Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
February 8, 2023

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Pharmacy and Therapeutics (P&T) Committee
Helpful Hints/Reference Document
P&T Charge

As defined by §22-6-122

The Medicaid Pharmacy and Therapeutics (P&T) Committee shall review and recommend classes of drugs to the Medicaid Commissioner for inclusion in the Medicaid Preferred Drug Plan. Class means a therapeutic group of pharmaceutical agents approved by the FDA as defined by the American Hospital Formulary Service.

The P&T Committee shall develop its preferred drug list recommendations by considering the clinical efficacy, safety and cost effectiveness of a product. Within each covered class, the Committee shall review and recommend drugs to the Medicaid Commissioner for inclusion on a preferred drug list. Medicaid should strive to insure any restriction on pharmaceutical use does not increase overall health care costs to Medicaid.

The recommendations of the P&T Committee regarding any limitations to be imposed on any drug or its use for a specific indication shall be based on sound clinical evidence found in labeling, drug compendia and peer reviewed clinical literature pertaining to use of the drug. Recommendations shall be based upon use in the general population. Medicaid shall make provisions in the prior approval criteria for approval of non-preferred drugs that address needs of sub-populations among Medicaid beneficiaries. The clinical basis for recommendations regarding the PDL shall be made available through a written report that is publicly available. If the recommendation of the P&T Committee is contrary to prevailing clinical evidence found in labeling, drug compendia and/or peer-reviewed literature, such recommendation shall be justified in writing.

Preferred Drug List/Program Definitions

Preferred Drug: Listed on the Agency's Preferred Drug Lists and will not require a prior authorization (PA).

Preferred with Clinical Criteria: Listed on the Agency's Preferred Drug Lists but will require a prior authorization. Clinical criteria must be met in order to be approved.

Non Preferred Drug: Covered by the Agency, if it is determined and supported by medical records to be medically necessary, but will require a PA.

Non Covered Drug: In accordance with Medicaid Drug Amendments contained in the Omnibus Budget Reconciliation Act of 1990 (OBRA 90 federal legislation), the Agency has the option to not cover (or pay for) some drugs. Alabama Medicaid does not cover/pay for the following:

- Drugs used for anorexia, weight loss or weight gain, with the exception of those specified by the Alabama Medicaid Agency
- Drugs used to promote fertility with the exception of those specified by the Alabama Medicaid Agency
- Drugs used for cosmetic purposes or hair growth
- Over-the-counter/non prescription drugs, with the exception of those specified by the Alabama Medicaid Agency
- Covered outpatient drugs when the manufacturer requires as a condition of sale that associated test and/or monitoring services be purchased exclusively from the manufacturer or designee
- DESI (Drug Efficacy Study Implementation [less than effective drugs identified by the FDA]) and IRS (Identical, Related and Similar [drugs removed from the market]) drugs which may be restricted in accordance with Section 1927(d) (2) of the Social Security Act
- Agents when used for the symptomatic relief of cough and colds except for those specified by the Alabama Medicaid Agency
- Prescription vitamin and mineral products, except prenatal vitamins and fluoride preparations and others as specified by the Alabama Medicaid Agency
- Agents when used for the treatment of sexual or erectile dysfunction, unless authorized for pulmonary hypertension.

(From Alabama Medicaid Agency Administrative Code, Chapter 16 and Alabama Medicaid Agency Provider Billing Manual, Chapter 27.)

Prior Authorization (PA): Process that allows drugs that require approval prior to payment to be reimbursed for an individual patient. Drugs may require PA if they are preferred with clinical criteria, are non-preferred status, or if they required PA prior to the PDL.

Medicaid may require prior authorization for generic drugs only in instances when the cost of the generic product is significantly greater than the net cost of the brand product in the same AHFS therapeutic class or when there is a clinical concern regarding safety, overuse or abuse of the product.

Although a product may require PA, the product is considered a covered product and Medicaid will pay for the product only once the PA has been approved.

Override: Process where drugs require approval prior to payment to be reimbursed for an individual patient if the claim falls outside a predetermined limit or criteria. Overrides differ from PA in that drugs or drug classes that require an override will automatically allow payment of the drug unless something on the claim hits a predetermined limit or criteria. The different types of overrides include:

Accumulation Edit
Brand Limit Switchover
Dispense As Written Override
Early Refill
Ingredient Duplication
Maintenance Supply Opt Out
Maximum Unit/Max Cost Limitations
Short Acting Opioid Naïve Override
Therapeutic Duplication

Electronic PA (EPA): The EPA system checks patient-specific claims history to determine if pharmacy and medical PA requirements are met at the Point-of-Sale claim submission for a non-preferred drug. If it is determined that all criteria are met and the request is approved, the claim will pay and no manual PA request will be required. Electronic PA results in a reduction in workload for providers because the claim is electronically approved within a matter of seconds with no manual PA required.

Prior Authorization Criteria Definitions

Appropriate Diagnosis: Diagnosis(es) that justifies the need for the drug requested. Diagnosis(es) **or** ICD-10 code(s) may be used. Use of ICD-10 codes provides specificity and legibility and will usually expedite review.

Prior Treatment Trials: Prior authorization requires that two (2) prescribed generic, OTC or brand name drugs have been utilized unsuccessfully relative to efficacy and/or safety within six (6) months prior to requesting the PA. The PA request must indicate that two (2) generic, OTC or other brand drugs have been utilized for a period of at least thirty (30) days each (14 days for Triptans, 3 days for EENT Vasoconstrictor Agents), **unless** there is an adverse/allergic response or contraindication. If the prescribing practitioner feels there is a medical reason for which the patient should not be on a generic, OTC or brand drug or drug trial, medical justification may be submitted in lieu of previous drug therapy. One prior therapy is acceptable in those instances when a class has only one preferred agent, either generic, OTC, or brand.

Stable Therapy: Allows for approval of a PA for patients who have been determined to be stable on a medication (same drug, same strength) for a specified timeframe and who continue to require therapy. Medications paid for through insurance, private pay or Medicaid are also counted toward the requirement. Providers will be required to document this information on the PA request form and note the program or method through which the medication was dispensed.

Medical Justification: An explanation of the reason the drug is required and any additional information necessary. Medical justification is documentation to support the physician's choice of the requested course of treatment. Documentation from the patient record (history and physical, tests, past or current medication/treatments, patient's response to treatment, etc) illustrates and supports the physician's request for the drug specified. For example, if a recommended therapy trial is contraindicated by the patient's condition or a history of allergy to a first-line drug, and the physician wants to order a non-preferred drug, documentation from the patient record would support that decision. In addition, medical justification may include peer reviewed literature to support the use of a non-preferred medication.

External Criteria

Skin and Mucous Membrane Agents

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trial

- The patient must also have failed 30-day treatment trials with at least two prescribed and preferred skin and mucous membrane agents in this class, either generic, OTC or brand, within the past 6 months, or one failed treatment trial when appropriate based on PDL preferred agents, or have a documented allergy or contraindication to all preferred agents in this class.

- For scabicides and pediculicides, the patient must have failed 14-day treatment trials with at least two prescribed and preferred skin and mucous membrane agents in this class, either generic, OTC or brand within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

- To meet prior usage requirements, drugs within this specific classification must be judged against others in the same class (AHFS specific).

    - For example, to qualify for a non-preferred topical anti-inflammatory agent, the patient must have met prior usage requirements of 30-day treatment trials with two other topical anti-inflammatory agents, either generic or brand.

Stable Therapy

- Approval may be given for children age 18 years and under who have been stable on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

- Skin and mucous membrane agents are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

AGENDA

ALABAMA MEDICAID AGENCY
PHARMACY AND THERAPEUTICS (P&T) COMMITTEE

February 8, 2023
1:00 p.m. – 3:00 p.m.

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1. Opening remarks……..……..…..…….……Chair
2. Approval of August 10, 2022 P&T Committee Meeting minutes…..…..…….……...…Chair
3. Pharmacy program update.....Alabama Medicaid
4. Oral presentations by manufacturers/manufacturers' representatives
   (prior to each respective class review)
5. Pharmacotherapy class re-reviews…University of Massachusetts Clinical Pharmacy Services
   - Skin and Mucous Membrane Antibacterials – AHFS 840404
   - Skin and Mucous Membrane Antivirals – AHFS 840406
   - Skin and Mucous Membrane Antifungals – AHFS 840408
   - Skin and Mucous Membrane Scabicides and Pediculicides – AHFS 840412
   - Skin and Mucous Membrane Local Anti-infectives, Miscellaneous – AHFS 840492
   - Skin and Mucous Membrane Corticosteroids – AHFS 840608
   - Skin and Mucous Membrane Nonsteroidal Anti-Inflammatory Agents – AHFS 840620
   - Skin and Mucous Membrane Anti-Inflammatory Agents, Misc – AHFS 840692
   - Skin and Mucous Membrane Antipruritics and Local Anesthetics – AHFS 840800
   - Skin and Mucous Membrane Astringents – AHFS 841200
   - Skin and Mucous Membrane Keratolytic Agents – AHFS 842800
   - Skin and Mucous Membrane Keratoplastic Agents – AHFS 843200
   - Skin and Mucous Membrane Agents, Miscellaneous – AHFS 849200
   - Skin and Mucous Membrane Cell Stimulants and Proliferants – AHFS 841600
   - Disease-Modifying Antirheumatic Agents – AHFS 923600
6. Results of voting announced…….....……...……..Chair
7. New Business……....……..……..……..Chair
   - Election of new Chair and Vice-Chair
8. Next meeting dates
   - May 3, 2023
   - August 2, 2023
   - November 8, 2023
9. Adjourn

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Antibacterials
AHFS Class 840404
February 8, 2023

I. Overview

The skin and mucous membrane antibacterials are approved for the treatment and/or prevention of various skin infections and bacterial vaginosis.[1-14] Humans are natural hosts for many microorganisms that colonize the skin as normal flora.[15,16] Bacterial infections of the skin are classified as either primary or secondary. Primary infections usually involve previously healthy skin and are typically caused by a single pathogen. Secondary infections occur in areas of previously damaged skin and are frequently polymicrobic.[15]

Bacterial vaginosis results from replacement of the normal hydrogen peroxide-producing *Lactobacillus* species in the vagina with anaerobic bacteria. Untreated vaginitis is associated with numerous health risks, such as pelvic inflammatory disease, cervicitis, postoperative infection, preterm delivery, postpartum endometritis, posthysterectomy infections, intrauterine infections, and other sexually transmitted infections.[17-20]

Impetigo is a contagious superficial skin infection seen predominantly in children. The most common causative organisms include *Staphylococcus aureus* and *Streptococcus pyogenes*. The goals of therapy are to relieve local symptoms, improve cosmetic appearance, as well as prevent spread and recurrence. Although impetigo usually heals spontaneously within two weeks without scarring, treatment may speed the time to resolution.[21]

Peritonitis is a complication that can occur in patients treated with peritoneal dialysis, which may result in sepsis and death. Peritoneal dialysis catheter-related infections are frequently related to direct contamination of the tubing or connection devices during exchanges. Exit-site infections predispose patients to peritonitis and the most common pathogens are *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Prevention of catheter infections is the primary goal of therapy, and antibiotic protocols have been developed to prevent exit-site infections.[22]

The skin and mucous membrane antibacterials that are included in this review are listed in Table 1. This review encompasses all topical dosage forms and strengths. Products solely indicated for the treatment of acne and/or rosacea are not covered by Alabama Medicaid. Therefore, these products are not included in this review. Most of the agents within this class are available in a generic formulation. This class was last reviewed in February 2021.

Table 1. Skin and Mucous Membrane Antibacterials Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Clindamycin	vaginal cream, vaginal gel, vaginal suppository	Cleocin®*, Clindesse®*, Xaciato®	clindamycin
Gentamicin	cream, ointment	N/A	gentamicin
Metronidazole	vaginal gel	MetroGel-Vaginal®*, Nuvessa®, Vandazole®*	metronidazole
Mupirocin	cream, ointment	Centany®*	mupirocin
Ozenoxacin	cream	Xepi®	none
Combination Products			
Neomycin and fluocinolone	cream	Neo-Synalar®	none
Neomycin and polymyxin B†	irrigation solution	N/A	neomycin and polymyxin B

*Generic is available in at least one dosage form or strength.

†Product is primarily administered in an institution and is included in Table 1 only.

N/A=Not available, PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the skin and mucous membrane antibacterials are summarized in Table 2.

Table 2. Treatment Guidelines Using the Skin and Mucous Membrane Antibacterials

Clinical Guideline	Recommendation(s)
Centers for Disease Control and Prevention: **Sexually Transmitted Diseases Treatment Guidelines (2021)**[17-19]	Genital herpes • Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management. • Systemic antiviral drugs can partially control the signs and symptoms of herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy. • Systemic antiviral drugs do not eradicate latent virus or affect the risk, frequency, or severity of recurrences after the drug is discontinued. • Randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes. • Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability. • Topical therapy with antiviral drugs provides minimal clinical benefit, and use is discouraged. • Newly acquired genital herpes can cause prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even patients with first episode herpes who have mild clinical manifestations initially can develop severe or prolonged symptoms. Therefore, all patients with first episodes of genital herpes should receive antiviral therapy. • Recommended regimens for first episodes of genital herpes: o acyclovir 400 mg orally three times daily for seven to 10 days o famciclovir 250 mg orally three times daily for seven to 10 days o valacyclovir 1,000 mg orally twice daily for seven to 10 days. • Treatment can be extended if healing is incomplete after 10 days of therapy. • Acyclovir 200 mg orally five times daily is also effective but is not recommended because of frequency of dosing. • Almost all patients with symptomatic first episode genital herpes simplex virus (HSV)-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection. • Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Suppressive therapy may be preferred because of the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners. • Long-term safety and efficacy have been documented among patients receiving daily acyclovir, valacyclovir, and famciclovir. • Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment. • Providers should discuss with patients on an annual basis whether they want to continue suppressive therapy because frequency of genital HSV-2 recurrence diminishes over time for many persons. • Discordant heterosexual couples in which a partner has a history of genital HSV-2 infection should be encouraged to consider suppressive antiviral therapy as part of a strategy for preventing transmission, in addition to consistent condom use and avoidance of sexual activity during recurrences. Suppressive antiviral therapy for persons with a history of symptomatic genital herpes also is likely to reduce transmission when used by those who

Clinical Guideline	Recommendation(s)
	have multiple partners. • Recommended regimens for suppressive therapy of genital herpes: o acyclovir 400 mg orally twice daily o famciclovir 250 mg orally twice daily o valacyclovir 500 mg orally once daily o valacyclovir 1,000 mg orally once daily. • Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens for persons who have frequent recurrences (i.e., ≥10 episodes/year). • Acyclovir, famciclovir and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding. Ease of administration and cost also are important to consider when deciding on prolonged treatment. • Because of the decreased risk for recurrences and shedding, suppressive therapy for HSV-1 genital herpes should be reserved for those with frequent recurrences through shared clinical decision-making between the patient and the provider. • Episodic treatment of recurrent herpes is most effective if initiation of therapy within one day of lesion onset or during the prodrome that precedes some outbreaks. Patients should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin. • Recommended regimens for episodic treatment of recurrent HSV-2 genital herpes: o acyclovir 800 mg orally twice daily for five days o acyclovir 800 mg orally three times daily for two days o famciclovir 1,000 mg orally twice daily for one day o famciclovir 500 mg orally once; followed by 250 mg orally twice daily for two days o famciclovir 125 mg orally twice daily for five days o valacyclovir 500 mg orally twice daily for three days o valacyclovir 1,000 mg orally once daily for five days. • Acyclovir 400 mg orally three times daily is also effective but is not recommended because of frequency of dosing. • Intravenous acyclovir should be provided to patients with severe HSV disease or complications that necessitate hospitalization or central nervous system complications. • HSV-2 meningitis is characterized clinically by signs of headache, photophobia, fever, meningismus, and cerebrospinal fluid (CSF) lymphocytic pleocytosis, accompanied by mildly elevated protein and normal glucose. • Optimal therapies for HSV-2 meningitis have not been well studied; however, acyclovir 5 to 10 mg/kg body weight IV every 8 hours until clinical improvement is observed, followed by high-dose oral antiviral therapy (valacyclovir 1 g 3 times/day) to complete a 10- to 14-day course of total therapy, is recommended. • Hepatitis is a rare manifestation of disseminated HSV infection, often reported among pregnant women who acquire HSV during pregnancy. Among pregnant women with fever and unexplained severe hepatitis, disseminated HSV infection should be considered, and empiric IV acyclovir should be initiated pending confirmation. • Consistent and correct condom use has been reported in multiple studies to decrease, but not eliminate, the risk for HSV-2 transmission from men to women. Condoms are less effective for preventing transmission from women to men.

Clinical Guideline	Recommendation(s)
	• Randomized clinical trials have demonstrated that PrEP with daily oral tenofovir disoproxil fumarate/emtricitabine decreases the risk for HSV-2 acquisition by 30% in heterosexual partnerships. Pericoital intravaginal tenofovir 1% gel also decreases the risk for HSV-2 acquisition among heterosexual women. • The patients who have genital herpes and their sex partners can benefit from evaluation and counseling to help them cope with the infection and prevent sexual and perinatal transmission. • Lesions caused by HSV are common among persons with human immunodeficiency virus (HIV) infection and might be severe, painful, and atypical. HSV shedding is increased among persons with HIV infection. • Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV infection among persons with HIV. • Recommended regimens for daily suppressive therapy of genital herpes in patients infected with HIV: o acyclovir 400 to 800 mg orally two to three times daily o famciclovir 500 mg orally twice daily o valacyclovir 500 mg orally twice daily • Recommended regimens for episodic treatment of genital herpes in patients infected with HIV: o acyclovir 400 mg orally three times daily for five to 10 days o famciclovir 500 mg orally twice daily for five to 10 days o valacyclovir 1,000 mg orally twice daily for five to 10 days • If lesions persist or recur in a patient receiving antiviral treatment, acyclovir resistance should be suspected, and a viral culture obtained for phenotypic sensitivity testing. • Foscarnet (40 to 80 mg/kg body weight IV every 8 hours until clinical resolution is attained) is the treatment of choice for acyclovir-resistant genital herpes. Intravenous cidofovir 5 mg/kg body weight once weekly might also be effective. • Imiquimod 5% applied to the lesion for 8 hours 3 times/week until clinical resolution is an alternative that has been reported to be effective. • Acyclovir can be administered orally to pregnant women with first-episode genital herpes or recurrent herpes and should be administered IV to pregnant women with severe HSV. • Suppressive acyclovir treatment starting at 36 weeks' gestation reduces the frequency of cesarean delivery among women who have recurrent genital herpes by diminishing the frequency of recurrences at term. However, such treatment might not protect against transmission to neonates in all cases. • Recommended regimen for suppression of recurrent genital herpes among pregnant women: o acyclovir 400 mg orally three times daily o valacyclovir 500 mg orally twice daily • Treatment recommended starting at 36 weeks' gestation. • Infants exposed to HSV during birth should be followed in consultation with a pediatric infectious disease specialist. • All newborn infants who have neonatal herpes should be promptly evaluated and treated with systemic acyclovir. The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 14 days if disease is limited to the skin and mucous membranes, or for 21 days for disseminated disease and disease involving the CNS. Pediculosis pubis (pubic lice infestation)

Clinical Guideline	Recommendation(s)

	• Recommended regimens:
	  ○ Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes.
	  ○ Piperonyl butoxide and pyrethrins applied to the affected area and washed off after 10 minutes.
	• Alternative regimens:
	  ○ Malathion 0.5% lotion applied for eight to 12 hours and washed off.
	  ○ Ivermectin 250 µg/kg orally and repeated in seven to 14 days.
	• Pregnant and lactating women should be treated with either permethrin or pyrethrin with piperonyl butoxide.
	
	<u>Scabies</u>
	• The first time a person is infested with *S. scabiei*, sensitization takes weeks to develop. However, pruritus might occur <24 hours after a subsequent reinfestation.
	• Scabies among adults frequently is sexually acquired, although scabies among children usually is not.
	• Recommended regimens:
	  ○ Permethrin 5% cream applied to all areas of the body from the neck down and washed off after eight to 14 hours.
	  ○ Ivermectin 200 µg/kg orally and repeated in two weeks.
	• Oral ivermectin has limited ovicidal activity; a second dose is required for eradication.
	• Alternative regimens:
	  ○ Lindane 1% lotion (1 oz) or cream (30 g) applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after eight hours.
	• Lindane is an alternative regimen because it can cause toxicity; it should be used only if the patient cannot tolerate the recommended therapies or if these therapies have failed.
	• Infants and children aged <10 years should not be treated with lindane.
	• Topical permethrin and oral and topical ivermectin have similar efficacy for cure of scabies. Choice of treatment might be based on patient preference for topical versus oral therapy, drug interactions with ivermectin, and cost.
	• Infants and young children should be treated with permethrin; the safety of ivermectin for children weighing <15 kg has not been determined.
	• Permethrin is the preferred treatment for pregnant women.
	• Crusted scabies is an aggressive infestation that usually occurs among immunodeficient, debilitated, or malnourished persons, including persons receiving systemic or potent topical glucocorticoids, organ transplant recipients, persons with HIV infection or human T-lymphotropic virus-1 infection, and persons with hematologic malignancies.
	• Combination treatment for crusted scabies is recommended with a topical scabicide, either 5% topical permethrin cream (full-body application to be repeated daily for 7 days then 2 times/week until cure) or 25% topical benzyl benzoate, and oral ivermectin 200 *u*g/kg body weight on days 1, 2, 8, 9, and 15. Additional ivermectin treatment on days 22 and 29 might be required for severe cases.
	
	<u>Bacterial vaginosis</u>
	• Bacterial vaginosis (BV) is a highly prevalent condition and the most common cause of vaginal discharge worldwide. However, in a nationally representative survey, the majority of women with BV were asymptomatic.
	• Treatment for BV is recommended for women with symptoms.

Clinical Guideline	Recommendation(s)
	• Established benefits of therapy among nonpregnant women are to relieve vaginal symptoms and signs of infection and reduce the risk for acquiring *C. trachomatis, N. gonorrhoeae*, *T. vaginalis*, *M. genitalium*, HIV, HPV, and HSV-2. • Recommended regimens for bacterial vaginosis include: o Metronidazole 500 mg orally twice daily for seven days. o Metronidazole 0.75% gel 5 g intravaginally once daily for five days. o Clindamycin 2% cream 5 g intravaginally at bedtime for seven days. • Alternative regimens include: o Tinidazole 2 g orally once daily for two days. o Tinidazole 1 g orally once daily for five days. o Clindamycin 300 mg orally twice daily for seven days. o Clindamycin 100 mg ovules intravaginally once at bedtime for three days. o Secnidazole 2 g oral granules in a single dose • Clindamycin ovules use an oleaginous base that might weaken latex or rubber products (e.g., condoms and diaphragms). Use of such products within 72 hours after treatment with clindamycin ovules is not recommended. • Oral granules should be sprinkled onto unsweetened applesauce, yogurt, or pudding before ingestion. A glass of water can be taken after administration to aid in swallowing. • Using a different recommended treatment regimen can be considered for women who have a recurrence; however, retreatment with the same recommended regimen is an acceptable approach for treating persistent or recurrent BV after the first occurrence. • BV treatment is recommended for all symptomatic pregnant women because symptomatic BV has been associated with adverse pregnancy outcomes, including premature rupture of membranes, preterm birth, intra-amniotic infection, and postpartum endometritis. <u>Uncomplicated vulvovaginal candidiasis</u> • Uncomplicated vulvovaginal candidiasis is defined as sporadic or infrequent vulvovaginal candidiasis, mild to moderate vulvovaginal candidiasis, candidiasis likely to be *Candida albicans*, or candidiasis in non-immunocompromised women. • Short-course topical formulations (i.e., single dose and regimens of one to three days) effectively treat uncomplicated vulvovaginal candidiasis. • Treatment with azoles results in relief of symptoms and negative cultures in 80 to 90% of patients who complete therapy. • Recommended regimens include: o Butoconazole 2% cream 5 g single intravaginal application. o Clotrimazole 1% cream 5 g intravaginally daily for seven to 14 days. o Clotrimazole 2% cream 5 g intravaginally daily for three days. o Miconazole 2% cream 5 g intravaginally daily for seven days. o Miconazole 4% cream 5 g intravaginally daily for three days. o Miconazole 100 mg vaginal suppository one suppository daily for seven days. o Miconazole 200 mg vaginal suppository one suppository for three days. o Miconazole 1,200 mg vaginal suppository one suppository for one day.

Clinical Guideline	Recommendation(s)
	○ Tioconazole 6.5% ointment 5 g single intravaginal application. ○ Terconazole 0.4% cream 5 g intravaginally daily for seven days. ○ Terconazole 0.8% cream 5 g intravaginally daily for three days. ○ Terconazole 80 mg vaginal suppository one suppository daily for three days. ○ Fluconazole 150 mg oral tablet in single dose. Complicated vulvovaginal candidiasis • Complicated vulvovaginal candidiasis is defined as recurrent vulvovaginal candidiasis, severe vulvovaginal candidiasis, non-albicans candidiasis, or candidiasis in women with diabetes, immunocompromising conditions, underlying immunodeficiency, or immunosuppressive therapy. • Most episodes of recurrent vulvovaginal candidiasis caused by *Candida albicans* respond well to short duration oral or topical azole therapy. • However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., seven to 14 days of topical therapy or a 100, 150, or 200 mg oral dose of fluconazole every third day for a total of three doses (day one, four, and seven) to attempt mycologic remission before initiating a maintenance antifungal regimen. • Recommended maintenance regimen is oral fluconazole (i.e., a 100-mg, 150-mg, or 200-mg dose) weekly for six months. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be considered. Severe vulvovaginal candidiasis • Severe vulvovaginal candidiasis is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy. • Either seven to 14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended. Non-albicans vulvovaginal candidiasis • The optimal treatment of non-albicans vulvovaginal candidiasis remains unknown. However, a longer duration of therapy (seven to 14 days) with a non-fluconazole azole drug (oral or topical) is recommended. • If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for three weeks. Genital warts • Treatment of anogenital warts should be guided by wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and provider experience. • There is no definitive evidence to suggest that any of the available treatments are superior to any other and no single treatment is ideal for all patients or all warts. • Because of uncertainty regarding the effect of treatment on future transmission of human papilloma virus and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution. • Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy. • In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment. • The treatment modality should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe.

Clinical Guideline	Recommendation(s)

	• Most genital warts respond within three months of therapy.
	• Recommended regimens for external anogenital warts (patient-applied):
	  ○ Podofilox 0.5% solution or gel.
	  ○ Imiquimod 3.75% or 5% cream.
	  ○ Sinecatechins 15% ointment.
	• Recommended regimens (provider administered):
	  ○ Cryotherapy with liquid nitrogen or cryoprobe.
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution
	  ○ Surgical removal
	• Fewer data are available regarding the efficacy of alternative regimens for treating anogenital warts, which include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir. Shared clinical decision-making between the patient and provider regarding benefits and risks of these regimens should be provided.
	• Podophyllin resin is no longer a recommended regimen because of the number of safer regimens available, and severe systemic toxicity has been reported when podophyllin resin was applied to large areas of friable tissue and was not washed off within 4 hours.
	
	<u>Cervical warts</u>
	• For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade squamous intraepithelial lesion must be performed before treatment is initiated.
	• Management of exophytic cervical warts should include consultation with a specialist.
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution
	
	<u>Vaginal warts</u>
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution
	
	<u>Urethral meatus warts</u>
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal
	
	<u>Intra-anal warts</u>
	• Management of intra-anal warts should include consultation with a colorectal specialist.
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal.
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution.

American College of Obstetricians and Gynecologists: **Vaginitis in Nonpregnant Patients (2020)**[20]	<u>Bacterial vaginosis</u> • Oral or intravaginal metronidazole or intravaginal clindamycin is recommended for the treatment of bacterial vaginosis. • Alternative treatments include oral secnidazole, oral tinidazole, or oral clindamycin. <u>Uncomplicated trichomoniasis</u>

Clinical Guideline	Recommendation(s)
	• Oral nitroimidazoles are recommended for the treatment of trichomoniasis. • Although a single dose of metronidazole has been the preferred treatment regimen for trichomoniasis, recent data from a randomized controlled trial show that a 7-day course of metronidazole is more effective. • Tinidazole single-dose therapy is an acceptable alternative to the metronidazole regimen. <u>Uncomplicated vulvovaginal candidiasis</u> • Because uncomplicated vulvovaginal candidiasis is effectively and safely treated with a variety of oral and topical treatments that are often available as over-the-counter and as short-course topical treatments, the choice of therapy should be individualized based on factors such as patient preference, cost, convenience, adherence, ease of use, and history of response or adverse reactions to previous treatments. • Over-the-counter intravaginal agents include clotrimazole, miconazole, and tioconazole. • Prescription options include intravaginal butoconazole, intravaginal terconazole, and oral single dose fluconazole. <u>Complicated vulvovaginal candidiasis</u> • Objective information in the form of culture is important to identify the yeast species and correlate with symptoms. • Most infections are secondary to *C. albicans*, which is responsive to both topical and oral azoles. Oral fluconazole is an effective and convenient treatment for complicated infections with *C. albicans*. <u>Recurrent vulvovaginal candidiasis</u> • Extended antifungal treatment is recommended for patients with recurrent vulvovaginal candidiasis to reduce the likelihood of persistent symptoms. After initial treatment of the acute infection, suppressive therapy with weekly doses of either an intravaginal or oral azole improves cure rates and decreases recurrence rates. • Prolonged antifungal treatment with fluconazole (150 mg weekly for six months) successfully controlled more than 90% of recurrent symptomatic episodes. • For patients who are unable or unwilling to take fluconazole, prolonged therapy with intermittent topical agents, such as clotrimazole (500 mg weekly or 200 mg twice a week), are acceptable options. <u>Severe vulvovaginal candidiasis</u> • These patients require a prolonged course with a topical intravaginal azole for 10 to 14 days or two to three doses of oral fluconazole taken orally three days apart. • An acute infection is treated with an extended course of a topical or oral azole. Topical agents can be extended to a 10 to 14-day intravaginal course. <u>Non-albicans vulvovaginal candidiasis</u> • Therapy with intravaginal boric acid (600-mg capsules daily for a minimum of 14 days) is effective for *C glabrata* and other atypical *Candida* species. • Patients with non-*albicans Candida* vulvovaginal candidiasis in whom boric acid therapy is ineffective should be referred to a subspecialist for further management. • Boric acid can be fatal if ingested orally and patients should be well counseled to use it only intravaginally, to place it out of the reach of children, and to use reliable contraception. • Topical flucytosine, 5 g nightly for two weeks, is another effective treatment for *C glabrata*.

Clinical Guideline	Recommendation(s)
American Academy of Family Physicians: **Impetigo: Diagnosis and Treatment (2014)[21]**	• Topical antibiotics (e.g., mupirocin 2% cream or ointment, retapamulin 1% ointment, and fusidic acid [not available in the United States]) are more effective than placebo and preferable to oral antibiotics for limited impetigo. • Retapamulin is a novel pleuromutilin antibacterial and the first new topical antibacterial in nearly 20 years. Retapamulin acts on three key aspects of bacterial protein synthesis, making it far less likely to induce resistant strains. It is approved for the treatment of impetigo due to *Staphylococcus aureus* (methicillin-susceptible isolates only) or *Streptococcus pyogenes* in adults and children at least nine months of age. • Oral penicillin should not be used for impetigo because it is less effective than other antibiotics. • Oral erythromycin and macrolides should not be used to treat impetigo because of emerging drug resistance. • There is insufficient evidence to recommend topical disinfectants for the treatment of impetigo. • There is insufficient evidence to recommend (or dismiss) popular herbal treatments for impetigo.
International Society for Peritoneal Dialysis: **Reducing Risks of Peritoneal Dialysis-Related Infections (2011)[22]**	<u>General considerations</u> • Prevention of catheter infections (and thus peritonitis) is the primary goal of exit-site care. • Antibiotic protocols against *Staphylococcus Aureus* are effective in reducing the risk of *Staphylococcus Aureus* catheter infections. <u>Antibiotic protocol options for preventing exit-site infections</u> • Mupirocin: o Daily after cleansing in all patients. o Daily after cleansing in carriers only. o In response to a positive exit-site culture for *Staphylococcus aureus* denoting carriage. o Mupirocin ointment should be avoided in patients with polyurethane catheters and mupirocin cream should be substituted. • Gentamicin cream: o Daily in all patients after cleansing.
European (International Union Against Sexually Transmitted Infections/ World Health Organization): **Guideline on the Management of Vaginal Discharge (2018)[23]**	<u>Bacterial vaginosis</u> • Recommended regimens for bacterial vaginosis: o Metronidazole 400 to 500 mg twice daily for five to seven days. o Intravaginal metronidazole 0.75% gel once daily for five days. o Intravaginal clindamycin 2% cream once daily for seven days. • Alternative regimens for bacterial vaginosis: o Metronidazole 2 g in a single dose. o Tinidazole 2 g in a single dose. o Tinidazole 1 g daily for five days. o Clindamycin 300 mg twice daily for seven days. o Dequalinium chloride 10 mg vaginal tablet once daily for six days. • Clindamycin and metronidazole have equal efficacy, comparing oral and vaginal formulations, both after one week and after one month of therapy. Approximately 58 to 88% will be cured after five days treatment with metronidazole or clindamycin. In most studies, clindamycin tended to have less adverse effects than metronidazole. • Single dose therapies have lower cure rates than prolonged treatment. Oral metronidazole for seven days has a significantly higher cure rate than single dose treatment (88 vs 54% and 82 vs 62% at three to four weeks after completion of therapy). • Intravaginal metronidazole is recommended for the treatment of persistent and recurrent bacterial vaginosis.

Clinical Guideline	Recommendation(s)
	Aerobic vaginitis • Recommended regimens for aerobic vaginitis: o 2% clindamycin cream 5 g intravaginally for seven to 21 days. o Combination use of intravaginal clindamycin and intravaginal steroids e.g., Hydrocortisone 300 to 500 mg intravaginally for seven to 21 days for more severe cases. o In cases with a significant atrophy component, local estrogens can be added. Vaginal candidiasis • Intravaginal and oral therapies are equally effective for vaginal candidiasis. • Treatment with azoles results in relief of symptoms and negative cultures among 80 to 90% of patients after either oral or topical treatment; only topical preparations should be used during pregnancy. • Recommended regimens for vaginal candidiasis: o Fluconazole 150 mg orally as a single dose. o Itraconazole 200 mg twice daily for one day. o Clotrimazole vaginal tablet 500 mg once or 200 mg once daily for three days. o Miconazole vaginal ovule 1,200 mg as a single dose or 400 mg once daily for three days. o Econazole vaginal pessary 150 mg as a single dose. • Standard single dose treatments are as effective as longer courses. • In a severely symptomatic attack, symptomatic benefit is with fluconazole 150 mg treatment repeated after three days. Trichomonas vaginalis • Recommended regimens for trichomonas vaginalis: o Metronidazole 400 to 500 mg orally twice daily for five to seven days. o Metronidazole 2 gram orally in a single dose. o Tinidazole 2 g orally in a single dose. • The nitroimidazoles are the only class of drugs useful for the oral or parenteral therapy of trichomoniasis and most strains are highly susceptible.
British Association for Sexual Health and Human Immunodeficiency Virus: **National Guideline for the Management of Bacterial Vaginosis (2012)[24]**	• Recommended regimens for bacterial vaginosis: o Metronidazole 400 mg twice daily for five to seven days. o Metronidazole 2 g in a single dose. o Intravaginal metronidazole 0.75% gel once daily for five days. o Intravaginal clindamycin 2% cream once daily for seven days. • Alternative regimens for bacterial vaginosis: o Tinidazole 2 g in a single dose. o Clindamycin 300 mg twice daily for seven days. • All these treatments have been shown to achieve cure rates of 70 to 80% after four weeks in controlled trials using placebo or comparison with oral metronidazole. Oral metronidazole treatment is established and usually well tolerated. Dosage and duration used in trials have varied from 400 mg twice daily for five days to 500 mg twice daily for seven days. The 2 g immediate dose may be slightly less effective at four week follow up. • Intravaginal metronidazole gel and clindamycin cream have similar efficacy. Metronidazole is less active against lactobacilli than clindamycin. Clindamycin is more active than metronidazole against most of the bacteria associated with bacterial vaginosis. • Oral clindamycin has only been evaluated in one study with short-term follow up, and in pregnant women. • Tinidazole has similar in vitro antibacterial activity and efficacy compared to

Clinical Guideline	Recommendation(s)
	metronidazole.
Infectious Diseases Society of America: **Clinical Practice Guidelines for the Treatment of Methicillin-resistant *Staphylococcus Aureus* Infections in Adults and Children (2011)**[25]	Impetigo and secondarily infected skin lesions (e.g., eczema, ulcers, or lacerations) in children • Topical mupirocin 2% ointment can be used. Methicillin-resistant *Staphylococcus Aureus* infections in neonates (neonatal pustulosis) • For mild cases with localized disease, topical treatment with mupirocin may be adequate in full-term neonates and young infants.
Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update (2014)**[26]	Impetigo and ecthyma • Bullous and nonbullous impetigo can be treated with oral or topical antimicrobials, but oral therapy is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission of infection. Treatment for ecthyma should be an oral antimicrobial. Treatment of bullous and nonbullous impetigo should be with either mupirocin or retapamulin twice daily for five days. Recurrent skin abscesses • A recurrent abscess at a site of previous infection should prompt a search for local causes such as a pilonidal cyst, hidradenitis suppurativa, or foreign material. Recurrent abscesses should be drained and cultured early in the course of infection. • After obtaining cultures of recurrent abscess, treat with a five to ten day course of an antibiotic active against the pathogen isolated. Consider a five day decolonization regimen twice daily of intranasal mupirocin, daily chlorhexidine washes, and daily decontamination of personal items such as towels, sheets, and clothes for recurrent *S. aureus* infection.
Society of Obstetricians and Gynecologists of Canada (SOGC): **Clinical practice guideline on vulvovaginitis − Screening for and management of trichomoniasis, vulvovaginal candidiasis, and bacterial vaginosis (2015)**[27]	• Following initial therapy, treatment success of recurrent vulvovaginal candidiasis is enhanced by maintenance of weekly oral fluconazole for up to six months. • Symptomatic vulvovaginal candidiasis treated with topical azoles may require longer courses of therapy to be resolved. • Test of cure following treatment of trichomoniasis with oral metronidazole is not recommended. • Higher-dose therapy may be needed for treatment-resistant cases of trichomoniasis. • Cure rates are equal at up to 88% for trichomoniasis treated with oral metronidazole 2 g once or 500 mg twice daily for seven days. Partner treatment, even without screening, enhances cure rates. • In pregnancy, treatment of symptomatic Trichomonas vaginalis with oral metronidazole is warranted for the prevention of preterm birth. • Bacterial vaginosis should be diagnosed using either clinical (Amsel's) or laboratory (Gram stain with objective scoring system) criteria. • Symptomatic bacterial vaginosis should be treated with oral metronidazole 500 mg twice daily for seven days. Alternatives include vaginal metronidazole gel and oral or vaginal clindamycin cream. • Longer courses of therapy for bacterial vaginosis are recommended for women with documented multiple recurrences.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the skin and mucous membrane antibacterials are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Skin and Mucous Membrane Antibacterials[1-14]

	Single-Entity Agents					Combination Products
Indication	**Clindamycin**	**Gentamicin**	**Metronidazole**	**Mupirocin**	**Ozenoxacin**	**Neomycin and Fluocinolone**
Skin Infections						
Treatment of impetigo due to *Staphylococcus aureus* and *Streptococcus pyogenes*				✔ *	✔	
Treatment of primary and secondary skin infections		✔				
Treatment of corticosteroid-responsive dermatoses with secondary infection						✔
Treatment of secondarily infected traumatic skin lesions due to susceptible strains of *S. aureus* and *S. pyogenes*				✔ †		
Vaginal Infections						
Treatment of bacterial vaginosis	✔		✔			

*Ointment formulation.
†Cream formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the skin and mucous membrane antibacterials are listed in Table 4. Pharmacokinetic properties of the combination products not listed in the table below would be in line with the properties of their individual components listed in the table below.

Table 4. Pharmacokinetic Parameters of the Skin and Mucous Membrane Antibacterials[1,3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Clindamycin	Vaginal cream: 5 Vaginal supp: 30	Not reported	Liver	Renal (<10)	1.5 to 11.0
Fluocinolone	Not reported	Not reported	Liver	Renal	Not reported
Gentamicin*	≤5	0 to 30	Not reported	Renal (65 to 100)	2 to 3.9
Metronidazole	56	<20	Liver	Renal (60 to 80)	6 to 12
Mupirocin	No measurable absorption	>97%	Not reported	Renal	0.28 to 0.6
Neomycin	3	0 to 30	Not reported	Fecal (97)	Not reported
Ozenoxacin	No measurable absorption	80 to 85	Liver (minimal)	Not reported	Not reported

*Greater absorption of drug with cream than ointment.

V. Drug Interactions

Major drug interactions with the skin and mucous membrane antibacterials are listed in Table 5.

Table 5. Major Drug Interactions with the Skin and Mucous Membrane Antibacterials[3]

Generic Name(s)	Interaction	Mechanism
Clindamycin	Erythromycin	Concurrent use of clindamycin and erythromycin may result in antagonistic antimicrobial effects.
Fluocinolone	Desmopressin	Concurrent use of fluocinolone and desmopressin may result in increased risk of severe hyponatremia.
Fluocinolone	Bemiparin	Concurrent use of fluocinolone and bemiparin may result in increased risk of bleeding
Fluocinolone	Nadroparin	Concurrent use of fluocinolone and nadroparin may result in increased risk of bleeding
Fluocinolone	Sargramostim	Concurrent use of fluocinolone and sargramostim may result in increased myeloproliferative effects of sargramostim.
Gentamicin	Lysine	Concurrent use of gentamicin and lysine may result in increased risk of nephrotoxicity.
Metronidazole	Amprenavir	Concurrent use of metronidazole and amprenavir may result in an increased risk of propylene glycol toxicity (seizures, tachycardia, lactic acidosis, renal toxicity, hemolysis).
Metronidazole	QT-interval prolonging drugs	Concurrent use of metronidazole and QT-interval prolonging drugs may result in increased risk of QT-interval prolongation and arrhythmias.
Metronidazole	Disulfiram	Concurrent use of metronidazole and disulfiram may result in CNS toxicity (psychotic symptoms, confusion).
Metronidazole	Dronabinol	Concurrent use of metronidazole and dronabinol may result in disulfiram-like reaction.

VI. Adverse Drug Events

The most common adverse drug events reported with the skin and mucous membrane antibacterials are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Antibacterials[1-14]

Adverse Events	Single-Entity Agents					Combination Products
	Clindamycin	Gentamicin	Metronidazole	Mupirocin	Ozenoxacin	Neomycin and Fluocinolone
Central Nervous System						
Depression	-	-	<1	-	-	-
Dizziness	<1	-	2	<1	-	-
Fatigue	<1	-	<1	-	-	-
Headache	7	-	2 to 7	2 to 9	-	-
Vertigo	<1	-	-	-	-	-
Dermatological						
Acneiform eruptions	-	-	-	-	-	✔
Acne vulgaris	-	-	<1	-	-	-
Burning		-	-	<4	-	✔
Cellulitis	-	-	-	<1	-	-
Contact dermatitis	✔	-	-	<1	-	✔
Dermatitis	-	-	-	<1	-	-
Dryness	-	-	-	<1	-	✔
Erythema	<1	✔	-	<1	-	-
Folliculitis	✔	-	-	-	-	✔
Hypertrichosis	-	-	-	-	-	✔
Hypopigmentation	-	-	-	-	-	✔
Irritation	✔	-	-	-	-	✔
Maceration of skin	-	-	-	-	-	✔
Miliaria	-	-	-	-	-	✔
Perioral dermatitis	-	-	-	-	-	✔
Pruritus	<1	✔	6	≤2	-	✔
Rash	<1	-	1	≤1	-	-
Rosacea-like face eruption	-	-	-	-	<1	-
Seborrhea	✔	-	-	-	-	-
Seborrheic dermatitis	-	-	-	-	<1	-
Skin atrophy	-	-	-	-	-	✔
Stinging	-	-	-	<2	-	-
Striae	-	-	-	-	-	✔
Tenderness	-	-	-	<1	-	-

Adverse Events	Single-Entity Agents					Combination Products
	Clindamycin	Gentamicin	Metronidazole	Mupirocin	Ozenoxacin	Neomycin and Fluocinolone
Urticaria	<1	-	<1	<1	-	-
Gastrointestinal						
Abdominal bloating	-	-	<1	-	-	-
Abdominal gas	-	-	<1	-	-	-
Abdominal pain/cramps	<1	-	1 to 5	<1	-	-
Appetite decreased	-	-	1	-	-	-
Clostridioides difficile colitis	✔	-	-	-	-	-
Clostridioides difficile-associated diarrhea	-	-	-	<1	-	-
Colitis	✔	-	-	-	-	-
Constipation	2	-	<1	-	-	-
Diarrhea	<1	-	1	<1	-	-
Dyspepsia	<1	-	<1	-	-	-
Flatulence	<1	-	<1	-	-	-
Halitosis	<1	-	-	-	--	-
Hematochezia	✔	-	-	-	-	-
Gastrointestinal discomfort/distress	-	-	7	-	-	-
Nausea	<1	-	≤4	1 to 5	-	-
Taste perversion	<1	-	2	3	-	-
Thirst	-	-	<1	-	-	-
Vomiting	<1	-	≤4	-	-	-
Xerostomia	-	-	<1	<1	-	-
Genitourinary						
Abnormal uterine bleeding	-	-	1	-	-	-
Cervical candidiasis	-	-	≤10	-	-	-
Dark urine	-	-	<1	-	-	-
Dysmenorrhea	<1	-	1 to 3	-	-	-
Dysuria	<1	-	<1	-	-	-
Heavy menstrual bleeding	-	-	<1	-	-	-
Nephrotoxicity	-	-	-	-	-	✔
Pelvic discomfort/pain	<1	-	3	-	-	-
Pyelonephritis	<1	-	<1	-	-	-
Salpingitis	-	-	<1	-	-	-
Trichomonal vaginitis	1	-	-	-	-	-
Urinary frequency	-	-	<1	-	-	-
Urinary tract infection	2	-	<1	-	-	-

Adverse Events	Single-Entity Agents					Combination Products
	Clindamycin	Gentamicin	Metronidazole	Mupirocin	Ozenoxacin	Neomycin and Fluocinolone
Uterine hemorrhage	<1	-	-	-	-	-
Vaginal burning/irritation	<1	-	9	-	-	-
Vaginal candidiasis	2 to 14	-	6 to 10	-	-	-
Vaginal discharge	✔	-	12	-	-	-
Vaginal discomfort	<1	-	-	-	-	-
Vaginal dryness	<1	-	-	-	-	-
Vaginal erythema	<1	-	-	-	-	-
Vaginal hemorrhage	✔					
Vaginal infection	✔	-	-	-	-	-
Vaginal pain	2	-	-	-	-	-
Vaginal swelling	✔	-	-	-	-	-
Vulvovaginal disorder	✔	-	-	-	-	-
Vulvovaginal pruritus	<1	-	2	-	-	-
Vulvovaginitis	4 to 6	-	≤10	-	-	-
Respiratory						
Asthma	-	-	<1	-	-	-
Cough	-	-	-	2	-	-
Pharyngitis	-	-	2	4	-	-
Respiratory tract congestion	-	-	-	5	-	-
Rhinitis	-	-	<1	6	-	-
Other						
Abnormal white blood cell differential	-	-	2	-	-	-
Allergic reaction	<1	-	-	-	-	-
Anorexia	-	-	<1	-	-	-
Aphthous stomatitis	-	-	-	<1	-	-
Bacterial infection	<1	-	1	-	-	-
Bacterial overgrowth syndrome, mycosis	-	-	-	-	-	-
Back pain	5	-	<1	-	-	-
Blepharitis	-	-	-	<1	-	-
Bloating	-	-	<1	-	-	-
Breast hypertrophy	-	-	<1	-	-	-
Diaphoresis	-	-	<1	-	-	-
Ear pain	-	-	-	<1	-	-
Edema	-	-	<1	<1	-	-
Endometriosis	<1	-	-	-	-	-

Adverse Events	Single-Entity Agents					Combination Products
	Clindamycin	Gentamicin	Metronidazole	Mupirocin	Ozenoxacin	Neomycin and Fluocinolone
Epistaxis	<1	-	-	<1	-	-
Eye pain	✔	-	-	-	-	-
Flank pain	<1	-	-	-	-	-
Fever	<1	-	-	-	-	-
Flu-like symptoms	-	-	<1	-	-	-
Fungal infection	≤1	-	12	-	-	-
Gingivitis	-	-	<1	-	-	-
Hypersensitivity	<1	-	<1	<1	-	-
Hyperthyroidism	<1	-	-	-	-	-
Increased thirst	-	-	<1	-	-	-
Increased wound secretion	-	-	-	<1	-	-
Insomnia	-	-	<1	-	-	-
Intermenstrual bleeding	<1	-	-	-	-	-
Lactation	-	-	<1	-	-	-
Leukorrhea	-	-	<1	-	-	-
Mastalgia	-	-	1	-	-	-
Menstrual disorder	<1	-	-	-	-	-
Metrorrhagia	<1	-	-	-	-	-
Mucous membrane disease	-	-	<1	-	-	-
Muscle cramps	-	-	1	-	-	-
Ototoxicity	-	-	-	-	-	✔
Pain	<1	-	<1	<2	-	-
Secondary infection	-	-	-	<1	-	✔

✔ Percent not specified.
- Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the skin and mucous membrane antibacterials are listed in Table 7.

Table 7. Usual Dosing Regimens for the Skin and Mucous Membrane Antibacterials[1-14]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single-entity Agents			
Clindamycin	Bacterial vaginosis: Vaginal cream: Cleocin®: insert one applicatorful intravaginally once daily at bedtime for three or seven days in non-pregnant patients and for seven days in pregnant patients Clindesse®: insert one applicatorful intravaginally once Vaginal gel: insert one applicatorful intravaginally once Vaginal suppository: insert one suppository intravaginally once daily at bedtime for three days	Bacterial vaginosis: Cream 2%: Limited data available: insert one applicatorful intravaginally at bedtime for 7 days Gel: insert one applicatorful intravaginally once Suppository: Insert one ovule intravaginally once daily at bedtime for 3 days	Vaginal cream: 2% Vaginal gel: 2% Vaginal suppository: 100 mg
Gentamicin	Primary and secondary skin infections: Cream or ointment: apply to the lesions three to four times daily	Primary and secondary skin infections: Cream or ointment: apply to the lesions three to four times daily	Cream: 0.1% Ointment: 0.1%
Metronidazole	Bacterial vaginosis: Vaginal gel: MetroGel-Vaginal®: insert one applicatorful intravaginally one to two times daily for five days. For once daily dosing, administer at bedtime Vandazole®: insert one applicatorful intravaginally once daily for five days. For once daily dosing, administer at bedtime Nuvessa®: insert one applicatorful intravaginally once at bedtime	Bacterial vaginosis: Vaginal gel 0.75%: Adolescents: one applicatorful intravaginally once daily at bedtime for 5 days Vaginal gel 1.3%: Children ≥12 years and adolescents: one applicatorful intravaginally once at bedtime as a single dose	Vaginal gel: 0.75% 1.3%
Mupirocin	Treatment of impetigo due to *Staphylococcus aureus* and *Streptococcus pyogenes*: Ointment: apply to the affected area two to three times daily for five days Treatment of secondarily infected traumatic skin lesions due to susceptible strains of *S. aureus* and *S. pyogenes*: Cream: apply to the affected area two to three times daily, typically for 7 to 14 days depending on severity and	Treatment of impetigo and minor skin infection in infants, children and adolescents: Cream, ointment: apply small amount 3 times daily for 5 to 10 days; patients not showing clinical response after 5 days should be reevaluated	Cream: 2% Ointment: 2%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	clinical response; if no response after three to five days, re-evaluate treatment		
Ozenoxacin	Treatment of impetigo due to *Staphylococcus aureus* and *Streptococcus pyogenes*: Cream: Apply a thin layer to the affected area (up to 100 cm^2) two times daily for five days	Treatment of impetigo due to *S. aureus* and *S. pyogenes* in children two months of age and older: Cream: Apply a thin layer to the affected area (up to 100 cm^2 for patients ≥12 years of age; or 2% of total body surface area not to exceed 100 cm^2 for patients <12 years of age) two times daily for five days	Cream: 1%
Combination Products			
Neomycin and fluocinolone	Treatment of corticosteroid-responsive dermatoses with secondary infection: Cream: apply to the affected area as a thin film two to four times daily	Refer to adult dosing. Dosage should be based on severity of disease and patient response; use smallest amount for shortest period of time. Therapy should be discontinued when control is achieved.	Cream: 0.5%-0.025%

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the skin and mucous membrane antibacterials are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Skin and Mucous Membrane Antibacterials

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Bacterial Vaginosis				
Nyirjesy et al.[28] (2007) Clindamycin 2% vaginal cream as a single dose vs metronidazole 0.75% vaginal gel BID for 5 days	RETRO Nonpregnant women ≥18 years of age with a clinical diagnosis of bacterial vaginosis	N=55 21 to 30 days	Primary: Microbiologic, clinical, and therapeutic cure of bacterial vaginosis Secondary: Not reported	Primary: There were significant reductions in mean *Mobiluncus* scores from baseline to the test-of-cure visit in both treatment groups (P<0.0001 for both groups). The mean *Mobiluncus* score in the clindamycin group was less than in the metronidazole group at the test-of-cure visit (0.05 vs 0.33; P<0.0471), indicating a significantly greater decrease in the presence of *Mobiluncus* in the clindamycin group compared to the metronidazole group. Significantly more patients in the clindamycin group compared to the metronidazole group achieved microbiologic (57.5 vs 26.7%; P=0.04) and clinical cure (57.5 vs 26.7%; P=0.04) of bacterial vaginosis. There was no significant difference between the clindamycin and metronidazole groups with regards to therapeutic cure rates (P=0.09). Secondary: Not reported
Nyirjesy et al.[29] (2006) Clindamycin 2% vaginal cream as a single dose vs clindamycin 2% vaginal cream QD for 7 days	RETRO Nonpregnant women ≥18 years of age with a clinical diagnosis of bacterial vaginosis	N=408 21 to 30 days	Primary: Change in *Lactobacillus* scores from baseline to the test-of-cure visit Secondary: Not reported	Primary: *Lactobacillus* scores were similar between the three treatment groups at the test-of-cure visit (P=0.71). The percentages of patients with a score of four (reflecting no observed *Lactobacillus* morphotypes) were reduced to 34, 36, and 39% in the clindamycin single-dose, clindamycin multi-dose, and metronidazole groups, respectively (P<0.0001 for all treatment groups). At the test-of-cure visit, 43, 38, and 38% of patients in the clindamycin single-dose, clindamycin multi-dose, and metronidazole groups, respectively, had *Lactobacillus* scores of zero (reflecting fully restored *Lactobacillus*). The three treatment groups were comparable with respect

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vs metronidazole 0.75% vaginal gel BID for 5 days				to the distributions of *Lactobacillus* scores within the groups. The changes in *Lactobacillus* scores from baseline to the test-of-cure visit were similar across the three treatment groups (P=0.50). Secondary: Not reported
Faro et al.[30] (2005) Clindamycin 2% vaginal cream (Clindesse®) as a single dose vs clindamycin 2% vaginal cream (Cleocin®) QD	AC, MC, PG, RCT, SB Non-pregnant women ≥18 years of age, with bacterial vaginosis infections	N=540 30 days	Primary: Investigator cure, clinical cure, and therapeutic cure Secondary: Not reported	Primary: There were no statistically significant differences found in the cure rates between the Clindesse® and the Cleocin® treatment groups. The P values for investigator cure, clinical cure, and therapeutic cure were P=0.702, P=0.945, and P=0.572, respectively. Secondary: Not reported
McCormack et al.[31] (2001) Clindamycin 2% vaginal cream QD vs sulfonamide vaginal cream BID	DB, MC, RCT Nonpregnant women ≥16 years of age with symptomatic bacterial vaginosis	N=159 7 days, with follow-up visits at days 5 to 10 and 25 to 39	Primary: Clinical cure or improvement Secondary: Not reported	Primary: Clinical cure or improvement was seen in 69.6% of patients in the clindamycin group compared to 41.8% of patients in the triple sulfonamide group (P<0.0001). Among patients with a history of bacterial vaginosis, the cure rates at five to 10 days after treatment for clindamycin and sulfonamide were 25 and 51%, respectively (P<0.001); and, at 25 to 39 days post-treatment, the cure rates for clindamycin and sulfonamide were 63.9 and 29.4%, respectively (P<0.0001). Among patients with no history of bacterial vaginosis, the cure rates at five to 10 days after treatment for clindamycin and sulfonamide were 27.9 and 42.9%, respectively; and, the improvement rates were 46.5 and 35.7%, respectively (P=0.4). At 25 to 39 days post-treatment, the cure rates for clindamycin and sulfonamide were 44.2 and 46.4%, respectively (P=0.11).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The Gram stain evaluation showed fewer stains consistent with bacterial vaginosis for the clindamycin group as compared to the sulfonamide group, at both post-treatment evaluations (P<0.002). Secondary: Not reported
Paavonen et al.[32] (2000) Clindamycin 100 mg vaginal ovules QD for 3 days vs metronidazole 500 mg capsules BID for 7 days	AC, DB, MC, RCT Adult women diagnosed with bacterial vaginosis	N=399 52 days	Primary: Overall clinical outcome, reported as cure, failure, and non-assessable efficacy rate Secondary: Clinical status, symptoms of vaginitis or cervicitis at each follow-up visit, patient evaluation of efficacy at second follow-up visit, and adverse effects	Primary: No statistically significant difference between the two treatment groups was observed regarding the primary endpoint (95% CI, -10.6 to 13.4; P=0.810). Secondary: There was no statistically significant difference in clinical status, at either the first or second follow-up visit, between the two treatment groups (P>0.5). There was no significant difference in the proportion of patients who rated their vaginal infection as cured in the metronidazole treatment group (79.6%) compared to clindamycin treatment group (78.3%). There was no difference in the number of patients reporting symptoms of vaginitis and cervicitis at either the first or second follow-up visit. Treatment-related adverse effects were more frequent in the metronidazole group (16.3%), compared to the clindamycin treatment group (10.3%), but this difference was not statistically significant (P=0.104).
Austin et al.[33] (2005) Clindamycin vaginal ovules QD for 3 days vs metronidazole vaginal gel QD for	AC, DB, RCT Premenopausal, non-pregnant women ≥18 years of age diagnosed with bacterial vaginosis	N=119 90 days	Primary: Overall clinical outcome, microbiologic response Secondary: Not reported	Primary: The clinical response rate did not differ between the two treatment groups. At seven to 12 days, cure rates were 79 and 88% for metronidazole and clindamycin, respectively (P=0.3). At 35 to 45 days, cure rates were 62 and 55%, respectively (P=0.5). The rates were 58 and 55%, respectively, at days 70 to 90 after therapy (P=0.8). While both therapies resulted in decreased colonization by *Gardnerella vaginalis* and *Mycoplasma hominis* (P<0.001), only the metronidazole treatment led to a significant decrease in the frequency and concentration of *Prevotella bivia* and black-pigmented *Prevotella* species (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
5 days				Women treated with metronidazole had a significant decrease in colonization by *Ureaplasma urealyticum* (P<0.001) compared to clindamycin-treated women (P=0.3). Both *Porphyromonas* and nonpigmented *Prevotella* species decreased significantly following treatment with either regimen (P<0.001). Clindamycin-resistant subpopulations of *P. bivia* and black-pigmented *Prevotella* species emerged seven to 12 days after therapy even among patients initially colonized by clindamycin-susceptible strains. Secondary: Not reported
Ferris et al.[34] (1995) Clindamycin 2% vaginal cream QD for 7 days vs metronidazole vaginal gel BID for 5 days vs metronidazole 500 mg capsules BID for 7 days	AC, DB, RCT Premenopausal, non-pregnant women ≥18 years of age diagnosed with bacterial vaginosis	N=101 14 days	Primary: Cure rate, post-treatment vulvovaginal candidiasis Secondary: Not reported	Primary: There was no significant difference in cure rates for oral metronidazole (84.2%), metronidazole vaginal cream (75.0%), or clindamycin vaginal cream (86.2%; P=0.548). There was no significant difference in the rates of post-treatment vulvovaginal candidiasis associated with oral metronidazole (12.5%), metronidazole vaginal cream (30.4%), or clindamycin vaginal cream (14.8%; P=0.272). Secondary: Not reported
Fischbach et al.[35] (1993) Clindamycin 2% vaginal cream QD for 7 days	AC, DB, MC, RCT Premenopausal, non-pregnant women ≥18 years of age diagnosed with	N=407 39 days	Primary: Cure rate, post-treatment vulvovaginal candidiasis	Primary: There was no significant difference in cure rate for oral metronidazole (78%) and clindamycin vaginal cream (83%). The incidence of drug-related adverse effects was similar in both groups, approximately 12%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs metronidazole 500 mg capsules BID for 7 days	bacterial vaginosis		Secondary: Not reported	There was no significant difference in the rates of post-treatment vulvovaginal candidiasis associated with oral metronidazole (4.7%) and clindamycin vaginal cream (8.5%). Secondary: Not reported
Tariq et al.[36] (2017) Clindamycin 2% vaginal cream multiple doses vs secnidazole 2 grams orally once	DB, RCT Non-pregnant women with symptomatic bacterial vaginosis (defined as milky white vaginal discharge, vaginal pH >4.5, and clue cells on microscopy	N=182 15 days	Primary: Therapeutic success (defined as normal Nugent score, negative Amine test, and no milky white discharge) Secondary: Not reported	Primary: On follow-up at 15th day of treatment, 92% of participants were completely free from vaginal discharge in the clindamycin group, and 96% had a negative amine test and clue cells. In the secnidazole group, 16% of participants were free from vaginal discharge. Amine test and clue cells were still positive in 69 and 77%, respectively. Overall, 96.6% participants in vaginal clindamycin group recovered from the bacterial vaginosis, while 23% patients were cured in oral secnidazole group (P<0.0001). Secondary: Not reported
Arredondo et al.[37] (1992) Metronidazole 500 mg capsules BID for 7 days vs clindamycin 2% vaginal cream BID for 7 days	DB, MC, RCT Women with symptomatic bacterial vaginosis	N=184 50 days	Primary: Total healing rate, relapse rate, failure rate, and adverse events Secondary: Not reported	Primary: Improvement in total healing was 87% for clindamycin and 79% for metronidazole (P>0.22). While 7% of patients randomized to the metronidazole group developed relapse of the disease following treatment, none of the patients receiving topical clindamycin experienced a relapse. The failure rates were 4.0 and 10.5% for clindamycin and 17.0 and 5.8% for metronidazole at first and second follow-up visits, respectively. Both drugs were well tolerated, with the most serious side effect, generalized rash, reported by a patient on metronidazole therapy. Secondary: Not reported
Andres et al.[38] (1992)	DB, PC, PRO, RCT Non-pregnant	N=60 30 days	Primary: Cure rate, improvement rate,	Primary: There was no statistically significant difference in the proportion of patients who have either improved or were cured post-treatment between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Metronidazole 500 mg capsules BID for 7 days vs clindamycin 2% vaginal cream BID for 7 days	women 18 to 60 years of age diagnosed with bacterial vaginosis		clinical failure assessed at the one-week and four-week follow-up visits, and adverse events Secondary: Not reported	the metronidazole (82%) and clindamycin (97%) study groups at the one-week follow-up visit. There was no statistically significant difference in the proportion of patients who had either improved or were cured post-treatment between the metronidazole (94.1%) and clindamycin (89.5%) study groups at the four-week follow-up visit. There was no statistically significant difference in clinical failure rates among patients randomized to receive either of the two study drugs. There was no statistically significant difference in side effects among patients randomized to receive either of the two study drugs. Secondary: Not reported
Schmitt et al.[39] (1992) Metronidazole 500 mg capsules BID for 7 days vs clindamycin 2% vaginal cream 5 g QD for 7 days	DB, PC, RCT Nonpregnant women 18 to 60 years of age diagnosed with bacterial vaginosis	N=61 30 days	Primary: Overall healing rate (clinical and microbiological), symptomatic failure rate at the one-week and four-week follow-up visits, adverse events, and *Candida* infections Secondary: Not reported	Primary: There was no statistically significant difference in the overall cure rate between the metronidazole (87%) and clindamycin (72%) study groups at the one-week follow-up visit (P=0.32). One month later, 61% of patients in both groups remained cured. Symptomatic failure occurred in one patient receiving clindamycin and in no one on metronidazole therapy. There were fewer asymptomatic failures in the metronidazole group compared to the clindamycin treatment arm; however this difference was not statistically significant (P=0.16). Symptomatic *Candida* yeast infections developed in 12% of clindamycin-treated patients and 9% of patients on metronidazole therapy. There was no statistically significant difference in side effects among patients randomized to receive either of the two study drugs. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Higuera et al.[40] (1993) Metronidazole 500 mg capsules BID for 7 days vs clindamycin 2% vaginal cream 5 g QD for 7 days	DB, PC, RCT Nonpregnant women 16 to 60 years of age diagnosed with bacterial vaginosis	N=82 50 days	Primary: Cure rate, improvement, clinical failure rate, and relapse rate Secondary: microbiological cure rate, vaginal fluid description, patient's efficacy evaluation, and adverse effects	Primary: There was no statistically significant difference in the proportion of patients who have either improved or were cured post-treatment between the metronidazole (82%) and clindamycin (86%) study groups at the one-week follow-up visit. There was no statistically significant difference in cure rate between the metronidazole (88%) and the clindamycin (90%) groups at the four-week follow-up visit. There was no statistically significant difference in failure rate between the metronidazole (17.9%) and clindamycin (14.3%) treatment groups at the one-week and four-week follow-up visits. Secondary: There was no statistically significant difference in microbiological cure rate between the metronidazole (82%) and the clindamycin (86%) groups at the first follow-up visit. There was no statistically significant difference in patient self-reported cure rate between the metronidazole (82%) and clindamycin (86%) groups. There was a significantly higher percentage of patients in the clindamycin group (10%) with a gram stain compatible with bacterial vaginosis at the second follow-up visit compared to the metronidazole group (4%; P<0.04). At the second follow-up visit, there were a greater number of patients in the clindamycin group (14%) exhibiting vaginal fluid odor compared to the metronidazole group (4%). There was no significant difference in the incidence of side effects between the metronidazole group (22%) and clindamycin (15%) group.
Chavoustie et al.[41] (2015)	MC, RCT Women ≥18 years	N=255 30 days	Primary: Proportion of patients with	Primary: The difference in therapeutic cure rates was not statistically different between groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Metronidazole vaginal gel 1.3% once daily for 1, 3, or 5 days vs metronidazole vaginal gel 0.75% once daily for 5 days	of age generally in good health and with a clinical diagnosis of bacterial vaginosis		therapeutic cure, defined as a clinical and a bacteriological cure Secondary: Proportion of patients with clinical cure, proportion of patients with bacteriological cure, time to resolution of symptoms, safety	Secondary: For all the efficacy analyses, the differences were not statistically significant. No clinically important differences were observed in the incidence of adverse events across treatment groups.
Impetigo				
Goldfarb et al.[42] (1988) Mupirocin 2% topical ointment TID for 8 days vs erythromycin ethylsuccinate 40 mg/kg/day QID for 8 days	AC, RCT Children ≥3 months of age with impetigo	N=62 15 days	Primary: Clinical response, bacteriologic response, and adverse events Secondary: Not reported	Primary: There was no statistically significant difference in clinical or bacteriologic response between the two treatment groups. Children randomized to mupirocin treatment were free of side effects while the most common side effect reported in the erythromycin group was diarrhea. Secondary: Not reported
Dagan et al.[43] (1992) Mupirocin 2% topical ointment TID for 7 days	AC, DB, RCT Children ≤16 years of age with impetigo	N=102 8 days	Primary: Cure rate or improved lesion, worsening of lesion, and appearance of new lesions	Primary: The mupirocin group exhibited a greater improvement compared to the erythromycin group in terms of cure rates, improved lesions, worsening of lesions, and bacterial colonization of the lesions ($P<0.05$). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs erythromycin ethylsuccinate suspension 50 mg/kg/day (up to maximum daily dose of 750 mg daily) TID for 7 days			Secondary: Not reported	
Koning et al.[44] (2012) Any program of topical or systemic treatment, including antibiotics, disinfectants or any other intervention for impetigo	SR Patients with primary and secondary impetigo	N=5,578 (68 trials) Variable duration	Primary: Cure as defined by clearance of crusts, blisters and redness as assessed by the investigator, and relief of symptoms as assessed by participants Secondary: Adverse effects	Primary: *Non-bullous impetigo* Topical antibiotics showed better cure rates or more improvement than placebo (pooled RR, 2.24; 95% CI, 1.61 to 3.13). This result was consistent for both mupirocin (RR, 2.21; 95% CI, 1.59 to 3.05) and retapamulin (RR, 1.64; 95% CI, 1.30 to 2.07). In one small study, bacitracin did not show a difference in cure rate compared to placebo (RR, 3.71; 95% CI, 0.16 to 84.29). No one topical antibiotic clearly showed greater efficacy over another. Pooling of 10 studies which compared topical mupirocin with oral erythromycin showed significantly better cure rates or more improvement with mupirocin (RR, 1.07; 95% CI, 1.01 to 1.13). No significant differences were observed between topical mupirocin and dicloxacillin, cephalexin or ampicillin. Bacitracin was significantly less effective than oral cephalexin in one small study, but no difference was seen between bacitracin and erythromycin or penicillin. *Bullous impetigo* Neomycin and bacitracin was significantly less effective than oral erythromycin (RR, 0.14; 95% CI, 0.02 to 0.99). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The reported number of side effects was low, with most being mild. Oral antibiotic treatment caused more side effects, especially gastrointestinal ones, than topical treatment.
Oranje et al.[45] (2007) Retapamulin 1% ointment BID for 5 days vs sodium fusidate 2% ointment TID for 7 days	MC, NI, RCT Patients ≥9 months of age with clinical diagnosis of primary bullous or nonbullous impetigo	N=519 14 days	Primary: Clinical response Secondary: Bacteriological responses at end of therapy and at follow-up	Primary: Patients in the clinical PP population had a statistically significant greater clinical success rate at the end of therapy with retapamulin treatment compared to sodium fusidate treatment (99.1 vs 94.0%; 95% CI, 1.1 to 9.0; P=0.003). Patients in the clinical ITT population had a clinical success rate of 94.8% at the end of therapy with retapamulin treatment compared to 90.1% observed with sodium fusidate treatment (95% CI, -0.4 to 9.7; P=0.062). Patients in the clinical PP population had a clinical success rate of 96.4% at follow-up with retapamulin treatment compared to 93.7% observed with sodium fusidate treatment (95% CI, -1.8 to 7.2; P=0.221). Patients in the clinical ITT population had a clinical success rate of 89.9% at follow-up with retapamulin treatment compared to 87.2% observed with sodium fusidate treatment (95% CI, -3.3 to 8.6; P=0.374). Secondary: Patients in the bacteriological PP population had a statistically significant greater bacteriological success rate at the end of therapy with retapamulin treatment compared to sodium fusidate treatment (99.2 vs 93.0%; 95% CI, 1.4 to 11.0; P=0.002). Patients in the bacteriological ITT population also had a statistically significant greater bacteriological success rate at the end of therapy with retapamulin compared to sodium fusidate treatment (95.1 vs 88.5%; 95% CI, 0.5 to 12.6; P=0.022). Patients in the bacteriological PP population had a bacteriological success rate of 96.6% at follow-up with retapamulin treatment compared to 92.5% observed with sodium fusidate treatment (95% CI, -1.4 to 9.6; P=0.106). Patients in the bacteriological ITT population had bacteriological success

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				rate of 90.1% at follow-up with retapamulin compared to 84.7% observed with sodium fusidate treatment (95% CI, -1.8 to 12.5; P=0.134).
Koning et al.[46] (2008) Retapamulin 1% ointment BID for 5 days vs placebo ointment BID for 5 days	DB, MC, PC, RCT Patients ≥9 months of age with a clinical diagnosis of primary impetigo (bullous or nonbullous)	N=213 14 days	Primary: Clinical response rate at the end of therapy (seven days) Secondary: Not reported	Primary: A clinical response of 'success' was achieved by 86% of the ITT population at the end of therapy for the retapamulin group compared to 52% of the placebo group (P<0.0001). The clinical success rate (ITT) 14 days after start of treatment was 76 and 39% for retapamulin and placebo, respectively (P<0.0001). Secondary: Not reported
Gropper et al.[47] (2014) Ozenoxacin 1% cream BID for 5 days vs retapamulin 1% ointment BID for 5 days vs. placebo cream BID for 5 days	AC, DB, MC, PC, PG, RCT Patients ≥2 years of age with a clinical diagnosis of bullous or nonbullous impetigo, a total skin infection rating scale score of at least 8 (including a pus exudate score of at least 1) and a total affected area of up to 100 cm^2 with surrounding erythema not exceeding 2 cm from the edge of the affected area	N=465 14 days	Primary: Clinical response rate in the ITT population at the end of therapy (7 days) Secondary: Clinical response rate in other populations (PP clinical and bacteriological and ITT bacteriological), skin infection rating scale score and size of affected area, and clinical and microbiological response according to baseline susceptibility	Primary: A clinical response (i.e., "success") among the ITT population was achieved by 34.8% of the ozenoxacin group at the end of therapy compared to 19.2% of the placebo group (P=0.003). Secondary: The cumulative clinical success rate at visit four (day 14) was 52.9% for the ozenoxacin group vs. 40.4% for placebo (P=0.027). A total of three individuals had a clinical relapse at day 14; one in the ozenoxacin group and two in the placebo group. At the end of the therapy, mean total skin infection rating scale scores were reduced by 81.7% from baseline in the ozenoxacin group and by 71.6% from baseline in the placebo group. The size of affected area ratio compared to baseline was smaller in the ozenoxacin group vs. placebo at all postbaseline visits (P<0.001). The microbiological success rate was 70.8% in the ozenoxacin group vs 38.2% in placebo after three to four days, and 79.2 and 56.6% after six to seven days, resulting in a statistically significant difference in success rates (P<0.0001 in both comparisons). Compared to the retapamulin control, ozenoxacin was reported to have a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			profile, microbiological response at visit 4, time to infection and bacterial eradication	more rapid microbiologic clearance based upon success rates of 74.7 vs 60.0% after three to four days (visit 2; P=0.0087) and 88.4 vs 88.7% after six to seven days (visit 3; P=1.0000). Clinical success as assessed by the absence of the treated lesions, improvement in lesions, or a reduction in the affected area such that no further antimicrobial therapy was required occurred in 85.2, 83.1, and 73.7% of ozenoxacin-treated, retapamulin-treated, and placebo-treated individuals, respectively.
Rosen et al.[48] (2018) Ozenoxacin 1% cream BID for 5 days vs. placebo cream BID for 5 days	DB, MC, PC, PG RCT Patients ≥2 months of age with a clinical diagnosis of impetigo and a total skin infection rating scale score ≥3	N=411 13 days	Primary: Clinical response rate in the ITT population at the end of therapy (day-6) Secondary: Clinical response at visit three incorporating combined criteria of clinical success, bacteriologic response, therapeutic response	Primary: A clinical response (i.e., "success") among the ITT population was achieved by 54.4% of the ozenoxacin group at the end of therapy compared to 37.9% of the placebo group (P=0.001). A clinical success response at visit 3 was achieved by 88.8% in the ozenoxacin group compared to 78.2% in the placebo group after incorporating combined criteria of clinical success (P=0.003). After two days of therapy, 75.7% of the ozenoxacin group achieved a positive clinical response (early cure or improvement) compared with 59.2% of the placebo group. Microbiological success was achieved by 87.2% of the ozenoxacin group and 63.9% of the placebo group at visit 2 (P=0.002) and 92.0% and 73.1% at visit 3, respectively (P=0.005). The overall therapeutic success rate (combined clinical and microbiological response) was 57.6% in the ozenoxacin group and 34.5% in the placebo group, corresponding to a difference in success rates of 0.226 (95% CI, 0.102 to 0.350; P<0.001). Therapeutic failure occurred in 40.8% of the ozenoxacin group and 61.3% of the placebo group.
Torrelo et al.[49] (2020) Ozenoxacin 1% cream BID for 5 days	Pooled analysis of two MC, DB, RCT Patients aged 6 months to <18 years with non-bullous impetigo	N=529 (total from both studies) 7 days	Primary: efficacy and safety of ozenoxacin in pediatric patients Secondary: Not reported	Primary: The clinical success rate in the pooled pediatric population after five days' treatment was significantly higher with ozenoxacin than vehicle (P<0.0001). In all of the stratified age groups, ozenoxacin was associated with a higher clinical success rate compared with vehicle. Respective clinical success rates by age group for ozenoxacin versus vehicle were: 100 versus 57.1% for 0.5 to <2 years; 88.0 versus 71.4% for 2 to <6 years;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs vehicle vs retapamulin 1% ointment				91.5 versus 77.4% for 6 to <12 years; and 93.3 versus 79.5% for 12 to <18 years. Results in the retapamulin control arm by age group were 93.5% for 2 to <6 years, 71.1% for 6 to <12 years, and 76.9% for 12 to <18 years, respectively. There were 34 mild (n=25) or moderate (n=9) adverse events (AEs) reported in 28 (5.3%) patients. No serious AEs were reported. A total of 15 AEs (12 mild, three moderate) were reported in 13 patients (5.4%) treated with ozenoxacin; six AEs (three mild, three moderate) were reported in six patients (3.0%) treated with vehicle, and 13 AEs (nine mild, four moderate) were reported in nine patients (10.1%) treated with retapamulin. Secondary: Not reported
Infections: Catheter-Related				
Lok et al.[50] (2003) Bacitracin (500 U/g), gramicidin (0.25 mg/g), and polymyxin B (10,000 U/g) ointment applied to the central venous catheter at the end of each dialysis session for 2 weeks and then with each dressing change vs placebo	DB, MC, RCT Patients ≥18 years of age with end-stage renal disease requiring hemodialysis, using a permanent cuffed catheter in the internal jugular vein as their primary source of vascular access	N=169 6 months	Primary: Incidence of infection, bacteremia, mortality, hospitalization, and catheter removal due to infections Secondary: Not reported	Primary: A smaller proportion of patients in the active group compared to placebo experienced an infection during the study duration (12 vs 34%; P=0.0013). It was calculated that treating five patients would prevent one infection (95% CI, 3 to 11). The proportion of patients experiencing a bacteremia was significantly higher in the placebo group compared to the active group (24 vs 10%; P=0.02). Treating seven patients would prevent one case of bacteremia (95% CI, 4 to 33). There were 13 deaths in the placebo group compared to three deaths in the treatment group during the study period (P=0.0041). It was calculated that treating eight patients would prevent one death (95% CI, 5 to 27). More patients in the placebo group compared to the active treatment group required hospitalization (24 vs 7%; P=0.0041). More patients in the placebo group compared to the active treatment group required catheter removal due to infections (27 vs 10%; P=0.0071).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Chu et al.[51] (2008) Gentamicin cream vs mupirocin ointment	PRO Adult peritoneal dialysis patients attending an outpatient clinic in Hong Kong	N=95 475.6 patient-months (gentamicin) 538.7 patient-months (mupirocin)	Primary: Incidence of ESI Secondary: Not reported	Primary: Fifteen episodes of ESI occurred in 12 patients in the gentamicin group. The overall rate was 0.38 episodes/patient-year. Nine episodes of ESI were recorded in seven patients in the mupirocin group. The over-all rate was 0.20 episodes/patient-year. No significant results were found. Six patients in the gentamicin group developed 13 peritonitis episodes, whereas 12 peritonitis episodes were reported in 10 patients in the mupirocin group. No significant results were found. Secondary: Not reported
Xu et al.[52] (2010) Mupirocin vs placebo or no prophylaxis	MA Patients ≥18 years of age undergoing peritoneal dialysis	N=2,450 (14 trials) Variable duration	Primary: Incidence of ESI and peritonitis due to *S. aureus* Secondary: Not reported	Primary: Treatment with mupirocin decreased the risk of ESI by 72% (95% CI, 0.60 to 0.81; P<0.0001) and the risk of peritonitis by 70% (95% CI, 0.52 to 0.81; P<0.0001) due to *S. aureus*. Treatment with mupirocin reduced the risk of ESI and peritonitis due to all organisms by 57% (95% CI, 0.46 to 0.66; P<0.00001) and 41% (95% CI, 0.24 to 0.54; P<0.0001), respectively. Secondary: Not reported
Bernardini et al.[53] (2005) Mupirocin calcium 2% topical cream applied to the catheter exit site QD vs gentamicin 0.1%	DB, MC, RCT Patients ≥18 years of age on peritoneal dialysis	N=133 12 months	Primary: *P. aeruginosa* and *S. aureus* catheter infection rates Secondary: Gram-negative and gram-positive peritonitis, overall catheter infection, peritonitis rate, causative	Primary: There was a statistically significant difference in *P. aeruginosa* catheter infection rate between the gentamicin and mupirocin treatment groups (0.0/year vs 0.11/year, respectively; P<0.003). *S. aureus* infections were infrequent in both the gentamicin and mupirocin treatment groups (0.06/year vs 0.08/year, respectively; P<0.44). Secondary: The rate of gram-positive and gram-negative catheter infections was lower in the gentamicin group compared to the mupirocin groups (0.23/year vs 0.54/year; P=0.005).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
topical cream, applied to the catheter exit site QD			organism, catheter removal, and time to first catheter infection	Time to first catheter infection was longer with gentamicin compared to the mupirocin cream (P=0.03). Patients receiving gentamicin cream experienced a statistically significant decrease in peritonitis rates compared to mupirocin group (0.34/year vs 0.52/year; P=0.03), with a significant decrease in gram-negative peritonitis (0.02/year vs 0.15/year; P=0.003). Catheter removal as a result of infection was similar between mupirocin (0.09/year) and gentamicin (0.15/year) groups (P=0.45).
Mahaldar et al.[54] (2009) Mupirocin vs gentamicin	RETRO Patients ≥18 years of age on peritoneal dialysis who were using topical mupirocin or gentamicin and who had ≥6 months of follow-up data	N=100 11.8 months and 14.3 months for mupirocin and gentamicin, respectively	Primary: Incidence of ESI and peritonitis Secondary: Not reported	Primary: The ESI rate was 0.002 episodes/patient–month in the gentamicin group and 0.004 episodes/patient–month in the mupirocin group (P=0.45). The rate of gram-positive ESI was 0.002 episodes/patient–month in the gentamicin group and 0.001 episodes/patient–month in the mupirocin group (P=0.75). The rate of gram-negative ESI was zero in the gentamicin group and 0.002 episodes/patient–month in the mupirocin group (P=0.22). The peritonitis rate was 0.06 episodes/patient–month in the gentamicin group and 0.02 episodes/patient–month in the mupirocin group (P=0.07). The rate of gram-positive peritonitis was 0.05 episodes/patient–month in the gentamicin group and 0.01 episodes/patient–month in the mupirocin group (P=0.08). The rate of gram-negative peritonitis was 0.009 episodes/patient–month in the gentamicin group and 0.008 episodes/patient–month in the mupirocin group (P=0.83). Secondary: Not reported
Aykut et al.[55] (2010) Mupirocin applied to the exit-site once weekly vs	PRO Adults undergoing peritoneal dialysis treatment	N=33 5 years	Primary: Incidence of ESI and peritonitis Secondary: Not reported	Primary: A total of 28 episodes of ESI (0.62 episodes/patient per year) and 41 episodes of peritonitis (0.76 episodes/patient per year) were seen in 33 patients prior to mupirocin treatment. A total of 14 episodes of ESI (0.20 episodes/patient per year) and 34 episodes of peritonitis (0.54 episodes/patient per year) were observed in all groups of patients who used mupirocin one or three times a week for five years. The decrease was 28% in peritonitis (P=0.07) and 64% in ESI (P=0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mupirocin applied to the exit-site three times weekly				In a subgroup analysis, patients were divided into those who used mupirocin once-a-week and those who used mupirocin three-times weekly. Among patients applying mupirocin once-weekly, there were 13 episodes of peritonitis and seven episodes of ESI. There were six episodes of peritonitis and one episode of ESI among patients applying mupirocin three times weekly. The rate of peritonitis was 56% lower (P=0.04) and the rate of ESI was 92% lower (P=0.03) in the group that applied mupirocin three times weekly compared to those who applied mupirocin once-weekly. Secondary: Not reported
Skin and Soft Tissue Infections				
Maddox et al.[56] (1985) Bacitracin, neomycin sulfate, and polymyxin B ointment applied to the wound TID vs placebo	DB, RCT Children with minor wounds	N=59 15 weeks	Primary: Prevention of streptococcal pyoderma Secondary: Not reported	Primary: Eighty-one percent of patients had positive normal skin cultures on one or more occasions. Nineteen children (32%) developed streptococcal pyoderma. Infection occurred in 47% of placebo-treated children compared to 15% of children treated with bacitracin, neomycin sulfate, and polymyxin B (NNT=32; P=0.01). Secondary: Not reported
Dire et al.[57] (1995) Bacitracin zinc, applied to the wound TID vs bacitracin, neomycin sulfate, and polymyxin B	DB, PC, PRO, RCT Patients with uncomplicated soft tissue wound admitted to the emergency department within 12 hours of injury	N=426	Primary: Wound infection rates Secondary: Not reported	Primary: Wound infection rates were 17.6% for petrolatum, 5.5% for bacitracin (NNT=8), 4.5% for bacitracin, neomycin sulfate, and polymyxin B (NNT=8), and 12.1% for silver sulfadiazine (NNT=18; P=0.0034). Sixty percent of the infections were stitch abscesses and were treated with local care only. There was no difference in rates of more serious infections between groups. One patient developed a hypersensitivity reaction to bacitracin, neomycin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ointment applied to the wound TID vs silver sulfadiazine, applied to the wound TID vs petrolatum, applied to the wound TID				sulfate, and polymyxin B. Secondary: Not reported
Leyden et al.[58] (1987) Bacitracin, neomycin sulfate, and polymyxin B "triple-antibiotic" ointment (Neosporin®) applied to the wound BID vs bacitracin and polymyxin B ointment (Polysporin®) applied to the wound BID vs	AC, OL, RCT Healthy volunteers, with induced intradermal blister wounds contaminated with *S. aureus*	N=48 22 days	Primary: Healing rate, overall ranking of clinical appearance and the healing rate of wounds, infection rate, and *S. aureus* count after two applications of each test agent Secondary: Not reported	Primary: Contaminated blister wounds treated with the triple antibiotic and the Polysporin® ointments healed significantly faster (mean 9.2 and 8.8 days, respectively) compared to patients treated with benzalkonium chloride spray (14.2 days), merbromin (13.1 days), or those receiving no antibacterial treatment (13.3 days; P<0.05). There was no statistically significant difference between the two antibacterial ointments in terms of the overall ranking of clinical appearance and the healing rate of wounds. There was no statistically significant difference in infection rate between the antiseptic-treated and no-treatment wounds. Neosporin® ointment was statistically better in terms of overall ranking of clinical appearance and the healing rate of wounds compared to all other products except the Polysporin® ointment (P<0.05). Following two applications of Neosporin® (triple-antibiotic) ointment, 83.3% of the wounds had a bacterial count of zero, significantly higher than seen with no treatment and all other products (P<0.05). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
benzalkonium chloride applied to the wound BID vs thimerosal applied to the wound BID vs hydrogen peroxide 3% applied to the wound BID vs tincture of iodine applied to the wound BID vs camphor and phenol applied to the wound BID vs merbromin applied to the wound BID vs wound protectant applied to the wound BID				Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs no treatment				
Berger et al.[59] (2000) Bacitracin, neomycin, and polymyxin B "triple-antibiotic" ointment (Neosporin®), applied to the wound BID vs bacitracin and polymyxin B "double-antibiotic" ointment (Polysporin®), applied to the wound BID vs non-occlusive gauze dressing	AC, PG, RCT Healthy volunteers >18 years of age, with dermabrasion wounds on the upper back, produced under anesthesia	N=70 14 days	Primary: Pigmentary composite score, textural composite score Secondary: Overall ranking of pigmentary changes, overall ranking of textural changes, and percentage area of the test site exhibiting scarring	Primary: The triple-antibiotic ointment treatment group had a statistically significant lower pigmentary composite score (2.6) at 90 days after study onset, compared to the group receiving gauze alone (4.2; P<0.001). Pigmentary composite score did not significantly differ between the double-antibiotic and the gauze-only group. The mean textural composite score at 45 days for the triple-antibiotic ointment group was statistically and clinically significantly different compared to the gauze treatment group (P<0.001). At 90 days, both the triple- and the double-antibiotic ointment groups had a statistically significantly lower textural composite score compared to the gauze-only group (P<0.001). Secondary: Both the pigmentary and the textural ranking significantly improved in the triple-antibiotic group compared to the gauze-treatment group at day 90 of the study (P<0.001). The double-antibiotic group exhibited significantly improved textural ranking compared to the gauze-treatment group at day 90 of the study (P<0.001). There was no statistical difference between any of the study groups in terms of percent area of scarring. Contact dermatitis was the most frequent reason for study withdrawal, occurring in 2.9% of patients receiving either one of the antibiotic ointments.
Kraus et al.[60] (1998)	DB, RCT	N=706	Primary: Clinical success	Primary: Clinical success at follow-up was equivalent in the two groups: 95.1 and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Mupirocin calcium 2% topical cream TID vs cephalexin 250 mg QID	Patients with secondarily infected wounds (small lacerations, abrasions, or sutured wounds)	10 days	rates at the end of therapy Secondary: Not reported	95.3% in the mupirocin cream and the cephalexin groups, respectively (95% CI, -4.0 to 3.6; P=0.89). The ITT success rate was 83.0% in both groups. Bacteriologic success at follow-up was also comparable: 96.9% in the mupirocin cream and 98.9% in the cephalexin groups (95% CI, -6.0 to 2.0; P=0.22). The occurrence of adverse experiences related to study treatment was similar for both groups, with fewer patients in the mupirocin cream group reporting diarrhea (1.1 vs 2.3% for cephalexin). Secondary: Not reported
Rist et al.[61] (2002) Mupirocin calcium 2% topical cream TID for 10 days vs cephalexin 250 mg QID for 10 days	DB, DD, MC, PG, RCT Patients ≥8 years of age, weighing >40 kg, with secondary eczema infection scored >8, on the total skin infection rating scale	N=159 10 days	Primary: Clinical response at the end of therapy Secondary: Bacteriological response, adverse events	Primary: There was no statistically significant difference in clinical response among the two treatment groups (P=0.29). Secondary: Bacteriological success, defined in terms of bacterial eradication, was statistically higher in the mupirocin group (50%) compared to the cephalexin group (28%; P=0.005). There was no significant difference in the incidence of adverse effects: diarrhea and nausea were the most common adverse events observed in the study (P=0.45).
Hood et al.[62] (2004) Mupirocin topical ointment applied to the wound TID vs neomycin, bacitracin, and	AC, RCT Emergency department patients with uncomplicated soft tissue wound 24 hours or less before study enrollment	N=99 7 days	Primary: Presence of infection seven days after study onset Secondary: Not reported	Primary: There was no statistically significant difference in wound infection incidence between the mupirocin and the neomycin, bacitracin, and polymyxin B treatment groups (4 vs 0%, respectively). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
polymyxin B ointment applied to the wound TID				
Parish et al.[63] (2006) Retapamulin 1% ointment BID for 5 days vs cephalexin 500 mg capsules BID for 10 days	DB, DD, MC, NI, RCT Patients ≥9 months of age with underlying inflammatory skin disease (atopic dermatitis, psoriasis, or allergic contact dermatitis) experiencing one or more signs or symptoms of secondarily infected dermatitis	N=547 17 to 19 days	Primary: Clinical response at follow-up (total resolution of all signs and symptoms of infection such that no additional antibiotic necessary) Secondary: Clinical response at end of therapy, microbiologic response at follow-up and end of therapy	Primary: Patients in the PP clinical population had a clinical success rate of 85.9% at follow-up with retapamulin treatment compared to 89.7% observed with oral cephalexin treatment (95% CI, -9.9 to 2.3). Patients in the ITT clinical population had a clinical success rate of 82.9% at follow-up with retapamulin treatment compared to 86.3% observed with oral cephalexin treatment (95% CI, –9.7 to 2.9). Secondary: Patients in the PP clinical population had similar clinical success rates at end of therapy between retapamulin and oral cephalexin (92.0 vs 93.8%, respectively). Patients in the ITT clinical population also had similar clinical success rates at end of therapy between retapamulin and oral cephalexin (92.3 vs 91.8%, respectively). Patients in the PP bacteriologic group had similar microbiologic success rates at the end of therapy between retapamulin and oral cephalexin (93.0 vs 94.1%, respectively) and at follow-up (87.2 vs 91.8%, respectively). Patients in the ITT bacteriologic population had similar microbiologic success rates at the end of therapy between retapamulin and oral cephalexin (93.4 vs 91.3%, respectively) and at follow-up (83.5 vs 87.8%, respectively).
Free et al.[64] (2006) Retapamulin 1% ointment BID for 5 days vs	DB, MC, RCT (two trials) Patients ≥9 months of age with a secondarily infected traumatic lesion (abrasion, small	N=1,904 17 to 19 days	Primary: Clinical response at follow-up in the PP clinical population for both studies Secondary:	Primary: Patients in the PP clinical population had comparable clinical success rates of 88.7 and 90.4% at follow-up with retapamulin treatment compared to 91.9 and 92.0% observed with oral cephalexin treatment (95% CI, -7.4 to 0.9) and (95% CI, -5.8 to 2.6) in each of the studies, respectively. Overall, clinical success rates for patients in the PP clinical population were 89.5% at follow-up with retapamulin treatment compared to 91.9%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cephalexin 500 mg capsules BID for 10 days	laceration, sutured wound)		Microbiologic response at follow-up in the PP clinical population for both studies	observed with oral cephalexin treatment combined for both studies (95% CI, -5.4 to 0.5). Secondary: Patients in the PP bacteriologic population had microbiologic success rates of 87.1 and 91.7% at follow-up with retapamulin treatment compared to 89.4 and 91.1% observed with oral cephalexin treatment in each of the studies, respectively. Overall, microbiologic success rates for patients in the PP bacteriologic population were 89.2% at follow-up with retapamulin treatment compared to 90.2% observed with oral cephalexin treatment combined for both studies.
Nelson et al.[65] (2021) Mupirocin ointment (0.5-inch ribbon) BID for 5 days vs placebo	PRO, DB, RCT *Staphylococcus aureus*-colonized infants in the neonatal intensive care unit (NICU)	N=205 ~3 years (October 2016 to December 2019)	Primary: Primary decolonization defined as the absence of *S. aureus* on PCR screen within two weeks of initial treatment Secondary: Proportion of recurrent colonization (defined as a positive *S. aureus* PCR screen recurring at any time following the first episode of decolonization) and subsequent decolonization (defined as the	Primary: Primary decolonization within two weeks of initial treatment occurred significantly more frequently in the mupirocin group compared with the placebo group (86 of 104 [83%] vs 20 of 101 [20%]; P<0.001) Secondary: Recurrent colonization after initial *S. aureus* decolonization occurred in most of the treated infants; approximately 75% of infants in both groups were again colonized with *S. aureus*. Mean time to recurrent *S. aureus* colonization was significantly longer in the mupirocin group compared with the control group (17 ± 11 days vs 9 ± 6 days; P=0.001). Subsequent decolonization within 2 weeks of repeat treatment occurred to a similar degree as that found for initial treatment and again resulted in significantly reduced colonization in infants treated with mupirocin vs those given placebo (38 of 49 [78%] vs 2 of 21 [10%]; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			absence of *S. aureus* on PCR screen within two weeks of retreatment)	

Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, ITT=intent-to-treat, MA=meta-analysis, MC=multicenter, NI=non inferiority, NNT=number needed to treat, OL=open-label, PC=placebo-controlled, PG=parallel-group, PP=per protocol, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single blinded, SR=systematic review
Miscellaneous Abbreviations: ESI=exit-site infections, *P. aeruginosa=Pseudomonas aeruginosa; S. aureus=Staphylococcus aureus*

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Skin and Mucous Membrane Antibacterials

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Clindamycin	vaginal cream, vaginal gel, vaginal suppository	Cleocin®*, Clindesse®*, Xaciato®	$-$$$$	$$$
Gentamicin	cream, ointment	N/A	N/A	$$$$
Metronidazole	vaginal gel	MetroGel-Vaginal®*, Nuvessa®, Vandazole®*	$$	$$
Mupirocin	cream, ointment	Centany®*	$	$
Ozenoxacin	cream	Xepi®	$$$$$	N/A
Combination Products				
Neomycin and fluocinolone	cream	Neo-Synalar®	$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The skin and mucous membrane antibacterials are approved for the treatment and/or prevention of various skin infections and bacterial vaginosis.[1-14] Most of the agents in this class are available in a generic formulation. Studies have demonstrated that prophylactic administration of topical antibiotics decreases infection rates in

minor wounds.[56,57,62] Studies comparing topical mupirocin or retapamulin to oral antibiotics in patients with secondarily infected wounds also demonstrated similar clinical response rates.[42,60,62,64]

Due to the complications associated with bacterial vaginosis, all symptomatic women should be treated. Guidelines recommend oral or vaginal metronidazole or vaginal clindamycin as initial therapy.[17-24] Cure rates do not differ between intravaginal clindamycin ovules and oral or intravaginal metronidazole formulations.[32,33] Clinical trials have demonstrated similar efficacy with metronidazole and clindamycin treatment regimens.[29,32-35,37-40]

Topical antibacterials have been shown to be effective for the treatment of impetigo in several clinical trials; however, there are relatively few studies that directly compare these agents.[42-46] According to the Infectious Diseases Society of America guidelines, treatment of impetigo should be with either mupirocin or retapamulin. An alternative that has been demonstrated as safe and efficacious for pediatric patients is ozenoxacin. Other agents, such as bacitracin and neomycin, are less effective for the treatment of impetigo. The guidelines also state that topical therapy with mupirocin is equivalent to oral antimicrobials and may be used when lesions are limited in number.[26] While there were no studies found in the medical literature directly comparing retapamulin and mupirocin, a 2012 Cochrane Systematic Review concluded that topical therapy consisting of mupirocin or retapamulin is probably equally effective in the treatment of impetigo. In contrast to mupirocin, no resistance has yet been reported with retapamulin.[21,44]

Topical antibacterials are also effective in preventing exit-site infections in patients receiving peritoneal dialysis; however, comparisons of different methods of exit-site care in randomized trials are limited.[51-55] The International Society for Peritoneal Dialysis guidelines recommend either mupirocin ointment or cream or gentamicin cream daily after cleansing in all patients. The use of mupirocin ointment at the exit-site should be avoided in patients with polyurethane catheters, as structural damage to the catheter has been reported.[22]

There is insufficient evidence to support that one brand skin and mucous membrane antibacterial is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand skin and mucous membrane antibacterials within the class reviewed are comparable to each other and to the generics products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand skin and mucous membrane antibacterial is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost-effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Antivirals
AHFS Class 840406
February 8, 2023

I. Overview

The skin and mucous membrane antivirals are approved for the treatment of herpes simplex virus types 1 and 2 (HSV-1 and HSV-2).[1-6] Infection with HSV is associated with chronic, life-long viral infections.[7] The two most common manifestations are genital herpes and labial herpes. Genital herpes typically results from infection with HSV-2; however, either HSV type can lead to genital ulcers.[7,8] Initial primary genital HSV infections tend to be more severe with lesions persisting for several weeks. Clinical manifestations include painful genital ulcers, itching, dysuria, headache, fever, malaise, and lymphadenopathy. Recurrent episodes are generally shorter and produce mainly localized vesicles, which progress through ulcerated and crusted stages for up to 10 days.[9] Labial herpes typically results from infection with HSV-1.[10] Initial primary episodes can be widespread and are associated with severe discomfort; recurrent episodes tend to be more localized.[8] Before skin lesions appear, there is often a prodrome phase consisting of pain, itching, tingling, and burning.[8,10] Papules then present on the lip and infrequently on the palate, chin, or oral mucosa. This is followed by progression through ulcerated, crusted, and healing stages within five days (for recurrent episodes).[10] Patients with recurrent labial herpes experience an average of one to six episodes per year.[8]

Treatment options for HSV infections include intravenous, oral, and topical antiviral agents. No antiviral agent will eradicate HSV; therefore, treatment is aimed at managing, rather than curing, the disease. Oral treatments are effective in reducing symptoms, while intravenous administration may be required in immunocompromised patients and in those with severe disseminated infection.[8] Topical antivirals reduce the duration of viral shedding and the length of time before all lesions become crusted; however, this route of administration is less effective than oral or intravenous routes.[8-12]

The skin and mucous membrane antivirals that are included in this review are listed in Table 1. This review encompasses all topical dosage forms and strengths. Acyclovir and penciclovir are available generically. This class was last reviewed in February 2021.

Table 1. Skin and Mucous Membrane Antivirals Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Acyclovir	cream, ointment	Zovirax®*	acyclovir, Zovirax® (cream)*
Penciclovir	cream	Denavir®*	penciclovir
Combination Product			
Acyclovir and hydrocortisone	cream	Xerese®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the skin and mucous membrane antivirals are summarized in Table 2.

Table 2. Treatment Guidelines Using the Skin and Mucous Membrane Antivirals

Clinical Guideline	Recommendation(s)
Centers for Disease Control and Prevention: **Sexually**	Genital herpes • Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management. • Systemic antiviral drugs can partially control the signs and symptoms of

Clinical Guideline	Recommendation(s)
Transmitted Diseases Treatment Guidelines (2022)[11-13]	herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy. • Systemic antiviral drugs do not eradicate latent virus or affect the risk, frequency, or severity of recurrences after the drug is discontinued. • Randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes. • Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability. • Topical therapy with antiviral drugs provides minimal clinical benefit, and use is discouraged. • Newly acquired genital herpes can cause prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even patients with first episode herpes who have mild clinical manifestations initially can develop severe or prolonged symptoms. Therefore, all patients with first episodes of genital herpes should receive antiviral therapy. • Recommended regimens for first episodes of genital herpes: o acyclovir 400 mg orally three times daily for seven to 10 days o famciclovir 250 mg orally three times daily for seven to 10 days o valacyclovir 1,000 mg orally twice daily for seven to 10 days. • Treatment can be extended if healing is incomplete after 10 days of therapy. • Acyclovir 200 mg orally five times daily is also effective but is not recommended because of frequency of dosing. • Almost all patients with symptomatic first episode genital herpes simplex virus (HSV)-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection. • Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Suppressive therapy may be preferred because of the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners. • Long-term safety and efficacy have been documented among patients receiving daily acyclovir, valacyclovir, and famciclovir. • Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment. • Providers should discuss with patients on an annual basis whether they want to continue suppressive therapy because frequency of genital HSV-2 recurrence diminishes over time for many persons. • Discordant heterosexual couples in which a partner has a history of genital HSV-2 infection should be encouraged to consider suppressive antiviral therapy as part of a strategy for preventing transmission, in addition to consistent condom use and avoidance of sexual activity during recurrences. Suppressive antiviral therapy for persons with a history of symptomatic genital herpes also is likely to reduce transmission when used by those who have multiple partners. • Recommended regimens for suppressive therapy of genital herpes: o acyclovir 400 mg orally twice daily o famciclovir 250 mg orally twice daily o valacyclovir 500 mg orally once daily o valacyclovir 1,000 mg orally once daily. • Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens for persons who have frequent recurrences (i.e., ≥10 episodes/year). • Acyclovir, famciclovir and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding. Ease of administration and cost also are

Clinical Guideline	Recommendation(s)
	important to consider when deciding on prolonged treatment. • Because of the decreased risk for recurrences and shedding, suppressive therapy for HSV-1 genital herpes should be reserved for those with frequent recurrences through shared clinical decision-making between the patient and the provider. • Episodic treatment of recurrent herpes is most effective if initiation of therapy within one day of lesion onset or during the prodrome that precedes some outbreaks. Patients should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin. • Recommended regimens for episodic treatment of recurrent HSV-2 genital herpes: o acyclovir 800 mg orally twice daily for five days o acyclovir 800 mg orally three times daily for two days o famciclovir 1,000 mg orally twice daily for one day o famciclovir 500 mg orally once; followed by 250 mg orally twice daily for two days o famciclovir 125 mg orally twice daily for five days o valacyclovir 500 mg orally twice daily for three days o valacyclovir 1,000 mg orally once daily for five days. • Acyclovir 400 mg orally three times daily is also effective but is not recommended because of frequency of dosing. • Intravenous acyclovir should be provided to patients with severe HSV disease or complications that necessitate hospitalization or central nervous system complications. • HSV-2 meningitis is characterized clinically by signs of headache, photophobia, fever, meningismus, and cerebrospinal fluid (CSF) lymphocytic pleocytosis, accompanied by mildly elevated protein and normal glucose. • Optimal therapies for HSV-2 meningitis have not been well studied; however, acyclovir 5 to 10 mg/kg body weight IV every 8 hours until clinical improvement is observed, followed by high-dose oral antiviral therapy (valacyclovir 1 g 3 times/day) to complete a 10- to 14-day course of total therapy, is recommended. • Hepatitis is a rare manifestation of disseminated HSV infection, often reported among pregnant women who acquire HSV during pregnancy. Among pregnant women with fever and unexplained severe hepatitis, disseminated HSV infection should be considered, and empiric IV acyclovir should be initiated pending confirmation. • Consistent and correct condom use has been reported in multiple studies to decrease, but not eliminate, the risk for HSV-2 transmission from men to women. Condoms are less effective for preventing transmission from women to men. • Randomized clinical trials have demonstrated that PrEP with daily oral tenofovir disoproxil fumarate/emtricitabine decreases the risk for HSV-2 acquisition by 30% in heterosexual partnerships. Pericoital intravaginal tenofovir 1% gel also decreases the risk for HSV-2 acquisition among heterosexual women. • The patients who have genital herpes and their sex partners can benefit from evaluation and counseling to help them cope with the infection and prevent sexual and perinatal transmission. • Lesions caused by HSV are common among persons with human immunodeficiency virus (HIV) infection and might be severe, painful, and atypical. HSV shedding is increased among persons with HIV infection. • Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV infection among persons with

Clinical Guideline	Recommendation(s)

	HIV.
	• Recommended regimens for daily suppressive therapy of genital herpes in patients infected with HIV:
	  ○ acyclovir 400 to 800 mg orally two to three times daily
	  ○ famciclovir 500 mg orally twice daily
	  ○ valacyclovir 500 mg orally twice daily
	• Recommended regimens for episodic treatment of genital herpes in patients infected with HIV:
	  ○ acyclovir 400 mg orally three times daily for five to 10 days
	  ○ famciclovir 500 mg orally twice daily for five to 10 days
	  ○ valacyclovir 1,000 mg orally twice daily for five to 10 days
	• If lesions persist or recur in a patient receiving antiviral treatment, acyclovir resistance should be suspected, and a viral culture obtained for phenotypic sensitivity testing.
	• Foscarnet (40 to 80 mg/kg body weight IV every 8 hours until clinical resolution is attained) is the treatment of choice for acyclovir-resistant genital herpes. Intravenous cidofovir 5 mg/kg body weight once weekly might also be effective.
	• Imiquimod 5% applied to the lesion for 8 hours 3 times/week until clinical resolution is an alternative that has been reported to be effective.
	• Acyclovir can be administered orally to pregnant women with first-episode genital herpes or recurrent herpes and should be administered IV to pregnant women with severe HSV.
	• Suppressive acyclovir treatment starting at 36 weeks' gestation reduces the frequency of cesarean delivery among women who have recurrent genital herpes by diminishing the frequency of recurrences at term. However, such treatment might not protect against transmission to neonates in all cases.
	• Recommended regimen for suppression of recurrent genital herpes among pregnant women:
	  ○ acyclovir 400 mg orally three times daily
	  ○ valacyclovir 500 mg orally twice daily
	• Treatment recommended starting at 36 weeks' gestation.
	• Infants exposed to HSV during birth should be followed in consultation with a pediatric infectious disease specialist.
	• All newborn infants who have neonatal herpes should be promptly evaluated and treated with systemic acyclovir. The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 14 days if disease is limited to the skin and mucous membranes, or for 21 days for disseminated disease and disease involving the CNS.
	
	<u>Bacterial vaginosis</u>
	• Bacterial vaginosis (BV) is a highly prevalent condition and the most common cause of vaginal discharge worldwide. However, in a nationally representative survey, the majority of women with BV were asymptomatic.
	• Treatment for BV is recommended for women with symptoms.
	• Established benefits of therapy among nonpregnant women are to relieve vaginal symptoms and signs of infection and reduce the risk for acquiring *C. trachomatis, N. gonorrhoeae*, *T. vaginalis*, *M. genitalium*, HIV, HPV, and HSV-2.
	• Recommended regimens for bacterial vaginosis include:
	  ○ Metronidazole 500 mg orally twice daily for seven days.
	  ○ Metronidazole 0.75% gel 5 g intravaginally once daily for five days.
	  ○ Clindamycin 2% cream 5 g intravaginally at bedtime for seven days.
	• Alternative regimens include:

Clinical Guideline	Recommendation(s)
	○ Tinidazole 2 g orally once daily for two days. ○ Tinidazole 1 g orally once daily for five days. ○ Clindamycin 300 mg orally twice daily for seven days. ○ Clindamycin 100 mg ovules intravaginally once at bedtime for three days. ○ Secnidazole 2 g oral granules in a single dose • Clindamycin ovules use an oleaginous base that might weaken latex or rubber products (e.g., condoms and diaphragms). Use of such products within 72 hours after treatment with clindamycin ovules is not recommended. • Oral granules should be sprinkled onto unsweetened applesauce, yogurt, or pudding before ingestion. A glass of water can be taken after administration to aid in swallowing. • Using a different recommended treatment regimen can be considered for women who have a recurrence; however, retreatment with the same recommended regimen is an acceptable approach for treating persistent or recurrent BV after the first occurrence. • BV treatment is recommended for all symptomatic pregnant women because symptomatic BV has been associated with adverse pregnancy outcomes, including premature rupture of membranes, preterm birth, intra-amniotic infection, and postpartum endometritis. <u>Uncomplicated vulvovaginal candidiasis</u> • Uncomplicated vulvovaginal candidiasis is defined as sporadic or infrequent vulvovaginal candidiasis, mild to moderate vulvovaginal candidiasis, candidiasis likely to be *Candida albicans*, or candidiasis in non-immunocompromised women. • Short-course topical formulations (i.e., single dose and regimens of one to three days) effectively treat uncomplicated vulvovaginal candidiasis. • Treatment with azoles results in relief of symptoms and negative cultures in 80 to 90% of patients who complete therapy. • Recommended regimens include: ○ Butoconazole 2% cream 5 g single intravaginal application. ○ Clotrimazole 1% cream 5 g intravaginally daily for seven to 14 days. ○ Clotrimazole 2% cream 5 g intravaginally daily for three days. ○ Miconazole 2% cream 5 g intravaginally daily for seven days. ○ Miconazole 4% cream 5 g intravaginally daily for three days. ○ Miconazole 100 mg vaginal suppository one suppository daily for seven days. ○ Miconazole 200 mg vaginal suppository one suppository for three days. ○ Miconazole 1,200 mg vaginal suppository one suppository for one day. ○ Tioconazole 6.5% ointment 5 g single intravaginal application. ○ Terconazole 0.4% cream 5 g intravaginally daily for seven days. ○ Terconazole 0.8% cream 5 g intravaginally daily for three days. ○ Terconazole 80 mg vaginal suppository one suppository daily for three days. ○ Fluconazole 150 mg oral tablet in single dose. <u>Complicated vulvovaginal candidiasis</u> • Complicated vulvovaginal candidiasis is defined as recurrent vulvovaginal candidiasis, severe vulvovaginal candidiasis, non-albicans candidiasis, or candidiasis in women with diabetes, immunocompromising conditions, underlying immunodeficiency, or immunosuppressive therapy. • Most episodes of recurrent vulvovaginal candidiasis caused by *Candida albicans* respond well to short duration oral or topical azole therapy.

Clinical Guideline	Recommendation(s)

	• However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., seven to 14 days of topical therapy or a 100, 150, or 200 mg oral dose of fluconazole every third day for a total of three doses (day one, four, and seven) to attempt mycologic remission before initiating a maintenance antifungal regimen.
	• Recommended maintenance regimen is oral fluconazole (i.e., a 100-mg, 150-mg, or 200-mg dose) weekly for six months. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be considered.
	
	Severe vulvovaginal candidiasis
	• Severe vulvovaginal candidiasis is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy.
	• Either seven to 14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended.
	
	Non-albicans vulvovaginal candidiasis
	• The optimal treatment of non-albicans vulvovaginal candidiasis remains unknown. However, a longer duration of therapy (seven to 14 days) with a non-fluconazole azole drug (oral or topical) is recommended.
	• If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for three weeks.
	
	Genital warts
	• Treatment of anogenital warts should be guided by wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and provider experience.
	• There is no definitive evidence to suggest that any of the available treatments are superior to any other and no single treatment is ideal for all patients or all warts.
	• Because of uncertainty regarding the effect of treatment on future transmission of human papilloma virus and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution.
	• Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy.
	• In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment.
	• The treatment modality should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe.
	• Most genital warts respond within three months of therapy.
	• Recommended regimens for external anogenital warts (patient-applied):
	  ○ Podofilox 0.5% solution or gel.
	  ○ Imiquimod 3.75% or 5% cream.
	  ○ Sinecatechins 15% ointment.
	• Recommended regimens (provider administered):
	  ○ Cryotherapy with liquid nitrogen or cryoprobe.
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution
	  ○ Surgical removal
	• Fewer data are available regarding the efficacy of alternative regimens for treating anogenital warts, which include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir. Shared clinical decision-making between the patient and provider regarding benefits and risks of these regimens should be provided.
	• Podophyllin resin is no longer a recommended regimen because of the number

Clinical Guideline	Recommendation(s)
	of safer regimens available, and severe systemic toxicity has been reported when podophyllin resin was applied to large areas of friable tissue and was not washed off within 4 hours. Cervical warts • For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade squamous intraepithelial lesion must be performed before treatment is initiated. • Management of exophytic cervical warts should include consultation with a specialist. • Recommended regimens: o Cryotherapy with liquid nitrogen. o Surgical removal o Trichloroacetic acid or bichloracetic acid 80 to 90% solution Vaginal warts • Recommended regimens: o Cryotherapy with liquid nitrogen. o Surgical removal o Trichloroacetic acid or bichloracetic acid 80 to 90% solution Urethral meatus warts • Recommended regimens: o Cryotherapy with liquid nitrogen. o Surgical removal Intra-Anal warts • Management of intra-anal warts should include consultation with a colorectal specialist. • Recommended regimens: o Cryotherapy with liquid nitrogen. o Surgical removal. o Trichloroacetic acid or bichloracetic acid 80 to 90% solution.
British Association for Sexual Health and Human Immunodeficiency Virus: **2014 UK national guideline for the management of anogenital herpes (2015)[14]**	First episode of genital herpes • Oral antiviral drugs are indicated within five days of the start of the episode, while new lesions are still forming, or if systemic symptoms persist. • Oral agents (acyclovir, valacyclovir, and famciclovir) all reduce the severity and duration of episodes. • Antiviral therapy does not alter the natural history of the disease in that frequency or severity of subsequent recurrences remains unaltered. • Topical agents are less effective than oral agents. • Combined oral and topical treatment is of no additional benefit over oral treatment alone. • Intravenous therapy is indicated only when the patient cannot swallow or tolerate oral medication because of vomiting. • There are no comparative studies to show benefit from therapy longer than five days. However, it may still be prudent to review the patient after five days and continue therapy if new lesions are still appearing at this time, or if systemic symptoms are still present, or if complications have occurred. Genital herpes with human immunodeficiency virus (HIV) infection • Standard systemic antiviral drugs, as used to treat genital herpes in HIV-uninfected patients, have been shown to successfully treat genital herpes in patients with HIV. • Resistance to antiherpes drugs is more common in those with HIV co-infection and is associated with treatment failure of genital herpes.

Clinical Guideline	Recommendation(s)
	• Oral acyclovir, valacyclovir, and famciclovir are recommended for treatment of genital herpes. • In severe cases, initiating therapy with acyclovir 5 to 10 mg/kg body weight intravenously every eight hours might be necessary.
World Health Organization: **Treatment of Genital Herpes Simplex Virus (2016)[15]**	<u>First clinical episode of genital Herpes Simplex Virus (HSV) infection</u> • For adults and adolescents with a first clinical episode of genital HSV infection, treatment is recommended over no treatment. • For adults and adolescents with a first clinical episode of genital HSV infection, a standard dose of acyclovir is suggested over valaciclovir or famciclovir. Dosages: o Acyclovir 400 mg orally thrice daily for 10 days (standard dose) o Acyclovir 200 mg orally five times daily for 10 days o Valaciclovir 500 mg orally twice daily for 10 days o Famciclovir 250 mg orally thrice daily for 10 days • Comparative trials of these medications suggest they have compatible clinical efficacy. • This recommendation also applies to people living with HIV, people who are immunocompromised, people with a severe episode and pregnant women. <u>Recurrent clinical episode of genital HSV infection (episodic therapy)</u> • For adults and adolescents with a recurrent clinical episode of genital HSV infection, treatment is suggested over no treatment. • Treatment should be given within the first 24 hours of the onset of symptoms or during the prodromal phase. • For adults and adolescents with a recurrent clinical episode of genital HSV infection, the use of acyclovir is suggested over valaciclovir or famciclovir. • Dosages for adults, adolescents and pregnant women: o Acyclovir 400 mg orally thrice daily for five days, 800 mg twice daily for five days, or 800 mg thrice daily for two days o Valaciclovir 500 mg orally twice daily for three days o Famciclovir 250 mg orally twice daily for five days • Dosages for people living with HIV and people who are immunocompromised: o Acyclovir 400 mg orally thrice daily for five days o Valaciclovir 500 mg orally twice daily for five days o Famciclovir 500 mg orally twice daily for five days • Although the benefits of the medicines are probably similar, the costs of valaciclovir and famciclovir are higher than acyclovir, and therefore acyclovir is preferred. <u>Recurrent clinical episodes of genital HSV infection that are frequent, severe or cause distress (suppressive therapy)</u> • For adults and adolescents with recurrent clinical episodes of genital HSV infection that are frequent, severe or cause distress, suppressive therapy is suggested over episodic therapy, and reassessment after one year. • For adults and adolescents with recurrent clinical episodes of genital HSV infection that are frequent, severe or cause distress, acyclovir is suggested over valaciclovir or famciclovir for suppressive therapy. • Dosages for adults, adolescents and pregnant women: o Acyclovir 400 mg orally twice daily o Valaciclovir 500 mg orally once daily o Famciclovir 250 mg orally twice daily • Dosages for people living with HIV and people who are immunocompromised: o Acyclovir 400 mg orally twice daily o Valaciclovir 500 mg orally twice daily o Famciclovir 500 mg orally twice daily • Individuals who have frequent recurrences (e.g., four to six times a year or more),

Clinical Guideline	Recommendation(s)
	severe symptoms or episodes which cause distress will likely choose suppressive therapy over episodic therapy. • Although the benefits of the medicines may be similar, the costs of valaciclovir and famciclovir are higher than acyclovir, and therefore acyclovir is preferred. The choice of medicine may also depend on compliance considerations.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the skin and mucous membrane antivirals are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Skin and Mucous Membrane Antivirals[1-6]

Indication	Single Entity Agents		Combination Product
	Acyclovir	Penciclovir	Acyclovir and Hydrocortisone
Herpes Simplex Virus Infections			
Management of initial genital herpes and in limited non–life-threatening mucocutaneous herpes simplex virus infections in immunocompromised patients	✔ †		
Treatment of recurrent herpes labialis	✔ *	✔	
Treatment of recurrent herpes labialis to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time			✔

*Cream formulation.
†Ointment formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the skin and mucous membrane antivirals are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Skin and Mucous Membrane Antivirals[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Acyclovir	Minimal	Not reported	Not reported	Not reported	Not reported
Penciclovir	Undetectable	Not reported	Not reported	Not reported	Not reported
Combination Product					
Acyclovir and hydrocortisone	Minimal	Not reported	Not reported	Not reported	Not reported

V. Drug Interactions

Due to limited systemic absorption with the skin and mucous membrane antivirals, no major drug interactions have been reported.[2]

VI. Adverse Drug Events

The most common adverse drug events reported with the skin and mucous membrane antivirals are listed in Table 5.

Table 5. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Antivirals[1-6]

Adverse Events	Single Entity Agents		Combination Product
	Acyclovir	Penciclovir	Acyclovir and Hydrocortisone
Dermatological			
Application site reaction	-	✔	-
Burning	30*, <1†	-	<1
Contact dermatitis	✔ †	-	<1
Cracked lips	<1†	-	-
Desquamation	<1†	-	-
Dry lips	<1†	-	<1
Dry skin	<1†	-	<1
Eczema	✔ †	-	-
Edema	✔ *	✔	-
Erythema	-	50	<1
Flakiness of the skin	<1†	-	<1
Local anesthesia	-	<1	-
Pigmentation changes	-	-	<1
Pruritus	4*, <1†	✔	-
Rash	✔ *	✔	-
Skin discoloration	-	✔	-
Stinging	30*, <1†	-	<1
Tingling	-	-	<1
Urticaria	-	✔	-
Other			
Anaphylaxis	✔ †	-	-
Angioedema	✔ †	-	-
Headache	-	5	-
Oropharyngeal edema	-	✔	-
Pain	30*	✔	-
Paresthesia	-	✔	-
Parosmia	-	✔	-

✔ Percent not specified.
- Event not reported or incidence <1%.
* Ointment formulation.
† Cream formulation.

VII. Dosing and Administration

The usual dosing regimens for the skin and mucous membrane antivirals are listed in Table 6.

Table 6. Usual Dosing Regimens for the Skin and Mucous Membrane Antivirals[1-6]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			

Acyclovir	Management of initial genital herpes and in limited non–life-threatening mucocutaneous herpes simplex virus infections in immunocompromised patients: Ointment: apply every three hours (six times/day) for seven days Recurrent herpes labialis in immunocompetent patients: Cream: Apply five times/day for four days	Recurrent herpes labialis in immunocompetent patients ≥12 years of age: Cream: apply five times/day for four days	Cream: 5% Ointment: 5%
Penciclovir	Recurrent herpes labialis: Cream: apply every two hours while awake for four days	Recurrent herpes labialis for individuals ≥12 years of age: Cream: apply every two hours while awake for four days	Cream: 1%
Combination Product			
Acyclovir and hydrocortisone	Recurrent herpes labialis to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time: Cream: apply five times/day for five days	Recurrent herpes labialis to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time for individuals ≥six years of age: Cream: apply five times/day for five days	Cream: 5%-1%

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the skin and mucous membrane antivirals are summarized in Table 7.

Table 7. Comparative Clinical Trials with the Skin and Mucous Membrane Antivirals

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Herpes Genitalis				
Luby et al.[16] (1984) Acyclovir 5% ointment applied 6 times/day at 3 hour intervals vs placebo	MC, PC, RCT Patients with recurrent genital herpes who experienced a prodrome more than 75% of the time before occurrence of actual lesions	N=309 5 days	Primary: Duration of viral excretion Secondary: Duration of ulceration/crusting of genital lesions, healing time of lesions, and duration of pain and itching	Primary: In female patients, the duration of viral excretion was less in the acyclovir group compared to placebo (1.1 vs 2.0 days; P=0.04). In male patients, there was no difference between the acyclovir and placebo groups (1.8 days). Secondary: There was no difference between placebo and acyclovir in ulceration and/or crusting time for male patients who had genital lesions present at the initial clinic visit (2.2 days). The mean duration of pain and itching in males treated with acyclovir compared to placebo was 3.7 and 3.8 days, respectively. The mean duration of pain and itching in females treated with acyclovir compared to placebo was 5.4 and 4.4 days, respectively.
Reichman et al.[17] (1983) Acyclovir 5% ointment applied 6 times/day at 3 hour intervals vs placebo	DB, PC, RCT Patients with culture-proven recurrent herpes simplex genitalis	N=88 5 days	Primary: Duration of virus shedding, time to crusting of lesions, time required for lesions to heal, time to cessation of pain Secondary: Not reported	Primary: The duration of virus shedding from lesions present at time of study entry was significantly reduced for men who received acyclovir compared to placebo (2.0 vs 3.2 days; P<0.05). In women, the duration of virus shedding was 1.6 days for those in the acyclovir group compared to 1.2 days for the placebo group. There was no significant difference between acyclovir and placebo in time to crusting, time required for lesion healing, time to cessation of pain, or frequency with which new lesions developed during the course of therapy. Secondary: Not reported
Corey et al.[18] (1982) Acyclovir 5%	DB, PC, RCT Patients with initial or	N=180 21 days	Primary: Mean duration of viral shedding from genital lesions, mean	Primary: Among acyclovir recipients with first episodes of genital herpes, the mean duration of viral shedding from genital lesions (2.0 vs 4.6 days), mean duration of local pain or itching (3.6 vs 6.7 days) and the mean time to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ointment applied 4 or 6 times/day vs placebo	recurrent episodes of genital herpes		duration of local pain or itching, mean time to healing of lesions Secondary: Not reported	healing of lesions (11.2 vs 15.8 days) were less than placebo (P<0.05). Among patients with recurrent genital herpes, the mean time to crusting and healing of lesions was 3.5 and 7.5 days, respectively, in acyclovir recipients compared to 5.0 days (P=0.03) and 9.7 days (P=0.07), respectively, in placebo recipients. Secondary: Not reported
Kinghorn et al.[19] (1983) Acyclovir 5% ointment applied 5 times/day vs placebo	DB, PC, RCT Patients diagnosed with a first or recurrent episode of genital herpes	N=113 14 days	Primary: Duration of pain, time to healing, duration of viral shedding, duration of new lesion formation Secondary: Not reported	Primary: For first episodes treated with acyclovir, the duration of pain (4 vs 8 days: P<0.05), time to healing (8 vs 14 days; P<0.001), duration of viral shedding (4 vs 11 days; P=0.001) and duration of new lesion formation (0 vs 2.5 days; P<0.001) were reduced compared to placebo. Patients with recurrent episodes in the acyclovir group showed reduced durations for all symptoms (3 vs 6 days; P<0.001), for time to healing (4 vs 6 days; P<0.01) and for the formation of new lesions (5 vs 29%; P<0.01) compared to placebo. Secondary: Not reported
Kinghorn et al.[20] (1986) Acyclovir 5% cream applied 5 times/day for 7 days and acyclovir 200 mg tablets 4 times/day vs placebo cream and acyclovir 200 mg tablets 4 times/day	DB, PC, RCT Patients ≥16 years of age who presented within 6 days of onset of symptoms of first episode genital herpes	N=49 7 days	Primary: Duration of viral shedding, duration of symptoms and time to healing of lesions Secondary: Not reported	Primary: Duration of viral shedding in the acyclovir cream group compared to placebo was not statistically significant (external lesions: 2.6 vs 2.0 days; urethra or cervix: 2.1 vs 1.7 days). The mean duration of viral shedding for women in the acyclovir cream group compared to placebo was not statistically significant (external lesions: 2.6 vs 2.8 days; cervix: 1.7 vs 1.8 days). The duration of symptoms of pain, dysuria and discharge showed no statistical significance between treatment groups. There was a decrease in the duration of itching with acyclovir cream compared to placebo (1.2 vs 2.2 days; P=0.08).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The mean duration of time to healing of lesions was not significantly different. Secondary: Not reported
Chen et al.[21] (2000) Penciclovir 1% cream applied 5 times/day vs acyclovir 3% cream applied 5 times/day	DB, MC, PG, RCT Patients 18 to 65 years of age with genital herpes and treatment was initiated within 24 hours of onset of the first sign of lesions	N=205 7 days	Primary: Time to healing, resolution of all symptoms, absence of blisters, cessation of new blisters, crusting and loss of crust Secondary: Not reported	Primary: A decrease in crusting time was noted in patients with primary first episodes of genital herpes with penciclovir compared to acyclovir (2.0 vs 3.0 days; P=0.03). The acyclovir group compared to the penciclovir group had a longer time to healing, absence of blisters, cessation of new blisters and loss of crust. None of these differences were found to be statistically significant. A comparison of clinical efficacy in terms of cure rate at day seven indicated that there was no difference between penciclovir and acyclovir treatment (P=0.53). Secondary: Not reported
Herpes Labialis				
Spruance et al.[22] (1984) Acyclovir 5% ointment applied 4 times/day for 5 days vs placebo	DB, PC Patients with herpes simplex labialis	N=208 5 days	Primary: Decrease in median virus titers in lesions between the first and second clinic visit Secondary: Not reported	Primary: Acyclovir had a greater decrease in median virus titers in lesions compared to placebo (P=0.04). Antiviral effect occurred in the subgroup of patients who entered the study 0 to eight hours after the onset of lesions. No differences were found in patients who began treatment nine to 25 hours after lesion onset. The acyclovir group had a mean number of episodes per month of 0.38 compared to 0.45 in the placebo group (P=0.22). Secondary: Not reported
Shaw et al.[23] (1985)	DB, PC, RCT Patients ≥18	N=45 5 days	Primary: Healing time of original lesions, and	Primary: No significant differences were found in the criteria used to examine efficacy between acyclovir and placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Acyclovir 5% cream applied 5 times/day vs placebo	years of age with at least three recurrences of herpes labialis a year		original lesion and fresh lesion combined; time to first crust on the original lesion and loss of crust from original lesion; duration of all symptoms Secondary: Not reported	The median healing times for acyclovir and placebo were nine and 10 days, respectively (P=0.82). The median duration of all symptoms was five days for the acyclovir group vs six days for the placebo group (P=0.33). Secondary: Not reported
Gibson et al.[24] (1986) Acyclovir 5% cream applied 4 times/day vs placebo	DB, PC, RCT Patients ≥16 years of age with six or more recurrences of herpes labialis per year	N=23 32 weeks (16 weeks of acyclovir application and 16 weeks of placebo)	Primary: Number of recurrent sores, number of days with sores present and number of days with signs/symptoms of disease present Secondary: Not reported	Primary: There was a significant difference in favor of the acyclovir group in mean number of doctor-confirmed recurrent sores (0.5 vs 1.1; P<0.05), mean number of sores present (9.5 vs 12.4; P<0.01) and mean number of days with no signs or symptoms of disease present (12.2 vs 17.4; P<0.001). There was no significant difference between the acyclovir and placebo groups in mean time to first patient recorded recurrence (40.7 vs 43.3), mean time to first doctor confirmed recurrence (64.2 vs 63.2) and mean number of patient recorded recurrent sores (1.6 vs 2.4). Secondary: Not reported
Raborn et al.[25] (1997) Acyclovir 5% cream applied 4 times/day at 4 hour intervals vs placebo	DB, MC, PC, RCT Patients ≥18 years of age who had experienced more than three episodes of sun-induced herpes labialis within the past year; first application	N=191 8 days	Primary: Number of lesions formed during treatment, number of lesions formed during follow-up Secondary: Not reported	Primary: The difference in the number of patients who had lesions form during treatment was not statistically significant in the acyclovir group compared to placebo (15/91 vs 23/90; P=0.20). During the four day follow-up period, a smaller percentage of patients with lesion formation were found in the acyclovir group compared to the placebo group (21 vs 40%; P<0.01). The proportion of patients with no lesion formation in either the treatment period or the four day follow-up was greater in the acyclovir group vs placebo (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	was to be applied 12 hours before intensive sun exposure			Secondary: Not reported
Spruance et al.[26] (2002) Acyclovir 5% cream applied 5 times daily vs placebo	DB, MC, PC, RCT (2 trials) Patients ≥18 years of age with a history of recurrent herpes labialis (at least three episodes in the past year)	N=1,385 4 days	Primary: Clinician-assessed duration of herpes labialis episode Secondary: Patient-assessed duration of pain, proportion of patients developing classical lesions (ulcers, vesicles, and crust)	Primary: The mean clinician-assessed duration of herpes labialis episode was significantly shorter for the patients treated with acyclovir cream vs patients treated with placebo cream in each of the two clinical trials (study 1; P=0.007, study 2; P=0.006). In study 1, the mean duration of herpes labialis episodes for patients with a known duration was 4.3 days in the acyclovir group compared to 4.8 days for the placebo group (P=0.010). In study 2, the durations of herpes labialis episodes for patients with a known duration was 4.6 days in the acyclovir group compared to 5.2 days for the placebo group (P=0.007). Secondary: The mean patient-assessed duration of pain was significantly shorter for patients in the acyclovir group compared to placebo in both studies (study 1; P=0.017, study 2; P=0.014). In study 1, the mean duration of pain was 2.9 days for patients in the acyclovir group compared to 3.2 days in the placebo group (P=0.024). In study 2, the mean duration of pain was 3.1 days for patients in the acyclovir group compared to 3.5 days for patients in the placebo group (P=0.027).
Evans et al.[27] (2002) Acyclovir-hydrocortisone 5%-1% cream applied 6 times/day for 5	DB, MC, RCT Patients ≥18 years of age who had a history of recurrent herpes labialis after exposure to	N=380 15 days	Primary: Development of lesions and time to healing, maximum lesion area, pain and tenderness Secondary:	Primary: Only 26% of patients developed delayed classical lesions (lesions that developed between 46 hours and seven days following UVR exposure) during treatment with acyclovir-hydrocortisone compared to 37% of patients treated with placebo (P=0.022). The patients in the acyclovir-hydrocortisone treatment group who developed delayed classical lesions had a median time to healing to normal skin of nine

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days vs placebo	sunlight in the previous 12 months or who had ≥2 cold sores in the previous 12 months		Not reported	days compared to 10.1 days with placebo (P=0.037). The healing time measured as the time to the loss of the hard crust was reduced 19% by acyclovir-hydrocortisone from 6.8 to 5.4 days (P=0.084). Acyclovir-hydrocortisone reduced the median maximal lesion area of the delayed classical lesions by 28% (P=0.072). No significant treatment effects with respect to pain were observed in the study. A total of 76% of patients receiving acyclovir-hydrocortisone experienced pain compared to 81% of patients receiving placebo. A total of 42 patients receiving acyclovir-hydrocortisone who developed delayed classical lesions experienced tenderness, whereas 65 patients who were in the control group and who developed delayed classical lesions experienced tenderness (P=0.11). The patient opinion was more favorable for the patients treated with acyclovir-hydrocortisone than for those treated with placebo (P=0.006). Secondary: Not reported
Hull et al.[7] (2011) Acyclovir-hydrocortisone 5%-1% cream applied 5 times/day for 5 days vs acyclovir 5% cream applied 5 times/day for 5	DB, MC, RCT Patients ≥18 years of age with herpes simplex labialis who had experienced at least three episodes in the last year	N=2,437 3 weeks	Primary: Prevention of ulcerative herpes simplex labialis lesions Secondary: Episode duration of ulcerative lesions, time to lesion healing of ulcerative lesions, maximum lesion area for ulcerative lesions during the vesicular, ulcerative, and hard	Primary: The proportion of patients with nonulcerative lesions was higher in the acyclovir-hydrocortisone group (42%) than in the acyclovir group (35%; P=0.014) or in the placebo group (26%; P<0.0001). Treatments were more effective when started at an early lesion stage. This was significant for acyclovir-hydrocortisone (P=0.023) and for acyclovir (P=0.002) compared to placebo. Secondary: In patients who developed an ulcerative lesion (58% in the acyclovir-hydrocortisone group, 65% in the acyclovir group, and 74% in the placebo group), the mean duration of the ulcerative lesions to loss of hard crust was shorter in patients receiving acyclovir-hydrocortisone (5.7 days) than in those receiving placebo (6.5 days; P=0.008). The mean duration of the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days vs placebo			crust stages, cumulative lesion area, duration of lesion tenderness	ulcerative lesions in patients receiving acyclovir was 5.9 days, which was not significantly different than acyclovir/hydrocortisone (P=0.365). The time for ulcerative lesions to heal was reduced by 1.4 days with acyclovir-hydrocortisone compared to placebo (P=0.002) and by 0.3 days compared to acyclovir (P=0.297). There was no significant difference in maximum lesion size of ulcerative lesions among the treatment groups. The cumulative lesion size of ulcerative lesions was not significantly different with acyclovir-hydrocortisone compared to acyclovir (P=0.096); however, favored acyclovir-hydrocortisone compared to placebo (P=0.005). The cumulative lesion size of "all lesions" favored acyclovir-hydrocortisone over acyclovir and placebo (P=0.014 and P<0.0001, respectively). The duration of tenderness of ulcerative lesions was five days with acyclovir-hydrocortisone and acyclovir compared to six days with placebo (P=0.019). There was no significant difference between acyclovir-hydrocortisone and acyclovir in the duration of tenderness of ulcerative lesions (P=0.838).
Strand et al.[28] (2012) Acyclovir-hydrocortisone 5%/1% cream applied topically 5 times a day for 5 days	MC, OL Patients 12 to 17 years of age with a history of herpes simplex labialis and ≥2 recurrences during the past year	N=134 4 weeks	Primary: Adverse events, categorization of the recurrence as ulcerative or nonulcerative maximum lesion area Secondary: Not reported	Primary: Five adverse events occurred in five patients. Three were rated as mild in intensity and two of moderate intensity. Only one adverse event was considered to be related to the study medication (application site inflammation of moderate severity), leading to withdrawal from the study. Herpes simplex labials recurrence consisted of a single lesion in 126 (95.5%) and two lesions in six (4.5%) patients respectively. Overall, 78 patients (59.5%) had nonulcerative recurrences and 53 patients (40.5%) had ulcerative recurrences. The mean maximum lesion area in the 53 patients with ulcerative herpes lesions was 38.8±40.8 mm^2 (range six to 260 mm^2). Lesions healed completely in all evaluable patients, with normal skin and no signs or symptoms at the follow-up visit.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Spruance et al.[29] (1997) Penciclovir 1% cream applied every 2 hours while awake vs placebo	DB, MC, PC, PG, PRO, RCT Patients with a history of frequent episodes of herpes labialis; treatment was self-initiated by the patient within one hour of the first sign or symptoms of recurrence	N=1,573 4 days	Primary: Lesion healing, proportion of patients who lost their lesions by days six to eight Secondary: Time to loss of lesion pain	Primary: Healing of classical lesions based on the investigator-assessed data was found to be one day faster in the patients who received penciclovir compared to the patients who received placebo (5 vs 6 days; P<0.001). Patient-assessed healing time was found to be 0.7 days faster for penciclovir-treated patients compared to those who received placebo (4.8 vs 5.5 days; P<0.001). Investigator-assessed proportion of patients who lost classical lesions by days six, seven, and eight in the penciclovir group compared to the placebo group increased by 11, 9, and 7%, respectively (P<0.001, P<0.001, P=0.001). In the patient-assessed data, the proportion of patients who lost classical lesions by days six, seven, and eight in the penciclovir group compared to the placebo group increased by 11, 10, and 6%, respectively (P<0.001, P<0.001and P=0.001). Secondary: Time to loss of pain (3.5 vs 4.1 days; P<0.001) resolved more quickly for penciclovir treated patients compared to patients who applied the placebo control.
Boon et al.[30] (2000) Penciclovir 1% cream applied every 2 hours while awake vs placebo	DB, PC, PG, RCT Patients 18 to 81 years of age with a history of sun-induced herpes labialis with at least three recurrences a year	N=541 4 days	Primary: Clinician-recorded time to lesion healing and severity Secondary: Patient-recorded time of healing and severity of pain as well as other lesion symptoms	Primary: Penciclovir was significantly more effective than placebo in decreasing the time to lesion healing (P<0.001). Analysis of healing times for penciclovir patients who developed immediate lesions demonstrated a reduction of two days in median healing time compared to the placebo group (P<0.001). Secondary: The lesion-associated symptoms of itching, tingling, burning, tenderness, and numbness resolved significantly faster with penciclovir treatment than with placebo (P=0.026). The median loss of symptoms was seven days for penciclovir patients vs eight days for patients using placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Fewer penciclovir treated patients rated their pain, itching, burning, and tenderness as moderate or severe compared to placebo (P<0.027).
Raborn et al.[31] (2002) Penciclovir 1% cream applied 6 times on day 1, then every 2 hours while awake vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with a history of recurrent herpes simplex labialis who had ≥3 episodes/year that manifested as classical lesions	N=4,573 4 days	Primary: Healing of classical lesions Secondary: Resolution of lesion pain and duration of viral shedding	Primary: Lesion healing occurred significantly faster in the penciclovir group (4.9 days) than in the placebo group (5.5 days; P=0.0001). The percentage of cases healed by day six was significantly greater in the penciclovir group (70%) than in the placebo group (59%; P=0.001). The percentage of cases healed by day eight was significantly greater in the penciclovir group (85%) than in the placebo group (78%) as determined by the investigator (P=0.012). A similar finding was reported by the patient at day eight with the penciclovir group at 84% and the placebo group at 76% (P=0.002). Secondary: Resolution of lesion pain (days) was significantly different between the penciclovir group and the placebo group (3.5 vs 4.2 days; P=0.0001). There was a significant difference in healing in favor of penciclovir over placebo for early (P=0.001), late (P=0.0001) and vesicle (P=0.0115) stages. Loss of lesion pain also showed a significant difference in favor of the penciclovir group relative to the placebo group for early (P=0.0004), late (P=0.0001) and vesicle (P=0.0023) stages.
Femiano et al.[32] (2001) Penciclovir 1% cream applied every 2 hours vs acyclovir 5% cream applied every 2 hours	RCT Patients 12 to 47 years of age who had a history of frequent episodes of recurrent herpes labialis (at least five each year)	N=40 4 days	Primary: Clinicians' judgment of the appearance of vesiculation to crusting and patients' experience of pain Secondary: Not reported	Primary: In the prodromal acyclovir group, labial lesions reached a crusting stage by six days, with pain ceasing at day five. In the prodromal penciclovir group, both phases were reached earlier. The crusting phase was reached and pain ceased by day four, a difference that was significant (P=0.002041). In the disease therapy (appearance of vesicles) group, the acyclovir patients' clinical evolution and symptoms were similar to those seen in the absence of any therapy. The penciclovir patients, however, benefited from a reduction of 30% in the time to lesional crusting and a 20% reduction of the duration of pain compared to baseline and acyclovir (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Lin et al.[33] (2002) Penciclovir 1% cream applied up to 5 times/day vs acyclovir 3% cream applied up to 5 times/day	DB, MC, PG, RCT Patients 18 to 65 years of age with clinical diagnosis of herpes simplex facialis/labialis	N=248 7 days	Primary: Time to healing, resolution of all symptoms, absence of blisters, cessation of new blisters, crusting and loss of crust Secondary: Not reported	Primary: There was a trend towards shorter times in the penciclovir-treated primary cases, but the differences were not found to be statistically significant (P<0.08). In all groups treated with study medication, there was a significant reduction in scores relative to baseline (P<0.01). On days five and seven of treatment, the clinical scores in penciclovir-treated patients were significantly lower than those in the acyclovir-treated patients (P<0.01 and P<0.05, respectively). On day seven evaluations, treatment was recorded as a clinical cure in 75.4% of the penciclovir-treated patients and 64.9% of the acyclovir-treated patients. The difference was not statistically significant. Secondary: Not reported
Herpes Simplex Virus in Immunocompromised Patients				
Whitley et al.[34] (1984) Acyclovir 5% ointment applied 6 times/day vs placebo	DB, PC, RCT Immuno-compromised patients diagnosed with herpes simplex virus infections regardless of type	N=63 28 days	Primary: Viral clearance, resolution of pain, total lesion healing Secondary: Not reported	Primary: Individuals in the acyclovir group experienced acceleration in the clearance of virus (P=0.0006), resolution of pain (P=0.004) and total healing (P=0.038). Median differences between groups averaged 6 days for each of these parameters. Secondary: Not reported

Study abbreviations: DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial
Miscellaneous Abbreviations: UVR=ultraviolet radiation

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 8. Relative Cost of the Skin and Mucous Membrane Antivirals

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Acyclovir	cream, ointment	Zovirax®*	$$$$$	$$$$
Penciclovir	cream	Denavir®*	$$$$	N/A
Combination Product				
Acyclovir and hydrocortisone	cream	Xerese®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The skin and mucous membrane antivirals are approved for the treatment of herpes simplex virus types 1 and 2 (HSV-1 and HSV-2).[1-6] Acyclovir and penciclovir are available generically.

Acyclovir ointment is approved for the treatment of genital herpes. Guidelines state that topical antiviral agents are less effective than oral agents, offer minimal clinical benefits, and do not recommend their use for this indication.[12-15] In clinical trials, topical acyclovir and penciclovir have been shown to be more effective than placebo.[16-20,22-26,29-31] One study directly compared topical formulations of acyclovir and penciclovir, which demonstrated similar efficacy among the agents.[21]

Acyclovir, penciclovir, and acyclovir-hydrocortisone are approved for the treatment of recurrent herpes labialis.[1-6] They have been shown to decrease lesion healing time and duration of pain in clinical trials compared to placebo.[7,24-27,29-31] Although the results were statistically significant, the clinical significance is unknown. Healing times and duration of pain were reduced by ≤1 day compared to placebo.[7,23,26,27,29-31] Two studies directly compared acyclovir and penciclovir for the topical treatment of herpes labialis. In one study, penciclovir resulted in a quicker time to crusting and cessation of pain compared to acyclovir; however, there was no significant difference in time to healing.[32] In a second study, acyclovir and penciclovir demonstrated similar efficacy with regards to clinical cure rates and time to healing.[33] Hull et al compared combination therapy with acyclovir-hydrocortisone and acyclovir monotherapy in patients with recurrent herpes labialis.[7] The proportion of patients with nonulcerative lesions was significantly higher in the acyclovir-hydrocortisone group compared to the acyclovir monotherapy group. In patients who developed ulcerative lesions, there was no difference in the mean duration of lesions with acyclovir-hydrocortisone (5.7 days) compared to acyclovir (5.9 days; P=0.365). There was also no significant difference in the time for ulcerative lesions to heal, maximum lesion size, cumulative lesion size or duration of tenderness of ulcerative lesions.

There is insufficient evidence to support that one brand skin and mucous membrane antiviral is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand skin and mucous membrane antivirals within the class reviewed are comparable to each other and to the generics products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand skin and mucous membrane antiviral is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Antifungals
AHFS Class 840408
February 8, 2023

I. Overview

The skin and mucous membrane antifungals are approved for the treatment of candidiasis, dermatitis, onychomycosis, and dermatophyte infections.[1-18] Local cutaneous and mucous membrane infections with *Candida* species are generally benign and are the result of changes in the normal flora.[19] Seborrheic dermatitis is an inflammatory skin condition characterized by the formation of white or yellow flaky scales, which appear on oily areas, such as the scalp, face, and upper trunk. Although the exact cause of seborrheic dermatitis is unknown, it is thought to be caused by a combination of overproduction of skin oil and colonization with *Malassezia*.[20] Onychomycosis is an infection of the nails which can be caused by any fungus, including dermatophytes, yeasts, and non-dermatophyte molds. Dermatophyte infections are named by location (e.g., tinea corporis, tinea pedis, tinea unguium, tinea capitis, tinea cruris, and tinea barbae). *Epidermophyton*, *Trichophyton,* and *Microsporum* are the three dermatophytes that cause the majority of infections.[21]

The antifungal agents are classified based upon their chemical structure: allylamines (naftifine, terbinafine); azoles (butoconazole, clotrimazole, econazole, efinaconazole, ketoconazole, luliconazole, miconazole, oxiconazole, sertaconazole, sulconazole, terconazole, tioconazole); benzylamines (butenafine); hydroxy pyridones (ciclopirox); oxaboroles (tavaborole); polyenes (nystatin); and thiocarbamates (tolnaftate).[1,2] Most of these agents share a similar mechanism of action. They primarily block the enzyme responsible for breaking down sterol precursors, thereby inhibiting the formation of key cell membrane components (e.g., ergosterol) of the fungus. This action compromises the integrity of the cell membrane leading to growth inhibition and/or cell death.[1,2]

There are several combination products that are currently available, including clotrimazole-betamethasone, miconazole-zinc oxide-white petrolatum, and nystatin-triamcinolone. The mechanism of action varies with each product. Products containing a corticosteroid (betamethasone and triamcinolone) help to control inflammation, which increases infection cure rates. Zinc oxide acts as a skin protectant and mild astringent with weak antiseptic properties.[1,2,18]

The skin and mucous membrane antifungals that are included in this review are listed in Table 1. This review encompasses all topical dosage forms and strengths. Many of the antifungals are available in a generic formulation. This class was last reviewed in February 2021.

Table 1. Skin and Mucous Membrane Antifungals Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Butenafine	cream	Mentax®	none
Butoconazole	vaginal cream	Gynazole-1®	none
Ciclopirox	cream, gel, shampoo, solution, suspension	Ciclodan®*, Loprox®*	ciclopirox
Clotrimazole	cream, solution, troche	N/A	clotrimazole
Econazole	cream	N/A	econazole
Efinaconazole	solution	Jublia®	none
Ketoconazole	cream, foam, shampoo	Extina®*	ketoconazole
Luliconazole	cream	Luzu®*	luliconazole
Miconazole	vaginal suppository	N/A	miconazole
Naftifine	cream, gel	Naftin®*	naftifine
Nystatin	cream, ointment, powder	N/A	nystatin
Oxiconazole	cream	N/A	oxiconazole
Sertaconazole	cream	Ertaczo®	none
Sulconazole	cream, solution	Exelderm®*	sulconazole

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Tavaborole	solution	Kerydin®*	tavaborole
Terconazole	vaginal cream, vaginal suppository	N/A	terconazole
Combination Products			
Clotrimazole and betamethasone	cream, lotion	N/A	clotrimazole and betamethasone
Miconazole, zinc oxide, and white petrolatum	ointment	Vusion®*	miconazole, zinc oxide, and white petrolatum
Nystatin and triamcinolone	cream, ointment	N/A	nystatin and triamcinolone

*Generic is available in at least one dosage form or strength.
N/A=Not available
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the skin and mucous membrane antifungals are summarized in Table 2.

Table 2. Treatment Guidelines Using the Skin and Mucous Membrane Antifungals

Clinical Guideline	Recommendation(s)
Infectious Diseases Society of America: **Clinical Practice Guidelines for the Management of Candidiasis (2016)**[22]	<u>Vulvovaginal candidiasis</u> • For the treatment of uncomplicated *Candida* vulvovaginitis, topical antifungal agents, with no one agent superior to another, are recommended. • Uncomplicated vulvovaginal candidiasis can be effectively treated with either single-dose or short-course therapy, both of which achieve >90% response. • Complicated vulvovaginal candidiasis (approximately 10% of cases) is defined as severe or recurrent disease, non-albicans candidiasis, and/or vulvovaginal candidiasis in an abnormal host. • Complicated vulvovaginal candidiasis requires topical therapy administered intravaginally daily for approximately seven days or multiple doses of fluconazole (150 mg every 72 hours for three doses). • For recurrent vulvovaginal candidiasis, 10 to 14 days of induction therapy with a topical or oral azole, followed by a suppressive regimen for at least 6 months, is recommended. The most convenient and well-tolerated regimen is once weekly oral fluconazole at a dose of 150 mg. If fluconazole therapy is not feasible, topical clotrimazole (200 mg twice weekly) or clotrimazole (500 mg vaginal suppository once weekly) or other intermittent topical azole treatments are recommended. <u>Oropharyngeal candidiasis</u> • For mild disease, clotrimazole troches, 10 mg five times daily, OR miconazole mucoadhesive buccal 50 mg tablet applied to the mucosal surface over the canine fossa once daily for seven to 14 days, are recommended. • Alternatives for mild disease include nystatin suspension (100,000 U/mL) 4 to 6 mL four times daily, OR 1 to 2 nystatin pastilles (200,000 U each) four times daily, for seven to 14 days. • For moderate to severe disease, oral fluconazole for seven to 14 days is recommended. • For fluconazole-refractory disease, either itraconazole solution or posaconazole suspension for up to 28 days is recommended. Voriconazole or amphotericin B is recommended when treatment with other agents has failed. Intravenous echinocandin or amphotericin B can be used in treating patients with refractory disease. • For denture-related candidiasis, disinfection of the denture, in addition to antifungal

Clinical Guideline	Recommendation(s)
	therapy, is recommended.
Centers for Disease Control and Prevention: **Sexually Transmitted Diseases Treatment Guidelines (2022)**[23-25]	Genital herpes • Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management. • Systemic antiviral drugs can partially control the signs and symptoms of herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy. • Systemic antiviral drugs do not eradicate latent virus or affect the risk, frequency, or severity of recurrences after the drug is discontinued. • Randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes. • Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability. • Topical therapy with antiviral drugs provides minimal clinical benefit, and use is discouraged. • Newly acquired genital herpes can cause prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even patients with first episode herpes who have mild clinical manifestations initially can develop severe or prolonged symptoms. Therefore, all patients with first episodes of genital herpes should receive antiviral therapy. • Recommended regimens for first episodes of genital herpes: o acyclovir 400 mg orally three times daily for seven to 10 days o famciclovir 250 mg orally three times daily for seven to 10 days o valacyclovir 1,000 mg orally twice daily for seven to 10 days. • Treatment can be extended if healing is incomplete after 10 days of therapy. • Acyclovir 200 mg orally five times daily is also effective but is not recommended because of frequency of dosing. • Almost all patients with symptomatic first episode genital herpes simplex virus (HSV)-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection. • Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Suppressive therapy may be preferred because of the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners. • Long-term safety and efficacy have been documented among patients receiving daily acyclovir, valacyclovir, and famciclovir. • Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment. • Providers should discuss with patients on an annual basis whether they want to continue suppressive therapy because frequency of genital HSV-2 recurrence diminishes over time for many persons. • Discordant heterosexual couples in which a partner has a history of genital HSV-2 infection should be encouraged to consider suppressive antiviral therapy as part of a strategy for preventing transmission, in addition to consistent condom use and avoidance of sexual activity during recurrences. Suppressive antiviral therapy for persons with a history of symptomatic genital herpes also is likely to reduce transmission when used by those who have multiple partners. • Recommended regimens for suppressive therapy of genital herpes: o acyclovir 400 mg orally twice daily o famciclovir 250 mg orally twice daily o valacyclovir 500 mg orally once daily o valacyclovir 1,000 mg orally once daily. • Valacyclovir 500 mg once a day might be less effective than other valacyclovir

Clinical Guideline	Recommendation(s)
	or acyclovir dosing regimens for persons who have frequent recurrences (i.e., ≥10 episodes/year). • Acyclovir, famciclovir and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding. Ease of administration and cost also are important to consider when deciding on prolonged treatment. • Because of the decreased risk for recurrences and shedding, suppressive therapy for HSV-1 genital herpes should be reserved for those with frequent recurrences through shared clinical decision-making between the patient and the provider. • Episodic treatment of recurrent herpes is most effective if initiation of therapy within one day of lesion onset or during the prodrome that precedes some outbreaks. Patients should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin. • Recommended regimens for episodic treatment of recurrent HSV-2 genital herpes: o acyclovir 800 mg orally twice daily for five days o acyclovir 800 mg orally three times daily for two days o famciclovir 1,000 mg orally twice daily for one day o famciclovir 500 mg orally once; followed by 250 mg orally twice daily for two days o famciclovir 125 mg orally twice daily for five days o valacyclovir 500 mg orally twice daily for three days o valacyclovir 1,000 mg orally once daily for five days. • Acyclovir 400 mg orally three times daily is also effective but is not recommended because of frequency of dosing. • Intravenous acyclovir should be provided to patients with severe HSV disease or complications that necessitate hospitalization or central nervous system complications. • HSV-2 meningitis is characterized clinically by signs of headache, photophobia, fever, meningismus, and cerebrospinal fluid (CSF) lymphocytic pleocytosis, accompanied by mildly elevated protein and normal glucose. • Optimal therapies for HSV-2 meningitis have not been well studied; however, acyclovir 5 to 10 mg/kg body weight IV every 8 hours until clinical improvement is observed, followed by high-dose oral antiviral therapy (valacyclovir 1 g 3 times/day) to complete a 10- to 14-day course of total therapy, is recommended. • Hepatitis is a rare manifestation of disseminated HSV infection, often reported among pregnant women who acquire HSV during pregnancy. Among pregnant women with fever and unexplained severe hepatitis, disseminated HSV infection should be considered, and empiric IV acyclovir should be initiated pending confirmation. • Consistent and correct condom use has been reported in multiple studies to decrease, but not eliminate, the risk for HSV-2 transmission from men to women. Condoms are less effective for preventing transmission from women to men. • Randomized clinical trials have demonstrated that PrEP with daily oral tenofovir disoproxil fumarate/emtricitabine decreases the risk for HSV-2 acquisition by 30% in heterosexual partnerships. Pericoital intravaginal tenofovir 1% gel also decreases the risk for HSV-2 acquisition among heterosexual women. • The patients who have genital herpes and their sex partners can benefit from evaluation and counseling to help them cope with the infection and prevent sexual and perinatal transmission.

Clinical Guideline	Recommendation(s)

	• Lesions caused by HSV are common among persons with human immunodeficiency virus (HIV) infection and might be severe, painful, and atypical. HSV shedding is increased among persons with HIV infection.
	• Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV infection among persons with HIV.
	• Recommended regimens for daily suppressive therapy of genital herpes in patients infected with HIV:
	  ○ acyclovir 400 to 800 mg orally two to three times daily
	  ○ famciclovir 500 mg orally twice daily
	  ○ valacyclovir 500 mg orally twice daily
	• Recommended regimens for episodic treatment of genital herpes in patients infected with HIV:
	  ○ acyclovir 400 mg orally three times daily for five to 10 days
	  ○ famciclovir 500 mg orally twice daily for five to 10 days
	  ○ valacyclovir 1,000 mg orally twice daily for five to 10 days
	• If lesions persist or recur in a patient receiving antiviral treatment, acyclovir resistance should be suspected, and a viral culture obtained for phenotypic sensitivity testing.
	• Foscarnet (40 to 80 mg/kg body weight IV every 8 hours until clinical resolution is attained) is the treatment of choice for acyclovir-resistant genital herpes. Intravenous cidofovir 5 mg/kg body weight once weekly might also be effective.
	• Imiquimod 5% applied to the lesion for 8 hours 3 times/week until clinical resolution is an alternative that has been reported to be effective.
	• Acyclovir can be administered orally to pregnant women with first-episode genital herpes or recurrent herpes and should be administered IV to pregnant women with severe HSV.
	• Suppressive acyclovir treatment starting at 36 weeks' gestation reduces the frequency of cesarean delivery among women who have recurrent genital herpes by diminishing the frequency of recurrences at term. However, such treatment might not protect against transmission to neonates in all cases.
	• Recommended regimen for suppression of recurrent genital herpes among pregnant women:
	  ○ acyclovir 400 mg orally three times daily
	  ○ valacyclovir 500 mg orally twice daily
	• Treatment recommended starting at 36 weeks' gestation.
	• Infants exposed to HSV during birth should be followed in consultation with a pediatric infectious disease specialist.
	• All newborn infants who have neonatal herpes should be promptly evaluated and treated with systemic acyclovir. The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 14 days if disease is limited to the skin and mucous membranes, or for 21 days for disseminated disease and disease involving the CNS.
	
	<u>Bacterial vaginosis</u>
	• Bacterial vaginosis (BV) is a highly prevalent condition and the most common cause of vaginal discharge worldwide. However, in a nationally representative survey, the majority of women with BV were asymptomatic.
	• Treatment for BV is recommended for women with symptoms.
	• Established benefits of therapy among nonpregnant women are to relieve vaginal symptoms and signs of infection and reduce the risk for acquiring *C. trachomatis, N. gonorrhoeae*, *T. vaginalis*, *M. genitalium*, HIV, HPV, and HSV-2.

Clinical Guideline	Recommendation(s)

	• Recommended regimens for bacterial vaginosis include:
	  ○ Metronidazole 500 mg orally twice daily for seven days.
	  ○ Metronidazole 0.75% gel 5 g intravaginally once daily for five days.
	  ○ Clindamycin 2% cream 5 g intravaginally at bedtime for seven days.
	• Alternative regimens include:
	  ○ Tinidazole 2 g orally once daily for two days.
	  ○ Tinidazole 1 g orally once daily for five days.
	  ○ Clindamycin 300 mg orally twice daily for seven days.
	  ○ Clindamycin 100 mg ovules intravaginally once at bedtime for three days.
	  ○ Secnidazole 2 g oral granules in a single dose
	• Clindamycin ovules use an oleaginous base that might weaken latex or rubber products (e.g., condoms and diaphragms). Use of such products within 72 hours after treatment with clindamycin ovules is not recommended.
	• Oral granules should be sprinkled onto unsweetened applesauce, yogurt, or pudding before ingestion. A glass of water can be taken after administration to aid in swallowing.
	• Using a different recommended treatment regimen can be considered for women who have a recurrence; however, retreatment with the same recommended regimen is an acceptable approach for treating persistent or recurrent BV after the first occurrence.
	• BV treatment is recommended for all symptomatic pregnant women because symptomatic BV has been associated with adverse pregnancy outcomes, including premature rupture of membranes, preterm birth, intra-amniotic infection, and postpartum endometritis.
	
	<u>Uncomplicated vulvovaginal candidiasis</u>
	• Uncomplicated vulvovaginal candidiasis is defined as sporadic or infrequent vulvovaginal candidiasis, mild to moderate vulvovaginal candidiasis, candidiasis likely to be *Candida albicans*, or candidiasis in non-immunocompromised women.
	• Short-course topical formulations (i.e., single dose and regimens of one to three days) effectively treat uncomplicated vulvovaginal candidiasis.
	• Treatment with azoles results in relief of symptoms and negative cultures in 80 to 90% of patients who complete therapy.
	• Recommended regimens include:
	  ○ Butoconazole 2% cream 5 g single intravaginal application.
	  ○ Clotrimazole 1% cream 5 g intravaginally daily for seven to 14 days.
	  ○ Clotrimazole 2% cream 5 g intravaginally daily for three days.
	  ○ Miconazole 2% cream 5 g intravaginally daily for seven days.
	  ○ Miconazole 4% cream 5 g intravaginally daily for three days.
	  ○ Miconazole 100 mg vaginal suppository one suppository daily for seven days.
	  ○ Miconazole 200 mg vaginal suppository one suppository for three days.
	  ○ Miconazole 1,200 mg vaginal suppository one suppository for one day.
	  ○ Tioconazole 6.5% ointment 5 g single intravaginal application.
	  ○ Terconazole 0.4% cream 5 g intravaginally daily for seven days.
	  ○ Terconazole 0.8% cream 5 g intravaginally daily for three days.
	  ○ Terconazole 80 mg vaginal suppository one suppository daily for three days.
	  ○ Fluconazole 150 mg oral tablet in single dose.
	
	<u>Complicated vulvovaginal candidiasis</u>
	• Complicated vulvovaginal candidiasis is defined as recurrent vulvovaginal

Clinical Guideline	Recommendation(s)

	candidiasis, severe vulvovaginal candidiasis, non-albicans candidiasis, or candidiasis in women with diabetes, immunocompromising conditions, underlying immunodeficiency, or immunosuppressive therapy.
	• Most episodes of recurrent vulvovaginal candidiasis caused by *Candida albicans* respond well to short duration oral or topical azole therapy.
	• However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., seven to 14 days of topical therapy or a 100, 150, or 200 mg oral dose of fluconazole every third day for a total of three doses (day one, four, and seven) to attempt mycologic remission before initiating a maintenance antifungal regimen.
	• Recommended maintenance regimen is oral fluconazole (i.e., a 100-mg, 150-mg, or 200-mg dose) weekly for six months. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be considered.
	
	Severe vulvovaginal candidiasis
	• Severe vulvovaginal candidiasis is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy.
	• Either seven to 14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended.
	
	Non-albicans vulvovaginal candidiasis
	• The optimal treatment of non-albicans vulvovaginal candidiasis remains unknown. However, a longer duration of therapy (seven to 14 days) with a non-fluconazole azole drug (oral or topical) is recommended.
	• If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for three weeks.
	
	Genital warts
	• Treatment of anogenital warts should be guided by wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and provider experience.
	• There is no definitive evidence to suggest that any of the available treatments are superior to any other and no single treatment is ideal for all patients or all warts.
	• Because of uncertainty regarding the effect of treatment on future transmission of human papilloma virus and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution.
	• Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy.
	• In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment.
	• The treatment modality should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe.
	• Most genital warts respond within three months of therapy.
	• Recommended regimens for external anogenital warts (patient-applied):
	  ○ Podofilox 0.5% solution or gel.
	  ○ Imiquimod 3.75% or 5% cream.
	  ○ Sinecatechins 15% ointment.
	• Recommended regimens (provider administered):
	  ○ Cryotherapy with liquid nitrogen or cryoprobe.
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution
	  ○ Surgical removal
	• Fewer data are available regarding the efficacy of alternative regimens for

Clinical Guideline	Recommendation(s)
	treating anogenital warts, which include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir. Shared clinical decision-making between the patient and provider regarding benefits and risks of these regimens should be provided. • Podophyllin resin is no longer a recommended regimen because of the number of safer regimens available, and severe systemic toxicity has been reported when podophyllin resin was applied to large areas of friable tissue and was not washed off within 4 hours. Cervical warts • For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade squamous intraepithelial lesion must be performed before treatment is initiated. • Management of exophytic cervical warts should include consultation with a specialist. • Recommended regimens: o Cryotherapy with liquid nitrogen. o Surgical removal o Trichloroacetic acid or bichloracetic acid 80 to 90% solution Vaginal warts • Recommended regimens: o Cryotherapy with liquid nitrogen. o Surgical removal o Trichloroacetic acid or bichloracetic acid 80 to 90% solution Urethral meatus warts • Recommended regimens: o Cryotherapy with liquid nitrogen. o Surgical removal Intra-Anal warts • Management of intra-anal warts should include consultation with a colorectal specialist. • Recommended regimens: o Cryotherapy with liquid nitrogen. o Surgical removal. o Trichloroacetic acid or bichloracetic acid 80 to 90% solution.
British Association for Sexual Health and Human Immunodeficiency Virus: **National Guideline for the Management of Vulvovaginal Candidiasis (2019)**[26]	Acute vulvovaginal candidiasis (VVC) • Recommended regimen: o Fluconazole* capsule 150 mg as a single dose, orally • Recommended topical regimen (if oral therapy contraindicated): o Clotrimazole pessary 500mg as a single dose, intravaginally** • Alternative regimens: o Clotrimazole vaginal cream (10%) 5g as a single dose, intravaginally** o Clotrimazole pessary 200 mg intravaginally at night for three consecutive nights** o Econazole pessary 150 mg intravaginally as a single dose or 150 mg intravaginally at night for three consecutive nights** o Fenticonazole capsule intravaginally as a single dose 600 mg or 200 mg intravaginally at night for three consecutive nights** o Itraconazole 200 mg orally twice daily for one day by mouth* o Miconazole capsule 1200mg intravaginally as a single dose, or 400 mg intravaginally at night for three consecutive nights** o Miconazole vaginal cream (2%) 5g intravaginally at night for seven

Clinical Guideline	Recommendation(s)
	consecutive nights** • Treatment choice: o All intravaginal imidazoles and oral azoles give a clinical and mycological cure rate of over 80% in acute VVC. o Intravaginal imidazoles and oral azoles are equally effective and tolerable in the management of acute VVC with no difference in treatment outcomes. o One RCT suggested that a single dose of oral fluconazole may be more effective than prolonged intravaginal clotrimazole 200mg (for six days) at clinical cure at seven days. • Treatment considerations: o *Oral therapies must be avoided in pregnancy, risk of pregnancy and breastfeeding; topical imidazoles are a safe and effective alternative in these situations. o **Intravaginal and topical treatments can also damage latex condoms and diaphragms with case reports of unplanned pregnancies; women must be appropriately counselled about this risk. o As there is minimal absorption of topically applied imidazoles from the vulvovaginal mucosae there is limited risk of systemic side effects. o Topical therapies can cause vulvovaginal irritation, and this should be considered if symptoms worsen or persist. o A medication history should be taken to advise women that oral fluconazole and other azoles can interact with medications. <u>Severe Vulvovaginal Candidiasis</u> • Recommended regimen: o Fluconazole 150 mg orally on day one and four • Alternative regimens: o Clotrimazole 500 mg pessary intravaginally on day one and four o Miconazole vaginal capsule 1,200 mg on day one and four • In patients with severe VVC (i.e., extensive vulval erythema, edema, excoriation, and fissure formation) regardless of a history of recurrence, fluconazole 150 mg should be repeated after three days as this improves symptomatic response but does not influence the risk or rate of recurrence. • There is no benefit of a seven-day topical treatment course over a single oral dose of fluconazole. <u>Recurrent VVC</u> • Recommended Regimen: o Induction: fluconazole 150 mg orally every 72 hours x three doses* o Maintenance: fluconazole 150 mg orally once a week for six months* • Alternative Regimens: o Induction: topical imidazole therapy can be increased to seven to 14 days according to symptomatic response o Maintenance for six months: ▪ Clotrimazole pessary 500 mg intravaginally once a week ▪ Itraconazole 50 to 100mg orally daily* • *Oral therapies must be avoided in pregnancy, risk of pregnancy and breastfeeding • Treatment duration: o There are no trials addressing the optimal duration of suppressive therapy with the majority of trials using six months maintenance as standard: ▪ If recurrences after maintenance regimen are infrequent, each episode should be treated independently. ▪ If recurrent disease is re-established the induction and maintenance regimens should be repeated. <u>Non-albicans Candida species and azole resistance</u>

Clinical Guideline	Recommendation(s)

	• Recommended Regimen:
	  ○ Nystatin pessaries 100,000 units intravaginally at night for 12 to 14 consecutive nights.
	• Alternative Regimens:
	  ○ Boric acid vaginal suppositories 600 mg daily for 14 days*
	  ○ Amphotericin B vaginal suppositories 50 mg once a day for 14 days
	  ○ Flucytosine 5g cream or 1g pessary intravaginally with amphotericin or nystatin daily for 14 days
	  ○ *Avoid in pregnancy or risk of pregnancy
	• Recurrent VVC due to azole resistant Candida:
	  ○ Nystatin pessaries 100,000 units intravaginally at night for 14 nights per month for six months
	  ○ Consider 14 days per month for six months of the alternative regimens

American College of Obstetricians and Gynecologists: **Vaginitis in Nonpregnant Patients (2020)**[27]	<u>Bacterial vaginosis</u> • Oral or intravaginal metronidazole or intravaginal clindamycin is recommended for the treatment of bacterial vaginosis. • Alternative treatments include oral secnidazole, oral tinidazole, or oral clindamycin. <u>Uncomplicated trichomoniasis</u> • Oral nitroimidazoles are recommended for the treatment of trichomoniasis. • Although a single dose of metronidazole has been the preferred treatment regimen for trichomoniasis, recent data from a randomized controlled trial show that a 7-day course of metronidazole is more effective. • Tinidazole single-dose therapy is an acceptable alternative to the metronidazole regimen. <u>Uncomplicated vulvovaginal candidiasis</u> • Because uncomplicated vulvovaginal candidiasis is effectively and safely treated with a variety of oral and topical treatments that are often available as over-the-counter and as short-course topical treatments, the choice of therapy should be individualized based on factors such as patient preference, cost, convenience, adherence, ease of use, and history of response or adverse reactions to previous treatments. • Over-the-counter intravaginal agents include clotrimazole, miconazole, and tioconazole. • Prescription options include intravaginal butoconazole, intravaginal terconazole, and oral single dose fluconazole. <u>Complicated vulvovaginal candidiasis</u> • Objective information in the form of culture is important to identify the yeast species and correlate with symptoms. • Most infections are secondary to *C albicans*, which is responsive to both topical and oral azoles. Oral fluconazole is an effective and convenient treatment for complicated infections with *C albicans*. <u>Recurrent vulvovaginal candidiasis</u> • Extended antifungal treatment is recommended for patients with recurrent vulvovaginal candidiasis to reduce the likelihood of persistent symptoms. After initial treatment of the acute infection, suppressive therapy with weekly doses of either an intravaginal or oral azole improves cure rates and decreases recurrence rates. • Prolonged antifungal treatment with fluconazole (150 mg weekly for six months) successfully controlled more than 90% of recurrent symptomatic episodes. • For patients who are unable or unwilling to take fluconazole, prolonged therapy

Clinical Guideline	Recommendation(s)
	with intermittent topical agents, such as clotrimazole (500 mg weekly or 200 mg twice a week), are acceptable options. Severe vulvovaginal candidiasis • These patients require a prolonged course with a topical intravaginal azole for 10 to 14 days or two to three doses of oral fluconazole taken orally three days apart. • An acute infection is treated with an extended course of a topical or oral azole. Topical agents can be extended to a 10 to 14-day intravaginal course. Non-albicans Candida species • Therapy with intravaginal boric acid (600-mg capsules daily for a minimum of 14 days) is effective for *C glabrata* and other atypical *Candida* species. • Patients with non-*albicans Candida* vulvovaginal candidiasis in whom boric acid therapy is ineffective should be referred to a subspecialist for further management. • Boric acid can be fatal if ingested orally and patients should be well counseled to use it only intravaginally, to place it out of the reach of children, and to use reliable contraception. • Topical flucytosine, 5 g nightly for two weeks, is another effective treatment for *C glabrata*.
European (International Union Against Sexually Transmitted Infections/ World Health Organization): **Guideline on the Management of Vaginal Discharge (2018)**[28]	Bacterial vaginosis • Recommended regimens for bacterial vaginosis: o Metronidazole 400 to 500 mg twice daily for five to seven days. o Intravaginal metronidazole 0.75% gel once daily for five days. o Intravaginal clindamycin 2% cream once daily for seven days. • Alternative regimens for bacterial vaginosis: o Metronidazole 2 g in a single dose. o Tinidazole 2 g in a single dose. o Tinidazole 1 g daily for five days. o Clindamycin 300 mg twice daily for seven days. o Dequalinium chloride 10 mg vaginal tablet once daily for six days. • Clindamycin and metronidazole have equal efficacy, comparing oral and vaginal formulations, both after one week and after one month of therapy. Approximately 58 to 88% will be cured after five days treatment with metronidazole or clindamycin. In most studies, clindamycin tended to have less adverse effects than metronidazole. • Single dose therapies have lower cure rates than prolonged treatment. Oral metronidazole for seven days has a significantly higher cure rate than single dose treatment (88 vs 54% and 82 vs 62% at three to four weeks after completion of therapy). • Intravaginal metronidazole is recommended for the treatment of persistent and recurrent bacterial vaginosis. Aerobic vaginitis • Recommended regimens for aerobic vaginitis: o 2% clindamycin cream 5 g intravaginally for seven to 21 days. o Combination use of intravaginal clindamycin and intravaginal steroids e.g. Hydrocortisone 300 to 500 mg intravaginally for seven to 21 days for more severe cases. o In cases with a significant atrophy component, local estrogens can be added. Vaginal candidiasis • Intravaginal and oral therapies are equally effective for vaginal candidiasis. • Treatment with azoles results in relief of symptoms and negative cultures among 80 to 90% of patients after either oral or topical treatment; only topical preparations

Clinical Guideline	Recommendation(s)
	should be used during pregnancy. • Recommended regimens for vaginal candidiasis: o Fluconazole 150 mg orally as a single dose. o Itraconazole 200 mg twice daily for one day. o Clotrimazole vaginal tablet 500 mg once or 200 mg once daily for three days. o Miconazole vaginal ovule 1,200 mg as a single dose or 400 mg once daily for three days. o Econazole vaginal pessary 150 mg as a single dose. • Standard single dose treatments are as effective as longer courses. • In a severely symptomatic attack, symptomatic benefit is with fluconazole 150 mg treatment repeated after three days. <u>Trichomonas vaginalis</u> • Recommended regimens for trichomonas vaginalis: o Metronidazole 400 to 500 mg orally twice daily for five to seven days. o Metronidazole 2 gram orally in a single dose. o Tinidazole 2 g orally in a single dose. • The nitroimidazoles are the only class of drugs useful for the oral or parenteral therapy of trichomoniasis and most strains are highly susceptible.
Finnish Medical Society Duodecim: **Seborrheic Dermatitis in the Adult (2020)**[29]	<u>General considerations</u> • No permanent results are usually achieved with treatment, which is symptomatic and needs to be repeated from time to time (a course lasting for one to two weeks) when symptoms worsen. • Maintenance therapy, perhaps once or twice weekly, should be continued in order to reduce the frequency of exacerbations. <u>Reduction of dandruff and sebo-suppression</u> • Seborrheic areas should be washed more often than normally (daily). • Basic topical ointments in gel form (e.g., products containing propylene glycol) to wash with, or basic topical ointments may be applied after washing. <u>Face and body</u> • Topical mild to moderately potent glucocorticoid creams. • Creams containing a combination of a glucocorticoid and an azole antifungal. • Glucocorticoid creams are used periodically, e.g., during periods of exacerbation once or twice daily in courses of one to two weeks. • Tacrolimus ointment or pimecrolimus cream as a periodical therapy one to two times daily for a period of three to four weeks or as maintenance therapy e.g., once or twice a week. • Creams, gels or shampoos containing topical antifungals (ketoconazole, clotrimazole, miconazole, tioconazole) or terbinafine ointment. • Antifungals may be used in acute exacerbations once or twice daily for one to two weeks, and they are suitable for prophylactic maintenance therapy once or twice a week. • Metronidazole or azelaic acid either as gel or cream in courses of three to four weeks and, if needed, as maintenance therapy one to two times a week. <u>Scalp</u> • Scalp plaques can be softened with 3 to 5% salicylic acid ointment in the evenings and washed away in the mornings. • Scalp may be washed with ketoconazole shampoo or selenium sulfide shampoo. • Corticosteroid solutions (equivalent doses) to the scalp (Class I–III). • In treatment-resistant cases, a sequential treatment schedule using a glucocorticoid shampoo in courses of three to four weeks may be tried.

Clinical Guideline	Recommendation(s)
	Ears and ear canals • Mild to moderately potent glucocorticoid ointments or solutions one to two times daily in courses of one to two weeks. Flexural areas • Mild to moderately potent glucocorticoid ointments. • A combination ointment of a glucocorticoid and an azole group antifungal. • Tacrolimus ointment or pimecrolimus cream periodically one to two times daily in courses of three to four weeks, or as maintenance therapy, e.g., one to two times a week. • The effect of the warm and moist environment can be reduced by application of talc or azole-containing powder after wash in the mornings and zinc paste after wash in the evenings. • Flexural areas can be painted with antiseptic solutions, many of which stain the skin (rarely used). • An application of a powder containing, for example, an azole antifungal in the morning and a corticosteroid ointment after washing at night for one to two weeks. • Systemic antifungals may be indicated in serious cases, for example fluconazole 50 mg once daily or 150 mg once weekly (for two to four weeks) or itraconazole 100 mg twice daily (for one to two weeks). Severe and treatment-resistant cases • A course of an oral antifungal drug may be combined with topical therapy, itraconazole 200 mg once daily for seven days, for example. Interactions with other medications must be checked. • Also oral fluconazole or terbinafine has been used as courses.
British Association of Dermatologists: **Guidelines for the Management of Onychomycosis (2014)[30]**	• Both topical and oral agents are available for the treatment of fungal nail infection. • Systemic therapy is almost always more successful than topical treatment. • While it is clearly possible to achieve clinical and mycological cure with topical nail preparations, these cure rates do not compare favorably with those obtained with systemic drugs. • Topical therapy can only be recommended for the treatment of superficial white onychomycosis and in early cases of distal and lateral subungual onychomycosis where the infection is confined to the distal edge of the nail. • Studies comparing the efficacy of topical treatments in onychomycosis are rare. • Systemic treatment in adults: o Itraconazole: first line treatment for dermatophyte onychomycosis. o Terbinafine: first line treatment for dermatophyte onychomycosis, and generally preferred over itraconazole. o Fluconazole: may be a useful alternative in patients unable to tolerate terbinafine or itraconazole. • Topical treatment in adults: o Amorolfine: useful for superficial and distal onychomycosis. o Ciclopirox: useful for superficial and distal onychomycosis and for patients in whom systemic therapy is contraindicated. o Tioconazole: useful for superficial and distal onychomycosis.
European Society for Pediatric Dermatology: **Guidelines for the Management of Tinea Capitis in Children (2010)[31]**	• Tinea capitis always requires systemic treatment because topical antifungal agents do not penetrate the hair follicle. • Topical treatment is only used as adjuvant therapy to systemic antifungals. • Griseofulvin has been the gold standard for systemic therapy of tinea capitis. The main disadvantage of griseofulvin is the long duration of treatment required (six to 12 weeks or longer) which may lead to reduced compliance. • The newer oral antifungal agents including terbinafine, itraconazole, and fluconazole appear to have efficacy rates and potential adverse effects similar to

Clinical Guideline	Recommendation(s)
	those of griseofulvin in children with tinea capitis due to *Trichophyton* species, while requiring much shorter duration of treatment. • Griseofulvin is still the treatment of choice for cases caused by *Microsporum* species. • Adjunctive topical therapies, such as selenium sulfide or ketoconazole shampoos, as well as fungicidal creams or lotions have been shown to decrease the carriage of viable spores responsible for the disease contagion and reinfection and may shorten the cure rate with oral antifungals. • The topical fungicidal cream or lotion should be applied to the lesions once daily for a week. The shampoo should be applied to the scalp and hair for five minutes twice weekly for two to four weeks or three times weekly until the patient is clinically and mycologically cured. The latter in conjunction with one week of topical fungicidal cream or lotion application is recommended.
British Association of Dermatologists: **Guidelines for the Management of Tinea Capitis (2014)[32]**	• The aim of treatment is to achieve a clinical and mycological cure as quickly and safely as possible. • Oral antifungal therapy is generally needed. Topical treatment alone is not recommended for the management of tinea capitis. Topical agents are used to reduce transmission of spores, and povidone–iodine, ketoconazole 2%, and selenium sulfide 1% shampoos have all shown efficacy in this context. • Oral therapy options include griseofulvin, terbinafine, itraconazole, fluconazole, and ketoconazole. • The optimal treatment regimen varies according to the dermatophyte involved. As a general rule, terbinafine is more efficacious against *Trichophyton* species (*T. tonsurans, T. violaceum, T. soudanense*), and griseofulvin more effective against *Microsporum* species (*M. canis, M. audouinii*). • Both griseofulvin and terbinafine have good evidence of efficacy and remain the most widely used first-line treatments. • If there has been no clinical response and signs persist at the end of the treatment period, then the options include: o Initially consider lack of compliance, suboptimal absorption of drug, relative insensitivity of the organism and reinfection. o In cases of clinical improvement but ongoing positive mycology, continue current therapy for a further two to four weeks. If there has been no initial clinical improvement, proceed to second-line therapy. • Itraconazole is safe, effective and has activity against both *Trichophyton* and *Microsporum* species. If itraconazole has been selected as first-line therapy, convert to terbinafine second line for *Trichophyton* infections or griseofulvin for *Microsporum* species. • For cases refractory to the above therapies, other modalities to be considered in exceptional circumstances include fluconazole and voriconazole. • Symptom-free carriers with light growth/low spore count on culture may be treated with topical treatment alone, but close follow-up is needed, with repeat mycology, to ensure that treatment has been effective. In asymptomatic carriers with a high spore load, oral therapy is usually justified. • The definitive end-point for adequate treatment is not clinical response but mycological cure; therefore, follow-up with repeat mycology sampling is recommended at the end of the standard treatment period and then monthly until mycological clearance is documented. Treatment should, therefore, be tailored for each individual patient according to response.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the skin and mucous membrane antifungals are noted in Tables 3 through 5. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Single Agent Skin and Mucous Membrane Antifungals (Drugs A-L)[1-18]

Indication	Butenafine	Butoconazole	Ciclopirox	Clotrimazole	Econazole	Efinaconazole	Ketoconazole	Luliconazole
Candidiasis								
Prophylactically to reduce the incidence of oropharyngeal candidiasis in immunocompromised patients				✔ *				
Treatment of cutaneous candidiasis			✔ †‡	✔ ‡§	✔		✔ ‡	
Treatment of oropharyngeal candidiasis				✔ *				
Treatment of vulvovaginal candidiasis		✔						
Dermatitis								
Topical treatment of seborrheic dermatitis							✔ ‡‖	
Treatment of seborrheic dermatitis of the scalp			✔ ¶#					
Dermatophyte Infections								
Treatment of interdigital tinea pedis and tinea corporis caused by *Trichophyton rubrum, Trichophyton mentagrophytes,* and *Epidermophyton floccosum*			✔ #					
Treatment of tinea pedis, tinea cruris, and tinea corporis caused by *E. floccosum* and *T. rubrum*								✔
Treatment of tinea pedis, tinea cruris, and tinea corporis caused by *E. floccosum, T. mentagrophytes,* and *T. rubrum*							✔ ‡	
Treatment of tinea pedis, tinea cruris, and tinea corporis caused by *E. floccosum, T. mentagrophytes, T. rubrum,* and *T. tonsurans*	✔							
Treatment of tinea pedis, tinea cruris, and tinea corporis caused by *T. rubrum*, *T. mentagrophytes*, *E. floccosum*, and *Microsporum canis*			✔ †‡					
Treatment of tinea pedis, tinea cruris, and tinea corporis caused by *T. rubrum*, *T. mentagrophytes*, *T. tonsurans*, *M. canis*, *Microsporum audouini*, *Microsporum gypseum*, and *E. floccosum*					✔			
Topical treatment of tinea versicolor caused by *Malassezia furfur*	✔		✔ †‡	✔ ‡§	✔		✔ ‡¶	
Onychomycosis								
Treatment of mild to moderate onychomycosis of fingernails and toenails without lunula involvement caused by *T. rubrum*			✔ §					
Treatment of onychomycosis of the toenail(s) due to *T. rubrum* and *T. mentagrophytes*						✔		

*Troche formulation.
†Suspension formulation.
‡Cream formulation.

§Solution formulation.
‖Foam formulation.
¶Shampoo formulation.
#Gel formulation.

Table 4. FDA-Approved Indications for the Single Agent Skin and Mucous Membrane Antifungals (Drugs M-Z)[1-18]

Indication	Miconazole	Naftifine	Nystatin	Oxiconazole	Sertaconazole	Sulconazole	Tavaborole	Terconazole
Candidiasis								
Treatment of cutaneous or mucocutaneous mycotic infections caused by *Candida. albicans* and other *Candida* species			✔					
Treatment of vulvovaginal candidiasis	✔							✔
Dermatophyte Infections								
Treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by *Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum*		✔ *						
Treatment of interdigital tinea pedis caused by *T. rubrum, T. mentagrophytes,* and *E. floccosum*		✔ †			✔			
Treatment of tinea pedis, tinea cruris, and tinea corporis caused by *T. rubrum*, *T. mentagrophytes*, and *E. floccosum*		✔ ‡		✔				
Treatment of tinea cruris and tinea corporis caused by *T. rubrum*, *T. mentagrophytes*, *E. floccosum*, and *Microsporum canis*						✔ ¶		
Treatment of tinea pedis, tinea cruris, and tinea corporis caused by *T. rubrum*, *T. mentagrophytes*, *E. floccosum*, and *M. canis*						✔ §		
Treatment of tinea pedis, tinea cruris, and tinea corporis caused by *T. rubrum, T. mentagrophytes, Trichophyton tonsurans,* and *E. floccosum*		✔ #						
Treatment of tinea versicolor caused by *Malassezia furfur*				✔		✔ §¶		
Onychomycosis								
Treatment of onychomycosis of the toenail(s) due to *T. rubrum* and *T. mentagrophytes*							✔	

*2% cream concentration.
†2% gel concentration.
‡1% cream concentration.
§Cream formulation.
¶Solution formulation.
#1% gel concentration.

Table 5. FDA-Approved Indications for the Combination Skin and Mucous Membrane Antifungals[1-18]

Indication	Clotrimazole and Betamethasone	Miconazole, Zinc Oxide and White Petrolatum	Nystatin and Triamcinolone
Candidiasis			
Treatment of cutaneous candidiasis			✔
Dermatitis			
Treatment of diaper dermatitis when complicated by documented candidiasis		✔	
Dermatophyte Infections			
Treatment of tinea pedis, tinea cruris and tinea corporis caused by *Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum*	✔		

IV. Pharmacokinetics

The pharmacokinetic parameters of the skin and mucous membrane antifungals are listed in Table 6. Pharmacokinetic properties of the combination products not listed in the table below would be in line with the properties of their individual components listed in the table below.

Table 6. Pharmacokinetic Parameters of the Skin and Mucous Membrane Antifungals[1-18]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Betamethasone	12 to 14	64	Liver	Renal	5.6
Butenafine	Minimal	Not reported	Liver	Renal	35
Butoconazole	5.5	Not reported	Not reported	Renal (2.7) Feces (2.8)	21 to 24
Ciclopirox	Solution: 1.3	94 to 98	Liver	Renal (<10)	Cream: 1.7 Gel: 5.5
Clotrimazole	Skin: <1	Not reported	Not reported	Renal (<1) Feces	3.5 to 5.0
Econazole	Minimal	98	Not reported	Renal (<1) Feces (<1)	Not reported
Efinaconazole	Not reported	Not reported	Not reported	Not reported	29.9
Ketoconazole	Negligible	Not reported	Not reported	Renal (13) Bile	Not reported
Luliconazole	Not reported	>99	Not reported	Not reported	Not reported
Miconazole	<2	90 to 93	Liver	Renal (<1) Feces (50)	Not reported
Naftifine	2.5 to 6.0	Not reported	Liver (14 to 29)	Renal (64) Feces (36)	48 to 72
Nystatin	Minimal	Not reported	Not reported	Feces	Not reported
Oxiconazole	Minimal	Not reported	Not reported	Renal (<1)	Not reported
Sertaconazole	Minimal	Not reported	Not reported	Not reported	Not reported
Sulconazole	8.7	Not reported	Not reported	Renal (6.7) Feces (2)	Not reported
Tavaborole	Not reported	Not reported	Not reported	Renal	Not reported
Terconazole	5 to 16	95	Liver	Renal (32 to 56) Feces (47 to 52)	6.9
Triamcinolone	Not reported	Not reported	Liver	Renal Bile	2 to 3

V. Drug Interactions

Major drug interactions with the skin and mucous membrane antifungals are listed in Table 7.

Table 7. Major Drug Interactions with the Skin and Mucous Membrane Antifungals[2]

Generic Name(s)	Interaction	Mechanism
Econazole and miconazole	Anticoagulants	Pharmacologic effects of anticoagulants may be increased by these agents, especially following application to the groin area in the elderly. Bleeding may occur.

VI. Adverse Drug Events

The most common adverse drug events reported with the skin and mucous membrane antifungals are listed in Tables 8 to 10.

Table 8. Adverse Drug Events (%) Reported with the Single Agent Skin and Mucous Membrane Antifungals (Drugs A-L)[1-18]

Adverse Events	Butenafine	Butoconazole	Ciclopirox	Clotrimazole	Econazole	Efinaconazole	Ketoconazole	Luliconazole
Central Nervous System								
Dizziness	-	-	-	-	-	-	✔ *	-
Headache	-	-	✔	-	-	-	✔ *	-
Dermatological								
Abnormal hair texture	-	-	-	-	-	-	✔ †	-
Acne	-	-	✔	-	-	-	✔ *	-
Allergic reaction	-	-	-	-	-	-	✔ *	-
Alopecia	-	-	✔	-	-	-	<1†	-
Blistering	-	-	-	✔ *‡	-	-	-	-
Burning	1	-	34§, <1*†‡ ‖	✔ *‡	3	-	4*, ✔ †¶	-
Cellulitis	-	-	-	-	-	-	-	<1
Contact dermatitis	<2	-	✔	-	-	2	✔	<1
Dry skin	-	-	✔	-	-	-	✔	-
Edema	-	-	-	✔ *‡	-	-	-	-
Erythema	<2	-	✔	✔ *‡	3	-	✔ *¶	-
Facial edema	-	-	✔	-	-	-	✔ *	-
Hair discoloration	-	-	✔	-	-	-	✔ †	-
Hypersensitivity reaction	-	-	-	-	-	-	✔ †	-
Impetigo	-	-	-	-	-	-	✔ *	-
Ingrown nail	-	-	-	-	-	2	-	-
Irritation	<2	-	✔	✔ *‡	-	-	✔ *, <1†	-
Nail discoloration	-	-	-	-	-	-	✔ *	-
Nail disorder	-	-	✔	-	-	-	-	-
Oily hair/skin	-	-	-	-	-	-	✔ †	-
Pain	-	-	✔	-	-	1	✔ *	-
Peeling	-	-	-	✔ *‡	-	-	-	-
Pruritus	<2	-	✔	✔	3	-	✔	-
Pustules	-	-	-	-	-	-	✔ *	-
Pyogenic granuloma	-	-	-	-	-	-	✔ *	-
Rash	-	-	✔	-	✔	-	✔ †¶	-
Scalp pustules	-	-	-	-	-	-	✔ †	-

Adverse Events	Butenafine	Butoconazole	Ciclopirox	Clotrimazole	Econazole	Efinaconazole	Ketoconazole	Luliconazole
Stinging	1	-	-	✔ *‡	3	-	5*	-
Urticaria	-	-	-	✔ *‡	-	-	✔ †	-
Vesicles	-	-	-	-	-	2	-	-
Gastrointestinal								
Abdominal cramping	-	✔	-	-	-	-	-	-
Abdominal pain	-	✔	-	-	-	-	-	-
Nausea	-	-	-	✔ #	-	-	-	-
Pelvic pain	-	✔	-	-	-	-	-	-
Unpleasant mouth sensation	-	-	-	✔ #	-	-	-	-
Vomiting	-	-	-	✔ #	-	-	-	-
Genitourinary								
Itching	-	✔	-	-	-	-	-	-
Soreness	-	✔	-	-	-	-	-	-
Swelling	-	✔	-	-	-	-	-	-
Vaginal irritation	-	-	-	-	-	-	-	-
Vulvar/vaginal burning	-	✔	-	-	-	-	-	-
Other								
Abnormal liver function tests	-	-	-	✔ #	-	-	-	-
Keratoconjunctivitis sicca	-	-	-	-	-	-	✔ *	-
Ocular irritation/swelling	-	-	-	-	-	-	✔ *	-

✔ Percent not specified.
- Event not reported or incidence <1%.
*Cream formulation.
†Shampoo formulation.
‡Solution formulation.
§Gel formulation.
‖Suspension formulation.
¶ Foam formulation.
# Troche formulation.

Table 9. Adverse Drug Events (%) Reported with the Single Agent Skin and Mucous Membrane Antifungals (Drugs M-Z)[1-18]

Adverse Events	Miconazole	Naftifine	Nystatin	Oxiconazole	Sertaconazole	Sulconazole	Tavaborole	Terconazole
Central Nervous System								
Headache	1	-	-	-	-	-	-	21 to 30
Dermatological								
Burning	-	5 to 6	-	≤1	✔	3	-	-
Contact dermatitis	-	-	✔	<1	✔	-	1	-
Desquamation	-	-	-	-	✔	-	-	-
Dry skin	-	3	-	-	✔	-	-	-

Adverse Events	Miconazole	Naftifine	Nystatin	Oxiconazole	Sertaconazole	Sulconazole	Tavaborole	Terconazole
Eczema	-	-	-	<1	-	-	-	-
Erythema	-	≤2	-	<1	✔	1	2	-
Exfoliation, local	-	-	-	-	-	-	3	-
Fissure	-	-	-	<1	-	-	-	-
Folliculitis	-	-	-	<1	-	-	-	-
Hyperpigmentation	-	-	-	-	✔	-	-	-
Hypersensitivity reaction	-	-	✔	-	-	-	-	-
Ingrown nail	-	-	-	-	-	-	3	-
Irritation	-	2	-	<1	-	-	✔	-
Maceration	-	-	-	<1	-	-	-	-
Nodules	-	-	-	<1	-	-	-	-
Pain	-	-	-	<1	-	-	-	-
Papules	-	-	-	<1	-	-	-	-
Pruritus	-	1 to 2	-	<2	✔	3	-	-
Rash	✔	<1	-	<1	-	-	-	-
Scaling	-	-	-	<1	-	-	-	-
Skin tenderness	-	<1	-	-	-	-	-	-
Stinging	-	5 to 6	-	<1	-	3	-	-
Stevens-Johnson syndrome	-	-	✔	-	-	-	-	-
Tenderness	-	-	-	-	✔	-	-	-
Gastrointestinal								
Abdominal cramping	2	-	-	-	-	-	-	-
Abdominal pain	-	-	-	-	-	-	-	3
Genitourinary								
Dysmenorrhea	-	-	-	-	-	-	-	6
Itching	2	-	-	-	-	-	-	-
Vaginal burning	2	-	-	-	-	-	-	5 to 15
Vaginal irritation	2	-	-	-	-	-	-	3
Vaginal itching	-	-	-	-	-	-	-	5
Vaginal pain	-	-	-	-	-	-	-	4
Other								
Chills	-	-	-	-	-	-	-	<2
Cough	-	-	-	-	-	-	-	1 to 3

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 10. Adverse Drug Events (%) Reported with the Combination Skin and Mucous Membrane Antifungals[1-18]

Adverse Events	Clotrimazole and Betamethasone	Miconazole, Zinc Oxide and White Petrolatum	Nystatin and Triamcinolone
Dermatological			
Acne	-	-	✔
Acneiform eruptions	✔	-	-
Blistering	✔	✔	-
Burning	2*	✔	✔
Contact dermatitis	✔	✔	✔
Dry skin	2*	✔	✔
Ecchymoses	✔	-	-
Edema	<1†	-	-
Erythema	✔	✔	-
Folliculitis	✔	-	✔
Hypertrichosis	✔	-	✔
Hypopigmentation	✔	-	✔
Inflammation	-	✔	-
Irritation	✔	-	✔
Maceration of skin	✔	-	✔
Miliaria	✔	-	-
Pain	-	✔	-
Peeling	✔	-	-
Perioral dermatitis	✔	-	-
Pruritus	✔	✔	✔
Rash	<1†	✔	
Skin atrophy	✔	-	✔
Skin exfoliation	-	✔	-
Stinging	<1*	-	-
Striae	✔	-	-
Urticaria	✔	-	-
Gastrointestinal			
Vomiting	-	✔	-
Other			
Benign intracranial hypertension	✔	-	-
Cushing's syndrome	✔	-	-
Growth retardation	✔	-	-
Paresthesia	2†	-	-
Secondary infection	<1†	-	✔
Sensitization	✔	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.
*Lotion formulation.
†Cream formulation.

VII. Dosing and Administration

The usual dosing regimens for the skin and mucous membrane antifungals are listed in Table 11.

Table 11. Usual Dosing Regimens for the Skin and Mucous Membrane Antifungals[1-18]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Butenafine	Treatment of interdigital tinea pedis caused by *E. floccosum, T. mentagrophytes, T. rubrum,* and *T. tonsurans*: Cream: apply twice daily for seven days or once daily for four weeks Treatment of tinea cruris and tinea corporis caused by *E. floccosum, T. mentagrophytes, T. rubrum,* and *T. tonsurans*: Cream: apply once daily for two weeks Topical treatment of tinea versicolor caused by *Malassezia furfur*: Cream: apply to the affected area once daily for two weeks	Treatment of interdigital tinea pedis caused by *E. floccosum, T. mentagrophytes, T. rubrum,* and *T. tonsurans* in patients ≥12 years of age: Cream: apply twice daily for seven days or once daily for four weeks Treatment of tinea cruris and tinea corporis caused by *E. floccosum, T. mentagrophytes, T. rubrum,* and *T. tonsurans* in patients ≥12 years of age: Cream: apply once daily for two weeks Topical treatment of tinea versicolor caused by *Malassezia furfur* in patients ≥12 years of age: Cream: apply to the affected area once daily for two weeks	Cream: 1%
Butoconazole	Vulvovaginal candidiasis: Vaginal cream: insert one applicatorful intravaginally once	Safety and efficacy in children have not been established.	Vaginal cream: 2%
Ciclopirox	Cutaneous candidiasis; Treatment of tinea pedis, tinea cruris, and tinea corporis caused by *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum*, and *Microsporum canis;* topical treatment of tinea versicolor caused by *Malassezia furfur*: Cream, suspension: apply to the affected area twice daily; if no improvement after four weeks of treatment, re-evaluate the diagnosis Treatment of interdigital tinea pedis and tinea corporis caused by *T. rubrum, T. mentagrophytes,* and *E. floccosum*: Gel: apply to the affected area twice daily for four weeks Treatment of mild to moderate onychomycosis of fingernails and	Cutaneous candidiasis; Treatment of tinea pedis, tinea cruris, and tinea corporis caused by *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum*, and *Microsporum canis;* topical treatment of tinea versicolor caused by *Malassezia furfur* in patients ≥10 years of age: Cream, suspension: apply to the affected area twice daily; if no improvement after four weeks of treatment, re-evaluate the diagnosis Treatment of interdigital tinea pedis and tinea corporis caused by *T. rubrum, T. mentagrophytes,* and *E. floccosum* in patients ≥16 years of age: Gel: apply to the affected area twice daily for four weeks	Cream: 0.77% Gel: 0.77% Shampoo: 1% Solution: 8% Suspension: 0.77%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	toenails without lunula involvement caused by *T. rubrum*: Solution: apply to the affected nails once daily Seborrheic dermatitis of the scalp: Gel: apply to the affected scalp area twice daily for four weeks Shampoo: wet hair and apply one to two teaspoons to scalp; lather and leave on hair and scalp for three minutes, then rinse off; repeat treatment twice per week for four weeks	Treatment of mild to moderate onychomycosis of fingernails and toenails without lunula involvement caused by *T. rubrum* in patients ≥12 years of age: Solution: apply to the affected nails once daily Seborrheic dermatitis of the scalp in patients ≥16 years of age: Gel: apply to the affected scalp area twice daily for four weeks Shampoo: wet hair and apply one to two teaspoons to scalp; lather and leave on hair and scalp for three minutes, then rinse off; repeat treatment twice per week for four weeks	
Clotrimazole	Treatment of cutaneous candidiasis; topical treatment of tinea versicolor caused by *M. furfur*: Cream, solution: apply to the affected area twice daily; if no improvement after four weeks of treatment, re-evaluate the diagnosis Prophylactically to reduce the incidence of oropharyngeal candidiasis in immunocompromised patients; treatment of oropharyngeal candidiasis: Troche: dissolve one troche in mouth five times daily for two weeks; for prophylaxis, dissolve one troche in mouth three times daily	Treatment of cutaneous candidiasis; topical treatment of tinea versicolor caused by *M. furfur* in patients two years of age and older: Cream, solution: apply to the affected area twice daily; if no improvement after four weeks of treatment, re-evaluate the diagnosis Treatment of oropharyngeal candidiasis in patients three years of age and older: Troche: dissolve one troche in mouth five times daily for two weeks	Cream: 1% Solution: 1% Troche: 10 mg
Econazole	Cutaneous candidiasis: Cream: apply to the affected area twice daily for two weeks Treatment of tinea cruris, and tinea corporis caused by *T. rubrum*, *T. mentagrophytes*, *T. tonsurans*, *M. canis*, *Microsporum audouini*, *Microsporum gypseum*, and *E. floccosum*; topical treatment of tinea versicolor caused by *M. furfur*: Cream: apply to the affected area once daily for two weeks Treatment of tinea pedis caused by	Cutaneous candidiasis: Cream: apply to the affected area twice daily for two weeks Treatment of tinea cruris, and tinea corporis caused by *T. rubrum*, *T. mentagrophytes*, *T. tonsurans*, *M. canis*, *M. audouini*, *M. gypseum*, and *E. floccosum*; topical treatment of tinea versicolor caused by *M. furfur*: Cream: apply to the affected area once daily for two weeks Treatment of tinea pedis caused by *T. rubrum*, *T. mentagrophytes*,	Cream: 1%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	T. rubrum, *T. mentagrophytes*, *T. tonsurans*, *M. canis*, *M. audouini*, *M. gypseum*, and *E. floccosum*: Cream: apply to the affected area once daily for one month	*T. tonsurans*, *M. canis*, *M. audouini*, *M. gypseum*, and *E. floccosum*: Cream: apply to the affected area once daily for one month	
Efinaconazole	Treatment of onychomycosis of the toenail(s) due to *T. rubrum* and *T. mentagrophytes*: Solution: apply to the affected toenails once daily for 48 weeks	Treatment of onychomycosis of the toenail(s) due to *T. rubrum* and *T. mentagrophytes* in patients ≥6 years of age: Solution: apply to the affected toenails once daily for 48 weeks	Solution: 10%
Ketoconazole	Cutaneous candidiasis: Cream: apply to the affected area once daily for two weeks Seborrheic dermatitis: Cream: apply to the affected area twice daily for four weeks or until clinical clearing Foam: apply to the affected area twice daily for four weeks Treatment of tinea cruris and tinea corporis caused by *E. floccosum, T. mentagrophytes,* and *T. rubrum:* Cream: apply to the affected area once daily for two weeks Treatment of tinea pedis caused by *E. floccosum, T. mentagrophytes,* and *T. rubrum*: Cream: apply to the affected area once daily for six weeks Topical treatment of tinea versicolor caused by *M. furfur*: Cream: apply to the affected area once daily for two weeks Shampoo: apply to the affected area and a wide margin surrounding this area; lather, leave in place for five minutes, and then rinse off with water; one application of the shampoo should be sufficient	Seborrheic dermatitis in patients ≥12 years of age: Foam: apply to the affected area twice daily for four weeks	Cream: 2% Foam: 2% Shampoo: 2%
Luliconazole	Treatment of tinea pedis due to *T. rubrum* and *E. floccosum*: Cream: apply to the affected area and approximately one inch of the immediate surrounding area once daily for two weeks Treatment of tinea cruris and tinea	Treatment of tinea pedis due to *T. rubrum* and *E. floccosum* in patients 12 years of age and older: Cream: apply to the affected area and approximately one inch of the immediate surrounding area once daily for two weeks	Cream: 1%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	corporis due to *T. rubrum* and *E. floccosum*: Cream: apply to the affected area and approximately one inch of the immediate surrounding area once daily for one week	Treatment of tinea cruris due to *T. rubrum* and *E. floccosum* in patients 12 years of age and older: Cream: apply to the affected area and approximately one inch of the immediate surrounding area once daily for one week Treatment of tinea corporis due to *T. rubrum* and *E. floccosum* in patients two years of age and older: Cream: apply to the affected area and approximately one inch of the immediate surrounding area once daily for one week	
Miconazole	Vulvovaginal candidiasis: Vaginal suppository: insert one suppository intravaginally at bedtime for three days	Vulvovaginal candidiasis in patients 12 years of age and older: Vaginal suppository: insert one suppository intravaginally at bedtime for three days	Vaginal suppository: 200 mg
Naftifine	Treatment of tinea corporis, tinea cruris, tinea pedis caused by susceptible species: Cream, gel: Apply to the affected area and surrounding skin once daily (cream) or twice daily (gel) for up to two weeks (2%) or up to four weeks (1%)	Treatment of tinea corporis caused by susceptible species in patients two years of age and older: Cream (2% only): Apply to the affected area and surrounding skin once daily for up to two weeks Treatment of tinea cruris caused by susceptible species in patients 12 years of age and older: Cream (2% only): Apply to the affected area and surrounding skin once daily for up to two weeks Treatment of tinea pedis caused by susceptible species in patients 12 years of age and older: Cream (2%), gel (2%): Apply to the affected area and surrounding skin once daily for up to two weeks	Cream: 1% 2% Gel: 1% 2%
Nystatin	Treatment of cutaneous or mucocutaneous mycotic infections caused by *Candida. albicans* and other *Candida* species: Cream, ointment, powder: apply to the affected area two to three times daily until healing is complete	Treatment of cutaneous or mucocutaneous mycotic infections caused by *Candida. albicans* and other *Candida* species in neonates and older: Cream, ointment, powder: apply to the affected area two to three times daily until healing is	Cream: 100,000 units/g Ointment: 100,000 units/g Powder: 100,000 units/g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		complete	
Oxiconazole	Treatment of tinea cruris, and tinea corporis caused by *T. rubrum*, *T. mentagrophytes*, and *E. floccosum*: Cream: apply to the affected area one to two times daily for two weeks Treatment of tinea pedis caused by *T. rubrum*, *T. mentagrophytes*, and *E. floccosum*: Cream: apply to the affected area one to two times daily for one month Treatment of tinea versicolor caused by *Malassezia furfur*: Cream: apply to the affected area once daily for two weeks	Treatment of tinea cruris, and tinea corporis caused by *T. rubrum*, *T. mentagrophytes*, and *E. floccosum*: Cream: apply to the affected area one to two times daily for two weeks Treatment of tinea pedis caused by *T. rubrum*, *T. mentagrophytes*, and *E. floccosum*: Cream: apply to the affected area one to two times daily for one month Treatment of tinea versicolor caused by *Malassezia furfur*: Cream: apply to the affected area once daily for two weeks	Cream: 1%
Sertaconazole	Treatment of interdigital tinea pedis caused by *T. rubrum, T. mentagrophytes,* and *E. floccosum*: Cream: apply to the affected area twice daily for four weeks	Treatment of interdigital tinea pedis caused by *T. rubrum, T. mentagrophytes,* and *E. floccosum* in patients ≥12 years of age: Cream: apply to the affected area twice daily for four weeks	Cream: 2%
Sulconazole	Treatment of tinea cruris, and tinea corporis caused by *T. rubrum*, *T. mentagrophytes*, *E. floccosum*, and *M. canis*; treatment of tinea versicolor caused by *Malassezia furfur*: Cream, solution: apply to the affected area one to two times daily for at least three weeks Treatment of tinea pedis caused by *T. rubrum*, *T. mentagrophytes*, *E. floccosum*, and *M. canis:* Cream: apply to the affected area twice daily for four weeks	Safety and efficacy in children have not been established.	Cream: 1% Solution: 1%
Tavaborole	Treatment of onychomycosis of the toenail(s) due to *T. rubrum* and *T. mentagrophytes*: Solution: apply to affected toenail(s) once daily for 48 weeks	Treatment of onychomycosis of the toenail(s) due to *T. rubrum* and *T. mentagrophytes* in patients ≥6 years of age: Solution: apply to affected toenail(s) once daily for 48 weeks	Solution: 5%
Terconazole	Vulvovaginal candidiasis: Vaginal cream (0.4%): insert one applicatorful once daily at bedtime for seven days Vaginal cream (0.8%): insert one applicatorful once daily at bedtime	Safety and efficacy in children have not been established.	Vaginal cream: 0.4% 0.8% Vaginal suppository: 80 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	for three days Vaginal suppository: insert one suppository intravaginally once daily at bedtime for three days		
Combination Products			
Clotrimazole and betamethasone	Treatment of tinea cruris and tinea corporis caused by *T. rubrum, T. mentagrophytes, and E. floccosum*: Cream, lotion: apply to the affected area twice daily for up to two weeks; maximum, 45 g per week Treatment of tinea pedis caused by *T. rubrum, T. mentagrophytes, and E. floccosum*: Cream, lotion: apply to the affected area twice daily for up to four weeks; maximum, 45 g per week	Treatment of tinea cruris and tinea corporis caused by *T. rubrum, T. mentagrophytes, and E. floccosum* in patients ≥17 years of age: Cream, lotion: apply to the affected area twice daily for up to two weeks; maximum, 45 g per week Treatment of tinea pedis caused by *T. rubrum, T. mentagrophytes, and E. floccosum* in patients ≥17 years of age: Cream, lotion: apply to the affected area twice daily for up to four weeks; maximum, 45 g per week	Cream: 1%-0.05% Lotion: 1%-0.05%
Miconazole, zinc oxide, and white petrolatum	Not applicable	Treatment of diaper dermatitis when complicated by documented candidiasis in patients four weeks of age and older: Ointment: apply to the affected area at each diaper change for seven days	Ointment: 0.25%-15%
Nystatin and triamcinolone	Treatment of cutaneous candidiasis: Cream, ointment: apply to the affected area twice daily for up to 25 days	Treatment of cutaneous candidiasis: Cream, ointment: apply to the affected area twice daily for up to 25 days	Cream: 100,000 units/g-0.1% Ointment: 100,000 units/g-0.1%

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the skin and mucous membrane antifungals are summarized in Table 12.

Table 12. Comparative Clinical Trials with the Skin and Mucous Membrane Antifungals

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Candidiasis (Cutaneous)				
Bagatell et al.[33] (1985) Ciclopirox 1% cream applied BID vs clotrimazole 1% cream applied BID vs placebo In study A, patients received either ciclopirox or vehicle. In study B, patients received either ciclopirox or clotrimazole.	2 DB, MC, PG, RCT Patients 12 to 75 years of age with stable or exacerbating skin lesions that were clinically and mycologically diagnosed as cutaneous candidiasis	N=240 28 days	Primary: Mycological cure, clinical cure Secondary: Adverse events	Primary: In the first week of therapy for study A, significant differences favoring the active drug were observed in patients treated with ciclopirox compared to placebo in terms of clinical and mycological cures (90 vs 50%, respectively; P<0.001). At the two-week follow-up period, 83 and 82 to 89% of patients treated with ciclopirox achieved clinical and mycological cure, respectively (P<0.001) compared to 14 and 34 to 46% of patients treated with vehicle achieved clinical and mycological cure, respectively (P<0.001). At the final post treatment visit, 27 and 12% of patients treated with ciclopirox and vehicle, respectively, achieved both clinical and mycological cure (P<0.001). After two weeks of therapy in study B, 17 and 0% of patients treated with ciclopirox and clotrimazole, respectively, achieved clinical cure (P<0.05). After three weeks, 38 and 21% of patients treated with ciclopirox and clotrimazole, respectively, achieved clinical cure (P<0.05). After four weeks of treatment, both treatment groups showed similar results. After two weeks of therapy, a greater proportion of patients treated with ciclopirox achieved both clinical and mycological cure compared to patients treated with clotrimazole (15 vs 0%; P=0.006). However, there was no significant difference between treatment groups relative to mycological cure. Secondary: No adverse events were reported.
Rajan et al.[34] (1983) Clotrimazole 1% cream applied BID	DB, PG, RCT Patients with clinically proven cutaneous candidiasis	N=41 3 weeks	Primary: Efficacy parameters (fungal culture, microscopic preparation,	Primary: At week two, 62.5 and 85.7% of patients treated with sulconazole and clotrimazole, respectively, had negative fungal cultures. At week three, 62.5 and 33.3% of patients treated with sulconazole and clotrimazole, respectively, had negative fungal cultures. At this time,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs sulconazole 1% cream applied QAM and placebo QHS			physician's assessment of overall improvement) Secondary: Adverse events	seven and three patients treated with sulconazole and clotrimazole, respectively, failed treatment. Although both treatment groups experienced improvement in certain symptoms of infection, there was no significant difference between the two treatment groups (erythema; P=0.45, scaling; P=0.69, itching; P=0.88). At week three, the physician's assessment of overall infection improvement for sulconazole- and clotrimazole-treated patients was 70.6 and 88.9%, respectively. Secondary: Five patients treated with sulconazole reported adverse effects, which included itching of various degrees of severity. No adverse effects were reported by patients treated with clotrimazole.
Tanenbaum et al.[35] (1983) Miconazole 2% cream applied BID vs sulconazole 1% cream applied QD vs sulconazole 1% cream applied BID vs placebo In study A, patients received either sulconazole	2 DB, PG, RCT Patients with cutaneous candidiasis	N=96 3 weeks	Primary: Mycological cure rate, signs of inflammation, itching, and clinician rated overall clinical status Secondary: Adverse effects	Primary: At the end of three weeks in study A, 100% of patients treated with sulconazole and 10% of patients who received the vehicle had negative results on the potassium hydroxide test; 100% of patients treated with sulconazole and 0% of patients who received the vehicle had negative cultures. At the end of three weeks in study B, 100% of patients receiving sulconazole and miconazole were negative on the potassium hydroxide test; 80 and 92% of sulconazole and miconazole patients, respectively, had negative cultures. At the end of three weeks in study A, 100% of patients treated with sulconazole and 26% of patients who received the vehicle were free of signs of inflammation; 89 and 21% of sulconazole and vehicle patients, respectively, were free of itching. At the end of three weeks in study B, 100 and 92% of sulconazole and miconazole patients, respectively, were free of signs of inflammation; 89 and 83% of sulconazole and miconazole patients, respectively, were free of itching. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
or vehicle given BID. In study B, patients received either sulconazole given QD or miconazole given BID.				One patient receiving the vehicle experienced itching. Erythema and/or pruritus was reported by six patients treated with sulconazole and three patients treated with miconazole.
Beveridge et al.[36] (1977) Nystatin cream vs nystatin-triamcinolone cream	DB, MC, PG, RCT Patients 6 months to 71 years of age with confirmed bilateral lesions of the flexures (secondary to *Candida*)	N=31 14 days	Primary: Eradication of *Candida*, clinical progress of lesions, patient preference for agent, and physician preference for agent Secondary: Adverse events	Primary: There was little difference in clinical cure (38.7 vs 45%) and mycological cure rates (87.1 vs 83.8%) between nystatin and nystatin-triamcinolone treatments, respectively. There was no significant difference in the preference for either treatment in terms of the patient's or physician's perspective (P>0.05). Secondary: Two patients treated with the creams reported burning and stinging. One patient treated with nystatin monotherapy complained of burning and one patient reported pustules.
Candidiasis (Oropharyngeal)				
Kirkpatrick et al.[37] (1978) Clotrimazole 10 mg troche five times daily vs placebo	DB, RCT Patients with chronic oral candidiasis for at least 6 months with poor response to nystatin or gentian violet	N=20 2 weeks	Primary: Clinical response, mycological response Secondary: Adverse events	Primary: Clinical and laboratory results were negative in more patients treated with clotrimazole compared to patients receiving placebo (six vs one, respectively; P<0.001). Secondary: No adverse events were reported with either study group.
Owens et al.[38] (1984) Clotrimazole 10 mg troche TID	DB, PRO, RCT Patients with leukemia or solid malignant	N=84 27 to 81 days	Primary: Signs and symptoms of oral candidiasis, culture	Primary: Oral thrush was observed after nine days in patients with leukemia, after three weeks in renal transplant patients, and after three weeks patients with solid malignant neoplasms (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	neoplasms who were treated with chemotherapy; renal transplant patients treated with an immunosuppressant to prevent graft rejection		Secondary: Adverse events	Oral candidiasis occurred in 13 and 57% of patients treated with clotrimazole and placebo, respectively (P<0.0005). Of the renal transplant patients, eight and 57% of patients treated with clotrimazole and placebo, respectively, had oral candidiasis (P<0.01). Of the leukemic patients, 37.5 and 62.5% of patients treated with clotrimazole and placebo, respectively, had oral candidiasis (P>0.05). Of the patients with solid malignant neoplasms, 0 and 67% of patients treated with clotrimazole and placebo, respectively, had oral candidiasis (P<0.05). Of the patients treated with clotrimazole, a significant improvement was observed in patients with malignant neoplasms (P<0.05) and renal transplant patients (P<0.05), but not patients with leukemia (P>0.05). Secondary: One case of abnormal jaw sensations and nausea was reported.
Vazquez et al.[39] (2010) Miconazole 50 mg buccal tablet QD (MBT) vs clotrimazole 10 mg troche 5 times daily (CT) Patients who were receiving antiretroviral therapy prior to the study were maintained on their regimen during the 14-day antifungal	DB, MC, RCT Patients ≥18 years of age with HIV infection and OPC	N=578 14 days	Primary: Clinical cure (defined as complete resolution of lesions and symptoms of OPC) at TOC visit (days 17 to 22) in the ITT and PP populations Secondary: Clinical cure at day seven, clinical success at day seven and at the TOC visit, mycological cure rate at the TOC visit, evidence of relapse by day 35,	Primary: The clinical cure rate in the MBT group was non-inferior to the CT group in both the ITT and PP populations at the TOC visit. In the ITT population, 61% of patients treated with MBT experienced clinical cure compared to 65% treated with CT (95% CI, -0.124 to 0.034). In the PP population, 68% of MBT-treated patients experienced clinical cure compared to 74% of CT-treated patients (95% CI, -0.140 to 0.022). Secondary: There were no significant differences between treatment groups in clinical cure rate at day seven, or in clinical success rate at day seven or at the TOC visit, in either the ITT or PP populations. At the TOC visit, mycological cure was not significantly different among the treatment groups (ITT and PP populations). In the ITT population, 27% of MBT patients and 25% of CT patients experienced mycological cure (P=0.58). In the PP population, 30% of MBT patients and 27% of CT patients experienced mycological cure (P=0.44). In the ITT population, 27.9% of patients receiving MBT experienced a relapse by day 35. In the CT group, relapse occurred in 28.1% of patients who were clinically cured at the TOC visit and evaluable for relapse (95%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
treatment.			and time to relapse	CI, -9.5 to 9.1; P=0.96). In the PP population, the percentages were 26.9 and 27.6% for the MBT and CT treatment groups, respectively (95% CI, -10.3 to 8.8; P=0.88). In the ITT population, the mean time to relapse was 16.0 and 15.5 days in the MBT and CT groups, respectively (P=0.7). In the PP population, the mean time to relapse was 16.2 days for MBT and 15.9 days for the CT group (P=0.7). Compliance was comparable between the treatment groups. The mean duration of adhesion was comparable between the MBT group and the CT group that received placebo buccal tablets. Total number of tablets that detached within the first six hours after placement was 6.3% of the MBTs and 5.7% of the placebo buccal tablets. An equal number of active and placebo buccal tablets were replaced in each treatment group. Adverse events were comparable between treatment groups. The most frequently reported treatment-emergent AEs were diarrhea, headache, nausea, and vomiting. The majority of patients in each treatment arm had no gingival inflammation at the application site at end of treatment. Patient-rated assessments for oral comfort were similar in both groups. There were decreases in severity for gum pain, dysgeusia, and dry mouth over the treatment period.
Candidiasis (Vulvovaginal)				
Droegemueller et al.[40] (1984) Butoconazole 2% cream insert 1 applicator full intravaginally QD vs clotrimazole 100 mg vaginal tablet insert 2 tablets intravaginally QD	DB, MC, PG, RCT Patients with confirmed vulvovaginal candidiasis	N=253 3 days	Primary: Clinical cure, microbiologic cure Secondary: Adverse effects	Primary: At eight days post treatment, 95 and 91% of patients treated with butoconazole and clotrimazole, respectively, achieved microbiologic cure. At 30 days post treatment, 80 and 74% of patients treated with butoconazole and clotrimazole, respectively, were infection-free. The difference in microbiologic cure between the two treatments was not significant (P value not reported). At eight days post treatment, 77 and 75% of patients treated with butoconazole and clotrimazole, respectively, achieved clinical cure. At 30 days post treatment, 82 and 74% of patients treated with butoconazole and clotrimazole, respectively, achieved clinical cure. The difference in clinical cure between the two treatments was not significant (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Eighty-two percent and 72% of patients treated with butoconazole and clotrimazole, respectively, had a complete absence of candidal signs and symptoms. Secondary: Patients treated with either butoconazole or clotrimazole reported increased local vulvar or vaginal irritation and burning.
Hajman et al.[41] (1988) Butoconazole 2% cream insert 1 applicator full intravaginally QHS (for 3 days) vs clotrimazole 1% cream insert 1 applicator full intravaginally QHS (for 6 days)	PG, RCT, SB Patients 19 to 63 years of age with confirmed vulvovaginal candidiasis	N=63 3 to 6 days	Primary: Clinical cure, microbiological cure, therapeutic cure Secondary: Adverse events	Primary: The difference between the clinical response of patients treated with butoconazole at the initial vs final visit was significant and indicated improvement in signs and symptoms of vulvovaginal candidosis, such as vaginal discharge, itching, burning, erythema, and swelling (P<0.001). Clinical response in patients treated with butoconazole was greater, though not clinically significant, compared to patients treated with clotrimazole (53.3 vs 38.7%, respectively). At seven days after treatment, 85.7 and 89.7% of patients treated with butoconazole and clotrimazole, respectively, achieved clinical cure. At this time, 93.3 and 77.4% of patients treated with butoconazole and clotrimazole, respectively, achieved microbiological cure (e.g., negative cultures). Likewise, 82.1 and 72.4% of patients treated with butoconazole and clotrimazole, respectively, achieved therapeutic cure. At one month after treatment, 86.7 and 96.4% of patients treated with butoconazole and clotrimazole, respectively, achieved clinical cure. At this time, 76.7 and 67.7% of patients treated with butoconazole and clotrimazole, respectively, achieved microbiological cure (e.g., negative cultures). Likewise, 66.7 and 64.5% of patients treated with butoconazole and clotrimazole, respectively, achieved therapeutic cure. There was no significant difference between treatment groups in terms of clinical, microbiological, and therapeutic cure rates. Secondary: No adverse events were reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Brown et al.[42] (1999) Butoconazole 2% cream insert 1 applicator full intravaginally QHS (for 1 day) vs miconazole 2% cream insert 1 applicator full intravaginally QHS (for 7 days)	MC, PG, RCT Patients with confirmed vulvovaginal candidiasis	N=205 1 to 7 days	Primary Clinical cure, microbiological cure Secondary: Adverse events	Primary: For butoconazole-treated patients, symptoms declined after treatment from 20 to 1% from day one to day seven since treatment initiation. At eight to 10 days post treatment, 92 and 87% of patient improved clinically and had negative cultures, respectively. At 30 days post treatment, 88 and 74% of patients improved clinically and had negative cultures, respectively. For the miconazole-treated patients, symptoms declined after treatment from 23 to 19% after the first dose. At eight to 10 days post treatment, 92 and 87% of patient improved clinically and had negative cultures, respectively. At 30 days post treatment, 86 and 77% of patients improved clinically and had negative cultures, respectively. All parameters between butoconazole and miconazole therapies were not different with the exception of the difference in the rapidity of severe symptom relief after the first dose of butoconazole compared to miconazole (P=0.01). Secondary: No systemic events were reported. Vulvovaginal irritation (e.g., burning, itching) was reported.
Kaufman et al.[43] (1989) Butoconazole 2% cream insert 1 applicator full intravaginally QHS (for 3 days) vs miconazole 2% cream insert 1 applicator full intravaginally QHS (for 7 days)	MC, PG, RCT Patients 18 to 61 years of age with confirmed vulvovaginal candidiasis	N=225 3 to 7 days	Primary: Microbiological cure, clinical cure Secondary: Adverse events	Primary: At days eight to 10 post treatment, 88 and 91% of patients treated with butoconazole and miconazole, respectively, were Candida free (P=0.888); 80 and 82% of patients treated with butoconazole and miconazole, respectively, were clinically cured (P=0.541). At 30 days post treatment, 73 and 69% of patients treated with butoconazole and miconazole, respectively, were Candida free (P=2.14); 78 and 80%, of patients treated with butoconazole and miconazole, respectively, were clinically cured (P=0.996); 59 and 52% of patients treated with butoconazole and miconazole experienced therapeutic cure. All parameters between butoconazole and miconazole therapies were not different. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Minimal side effects were reported from both butoconazole- and miconazole-treated patients including vaginal irritation.
Jacobson et al.[44] (1985) Butoconazole 1% cream insert 1 applicator full (5 g) intravaginally QD vs butoconazole 2% cream insert 1 applicator full (5 g) intravaginally QD vs miconazole 2% cream insert 1 applicator full (5 g) intravaginally QD	DB, MC, PG, RCT Patients 13 to 39 years of age with confirmed vulvovaginal candidiasis	N=130 6 days	Primary: Microbiological cure, clinical cure, and relapse rate Secondary: Adverse effects	Primary: On day eight, 98, 91, and 83% of patients treated with butoconazole 2%, butoconazole 1%, and miconazole 2%, respectively, achieved negative fungal cultures. Likewise, 78, 75, and 68% of patients treated with butoconazole 2%, butoconazole 1%, and miconazole 2%, respectively, achieved clinical cure at this visit. After 30 days from the end of treatment, 82, 80 and 68% of patients treated with butoconazole 2%, butoconazole 1%, and miconazole 2%, respectively, maintained negative fungal cultures; therefore, relapse rate was low. Likewise, 73, 67, and 66% of patients treated with butoconazole 2%, butoconazole 1%, and miconazole 2%, respectively, maintained clinical cure at this visit. The differences between cure rates of the three treatment groups were not significant (P values not reported). Secondary: Two patients in each treatment group reported side effects (i.e., headache, vaginal burning, leakage of cream, and bleeding).
Brown et al.[45] (1986) Butoconazole 1% cream insert 1 applicator full intravaginally QD (for 3 days) vs	DB, MC, PG, RCT Patients 17 to 67 years of age with confirmed vulvovaginal candidiasis	N=580 3 to 6 days	Primary: Microbiological cure, clinical cure, and therapeutic cure Secondary: Adverse events	Primary: Clinical and microbiological cure rates were greater in all butoconazole- and miconazole-treated patients compared to placebo (P<0.003 for each comparison). There was no significant difference in microbiologic and clinical cure rate between different butoconazole regimens and butoconazole compared to miconazole. There was no significance difference in therapeutic cure rates in patients treated with butoconazole 1% for six days and placebo. All other treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
butoconazole 1% cream insert 1 applicator full intravaginally QD (for 6 days) vs butoconazole 2% cream insert 1 applicator full intravaginally QD (for 3 days) vs butoconazole 2% cream insert 1 applicator full intravaginally QD (for 6 days) vs miconazole 2% cream insert 1 applicator full intravaginally QD (for 6 days) vs placebo				groups demonstrated statistical significance in this parameter (P<0.001). Secondary: Systemic adverse events were not observed. The most common adverse events associated with all study groups were local side effects.
Hirsch et al.[46] (1989) Clotrimazole 200	MA Patients with confirmed	N=1,800 (16 trials) 1 to 7 days	Primary: Clinical cure rate Secondary:	Primary: According to the MA, the most effective regimens of terconazole were the 80 mg suppository for three days, 240 mg suppositories for one day, and the 0.4% cream for seven days. The 240 mg suppository for one day was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg vaginal tablets insert 1 tablet intravaginally QD (for 3 days) vs clotrimazole 1% cream insert 1 applicator full (5 g) intravaginally QHS (for 7 days) vs econazole 150 mg suppositories* (for 3 days) vs miconazole 2% cream insert 1 applicator full (5 g) intravaginally QHS (for 7 days) vs terconazole 40 to 240 mg vaginal suppositories or terconazole 0.2% to 0.8% vaginal cream	vulvovaginal candidiasis		Adverse effects	more effective than the 80 mg suppository for three days. The clinical efficacies of the 0.4% and 0.8% cream formulations for seven days were comparable. At four weeks from the start of treatment, 92% patients receiving terconazole 80 mg suppositories achieved clinical cure; 88% for terconazole 240 mg suppository for one day, 94% for terconazole 0.8% cream for five days, 90% for terconazole 0.4% cream for seven days. After four weeks, mycological cure rates with terconazole 0.2% cream were similar to miconazole 2% cream but less compared to terconazole 0.4% cream. After four weeks, mycological cure rates were 100 and 80% for terconazole 0.4% cream and clotrimazole 1% cream, respectively, for nonpregnant patients. After four weeks, mycological cure rates were 92 and 89% for terconazole 0.4% cream and clotrimazole 1% cream, respectively, for pregnant patients. After four weeks, mycological cure rates were similar between terconazole 80 mg suppositories and econazole 150 mg suppositories for pregnant and nonpregnant patients. After four weeks, mycological cure rates were similar between terconazole 80 mg and 240 mg suppositories and clotrimazole 240 mg tablets. Secondary: Vaginal burning was reported by 2, 2, and 1% of patients taking terconazole 80 mg vaginal suppositories, terconazole 0.4% vaginal cream, and terconazole 0.8% vaginal cream, respectively. Regimens comprised of terconazole 240 mg vaginal suppository were well tolerated.
Young et al.[47] (2001)	MA	10 trials	Primary: Clinical cure rate	Primary: According to data from five trials, patients treated with topical azoles

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Clotrimazole vs econazole* vs hydrargaphen* vs miconazole vs nystatin vs terconazole vs placebo	Patients with vulvovaginal candidiasis	Variable duration	Secondary: Not reported	achieved greater cure compared to patients treated with nystatin (OR, 0.21; 95% CI, 0.06 to 0.29). According to data from one trial, there was no significant difference between patients treated with nystatin compared to hydrargaphen* (OR, 0.14; 95% CI, 0.05 to 1.84). According to data from trials with clotrimazole, the following results were reported: treatment with clotrimazole was more effective than placebo (OR, 0.14; 95% CI, 0.06 to 0.31); treatment with clotrimazole was similar regardless of single or multiple (i.e., three to four days) dosing; treatment with clotrimazole for seven days was more efficacious compared to treatment for four days (OR, 11.7; 95% CI, 4.21 to 29.15); treatment with clotrimazole was similar regardless of seven-day or 14-day treatment duration (OR, 0.41; 95% CI, 0.16 to 1.05); treatment with clotrimazole and terconazole had similar efficacy (OR, 1.41; 95% CI, 0.28 to 7.10). Secondary: Not reported
Thomason et al.[48] (1990) Miconazole 100 mg vaginal suppositories insert 1 suppository intravaginally QHS	DB, RCT Patients with confirmed vulvovaginal candidiasis	N=29 7 days	Primary: Microbiologic cure, clinical cure, and therapeutic cure Secondary: Adverse events	Primary: At eight to 10 days, 100% of patients treated with terconazole achieved clinical, microbiologic, and therapeutic cure. At that time, 100, 89, and 89% of patients treated with miconazole achieved clinical, microbiologic, and therapeutic cure, respectively. At that time, 44, 33, 33% of patients receiving placebo achieved clinical, microbiologic, and therapeutic cure, respectively. Terconazole and miconazole treatment groups showed significant improvements in clinical, microbiologic, and therapeutic cure compared to placebo ($P<0.05$). There was no significant difference in cure rates

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs terconazole 80 mg vaginal suppositories insert 1 suppository intravaginally QHS (for 3 days) vs placebo				between miconazole and terconazole treatment groups. Secondary: No adverse events were reported.
Corson et al.[49] (1991) Miconazole 2% cream insert 1 applicator full (5 g) intravaginally QD vs terconazole 0.4% cream insert 1 applicator full (5 g) intravaginally QD vs terconazole 0.8% cream insert 1 applicator full (5 g) intravaginally QD	DB, MC, RCT Patients 17 to 61 years of age with signs and symptoms of vulvovaginal candidiasis, microbiologically-confirmed vulvovaginal candidiasis, and either history of being postmenopausal for 2 years or using an effective means of contraception	N=574 7 days	Primary: Clinical response, microbiological response, therapeutic cure, and relapse Secondary: Adverse events	Primary: Relative to demographics, the use of contraceptives appears to have a negative effect on cure rate across all treatment groups; patients not on contraceptives achieved a higher cure rate (P=0.01). Between eight to 10 days post treatment (visit one), the microbiologic cure rates for terconazole 0.4%, terconazole 0.8%, and miconazole 2% were 91.1, 86.9, and 83.6%, respectively; clinical cure rates were 95.5, 93.4, and 91.6%, respectively; the therapeutic cure rates were 87.9, 83.8, and 81.3%, respectively. The microbiologic cure rates of patients treated with terconazole 0.4% were higher than that of patients treated with miconazole 2% (91.1 vs 83.6%; P=0.02). There was no significant difference for other comparisons. After seven days of treatment, patients treated with terconazole 0.4%, terconazole 0.8%, and miconazole 2% had complete symptom relief rates of 83.3, 77.0, and 79.5%, respectively. There was no significant difference between treatment groups. After seven days of treatment, patients treated with terconazole 0.4%, terconazole 0.8%, and miconazole 2% had combined clinical and microbiological cure rates of 87.9, 83.8, and 81.3%, respectively. There was no significant difference between treatment groups. Between 30 to 35 days post treatment (visit two), there were no significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				differences in microbiologic, clinical, or therapeutic cure rates in the treatment groups. Secondary: There was no significant difference in the number of patients who reported adverse effects in the terconazole 0.4%, terconazole 0.8%, and miconazole 2% treatment groups (61.1, 62.2, 57.2%), respectively. Adverse reactions most commonly reported involved the central nervous system or genital-reproductive system. Although no P values were provided, investigators claim that patients treated with terconazole 0.4% had significantly less side effects associated with the genital- reproductive system compared to the other groups, that patients treated with the lower strength of terconazole had significantly lower rates of pruritus and metrorrhagia, that patients treated with miconazole experienced more vulvovaginal symptoms and rhinorrhea compared to both terconazole groups, that patients treated with terconazole 0.4% experienced more pyrexia compared to the other groups.
Thomason et al.[50] (1989) Miconazole 2% vaginal cream (for 7 days) vs miconazole 100 mg vaginal suppositories (for 7 days) vs terconazole 0.4% vaginal cream (for 7 days)	MA Patients ≥18 years of age with vulvovaginal candidiasis	N=1,259 3 to 7 days	Primary: Clinical cure rate, mycological cure rate, and relapse rate Secondary: Adverse events	Primary: Terconazole cream and suppository formulations were more efficacious compared to placebo (P<0.001 for both comparisons). Studies of terconazole cream showed 87.3 to 95.5%, 76.9 to 91.1%, and 10.4 to 22.2% in terms of clinical, microbiologic cure, and relapse (at day 35) rates, respectively. After 10 days, mycological cure rates were similar between terconazole 0.4% cream and 2% miconazole cream; however, in trials with a large number of patients, microbiologic cure rates were higher in terconazole- vs, miconazole-treated patients. Studies of terconazole 80 mg suppositories showed ranges of 90 to 92.2% for rates of clinical cure, 80.4 to 85% for rates of microbiologic cure, and 20.0 to 28.1% for relapse rates (at day 35). After 10 days, mycological cure rates were similar between terconazole 80 mg suppositories and miconazole 100 mg suppositories used for seven days. Secondary: The adverse effects associated with terconazole therapies were minimal. Frequency of common adverse effects was similar between terconazole

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs terconazole 80 mg vaginal suppositories (for 3 days) vs terconazole 80 mg vaginal suppositories (for 3 days) vs placebo				and miconazole suppositories. Relative to cream formulations, skin rash was associated with terconazole and rhinorrhea, pain and burning was associated with miconazole.
Martins et al.[51] (2012) Nystatin vaginal cream 25,000 U/g QD for 7 days vs fluconazole 150 mg orally once weekly for 2 weeks	OL, PG Patients 15 to 83 years of age with vaginal *Candida* species	N=60 1 to 2 weeks	Primary: Mycological cure Secondary: Not reported	Primary: Treatment with nystatin resulted in similar overall mean cure rate compared to treatment with fluconazole (74 vs 87%; P>0.05). Treatment with nystatin resulted in 93% cure rate for *C. albicans* and 44.4% cure rate for non-*albicans* species. Treatment with fluconazole resulted in 82.4% cure rate for *C. albicans* and 100% cure rate for non-*albicans* species. Secondary: Not reported
Li et al.[52] (2015) Terconazole vaginal suppository (80 mg) six-day course	OL, PRO, RCT Patients 18 to 50 years of age with severe vulvovaginal candidiasis	N=140 35 days	Primary: Clinical cure rates, mycological cure rates, adverse events Secondary:	Primary: The clinical cure rates of the terconazole group and the fluconazole group were, respectively, 81.0 and 75.8% at follow-up day seven to 14 and 60.3 and 56.1% at day 30 to 35. The mycological cure rates of the two groups were, respectively, 79.3 and 71.2% at follow-up day seven to 14 and 62.1 and 53.0% at day 30 to 35 (P>0.05 for all). Local irritation was the primary adverse event associated with terconazole, whereas systemic side

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs oral fluconazole (150 mg) two doses			Not reported	effects were associated with fluconazole; however, these effects were minimal. Secondary: Not reported
Onychomycosis				
Gupta et al.[53] (2000) Ciclopirox 8% nail lacquer applied QD vs placebo	2 DB, MC, PC, PG Patients 18 to 70 years of age with mild to moderate toenail onychomycosis caused by dermatophytes	N=560 48 weeks	Primary: Mycological cure rate, treatment success, treatment cure, and negative culture Secondary: Adverse effects	Primary: In study A, there was significant improvement in mycological cure in patients treated with ciclopirox compared to patients receiving the vehicle throughout the 48-week treatment period (29 vs 11%, respectively; P<0.001). In study B, there was significant improvement in mycological cure in patients treated with ciclopirox compared to patients receiving the vehicle throughout the 48-week treatment period (36 vs 9%, respectively; P<0.001). In study A, there was significant improvement in culture results in patients treated with ciclopirox compared to patients receiving the vehicle throughout the 48-week treatment period (84 vs 37%, respectively; P<0.001). In study B, there was significant improvement in culture results in patients treated with ciclopirox compared to patients receiving the vehicle throughout the 48-week treatment period (84 vs 44%, respectively; P<0.001). In study A, there was a significant difference between ciclopirox and the vehicle in terms of treatment success (6.5 vs 0.9%, respectively; P=0.031). In study B, there was significant improvement in treatment success in patients treated with ciclopirox compared to patients receiving the vehicle throughout the 48-week treatment period (12 vs 0.9%, respectively; P=0.001). In study A, there was no significant difference between ciclopirox and the vehicle in terms treatment cure (5.5 vs 0.9%, respectively; P=0.059). In study B, there was significant improvement in treatment cure in patients treated with ciclopirox compared to patients receiving the vehicle throughout the 48-week treatment period (8.5 vs 0%, respectively; P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: In study A, adverse effects associated with ciclopirox compared to vehicle were mainly localized site reactions including erythema (4 vs 1%, respectively); tingling sensation, pain or intermittent burning (3 vs 2%, respectively) and changes in nail shape or color (2 vs 1%, respectively). In study B, adverse effects associated with ciclopirox compared to vehicle were mainly localized site reactions including erythema (10 vs 2%, respectively); tingling sensation, pain or intermittent burning (0 vs 1%, respectively) and changes in nail shape or color (3 vs 3%, respectively).
Brenner et al.[54] (2007) Ciclopirox 8% nail lacquer applied QD	MC, OL Diabetic patients with distal subungual onychomycosis	N=49 48 weeks	Primary: Clinical improvement as determined by involved area, severity, subungual hyperkeratosis, and signs or symptoms Secondary: Not reported	Primary: After 48 weeks of treatment, 63.4% of patients experienced clinical improvement, success, or cure with ciclopirox. At the end of the study, 85.7% of patients had at least a mycologic improvement; 54.3% achieved mycologic cure. Treatment improvement, success, or cure was achieved in 84.4% of patients at the end of the study. Patients experienced improvement in the diseased area of the nail (63.4%), nail surface (56.1%), nail color (48.8%), and nail thickness (65.9%). Physicians rated most patients (78.9%) as experiencing at least a slight improvement in the target nail; 52.6% of patients were rated as experiencing a fair-to-good improvement, and 7.9% were rated as experiencing an excellent improvement. Patient-rated effectiveness was good or excellent in 73.7% of patients. Secondary: Not reported
Shemer et al.[55] (2010) Ciclopirox 8% nail	OL Patients with DLSO and LSO	N=40 9 months	Primary: Clinical nail status, KOH examination and mycological	Primary: After nine months, eight patients (22%) had complete cure (clinical and mycological) of the toenails. Five patients had both marked clinical improvement of their toenails and mycological cure. Nine patients had

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
lacquer applied QD			culture Secondary: Not reported	mild improvement and three patients had moderate improvement of their toenail status. Eight patients (66%) still showed fungal hyphae at KOH examination and/or positive culture. Eleven patients (31%) had no clinical improvement in their toenails and all had positive mycological cultures at the end of the study. No adverse effects were noted throughout the treatment period. Secondary: Not reported
Gupta et al.[53] (2000) Ciclopirox 8% nail lacquer applied QD vs placebo	MA Randomized trials, mostly OL and MC, conducted in Europe, Asia, North America, and South America with patients with extensive finger and/or toe nail involvement of onychomycosis caused by dermatophytes or non-dermatophytes (e.g., *Candida* species)	N=2,075 (13 trials) 6 months	Primary: Mycological cure, clinical cure, and clinical response for ciclopirox therapies Secondary: Adverse effects	Primary: Mycological cure rates ranged from 46.7 to 85.7%, clinical cure ranged from zero to 56.9%, and clinical response ranged from 36.7 to 86% when ciclopirox was used according to dosing regimens ranging from QD to twice weekly. The lowest-reported clinical cure and response rates were associated with the twice-weekly regimens. The highest reported clinical cure and response rates were associated with the QD regimens. Average relapse rate was 20.7% at up to six months of treatment. Secondary: Minimal local side effects were associated with ciclopirox therapy. Reported side effects included nail changes, burning, stinging, erythema, pain, and skin reactions.
Elewski et al.[56] (2013) Efinaconazole 10% solution vs	2 DB, MC, PRO, RCTs Patients 18 to 70 years of age with distal lateral subungual onychomycosis	N=1655 52 weeks	Primary: Complete cure rate Secondary: Mycologic cure, treatment success (<10% clinical involvement of the	Primary: At week 52, 17.8% (study 1) and 15.2% (study 2) of patients had a complete cure on efinaconazole compared with 3.3% and 5.5%, respectively, of patients on placebo (both P<0.001). Secondary: At week 52, 55.2% (study 1) and 53.4% (study 2) of patients achieved mycologic cure on efinaconazole compared with 16.8% (study 1) and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			target toenail), complete or almost complete cure (≤5% clinical involvement and mycologic cure), and unaffected toenail growth (change from baseline)	16.9% (study 2) on placebo (both P<0.001). More patients treated with efinaconazole (study 1: 26.4% and study 2: 23.4%) achieved a complete or almost complete cure compared with placebo (study 1: 7.0% and study 2: 7.5%; both P<0.001). At week 52, 35.7% (study 1) and 31.0% (study 2) of patients on efinaconazole had treatment success compared with 11.7% (study 1) and 11.9% (study 2) on vehicle (P<0.001). Mean unaffected new toenail growth (study 1: 5.0 mm, study 2: 3.8 mm) was greater for efinaconazole than vehicle (study 1: 1.6 mm, study 2: 0.9 mm; P<0.001).
Rich, P.[57] (2015) Efinaconazole 10% solution vs placebo Patients were categorized based on disease duration at baseline (<1 year, 1 to 5 years, and >5 years)	2 DB, MC, PRO, RCTs Patients 18 to 70 years of age with mild to moderate toenail onychomycosis	N=1655 52 weeks	Primary: Complete cure rate Secondary: Mycologic cure, treatment success (<10% clinical involvement of the target toenail), complete or almost complete cure (≤5% clinical involvement and mycologic cure), and unaffected toenail growth (change from baseline)	Primary: Efinaconazole 10% solution was more effective than placebo irrespective of disease duration. At week 52, 42.6% of patients with a baseline disease duration of <1 year had a complete cure with efinaconazole compared to 16.7% on placebo (P value not reported). In addition, 17.1% of patients with a baseline duration of one to five years had a complete cure with efinaconazole compared with 4.4% on placebo (P<0.001). For patients with disease duration >5 years, 16.2% of patients had a complete cure with efinaconazole compared with 2.5% on placebo (P<0.001). Secondary: At week 52, 66.0, 59.0, and 53.8% of patients respectively achieved mycologic cure with efinaconazole compared with 27.8, 14.7, and 14.4% on placebo (last two P<0.001). More patients also achieved a complete or almost complete cure with efinaconazole (48.9, 28.3, 24.4% respectively) compared to placebo (22.2, 7.4, 5.0%), again with treatment benefits reducing with increased baseline disease duration. At week 52, all of the patients with early disease (<1 year) who achieved mycologic cure were considered treatment successes (≤10% affected target toenail) irrespective of treatment. By contrast, 83.7% of patients with a disease duration of one to five years and 78.5% with a disease duration >5 years, and who were mycologic cures were treatment successes at week 52, were considered treatment successes.
Iozume et al.[58] (2019) Eficonazole 10%	MC, SA Patients ≥20 years of age who provided	N=219 Up to 72 weeks	Primary: Changes over time in treatment success rate,	Primary: The changes in treatment success rate in the full analysis set were 9.1%, 27.9%, 39.3%, 47.9%, 51.1% and 53.4% at weeks 12, 24, 36, 48, 60 and 72 after starting the eficonazole application, respectively, showing an

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solution	written consent and were diagnosed with onychomycosis in either the left or right great toenail		defined as a reduction in clinical involvement to ≤10% of the target nail Secondary: Changes over time in complete cure rate, mycological cure rate, decrease rate of clinical involvement and clinical involvement	increase in efficacy rate over time. The treatment success rate at the final assessment was 56.6% (95% CI, 50.0 to 63.0%). Secondary: Changes in the complete cure rate in the full analysis set were confirmed to increase over time until week 72 after starting eficonazole application, like the treatment success rate, achieving 31.1% at the final assessment. Changes in the mycological cure rate increased earlier than the treatment success and complete cure rates, increasing to 38.8% at week 24, 50.7% at week 36 and 55.3% at week 72 after starting eficonazole application. The mycological cure rate at the final assessment was 61.6%. Changes in clinical involvement started to increase to 11.1%±13.27% (clinical involvement, 49.1%±23.14% at the start of eficonazole application) from week 12 after starting eficonazole application, reaching up to 21.0%±18.40% at week 24 and then 31.9%±24.32% at week 72. For the decreased rate of clinical involvement, the proportion of subjects with improvement (reduction of involvement area by ≥50%) was 74.9% at the time of final assessment.
Eichenfield et al.[59] (2021) Eficonazole 10% solution	MC, OL Patients 6 to 16 years old with distal lateral subungual onychomycosis	N=62 52 weeks	Primary: Tolerability Secondary: Not reported	Primary: Of 62 enrolled participants, 12 (19.4%) discontinued the study (withdrawal by parent/guardian, n=6; lost to follow-up, n=5; participant request, n=1). None of the treatment-emergent adverse events (TEAEs) led to study discontinuation. The only treatment-related TEAE was ingrown nail. No safety signals or trends associated with local skin reactions were observed. Secondary: Not reported
Elewski et al.[60] (2015) Tavaborole 5% solution vs placebo	2 DB, MC, PG, RCTs Patients 18 years of age or older with distal subungual toenail onychomycosis	N=1198 52 weeks	Primary: Complete cure rate Secondary: Completely or almost clear nail, negative mycology, and completely or	Primary: A significantly greater proportion of patients achieved complete cure with tavaborole vs placebo in study 1 (6.5 vs 0.5%; P=0.001) and study 2 (9.1 vs 1.5%; P<0.001). Secondary: Rates of completely or almost clear nail at week 52 with tavaborole were 26.1 and 27.5% in study 1 and study 2, respectively, vs 9.3 and 14.6% with placebo (both P<0.001). Negative mycology rates with tavaborole

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			almost clear nail plus negative mycology; safety	were 31.1 and 35.9% in study 1 and study 2, respectively, vs 7.2 and 12.2% with placebo (both P<0.001). Rates of completely or almost clear nail plus negative mycology were significantly greater for tavaborole vs placebo (P<0.001). The incidence of treatment-emergent adverse events with tavaborole vs vehicle was similar.
Rich et al.[61] (abstract only) (2019) Tavaborole 5% solution	OL, SA Patients 6 to <17 years of age with distal subungual onychomycosis affecting greater than equal to 20% of the target great toenail	N=not available 48 weeks	Primary: Safety Secondary: Efficacy	Primary: Treatment-emergent adverse events were reported by 55.6% of patients; the most frequently reported (≥5% of patients) were nasopharyngitis, contusion, sinusitis and vomiting. Most treatment-emergent adverse events and local treatment reactions were mild or moderate and considered unrelated to treatment. There was one serious adverse event (severe appendicitis, considered unrelated to treatment) and there were no deaths, discontinuations because of adverse events or dose adjustments because of adverse events. The most frequently reported local treatment reactions were erythema and scaling. The incidence of local treatment reactions diminished over time. Secondary: For efficacy, 8.5% of patients achieved complete cure (clear nail and negative mycology [negative fungal culture and negative potassium hydroxide wet mount]) at week 52, and 14.9% achieved complete/almost complete cure at week 52 (clear or almost clear nail [≤5% dystrophic or discolored distal toenail plate] and negative mycology).
Seborrheic Dermatitis				
Aly at el.[62] (2003) Ciclopirox 0.77% gel applied BID vs placebo	DB, MC, PC, RCT Patients 19 to 85 years of age with moderate, stable or exacerbating, inflammatory seborrheic dermatitis of the scalp	N=178 28 days	Primary: Clinical evaluation, efficacy evaluation Secondary: Adverse events	Primary: At days 22, 29, and at the study endpoint (final visit, up to day 33), patients treated with ciclopirox achieved greater than 75% improvement in global evaluation scores compared to those treated with placebo (P=0.01). At days 15 (P=0.01), 22 (P=0.001), 29 (P=0.001), and at the study endpoint (P=0.001), total patient signs and symptom scores were higher in patients treated with ciclopirox compared to placebo. Twenty-nine percent of patients treated with ciclopirox rated the medication as cosmetically acceptable. Secondary:

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				A burning sensation was reported in 13 and 9% in ciclopirox and placebo-treated patients, respectively.
Vardy et al.[63] (2000) Ciclopirox 1% shampoo applied twice weekly vs placebo	DB, PC, PRO, RCT Patients ≥15 years of age with mild to moderate seborrheic dermatitis of the scalp	N=82 4 weeks	Primary: Symptom scores, clinical cure, and clinical assessments Secondary: Not reported	Primary: At the end of four weeks of treatment, 93 and 41% of patients treated with ciclopirox and placebo, respectively, had improvement or clearing of infections (P<0.00001). No recurrence was observed at two weeks post treatment. At the two-week checkup, four-week checkup, and at two weeks post treatment, there was greater improvement in overall symptoms scores in patients treated with ciclopirox compared to patients treated with placebo (P=0.022, P<0.001, and P=0.014, respectively). After four weeks of treatment, both patient and physician assessment scores showed a significant difference in clinical response favoring ciclopirox at weeks four (P=0.00001 for both comparisons) and six (P=0.00059 and P<0.00023, respectively). Secondary: Not reported
Lebwohl et al.[64] (2004) Ciclopirox 1% shampoo applied twice weekly vs placebo	DB, PC, RCT Patients with a mild to pronounced expression of stable or exacerbating seborrheic dermatitis of the scalp	N=499 4 weeks	Primary: Effective treatment for status, scaling, and erythema Secondary: Clearance and improvement, sum scores of scaling, itching, and erythema	Primary: Effective treatment was noted in 65 subjects (26.0%) in the ciclopirox group compared to 32 patients (12.9%) in the vehicle group (OR, 2.383; 95% CI, 1.494 to 3.799; P=0.0001). Secondary: Clearance was obtained for 10.0% of patients in the ciclopirox group and 3.2% of patients in the vehicle group. Improvement of disease status from baseline by ≥3 points occurred in 42.4% of patients in the ciclopirox group and 24.1% of patients in the vehicle group (P<0.001). At the end of treatment period, there was no significant difference in the changes in the status of seborrheic dermatitis between the two groups. Sum scores of scaling, itching and erythema during the study period in the

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				ciclopirox group were reduced from a mean of 8.5 to a mean of 4.6 (3.9-point reduction) at week four. Reductions of means in the vehicle group were from 8.7 to 6.1 at week four (2.6-point reduction). This difference between groups was significant in favor of ciclopirox at both week two (P=0.0003) and week four (P<0.0001).
Shuster et al.[65] (2005) Study Segment A Ciclopirox 1% shampoo applied once or twice weekly for 4 weeks vs placebo Study Segment B Ciclopirox 1% shampoo applied prophylactically once weekly or every 2 weeks for 12 weeks vs placebo	DB, MC, PC, RCT Patients 18 to 88 years of age with stable or exacerbating seborrheic dermatitis of the scalp	Study Segment A N=949 4-weeks Study Segment B N=428 12-weeks	Study Segment A Primary: Effectively treated for status, scaling, and inflammation Secondary: Cleared for status, scaling, inflammation, and itching Study Segment B Primary: Relapse rate Secondary: Not reported	Study Segment A Primary: Ciclopirox was more effective than vehicle. Twice- and once-weekly shampooing produced response rates of 58.5 and 45.5%, respectively, compared to 31.6% in the vehicle treatment group (P<0.001 and P<0.001, respectively). Secondary: Higher response rates were demonstrated with ciclopirox than with placebo (ciclopirox twice weekly, 23.1% [P<0.001)]; ciclopirox once weekly, 17% [P=0.4]; placebo, 10%). Study Segment B Primary: Relapses occurred in 14.7% of patients using prophylactic ciclopirox once weekly, 22.1% of those using prophylactic ciclopirox once every two weeks, and 35.5% in the placebo group (P<0.001 and P<0.001, respectively). Secondary: Not reported
Green et al.[66] (1987) Ketoconazole 2% cream applied to the affected skin area and	DB, PC, RCT Patients 16 to 78 years of age with seborrheic dermatitis of the face and possible	N=20 4 weeks	Primary: Degree of seborrheic dermatitis, patient assessment of facial rash, scalp itching, and scalp	Primary: After four weeks, patients treated with ketoconazole experienced a significant improvement in seborrheic dermatitis of the face (P<0.01) according to clinical assessment grading. As opposed to patients receiving the placebo agents, patients treated with ketoconazole showed improved visual analog scores for facial rash at three weeks (P<0.05) and four weeks (P<0.01).

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ketoconazole 2% shampoo applied to the hair two to three times weekly vs placebo	seborrheic dermatitis of the scalp and/or chest/back		scaling Secondary: Not reported	Six out of ten patients receiving ketoconazole experienced significant reduction in scalp scaling (P<0.05). Patients receiving the placebo experienced no change or improvement in clinical or visual analog scores. Secondary: Not reported
Piérard-Franchimont et al.[67] (2001) Ketoconazole 1% shampoo applied to the hair twice weekly vs ketoconazole 2% shampoo applied to the hair twice weekly	OL, PG, RCT Patients 20 to 69 years of age with severe dandruff and seborrheic dermatitis	N=66 4 weeks	Primary: Squamometry *Malassezia* spp. counts, clinical assessment Secondary: Adverse events, relapse rate	Primary: After two and four weeks of treatment, ketoconazole 2% was more effective than ketoconazole 1% relative to decreasing flakiness and *Malassezia* spp. counts (P<0.001). At week two, at treatment endpoint, and at the follow-up, ketoconazole 2% was associated with a greater improvement on *Malassezia* spp. counts compared to patients on ketoconazole 1% (P=0.001, P<0.001, and P=0.001, respectively). At week 2, at treatment endpoint, and at the follow-up, ketoconazole 2% was associated with a greater improvement of global clinical evaluation scores compared to patients on ketoconazole 1% (P<0.001, P<0.001, P<0.001, respectively). Secondary: One patient treated with ketoconazole 1% reported seborrhea. During follow-up, there were less relapses for patients previously treated with ketoconazole 2% compared to ketoconazole 1%.
Carr et al.[68] (1987) Ketoconazole 2% shampoo applied to the hair QD for 4 weeks, then Johnson's® baby shampoo applied	DB, PC, RCT, XO Patients 25 to 65 years of age with seborrheic dermatitis on the scalp	N=20 12 weeks	Primary: Degree of scalp scaling, patient assessment of scalp itching and scaling Secondary: Not reported	Primary: Seventy-four percent of patients treated with ketoconazole 2% shampoo experienced a significant improvement in clinical scores characterizing the degree of scalp scaling compared to patients receiving placebo (P<0.01). Patients treated with ketoconazole 2% shampoo experienced a significant improvement in scalp itching (P<0.01) and scalp scaling (P<0.05); there was no difference found in patients receiving the placebo shampoo.

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to the hair for 4 weeks, then placebo for 4 weeks vs placebo for 4 weeks, then Johnson's® baby shampoo applied to the hair for 4 weeks, then ketoconazole 2% shampoo applied to the hair QD for 4 weeks				Secondary: Not reported
Ratnavel et al.[69] (2007) Ketoconazole 2% shampoo applied 3 times per week for 4 weeks vs ciclopirox 1.5% shampoo applied 3 times per week for 4 weeks vs placebo	DB, PG, RCT Patients with seborrheic dermatitis of the scalp	N=350 8 weeks	Primary: Scalp area affected, severity of scaling, erythema, itching and scaling, and overall signs and symptoms Secondary: Not reported	Primary: The reductions in affected scalp area from day one to days 15, 29, and 43 were all significantly greater with ciclopirox shampoo than with placebo (P=0.001), but did not differ significantly from the reductions observed with ketoconazole. Ciclopirox was non-inferior to ketoconazole. The percentage reduction in the patients' assessments of itching and scaling of the scalp was significantly greater with ciclopirox than placebo at day 29 (P=0.011 and P=0.003, respectively), but there were no significant differences between the two active shampoos. At day 29, the improvement in the patients' assessments of overall signs and symptoms was significantly greater with ciclopirox shampoo than with placebo (P<0.001) or ketoconazole (P=0.030). The improvement was also greater with ciclopirox than placebo at day 15 (P<0.05). The technician's assessment of scaling showed a greater reduction from day one to day 29 with ciclopirox than placebo (P=0.022) as was the reduction from day one to day 43 (P=0.012). The reduction in erythema was also greater with ciclopirox than placebo at day 29 (P=0.019). There

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				were no significant differences between active and placebo treatment with respect to erythema. The technician's assessment of global change showed ciclopirox shampoo to be better than placebo at day 29 and day 43 (P<0.001 for both days); no differences between the two active shampoos were detected. Secondary: Not reported
Squire et al.[70] (2002) Ketoconazole 2 % shampoo applied 3 times per week for 4 weeks vs ciclopirox 1.5% and salicylic acid 3% shampoo applied 3 times per week for 4 weeks	RCT, SB, SC Patients 12 to 70 years of age mild, moderate or severe dandruff and/or seborrheic dermatitis of the scalp	N=161 8 weeks	Primary: Clinical assessments of dandruff and safety Secondary: Not reported	Primary: For both treatment groups, there was a significant decrease in the clinical assessment of dandruff scores at day 29 compared to day one (P<0.001). However, there was no significant difference among the treatment groups. Scores remained significantly lower after the cessation of therapy for two weeks (day 43) than on day one (P<0.05). Both treatments significantly improved clinical assessments of seborrheic dermatitis, patients' self-assessments of dandruff, overall scalp itching, and itching of area of seborrheic dermatitis (P<0.05). Scores remained significantly lower after the cessation of treatment for two weeks (day 43) than at the start of treatment (day one; P<0.05). For both treatment groups, the mean scores for the global evaluation of clinical change indicated an improvement in condition over time, with scores lower than five (no change), at each assessment day after the start of treatment. Only the between-treatment change at day 43 was statistically significant (P<0.05), with lower mean scores in the ketoconazole group. There were similar mean scores for both treatment groups for the patients' overall rating of treatment at the end of treatment (day 29), with 72% of patients in the ciclopirox/salicylic acid group and 56% of patients in the ketoconazole group rating their treatment as 'good', 'very good' or 'excellent'. The between-treatment comparison was not statistically significant (P>0.05). The most common adverse events were pruritus, rhinitis, seborrhea and

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				skin irritation. Secondary: Not reported
Koc et al.[71] (2009) Ketoconazole 2% cream applied BID vs pimecrolimus 1% cream applied BID	OL, RCT Patients with mild to moderate seborrheic dermatitis	N=48 6 weeks	Primary: Treatment efficacy (symptoms of erythema, scaling and infiltration) Secondary: Not reported	Primary: In both treatment groups, there was a significant decrease in erythema, scaling and infiltration criteria (P<0.05). Clinical improvements were as follows: 81.4 and 78.3% for erythema, 86.1 and 87.2% for scaling, and 93.3 and 94.6% for infiltration in the pimecrolimus and ketoconazole groups, respectively. The mean percentage decrease in the total clinical severity scores was 86.2 and 86.1% in the pimecrolimus and ketoconazole groups, respectively (P>0.05). Adverse events were observed in 12 patients in the pimecrolimus group and four patients in the ketoconazole group. Burning sensation, pruritus, irritation, and erythema were more common in the pimecrolimus group than in the ketoconazole group (P<0.05). Secondary: Not reported
Pierard-Franchimont et al.[72] (2002) Ketoconazole 2% shampoo twice applied to the hair weekly for 4 weeks vs zinc pyrithione 1% shampoo applied	MC, OL, PG, RCT Adults with seborrheic dermatitis of the scalp or severe noninflammatory dandruff	N=343 4 week treatment phase 4 week follow-up phase	Primary: Overall cure Secondary: Relapses, TDSS	Primary: The proportions of clinical responders who experienced marked improvement or clearing of their scalp condition at the treatment endpoint were similar for the ketoconazole (86%) and zinc pyrithione (82%) groups. The shift in the global scores was significantly greater for ketoconazole both at the end of treatment and at completion of the follow-up phase (P<0.05). The overall clearing was greater in the ketoconazole group (57%) than in the zinc pyrithione group (44%; P<0.01). Secondary: Relapse rates were 39% in the ketoconazole group compared to 51% in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to the hair at least twice weekly for 4 weeks				zinc pyrithione group (P<0.03). The ketoconazole group showed a significantly greater improvement from baseline in TDSS than the zinc pyrithione at treatment endpoint (P<0.02) and at the end of the follow-up period (P<0.04).
Tinea Infections				
Reyes et al.[73] (1998) Butenafine 1% cream applied QD vs placebo	DB, MC, PC, RCT Patients with interdigital tinea pedis rated with a minimum erythema score of 2 and a minimum score of 2 for either pruritus or scaling	N=105 4 weeks	Primary: Mycological cure, investigator global assessment of clinical response, patient's assessment of change, and effective treatment Secondary: Adverse effects	Primary: Patients who received butenafine were more likely to experience mycological cure at four weeks compared to placebo (91 vs 63%, respectively; P<0.01). Mycological cure persisted in patients receiving butenafine four weeks after the end of the four-week treatment period compared to the placebo (83 vs 38%, respectively; P<0.001). According to the investigator global response, patients receiving butenafine had significantly better clinical response to compared to placebo at four (P=0.03) and eight weeks (P<0.001). According to the patient's assessment of clinical response, a greater number of patients receiving butenafine described improvement in signs and symptoms compared to those receiving placebo (P<0.001). Effective treatment as determined by mycological cure rate and sign/symptom improvement was greater with patients receiving butenafine compared to patients who received placebo at four (58 vs 31%, respectively; P<0.01) and eight weeks (68 vs 25%, respectively; P<0.001). Secondary: One patient receiving butenafine experienced moccasin-type tinea pedis of the plantar surface; one patient experienced hyperbilirubinemia.
Tschen et al.[74] (1997) Butenafine 1% cream applied QD vs	DB, PC, RCT Patients with interdigital tinea pedis with a minimum erythema score of 2 and a minimum score of 2	N=80 4 weeks	Primary: Mycological cure, investigator global assessment of clinical response, patient's assessment of change, and	Primary: Patients who received butenafine were more likely to experience mycological cure at four weeks compared to placebo (88 vs 33%). According to the investigator global response, patients receiving butenafine had significantly better clinical response as compared to those treated with placebo at four weeks (P<0.01) and at eight weeks (P=0.001). Effective clinical response persisted in patients receiving butenafine

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	for either pruritus and scaling		effective treatment Secondary: Safety, tolerability	compared to placebo at eight weeks (clinical response at four weeks was 68 vs 40%, respectively; [P<0.01]; at eight weeks was 78 vs 35%, respectively; [P<0.001]). According to the patient's assessment of clinical response, a greater number of patients receiving butenafine described somewhat or great improvement in signs and symptoms compared to those receiving placebo at four weeks (P=0.003) and eight weeks (P<0.001). Effective treatment as determined by mycological cure rate and sign/symptom improvement was greater with patients receiving butenafine compared to patients who received placebo at two weeks (55 vs 23%, respectively; P=0.001) and eight weeks (70 vs 23%, respectively; P=0.012). Secondary: One patient receiving butenafine experienced mild burning sensations at the site of application, whereas four patients receiving placebo experienced burning, itching, stinging, a red streak, and/or a high serum lactate dehydrogenase concentration.
Singal et al.[75] (2005) Butenafine 1% cream applied QD for 2 weeks vs clotrimazole 1% cream applied BID for 4 weeks	DB, RCT Patients ≥14 years of age with localized tinea cruris and localized tinea corporis	N=80 8 weeks	Primary: Clinical and mycological cure Secondary: Not reported	Primary: The clinical assessment score, clinical cure rates, and mycological cure rates were similar for the butenafine and clotrimazole treatment groups at four and eight weeks of treatment. In the butenafine group, relapse was not observed in any patient, while two patients in the clotrimazole group became KOH-positive again at eight weeks and one of them also had evidence of clinical relapse. Secondary: Not reported
Aly et al.[76] (2003) Ciclopirox 0.77% gel applied BID	2 DB, MC, RCT Patients 16 to 80 years of age with clinically	N=317 28 days	Primary: Treatment success (mycological and clinical cure)	Primary: At the end of the study, 60 and 6% of patients treated with ciclopirox and placebo, respectively, achieved treatment success, greater than 75% clinical improvement (P=0.05). This significant difference in treatment success between ciclopirox and placebo was observed at days 26, 43 and

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vs placebo	diagnosed, stable or exacerbating interdigital tinea pedis with or without plantar involvement with positive culture and potassium hydroxide test		Secondary: Global clinical response, signs and symptoms severity scores, mycological evaluation, mycological cure, and treatment cure	at the study endpoint (final visit, up to day 50; P=0.05). Secondary: At the end of the study, 40 and 4% of the patients treated with ciclopirox and placebo, respectively, had complete clinical cure. This significant difference in clinical cure between ciclopirox and placebo was observed at days 26, 43 and at the study endpoint (P=0.05). At the end of the study, 66 and 16% of patients treated with ciclopirox and placebo, respectively, had either cleared or excellent improvement relative to the infection (P=0.05). At two weeks post treatment, 85 and 16% of patients treated with ciclopirox and placebo, respectively, were mycologically cured (P=0.05). At the end of the treatment, 46 and 24% of patients treated with ciclopirox and placebo, respectively, described treatment as cosmetically acceptable.
Gupta et al.[77] (2005) Ciclopirox 0.77% gel applied QD vs ciclopirox 0.77% gel applied BID vs placebo	DB, PC, PRO, RCT Patients 18 to 70 years of age with moderate interdigital tinea pedis and secondary bacterial infection	N=100 8 weeks	Primary: Global clinical evaluation score, subject clinical evaluation score, clinical cure, mycological cure, and complete cure; clinical evaluation scores ranged from one excellent to seven worse Secondary: Adverse effects	Primary: There was no significant difference in improved evaluation scores between QD or BID applications of ciclopirox. However, both QD and BID ciclopirox treatment groups showed significant improvement in evaluation scores compared to placebo at week eight (2.06 vs 6.17; P=0.0003 and 2.41 vs 6.17; P=0.0036, respectively). There was no significant difference in improved mycological cure rates between QD or BID applications of ciclopirox. However, both QD and BID ciclopirox treatment groups showed significant improvement in mycological cure rate compared to placebo at week eight (82.8 vs 43.8%; P=0.013 and 80.8 vs 43.8%; P=0.007, respectively). There was a significant difference in complete cure rate between twice-daily ciclopirox and placebo (50.0 vs 12.5%, respectively; P=0.014). Other comparisons were not significant. Secondary: The most common reported adverse effects were local site reactions of burning or itching. There was no significant difference in the incidence of

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				adverse effects between treatment groups.
Aly et al.[78] (1989) Ciclopirox 1% cream applied BID vs ciclopirox 1% lotion applied BID vs placebo	DB, MC, PG, RCT Patients with clinically and mycologically confirmed plantar, interdigital, or vesicular tinea pedis	N=134 28 days	Primary: Clinical cure, mycological cure Secondary: Adverse events	Primary: On day 29, patients treated with ciclopirox lotion experienced greater mycological response compared to patients receiving the placebo (P<0.001). On day 43, patients treated with ciclopirox lotion compared to placebo achieved greater clinical cure (45 vs 27%, respectively; P=0) and mycological cure (76 vs 43%, respectively; P=0). Secondary: Pruritus and burning were reported with ciclopirox use.
Wu et al.[79] (1991) Ciclopirox 1% cream applied BID to TID	OL, OS Patients living in temperate climates with culture or microscopically confirmed onychomycosis and/or tinea pedis	N=49 3 to 24 months	Primary: Clinical cure, mycological cure Secondary: Adverse effects	Primary: For onychomycosis, 14 and 36% of patients treated with ciclopirox were cured and showed improvement, respectively. Cure was influenced by the degree of nail plate affected; moderate involvement correlated to a better cure rate. For tinea pedis, 42 and 45% of patients treated with ciclopirox were cured and showed improvement, respectively. Secondary: Paronychia was reported as a side effect, possibly due to excessive application of the agent.
Bogaert et al.[80] (1986) Ciclopirox 1% cream applied BID vs clotrimazole 1% cream applied BID	2 DB, MC, PG, RCT Patients with tinea corporis or tinea cruris	N=229 28 weeks	Primary: Clinical evaluation, assessment of treatment response Secondary: Safety, tolerance	Primary: In study A, patients treated with ciclopirox demonstrated significant improvement in clinical and mycological cure rate compared to the patients receiving placebo at six weeks (61 vs 15%; P<0.001). In study B, there was no significant difference in clinical and mycological cure rate between treatment groups receiving ciclopirox or clotrimazole creams (64 vs 69%; P value not reported). Secondary: In study A, no side effects associated with ciclopirox were reported; one

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo In study A, patients received either ciclopirox 1% cream BID or placebo. In study B, patients received either ciclopirox 1 % cream BID or clotrimazole 1 % cream BID.				patient receiving placebo reported transient burning. In study B, one patient receiving ciclopirox reported pruritus and one patient receiving clotrimazole reported burning, pruritus, and worsening of lesions.
Chen et al.[81] (2010) Ciclopirox 1% shampoo applied twice weekly vs selenium sulfide 1% shampoo applied twice weekly Treatments were an adjunct to an 8-week course of ultra micronized griseofulvin, which was dosed	DB, RCT Children 1 to 12 years of age with a clinical diagnosis of tinea capitis	N=44 Treatment: 8 to 12 weeks Follow-up: 4 weeks post-treatment	Primary: Mycological cure (defined as having zero dermatophyte colonies on Mycosel agar) Secondary: Not reported	Primary: Overall, 30.3% of children had negative cultures at two weeks, 42.4% of children at four weeks, 18.2% of children at eight weeks, and 3.0% of children at 12 weeks, for a total of 93.9% of children mycologically cured by 12 weeks. Among children treated with griseofulvin and selenium sulfide shampoo, 25.0% demonstrated negative cultures at two weeks, 50.0% of children at four weeks, 16.7% of children at eight weeks, and no additional children at 12 weeks, for a total of 91.7% of children mycologically cured by eight weeks. Among children treated with griseofulvin and ciclopirox shampoo, 33.3% demonstrated negative cultures at two weeks, 38.1% of children at four weeks, 19.0% of children at eight weeks, and 4.7% of children at 12 weeks, for a total of 95.2% of children mycologically cured by 12 weeks. There was no significant difference among the treatment groups at two weeks (P=0.71), four weeks (P=1.0), eight weeks (P=1.0), or 12 weeks (P=1.0). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
10 to 12 mg/kg/day.				
Wortzel et al.[82] (1982) Clotrimazole applied BID vs betamethasone dipropionate applied BID vs betamethasone dipropionate and clotrimazole combination cream applied BID	DB, MC, RCT Patients with confirmed tinea cruris	N=45 2 weeks	Primary: Clinical cure, microbiological cure Secondary: Adverse events	Primary: At the end of two weeks, 80, 20 and 13% of patients treated with the combination product, clotrimazole only, and betamethasone only, respectively, achieved either complete cure or excellent response to therapy. At the end of two weeks, 87, 100 and 46% of patients treated with the combination product, clotrimazole only, and betamethasone only, respectively, had negative culture. Two weeks after treatment, 93, 100 and 40% of patients treated with the combination product, clotrimazole only, and betamethasone only, respectively, achieved either complete cure or excellent response to therapy. Relative to overall clinical rating of the treatment, the combination product was better than clotrimazole (P=0.013) and betamethasone (P=0.001); clotrimazole was better than betamethasone (P=0.001). Secondary: One patient treated with betamethasone reported severe burning and tingling.
Katz et al.[83] (1984) Clotrimazole 1 cream applied BID vs betamethasone dipropionate 0.05% cream applied BID	DB, MC, PG, RCT Patients with a confirmed diagnosis of moderate to severe tinea cruris or tinea corporis	N=331 2 weeks	Primary: Total signs and symptoms severity score/clinical response ratings, and mycologic findings Secondary: Adverse events	Primary: Patients treated with clotrimazole had higher total signs and symptoms scores at baseline (P<0.05). At days seven, 14, and 28, patients diagnosed with tinea cruris and treated with the combination product had better total signs and symptoms scores compared to patients treated with clotrimazole (P<0.05). At days 14 and 28, patients diagnosed with tinea cruris and treated with the combination product had better total signs and symptoms scores compared to patients treated with betamethasone dipropionate (P<0.05). At days seven and 28, patients diagnosed with tinea corporis and treated with the combination product had better total signs and symptoms scores

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs betamethasone dipropionate 0.05% and clotrimazole 1% combination cream applied BID				compared to patients treated with clotrimazole (P<0.05). At days 14 and 28, patients diagnosed with tinea corporis and treated with the combination product had better total signs and symptoms scores compared to patients treated with betamethasone dipropionate (P<0.05). According to mycologic responses, the combination product and clotrimazole were more effective than betamethasone dipropionate (63 and 51 vs 32%, respectively; P<0.05). Secondary: Two patients treated with the combination product reported mild macular papular eruption and/or mild paresthesia. Eight patients treated with betamethasone dipropionate reported paresthesia and/or severe pain followed by a papular eruption. Three patients treated with clotrimazole reported paresthesia.
Kamalam et al.[84] (1980) Clotrimazole vs econazole	DB, OS Patients 45 days to 36 years of age with confirmed tinea infections	N=45 3 to 60 days	Primary: Clinical cure, microscopically negative results Secondary: Adverse events	Primary: At six weeks post treatment, 98 and 2% of all patients achieved complete or partial cure, respectively, regardless of treatment with either clotrimazole or econazole. For econazole-treated patients, clinical cure was observed in approximately 14 days (range, five to 29 days) and microscopically negative results were seen in one to two weeks. At six weeks post treatment, all cases were cured. For clotrimazole-treated patients, clinical cure was observed in approximately 16.5 days (range, three to 44 days) and microscopically negative results were seen in one to six weeks. At six weeks post treatment, there was one case not cured. Secondary: No adverse effects were reported. There was one report of a recurrence after two weeks of stopping therapy.
Dehghan et al.[85] (2010) Clotrimazole 1%	DB, RCT Patients with hyperpigmented	N=120 Treatment: 2 weeks	Primary: Clinical response Secondary:	Primary: At week two in the fluconazole group, 30 and 66% of patients showed complete and incomplete clinical response, respectively. Clinical response was not seen in 4% of patients. In the clotrimazole group, 49.1 and 47.3%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cream applied BID for 2 weeks vs fluconazole 400 mg orally as a single dose	tinea versicolor	Follow-up: 12 weeks	Not reported	of patients showed complete and incomplete clinical response, respectively. Clinical response was not seen in 3.6% of patients. At week four in the fluconazole group, 81.2 and 18.8% of patients showed complete and incomplete clinical response, respectively. In the clotrimazole group, 94.9 and 5.1% of patients showed complete and incomplete clinical response, respectively (P=0.044). At week 12 in the fluconazole group, 92 and 2% of patients showed complete and incomplete clinical response, respectively. Recurrence or no clinical response was seen in 6% of patients. In the clotrimazole group, 81.8 and 0% of patients showed complete and incomplete clinical response, respectively. Recurrence or no clinical response was seen in 18.2% of patients (P=0.77). No complications were seen in either group. Secondary: Not reported
Sivayathorn et al.[86] (1979) Clotrimazole 1% cream applied TID vs miconazole 2% cream applied TID vs tolnaftate 2% cream applied TID vs	DB, RCT Patients 2 to 72 years of age with superficial dermatophytoses	N=101 2 weeks	Primary: Clinical response, mycological cure Secondary: Adverse events	Primary: Satisfactory clinical response was reported in 50, 73.68, 77.78, and 81.48% of patients treated with Whitfield's Ointment®, tolnaftate, clotrimazole, and miconazole, respectively. Mycological cure was reported in 21.42, 63.16, 59.26, and 77.78% of patients treated with Whitfield's Ointment®, tolnaftate, clotrimazole, and miconazole, respectively. Although miconazole demonstrated the highest clinical and mycological cure rate, there was no significant difference between clotrimazole, miconazole, and tolnaftate treatment groups (P>0.05). Clotrimazole, miconazole, and tolnaftate therapies were more efficacious compared to Whitfield's Ointment® (P<0.05). Secondary: There were no reported adverse reactions.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Whitfield's Ointment® (3% salicylic acid, 6% benzoic acid) applied TID				
Clayton et al.[87] (1973) Clotrimazole 1% cream applied BID vs nystatin 100,000 U/g ointment applied BID vs Whitfield's Ointment® (3% salicylic acid, 6% benzoic acid) applied BID	AC, DB, RCT Patients 13 to 63 years of age with either confirmed tinea corporis, tinea pityriasis, erythrasma, or *Candida* infections	N=103 4 weeks	Primary: Clinical cure, mycological cure Secondary: Not reported	Primary: Relative to patients with confirmed tinea corporis, there was no significant difference in efficacy in patients treated with clotrimazole or Whitfield's Ointment®. Relative to patients with confirmed tinea pityriasis, there was no significant difference in efficacy in patients treated with clotrimazole or Whitfield's Ointment®. Relative to patients with confirmed erythrasma, there was no significant difference in efficacy in patients treated with clotrimazole or Whitfield's Ointment®. Relative to patients with Candida infections, there was no significant difference in efficacy in patients treated with clotrimazole or nystatin. Secondary: Not reported
Lassus et al.[88] (1983) Clotrimazole 1% cream applied BID vs sulconazole 1% cream applied BID	DB, PG Patients with microbiologically confirmed dermatomycosis	N=40 4 weeks	Primary: Clinical signs and symptoms, overall clinical improvement, and cosmetic acceptability Secondary: Adverse events	Primary: Patients with signs and symptoms of scaling and erythema responded better to sulconazole than clotrimazole at weeks two ($P<0.05$), three ($P<0.01$), and four ($P<0.05$) of treatment. There was no significant difference in the other signs and symptoms regardless of therapy. Overall clinical improvement at weeks two, three, and four was greater with sulconazole (94.8, 100, and 100%, respectively) compared to clotrimazole (73.7, 78.9, and 83.4%, respectively). Secondary: One patient from each treatment group experienced an allergic reaction during the first week of therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tanenbaum et al.[89] (1989) Clotrimazole 1% cream applied BID vs sulconazole 1% cream applied QAM and placebo QPM vs sulconazole 1% cream applied BID vs placebo In study A, patients received either sulconazole applied QAM and placebo QPM or clotrimazole applied BID. In study B, patients received either sulconazole applied BID or placebo BID.	2 DB, PG, RCT Male patient with tinea cruris or tinea corporis	N=117 3 weeks	Primary: Microbiological cure, culture conversion, and overall clinical evaluation Secondary: Adverse events	Primary: In study A, there was no significant difference between treatment groups throughout the study relative to microbiological cure or culture conversion. In study B, there was a significant improvement in culture conversion and microbiological cure for patients treated with sulconazole compared to placebo at week two (P=0.0001) and week three (P=0.0001). By week three, 100% of patients treated with either clotrimazole or sulconazole achieved complete or partial clearing compared to 30% of patients receiving placebo; there was no statistical difference between active treatment groups. In study B, patients treated with sulconazole had a significant improvement in overall clinical evaluation compared to placebo (P=0.0001). Secondary: In study A, four patients receiving clotrimazole cream reported moderate to severe side effects, including erosive primary irritation, fissuring, and erythema. In study B, six patients receiving placebo experienced primary irritant reactions (erosions, burning).
Tham et al.[90] (1987)	RCT	N=84	Primary: Clinical	Primary: Reduced rates of itching, scaling, and erythema did not differ between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Clotrimazole 1% solution applied BID vs sulconazole 1% solution applied QAM and placebo QHS	Patients 14 to 62 years of age with microscopically confirmed tinea versicolor	3 weeks	assessment, investigator assessment, patient assessment, and negative microscopy Secondary: Adverse effects	treatment groups at weeks two and three (P>0.05). Potassium hydroxide results did not differ (P>0.05) between patients treated with sulconazole or clotrimazole at weeks two (67 vs 72%, respectively) and three (76 vs 93%, respectively). Investigator assessed clinical efficacy was 63 and 65% in patients treated with sulconazole and clotrimazole, respectively (P=0.8911). Overall evaluation by the patients was similar (P=0.2197). After six weeks post treatment, negative microscopy was maintained by 79 and 92% of patients taking sulconazole and clotrimazole, respectively. This difference was not significant. Secondary: Five patients who were treated with sulconazole reported adverse effects which included mild itching and burning. Eight patients who were treated with clotrimazole reported adverse effects such as severe itching, biting sensation, stickiness of product, and skin peeling.
Patel et al.[91] (1999) Clotrimazole 1% cream applied BID for 4 weeks vs terbinafine 1% cream applied BID for 1 week, then placebo for 3 weeks	DB, MC, PG, RCT Patients with confirmed interdigital tinea pedis	N=104 4 weeks	Primary: Mycological cure Secondary: Effective treatment, complete cure, perceived efficacy, relapse rate, and adverse events	Primary: After one week of treatment, 84.6 and 55.8% of patients treated with terbinafine and clotrimazole, respectively, were culture negative (P=0.001). There was no significant difference between study groups with regards to mycological cure at weeks four, eight, and 12 weeks. Secondary: There was no significant difference in effective treatment and complete cure between the treatment groups. Throughout the study, both patients and investigators evaluated the treatments as very good to good in 75 to 80% of cases. Relapse rate was 15 and 19% in patients treated with terbinafine and clotrimazole, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Most commonly reported adverse effects included burning, hypersensitivity, stinging, and exacerbation of pruritus.
Lassus et al.[92] (1984) Econazole 1% cream applied BID vs sulconazole 1% cream applied BID	DB, PG, RCT Patients with confirmed dermatophytoses	N=38 4 weeks	Primary: Microbiological cure, clinical cure, overall clinical improvement, relapse, and cosmetic acceptability Secondary: Adverse effects	Primary: By week two, every patient achieved microbiological cure with the exception of one patient treated with sulconazole. By week four, all patients achieved microbiological cure. Both treatment groups responded well to treatment leading to significant reductions in itching, scaling, and erythema. However, by week four, two and three patients treated with sulconazole and econazole, respectively, were still mildly symptomatic. There was no significant difference between treatment groups in terms of overall clinical improvement. The diagnosis of tinea pedis in 80% of the study patients did not influence the study results. At week 10, all patients treated with sulconazole remained symptom- and microbiologically-free of infection, whereas three patients treated with econazole experienced clinical relapses. Relative to cosmetic acceptability, 90 and 79% of patients treated with sulconazole and econazole, respectively, rated the acceptability as excellent. There was no significant difference in cosmetic acceptability. Secondary: One patient treated with econazole reported an allergic reaction. One patient treated with sulconazole reported a case of eczema.
Bonifaz et al.[93] (2000) Ketoconazole 2% cream applied QD for 14 days vs terbinafine 1% gel applied QD for 7	OL, PG, PRO, RCT Patients 12 to 79 years of age with confirmed tinea corporis and tinea cruris	N=65 7 to 14 days	Primary: Mycological cure, clinical cure Secondary: Adverse events	Primary: Clinical cure was not significant between the two treatment groups (P=0.088). Mycological cure was achieved in 94 and 69% of patients treated with terbinafine and ketoconazole, respectively (P=0.027) Combined clinical and mycological overall cure was achieved in 72 and 31% of patients treated with terbinafine and ketoconazole, respectively (P=0.002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days				Of note, the demographic data revealed an unequal distribution of patients in terms of gender (P=0.015); the ketoconazole study group had more male patients compared to the terbinafine study group. Secondary: One patient treated with terbinafine and three patients treated with ketoconazole reported dermatitis-like side effects. Terbinafine was better tolerated than ketoconazole (P=0.003)
Jones et al.[94] (2014) Luliconazole 1% cream once daily for 7 days vs placebo	DB, PG, RCT Patients ≥12 years of age with a diagnosis of tinea cruris and clinical evidence of tinea infection	N=256 28 days	Primary: Complete clearance at day 28 (21 days posttreatment) Secondary: Safety	Primary: Complete clearance was obtained in 21.2% (35/165) of patients treated with luliconazole cream compared with 4.4% (4/91) treated with placebo (P<0.001). Secondary: Overall, treatment emergent adverse events were reported by a numerically smaller percentage of patients treated with luliconazole cream (11.3% [35/311] vs 16.9% [27/160]) compared with placebo cream.
Jarratt et al.[95] (2014) Luliconazole 1% cream once daily for 14 days vs placebo	DB, PG, RCT Patients ≥12 years of age with a diagnosis of tinea pedis and clinical evidence of tinea infection	N=321 42 days	Primary: Complete clearance Secondary: Safety	Primary: Complete clearance at day 42 was achieved in 26.4% (28/106) of patients treated with luliconazole cream 1% compared with 1.9% (2/103) of patients treated with vehicle (P<0.001). Secondary: Treatment emergent adverse events were reported in 15.1% of patients treated with luliconazole cream and 17.0% of patients treated with placebo cream.
Tanenbaum et al.[96] (1982) Miconazole 2% cream applied BID vs	DB, PG, RCT Patients 18 to 65 years of age with cutaneous dermatomycosis	N=96 3 to 4 weeks	Primary: Mycological cure, clinical cure, and relapse rate Secondary: Adverse events	Primary: At the end of four weeks in patients treated for tinea pedis, 100% of patients treated with sulconazole and 67% of patients treated with miconazole were mycologically cured. After the end of three weeks in patients treated for tinea cruris/corporis, 91% of patients treated with sulconazole and 100% of patients treated with miconazole were mycologically cured.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sulconazole 1% cream applied BID				At the end of three weeks, 91 and 100% of patients treated with sulconazole and miconazole, respectively, reported significant or complete clearing of symptoms. Relapse rates were reported as 16 and 35% in patients treated with sulconazole and miconazole, respectively. Secondary: Two patients treated with miconazole reported severe irritant dermatitis. One patient treated with sulconazole experiences moderate-to-severe itching.
Tanenbaum et al.[97] (1984) Miconazole 2% cream applied BID vs sulconazole 1% cream applied BID	DB, MC, PG, RCT Patients with confirmed tinea versicolor	N=181 3 weeks	Primary: Clinical cure, mycological cure Secondary: Adverse events	Primary: At the end of the study, 93 and 87% of patients treated with sulconazole and miconazole were mycologically cured (P=0.6198). At this time, clinical cure was achieved in 89 and 82% of patients treated with sulconazole and miconazole (P=0.2431). Secondary: Patients treated with miconazole reported stinging, itching, dermatitis, or irritation. Patients treated with sulconazole reported itching, stinging/burning, dryness/scaling, and fissure/cracking.
Jordon at el.[98] (1990) Naftifine 1% cream applied QD vs placebo	DB, RCT Patients 14 to 67 years of age with confirmed tinea cruris or tinea corporis	N=70 4 weeks	Primary: Mycological cure, clinical cure Secondary: Adverse events	Primary: After two weeks, 79 and 31% of patients treated with naftifine and placebo, respectively, achieved mycological cure (P<0.001). At this time, patients treated with naftifine had better resolution of erythema (P<0.001), scaling (P=0.007), and pruritus (P<0.001) compared to patients using placebo. This significant trend favoring naftifine persisted throughout the treatment period (86 vs 30%, respectively; P<0.001) and two weeks post treatment (66 vs 26%, respectively; P=0.002). Secondary: Two patients treated with placebo reported adverse events, while none were reported by patients treated with naftifine.
Parish et al.[99] (2011)	DB, MC, PC, RCT Patients 12 years of	N=334 4 weeks	Primary: Complete cure	Primary: At week two, complete cure was achieved by 5% of patients treated with naftifine compared to 0% of patients treated with placebo (P<0.025). At

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Naftifine 2% cream QD for 2 weeks vs placebo	age and older with a clinical diagnosis of *T. cruris*		Secondary: Mycological cure, treatment effectiveness, clinical cure, and clinical success	week four, complete cure was achieved by 25% of patients treated with naftifine compared to 3% of patients treated with placebo (P<0.001). Secondary: At week two, mycological cure was achieved by 67% of patients treated with naftifine compared to 11% of patients treated with placebo (P<0.001). At week four, mycological cure was achieved by 72% of patients treated with naftifine compared to 16% of patients treated with placebo (P<0.001). At week two, treatment effectiveness was achieved by 52% of patients treated with naftifine compared to 9% of patients treated with placebo (P<0.001). At week four, treatment effectiveness was achieved by 60% of patients treated with naftifine compared to 10% of patients treated with placebo (P<0.001). At week two, clinical cure was achieved by 10% of patients treated with naftifine compared to 5% of patients treated with placebo (P<0.257). At week four, clinical cure was achieved by 33% of patients treated with naftifine compared to 10% of patients treated with placebo (P<0.001). At week two, clinical success was achieved by 74% of patients treated with naftifine compared to 5% of patients treated with placebo (P<0.001). At week four, clinical success was achieved by 84% of patients treated with naftifine compared to 10% of patients treated with placebo (P<0.001).
Parish et al.[100] (2011) Naftifine 2% cream QD for 2 weeks vs naftifine 1% cream QD for 4 weeks	DB, MC, PC, RCT Patients 12 years of age and older with a clinical diagnosis of *T. pedis*	N=709 6 weeks	Primary: Complete cure Secondary: Mycological cure, treatment effectiveness, clinical cure, and clinical success	Primary: At week six, a greater proportion of patients treated with naftifine 2% achieved complete cure compared to patients treated with placebo (18 vs 7%; P<0.010). The complete cure rates were not statistically significantly different between naftifine 2% and placebo at weeks two (P=0.100) and four (P=0.234). At week six, a greater proportion of patients treated with naftifine 1% achieved complete cure compared to patients treated with placebo (16 vs 3%; P<0.001). The complete cure rates were not statistically significantly different between naftifine 1% and placebo at weeks two (P=0.097) and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo for 2 weeks vs placebo for 4 weeks				four (P=0.143). Secondary: Compared to placebo, a greater proportion of patients treated with naftifine 2% achieved mycological cure at week two (28 vs 19%; P<0.049), at week four (54 vs 20%; P<0.001), and at week six (67 vs 21%; P<0.001). Similarly, compared to placebo, a greater proportion of patients treated with naftifine 1% achieved mycological cure at week two (32 vs 19%; P<0.028), at week four (53 vs 9%; P<0.001), and at week six (71 vs 22%; P<0.001). Compared to placebo, a greater proportion of patients treated with naftifine 2% achieved treatment effectiveness at week four (35 vs 10%; P<0.001) and at week six (57 vs 20%; P<0.001). Treatment effectiveness was not statistically significantly different between naftifine 2% and placebo at week two (P=0.460). Compared to placebo, a greater proportion of patients treated with naftifine 1% achieved treatment effectiveness at week two (18 vs 6%; P<0.011), at week four (36 vs 6%; P<0.001), and at week six (59 vs 14%; P<0.001). At week six, a greater proportion of patients treated with naftifine 2% achieved clinical cure compared to patients treated with placebo (22 vs 11%; P<0.040). The clinical cure rates were not statistically significantly different between naftifine 2% and placebo at week two (P=0.213) and at week four (P=0.987). At week six, a greater proportion of patients treated with naftifine 1% achieved clinical cure compared to patients treated with placebo (22 vs 8%; P<0.008). The clinical cure rates were not statistically significantly different between naftifine 1% and placebo at week two (P=0.193) and at week four (P=0.564). Compared to placebo, a greater proportion of patients treated with naftifine 2% achieved clinical success at week four (57 vs 35%; P<0.001) and at week six (78 vs 49%; P<0.001). Clinical success rates were not statistically significantly different between naftifine 2% and placebo at week two (P=0.482). Compared to placebo, a greater proportion of patients treated with naftifine 1% achieved clinical success at week two (44 vs 27%; P<0.007) and at week six (84 vs 44%; P<0.001). Clinical

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				success rates were not statistically significantly different between naftifine 1% and placebo at week four (P<0.078).
Ramelet et al.[101] (1987) Oxiconazole cream applied QAM and placebo QPM vs oxiconazole cream applied BID	DB, MC, RCT Patients 8 to 80 years of age with confirmed dermatomycoses or erythrasma	N=138 7 to 60 days	Primary: Mycological cure, clinical cure Secondary: Adverse events	Primary: At the conclusion of the study, 69 and 70 patients treated with oxiconazole QD and BID, respectively, achieved cure. The cure rates were 92.0 and 93.3% for patients treated with oxiconazole QD and BID, respectively; no significant difference found between treatment groups. Secondary: Adverse effects were negligible. Three patients reported adverse events which included irritation with erythema and pruritus near the infected area and burning sensations.
Pariser et al.[102] (1994) Oxiconazole 1% lotion applied BID vs placebo QAM, then oxiconazole 1% lotion applied QPM vs placebo	DB, MC, PC, RCT Patients 12 to 82 years of age with confirmed tinea pedis	N=332 6 weeks	Primary: Mycological cure, clinical cure, overall cure, and global response score Secondary: Adverse events	Primary: At the end of the study, 67 and 31% of patients treated with oxiconazole and placebo, respectively, experienced mycological cure. At the end of the study, >80 and 50% of patients treated with oxiconazole and placebo, respectively, experienced good to excellent improvement in clinical signs and symptoms of tinea pedis as well as global response. A significant improvement was observed in patients treated with oxiconazole compared to placebo relative to overall cure. Secondary: Adverse effects reported were similar across study groups. Commonly reported adverse events included burning, stinging, dyshidrotic eczema, pain, scaling on dorsum of feet, and tingling.
Van Esso et al.[103] (1995) Sertaconazole 2% cream applied QD vs	MC, OL Patients 2 to 16 years of age with tinea corporis, tinea cruris, or tinea pedis	N=16 2 weeks	Primary: Symptoms, clinical cure Secondary: Adverse effects	Primary: The number of patients experiencing symptoms of tinea infections decreased throughout the treatment duration of two weeks; exact percentages were not provided. All of the patients treated with sertaconazole achieved clinical cure after four weeks since start of treatment; 31% achieved cure at week one and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				75% achieved cure at week two. Secondary: No local or systemic adverse effects were observed.
Sharma et al.[104] (2011) Sertaconazole 2% cream applied BID for 2 weeks vs miconazole 2% cream applied BID for 2 weeks	DB, MC, PG, RCT Patients 18 to 70 years of age with a clinical diagnosis of cutaneous dermatophytosis	N=260 2 weeks	Primary: Physician global assessment of clinical response regarding complete clinical cure Secondary: Clinical evaluation of the disease condition	Primary: Overall global assessment showed that clinical cure was achieved in 62.3% of patients receiving sertaconazole and in 44.6% of patients receiving miconazole (P<0.05). Secondary: After one week, 76.3% of patients receiving sertaconazole reported improvement in their pruritus symptoms to be 'better' or 'much better' compared to 49.2% of patients in the miconazole group (P<0.05). After two weeks, clinical cure of pruritus was reported by 45.9% of patients receiving sertaconazole compared to 36.7% of patients receiving miconazole group (P=NS). After one week, 79.5% of patients in the sertaconazole group reported 'better' to 'much better' relief of erythema compared to 45.3% of patients in the miconazole group (P<0.05). After two weeks, 51.6% of patients receiving sertaconazole reported clinical cure of erythema compared to 30.5% of patients receiving miconazole (P<0.05). After one week, 79.5% of patients reported improvement in desquamation and reported it to be 'better' or 'much better' following therapy with sertaconazole compared to 46.9% of patients in the miconazole group. After two weeks, 45.1% of patients receiving sertaconazole reported clinical cure of desquamation compared to 22.7% of patients receiving miconazole (P=NS). After two weeks of therapy, changes in mean scores of erythema/itching, burning/weeping and scaling/pustules were significantly lower with sertaconazole (73.3%) than with miconazole (69.6%; P<0.05). There was a significant improvement in the mean total score at the end of week two by 74.1% in the sertaconazole group compared to 69.3% in the miconazole group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Both treatments were well tolerated. Only 4.5% of patients receiving sertaconazole reported adverse events compared to 8.2% of patients receiving miconazole. The most common adverse events were dry skin, erythema, burning, itching, irritation, and hyperpigmentation.
Ghaninejad et al.[105] (2009) Sertaconazole 2% cream applied BID for 4 weeks vs miconazole 2% cream applied BID for 4 weeks	DB, RCT Patients ≥18 years of age with a clinical diagnosis of cutaneous dermatophytosis	N=100 43 days	Primary: Cure, adverse events Secondary: Not reported	Primary: At day 15 in the ITT population, cure rates were 20.0 and 23.6% in the miconazole and sertaconazole groups, respectively (P=0.66). In the PP population, cure rates were 2.2 and 13.0% in the miconazole and sertaconazole groups, respectively (P<0.01). At day 29 in the ITT population, cure rates were 66.7 and 69.1% in the miconazole and sertaconazole groups, respectively (P=0.80). In the PP population, cure rates were 73.2 and 82.6% in the miconazole and sertaconazole groups, respectively (P=0.36). At day 43 in the ITT population, cure rates were 88.9 and 76.4% in the miconazole and sertaconazole groups, respectively (P=0.09). In the PP population, cure rates were 100.0 and 100.0% in the miconazole and sertaconazole groups, respectively (P=1.0). Adverse events were reported by 22 patients in the sertaconazole group and 15 patients in the miconazole group (P=0.28). Their symptoms did not require cessation of therapy. The most commonly reported adverse event was pruritus. Secondary: Not reported
Chatterjee et al.[106] (2016) Sertaconazole 2% cream once daily versus terbinafine 1% cream once daily	RCT, SB Patients 18 to 65 years of age presenting with localized tinea lesions, without nail or scalp involvement, and without any	N=179 2 weeks	Primary: Clinical cure rate (complete absence of erythema, scaling, and pruritus and the dermatologist's impression of a "cleared" lesion)	Primary: After the first two weeks of topical therapy, the clinical cure rates of sertaconazole (77.27%; 95% CI, 68.52 to 86.03%) and terbinafine (73.63%; 95% CI, 64.57 to 82.68%) did not differ significantly between groups (P=0.606). Partial improvement occurred in 28 patients (14 in each group) after two weeks of treatment. All these 28 patients who needed topical therapy beyond two weeks ultimately achieved complete clinical cure within four weeks. The overall cure rates achieved were thus 82 out of 88 for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	secondary bacterial infection over the lesions		Secondary: Not reported	sertaconazole (93.18%; 95% CI, 88.75 to 97.62%) and 81 out of 91 for terbinafine (89.01%; 95% CI, 82.59 to 95.44%), which was statistically not a significant difference (P=0.914). Secondary: Not reported
Borelli et al.[107] (2010) Sertaconazole 2% cream applied BID for 4 weeks	OL, MC, RCT (subgroup analysis) Patients 18 to 70 years of age with tinea pedis interdigitalis of dermatophyte origin	N=92 4 weeks	Primary: Eradication of the pathogen and reduction in total clinical score of at least two points Secondary: Reduction in sign and symptoms, adverse events	Primary: After four weeks, 89.9% of patients had eradication of the pathogen and 97.8% had reduction in total clinical score of at least two points. Overall, 88.8% of patients achieved both primary end points for successful treatment. Secondary: After four weeks, 63.7% of patients were free of erythema, 33.0% of patients were free of desquamation, and 91.2% of patients were free of itch. Most patients had either absent or mild symptoms by the end of the study. Adverse events were reported by 8.7% of patients during the study and none were considered serious.
Rotta et al.[108] (2013) Amorolfine* vs bifonazole* vs butenafine vs ciclopirox	MA Patients with mycologically determined diagnosis of dermatophytosis, excluding onychomycosis and tinea capitis	N=7,629 (65 trials) 5 to 42 days	Primary: Mycologic cure at the end of treatment, sustained cure rate Secondary: Not reported	Primary: No statistically significant difference was found between any antifungal for the mycologic cure at the end of treatment. There was no statistically significant difference between placebo and the amorolfine (OR, 3.04; 95% CrI, 0.14 to 65.66), bifonazole (OR, 3.77; 95% CrI, 0.60 to 23.67), flutrimazole (OR, 5.70; 95% CrI, 0.86 to 31.11), ketoconazole (OR, 9.40; 95% CrI, 0.89 to 99.46), and oxiconazole (OR, 3.86; 95% CrI, 0.83 to 18.04) for the mycologic cure at the end of treatment outcome. For all comparisons with placebo (except oxiconazole vs placebo), the results were determined with indirect comparisons due to the lack of head-to-head RCTs. For the sustained cure outcome, treatment with butenafine was more effective compared to the azoles clotrimazole (OR, 2.76; 95% CrI, 1.20 to 6.36), oxiconazole (OR, 4.26; 95% CrI, 1.40 to 12.93), and sertaconazole (OR, 3.44; 95% CrI, 1.04 to 11.34), respectively. Treatment with the same azoles clotrimazole (OR, 0.36; 95% CrI, 0.20 to 0.67), oxiconazole (OR,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs clotrimazole vs econazole vs fenticonazole* vs flutrimazole* vs isoconazole* vs ketoconazole vs miconazole vs naftifine vs oxiconazole vs				0.24; 95% CrI, 0.09 to 0.62), and sertaconazole (OR, 0.29; 95% CrI, 0.10 to 0.87) was significantly inferior compared to terbinafine. Treatment with ciclopirox was significantly inferior to treatment with terbinafine (OR, 0.45; 95% CrI, 0.22 to 0.93). Treatment with naftifine was more effective compared to oxiconazole (OR, 3.13; 95% CrI, 1.09 to 8.95). Compared to placebo, treatment with amorolfine (OR, 10.77; 95% CrI, 1.00 to 116.38), ketoconazole (OR, 3.90; 95% CrI, 0.77 to 19.70), and tioconazole (OR, 3.24; 95% CrI, 0.14 to 76.18) had no statistically significant difference for sustained cure outcome. For all comparisons with placebo, the results were determined with indirect comparisons due to the lack of head-to-head RCTs. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sertaconazole vs terbinafine vs tioconazole vs placebo				
Rotta et al.[109] (2012) Amorolfine* vs bifonazole* vs butenafine vs ciclopiroxolamine vs clotrimazole vs	MA, SR Patients with dermatophytosis, including cutaneous candidiasis and that of *T. pedis, T. corporis, T. cruris* and *T. versicolor; p*atients with onychomycosis or *T. capitis* were excluded	N=15,795 (104 trials) 1 to 6 weeks	Primary: Mycologic cure at the end of treatment, sustained cure rate Secondary: Not reported	Primary: Data from 26 RCTs showed that treatment with azoles (bifonazole, clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, sertaconazole, and tioconazole) was more effective in achieving mycological cure at the end of treatment compared to placebo (OR, 10.25; 95% CI, 6.88 to 15.27; I^2=71%). Data from 20 RCTs showed that treatment with allylamines (naftifine and terbinafine) was more effective in achieving mycological cure at the end of treatment compared to placebo (OR, 6.15; 95% CI, 3.47 to 10.91; I^2=75%). Data from 12 PC RCTs showed that treatment with butenafine and ciclopiroxolamine was more effective in achieving mycological cure at the end of treatment compared to placebo (OR, 6.63; 95% CI, 4.12 to 10.67; I^2=67%). Data from 15 RCTs showed that treatment with azoles (bifonazole, clotrimazole, econazole, fenticonazole, miconazole, and oxiconazole) was not statistically different from treatment with allylamines (naftifine and terbinafine) in achieving mycological cure at the end of treatment (OR, 0.78; 95% CI, 0.48 to 1.24; I^2=45%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
econazole vs fenticonazole* vs flutrimazole* vs isoconazole* vs ketoconazole vs miconazole vs naftifine vs oxiconazole vs sertaconazole vs terbinafine				Data from 10 RCTs showed that treatment with azoles (bifonazole, clotrimazole, and fenticonazole) was not statistically different from treatment with antifungals other than allylamines in achieving mycological cure at the end of treatment (OR, 0.64; 95% CI, 0.40 to 1.01; I^2=7%). Data from 13 RCTs showed that treatment with azoles (bifonazole, clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, sertaconazole, and tioconazole) was more effective in achieving sustained cure compared to placebo (OR, 7.25; 95% CI, 5.15 to 10.20; I^2=5%). Data from 25 RCTs showed that treatment with allylamines (naftifine and terbinafine) was more effective in achieving sustained cure compared to placebo (OR, 12.67; 95% CI, 8.99 to 17.84; I^2=42%). Data from 12 PC RCTs showed that treatment with butenafine and ciclopiroxolamine was more effective in achieving sustained cure compared to placebo (OR, 6.63; 95% CI, 4.12 to 10.67; I^2=67%). Data from 15 RCTs showed that treatment with azoles (bifonazole, clotrimazole, econazole, fenticonazole, miconazole, and oxiconazole) was more effective in achieving sustained cure compared to treatment with allylamines (naftifine and terbinafine) (OR, 0.55; 95% CI, 0.33 to 0.89; I^2=60%); however, no statistically significant difference was observed when one study accounting for high heterogenicity was hypothetically removed, decreasing the I^2 to 50%. Data from 10 RCTs showed that treatment with azoles (bifonazole, clotrimazole, and fenticonazole) was not statistically different from treatment with antifungals other than allylamines in achieving sustained cure (OR, 0.79; 95% CI, 0.50 to 1.26; I^2=0%). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs tioconazole vs placebo				
Miscellaneous				
Grigoriu et al.[110] (1983) Econazole 1% cream applied BID vs tioconazole 1% cream applied BID	DB, RCT Patients with confirmed fungal skin infection or erythrasma	N=61 Mean 38 to 40 days	Primary: Clinical response, mycological response, combined clinical and mycological cure Secondary: Adverse effects	Primary: In 28 days or less, 46.7 and 41.7% of patients treated with tioconazole and econazole, respectively, achieved symptomatic improvement. After 14 days of treatment, 23 and 25 patients treated with tioconazole and econazole, respectively, were cured. Combined clinical and mycological cure was achieved in 93.1 and 93.5% of patients treated with tioconazole and econazole, respectively. There was no significant difference in rate of improvement, mycologically or clinically, between the two treatment groups. Overall response rate was 90% observed in both treatment groups. Secondary: Reported adverse event included mild intermittent pruritus, which was identified in a patient treated with econazole.
Concannon et al.[111] (2001) Miconazole 0.25% in zinc oxide-petrolatum base applied to rash at each diaper change and after infant's bath vs	DB, PC, PG, RCT Patients 2 to 13 months of age with acute diaper dermatitis	N=188 7 days	Primary: Number of rash sites, mean total rash score Secondary: Adverse events	Primary: On days five and seven, patients treated with miconazole-zinc oxide-petrolatum had fewer rash sites and lower mean total rash scores than patient receiving zinc oxide-petrolatum alone (P<0.001). By day seven, patients treated with miconazole-zinc oxide-petrolatum had a greater number of mild or no cases of diaper dermatitis compared to the zinc oxide-petrolatum group (94 vs 72%, respectively; P<0.001). For patients with mild diaper dermatitis at baseline, there was a significant difference between treatment groups in mean total rash scores favoring the miconazole-zinc oxide-petrolatum study group (0.78 vs 1.65, respectively; P=0.031) on day seven.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
zinc oxide-petrolatum base applied to rash at each diaper change and after infant's bath				For patients with moderate diaper dermatitis at baseline, there was a significant difference between treatment groups in mean total rash scores favoring the miconazole-zinc oxide-petrolatum study group on days three (P=0.006), five (P<0.001), and seven (P<0.001). For patients with severe diaper dermatitis at baseline, there was no significant difference between treatment groups in mean total rash scores due to the limited study size. For patients with Candida-positive rash cultures, there was a significant difference between treatment groups in mean total rash scores favoring the miconazole-zinc oxide-petrolatum study group on days three, five, and seven (P<0.001). In this patient population, microbiologic response was greater in patients treated with miconazole-zinc oxide-petrolatum (P<0.001). Secondary: No serious adverse events were noted with either treatment group.
Spraker et al.[112] (2006) Miconazole 0.25% in zinc oxide-petrolatum ointment applied to rash at each diaper change and after infant's bath vs zinc oxide-petrolatum ointment applied to rash at each diaper change and	DB, PC, PG, RCT Patients with diaper dermatitis complicated by candidiasis with a severity score of 3 or higher	N=236 7 days	Primary: Clinical cure, microbiologic cure, overall rate of cure, and diaper dermatitis index score Secondary: Adverse events	Primary: On day 14, patients treated with miconazole-zinc oxide-petrolatum had a higher clinical cure compared to patients treated with zinc oxide/petrolatum (38 vs 11%, respectively; P<0.001). On day 14, patients treated with miconazole-zinc oxide-petrolatum had a higher microbiologic cure compared to patients treated with zinc oxide/petrolatum (50 vs 23%, respectively). On day 14, patients treated with miconazole-zinc oxide-petrolatum had a higher overall rate of cure compared to patients treated with zinc oxide/petrolatum (23 vs 20%, respectively; P=0.005). From days three through 14, patients treated with miconazole-zinc oxide-petrolatum had a lower diaper dermatitis severity index score compared to patients treated with zinc oxide-petrolatum (P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
after infant's bath				There was no statistical difference in the percentage of patients with adverse events between the study groups (P=0.585).
Hart et al.[113] (1999) Allylamines vs azoles vs ciclopirox vs tolnaftate vs undecenoic acid vs tea tree oil vs placebo	MA Patients with confirmed superficial fungal infection of the skin and toenails	72 trials	Primary: Relative risk of failure to cure for topical antifungal agents Secondary: Not reported	Primary: According to a MA of 17 trials comparing topical azoles to placebo, the pooled relative risk of failure to cure was 0.54 (95% CI, 0.42 to 0.68). According to a MA of 12 trials comparing allylamines to placebo, the pooled relative risk of failure to cure was 0.30 (95% CI, 0.24 to 0.38). According to a MA of 12 trials comparing azoles to allylamines given QD or BID for greater than or equal to four weeks, the pooled risk for failure to cure was 0.88 (95% CI, 0.78 to 0.99) with study results favoring the allylamines. It is important to note that there was a significance difference in both the clinical efficacy of the azoles and duration of use as well as the relative risk estimates reported by English and foreign language papers. No difference was detected between individual azoles and allylamines. According to a MA of three trials comparing tolnaftate to placebo, the pooled risk for failure to cure was 0.46 (95% CI, 0.17 to 1.22). Data showed that tolnaftate was not as effective as haloprogin or clotrimazole. According to a MA of four trials comparing undecenoic acid to placebo or active control, the pooled risk for failure to cure was 0.28 (95% CI, 0.11 to 0.74). In nail trials, ciclopirox was shown to be significantly more effective than placebo with the pooled risk for failure to cure of 0.14 (95% CI, 0.06 to 0.32) and more effective than clotrimazole though not significantly, with the pooled risk for failure to cure of 0.89 (95% CI, 0.72 to 1.10). One trial showed that both clotrimazole solution and tea tree oil achieved a cure rate of 10% after six months. Secondary: Not reported
Crawford et al.[114] (2007)	MA Patients with fungal	67 trials Duration	Primary: Pooled relative risks of failure to	Primary: Among the PC trials, the pooled relative risks of failure to cure for skin infections were as follows for the topical antifungal agents: allylamines

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Allylamines vs azoles vs ciclopiroxolamine vs griseofulvin* vs haloprogin* vs tea tree oil vs tolnaftate vs undecenoates vs placebo	infections of the skin and toenails	varied	cure for topical antifungal agents Secondary: Not reported	0.33 (95% CI, 0.24 to 0.44), azoles 0.30 (95% CI, 0.20 to 0.45), ciclopiroxolamine 0.27 (95% CI, 0.11 to 0.66), tolnaftate 0.19 (95% CI, 0.08 to 0.44), butenafine 0.33 (95%, CI 0.24 to 0.45), undecenoates 0.29 (95% CI, 0.12 to 0.70). In the MA of 11 trials comparing allylamines and azoles, the pooled relative risks of failure to cure for skin infections was 0.63 (95% CI, 0.42 to 0.94) in favor of allylamines. Secondary: Not reported

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, QAM=every morning, QD=once daily, QHS=at bedtime, QPM=every evening, TID=three times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, CrI=credible interval, DB=double-blind, DLSO=distal and lateral subungual onychomycosis, HIV=human immunodeficiency virus, ITT=intention-to-treat, LSO=lateral subungual onychomycosis, MA=meta-analysis, MC=multicenter, OL=open-label, OPC=oropharyngeal candidiasis, OR=odds ratio, OS=observational study,

PC=placebo-controlled, PG=parallel-group, PP=per protocol, PRO=prospective, RCT=randomized controlled trial, SB=single blinded, SC=single center, SR=systematic review, TCS=total clinical score, TDSS=total dandruff severity score, TOC=test of cure, XO=crossover

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 13. Relative Cost of the Skin and Mucous Membrane Antifungals

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Butenafine	cream	Mentax®	$$$$$	N/A
Butoconazole	vaginal cream	Gynazole-1®	$$$	N/A
Ciclopirox	cream, gel, shampoo, solution, suspension	Ciclodan®*, Loprox®*,	$$$-$$$$$	$
Clotrimazole	cream, solution, troche	N/A	N/A	$
Econazole	cream	N/A	N/A	$
Efinaconazole	solution	Jublia®	$$$$	N/A
Ketoconazole	cream, foam, shampoo	Extina®*	$$-$$$$$	$
Luliconazole	cream	Luzu®*	$$$$$	$$$$$
Miconazole	vaginal suppository	N/A	N/A	$$
Naftifine	cream, gel	Naftin®*	$$$$$	$$$$
Nystatin	cream, ointment, powder	N/A	N/A	$
Oxiconazole	cream	N/A	N/A	$$$$
Sertaconazole	cream	Ertaczo®	$$$$$	N/A
Sulconazole	cream, solution	Exelderm®*	$$$$$	N/A

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Tavaborole	solution	Kerydin®*	$$$$$	$$$$$
Terconazole	vaginal cream, vaginal suppository	N/A	N/A	$$
Combination Products				
Clotrimazole and betamethasone	cream, lotion	N/A	N/A	$
Miconazole, zinc oxide, and white petrolatum	ointment	Vusion®*	$$$$$	$$$$$
Nystatin and triamcinolone	cream, ointment	N/A	N/A	$

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The skin and mucous membrane antifungals are approved for the treatment of candidiasis, dermatitis, onychomycosis, and dermatophyte infections.[1-18] Many of the products are available in a generic formulation.

Clotrimazole troches are approved for the treatment oropharyngeal candidiasis. The Infectious Diseases Society of America guidelines recommend the use of clotrimazole troches or miconazole buccal tablets as initial therapy for patients with mild oropharyngeal candidiasis and oral nystatin as an alternative treatment. Oral fluconazole is recommended for patients with moderate to severe disease.[22]

There are several antifungals available that effectively treat vulvovaginal candidiasis, and no agent or regimen has been shown to be more effective than another. Patients with uncomplicated vulvovaginal candidiasis can be treated with vaginal antifungals for one to three days (short-course therapy). Patients with complicated vulvovaginal candidiasis require a longer duration of therapy with vaginal antifungals (seven to 14 days) or multiple doses of oral fluconazole. Prolonged maintenance therapy with oral fluconazole is recommended for recurrent vulvovaginal candidiasis; however, the use of intermittent vaginal antifungals is also acceptable. Guidelines do not give preference to one vaginal antifungal agent over another for the treatment of vulvovaginal candidiasis.[22-28] Clinical trials have demonstrated similar efficacy among the azole antifungals for the treatment of vulvovaginal candidiasis; however, the azoles have been shown to be more effective than nystatin.[26,40-51]

Ciclopirox and ketoconazole are approved for the treatment of seborrheic dermatitis. The Finnish Medical Society Duodecim guidelines recommend the use of salicylic acid to soften scales. To decrease fungal growth, the scalp should be treated with topical azole antifungals or corticosteroid solution.[29] Treatment with ciclopirox and ketoconazole significantly improved clinical cure rates compared to placebo.[62-69]

Miconazole-zinc oxide-white petrolatum is approved for the treatment of diaper dermatitis.[1,18] It is recommended that the underlying cause of diaper dermatitis be identified and treated. Topical antifungals should be used to treat diaper dermatitis complicated by *Candida albicans*. Injured skin should also be protected with a barrier cream or paste, such as zinc oxide.[115] Studies have demonstrated greater clinical cure rates with miconazole-zinc oxide-white petrolatum than zinc oxide-white petrolatum.[111,112] There were no studies found in the medical literature that directly compared the miconazole-zinc oxide-white petrolatum combination product with the coadministration of miconazole and zinc oxide and white petrolatum as separate formulations.

Ciclopirox 8% solution, efinaconazole, and tavaborole are approved for the treatment of onychomycosis.[1,7,8,16] Oral antifungals are more effective than topical agents for the treatment of onychomycosis. Topical monotherapy is recommended when the matrix area is not involved. Oral monotherapy or the combination of oral and topical therapy is recommended when at least 50% of the distal nail plate is involved, when the nail matrix area is involved, or if mycological criteria are known.[30] Ciclopirox 8% solution, efinaconazole 10% solution, and tavaborole 5% solution have been shown to improve clinical and mycological cure rates compared to placebo in clinical trials.[53-57,60] Data from a meta-analysis demonstrated that mycological cure rates ranged from 46.7 to

85.7%, clinical cure rates ranged from 0 to 56.9%, and clinical response rates ranged from 36.7 to 86.0% when ciclopirox was used in various dosing regimens.[53]

For the treatment of dermatophyte infections, studies have demonstrated similar efficacy among the various topical antifungals.[75,80,84,86,87,89-93,96-97,105,106] Luliconazole, which is approved for the treatment of tinea pedis, tinea cruris, and tinea corporis, demonstrated higher rates of complete clearance of tinea infections compared to placebo, with a similar incidence of adverse events, in two clinical trials.[94,95] A mixed-treatment comparison meta-analysis of randomized controlled trials that included patients with dermatophytosis (excluding onychomycosis and tinea capitis) found no significant difference among the antifungals with respect to mycologic cure at the end of treatment. Butenafine, naftifine, and terbinafine were the most effective therapies for maintaining cured status. Since the efficacy difference was not very large between antifungal classes, the authors recommended cost-effectiveness studies to compare the various treatment strategies.[108] Clotrimazole-betamethasone was found to be more effective than monotherapy with clotrimazole or betamethasone.[82,83] There were no studies found in the medical literature that directly compared the clotrimazole-betamethasone combination product with the coadministration of clotrimazole and betamethasone as separate formulations.

There is insufficient evidence to support that one brand skin and mucous membrane antifungal is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand skin and mucous membrane antifungals within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand skin and mucous membrane antifungal is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Scabicides and Pediculicides
AHFS Class 840412
February 8, 2023

I. Overview

The skin and mucous membrane scabicides and pediculicides are approved to treat pediculosis and scabies.[1-8] Pediculosis is a transmissible infection, which is caused by three different kinds of lice depending on the location: head (*Pediculus humanus capitis*), body (*Pediculus humanus corporis*), and pubic region (*Phthirus pubis*). Pediculosis is often asymptomatic; however, itching may occur due to hypersensitivity to lice saliva.[9] Scabies is also a transmissible skin infection caused by the mite *Sarcoptes scabiei.* Mites burrow into the skin and lay eggs, which when hatched will crawl to the skin's surface and begin to make new burrows. The most common clinical manifestation of scabies is itching, which is due to a hypersensitivity reaction to the mite or mite excrement.[10]

When treating scabies and lice, the goal of therapy is to eradicate the parasite. Crotamiton has scabicidal and antipruritic actions; however, the exact mechanism of action is unknown.[3] Lindane is a central nervous system stimulant, which causes convulsions and death of the arthropod.[1,2] Malathion is an organophosphate agent, which inhibits cholinesterase activity.[4] Permethrin disrupts the sodium channel current, which leads to delayed repolarization and paralysis of the arthropod.[1,2] Spinosad causes neuronal excitation, which leads to paralysis and death.[5] Retreatment with permethrin is required after seven to 10 days to eradicate the infestation. The newest agent in the class, ivermectin, is pediculicidal but not ovicidal, and it is approved as a single application product only.[6]

The skin and mucous membrane scabicides and pediculicides that are included in this review are listed in Table 1. This review encompasses all topical dosage forms and strengths. All of the products are available in a generic formulation. This class was last reviewed in February 2021.

Table 1. Skin and Mucous Membrane Scabicides and Pediculicides Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Crotamiton	cream, lotion*	Eurax®*	crotamiton
Ivermectin	lotion	Sklice®#	none
Lindane	shampoo	N/A	none†
Malathion	lotion	Ovide®*	malathion
Permethrin	cream	N/A	permethrin
Spinosad	suspension	Natroba®*	spinosad

*Generic is available in at least one dosage form or strength.
†Generic lindane requires prior authorization.
#Generic available OTC.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the skin and mucous membrane scabicides and pediculicides are summarized in Table 2.

Table 2. Treatment Guidelines Using the Skin and Mucous Membrane Scabicides and Pediculicides

Clinical Guideline	Recommendation(s)
American Academy of Pediatrics: **Clinical Report - Head Lice (2022)**[11,12]	Treatment • Treatment should be initiated only if there is diagnosis of active head lice infestation. Ideal treatment should be safe, free of toxic chemicals, readily available, simple to apply, effective and inexpensive. • Topical agents that are FDA-approved for head lice treatment should be safe to

Clinical Guideline	Recommendation(s)
	use in pregnant or lactating persons. Topical formulations against head lice have little systemic absorption, and risk of harm to the fetus or breastfeeding child from topical head lice treatment is expected to be minimal. • Permethrin, a pyrethroid, is the most widely used and studied pediculicide in the United States. • Permethrin is approved for use for individuals two months and older and is regarded as the drug of choice for treatment of head lice during pregnancy. • Pyrethrin is often synergized with piperonyl butoxide (RID and generics) to enhance activity. These products are available OTC in shampoo or mousse formulations for people 24 months and older. • Ivermectin was approved in a lotion form (Sklice) by the FDA in 2012 for people six months and older for head lice and was approved for OTC use in late 2020. • The oral formulation of ivermectin (Stromectol) is FDA-approved for treatment of head lice in adult patients, although it does not have this indication in pediatrics. However, it is approved for treatment of other infections in pediatric patients, so it can be used for the treatment of head lice in pediatric patients. • Oral ivermectin is only available by prescription and should only be used if head lice is resistant to all topical FDA-approved treatments. • Malathion has been used for the treatment of head lice in the United States since 1999 for individuals six years and older. It is available only by prescription. • When compared with pyrethrins and permethrin, malathion was the most pediculicidal and ovicidal agent with highest cure rates after one application. • Safety and effectiveness of malathion lotion have not been established in children younger than six years. • Spinosad (Natroba) has a broad spectrum of activity against insects, including many species of lice. Spinosad was approved by the FDA for topical use in people six months and older. It is available by prescription only. It is not recommended for children younger than six months, because it contains benzyl alcohol, and systemic absorption may lead to benzyl alcohol toxicity. • Although available and FDA-approved for pediculosis capitis in adults, lindane is not recommended by the American Academy of Pediatrics (AAP), the Centers for Disease Control and Prevention (CDC), or the *Medical Letter* for use as treatment of head lice because of its neurotoxicity. • All topical pediculicides should be rinsed from the hair over a sink rather than in the shower or bath to limit skin exposure and with warm rather than hot water to minimize skin absorption attributable to vasodilation. Hair should not be shampooed as part of the initial rinse process, and for most products, the hair should not be washed for 24 to 48 hours after rinsing. • Itching or mild burning of the scalp caused by inflammation of the skin in response to topical pharmaceutical agents can persist for many days after head lice are killed and is not a reason for retreatment. Topical corticosteroids or oral antihistamines may be taken to relieve these signs and symptoms if itching or burning is very uncomfortable or persistent. • Permethrin, or pyrethrin–piperonyl butoxide are first-line treatments for head lice. If treatment failure is not attributable to improper use of an OTC pediculicide, then a full course of topical treatment from a different class of medication is recommended (e.g. topical ivermectin lotion, spinosad suspension, malathion lotion). • When head lice are resistant to all topical agents, oral ivermectin may be used in children weighing more than 15 kg.
Centers for Disease	Genital herpes

Clinical Guideline	Recommendation(s)

Control and Prevention: **Sexually Transmitted Diseases Treatment Guidelines (2021)**[13-15]	• Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management.
	• Systemic antiviral drugs can partially control the signs and symptoms of herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy.
	• Systemic antiviral drugs do not eradicate latent virus or affect the risk, frequency, or severity of recurrences after the drug is discontinued.
	• Randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes.
	• Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability.
	• Topical therapy with antiviral drugs provides minimal clinical benefit, and use is discouraged.
	• Newly acquired genital herpes can cause prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even patients with first episode herpes who have mild clinical manifestations initially can develop severe or prolonged symptoms. Therefore, all patients with first episodes of genital herpes should receive antiviral therapy.
	• Recommended regimens for first episodes of genital herpes:
	  ○ acyclovir 400 mg orally three times daily for seven to 10 days
	  ○ famciclovir 250 mg orally three times daily for seven to 10 days
	  ○ valacyclovir 1,000 mg orally twice daily for seven to 10 days.
	• Treatment can be extended if healing is incomplete after 10 days of therapy.
	• Acyclovir 200 mg orally five times daily is also effective but is not recommended because of frequency of dosing.
	• Almost all patients with symptomatic first episode genital herpes simplex virus (HSV)-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection.
	• Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Suppressive therapy may be preferred because of the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners.
	• Long-term safety and efficacy have been documented among patients receiving daily acyclovir, valacyclovir, and famciclovir.
	• Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment.
	• Providers should discuss with patients on an annual basis whether they want to continue suppressive therapy because frequency of genital HSV-2 recurrence diminishes over time for many persons.
	• Discordant heterosexual couples in which a partner has a history of genital HSV-2 infection should be encouraged to consider suppressive antiviral therapy as part of a strategy for preventing transmission, in addition to consistent condom use and avoidance of sexual activity during recurrences. Suppressive antiviral therapy for persons with a history of symptomatic genital herpes also is likely to reduce transmission when used by those who have multiple partners.
	• Recommended regimens for suppressive therapy of genital herpes:
	  ○ acyclovir 400 mg orally twice daily
	  ○ famciclovir 250 mg orally twice daily
	  ○ valacyclovir 500 mg orally once daily
	  ○ valacyclovir 1,000 mg orally once daily.
	• Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens for persons who have frequent recurrences (i.e.,

Clinical Guideline	Recommendation(s)
	≥10 episodes/year). • Acyclovir, famciclovir and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding. Ease of administration and cost also are important to consider when deciding on prolonged treatment. • Because of the decreased risk for recurrences and shedding, suppressive therapy for HSV-1 genital herpes should be reserved for those with frequent recurrences through shared clinical decision-making between the patient and the provider. • Episodic treatment of recurrent herpes is most effective if initiation of therapy within one day of lesion onset or during the prodrome that precedes some outbreaks. Patients should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin. • Recommended regimens for episodic treatment of recurrent HSV-2 genital herpes: o acyclovir 800 mg orally twice daily for five days o acyclovir 800 mg orally three times daily for two days o famciclovir 1,000 mg orally twice daily for one day o famciclovir 500 mg orally once; followed by 250 mg orally twice daily for two days o famciclovir 125 mg orally twice daily for five days o valacyclovir 500 mg orally twice daily for three days o valacyclovir 1,000 mg orally once daily for five days. • Acyclovir 400 mg orally three times daily is also effective but is not recommended because of frequency of dosing. • Intravenous acyclovir should be provided to patients with severe HSV disease or complications that necessitate hospitalization or central nervous system complications. • HSV-2 meningitis is characterized clinically by signs of headache, photophobia, fever, meningismus, and cerebrospinal fluid (CSF) lymphocytic pleocytosis, accompanied by mildly elevated protein and normal glucose. • Optimal therapies for HSV-2 meningitis have not been well studied; however, acyclovir 5 to 10 mg/kg body weight IV every 8 hours until clinical improvement is observed, followed by high-dose oral antiviral therapy (valacyclovir 1 g 3 times/day) to complete a 10- to 14-day course of total therapy, is recommended. • Hepatitis is a rare manifestation of disseminated HSV infection, often reported among pregnant women who acquire HSV during pregnancy. Among pregnant women with fever and unexplained severe hepatitis, disseminated HSV infection should be considered, and empiric IV acyclovir should be initiated pending confirmation. • Consistent and correct condom use has been reported in multiple studies to decrease, but not eliminate, the risk for HSV-2 transmission from men to women. Condoms are less effective for preventing transmission from women to men. • Randomized clinical trials have demonstrated that PrEP with daily oral tenofovir disoproxil fumarate/emtricitabine decreases the risk for HSV-2 acquisition by 30% in heterosexual partnerships. Pericoital intravaginal tenofovir 1% gel also decreases the risk for HSV-2 acquisition among heterosexual women. • The patients who have genital herpes and their sex partners can benefit from evaluation and counseling to help them cope with the infection and prevent sexual and perinatal transmission. • Lesions caused by HSV are common among persons with human

Clinical Guideline	Recommendation(s)
	immunodeficiency virus (HIV) infection and might be severe, painful, and atypical. HSV shedding is increased among persons with HIV infection. • Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV infection among persons with HIV. • Recommended regimens for daily suppressive therapy of genital herpes in patients infected with HIV: o acyclovir 400 to 800 mg orally two to three times daily o famciclovir 500 mg orally twice daily o valacyclovir 500 mg orally twice daily • Recommended regimens for episodic treatment of genital herpes in patients infected with HIV: o acyclovir 400 mg orally three times daily for five to 10 days o famciclovir 500 mg orally twice daily for five to 10 days o valacyclovir 1,000 mg orally twice daily for five to 10 days • If lesions persist or recur in a patient receiving antiviral treatment, acyclovir resistance should be suspected, and a viral culture obtained for phenotypic sensitivity testing. • Foscarnet (40 to 80 mg/kg body weight IV every 8 hours until clinical resolution is attained) is the treatment of choice for acyclovir-resistant genital herpes. Intravenous cidofovir 5 mg/kg body weight once weekly might also be effective. • Imiquimod 5% applied to the lesion for 8 hours 3 times/week until clinical resolution is an alternative that has been reported to be effective. • Acyclovir can be administered orally to pregnant women with first-episode genital herpes or recurrent herpes and should be administered IV to pregnant women with severe HSV. • Suppressive acyclovir treatment starting at 36 weeks' gestation reduces the frequency of cesarean delivery among women who have recurrent genital herpes by diminishing the frequency of recurrences at term. However, such treatment might not protect against transmission to neonates in all cases. • Recommended regimen for suppression of recurrent genital herpes among pregnant women: o acyclovir 400 mg orally three times daily o valacyclovir 500 mg orally twice daily • Treatment recommended starting at 36 weeks' gestation. • Infants exposed to HSV during birth should be followed in consultation with a pediatric infectious disease specialist. • All newborn infants who have neonatal herpes should be promptly evaluated and treated with systemic acyclovir. The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 14 days if disease is limited to the skin and mucous membranes, or for 21 days for disseminated disease and disease involving the CNS. <u>Pediculosis pubis (pubic lice infestation)</u> • Recommended regimens: o Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes. o Piperonyl butoxide and pyrethrins applied to the affected area and washed off after 10 minutes. • Alternative regimens: o Malathion 0.5% lotion applied for eight to 12 hours and washed off. o Ivermectin 250 µg/kg orally and repeated in seven to 14 days. • Pregnant and lactating women should be treated with either permethrin or

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	pyrethrin with piperonyl butoxide. Scabies • The first time a person is infested with *S. scabiei*, sensitization takes weeks to develop. However, pruritus might occur <24 hours after a subsequent reinfestation. • Scabies among adults frequently is sexually acquired, although scabies among children usually is not. • Recommended regimens: o Permethrin 5% cream applied to all areas of the body from the neck down and washed off after eight to 14 hours. o Ivermectin 200 µg/kg orally and repeated in two weeks. • Oral ivermectin has limited ovicidal activity; a second dose is required for eradication. • Alternative regimens: o Lindane 1% lotion (1 oz) or cream (30 g) applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after eight hours. • Lindane is an alternative regimen because it can cause toxicity; it should be used only if the patient cannot tolerate the recommended therapies or if these therapies have failed. • Infants and children aged <10 years should not be treated with lindane. • Topical permethrin and oral and topical ivermectin have similar efficacy for cure of scabies. Choice of treatment might be based on patient preference for topical versus oral therapy, drug interactions with ivermectin, and cost. • Infants and young children should be treated with permethrin; the safety of ivermectin for children weighing <15 kg has not been determined. • Permethrin is the preferred treatment for pregnant women. • Crusted scabies is an aggressive infestation that usually occurs among immunodeficient, debilitated, or malnourished persons, including persons receiving systemic or potent topical glucocorticoids, organ transplant recipients, persons with HIV infection or human T-lymphotropic virus-1 infection, and persons with hematologic malignancies. • Combination treatment for crusted scabies is recommended with a topical scabicide, either 5% topical permethrin cream (full-body application to be repeated daily for 7 days then 2 times/week until cure) or 25% topical benzyl benzoate, and oral ivermectin 200 *u*g/kg body weight on days 1, 2, 8, 9, and 15. Additional ivermectin treatment on days 22 and 29 might be required for severe cases. Bacterial vaginosis • Bacterial vaginosis (BV) is a highly prevalent condition and the most common cause of vaginal discharge worldwide. However, in a nationally representative survey, the majority of women with BV were asymptomatic. • Treatment for BV is recommended for women with symptoms. • Established benefits of therapy among nonpregnant women are to relieve vaginal symptoms and signs of infection and reduce the risk for acquiring *C. trachomatis, N. gonorrhoeae*, *T. vaginalis*, *M. genitalium*, HIV, HPV, and HSV-2. • Recommended regimens for bacterial vaginosis include: o Metronidazole 500 mg orally twice daily for seven days. o Metronidazole 0.75% gel 5 g intravaginally once daily for five days. o Clindamycin 2% cream 5 g intravaginally at bedtime for seven days. • Alternative regimens include: o Tinidazole 2 g orally once daily for two days.

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	○ Tinidazole 1 g orally once daily for five days. ○ Clindamycin 300 mg orally twice daily for seven days. ○ Clindamycin 100 mg ovules intravaginally once at bedtime for three days. ○ Secnidazole 2 g oral granules in a single dose • Clindamycin ovules use an oleaginous base that might weaken latex or rubber products (e.g., condoms and diaphragms). Use of such products within 72 hours after treatment with clindamycin ovules is not recommended. • Oral granules should be sprinkled onto unsweetened applesauce, yogurt, or pudding before ingestion. A glass of water can be taken after administration to aid in swallowing. • Using a different recommended treatment regimen can be considered for women who have a recurrence; however, retreatment with the same recommended regimen is an acceptable approach for treating persistent or recurrent BV after the first occurrence. • BV treatment is recommended for all symptomatic pregnant women because symptomatic BV has been associated with adverse pregnancy outcomes, including premature rupture of membranes, preterm birth, intra-amniotic infection, and postpartum endometritis. <u>Uncomplicated vulvovaginal candidiasis</u> • Uncomplicated vulvovaginal candidiasis is defined as sporadic or infrequent vulvovaginal candidiasis, mild to moderate vulvovaginal candidiasis, candidiasis likely to be *Candida albicans*, or candidiasis in non-immunocompromised women. • Short-course topical formulations (i.e., single dose and regimens of one to three days) effectively treat uncomplicated vulvovaginal candidiasis. • Treatment with azoles results in relief of symptoms and negative cultures in 80 to 90% of patients who complete therapy. • Recommended regimens include: ○ Butoconazole 2% cream 5 g single intravaginal application. ○ Clotrimazole 1% cream 5 g intravaginally daily for seven to 14 days. ○ Clotrimazole 2% cream 5 g intravaginally daily for three days. ○ Miconazole 2% cream 5 g intravaginally daily for seven days. ○ Miconazole 4% cream 5 g intravaginally daily for three days. ○ Miconazole 100 mg vaginal suppository one suppository daily for seven days. ○ Miconazole 200 mg vaginal suppository one suppository for three days. ○ Miconazole 1,200 mg vaginal suppository one suppository for one day. ○ Tioconazole 6.5% ointment 5 g single intravaginal application. ○ Terconazole 0.4% cream 5 g intravaginally daily for seven days. ○ Terconazole 0.8% cream 5 g intravaginally daily for three days. ○ Terconazole 80 mg vaginal suppository one suppository daily for three days. ○ Fluconazole 150 mg oral tablet in single dose. <u>Complicated vulvovaginal candidiasis</u> • Complicated vulvovaginal candidiasis is defined as recurrent vulvovaginal candidiasis, severe vulvovaginal candidiasis, non-albicans candidiasis, or candidiasis in women with diabetes, immunocompromising conditions, underlying immunodeficiency, or immunosuppressive therapy. • Most episodes of recurrent vulvovaginal candidiasis caused by *Candida albicans* respond well to short duration oral or topical azole therapy.

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	• However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., seven to 14 days of topical therapy or a 100, 150, or 200 mg oral dose of fluconazole every third day for a total of three doses (day one, four, and seven) to attempt mycologic remission before initiating a maintenance antifungal regimen. • Recommended maintenance regimen is oral fluconazole (i.e., a 100-mg, 150-mg, or 200-mg dose) weekly for six months. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be considered. Severe vulvovaginal candidiasis • Severe vulvovaginal candidiasis is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy. • Either seven to 14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended. Non-albicans vulvovaginal candidiasis • The optimal treatment of non-albicans vulvovaginal candidiasis remains unknown. However, a longer duration of therapy (seven to 14 days) with a non-fluconazole azole drug (oral or topical) is recommended. • If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for three weeks. Genital warts • Treatment of anogenital warts should be guided by wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and provider experience. • There is no definitive evidence to suggest that any of the available treatments are superior to any other and no single treatment is ideal for all patients or all warts. • Because of uncertainty regarding the effect of treatment on future transmission of human papilloma virus and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution. • Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy. • In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment. • The treatment modality should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe. • Most genital warts respond within three months of therapy. • Recommended regimens for external anogenital warts (patient-applied): o Podofilox 0.5% solution or gel. o Imiquimod 3.75% or 5% cream. o Sinecatechins 15% ointment. • Recommended regimens (provider administered): o Cryotherapy with liquid nitrogen or cryoprobe. o Trichloroacetic acid or bichloracetic acid 80 to 90% solution o Surgical removal • Fewer data are available regarding the efficacy of alternative regimens for treating anogenital warts, which include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir. Shared clinical decision-making between the patient and provider regarding benefits and risks of these regimens should be provided. • Podophyllin resin is no longer a recommended regimen because of the number

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	of safer regimens available, and severe systemic toxicity has been reported when podophyllin resin was applied to large areas of friable tissue and was not washed off within four hours. Cervical warts • For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade squamous intraepithelial lesion must be performed before treatment is initiated. • Management of exophytic cervical warts should include consultation with a specialist. • Recommended regimens: o Cryotherapy with liquid nitrogen. o Surgical removal o Trichloroacetic acid or bichloracetic acid 80 to 90% solution Vaginal warts • Recommended regimens: o Cryotherapy with liquid nitrogen. o Surgical removal o Trichloroacetic acid or bichloracetic acid 80 to 90% solution Urethral meatus warts • Recommended regimens: o Cryotherapy with liquid nitrogen. o Surgical removal Intra-Anal warts • Management of intra-anal warts should include consultation with a colorectal specialist. • Recommended regimens: o Cryotherapy with liquid nitrogen. o Surgical removal. o Trichloroacetic acid or bichloracetic acid 80 to 90% solution.
Centers for Disease Control and Prevention: **Treatment of Head Lice (2019)**[16]	• Treatment for head lice is recommended for persons diagnosed with an active infestation. All household members and other close contacts should be checked; those persons with evidence of an active infestation should be treated. • Some experts believe prophylactic treatment is prudent for persons who share the same bed with actively-infested individuals. All infested persons (household members and close contacts) and their bedmates should be treated at the same time. • For pediculicides that are only weakly ovicidal or not ovicidal, routine retreatment is recommended. For those that are more strongly ovicidal, retreatment is recommended only if live lice are still present several days after treatment. To be most effective, retreatment should occur after all eggs have hatched but before new eggs are produced. o When treating head lice, non-pharmacologic measures can be combined with recommended medicine; however, such measures generally are not required to eliminate a head lice infestation. Over-the-counter medications • Pyrethrin or permethrin-containing products are approved by the FDA for the treatment of head lice and are available over-the-counter. • Pyrethrins only kill live lice, not unhatched eggs (nits). A second treatment is recommended nine to ten days after the first treatment to kill newly hatched lice before they produce new eggs.

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	• Permethrin is a synthetic pyrethroid similar to naturally occurring pyrethrins. Permethrin kills live lice but not unhatched eggs. Permethrin may continue to kill newly hatched lice for several days after treatment. A second treatment often is necessary on day nine to kill newly hatched lice before they produce new eggs. Prescription medications • Benzyl alcohol lotion 5% kills live lice but does not kill unhatched lice eggs. A second treatment is required seven days after the first treatment to kill any newly hatched lice before they can produce new eggs. • Ivermectin is not ovicidal, but appears to prevent nymphs (newly hatched lice) from surviving. It is effective when given as a single application on dry hair without nit combing. Retreatment should not occur before discussions with the health care provider. • Malathion is pediculicidal and partially ovicidal. A second treatment is recommended if live lice still are present seven to nine days after treatment. • Spinosad kills live lice and unhatched eggs and as a result, retreatment is usually not needed and nit combing is not required. Treatment should not be repeated if live (crawling) lice are seen seven days after the first treatment. • For second-line treatment only: Lindane is an organochloride. The American Academy of Pediatrics no longer recommends using this agent for the treatment of lice. Incorrect use of lindane can be neurotoxic; its use should be restricted to patients for whom prior treatments have failed or who cannot tolerate safer medications. Lindane should not be used to treat premature infants, persons with human immunodeficiency virus, a seizure disorder, women who are pregnant or breast-feeding, persons who have very irritated skin or sores where the lindane will be applied, infants, children, the elderly, and persons who weigh less than 110 lbs. Retreatment with lindane should be avoided.
Centers for Disease Control and Prevention: **Treatment of Scabies (2018)**[17]	Suggested general guidelines • Scabicides should be applied to all areas of the body from the neck down to the feet and toes. When treating infants and young children, scabicide lotion or cream also should be applied to their entire head and neck because scabies can affect their face, scalp, and neck, as well as the rest of their body. The lotion or cream should be applied to a clean body and left on for the recommended time before washing it off. Clean clothing should be worn after treatment. Medications • Permethrin is the drug of choice for the treatment of scabies and is approved in persons at least two months of age. Permethrin kills the scabies mite and eggs. Two (or more) applications may be necessary to eliminate all mites, particularly when treating crusted (Norwegian) scabies. • Crotamiton is approved for the treatment of scabies in adults. Crotamiton is not approved for use in children. This agent is frequently associated with treatment failure. • Sulfur ointment is used to treat scabies in both adults and children, including infants under two months of age. Reported side effects are primarily skin irritation. The odor and cosmetic quality may make its use unpleasant. • Lindane is not recommended as a first-line therapy. Overuse, misuse, or accidentally swallowing lindane can be toxic to the brain and other parts of the nervous system. Use should be restricted to patients who have failed recommended therapies or who cannot tolerate recommended treatments. Lindane should not be used to treat premature infants, persons with a seizure disorder, women who are pregnant or breast-feeding, persons who have very irritated skin or sores where the lindane will be applied, infants, children, the elderly, and persons who weigh less than 110 lbs. • Oral ivermectin may be safe and effective for the treatment of scabies; however,

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	ivermectin is not approved for this use. Oral ivermectin has been reported effective in the treatment of crusted scabies; its use should be considered for patients who have failed treatment with or who cannot tolerate topical medications for the treatment of scabies. The dosage of ivermectin is 200 µg/kg orally. Two or more doses at least seven days apart may be necessary to eliminate a scabies infestation. The safety of ivermectin in children weighing less than 15 kg and in pregnant women has not been established.
Centers for Disease Control and Prevention: **Treatment of Pubic Lice (2019)**[18]	Medications • A lice-killing lotion containing 1% permethrin or a mousse containing pyrethrins and piperonyl butoxide can be used to treat pubic lice. These products are available over-the-counter without a prescription and are safe and effective when used exactly according to instructions on the package. • Lindane shampoo is a prescription medication that can kill lice and lice eggs. However, lindane is not recommended as a first-line therapy. Lindane can be toxic to the brain and other parts of the nervous system; its use should be restricted to patients who have failed treatment with recommended therapies. Lindane should not be used to treat premature infants, persons with a seizure disorder, women who are pregnant or breast-feeding, persons who have very irritated skin or sores where the lindane will be applied, infants, children, the elderly, and persons who weigh less than 110 lbs. • Malathion lotion is a prescription medication that can kill lice and some lice eggs but has not been approved by the FDA for this indication. • Both topical and oral ivermectin have been used successfully to treat lice; however, only topical ivermectin lotion currently is approved by the FDA for treatment of lice. Oral ivermectin is not FDA-approved for treatment of lice.
British Association of Sexual Health and Human Immunodeficiency Virus: **United Kingdom National Guideline on the Management of *Phthirus pubis* Infestation (2007)**[19]	General considerations • A number of treatments are available. The recommendation of some agents is based on successful results when treating head lice; there is no evidence to give an efficacy rate for public lice. • Lotions are likely to be more effective than shampoos, and should be applied to all body hair including the beard and moustache if necessary. • A second application after three to seven days is advised. Recommended regimens • Malathion 0.5%: Apply to dry hair and wash out after at least two, and preferably, 12 hours (overnight). • Permethrin 1% cream rinse: Apply to damp hair and wash out after 10 minutes. • Infestation of eyelashes can be treated with permethrin 1% lotion, keeping the eyes closed during the 10 minute application.
British Association of Sexual Health and Human Immunodeficiency Virus: **United Kingdom National Guideline on the Management of Scabies (2016)**[20]	• Four scabicides have been used for the treatment of scabies: permethrin 5% cream, malathion aqueous 0.5% liquid, benzyl benzoate 25% emulsion and oral ivermectin [topical ivermectin is not available in the UK]. • Benzyl benzoate is generally no longer recommended as it is not as effective as Permethrin or Malathion and may cause skin irritation. • Single dose oral ivermectin is less effective than permethrin. • Itching may continue for up to two weeks after successful treatment for scabies, but treatment failure should be suspected if new burrows appear or if the itching persists for longer than two to four weeks after the last application of scabicide. • Treat post-scabetic itch with crotamiton 10% cream (two to three times a day) or, if the scabies mites have definitely been eradicated, with topical hydrocortisone 1%.
Canadian Paediatric Society: **Position statement – Scabies**	Treatment • All household contacts, even those without symptoms, must be treated simultaneously to avoid reinfestation and transmission. The main reason for treatment of household contacts is that scabies symptoms can take several

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(2015, reaffirmed 2018)[21]	weeks to appear, especially in new cases. • Topical lotions are the mainstay of scabies treatment, although oral ivermectin has been used more recently in special circumstances. First-line treatment continues to be 5% permethrin cream or lotion, which is applied to the skin from neck to toes, usually for several hours – often overnight – then washed off. • Retreatment in seven days improves efficacy. The appearance of new lesions should be considered as a sign of persistent infection and a signal to retreat. • A second treatment is usually given one week later to eliminate recently hatched eggs. Benzyl benzoate (28% for adults, and 10% to 12.5% for children) has high efficacy and a lower cost and is widely used outside of North America. • Lindane has been withdrawn from the market in many parts of the world because of neurotoxicity concerns. It is only considered when other therapies have failed. • Sulphur precipitated in petroleum jelly has been used safely in young children and pregnant women, although its odor and messy application can compromise adherence to treatment. • Oral ivermectin has proven effective in managing institutional or community outbreaks, with rapid reduction of scabies symptoms. It has also been used very effectively in managing crusted scabies, especially with recurrent disease, and often in combination with keratolytics (to break down the keratin in the scales) or with topical 5% permethrin.
Canadian Paediatric Society: **Practice point on head lice infestations – A clinical update (2018)[22]**	Treatment • Well-established treatment options for a proven head lice infestation include topical insecticides and oral agents. • First line therapies: pyrethrin and permethrin • Both pyrethrins and permethrin have minimal percutaneous absorption and favorable safety profiles • Malathion and crotamiton lotion are also treatment options. • Lindane is no longer considered acceptable therapy for head lice because of the potential risks for neurotoxicity and bone marrow suppression following percutaneous absorption • The WHO has recategorized lindane as a probable carcinogen. • Topical ivermectin 0.5% is also an available treatment option and has minimal side effects (minor eye irritation and mild skin burning). • Treatment with an approved, properly applied, topical head lice insecticide (two applications 7 to 10 days apart) is recommended when a case of active infestation is detected. • When there is evidence of treatment failure (detection of live lice), using a full course of topical treatment from a different class of medication is recommended. • For children ≥2 months of age, permethrin and pyrethrins are acceptable treatments for confirmed cases of head lice.
European Academy of Dermatology and Venereology: **European guideline for the management of scabies (2017)[23]**	Treatment • Topical treatment should be applied to all skin regions including scalp, groin, navel, external genitalia, finger and toe web spaces and the skin beneath the ends of the nails at night and left in place for 8 to 12 hours. The skin should be cool and dry. A second application is recommended after 7 to 14 days. • After applying treatment, patients should change into clean clothing. All the patient's close personal contacts should be treated simultaneously to avoid re-infestation. • Clothing, bedding, towels and other items should be machine washed (at 50°C or higher), dry-cleaned, or sealed and stored in plastic bag for one week.

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	• The infestation is considered cleared if one week after the end of treatment there are no manifestations of active scabies (no active lesions, no nocturnal pruritus). • Post-treatment itch may persist for up to two to four weeks. • Recommended treatments: permethrin 5% cream applied head to toe and washed off after 8 to 12 hours. The treatment must be repeated after 7 to 14 days. • Oral ivermectin (taken with food) is also a recommended treatment - 200 micrograms/kg as two doses one week apart. • Third recommended treatment: benzyl benzoate lotion 10 to 25% applied once daily at night on two consecutive days with re-application at seven days. • Alternative treatment options include: malathion 0.5% lotion, ivermectin 1% lotion (reported to be as effective as permethrin 5% cream), sulphur 6 to 33% cream/lotion/ointment, and synergized pyrethrins. • Lindane is no longer recommended due to potential to cause neurotoxicity. • For crusted scabies, recommended treatment is a topical scabicide (permethrin 5% cream or benzyl benzoate lotion 25%) repeated daily for seven days then 2x weekly until cure. • For crusted scabies, the topical scabicide should be used in conjunction with oral ivermectin 200 micrograms/kg on days one, two and eight. • A follow-up visit two weeks after completion of treatment is recommended for a test of cure by microscopy examination. • Permethrin is safe in pregnancy lactation and is licensed for use in children from age two months onwards. • Benzyl benzoate and sulphur are considered safe in pregnancy. • Ivermectin should not be used during pregnancy or in children weighing less than 15 kg.
European Academy of Dermatology and Venereology: **European guideline for the management of pediculosis pubis (2017)**[24]	Treatment • Topical treatment is applied to all suspected infected regions: genital and anal areas, thighs, trunk, axillae, moustache and beard areas. • Skin must be cool and dry to minimize percutaneous absorption. • Nits must be removed from hair with comb or tweezers. • Clothing, bedding, towels and other items should be machine washed (at 50°C or higher) or dry-cleaned or sealed and stored in a plastic bag for three days. • Topical medication must be applied as mentioned in the drug package insert leaflet or as indicated on the medication box. Insufficient application of the insecticide or poor compliance is frequent cause for treatment failure. • Resistance to topical and systemic pediculicide treatment has been reported. If the infestation persists, a different class of pediculicide should be applied. • First-line therapies: permethrin cream 1% or pyrethrins with piperonyl butoxide. • Second-line therapies: phenothrin 0.2% lotion, malathion 0.5% lotion, or ivermectin. • Topical ivermectin is an alternative treatment option. • Lindane was withdrawn, should not be applied a second time or used in pregnant/lactating women or children. • Permethrin is safe in pregnancy.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the skin and mucous membrane scabicides and pediculicides are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Skin and Mucous Membrane Scabicides and Pediculicides[1-8]

Indication	Crotamiton	Ivermectin	Lindane	Malathion	Permethrin	Spinosad
Lice						
Treatment of head lice infestation		✔			✔ †	✔
Treatment of patients infected with head lice and their ova of the scalp hair				✔		
Treatment of infestations of head lice, crab lice, and their eggs only in patients who cannot tolerate other approved therapies, or have failed treatment with other approved therapies			✔			
Scabies						
Treatment of infestations of scabies					✔ §	✔
Treatment of infestations of scabies and for symptomatic treatment of pruritic skin	✔					

†Liquid formulation.
§Cream formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the skin and mucous membrane scabicides and pediculicides are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Skin and Mucous Membrane Scabicides and Pediculicides[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life
Crotamiton	Not reported	Not reported	Not reported	Not reported	Not reported
Ivermectin	Not reported	>99	Liver	Renal	6.5 days
Lindane	~10	Not reported	Liver	Renal	17.9 to 21.4 hours
Malathion	8	Not reported	Not reported	Not reported	Not reported
Permethrin	≤2	Not reported	Liver	Renal	Not reported
Spinosad	0	Not reported	Not reported	Not reported	Not reported

V. Drug Interactions

There are no major drug interactions with the scabicides and pediculicides.[1-8] Lindane should be used with caution with any drug that is known to lower the seizure threshold. These include antipsychotics, antidepressants, theophylline, cyclosporine, mycophenolate, tacrolimus, penicillins, imipenem, fluoroquinolones, chloroquine, isoniazid, meperidine, radiographic contrast media, centrally active anticholinesterases and methocarbamol.[1,2]

VI. Adverse Drug Events

The most common adverse drug events reported with the skin and mucous membrane scabicides and pediculicides are listed in Table 5. The boxed warning for lindane is listed in Table 6. Malathion is an organophosphate agent. Inadvertent transdermal absorption has occurred from agricultural use. Acute toxicity was manifested by excessive cholinergic activity (i.e., increased sweating, salivary and gastric secretion, gastrointestinal and uterine motility, and bradycardia).[4]

Table 5. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Scabicides and Pediculicides[1-8]

Adverse Events	Crotamiton	Ivermectin	Lindane	Malathion	Permethrin	Spinosad
Central Nervous System						
Dizziness	-	-	✔	-	-	-
Headache	-	-	✔	-	-	-
Pain	-	-	✔	-	-	≤3
Paresthesia	-	-	✔	-	-	-
Restlessness	-	-	✔	-	-	-
Seizures	-	-	✔	-	-	-
Dermatological						
Allergic sensitivity reaction	✔	-	-	-	-	-
Alopecia	-	-	✔	-	-	<1
Dandruff	-	<1	-	-	-	-
Dermatitis	✔	<1	✔	-	-	-
Dryness	-	<1	✔	-	-	2
Erythema	-	-	-	-	1 to 10	3
Exfoliation	-	-	-	-	-	<1
Irritation	✔	≤1	-	✔	-	≤3
Mild transient burning/stinging	-	≤1		✔	1 to 10	≤3
Numbness	-	-	-	-	1 to 10	-
Pruritus	✔	-	✔	-	1 to 10	-
Rash	✔	-	✔	-	1 to 10	-
Scalp discomfort	-	-	-	-	1 to 10	-
Tingling of skin	-	-	-	-	1 to 10	-
Urticaria	-	-	✔	-	-	-
Warm sensation	✔	-	-	-	-	-
Other						
Aplastic anemia	-	-	✔	-	-	-
Chemical burn	-	-	-	✔	-	-
Conjunctivitis (if eye contact)	-	<1	-	✔	-	-
Edema	-	-	-	-	1 to 10	-
Erythema of eyelid	-	-	-	-	-	2
Ocular edema	-	-	-	-	-	2

Adverse Events	Crotamiton	Ivermectin	Lindane	Malathion	Permethrin	Spinosad
Ocular irritation/hyperemia	-	<1	-	-	-	-

✔ Percent not specified.
- Event not reported.

Table 6. Boxed Warning for Lindane[1,8]

WARNING
Only use lindane in patients who cannot tolerate or have failed first-line treatment with safer medications for the treatment of scabies. **Neurologic toxicity:** Seizures and deaths have been reported following lindane use with repeat or prolonged application, but also in rare cases following a single application used according to directions. Exercise caution when using lindane in infants, children, the elderly, and individuals with other skin conditions (e.g., atopic dermatitis, psoriasis) and in those who weigh less than 110 lbs (50 kg) as they may be at risk of serious neurotoxicity. **Contraindications:** Lindane is contraindicated in premature infants and individuals with known uncontrolled seizure disorders. **Proper use:** Instruct patients on the proper use of lindane, the amount to apply, how long to leave it on, and avoiding retreatment. Inform patients that itching occurs after the successful killing of scabies and is not necessarily an indication for retreatment with lindane.

VII. Dosing and Administration

The usual dosing regimens for the skin and mucous membrane scabicides and pediculicides are listed in Table 7.

Table 7. Usual Dosing Regimens for the Skin and Mucous Membrane Scabicides and Pediculicides[1-8]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Crotamiton	Scabies: Cream, lotion: prior to application, patients should bathe or shower; shake the lotion well before using; thereafter, a thin layer of the cream or lotion should be thoroughly massaged into all skin surfaces from the chin down to the toes including all skin folds and creases; crotamiton is left on the skin and a second application is advisable 24 hours later; the patient should take a cleansing bath 48 hours after the last application to remove any remaining drug; patients can be retreated after seven days if live mites appear or if no clinical improvement is observed	Scabies: Limited data available: Infants, children, and adolescents: Topical: Apply a thin layer onto skin of entire body from neck to toes; apply once daily for 3 days followed by a cleansing bath 48 hours after the last application; treatment may be repeated after 7 days if mites appear; not typically first-line therapy as other agents have shown greater efficacy. Longer duration of treatment (5 days) has also been reported and was well tolerated	Cream: 10% Lotion: 10%
Ivermectin	Head lice: Lotion: apply to dry hair in an amount sufficient (up to one tube) to thoroughly coat the hair and scalp; leave lotion in place for 10 minutes and then rinse off with water	Head lice ≥6 months of age: Lotion: apply to dry hair in an amount sufficient (up to one tube) to thoroughly coat the hair and scalp; leave lotion in place for 10 minutes and then rinse off with water	Lotion: 0.5%
Lindane	Head lice: Shampoo: apply shampoo directly to dry hair without adding water; work thoroughly into the hair and allow it to remain in place for four minutes only; special attention should be given to the fine hairs along the neck; after	Although FDA approved, lindane is not recommended as a treatment option for head lice in pediatric patients <50 kg due to safety concerns and use should be avoided if possible. Alternative agents should be considered.	Shampoo: 1%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	four minutes, add small quantities of water to hair until a good lather forms; immediately rinse all lather away, towel dry hair and comb with a fine tooth comb to remove nits; avoid unnecessary contact of lather with other body surfaces; do not use hot water; do not retreat. Amount of shampoo is based on length and density of hair; most patients will require only one ounce. Do not prescribe more than two ounces for larger adults.	Head lice: Shampoo: apply shampoo directly to dry hair without adding water; work thoroughly into the hair and allow it to remain in place for four minutes only; special attention should be given to the fine hairs along the neck; after four minutes, add small quantities of water to hair until a good lather forms; immediately rinse all lather away, towel dry hair and comb with fine tooth comb to remove nits; avoid unnecessary contact of lather with other body surfaces; do not use hot water; do not retreat. Amount of shampoo is based on length and density of hair; most patients will require only one ounce; maximum dose two ounces.	
Malathion	Head lice: Lotion: apply on dry hair in an amount just sufficient to thoroughly wet the hair and scalp; allow hair to dry naturally, do not use an electric heat source, and allow hair to remain uncovered; after eight to 12 hours, the hair should be shampooed; rinse and use a fine-toothed (nit) comb to remove dead lice and eggs; if lice are still present after seven to nine days, repeat with a second application of lotion	Headlice in children 2 to 5 years: Limited data available: Note: Only use for head lice resistant to permethrin/pyrethrins or previously failed courses: Lotion: Apply sufficient amount to cover and thoroughly moisten dry hair and scalp, leave on for 8 to 12 hours (typically overnight application); may shampoo upon completion; during clinical trials, a maximum dose of ~60 mL (2 fluid ounces) was used Head lice ≥6 years of age: Lotion: apply on dry hair in an amount just sufficient to thoroughly wet the hair and scalp; allow hair to dry naturally, do not use an electric heat source, and allow hair to remain uncovered; after eight to 12 hours, the hair should be shampooed; rinse and use a fine-toothed (nit) comb to remove dead lice and eggs; if lice are still present after seven to nine days, repeat with a second application of lotion	Lotion: 0.5%
Permethrin	Scabies: *Classic scabies:* Thoroughly massage cream (30 g for average adult) from head to soles of feet; leave on for 8 to 14 hours before removing (shower or bath); for elderly patients, also apply	Scabies >2 months of age: Apply and massage in cream from head to toe (average adult requires 30 g); leave on for 8 to 14 hours before washing off with water; for infants, also apply on	Cream: 5%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	on the hairline, neck, scalp, temple, and forehead; may repeat if living mites are observed 14 days after first treatment; one application is generally curative. *Crusted scabies:* Apply to entire body; leave on for 8 to 14 hours before washing off with water. Repeat this regimen daily for 7 days, and then twice weekly until symptoms have resolved. Ivermectin should be given concomitantly on days 1, 2, 8, 9, and 15 (and potentially on days 22 and 29 for severe cases)	the hairline, neck, scalp, temple, and forehead; may reapply in 14 days if live mites appear.	
Spinosad	Head lice: Apply a sufficient amount to adequately cover dry scalp and hair; rinse off with warm water after 10 minutes; if live lice are seen seven days after the first treatment, a second treatment should be applied Scabies: Apply a sufficient amount to skin to completely cover the body from the neck to the toes (including the soles of the feet); allow to absorb into the skin and dry for 10 minutes before getting dressed; leave on the skin for at least 6 hours before showering or bathing. For patients with balding scalp, also apply product to the scalp, hairline, temples, and forehead.	Head lice ≥6 months of age: Apply a sufficient amount to adequately cover dry scalp and hair; rinse off with warm water after 10 minutes; if live lice are seen seven days after the first treatment, a second treatment should be applied Scabies ≥4 years of age: Apply a sufficient amount to skin to completely cover the body from the neck to the toes (including the soles of the feet); allow to absorb into the skin and dry for 10 minutes before getting dressed; leave on the skin for at least 6 hours before showering or bathing	Suspension: 0.9%

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the skin and mucous membrane scabicides and pediculicides are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Skin and Mucous Membrane Scabicides and Pediculicides

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Head, Body, or Pubic Lice				
Barker et al.[25] (2010) Benzyl alcohol 5% lotion applied three times, at weekly intervals, (on day 0, day 7 and day 14) vs pyrethrins and piperonyl butoxide aerosol mousse applied twice (on day 0 and day 7) vs tea tree oil and lavender oil solution applied three times, at weekly intervals, (on day 0, day 7 and day 14) Nit combining was not allowed.	RCT, SB Primary school-aged children four to 12 years of age and their siblings with live head lice in their hair or on their scalp	N=132 8 or 15 days (one day after the last treatment)	Primary: Louse free rate assessed one day after the last treatment Secondary: Louse free rate on day one (one day after the first application)	Primary: In the ITT population, 97.6% of patients receiving tea tree oil and lavender oil solution and 97.6% of patients receiving benzyl alcohol were louse-free one day after the last treatment compared to 25.0% of patients receiving pyrethrins and piperonyl butoxide (both, P<0.0001). In the PP population, 97.6% of patients receiving tea tree oil and lavender oil solution and 100% of patients receiving benzyl alcohol were louse-free one day after the last treatment compared to 33.3% of patients receiving pyrethrins and piperonyl butoxide (both, P<0.0001). Secondary: In the ITT population, 90.3% of patients receiving tea tree oil and lavender oil solution and 69.4% of patients receiving benzyl alcohol were louse-free on day one compared to 43.3% of patients receiving pyrethrins and piperonyl butoxide (P=0.001 and P=0.0329, respectively). The difference in the louse-free rates for tea tree oil and lavender oil solution and benzyl alcohol was not significant (P=0.1009). In the PP population, 90.0% of patients receiving tea tree oil and lavender oil solution and 72.4% of patients receiving benzyl alcohol were louse-free on day one compared to 57.1% of patients receiving pyrethrins and piperonyl butoxide (P=0.0196 and P=0.2986, respectively). The most commonly reported adverse events with tea tree oil and lavender oil solution were stinging, flaky scalp/dry scalp and erythema. The most common adverse event with benzyl alcohol was flaky scalp/dry scalp. In the pyrethrins/piperonyl butoxide group, flaky scalp/dry scalp and erythema were reported.
Meinking et al.[26]	AC, PC, RCT, SB	N=459	Phase II Trials	Phase II Trials

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2010) Phase II Trials Benzyl alcohol 2.5 to 10% lotion applied on day 0 and day 7 (BAL) vs placebo or active control (RID®) Phase III Trials Benzyl alcohol 5% lotion applied on day 0 and day 7 (BAL) vs placebo OL ES Trial Benzyl alcohol 5% lotion applied on day 0 and day 7 (BAL)	(3 Phase II trials) and DB, PC, RCT (2 Phase III trials) and EL, OL (1 trial) Phase II Trials Patients two to 70 years of age with head lice Phase III Trials and EL, OL Trial Children six months of age and older with head lice	(6 trials) Up to 21 days	Primary: Treatment success seven days after final treatment Secondary: Not reported Phase III Trials Primary: Treatment success 14 days after final treatment Secondary: Treatment failure assessed one day after the second treatment ES OL Trial Primary: Treatment success 14 days after final treatment Secondary: Treatment failure assessed one day after the second treatment	Primary: In the Phase IIa study, the BAL 5%, BAL 10% and RID® treatment groups had fewer live lice in comparison with the placebo group (P=0.004). The kill rate (ratio of total lice minus live lice/total lice) was >80% in the patients who received any of the active treatments and <20% in patients who received placebo (P<0.001). No significant differences were observed among the groups at day 15; however, the placebo group was treated with the active treatment at the day eight visit. The efficacy outcome one week later showed 70% overall success with BAL 5%, BAL 10%, and RID®, while the vehicle group demonstrated 53% success after one week treatment. In the Phase IIb study, all patients treated achieved 100% treatment success one week after treatment regardless of treatment duration. In the Phase IIc study, BAL 5% was more effective than BAL 2.5%, although not statistically significant, with treatment success rates of 90.5% and 81%, respectively (P=0.663). Secondary: Not reported Phase III Trials Primary: BAL 5% demonstrated greater treatment success 14 days after treatment in all subgroups compared to placebo (P<0.001). Secondary: In study 1, 3.3% of the BAL 5% ITT group were treatment failures, compared to 83.6% in the placebo group (P<0.001). In study 2, 14.3% of BAL 5% ITT patients were treatment failures, compared to 60.7% of patients treated with vehicle alone (P<0.001). ES OL Trial Primary: An overall 75.0% treatment success was demonstrated with BAL at the end

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				of study (14 days after the second treatment). Secondary: Treatment success measured one day after the second treatment (day eight) showed 92.2% success.
Brandenberg et al.[27] (1986) Lindane 1% shampoo vs permethrin 1% creme rinse	RCT Patients with head lice	N=573 2 weeks	Primary: Efficacy Secondary: Tolerance	Primary: Of the 257 patients treated with 1% permethrin cream rinse, 99% were lice free at 14 days; of the 251 patients treated with 1% lindane shampoo, 85% were lice free at 14 days (P<0.001). Secondary: For both treatments, adverse experiences were infrequent, mild, and usually difficult to distinguish from the symptoms of head lice infestation.
Bowerman et al.[28] (1987) Lindane shampoo vs permethrin 1% creme rinse	RCT Patients with head lice	N=1,040 2 weeks	Primary: Efficacy Secondary: Adverse effects	Primary: One patient in each of the 296 family groups was designated as the index patient. Among index patients 98% treated with permethrin and 76% treated with lindane were louse-free 2 weeks after treatment (P<0.001). Comparable results were found with non-index patients as well. Secondary: Mild dermal reactions occurred in 1.2% of permethrin-treated patients and 2.6% of lindane-treated patients. There were no reports of central nervous system adverse effects or conjunctivitis.
Kalter et al.[29] (1987) Lindane 1% shampoo vs permethrin 1% creme rinse	RCT Men with the diagnosis of pediculosis pubis	N=53 10 days	Primary: Efficacy Secondary: Tolerability	Primary: In the lindane group, 10 (40%) of 25 patients were infested at the final assessment. In the permethrin group, 12 (43%) of 28 patients were infested at the final assessment. The difference was not statistically significant. Secondary: Both treatments were well tolerated.
Roberts et al.[30]	RCT	N=81	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2000) Malathion lotion vs wet combing	Children three to 14 years of age with head lice	2 weeks	Efficacy Secondary: Not reported	The cure rate was 38% for wet combing and 78% for malathion. Children assigned wet combing were 2.8 times more likely than those assigned to malathion to have lice at the end of treatment (P=0.0006). Secondary: Not reported
Chosidow et al.[31] (2010) Malathion 0.5% lotion applied on day 1 and day 8 vs ivermectin 400 µg/kg on day 1 and day 8 Patients who still had a head lice infestation on day 15 received the alternative treatment.	DB, MC, RCT Patients two years of age and older and ≥15 kg with live lice and previously failed treatment despite topical application of a pyrethroid-based or malathion insecticide two to six weeks before enrollment	N=812 Up to 29 days	Primary: Absence of live lice on day 15 Secondary: Absence of live head lice on days two and eight and days 22 and 29 for patients who entered the extension stage; treatment preference	Primary: In the ITT population, 95.2% of patients receiving ivermectin were lice-free on day 15, as compared to 85.0% of those receiving malathion (P<0.001). In the PP population, 97.1% of patients in the ivermectin group were lice-free on day 15, as compared to 89.8% of those in the malathion group (P=0.002). Secondary: On day 15, 39 patients (eight in the ivermectin group and 31 in the malathion group) had persistent infestation and entered the extension phase. At day 29, 100% of patients receiving malathion and 96.8% of patients receiving ivermectin no longer had head lice. A total of 78.3% of the patients preferred tablets, 13.0% preferred lotion, and 8.7% had no preference. A total of 1.8% of patients in the ivermectin group and 1.2% of patients in the malathion group discontinued treatment due to an adverse event.
Meinking et al.[32] (2004) Malathion 0.5% lotion applied for 20 minutes vs permethrin 1% creme rinse	RCT, SB Patients six to 70 years of age with head lice	N=66 15 days	Primary: Efficacy Secondary: Not reported	Primary: On day eight, live lice were found on eight of the 41 malathion patients (19.5%) and nine of the 22 permethrin patients (40.9%; P=0.08). For patients who required re-treatment on day eight, 88% in the malathion group and 33% in the permethrin group were lice-free on day 15 (P=0.05). At the end of the study, 98% of malathion-treated patients were lice-free compared to 55% of permethrin-treated patients (P<0.0001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
applied for 10 minutes				Not reported
Meinking et al.[33] (2007) Malathion 0.5% gel for 30, 60 and 90 minute application period vs malathion 0.5% lotion for an eight to 12 hour application period vs permethrin 1% creme rinse for a 10-minute application period	AC, RCT, SB Patients with head lice	N=172 23 days	Primary: Treatment success Secondary: Retreatment requirements and adverse events	Primary: In the ITT population, the treatment success rates were 98% for the 30-minute malathion gel (P<0.0001), 93% for the 60-minute malathion gel (P=0.001), 86% for the 90-minute malathion gel (P=0.01), 97% for malathion lotion (P=0.0006), and 45% for permethrin. In the PP population, there were no significant differences in treatment success rates between the malathion gel groups and the malathion lotion group. Secondary: The proportions of patients requiring retreatment on day eight was greater for those treated with permethrin than for those treated with malathion gels or malathion lotion. The incidence of adverse events among the treatment groups was not significantly different.
Taplin et al.[34] (1986) Permethrin 1% creme rinse vs lindane 1% shampoo vs placebo	DB, PC, RCT Patients with head lice	N=93 2 weeks	Primary: Efficacy Secondary: Safety	Primary: At 14 days after treatment, 97% of patients treated with permethrin were free of lice compared to 6% of placebo-treated patients (P<0.001) and 43% of the lindane-treated patients. Permethrin was 70% ovicidal compared to 14% for placebo (P<0.001) and 45% for lindane. The differences between lindane and the other groups (permethrin and placebo), were not subject to statistical analysis since lindane-treated patients were not included in the pre-study blinded randomization of treatments. Secondary: No adverse experiences were noted during this study.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Carson et al.[35] (1988) Permethrin 1% creme rinse vs pyrethrins and piperonyl butoxide	RCT Patients four years of age and older with head lice	N=58 2 weeks	Primary: Efficacy (cure rate) Secondary: Tolerability	Primary: Seven days after the initial visit, permethrin was determined to be significantly better than pyrethrins with piperonyl butoxide for eradicating the lice infestation. Of the 27 patients receiving permethrin, 26 were lice free vs 14 of the 31 piperonyl butoxide and pyrethrin-treated patients (P<0.005). At day 14, there was no statistically significant difference (P>0.01) in the treatments (27 of 27 permethrin-treated vs 29 of 31 pyrethrins with piperonyl butoxide-treated patients were lice free). Secondary: Both treatments were well tolerated, and no subject experienced adverse reactions.
DiNapoli et al.[36] (1988) Permethrin 1% creme rinse vs pyrethrins and piperonyl butoxide	RCT Patients with head lice	N=435 2 weeks	Primary: Efficacy Secondary: Adverse effects	Primary: Seven days after the treatment, 98% of the permethrin-treated and 85% of the pyrethrins combined with piperonyl butoxide-treated patients were free of lice. At 14 days, prior to nit removal, 96% of the permethrin-treated and 62% of the pyrethrins combined with piperonyl butoxide-treated patients were still lice free. Secondary: Seventeen (7%) permethrin-treated and 32 (16%) pyrethrins combined with piperonyl butoxide-treated patients were reported to have adverse experiences.
Hipolito et al.[37] (2001) Permethrin 1% creme rinse vs trimethoprim/ sulfamethoxazole vs	MC, RCT Children two to 13 years of age with head lice	N=115 1 month	Primary: Efficacy Secondary: Adverse effects	Primary: At the two-week follow-up visit, successful treatment for groups one, two, and three was 79.5, 83.0, and 95.0%, respectively. At the four-week follow-up, successful treatment was 72.0, 78.0, and 92.5% for groups one, two, and three, respectively. The absolute risk reduction for recurrence comparing group one vs group two was 6%, group two vs group three was 14%, and group one vs group three was 20%. Secondary: No major adverse complications were seen in any treatment group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
permethrin 1% creme rinse 1% plus trimethoprim/ sulfamethoxazole				There were three trimethoprim/sulfamethoxazole-related rashes. Of the 115 patients, eight had minor adverse reactions to the treatment.
Stough et al.[38] (2009) Spinosad 0.9% topical suspension without nit combing vs permethrin 1% topical solution with nit combing vs spinosad 0.9% topical suspension with nit combing	2 AC, MC, PG, RCT, SB Patients six months of age and older with head lice	N=1,038 14 days (up to 21 days for patients who received a second course of treatment)	Primary: Efficacy (cure rate) Secondary: Proportion of patients requiring one or two treatments	Primary: Treatment with spinosad without nit combing resulted in a significantly greater proportion of lice-free patients 14 days after treatment compared to permethrin with nit combining (P<0.001 for both trials). Results were similar when data from all of the patients (primary and nonprimary) were analyzed regardless of how many treatments were received. Both treatments were well tolerated, and no severe adverse events were reported. The most common adverse events were eye and scalp irritation. Overall, spinosad-treated patients had fewer adverse events; however, only application site erythema was significantly more frequent with permethrin-treated patients (P=0.007). Secondary: Overall, the majority of spinosad-treated patients (with or without nit combining) required only one treatment application for complete eradication of lice, whereas the majority of permethrin-treated patients required two treatments. In trial one, 94.2 and 68.1% of spinosad without nit combining- and permethrin with nit combing-treated patients required only one treatment (P value not reported). The corresponding numbers in trial two were 93.1 and 62.4%, respectively (P value not reported). After two treatments, 55.7 and 64.3% of spinosad without nit combing-treated patients were lice-free in both trials, compared to 33.3 and 27.1% of permethrin with nit combing-treated patients (P values not reported).
Pariser et al.[39] (2012) Ivermectin lotion 0.5% vs	2 DB, MC, PC, RCT Patients six months of age and older with head lice who agreed not to use any	N=765 15 days	Primary: Number of index patients who were louse-free by day two and remained louse-free through days eight and 15	Primary: Significantly more patients treated with ivermectin were free of live lice at the first post-application observation on day two and at the subsequent observations through day 15 (P<0.001 for all). The combined ITT analysis showed that significantly more patients in the ivermectin group were lice-free on day two (94.9 vs 31.3%), day eight (85.2 vs 20.8%) and day 15 (73.8 vs 17.6%) compared to the vehicle group (P<0.001 for each day).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vehicle	other louse treatment, comb out nits, or cut or chemically treat hair		(ITT population) Secondary: Number of index patients plus all enrolled household members who were louse-free by day two and remained louse-free through days eight and 15 (extended ITT population) and safety	Secondary: Results were consistent when cure rates in the extended ITT populations were analyzed (95.5 vs 35.3% at day two, 88.6 vs 26.2% at day eight and 78.7 vs 22.2% at day 15; P<0.001 for all comparisons). Pruritus, excoriation and erythema were the most common adverse events, occurring in >1% in the vehicle group and <1% in the ivermectin group. There was one severe adverse event (pain in an extremity with vehicle) and no serious adverse events. All other adverse events were mild to moderate. The frequency and severity of adverse events were similar in the two study groups and across age groups. Ocular irritation was noted in seven patients in the ivermectin group and five in the vehicle-control group on day two.
Nofal et al.[40] (2010) Malathion lotion 0.5% vs oral ivermectin in a single oral dose of 200 µg/kg	AC, RCT Children with head lice who were attending an outpatient clinic	N=80 29 days	Primary: Presence of live lice and any side effects at day eight, 15 and 29 Secondary: Not reported	Primary: At day eight (after a single dose) there was a trend towards a higher cure rate in the malathion group compared to the ivermectin group, however, the difference was not statistically significant (87.5 vs 77.5%; P>0.05). The cure rate increased in both treatment groups after nonresponders were given a second dose (day 15), but the difference remained nonsignificant (95.0 vs 92.5% for malathion and ivermectin, respectively; P>0.05). By day 29, cure rates remained similar between the malathion and ivermectin treatment groups (80 vs 75%, respectively; P>0.05). Secondary: Not reported
Scabies				
Goldust et al.[41] (2014) Crotamiton 10% cream applied twice daily for five	SB, RCT Patients with scabies aged two years and older	N=340 4 weeks	Primary: Efficacy Secondary: Not reported	Primary: At the two week follow-up, the treatment was effective in 110 (64.7%) patients in the ivermectin group and 70 patients (41.2%) in the crotamiton group (P=0.72). The treatment was repeated for the 160 patients (90 male, 70 female; 60 in the ivermectin group and 100 in the crotamiton group) who still had infestation.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
consecutive days for about six hours vs ivermectin 1% applied topically to the affected skin the entire night; the dose was 400 µg/kg, repeated once the following week				At the second follow-up, at four weeks, 30 of the 70 patients in the ivermectin group still had severe itching and skin lesions, compared with 60 of the 100 patients in the crotamiton group. Thus, the overall cure rate was 140 of 170 patients (82.3%) in the ivermectin group and 110 of 170 (64.7%) in the crotamiton group (P=0.043). Secondary: Not reported
Haustein et al.[42] (1989) Lindane 1% and 0.3% vs permethrin 5 and 2.5% vs benzyl benzoate 20 and 10%	OL Patients with scabies	N=194 3 weeks	Primary: Efficacy Secondary: Side effects	Primary: Cure rates were 92% for lindane, 100% for permethrin and 100% for benzyl benzoate. Lindane was less effective than the other treatments (P<0.025). Secondary: Benzyl benzoate had more immediate (22%) and late (42%) adverse effects.
Schultz et al.[43] (1990) Lindane 1% lotion vs permethrin 5% cream	MC, RCT Patients with scabies	N=467 28 days	Primary: Clinical cure Secondary: Pruritus and adverse events	Primary: Complete resolution occurred in 91% of patients treated with permethrin (P=0.18) and in 86% of patients treated with lindane (P=0.30). Secondary: Pruritus was reported in 13.9 and 24.8% of patients treated with permethrin and lindane at the end of the study period, respectively (95% CI, 0.37 to 0.86).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The most frequent adverse effects were new or increased pruritus and mild, transient burning or stinging.
Zargari et al.[44] (2006) Lindane 1% cream vs permethrin 5% cream	DB, RCT Patients older than 5 years of age with scabies	N=99 4 weeks	Primary: Efficacy and pruritus; adverse events Secondary: Not reported	Primary: At the two-week post-treatment follow-up, permethrin was effective in 84.6% of treated patients compared to 48.9% of lindane-treated patients (P<0.05). At the four-week post-treatment follow-up, one patient in the permethrin group who showed no response at the first follow-up and was subsequently treated with lindane still had severe itching. In contrast, all 15 patients not responding to lindane who were then treated with permethrin showed improvement in itching and skin lesions. The better response to permethrin was partially related to its properties in reducing pruritus. Only three patients (two in permethrin group and one in lindane group) experienced irritation after application of the drug, but none had allergic reactions. Secondary: Not reported
Taplin et al.[45] (1986) Lindane 1% lotion vs permethrin 5% cream	RCT Patients with scabies	N=23 1 month	Primary: Efficacy Secondary: Not reported	Primary: Only 13% of patients treated with 1% lindane lotion were free of scabies two weeks after a single treatment and 65% of patients were cured at one month. Forty-eight percent of patients treated with permethrin cream were cured in two weeks and 91% were cured at one month (P<0.025). Secondary: Not reported
Rezaee et al.[46] (2015) Lindane 1% lotion vs	DB, RCT Patients with scabies aged two years and older	N=120 4 weeks	Primary: Efficacy Secondary: Not reported	Primary: At two weeks post-treatment, treatment was effective in 80% of patients in the permethrin group and 46.6% of patients in the lindane group (P=0.002). The 44 patients who had not improved at two weeks were crossed to the other group. At four weeks, two patients in the permethrin group who were subsequently treated with lindane still had severe itching. All 32 patients not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
permethrin 5% cream				responding to lindane who were then treated with permethrin showed improvement in itching and skin lesions. Secondary: Not reported
Amer et al.[47] (1992) Lindane 1% vs permethrin 5% vs crotamiton 10%	RCT Patients with microscopically confirmed detection of mites from at least one body site with no significant impetiginization	N=150 28 days	Primary: Clinical cure Secondary: Adverse effects	Primary: After four weeks of observation, the cure rates for the three treatment arms were as follows: permethrin 98%, crotamiton 88%, and lindane 84%. Secondary: No reported systemic, neurologic or local irritations, or adverse effects to the medications used in the trial.
Chouela et al.[48] (1999) Lindane 1% solution vs ivermectin 150-200 µg/kg	DB, PG, PRO, RCT Patients with scabies	N=53 1 month	Primary: Clinical healing Secondary: Adverse effects	Primary: At day 15, 74% of patients in the group receiving ivermectin showed healing of their scabies (95% CI, 48.8 to 90.8) compared to 54% of patients in the group treated with lindane (95% CI, 32.8 to 74.4). At 29 days, both treatments resulted in equivalent therapeutic efficacy. Ninety-five percent were healed with ivermectin (95% CI, 74.0 to 99.9) and 96% were healed with lindane (95% CI, 78.9 to 99.9%). Secondary: Adverse effects from the treatments were few, mild and transient.
Madan et al.[49] (2001) Lindane 1% lotion vs ivermectin 200 µg/kg	RCT Patients with scabies	N=200 1 month	Primary: Efficacy Secondary: Adverse effects	Primary: After a period of four weeks, 82.60% of the patients in the ivermectin group showed marked improvement; only 44.44% of the patients in the lindane group showed a similar response. Secondary: One severe headache from ivermectin was noted.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Taplin et al.[50] (1990) Permethrin 5% cream vs crotamiton 10% cream	DB, RCT Treatment of scabies in children two months to five years of age	N=47 28 days	Primary: Clinical cure Secondary: Pruritus	Primary: After 14 days, 30% of the children were cured with permethrin 5% cream compared to 13% of children treated with crotamiton (P=0.001). After 28 days, 89% of children treated with permethrin 5% cream compared to 60% of children treated with crotamiton were cured (P=0.002) After 14 days, 47 and 79% of patients in the permethrin group and crotamiton group were experiencing pruritus, respectively. After 28 days, 11 and 24% of patients in the permethrin group and crotamiton group were experiencing pruritus, respectively. In the permethrin group, 27% of patients (≤12 months of age) were not completely cured at 28 days. In the corresponding age group treated with crotamiton, 56% of patients were treatment failures. In children age one to five years the failure rates were 6% for permethrin and 32% for crotamiton. Five patients who were treated with permethrin but were not completely cured were dramatically improved compared to their baseline evaluations. At the end of 28 days they had a 73% reduction in the number of active lesions. In contrast, 10 of the 19 treatment failures in the crotamiton group became clinically worse after therapy, and the remaining nine were only marginally improved.
Rao et al.[51] (2019) Permethrin 5% cream vs crotamiton 10% cream	RCT Patients 13 to 65 years of age with scabies (diagnosis made by scraping the burrows to extract mite, larvae or eggs and to see them under light microscope)	N=160 4 weeks	Primary: Efficacy Secondary: Not reported	Primary: Treatment was effective in 81.3% patients being treated with 5% permethrin and 53.8% in 10% crotamiton group. Comparison of treatment showed superiority of 5% permethrin over 10% crotamiton (P=0.001). Secondary: Not reported
Usha et al.[52] (2000)	RCT	N=85	Primary: Efficacy	Primary: A single dose of ivermectin provided a cure rate of 70%, which increased to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Permethrin 5% cream vs ivermectin 200 µg/kg	Patients with scabies and their family contacts older than five years of age	2 months	Secondary: Not reported	95% with two doses at a two-week interval. A single application of permethrin was effective in 97.8% of patients. One patient responded to two applications at a two-week interval. Permethrin-treated patients recovered earlier. Secondary: Not reported
Goldust et al.[53] (2012) Permethrin cream 5% vs ivermectin in a single oral dose of 200 µg/kg body weight	AC, RCT Patients aged two to 84 years of age with a diagnosis of scabies and family contacts	N=242 4 weeks	Primary: Efficacy (cure rate) Secondary: Not reported	Primary: Two weeks following treatment, a similar proportion of patients treated with permethrin cream or oral ivermectin experienced a cure (92.5 vs 85.9%; P=0.42). Twenty six patients who had not improved were crossed over to the other treatment group. When crossed over, seven patients in the permethrin 5% group who experienced treatment failure continued to have severe itching when treated with ivermectin. In contrast, all 17 patients not responding to ivermectin who were then treated with permethrin showed improvement in itching and skin lesions. Secondary: Not reported
Chhaiya et al.[54] (2012) Permethrin cream 5% vs ivermectin in a single oral dose of 200 µg/kg body weight vs	AC, OL, PG, RCT Patients five to 80 years of age with clinically-diagnosed scabies and presence of typical scabei lesions like papules, nodules or vesicles at classical sites	N=315 4 weeks	Primary: Efficacy (cure rate) Secondary: Complete relief of pruritus	Primary: Significantly fewer patients treated with oral ivermectin compared to ivermectin lotion or permethrin cream were cured at one week (30.0 vs 69.3 and 74.8%, respectively; P<0.05) and two weeks (63 vs 100 and 99%, respectively; P<0.05). There was no statistically significant difference in cure rates between the three treatments by three or four weeks following treatment (P>0.05 for both). Secondary: Patients treated with ivermectin lotion and permethrin cream experienced significantly higher pruritus cure rates compared to oral ivermectin at two (P<0.05) and three weeks (P<0.05). By week four, 95, 99 and 98% of patients treated with oral ivermectin, ivermectin lotion and permethrin cream, respectively, were cured of pruritus (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ivermectin lotion 1%				
Seiler et al.[55] (2021) Spinosad 0.9% suspension vs vehicle	Pooled analysis of two MC, DB, VC, RCT Index subjects (the youngest member in a household [4 years of age or older]) who had an active scabies infestation and up to 5 additional members of their household (regardless of infestation status)	N=120 in each study 28 days	Primary: Percentage of index subjects with complete cure on day 28 Secondary: Efficacy with clinical cure, microscopic cure and lesion counts	Primary: Spinosad at 0.9% is not equivalent to vehicle in the percentage of index subjects achieving complete cure on day 28 (78.1% vs 39.6%, respectively; P<0.0001). Secondary: Spinosad 0.9% showed greater efficacy relative to vehicle based on the percentages of index subjects with clinical cure (79.6% vs 41.2%, respectively; P<0.001). Spinosad 0.9% showed greater efficacy relative to vehicle based on the percentages of index subjects with microscopic cures (85.9% vs 52.6%, respectively; P<0.001). Index subjects in the 0.9% spinosad group relative to the vehicle group were also less likely to develop new lesions (P<0.001); spinosad at 0.9% was favored over vehicle in the mean change from baseline in total lesion counts (P=0.001).

Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, ES=extension study, ITT=intent-to-treat, MC=multicenter, OL=open-label, PC=placebo controlled, PG=parallel-group, PP=per-protocol, PRO=prospective, RCT=randomized controlled trial, SB=single-blind, VC=vehicle controlled

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 9. Relative Cost of the Skin and Mucous Membrane Scabicides and Pediculicides

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Crotamiton	cream, lotion*	Eurax®*	$$$$$	$$$$$
Ivermectin	lotion	Sklice®#	$$$$$	$$$$
Lindane	shampoo	N/A	N/A	$$$$
Malathion	lotion	Ovide®*	$$$$$	$$$$
Permethrin	cream	N/A	N/A	$
Spinosad	suspension	Natroba®*	$$$$$	$$$$$

*Generic is available in at least one dosage form or strength.
#Generic available OTC.
N/A=Not available

X. Conclusions

The skin and mucous membrane scabicides and pediculicides are approved to treat pediculosis and scabies.[1-8] All of the products are available in a generic formulation.

Permethrin products are recommended as first-line therapy for treatment of scabies and lice, despite increasing resistance in the United States.[11,12,16,56] The topical insecticides exert their pediculicidal and scabicidal effects through their neurotoxic actions on lice. Ivermectin and spinosad are two newer agents approved for the treatment

of head lice.[5,6] Spinosad is not extensively metabolized, and therefore it is still present, and able to exert its effect, when the lice eggs hatch and the nervous system develops. This may prevent the need for a second administration if no live lice are observed several days following the initial application.[5] Ivermectin has been approved for one-time use.[6] Lindane is no longer recommended by the American Academy of Pediatrics for use as treatment of pediculosis capitis.[11,12] Lindane is reserved as an alternative therapy by the Centers for Disease Control (CDC): Lindane should not be used to treat premature infants, persons with human immunodeficiency virus, a seizure disorder, women who are pregnant or breast-feeding, persons who have very irritated skin or sores where the lindane will be applied, infants, children, the elderly, and persons who weigh less than 110 pounds.[16] It carries a Boxed Warning describing risk of neurotoxicity associated with its use. Other available agents offer alternative options should a resistant case occur, or if a patient fails first-line product.[11,12,16,56]

Overall, the comparative success rates of topical pediculicides have been shown to be approximately 57 to 99% with permethrin, 45 to 95% with piperonyl butoxide and pyrethrins, 60 to 88% with lindane, and 78% with malathion. The newer agents, which include benzyl alcohol, ivermectin, and spinosad, have shown cure rates of 75%, 71 to 75% and 93 to 94%, respectively, although there is limited published literature confirming these results.[6,38] Permethrin and oral ivermectin are recommended as first-line therapy for the treatment of scabies in the guidelines by the CDC.[17,56] Spinosad was recently FDA-approved in 2021 for the topical treatment of scabies in adults and children four years of age and older. This agent's efficacy and safety has yet to be compared to the other available therapies for the indication of scabies. Crotamiton also has a role as an antipruritic for those with this condition.[16] All patients treated for scabies should expect the rash and itching to continue for approximately two weeks after treatment.[57] The CDC recommends permethrin, piperonyl butoxide and pyrethrins for pediculosis pubis. Malathion and oral ivermectin are recommended as alternative regimens.[18]

Therefore, all brand skin and mucous membrane scabicides and pediculicides within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Lindane possesses an extensive adverse effect profile compared to the other brands and generics in the class (if applicable).

XI. Recommendations

No brand skin and mucous membrane scabicide or pediculicide is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost-effective products and possibly designate one or more preferred brands.

Lindane should not be placed in preferred status regardless of cost.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Local Anti-infectives, Miscellaneous
AHFS Class 840492
February 8, 2023

I. Overview

The skin and mucous membrane miscellaneous local anti-infectives are approved for the treatment of antiseptic cleansing and prevention/treatment of burn wounds.[1-5] Burn patients are predisposed to infections due to a loss of the protective barrier function of the skin, which leads to the entry of microorganisms. *Streptococci* and *Staphylococci* are the main organisms involved in burn wound infections; however, the incidence of *Pseudomonas* and fungal infections are increasing due to the use of broad-spectrum antibiotics.[6,7] Topical antimicrobial therapy remains one of the most important components of wound care in hospitalized burn patients. The goal of prophylactic topical antimicrobial therapy is to control microbial colonization and prevent infections. Mafenide, silver nitrate, and silver sulfadiazine are used for the prevention and treatment of burn wound infections and all three have a broad spectrum of activity. Mafenide is a sulfonamide, which exerts bacteriostatic action by preventing bacterial folic acid synthesis.[3,5] Silver nitrate inhibits the growth of bacteria, which is due to the precipitation of bacterial proteins by liberated silver ions. It also coagulates cellular proteins to form an eschar, which is why it has been used for the destruction of exuberant granulations. Silver sulfadiazine is formed by combining sulfadiazine with silver nitrate, which exhibits both bactericidal and bacteriostatic actions.[1,2]

The skin and mucous membrane miscellaneous local anti-infectives that are included in this review are listed in Table 1. This review encompasses all topical dosage forms and strengths. Products indicated solely for the treatment of acne and/or rosacea are not covered by Alabama Medicaid. Therefore, these products are not included in this review. All products are available in a generic formulation. This class was last reviewed in February 2021.

Table 1. Skin and Mucous Membrane Local Anti-infectives, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Mafenide	cream, packet	Sulfamylon®*	mafenide
Silver nitrate	solution	N/A	silver nitrate
Silver sulfadiazine	cream	Silvadene®*, SSD®*	silver sulfadiazine

*Generic is available in at least one dosage form or strength.
N/A=Not available
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the skin and mucous membrane miscellaneous local anti-infectives are summarized in Table 2.

Table 2. Treatment Guidelines Using the Skin and Mucous Membrane Local Anti-infectives, Miscellaneous

Clinical Guideline	Recommendation(s)
Centers for Disease Control and Prevention: **Guideline for Hand Hygiene in Health-Care Settings (2002)**[8]	• Alcohol-based products are more effective for standard handwashing or hand antisepsis than soap or antimicrobial soaps. • Alcohol-based hand rubs are more effective at reducing bacteria on hands, cause less irritation, require less time, and more accessible compared to soap and water. • No recommendation can be made regarding the routine use of non-alcohol-based hand rubs for hand hygiene in health-care settings. • Studies of hexachlorophene as a hygienic hand wash and surgical scrub demonstrated only modest efficacy after a single hand wash. • Hexachlorophene has residual activity for several hours after use and gradually reduces bacterial counts on hands after multiple uses (i.e., it has a cumulative effect).

Clinical Guideline	Recommendation(s)
	• With repeated use of 3% hexachlorophene preparations, the drug is absorbed through the skin. • Because hexachlorophene is absorbed into the blood after repeated use, it is seldom used as a surgical scrub. • Current guidelines recommend against the routine bathing of neonates with hexachlorophene because of its potential neurotoxic effects. • Hexachlorophene is classified by the Food and Drug Administration Tentative Final Monograph as not generally recognized as safe and effective for use as an antiseptic hand wash. • Hexachlorophene should not be used to bathe patients with burns or extensive areas of susceptible, sensitive skin.

New Zealand Guidelines Group: **Management of Burns and Scalds in Primary Care (2007)[9]**	<u>First aid - initial coverings</u>
	• Following cooling, polyvinyl chloride film may be used as a temporary cover prior to hospital assessment.
	• Topical creams should not be applied as they may interfere with subsequent assessment.
	
	<u>Management of superficial and mid dermal burns or scalds</u>
	• Preventing infection:
	  o Products with antimicrobial action (such as silver sulfadiazine cream) should be used on all burns for the first 72 hours after burn injury. If infection is suspected, longer-term use of silver sulfadiazine may be indicated.
	  o Burn wounds with signs of mild cellulitis can be treated with topical silver sulfadiazine and/or oral antibiotics.
	• Wound healing:
	  o Use dressings that encourage re-epithelialization by moist wound healing.
	  o The prolonged use of silver sulfadiazine cream (more than seven days) may delay healing and should be avoided in non-infected burns.
	  o Following initial silver sulfadiazine cream or antimicrobial dressing, a technique that promotes moist wound healing (such as a hydrocolloid dressing) is recommended.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the skin and mucous membrane miscellaneous local anti-infectives are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Skin and Mucous Membrane Local Anti-infectives, Miscellaneous[1-5]

Indication	Mafenide	Silver Nitrate	Silver Sulfadiazine
Wound Care			
Adjunct for the prevention and treatment of wound sepsis in patients with second- and third-degree burns			✔
Adjunctive therapy of patients with second- and third-degree burns	✔ †		
Adjunctive topical antimicrobial agent to control bacterial infection when used under moist dressing over meshed autografts on excised burn wounds	✔ ‡		
Treatment of indolent wounds, perianal and intergluteal dermatitis, fissures, cutaneous warts and lesions		✔	
Reduction of exuberant granulations		✔	

†Cream formulation.
‡Solution formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the skin and mucous membrane miscellaneous local anti-infectives are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Skin and Mucous Membrane Local Anti-infectives, Miscellaneous[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Mafenide	80	Not reported	Not reported	Renal	Not reported
Silver nitrate	Minimal	Not reported	Not reported	Not reported	Not reported
Silver sulfadiazine	Not reported	Not reported	Not reported	Renal (60)	10

V. Drug Interactions

Due to limited systemic absorption with the skin and mucous membrane miscellaneous local anti-infectives, no major drug interactions have been reported.[1,2]

VI. Adverse Drug Events

The most common adverse drug events reported with the skin and mucous membrane miscellaneous local anti-infectives are listed in Table 5.

Table 5. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Local Anti-infectives, Miscellaneous[1-5]

Adverse Events	Mafenide	Silver Nitrate	Silver Sulfadiazine
Dermatologic			
Burning	✔	-	-
Dermatitis	✔	-	-
Discoloration of skin	-	✔	✔
Dryness	✔	-	-
Edema	✔	-	-
Erythema	✔	✔	-
Erythema multiforme	-	-	✔
Excoriation	✔	-	-
Facial edema	✔	-	-
Hives	✔	-	-
Irritation	✔	✔	-
Maceration	✔	-	-
Photosensitivity	-	-	✔
Pruritus	✔	-	✔
Rash	✔	-	✔
Sensitivity reaction	✔	-	-
Urticaria	✔	-	-
Endocrine and Metabolic			
Hyperchloremia	✔	-	-
Hyponatremia	-	✔	-
Metabolic acidosis	✔	-	-
Hematologic			
Agranulocytosis	-	-	✔
Aplastic anemia	-	-	✔
Bleeding	✔	-	-
Bone marrow suppression	✔	-	-
Eosinophilia	✔	-	-
Hemolytic anemia	✔	-	✔
Leukopenia	-	-	✔
Methemoglobinemia	-	✔	-
Porphyria	✔	-	-

Adverse Events	Mafenide	Silver Nitrate	Silver Sulfadiazine
Respiratory			
Dyspnea	✔	-	-
Hyperventilation	✔	-	-
Tachypnea	✔	-	-
Other			
Allergic reactions	-	-	✔
Hepatitis	-	-	✔
Hypersensitivity	✔	-	-
Interstitial nephritis	-	-	✔

✔ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the skin and mucous membrane miscellaneous local anti-infectives are listed in Table 6.

Table 6. Usual Dosing Regimens for the Skin and Mucous Membrane Local Anti-infectives, Miscellaneous[1-5]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Mafenide	Adjunctive therapy for burn wounds: Cream: apply to the affected area one to two times daily Packet: Wet burn dressing with mafenide solution using an irrigation syringe and/or irrigation tubing until leaking is noticeable. The gauze dressing should be kept wet.	Adjunctive therapy for burn wounds: Cream: apply to the affected area one to two times daily Packet: Wet burn dressing with mafenide solution using an irrigation syringe and/or irrigation tubing until leaking is noticeable. The gauze dressing should be kept wet.	Cream: 8.5% Packet: 50 g
Silver nitrate	Adjunctive therapy for burn wounds: Solution: apply a cotton applicator dipped in solution on the affected area one to three times a week for two to three weeks	Adjunctive therapy for burn wounds: Solution: apply a cotton applicator dipped in solution on the affected area one to three times a week for two to three weeks	Solution: 0.5%
Silver sulfadiazine	Adjunctive therapy for burn wounds: Cream: apply to the affected area one to two times daily	Adjunctive therapy for burn wounds: Cream: apply to the affected area one to two times daily	Cream: 1%

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the skin and mucous membrane miscellaneous local anti-infectives are summarized in Table 7.

Table 7. Comparative Clinical Trials with the Skin and Mucous Membrane Local Anti-infectives, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Burn Wound Care				
Heinle et al.[10] (2001) Mafenide 5% solution administered until autograft vascularization was observed vs historical control treated with similar protocol but without mafenide	RETRO Patients with necrotizing fasciitis admitted to the burn unit after undergoing debridement and grafting	N=74 6 years	Primary: First time successful wound closure, mean debridements, mean wound closure procedures, mortality rate Secondary: Not reported	Primary: The mafenide group exhibited a higher percentage of first-time successful wound closures compared to the control group (P=0.039). There was no significant difference in the mean number of debridements performed in each patient between the mafenide (3.7) and the control groups (5.4). There was no significant difference in the mean number of wound closure procedures performed between the two groups. There was no significant difference in the mortality between the two groups (P=0.158). Secondary: Not reported
Kucan et al.[11] (1993) Mafenide 5% topical solution	PRO Patients with burn wounds requiring topical antibacterial therapy	N=669 7 years	Primary: Burn wound biopsy, infection, sepsis, adverse effects Secondary: Not reported	Primary: Eighteen percent of the patients receiving mafenide 5% topical solution had at least one positive burn wound biopsy. Forty-two patients exhibited systemic signs of sepsis. Use of mafenide 5% topical solution was not associated with acid-base disturbances. Discontinuation of therapy because of the patient's pain was necessary in less than 1% of patients. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
MacMillan et al.[12] (1967) Mafenide acetate 10% applied once daily with replenishment as needed vs silver nitrate 0.5% dressings changed twice daily and saturated every two hours vs gentamicin ointment applied as an occlusive dressing and changed every two to three days vs control group treated with occlusive dressings and no topical drugs Patients also received systemic antibiotic and	OL Patients with second-and third-degree burn wounds requiring topical antibacterial therapy	N=52 Variable duration	Primary: Bacterial flora of the burn wounds and complications Secondary: Not reported	Primary: Of 13 patients treated with mafenide, two died of pneumonia (15%). One patient in this group developed *Pseudomonas* septicemia, but recovered. Of 18 patients treated with silver nitrate, two (11%) died, both of whom developed *Pseudomonas* septicemia. Of 10 patients treated with gentamicin, none died, but two developed septicemia, one due to *Pseudomonas* and one due to *Aerobacter* and *Klebsiella*. In a control group of 11 patients treated with occlusive dressings and no topical drugs, four (36%) died, three from *Pseudomonas aeruginosa* septicemia and one from *Paracolobactrum aerogenoides* septicemia. It was documented that 100% of the patients with no topical drug treatment had wound colonization with *Paracolobactrum aerogenoides*, whereas 25% receiving mafenide, 42% of those receiving silver nitrate, and 75% receiving gentamicin, respectively, demonstrated this species. Mafenide was found to be at least as effective in containing burn wound sepsis as silver nitrate and gentamicin. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
gamma globulin therapy.				
Pegg et al.[13] (1979) Mafenide vs silver sulfadiazine vs control	OL Patients >12 years of age with burn injuries requiring admission	N=645 9 years of follow-up	Primary: Wound infection and complications Secondary: Not reported	Primary: There were 78 patients with clinical wound infections. Patients treated with silver sulfadiazine had significantly fewer positive cultures than the control group (No growth [P<0.001], *Pseudomonas* [P<0.01], Staphylococcus [P<0.01], *Proteus* [P<0.01], *Klebsiella* [P<0.01], *Escherichia coli* [P<0.01], *Candia albicans* [P<0.01]). Patients treated with mafenide has significantly fewer positive cultures than the control group (*Streptococcus* [P<0.01], *Proteus* [P<0.025], *Klebsiella* [P<0.01], *Escherichia coli* [P<0.01], *Candia* albicans [P<0.01]). Silver sulfadiazine was more effective than mafenide in reducing the clinical infection rate of *Pseudomonas* and *Staphylococcus*. Both treatment groups were comparable in reducing *Escherichia coli* and *Candida albicans*; however, pneumonias were increased in the treatment groups. There was no difference in the number of patients requiring grafting between the groups. There was no difference in the average days in the hospital between the groups. Mortality was reduced in the silver sulfadiazine group compared to control (P<0.01). Secondary: Not reported
Livingston et al.[14] (1990) Silver nitrate 0.5%	RCT Patients admitted to the adult burn unit with thermal injury	N=52 Variable follow-up	Primary: Prevention of autogenous skin-graft loss due to infection	Primary: Graft loss of 10% or more occurred in 33% of patients. Graft loss of 10% or more occurred in 12% of patients with small burns (<20% total body surface area).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs neomycin (1 g/L) and bacitracin (50,000 units/L) (NB) vs ringers lactate	who required skin grafting		Secondary: Not reported	Graft loss of 10% or more occurred in 67% of patients with large burns (>40% total body surface area). There was no difference in the incidence of graft loss between the treatments. In patients with 20 to 40% total body surface area burns, the use of either antimicrobial (silver nitrate or neomycin/bacitracin) resulted in a 7% graft loss rate compared to a 67% graft loss rate in the ringers lactate group (P<0.05). The rate of graft loss in the silver nitrate group was significantly lower than in the ringers lactate group (P=0.02). There was no difference in the rate of graft loss between the neomycin/bacitracin and ringers lactate treatment groups (P=0.10) Infection in the area of graft loss was caused by antibiotic-resistant organisms or yeast in 50% of the ringers lactate group and the entire neomycin plus bacitracin group. No graft infections were caused by resistant organisms or yeast in the silver nitrate group. Secondary: Not reported
Khorasani et al.[15] (2009) Silver sulfadiazine 1% cream applied twice daily vs aloe vera cream applied twice daily Each patient had one burn treated with silver sulfadiazine and one burn treated	DB, RCT Patients with second degree burns at two sites on different parts of the body and <40% total burn surface are burns	N=30 21 days	Primary: Time to wound healing and average wound size Secondary: Not reported	Primary; The mean times for healing were 18.73 days for SSD cream and 15.90 days for aloe cream (P<0.0001). The sites treated with aloe healed ~3 days sooner than the sites treated with silver sulfadiazine in all the patients. There was a significant difference in the average wound size among the treatment groups 10, 13, and 16 days after treatment, which favored aloe cream (P<0.01). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
with aloe cream.				
Muangman et al.[16] (2010) Silver sulfadiazine 1% applied daily vs Aquacel® Ag (Hydrofiber® dressing and 1.2% ionic silver) applied every three days	RCT Patients with superficial second-degree burns covering <15% total body surface area	N=70 Up to 21 days	Primary: Time to wound healing Secondary: Pain during dressing changes	Primary: Time-to-wound closure was significantly shorter in the Aquacel® Ag group compared to the silver sulfadiazine group (10.0 vs 13.7 days, respectively; P<0.02). Secondary: The average pain scores in the Aquacel® Ag group were significantly lower than in the silver sulfadiazine group on days one, three and seven (4.1, 2.1, and 0.9 vs 6.1, 5.2, and 3.3, respectively; P<0.02).
Barret et al.[17] (2000) Silver sulfadiazine 1% applied twice daily vs Biobrane® (bilaminar temporary skin substitute) applied twice daily	AC, RCT Patients ≤17 years of age with second-degree noninfected burns admitted within 24 hours of the burn, with total body surface area burned 2 to 29%	N=20 3 days	Primary: Pain relief, length of stay, wound healing time, pain and anxiolytic medication use Secondary: Not reported	Primary: Patients treated with Biobrane® had a significantly shorter length of stay, wound healing time, and decreased requirement of pain medications compared to patients in the silver sulfadiazine group (P<0.05). While patients in the Biobrane® treatment group experienced significant pain relief compared to baseline (P<0.001), patients treated with silver sulfadiazine maintained constant high pain scores during their hospital stay. No differences between groups were noted in terms of anxiolytic medication use, infection rate, or autographing needs. Secondary: Not reported
Glat et al.[18] (2009) Silver sulfadiazine 1% cream applied every two to three days	RCT Patients two months to 18 years of age with superficial or mid-dermal burns covering <40% of	N=24 Up to 21 days	Primary: Time to full reepithelialization, pain during dressing changes, number of dressing changes, and	Primary: No significant difference was found between the treatment groups in the time to re-epithelialization (P=0.949). Pain ratings were significantly less in the SilvaSorb® group compared to the silver sulfadiazine group (2.33 vs 5.33; P<0.0001). More patients in the SilvaSorb group (50%) experienced less pain (in the range one to four)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs SilvaSorb® gel applied every two to three days	total body surface area		patient satisfaction Secondary: Not reported	compared to the silver sulfadiazine group (17%). There was no significant difference in the number of dressing changes among the treatment groups (P=0.449). Patients receiving silver sulfadiazine had lower satisfaction scores compared to patients in the SilvaSorb® group (P=0.004). Secondary: Not reported
Muangman et al.[19] (2009) Silver sulfadiazine 1% applied daily vs Urgotul SSD® (hydrocolloid dressing material impregnated with silver sulfadiazine) applied every 2 days	RCT Patients >17 years of age with partial thickness burns covering <15% total body surface area	N=68 Up to 21 days	Primary: Pain relief and time of wound healing Secondary: Rate of wound infections	Primary: Patients treated with Urgotul SSD® had significantly lower pain scores (P=0.02), follow-up times (P=0.03) and time of burn wound closure (P=0.04) compared to silver sulfadiazine. Patients treated with Urgotul SSD® had decreased requirements for pain medications (P=0.04) compared to patients receiving silver sulfadiazine. Secondary: Two patients developed wound infection; one patient in the Urgotul SSD® group and one patient in the silver sulfadiazine group. There was no growth of organism in either patient.
Gravante et al.[20] (2009) Silver sulfadiazine vs nanocrystalline silver	MA Patients with burn wounds	N=285 (5 trials) Up to 21 days	Primary: Differences in the infection rate of burns Secondary: Differences in pain and length of hospitalizations	Primary: The nanocrystalline silver group had a significantly lower incidence of infections compared to the silver sulfadiazine group (9.5 vs 27.8%; P<0.001). Secondary: When data were available, decreased pain scores were observed with nanocrystalline silver compared to silver sulfadiazine (P<0.0001). There were contrasting results for length of hospitalizations among the studies.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Genuino et al.[21] (2014) Silver sulfadiazine with gauze top dressings vs petrolatum gel without top dressings	PG, RCT Adults 18 to 45 years of age with superficial partial thickness (second degree) burns ≤10% total body surface area seen within 24 hours of the injury	N=38 Time to re-epithelialization	Primary: Time to full re-epithelialization, incidence of wound infection, and incidence of adverse reactions including allergic contact dermatitis Secondary: Dressing adherence, ease of dressing removal, time taken to change dressing, number of dressing changes and reapplications during the day, and pain during dressing changes and removal of dressings	Primary: Mean time to re-epithelialization was shorter in the petrolatum group by more than one day (t-test: CI, -0.01 to 3.26; P=0.050). Shapiro–Wilk tests suggested that healing outcome data were normally distributed in all participants combined and in the silver group, but not in the petrolatum group, in which data were skewed toward shorter healing times. A non-parametric Mann–Whitney U test suggests a statistically significant difference in healing time (P=0.030). None of the participants in either group exhibited clinical signs of wound infection, or other adverse events including allergic contact dermatitis. Secondary: Scores for adherence to the wound dressing, ease of dressing removal, and time required to change dressings were more favorable in the petrolatum treatment arm (P<0.01 for all comparisons). Although patient reported VAS pain scores were generally lower in the petrolatum group, the differences were not statistically significant.
Rashaan et al.[22] (2014) Silver sulfadiazine vs nonsilver treatment	MA (7 RCTs) Pediatric patients 0 to 18 years of age with partial-thickness burns randomized within 48 hours after injury	N=473 Variable	Primary: Time to wound healing, need for grafting Secondary: Infection or colonization, number of dressing changes, pain, length of hospital stay, and scarring	Primary: Use of nonsilver treatment led to shorter wound healing time (weighted mean difference, −3.43 days, 95% CI, −4.78 to −2.07) compared with silver sulfadiazine treatment. No difference was found in the incidence of grafting. Secondary: Use of nonsilver treatment led to less dressing changes (weighted mean difference, −19.89 dressing changes; 95% CI, −38.12 to −1.66) and shorter length of hospital stay (weighted mean difference, −2.07 days; 95% CI, −2.63 to −1.50) compared with silver sulfadiazine treatment. No difference in the incidence of wound infection was found.
Miscellaneous Wound Care				

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dire et al.[23] (1995) Bacitracin zinc, applied to the wound three times a day vs bacitracin, neomycin sulfate, and polymyxin B ointment applied to the wound three times a day vs silver sulfadiazine, applied to the wound three times a day vs petrolatum, applied to the wound three times a day	DB, PC, PRO, RCT Patients with uncomplicated soft tissue wound admitted to the emergency department within 12 hours of injury	N=426	Primary: Wound infection rates Secondary: Not reported	Primary: Wound infection rates were 17.6% for petrolatum, 5.5% for bacitracin (NNT=8), 4.5% for bacitracin, neomycin sulfate, and polymyxin B (NNT=8), and 12.1% for silver sulfadiazine (NNT=18; P=0.0034). Sixty percent of the infections were stitch abscesses and were treated with local care only. There was no difference in rates of more serious infections between groups. One patient developed a hypersensitivity reaction to bacitracin, neomycin sulfate, and polymyxin B. Secondary: Not reported
Skin Cleanser or Surgical Scrub				
Smylie et al.[24] (1973) Period 1: Hexachlorophene 3%	OL Operating team consisting of surgeons, nurses, and assistants	Period 1: 154 operations Period 2: 228 operations	Primary: Reduction of postoperative CFUs Secondary:	Primary: During periods 1, 2, and 3, there was no difference between hexachlorophene and chlorhexidine (P>0.1). There was no difference between the two hexachlorophene treatment periods (P>0.1). Combining the two baseline measurement periods for hexachlorophene

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Period 2: chlorhexidine 4% Period 3: hexachlorophene 3% Period 4: povidone-iodine		Period 3: 262 operations Period 4: 222 operations	Not reported	treatment and comparing that with period 2, chlorhexidine appeared to be a better treatment, although of only marginal significance (P=0.05). The major difference was for period 4 with povidone-iodine treatment, which gave counts above five significantly more often than did the other periods (P<0.001). The members of the team found chlorhexidine to be more acceptable for use than either povidone-iodine or hexachlorophene. Secondary: Not reported
Bodey et al.[25] (1976) Hexachlorophene 3% vs P-300® (tribromsalan and triclosan)	AC, RCT Patients with acute leukemia hospitalized in isolation units	N=26 ≤14 weeks	Primary: Reduction of CFUs Secondary: Not reported	Primary: Bathing with either P-300® or hexachlorophene resulted in a major reduction in the number of CFUs on each body site. After one week of bathing, the median number of CFUs was reduced to 0 to 100 per body site in the P-300® group and to 0 to 50 in the hexachlorophene treatment group. Secondary: Not reported

Study design abbreviations: AC=active-control, DB=double-blind, MA=meta-analysis, NNT=number needed to treat, OL=open-label, PC=placebo-controlled, PG=parallel group, PRO=prospective, RCT=randomized trial, RETRO=retrospective, VAS=visual analog scale
Miscellaneous abbreviations: CFUs=colony-forming units

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 8. Relative Cost of the Skin and Mucous Membrane Local Anti-infectives, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Mafenide	cream, packet	Sulfamylon®*	$$$$	$$$$
Silver nitrate	solution	N/A	N/A	$$$
Silver sulfadiazine	cream	Silvadene®*, SSD®*	$$	$

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The skin and mucous membrane miscellaneous local anti-infectives are approved for the treatment of antiseptic cleansing and prevention/treatment of burn wounds.[1-5] All products are available in a generic formulation.

Topical antimicrobial therapy remains one of the most important components of wound care in hospitalized burn patients. Mafenide, silver nitrate, and silver sulfadiazine are effective for the prevention and treatment of burn wounds. Silver sulfadiazine is the most frequently used agent because of its low toxicity and ease of use. Mafenide rapidly penetrates burn eschar; however, the application must be limited because of systemic toxicity associated with prolonged use.[26] Mafenide is a strong carbonic anhydrase inhibitor, which can lead to acid-base abnormalities. Pain or burning following mafenide application is the most frequently reported adverse event. Silver nitrate does not penetrate the eschar due to precipitation upon contact with exudates. Therefore, it is only

used for prevention of infection and is not effective in treating wound infections. Silver nitrate may be an effective treatment option for patients with an allergy to sulfonamides. There are very few studies that directly compared the efficacy and safety of the miscellaneous local anti-infectives for the prevention/treatment of burn wounds.[10-25] MacMillan et al. reported similar efficacy with mafenide and silver nitrate in patients with second-and third-degree burn wounds who required topical antibacterial therapy.[12] Pegg et al. demonstrated similar efficacy with mafenide and silver sulfadiazine in patients with burn injuries requiring admission.[13]

There is insufficient evidence to support that one brand skin and mucous membrane miscellaneous local anti-infective is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand skin and mucous membrane miscellaneous local anti-infectives within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand skin and mucous membrane miscellaneous local anti-infective is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Corticosteroids
AHFS Class 840608
February 8, 2023

I. Overview

The skin and mucous membrane corticosteroids are approved for the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.[1-3] While systemic corticosteroids are more effective for dermatologic inflammatory conditions, they are generally reserved for more widespread and advanced conditions. Topical treatment is preferred in most cases with limited or localized involvement to help minimize systemic adverse events.[4]

The mechanism of action of corticosteroids is complex and is thought to include binding to intracellular corticosteroid receptors and regulation of gene transcription; in particular those which code for proinflammatory cytokines.[4] These agents have the potential to elicit a wide variety of biologic responses. Corticosteroids reduce inflammation, possess antimitotic activity, and induce cutaneous vasoconstriction.[4,5]

The topical corticosteroids are classified based on their relative potency: super high potency (Class I), high potency (Classes II to III), medium potency (Classes IV to V), and low potency (Classes VI to VII).[5] The super high potency agents are used to treat severe dermatoses over non-facial and non-intertriginous areas.[5] Medium to high potency agents are often used for the treatment of mild to moderate non-facial and non-intertriginous dermatoses. Low to medium potency agents are used when large areas need to be treated due to the potential for systemic absorption. Only low potency agents should be used on the eyelids and genital areas.[5]

The efficacy and safety of topical corticosteroids depends on a variety of factors, including potency, type and location of lesions being treated, vehicle used, application method, and patient factors (e.g., age). The topical corticosteroids are available in a variety of vehicles, including cream, foam, gel, lotion, ointment, paste, shampoo, solution, spray, and tape.[5] Ointments are semiocclusive and are considered the most potent vehicle; however, they are greasy and difficult to use on hairy areas. Creams are less potent than ointments, but are stronger than lotions. They can be easily washed off with water and are the most cosmetically appealing vehicle for applying topical medications. Lotions are considered the least potent of all of the vehicles, but are easier to apply to large or hairy areas. Solutions are often used as bath soaks and for wet dressings. Gels are greaseless and dry as a thin film after application. Foams spread easily and are often easier to apply than other vehicles, especially to hairy areas. Unlike other vehicles, foams require a special delivery system due to the pressurized nature of the product.[5]

The skin and mucous membrane corticosteroids are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. The relative potency ratings of the topical corticosteroids are listed in Table 2. There is at least one topical corticosteroid available in a generic formulation in each potency category. Hydrocortisone is also available over-the-counter. This class was last reviewed in February 2021.

Table 1. Skin and Mucous Membrane Corticosteroids Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Alclometasone	cream, ointment	N/A	alclometasone
Amcinonide	cream	N/A	amcinonide
Betamethasone dipropionate	cream*, gel*, lotion*, ointment*	N/A	betamethasone dipropionate
Betamethasone valerate	cream, foam, lotion, ointment	Luxiq®*	betamethasone valerate
Clobetasol	cream, foam, gel, lotion, ointment, shampoo, solution, spray	Clodan®*, Impeklo®, Olux®*, Olux-E®*, Temovate®*, Tovet®*	clobetasol
Clocortolone	cream	Cloderm®*	clocortolone
Desonide	cream, lotion, ointment	N/A	desonide

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Desoximetasone	cream, gel, ointment, spray	Topicort®*	desoximetasone
Diflorasone	cream, ointment	N/A	diflorasone
Fluocinolone	cream, oil, ointment, solution	Derma-Smoothe/FS®*, Synalar®*	fluocinolone, Capex Shampoo®
Fluocinonide	cream, gel, ointment, solution	Vanos®*	fluocinonide
Flurandrenolide	cream*, lotion*, ointment*	N/A	flurandrenolide
Fluticasone	cream, lotion, ointment	Beser®*	fluticasone
Halcinonide	cream*, ointment, solution	Halog®*	halcinonide
Halobetasol	cream*, foam*, lotion, ointment*	Bryhali®, Lexette®*, Ultravate®	halobetasol
Hydrocortisone	cream, lotion, ointment, rectal cream, rectal enema, solution	Anusol-HC®*, Cortenema®*, Texacort®	hydrocortisone
Hydrocortisone acetate	rectal foam	Cortifoam®	none
Hydrocortisone butyrate	cream, lotion, ointment, solution	Locoid®*, Locoid Lipocream®*	hydrocortisone butyrate
Hydrocortisone probutate	cream	Pandel®	none
Hydrocortisone valerate	cream, ointment	N/A	hydrocortisone valerate
Mometasone	cream, ointment, solution	N/A	mometasone
Prednicarbate	cream, ointment	N/A	prednicarbate
Triamcinolone	aerosol, cream, dental paste, lotion, ointment	Kenalog®*, Oralone®*	triamcinolone
Combination Products			
Betamethasone dipropionate and propylene glycol	cream, lotion, ointment	Diprolene®*	betamethasone dipropionate and propylene glycol
Hydrocortisone acetate and pramoxine	rectal foam	ProctoFoam-HC®	none

*Generic is available in at least one dosage form or strength.
N/A=Not available
PDL=Preferred Drug List

Table 2. Relative Potency Ratings of the Skin and Mucous Membrane Corticosteroids[5]

Group	Generic Name(s)	Strength	Formulations
I	betamethasone dipropionate	0.05%	ointment
I	clobetasol	0.05%	cream, foam, gel, lotion, ointment, shampoo, solution, spray
I	desoximetasone	0.25%	spray
I	fluocinonide	0.1%	cream
I	flurandrenolide	4 µg/cm^2	tape
I	halobetasol	0.05%	cream, lotion, ointment
II	betamethasone dipropionate	0.05%	cream, gel
II	desoximetasone	0.25%	cream, ointment, spray
II	diflorasone	0.05%	ointment
II	fluocinonide	0.05%	cream, gel, ointment, solution
II	halcinonide	0.1%	cream, ointment, solution
III	amcinonide	0.1%	cream, lotion
III	betamethasone valerate	0.1%	ointment
III	diflorasone diacetate	0.05%	cream
III	fluticasone	0.005%	ointment
III	mometasone	0.1%	ointment
III	triamcinolone	0.5%	cream, ointment
IV	betamethasone valerate	0.12%	foam
IV	clocortolone	0.1%	cream
IV	desoximetasone	0.05%	cream, ointment, gel
IV	fluocinolone	0.025%	ointment
IV	fluocinolone	0.2%	cream
IV	flurandrenolide	0.05%	ointment
IV	hydrocortisone valerate	0.2%	ointment
IV	mometasone	0.1%	cream, solution
IV	triamcinolone	0.1%	ointment
V	betamethasone dipropionate	0.05%	lotion
V	betamethasone valerate	0.1%	cream, lotion
V	desonide	0.05%	lotion
V	fluocinolone	0.01%	shampoo
V	fluocinolone	0.025%	cream
V	fluocinolone	0.03%	cream
V	flurandrenolide	0.05%	cream, lotion
V	fluticasone	0.05%	cream, lotion
V	hydrocortisone butyrate	0.1%	cream, ointment, solution
V	hydrocortisone valerate	0.2%	cream
V	hydrocortisone probutate	0.1%	cream
V	prednicarbate	0.1%	cream, ointment
V	triamcinolone	0.1%	cream, lotion
VI	alclometasone	0.05%	cream, ointment
VI	betamethasone valerate	0.05%	cream, ointment
VI	desonide	0.05%	cream, foam, lotion, ointment
VI	fluocinolone	0.01%	cream, oil, solution
VII	Hydrocortisone (base)	0.5%	cream, ointment
VII	Hydrocortisone (base)	1%	cream, lotion, ointment, spray
VII	hydrocortisone (base)	2.5%	cream, lotion, ointment, solution

Group	Generic Name(s)	Strength	Formulations
VII	Hydrocortisone acetate with pramoxine 1% combination	1%	cream, foam, lotion, ointment

I=Highest Potency; VII=Lowest Potency

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the skin and mucous membrane corticosteroids are summarized in Table 3.

Table 3. Treatment Guidelines Using the Skin and Mucous Membrane Corticosteroids

Clinical Guideline	Recommendation(s)
Scottish Intercollegiate Guidelines Network: **Management of Atopic Eczema in Primary Care (2011)**[6]	Emollient therapy • Patients with atopic eczema should receive ongoing treatment with emollients. Topical corticosteroid therapy • Patients should continue with emollient therapy during treatment with topical corticosteroids. • Patients with atopic eczema should be advised to apply topical corticosteroids once daily. • Twice weekly maintenance therapy with a topical corticosteroid should be considered in patients with moderate to severe atopic eczema experiencing frequent relapses. • There is no good quality evidence to assist in the choice of topical corticosteroid potency in the treatment of atopic eczema. • The choice of topical corticosteroid potency should be tailored to the age of the patient, the body region being treated, and the degree to which the skin is inflamed. For delicate areas of skin, such as the face and flexures, only mild or moderately potent preparations should be used. On the face, especially in children, it is reasonable to start with a mildly potent topical corticosteroid. • Topical corticosteroids should be used with caution in the periocular region. Topical calcineurin inhibitors • Tacrolimus should be considered for short-term, intermittent treatment of moderate to severe atopic eczema that has not been controlled by topical corticosteroids, or if there is a serious risk of important adverse effects from further topical corticosteroid use (e.g., skin atrophy). • Topical calcineurin inhibitors should not be applied to skin which appears actively infected. • Due to long-term safety issues, topical calcineurin inhibitors should not be used as first-line treatment unless there is a specific reason to avoid or reduce the use of topical corticosteroids. Antihistamines • Short-term bedtime use of sedating antihistamines should be considered in patients with atopic eczema when there is sleep disturbance.
Primary Care Dermatology Society: **Clinical Guidance for Eczema: Atopic Eczema (2019)**[7] Reaffirmed June	Emollients • Emollients are the mainstay of therapy and without them it is not possible to manage eczema effectively. • Good evidence shows that the more emollients are used, the less topical steroids are needed. • Compliance is essential and so always review patients to check they are happy with what has been prescribed - it may be necessary to try a range of emollients before the patient settles on the best combination.

Clinical Guideline	Recommendation(s)

2022	Topical Steroids
	• Use the lowest appropriate potency and only apply thinly to inflamed skin.
	• Allow moisturizers to dry into skin for 20 minutes before applying the steroid.
	• Avoid using combined steroid-antibiotic preparations on a regular basis as it will increase the risk of antibiotic resistance.
	• Amount of steroid needed can be determined by the Finger Tip Unit method.
	• Strength of steroid to be determined by the age of patient, site and severity:
	  ○ Child face: mild potency (e.g., 1% hydrocortisone).
	  ○ Child trunk and limbs: moderate potency (e.g., clobetasone butyrate 0.05% or betamethasone valerate 0.025%).
	  ○ Adult face: mild or moderate potency (e.g., clobetasone butyrate 0.05%)
	  ○ Adult trunk and limbs: potent (e.g., betamethasone valerate 0.1%, mometasone).
	  ○ Palms and soles: potent or very potent (e.g., clobetasol propionate 0.05%)
	• If used appropriately it is uncommon to develop steroid atrophy, however extra care needs to be taken in the following sites:
	  ○ Around the eyes: unless used very infrequently topical steroid preparations should be avoided due to the risks of glaucoma.
	  ○ The face - the regular use of topical steroids should be avoided.
	  ○ Lower legs in older patients / others at risk of leg ulcers - the regular use of topical steroids should be avoided.
	
	Immunomodulatory treatments
	• Immunomodulatory agents (e.g., tacrolimus or pimecrolimus) are calcineurin inhibitors.
	• Their main benefit is that they are not steroid based and so do not cause skin atrophy.
	• Formulations include tacrolimus 0.03% ointment and pimecrolimus approved for ages two years and above and tacrolimus 0.1% ointment is approved for 16 years of age and above.
	• Local adverse effects include stinging, burning, itch, irritation and slight photosensitivity - appropriate sun protection is recommended. Adverse effects are more common with tacrolimus but in many patients are transient. Immunomodulators should be temporarily discontinued when the skin is infected.
	• When to consider immunomodulators:
	  ○ Eczema involving the eyelids and peri-orbital skin.
	  ○ Patients regularly using topical steroids on the face.
	  ○ Patients regularly using topical steroids on the lower legs in elderly patients and others at risk of leg ulcers.
	  ○ Any signs of skin atrophy.
	• In milder cases use pimecrolimus cream, although if this is ineffective or in the first instance the eczema is of a greater severity consider tacrolimus ointment.
	• While short-term data has showed no serious adverse effects, the possible long-term adverse effects of immunomodulators are not yet known - however the risks are likely to be minimal especially when the treatments are used in the ways described above.
	
	Other treatments
	• There is almost no role for non-sedating antihistamines in the management of eczema; the only exception is patients needing treatment for co-existent hay fever.
	• For the management of scalp eczema, wash with a mild tar-based shampoo. In young children (e.g., 18 months and under) it is often better to use an emollient bath oil to wash the hair rather than using a specific scalp treatment.

European Academy of Dermatology	• Emollients should be prescribed in adequate amounts, and these should be used liberally and frequently, in a minimum amount of 250 g per week for adults.

Clinical Guideline	Recommendation(s)
and Venereology: **Consensus-based European Guidelines for Treatment of Atopic Eczema (Atopic Dermatitis) in Adults and Children (2018)[8]**	• Emollient bath oils and soap substitutes should also be used. Emollients with a higher lipid content are preferable in winter time. • A regular use of emollient has a short- and long-term steroid sparing effect in mild-to-moderate atopic eczema. An induction of remission with topical corticosteroids or topical calcineurin inhibitors is required first. • Topical corticosteroids are important anti-inflammatory drugs to be used in atopic eczema, especially in the acute phase. • Topical corticosteroids with an improved risk/benefit ratio are recommended in atopic eczema. • Diluted topical corticosteroids may be used under wet wraps for short-term periods in acute atopic eczema to increase their efficacy. • Proactive therapy, e.g., twice-weekly application in the long-term follow-up, may help to reduce relapses. • Proactive therapy with topical corticosteroids may be used safely for at least 20 weeks, which is the longest duration of trials. • Patient fear of side-effects of corticosteroids should be recognized and adequately addressed to improve adherence and avoid undertreatment. • Topical calcineurin inhibitors are important anti-inflammatory drugs to be used in atopic eczema. Instead of treating acute flares with topical calcineurin inhibitors, initial treatment with topical corticosteroids before switching to topical calcineurin inhibitors should be considered. • Topical calcineurin inhibitors are especially indicated in sensitive skin areas (face, intertriginous sites, anogenital area). • Proactive therapy with twice-weekly application of tacrolimus ointment may reduce relapses. • Effective sun protection should be recommended inpatients treated with topical calcineurin inhibitors. • Topical corticosteroids are recommended to control pruritus in the initial phase of atopic eczema exacerbation. • Topical calcineurin inhibitors are recommended to control pruritus in atopic eczema until clearance of eczema. • Topical polidocanol may be used to reduce pruritus in atopic eczema patients. • Routine clinical use of topical antihistamines including doxepin, topical cannabinoid receptor agonists, topical μ-opioid receptor antagonists or topical anaesthetics cannot be recommended as an adjuvant antipruritic therapy in atopic eczema. • There is not enough data available to recommend the use of capsaicin in management of itch in atopic eczema patients. • If emollients and anti-inflammatory topical preparations must be applied to the same location, the cream formulation should be applied first and only 15 minutes later the ointment formulation. • For routine treatment of flares once daily application of a potent topical corticosteroid is sufficient, usually for three to six days. • With mild disease activity, a small amount of topical corticosteroids two to three times weekly, associated with a liberal use of emollients, generally allows a good maintenance with SCORAD values below 15 to 20 (indicating mild disease). • The most constructive way to spare topical corticosteroids and avoid steroid-related side-effects is not to spare them during acute flares, but through consequent baseline emollient skin care combined with early anti-inflammatory intervention in order to stabilize the disease, and prevent treatment-intensive flares. • The two steroid-free topical calcineurin inhibitors, tacrolimus ointment and pimecrolimus cream, have demonstrated efficacy against placebo in clinical trials for short-term and long-term use. • Proactive tacrolimus ointment therapy has been shown to be safe and effective for up to one year in reducing the number of flares and improving the quality of life in adult patients and children.

Clinical Guideline	Recommendation(s)
	• The anti-inflammatory potency of 0.1% tacrolimus ointment is similar to a topical corticosteroid with intermediate activity, while the latter is clearly more active than 1.0% pimecrolimus cream. • The topical calcineurin inhibitors do not induce skin atrophy like corticosteroids, which favors their use on delicate skin areas like the eyelids, perioral skin, genital areas, inguinal fold, and for topical long-term management. • Clinical and preclinical data do not indicate an increased risk of the induction of lymphoma or other types of malignancies, or photocarcinogenicity for topical calcineurin inhibitors, but since the continuous oral administration of the calcineurin inhibitor cyclosporine is associated with an increased photocarcinogenicity risk in solid organ transplant patients, UV protection, (e.g., with sunscreens) is recommended.

National Institute for Health and Clinical Excellence: **Management of Atopic Eczema in Children From Birth Up to the Age of 12 Years (2007)**[9]
 	
Reaffirmed March 2021
	<u>General considerations</u>
	• A stepped approach should be used for managing atopic eczema in children. Treatment should be tailored based on the severity of the atopic eczema.
	• Emollients should always be used, even when the atopic eczema is clear. Treatment can be stepped up or down, according to the severity of symptoms, with the addition of the other treatments as necessary as follows:
	  ○ Mild atopic eczema: emollients and mild potency topical corticosteroids.
	  ○ Moderate atopic eczema: emollients, moderate potency topical corticosteroids, topical calcineurin inhibitors, and bandages.
	  ○ Severe atopic eczema: emollients, potent topical corticosteroids, topical calcineurin inhibitors, bandages, phototherapy, and systemic therapy.
	
	<u>Emollients</u>
	• Emollients should be used on the whole body when the atopic eczema is clear and while using all other treatments.
	
	<u>Topical corticosteroids</u>
	• Use mild potency topical corticosteroids on the face and neck, except for short-term (three to five days) use of moderate potency agents for severe flares.
	• Use moderate or potent topical corticosteroids for short periods only (seven to 14 days) for flares in sites such as axillae and groin.
	• Do not use very potent preparations in children without specialist dermatological advice.
	• Topical corticosteroids for atopic eczema should be prescribed for application only once or twice daily.
	• In children ≥12 months of age, potent topical corticosteroids should be used for the shortest amount of time as possible; no longer than 14 days. They should not be used on the face or neck. Potent topical corticosteroids should not be used in children <12 months of age without specialist dermatological supervision.
	• Consider treating problem areas with topical corticosteroids for two consecutive days per week to prevent flares, rather than treating flares as they arise, in children with frequent flares (two or three per month), once the eczema has been controlled.
	• A different topical corticosteroid of the same potency should be considered as an alternative to stepping up treatment if tachyphylaxis to a topical corticosteroid is suspected.
	
	<u>Topical calcineurin inhibitors</u>
	• Topical tacrolimus and pimecrolimus are not recommended for the treatment of mild atopic eczema or as first-line treatments for atopic eczema of any severity.
	• Topical tacrolimus is recommended as an option for the second-line treatment of moderate to severe atopic eczema in adults and children aged two years and older that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly

Clinical Guideline	Recommendation(s)
	irreversible skin atrophy. • Pimecrolimus is recommended as an option for the second-line treatment of moderate atopic eczema on the face and neck in children aged two to 16 years that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy. • Treatment with tacrolimus or pimecrolimus should only be initiated by physicians (including general practitioners) with a special interest and experience in dermatology. • For facial atopic eczema in children that requires long-term or frequent use of mild topical corticosteroids, consider stepping up treatment to topical calcineurin inhibitors. <u>Antihistamines</u> • Oral antihistamines should not be used routinely in the management of atopic eczema in children. • A one-month trial of a nonsedating antihistamine should be offered to children with severe atopic eczema or children with mild or moderate atopic eczema where there is severe itching or urticaria. Treatment can be continued, if successful, while symptoms persist, and should be reviewed every three months. • A seven to 14 day trial of an age-appropriate sedating antihistamine should be offered to children aged six months or over during an acute flare of atopic eczema if sleep disturbance has a significant impact on the child or parents or carers. This treatment can be repeated during subsequent flares if successful. <u>Phototherapy and systemic treatments</u> • Phototherapy or systemic treatments should be considered for the treatment of severe atopic eczema in children when other management options have failed or are inappropriate and where there is a significant negative impact on quality of life.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma and Immunology/ Joint Council on Allergy, Asthma and Immunology: **Disease Management of Atopic Dermatitis: An Updated Practice Parameter (2012)**[10]	<u>General considerations</u> • The intensity of management and treatment of atopic dermatitis is dictated by the severity of illness, which relates to the effect of atopic dermatitis on the quality of life on the patient and his or her family. • The management of atopic dermatitis requires multiple therapeutic approaches including antipruritic therapy, skin hydration, topical anti-inflammatory medications, antibacterial measures, and the identification/elimination of exacerbating factors. <u>Skin hydration</u> • Hydration with warm soaking baths for at least 10 minutes followed by the application of a moisturizer is recommended. • Moisturizers should be recommended as first-line therapy. <u>Topical corticosteroids</u> • Topical corticosteroids are an effective treatment option for atopic dermatitis. If atopic dermatitis is not controlled by moisturizers alone, then the clinician should recommend a topical corticosteroid. • Low-potency corticosteroids are recommended for maintenance therapy, whereas intermediate-and high-potency corticosteroids should be used for the treatment of exacerbation and applied to affected areas over short periods of time. • Potent fluorinated corticosteroids should not be used on the face, eyelids, genitalia, and intertriginous areas or in young infants. • Ultrahigh-potency corticosteroids should be used only for very short periods of time (several days) and in nonfacial non-skinfold areas. • The degree of corticosteroid absorption through the skin and the potential for

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	systemic adverse effects are directly dependent on the surface area of the skin involved, thickness of the skin, the use of occlusive dressing, and the potency of the corticosteroid preparation. Topical calcineurin inhibitors • Tacrolimus ointment has been shown to be effective and safe in both adults and children older than two years of age, with most patients experiencing a reduction of pruritus within three days of initiating therapy. • Tacrolimus ointment does not cause atrophy for eczema on the face, eyelid, and skin folds that is unresponsive to low-potency topical steroids. • Once a flare is controlled, tacrolimus ointment twice daily, twice weekly to eczema-prone areas may prevent future flares. • Pimecrolimus cream decreases the number of flares of atopic dermatitis, reduces the need for corticosteroids, and controls pruritus. Tar preparations • There are no randomized studies that have demonstrated the efficacy of tar preparations, despite their widespread use for the treatment of atopic dermatitis. • Newer coal tar products have been developed that are more cosmetically acceptable than older products. • Coal preparations should not be recommended for acutely inflamed skin because this might result in additional skin irritation. Antihistamines • Patients may benefit from the use of oral antihistamines for the relief of pruritus associated with atopic dermatitis. Treatment of atopic dermatitis with topical antihistamines is generally not recommended because of potential cutaneous sensitization. Vitamin D • Patients with atopic dermatitis might benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake. Dilute bleach baths • The addition of dilute bleach baths twice weekly may reduce the severity of atopic dermatitis, especially in patients with recurrent skin infections. Microbes • Skin infections with *Staphylococcus aureus* are a recurrent problem in patients with atopic dermatitis, and patients with moderate-to-severe atopic dermatitis have been found to make IgE antibodies against staphylococcal toxins present in their skin. • A short course of an appropriate systemic antibiotic for patients who are clinically infected with *Staphylococcus aureus* should be prescribed. In areas with high levels of methicillin-resistant *Staphylococcus aureus*, treatment with clindamycin, doxycycline, or sulfamethoxazole-trimethoprim may be initiated while awaiting skin culture results. • Atopic dermatitis can be complicated by recurrent viral skin infections, such as herpes simplex, warts, and molluscum contagiosum. Herpes simplex or eczema herpeticum should be diagnosed and promptly treated with systemic antiviral agents. • Fungal infections can complicate atopic dermatitis and might contribute to exacerbations. Systemic Immunomodulating Agents • Immunosuppressive agents such as cyclosporine, interferon gamma, mycophenolate mofetil, azathioprine, and corticosteroids have been shown to provide benefit for

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	certain cases of severe refractory atopic dermatitis, but potential benefits should be weighed against their potentially serious adverse effects. Phototherapy • Ultraviolet therapy can be a useful treatment for recalcitrant atopic dermatitis. Allergen immunotherapy • Select patients with atopic dermatitis with aeroallergen sensitivity may benefit from allergen immunotherapy.
American Academy of Dermatology: **Guidelines of Care for the Management of Atopic Dermatitis (2014)**[11]	Topical corticosteroids • Topical corticosteroids are the mainstay of anti-inflammatory therapy for the management of atopic dermatitis. • They are typically introduced into the treatment regimen after failure of lesions to respond to good skin care and regular use of moisturizers alone. • Comparative trials are limited in duration and scope (i.e., they mainly involve two, and occasionally three, agents), and as a result, there are no data to support one or a few specific agents as being more efficacious than others. • A variety of factors should be considered when choosing a particular topical corticosteroid for the treatment of atopic dermatitis, including patient age, areas of the body to which the medication will be applied, and other patient factors such as degree of xerosis, patient preference, and cost of medication. • Twice-daily application of corticosteroids is generally recommended for the treatment of atopic dermatitis; however, evidence suggests that once-daily application of some corticosteroids may be sufficient. • Proactive, intermittent use of topical corticosteroids as maintenance therapy (one to two times/week) on areas that commonly flare is recommended to help prevent relapses and is more effective than use of emollients alone. • The potential for both topical and systemic side effects, including possible hypothalamic-pituitary-adrenal axis suppression, should be considered, particularly in children with atopic dermatitis in whom corticosteroids are used. • Monitoring by physical examination for cutaneous side effects during long-term, potent steroid use is recommended. • No specific monitoring for systemic side effects is routinely recommended for patients with atopic dermatitis. • Patient fears of side effects associated with the use of topical corticosteroids for atopic dermatitis should be recognized and addressed to improve adherence and avoid undertreatment. Topical calcineurin inhibitors • Topical calcineurin inhibitors are recommended and effective for acute and chronic treatment, along with maintenance, in both adults and children with atopic dermatitis, and are particularly useful in selected clinical situations, including recalcitrance to steroids, use on sensitive areas (e.g., face, anogenital, skin folds), steroid-induced atrophy, and long-term uninterrupted topical steroid use. • Topical calcineurin inhibitors are recommended for use on actively affected areas as a steroid-sparing agent for the treatment of atopic dermatitis. • For patients with atopic dermatitis <2 years of age with mild to severe disease, off-label use of 0.03% tacrolimus or 1% pimecrolimus ointment can be recommended. • Pimecrolimus cream and tacrolimus ointment may cause skin burning and pruritus, especially when applied to acutely inflamed skin. Initial treatment of patients with atopic dermatitis using topical corticosteroids should be considered to minimize topical calcineurin inhibitor application site reactions. Patients with atopic dermatitis should be counseled about the possibility of these reactions. • Proactive, intermittent use of topical calcineurin inhibitor as maintenance therapy (two to three times per week) on areas that commonly flare is recommended to help

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	prevent relapses while reducing the need for topical corticosteroids, and is more effective than the use of emollients alone. • The concomitant use of a topical corticosteroid with a topical calcineurin inhibitor may be recommended for the treatment of atopic dermatitis. • No consistent increases in the prevalence of cutaneous viral infections have been seen with continuous or intermittent use of topical calcineurin inhibitor for up to five years; however, physicians should inform their patients of these theoretical cutaneous risks, given the lack of safety data for longer periods of time. • Clinicians should be aware of the black-box warning on the use of topical calcineurin inhibitor for patients with atopic dermatitis and discuss as warranted. • Routine blood monitoring of tacrolimus and pimecrolimus levels in patients with atopic dermatitis who are applying these agents is not recommended at this time. <u>Topical antimicrobials and antiseptics</u> • Except for bleach baths with intranasal mupirocin, no topical antistaphylococcal treatment has been shown to be clinically helpful in patients with atopic dermatitis, and is not routinely recommended. • In patients with moderate to severe atopic dermatitis and clinical signs of secondary bacterial infection, bleach baths and intranasal mupirocin may be recommended to reduce disease severity. <u>Other topical agents</u> • Topical antihistamines have been tried for the treatment of atopic dermatitis but have demonstrated little utility and are not recommended. • There are not adequate data to make a recommendation regarding the use of coal tar topical agents.
British Association of Dermatologists: **Guidelines for the Management of Contact Dermatitis (2017)**[12]	• Avoidance of allergens and irritants is the cornerstone of the management of occupational skin disease. • Personal protective equipment such as clothing or gloves may be an adequate solution, although less likely to be effective with potent sensitizers and airborne allergens/irritants. • Replacement of soaps and detergents with emollients is useful, even if they are not the cause of the dermatitis, as they are irritants which will compound the situation. • Therapy for contact dermatitis persisting despite allergen/irritant removal and skin protection largely follows the management of atopic/endogenous dermatitis. • Studies support the efficacy of topical steroids and topical tacrolimus in the treatment of contact dermatitis. • Second-line treatment includes phototherapy and systemic immunomodulators such as methotrexate and mycophenolate mofetil. • Psoralen plus UVA, ciclosporin and alitretinoin have been demonstrated to be useful in chronic hand dermatitis, and azathioprine in chronic actinic dermatitis, but none has been assessed specifically in the treatment of contact dermatitis.
American Academy of Dermatology/ National Psoriasis Foundation: **Guidelines of Care for the Management and Treatment of Psoriasis with Topical Therapy and Alternative**	• Topical corticosteroids, which provide high efficacy and good safety, play a key role in the treatment of psoriasis, especially for localized disease. • Choosing a corticosteroid with appropriate potency plus the appropriate vehicle should be based on the disease severity, disease location, patient preference, as well as the age of the patient. • Lower potency corticosteroids should be used on the face, intertriginous areas, and areas that are susceptible to steroid atrophy (e.g., forearms) and other adverse effects. • The use of class 1, class 2, and class 3 to 5 topical steroids for up to four weeks is recommended for the treatment of plaque psoriasis not involving intertriginous areas. • The use of class 1 to 7 topical steroids for a minimum of up to four weeks is

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Medicine Modalities for Psoriasis Severity Measures (2020)[13]	recommended as initial and maintenance treatment of scalp psoriasis. • The use of topical corticosteroids for > 12 weeks can be considered if done under the careful supervision of a physician. • While not FDA approved for psoriasis, the topical calcineurin inhibitors tacrolimus and pimecrolimus are often employed in the treatment of psoriasis. They are especially helpful on thinner skin such as facial and intertriginous areas and used as steroid-sparing agents for prolonged use (> 4 weeks). The majority of the data regarding these medications are derived from their extensive use in atopic dermatitis. • The off-label use of 0.1% tacrolimus for psoriasis involving the face as well as inverse psoriasis for up to eight weeks can be considered. • The off-label use of pimecrolimus for inverse psoriasis for four to eight weeks is recommended. • Long term use of tacrolimus or pimecrolimus can be considered for inverse psoriasis treatment as off-label use. • The off-label combination of tacrolimus and 6% salicylic acid for 12 weeks may be used for the treatment of plaque psoriasis. • The long-term use of topical vitamin D analogues (up to 52 weeks) including calcipotriene/calcipotriene, calcitriol, tacalcitol, and maxacalcitol is recommended for the treatment of mild to moderate psoriasis. • Use of calcipotriene foam and calcipotriene plus betamethasone dipropionate gel is recommended for 4 to 12 weeks for the treatment of mild to moderate scalp psoriasis. • Topical tacalcitol ointment or calcipotriene combined with hydrocortisone for eight weeks can be used for the treatment of facial psoriasis. • Use of combination treatments with vitamin D analogues and potent Class II and Class III topical steroids up to 52 weeks is recommended for the treatment of psoriasis. • Use of combination products with calcipotriol and corticosteroids is recommended for the treatment of psoriasis. • The application of vitamin D analogues twice daily on weekdays in conjunction with high potency topical steroids twice daily on weekends can be considered for maintenance treatment for psoriasis. • The application of morning high potency topical steroids and evening topical vitamin D analogues is an effective treatment regimen that can be considered for the treatment of psoriasis. • Topical tazarotene can be used for the treatment of mild to moderate psoriasis and nail psoriasis. • The combination of topical tazarotene and NB-UVB has been shown to be effective and allow a reduction in total usage of NB-UVB. • The use of mid-potency or high potency topical steroid in combination with tazarotene for 8 to 16 weeks is more effective than monotherapy with tazarotene and is recommended for the treatment of mild to moderate psoriasis. • The use of topical steroids along with tazarotene is recommended to decrease the duration of treatment as well as increase the length of remission. • The use of an emollient in conjunction with topical corticosteroids for four to eight weeks can be used to help reduce itching, desquamation, and total body surface area and prevent quick relapse of psoriasis when topical corticosteroids are discontinued. • Topical salicylic acid can be used for 8 to 16 weeks for the treatment of mild to moderate psoriasis. • The combination of salicylic acid with topical corticosteroids can be used for the treatment of moderate to severe psoriasis (BSA ≤ 20%). • Topical anthralin for 8 to 12 weeks can be used for the treatment of mild to moderate psoriasis. Short contact (up to two hours per day) anthralin is recommended to limit side effects.

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	• Coal tar preparations are recommended for the treatment of mild to moderate psoriasis. • The addition of an ultra-high potency (Class 1) topical corticosteroid to standard dose etanercept for 12 weeks is recommended for the treatment of moderate to severe psoriasis. • The addition of calcipotriene/betamethasone to standard dose adalimumab for 16 weeks is recommended for the treatment of moderate to severe psoriasis to accelerate clearance of psoriatic plaques. • All topical steroids can be used in combination with any biologics for the treatment of moderate to severe psoriasis. • The addition of topical calcipotriene to standard dose methotrexate therapy is recommended for the treatment of moderate to severe psoriasis. It may lead to lower cumulative doses of methotrexate and increased time to relapse following methotrexate discontinuation. • The addition of calcipotriene/betamethasone dipropionate ointment to low dose (2 mg/kg/day) cyclosporine can be used for the treatment of moderate to severe psoriasis. • The addition of calcipotriene to standard dose acitretin is recommended for the treatment of moderate to severe psoriasis.
Finnish Medical Society Duodecim: **Seborrheic Dermatitis in the Adult (2020)**[14]	<u>General considerations</u> • No permanent results are usually achieved with treatment, which is symptomatic and needs to be repeated from time to time (a course lasting for one to two weeks) when symptoms worsen. • Maintenance therapy, perhaps once or twice weekly, should be continued in order to reduce the frequency of exacerbations. <u>Reduction of dandruff and sebo-suppression</u> • Seborrheic areas should be washed more often than normally (daily). • Basic topical ointments in gel form (e.g. products containing propylene glycol) to wash with, or basic topical ointments may be applied after washing. <u>Face and body</u> • Topical mild to moderately potent glucocorticoid creams. • Creams containing a combination of a glucocorticoid and an azole antifungal. • Glucocorticoid creams are used periodically, e.g., during periods of exacerbation once or twice daily in courses of one to two weeks. • Tacrolimus ointment or pimecrolimus cream as a periodical therapy one to two times daily for a period of three to four weeks or as maintenance therapy e.g., once or twice a week. • Creams, gels or shampoos containing topical antifungals (ketoconazole, clotrimazole, miconazole, tioconazole) or terbinafine ointment. • Antifungals may be used in acute exacerbations once or twice daily for one to two weeks, and they are suitable for prophylactic maintenance therapy once or twice a week. • Metronidazole or azelaic acid either as gel or cream in courses of three to four weeks and, if needed, as maintenance therapy one to two times a week. <u>Scalp</u> • Scalp plaques can be softened with 3 to 5% salicylic acid ointment in the evenings and washed away in the mornings. • Scalp may be washed with ketoconazole shampoo or selenium sulfide shampoo. • Corticosteroid solutions (equivalent doses) to the scalp (Class I–III). • In treatment-resistant cases, a sequential treatment schedule using a glucocorticoid shampoo in courses of three to four weeks may be tried.

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	Ears and ear canals • Mild to moderately potent glucocorticoid ointments or solutions one to two times daily in courses of one to two weeks. Flexural areas • Mild to moderately potent glucocorticoid ointments. • A combination ointment of a glucocorticoid and an azole group antifungal. • Tacrolimus ointment or pimecrolimus cream periodically one to two times daily in courses of three to four weeks, or as maintenance therapy, e.g., one to two times a week. • The effect of the warm and moist environment can be reduced by application of talc or azole-containing powder after wash in the mornings and zinc paste after wash in the evenings. • Flexural areas can be painted with antiseptic solutions, many of which stain the skin (rarely used). • An application of a powder containing, for example, an azole antifungal in the morning and a corticosteroid ointment after washing at night for one to two weeks. • Systemic antifungals may be indicated in serious cases, for example fluconazole 50 mg once daily or 150 mg once weekly (for two to four weeks) or itraconazole 100 mg twice daily (for one to two weeks). Severe and treatment-resistant cases • A course of an oral antifungal drug may be combined with topical therapy, itraconazole 200 mg once daily for seven days, for example. Interactions with other medications must be checked. • Also oral fluconazole or terbinafine has been used as courses.
American Gastroenterological Association: **Medical Position Statement: Diagnosis and Treatment of Hemorrhoids (2004)**[15]	• Treatment of hemorrhoids depends on their severity. • The cornerstone of medical therapy is fiber and water. • Topical corticosteroids and analgesics are useful for managing perianal skin irritation due to poor hygiene, mucus discharge, or fecal seepage. • Prolonged use of potent corticosteroid preparations may be harmful and should be avoided.
American Gastroenterological Association: **Technical Review on the Diagnosis and Treatment of Hemorrhoids (2004)**[16]	• Add dietary fiber and avoid straining at stool. • Over-the-counter topical agents and suppositories have become equally ubiquitous in the empirical treatment of hemorrhoidal symptoms, but data supporting their use are lacking. • Topical analgesics may bring relief of local pain and itching. • Corticosteroid creams may ameliorate local perianal inflammation, but no data suggest that they actually reduce hemorrhoidal swelling, bleeding, or protrusion. • Long-term use of high-potency corticosteroid creams is deleterious and should be avoided.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the skin and mucous membrane corticosteroids are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Skin and Mucous Membrane Corticosteroids[1-3]

Generic Name(s)	Relief of Inflammatory and Pruritic Manifestations of Corticosteroid-Responsive Dermatoses*
Single Entity Agents	
Alclometasone	✔
Amcinonide	✔
Betamethasone dipropionate	✔
Betamethasone valerate	✔
Clobetasol	✔
Clocortolone	✔
Desonide	✔
Desoximetasone	✔
Diflorasone	✔
Fluocinolone	✔
Fluocinonide	✔
Flurandrenolide	✔
Fluticasone	✔
Halcinonide	✔
Halobetasol	✔
Hydrocortisone	✔ †‡
Hydrocortisone acetate	✔ †§
Hydrocortisone butyrate	✔
Hydrocortisone valerate	✔
Mometasone	✔
Prednicarbate	✔
Triamcinolone	✔ ‖
Combination Products	
Betamethasone dipropionate and propylene glycol	✔
Hydrocortisone acetate and pramoxine	✔

*Dermatoses include anogenital and anorectal pruritus, atopic dermatitis, psoriasis, seborrheic dermatitis, and inflammatory phase of xerosis.
†Over the counter topical products are used for the temporary relief of itching associated with minor skin irritations, inflammation, and rashes.
‡Rectal enema is indicated as adjunctive therapy in the treatment of ulcerative colitis.
§Rectal foam is indicated as adjunctive therapy in the topical treatment of ulcerative proctitis of the distal portion of the rectum in patients who cannot retain hydrocortisone or other corticosteroid enemas.
‖Dental paste is indicated for adjunctive treatment and for the temporary relief of symptoms associated with oral inflammatory lesions and ulcerative lesions resulting from trauma.

IV. Pharmacokinetics

The pharmacokinetic parameters of the skin and mucous membrane corticosteroids are listed in Table 5. Pharmacokinetic properties of the combination products not listed in the table below would be in line with the properties of their individual components listed in the table below.

Table 5. Pharmacokinetic Parameters of the Skin and Mucous Membrane Corticosteroids[1-3]

Generic Name(s)	Bioavailability* (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Alclometasone	3	Not reported	Liver	Renal	Not reported
Amcinonide	Not reported	Not reported	Liver	Renal	Not reported
Betamethasone	12 to 14	64	Liver	Renal	Not reported
Clobetasol	Not reported	Variable	Liver	Renal, Bile	Not reported
Clocortolone	Not reported	Variable	Liver	Renal, Bile	Not reported
Desonide	Not reported	Not reported	Liver	Renal, Bile	Not reported
Desoximetasone	Variable	Variable	Liver	Renal, Feces, Bile	15 to 17
Diflorasone	1	Not reported	Liver	Renal, Bile	Not reported
Fluocinolone	Variable	>90	Not reported	Renal, Bile	Not reported

Generic Name(s)	Bioavailability* (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Fluocinonide	Not reported	Variable	Liver	Renal, Feces	Not reported
Flurandrenolide	Variable	Variable	Liver	Renal, Bile	Not reported
Fluticasone	Not reported	91	Liver	Renal, Feces	7.2
Halcinonide	Not reported	Note reported	Liver	Renal, Bile	Not reported
Halobetasol	3	Not reported	Not reported	Not reported	Not reported
Hydrocortisone	Not reported	90	Liver	Renal	1 to 2
Mometasone	0.7	Not reported	Liver	Renal, Feces	Not reported
Prednicarbate	Poor	Not reported	Not reported	Not reported	Not reported
Triamcinolone	Not reported	Not reported	Liver	Renal, Bile	2 to 3

*There is large variation in absorption of topical corticosteroids among individuals and anatomical sites.

V. Drug Interactions

Due to limited systemic absorption with the skin and mucous membrane corticosteroids, no major drug interactions have been reported.[2]

VI. Adverse Drug Events

The most common adverse drug events reported with the skin and mucous membrane corticosteroids are listed in Tables 6 and 7. Adverse drug events of the combination products not listed in the tables below would be in line with the properties of their individual components listed in the table below.

Table 6. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Corticosteroids (Drugs A to F)[1-3]

Adverse Events	Alclometasone	Amcinonide	Betamethasone	Clobetasol	Clocortolone	Desonide	Desoximetasone	Diflorasone	Fluocinolone
Dermatological									
Acneform eruptions	✔	✔	✔	✔	✔	✔	✔	✔	✔
Allergic contact dermatitis	✔	✔	✔	✔	✔	✔	✔	✔	✔
Alopecia	-	-	-	✔	-	-	-	-	-
Asteatotic eczema	-	-	-	✔	-	-	-	-	-
Atopic dermatitis (secondary)	-	-	-	-	-	-	-	-	✔
Atrophy	-	-	-	-	-	✔	-	-	-
Burning	✔	✔	✔	✔	✔	✔	✔	✔	✔
Cracking	-	-	-	✔	-	-	-	-	-
Dermatitis	-	-	-	-	-	✔	-	-	-
Dryness	✔	✔	✔	✔	✔	✔	✔	✔	✔
Erythema	✔	-	✔	✔	-	✔	✔	-	✔
Folliculitis	✔	✔	✔	✔	✔	✔	✔	✔	✔
Hypertrichosis	✔	✔	✔	✔	✔	✔	✔	✔	✔
Hypopigmentation	✔	✔	-	✔	✔	✔	✔	✔	✔
Irritation	✔	✔	✔	✔	✔	✔	✔	✔	✔
Keratosis pilaris	-	-	-	-	-	-	-	-	✔
Maceration of the skin	✔	✔	-	✔	✔	-	✔	✔	-
Miliaria	✔	✔	✔	✔	✔	✔	✔	✔	✔
Numbness	-	-	-	✔	-	-	-	-	-
Papular rash	✔	-	-	-	-	-	-	-	-
Papules	-	-	-	-	-	-	-	-	✔
Peeling of skin	-	-	-	-	-	✔	-	-	-
Perioral dermatitis	✔	-	-	✔	✔	✔	✔	✔	✔
Pruritus	✔	✔	✔	✔	✔	✔	✔	✔	✔
Pustules	-	-	-	-	-	-	-	-	✔
Rash	-	-	-	-	-	✔	-	-	-
Scaly skin	-	-	-	-	-	✔	-	-	-
Shiny skin	-	-	-	-	-	-	-	-	✔
Skin atrophy	✔	✔	✔	✔	✔	✔	✔	✔	✔
Stinging	-	-	-	✔	-	✔	-	-	-
Striae	✔	✔	✔	-	✔	✔	✔	✔	✔
Telangiectasia	✔	✔	-	✔	-	✔	-	-	✔
Urticaria	-	-	-	✔	-	-	-	-	-
Vesiculation	-	-	✔	-	-	-	✔	-	-
Endocrine and Metabolic									
Adrenal suppression	-	-	-	✔	-	-	-	-	-
Cushing's Syndrome	✔	✔	✔	✔	-	✔	-	-	✔

Adverse Events	Alclometasone	Amcinonide	Betamethasone	Clobetasol	Clocortolone	Desonide	Desoximetasone	Diflorasone	Fluocinolone
Growth retardation	✔	✔	✔	-	-	✔	-	-	-
Hypothalamic-pituitary-adrenal suppression	✔	✔	✔	-	-	✔	-	-	✔
Hyperglycemia	-	✔	✔	✔	-	✔	-	-	-
Weight gain delayed	-	-	-	-	-	✔	-	-	-
Respiratory									
Asthma	-	-	-	-	-	✔	-	-	-
Cough	-	-	-	-	-	✔	-	-	-
Pharyngitis	-	-	-	✔	-	✔	-	-	-
Upper respiratory tract infection	-	-	-	✔	-	✔	-	-	-
Other									
Arthralgia	-	-	-	-	-	-	✔	-	-
Ear infection	-	-	-	-	-	-	-	-	✔
Edema	-	-	-	✔	-	-	-	-	-
Glucosuria	-	-	-	✔	-	-	-	-	-
Headache	-	-	-	-	-	✔	-	-	-
Herpes simplex	-	-	-	-	-	-	-	-	✔
Hypertension	-	-	-	-	-	✔	-	-	-
Intracranial hypertension	-	-	-	-	-	✔	-	-	✔
Irritability	-	-	-	-	-	✔	-	-	-
Muscle atrophy	-	-	-	-	-	-	-	✔	-
Secondary infection	✔	✔	-	✔	✔	✔	✔	✔	✔

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 7. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Corticosteroids (Drugs F to T)[1-3]

Adverse Events	Fluocinonide	Flurandrenolide	Fluticasone	Halcinonide	Halobetasol	Hydrocortisone	Mometasone	Prednicarbate	Triamcinolone
Dermatological									
Acneform eruptions	✔	✔	✔	✔	✔	✔	-	<1	✔
Allergic contact dermatitis	✔	✔	✔	✔	✔	<1	-	<1	✔
Bacterial skin infection	-	-	-	-	-	-	1 to 10	-	-
Burning	✔	✔	-	✔	1 to 4	<1	1 to 10	<1	✔
Dryness	✔	✔	1	✔	✔	2	-	-	✔
Edema	-	-	✔	-	-	-	-	<1	-
Eczema exacerbation	-	-	2	-	-	13	-	-	-
Erythema	-	-	-	-	✔	-	-	-	-
Folliculitis	✔	✔	✔	✔	-	<1	<1	<1	✔
Furunculosis	-	-	-	-	-	-	1 to 10	-	-
Hyperpigmentation	-	✔	-	-	-	-	-	-	-
Hypertrichosis	✔	✔	-	✔	-	✔	-	-	✔
Hypopigmentation	✔	-	✔	-	✔	<1	<1	<1	✔
Irritation	✔	✔	3	-	-	-	-	-	✔
Leukoderma	-	-	-	-	✔	-	-	-	-
Maceration of the skin	✔	✔	-	✔	-	-	-	-	✔

Adverse Events	Fluocinonide	Flurandrenolide	Fluticasone	Halcinonide	Halobetasol	Hydrocortisone	Mometasone	Prednicarbate	Triamcinolone
Miliaria	✔	✔	✔	✔	✔	-	-	<1	✔
Paresthesia	-	-	-	-	-	-	<1	<1	-
Perioral dermatitis	✔	✔	✔	✔	✔	-	-	<1	✔
Pruritus	✔	✔	3	✔	1 to 4	6	1 to 10	<1	✔
Pustules	-	-	✔	-	✔	-	-	-	-
Rash	-	-	-	-	✔	-	-	<1	-
Rosacea	-	-	-	-	-	-	<1	-	-
Shininess	-	-	-	-	-	-	-	3	-
Skin atrophy	✔	✔	✔	✔	✔	<1	1 to 10	1 to 10	✔
Stinging	-	-	-	-	1 to 4	2	1 to 10	-	-
Striae	✔	✔	✔	✔	✔	<1	-	<1	✔
Telangiectasia	✔	-	-	-	-	-	-	5	-
Thinness	-	-	-	-	-	-	-	3	-
Urticaria	-	-	✔	-	-	-	-	<1	-
Vesicles	-	-	-	-	✔	-	-	-	-
Endocrine and Metabolic									
Cushing's Syndrome	✔	✔	✔	✔	-	-	-	-	-
Growth retardation	✔	✔	-	✔	-	-	<1	-	-
Hypothalamic-pituitary-adrenal suppression	✔	✔	-	✔	✔	✔	<1	-	✔
Hyperglycemia	✔	-	✔	✔	-	✔	-	-	✔
Hypokalemia	-	-	-	-	-	✔	-	-	✔
Respiratory									
Nasal congestion	✔	-	-	-	-	-	-	-	-
Pharyngitis	✔	-	-	-	-	-	-	-	-
Other									
Blurred vision	-	-	✔	-	-	-	-	-	-
Cataract formation	-	-	-	-	-	-	<1	-	-
Glucosuria	✔	-	✔	-	-	-	-	-	-
Hemorrhage	-	-	✔	-	-	-	-	-	-
Hypersensitivity	-	-	-	-	-	✔	-	-	-
Intracranial hypertension	✔	✔	-	✔	-	-	-	-	-
Immunosuppression	-	-	✔	-	-	-	-	-	-
Leukopenia	-	-	✔	-	-	-	-	-	-
Moniliasis	-	-	-	-	-	-	<1	-	-
Numbness of fingers	-	-	1	-	-	-	-	-	-
Rectal bleeding	-	-	-	-	-	✔	-	-	-
Rectal pain	-	-	-	-	-	✔	-	-	-
Secondary infection	✔	✔	✔	✔	✔	✔	-	<1	✔
Sepsis	-	-	✔	-	-	-	-	-	-
Thrombocytopenia	-	-	✔	-	-	-	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the skin and mucous membrane corticosteroids are listed in Table 8.

Table 8. Usual Dosing Regimens for the Skin and Mucous Membrane Corticosteroids[1-3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Alclometasone	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment: apply to the affected area two to three times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses for children >1 year of age:* Cream, ointment: apply to the affected area two to three times daily	Cream: 0.05% Ointment: 0.05%
Amcinonide	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream: apply to the affected area two to three times daily Lotion: apply to the affected area two times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream: apply to the affected area two to three times daily Lotion: Apply to the affected area two times daily	Cream: 0.1% Lotion: 0.1%
Betamethasone dipropionate	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, gel, ointment: apply to the affected area one to two times daily Lotion: apply a few drops to the affected area one to two times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses for children >13 years of age:* Cream, gel, ointment: apply to the affected area one to two times daily Lotion: apply a few drops to the affected area one to two times daily	Cream: 0.05% Gel: 0.05% Lotion: 0.05% Ointment: 0.05%
Betamethasone valerate	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment: apply to the affected area one to three times daily Foam: apply to the affected scalp area two times daily Lotion: apply a few drops to the affected area two times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment: apply to the affected area one to three times daily Foam: apply to the affected scalp area two times daily Lotion: apply a few drops to the affected area two times daily	Cream: 0.1% Foam: 0.12% Lotion: 0.1% Ointment: 0.1%
Clobetasol	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, foam, gel, lotion, ointment, spray: apply to the affected area two times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses for children >12 years of age:* Cream, foam, gel, ointment: apply to the affected area two	Cream: 0.05% Foam: 0.05% Gel:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Shampoo: apply to dry scalp once daily Solution: apply to the affected scalp area two times daily	times daily Solution: apply to the affected scalp area two times daily	0.05% Lotion: 0.05% Ointment: 0.05% Shampoo: 0.05% Solution: 0.05% Spray: 0.05%
Clocortolone	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream: apply to the affected area three times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream: apply to the affected area three times daily	Cream: 0.1%
Desonide	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, lotion, ointment: apply to the affected area two to three times daily	Safety and efficacy of the cream/lotion/ointment have not been established in children.	Cream: 0.05% Lotion: 0.05% Ointment: 0.05%
Desoximetasone	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Topical formulations: apply to the affected area two times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, gel, ointment (0.05%): apply to the affected area two times daily ≥10 years of age: Ointment (0.25%): apply to the affected area two times daily	Cream: 0.05% 0.25% Gel: 0.05% Ointment: 0.05% 0.25% Spray: 0.25%
Diflorasone	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment: apply to the affected area one to three times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Ointment: apply to the affected area one to three times daily	Cream: 0.05% Ointment: 0.05%
Fluocinolone	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment, solution: apply to the affected area three to four	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment, solution: apply to the affected area two	Cream: 0.01% 0.025% Oil: 0.01%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	times daily Oil (body): apply to the affected area three times daily Oil (scalp): wet or dampen hair and scalp thoroughly; apply a thin film on the scalp, massage well, and cover scalp with the supplied shower cap; leave on overnight or for a minimum of four hours before washing off; wash hair with regular shampoo and rinse thoroughly Shampoo: apply no more than approximately one ounce to the scalp area once daily, work into a lather, and allow it to remain on the scalp for approximately five minutes; the hair and scalp should then be rinsed thoroughly with water	to four times daily ≥3 months of age: Oil (body): apply to the affected area two times daily ≥2 years of age: Oil (scalp): apply to the affected area two times daily	Ointment: 0.025% Shampoo: 0.01% Solution: 0.01%
Fluocinonide	<u>Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:*</u> Cream, gel, ointment (0.05%): apply to the affected area two to four times daily Cream (0.1%): apply to the affected area one to two times daily	<u>Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:*</u> Cream, gel, ointment (0.05%): apply to the affected area two to four times daily ≥12 years of age: Cream (0.1%): apply to the affected area one to two times daily	Cream: 0.05% 0.1% Gel: 0.05% Ointment: 0.05% Solution: 0.05%
Flurandrenolide	<u>Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:*</u> Cream, lotion, ointment: apply to the affected area two to three times daily	<u>Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:*</u> Cream, lotion, ointment: apply to the affected area two to three times daily	Cream: 0.05% Lotion: 0.05% Ointment: 0.005%
Fluticasone	<u>Atopic dermatitis:</u> Cream: apply to the affected area one to two times daily <u>Corticosteroid-responsive dermatoses:</u> Cream, ointment: apply to the affected area twice daily Lotion: apply to the affected area once daily	<u>Atopic dermatitis:</u> ≥3 months of age: Cream: apply to the affected area one to two times daily >1 year of age: Lotion: apply to the affected area once daily <u>Corticosteroid-responsive dermatoses:</u> ≥3 months of age:	Cream: 0.05% Lotion: 0.05% Ointment: 0.005%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		Cream: apply to the affected area twice daily ≥1 year of age: Lotion: apply to the affected area once daily	
Halcinonide	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment, solution: apply to the affected area two to three times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment, solution: apply to the affected area two to three times daily	Cream: 0.1% Ointment: 0.1% Solution: 0.1%
Halobetasol	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, foam, lotion, ointment: apply to the affected area one to two times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in children >12 years of age:* Cream, ointment: apply to the affected area one to two times daily	Cream: 0.05% Foam: 0.05% Lotion: 0.01% 0.05% Ointment: 0.05%
Hydrocortisone	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, lotion, ointment, solution: apply to affected area two to four times daily Rectal enema:† one enema nightly for 21 days or until remission occurs	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses for children >2 years of age:* Cream, lotion, ointment: apply to affected area two to four times daily	Cream: 1% 2.5% Lotion: 2.5% Ointment: 1% 2.5% Rectal cream: 1% 2.5% Rectal enema: 100 mg/60 mL Solution: 2.5%
Hydrocortisone acetate	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Rectal foam:‡ apply one applicator full once or twice daily for two or three weeks, and every second day thereafter	Safety and efficacy of the rectal foam have not been established in children.	Rectal foam: 10%
Hydrocortisone butyrate	Relief of inflammatory and pruritic manifestations of	Relief of inflammatory and pruritic manifestations of	Cream: 0.1%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	corticosteroid-responsive dermatoses:* Cream, ointment, solution: apply to affected area two to three times daily Lotion: apply thin film to affected area twice daily	corticosteroid-responsive dermatoses:* Cream, ointment, solution: apply to affected area two to three times daily Lotion: apply thin film to affected area twice daily	Lotion: 0.1% Ointment: 0.1% Solution: 0.1%
Hydrocortisone probutate	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream: apply to affected area one to two times daily	Safety and efficacy in children have not been established.	Cream: 0.1%
Hydrocortisone valerate	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment: apply to affected area two to three times daily	Safety and efficacy in children have not been established.	Cream: 0.2% Ointment: 0.2%
Mometasone	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment: apply to the affected area once daily Solution: apply a few drops to affected area once daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* ≥2 years of age: Cream, ointment: apply a thin film to affected area of the skin once daily ≥12 years of age: Solution: apply a few drops to affected area once daily	Cream: 0.1% Ointment: 0.1% Solution: 0.1%
Prednicarbate	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment: apply to the affected area twice daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* ≥1 year of age: Cream: apply to the affected area twice daily ≥10 years of age: Ointment: apply to the affected area twice daily	Cream: 0.1% Ointment: 0.1%
Triamcinolone	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Aerosol: apply to the affected area three to four times daily Cream, lotion, ointment: <0.1%: apply to the affected area two to four times daily ≥0.1%: apply to the affected area	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Aerosol: apply to the affected area three to four times daily Cream, lotion, ointment (<0.1%): apply to the affected area two to four times daily	Aerosol: 0.147 mg/g Cream: 0.025% 0.1% 0.5% Dental paste: 0.1%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	two to three times daily Dental paste:§ press a small amount (1/4 inch) to the lesion until a thin film develops up to three times daily	Dental paste:§ press a small amount (1/4 inch) to the lesion until a thin film develops up to three times daily	Lotion: 0.025% 0.1% Ointment: 0.025% 0.05% 0.1% 0.5%
Combination Products			
Betamethasone dipropionate and propylene glycol	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Cream, ointment: apply to the affected area one to two times daily Lotion: apply a few drops to the affected area one to two times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses for children >13 years of age:* Cream, ointment: apply to the affected area one to two times daily Lotion: apply a few drops to the affected area one to two times daily	Cream: 0.05% Lotion: 0.05% Ointment: 0.05%
Hydrocortisone acetate and pramoxine	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Rectal foam: apply to affected area three to four times daily	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses:* Rectal foam: apply to affected area three to four times daily	Rectal foam: 1%-1%

*Dermatoses include anogenital and anorectal pruritus, atopic dermatitis, psoriasis, seborrheic dermatitis, and inflammatory phase of xerosis.
†Rectal enema is indicated as adjunctive therapy in the treatment of ulcerative colitis.
‡Rectal foam is indicated as adjunctive therapy in the topical treatment of ulcerative proctitis of the distal portion of the rectum in patients who cannot retain hydrocortisone or other corticosteroid enemas.
§Dental paste is indicated for adjunctive treatment and for the temporary relief of symptoms associated with oral inflammatory lesions and ulcerative lesions resulting from trauma.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the skin and mucous membrane corticosteroids are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Skin and Mucous Membrane Corticosteroids

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Atopic Dermatitis				
Kuokkanen et al.[17] (1987) Alclometasone 0.05% ointment applied BID vs hydrocortisone 1% ointment applied BID	DB, RCT Children with eczema	N=34 3 weeks	Primary: Potential for induction of cutaneous atrophy; severity of erythema, induration, pruritus; global evaluation Secondary: Not reported	Primary: At study endpoint, the percent improvement in signs and symptoms in the alclometasone and hydrocortisone treatment sides were 88 and 86%, respectively. Secondary: Not reported
Lassus et al.[18] (1984) Alclometasone 0.05% cream applied BID vs clobetasol butyrate 0.05% cream applied BID	DB, PG, RCT Children with stable or worsening AD	N=43 2 weeks	Primary: Erythema, induration, pruritus, physician global evaluation Secondary: Not reported	Primary: The average percent reduction in disease signs was similar with clobetasol (86%) and alclometasone (85%; P>0.10). Physicians deemed nine of 22 patients in the alclometasone group cleared compared to 10 of 21 patients in the clobetasol group (P>0.10). Secondary: Not reported
Bickers et al.[19] (1984) Amcinonide 0.1% cream applied BID vs	DB, PG, RCT Patients 17 to 84 years of age with acute or subacute eczematous dermatitis	N=33 2 weeks	Primary: Itching, burning, pain, erythema, edema, excoriation, vesiculation, crusting, scaling,	Primary: The amcinonide group had a greater improvement in edema compared to the halcinonide group at endpoint (P=0.04). All other primary endpoints were not significantly different between the two treatment groups (P≤0.82). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
halcinonide 0.1% cream applied BID			lichenification, plaques, pigmentation changes, secondary skin infection, fissuring Secondary: Cosmetic acceptability questionnaire	No significant difference in cosmetic acceptability was seen between the two treatment groups (P=0.92).
Guenther et al.[20] (1981) Amcinonide 0.1% cream applied BID vs halcinonide 0.1% cream applied BID	DB, PG Patients 16 to 71 years of age with eczematous dermatitis for at least one year with slow exacerbation of disease	N=29 2 weeks	Primary: Erythema, scaling, lichenification, plaques, fissuring, oozing, crusting, excoriation, pigmentation changes, itching and burning and/or pain Secondary: Investigator's overall evaluation, patient's overall evaluation and patient's acceptability evaluation	Primary: All signs and symptoms, and the total score, yielded statistically significant improvements in both treatment groups at both weeks one and two, with the exception of pigmentation changes at week one (P=0.10 to 0.001). Halcinonide-treated patients had significantly greater improvements in fissuring at week one; however, there was no apparent difference at week two. At week two, the amcinonide group had much greater improvement in burning/pain, and this was repeated in the evaluation of the number of patients experiencing complete burning/pain relief (all 11 patients treated with amcinonide reported complete relief compared to four of seven halcinonide patients). There were no major differences among other signs and symptoms between the groups at week two. Secondary: No significant difference was reported between the two treatment groups.
Breneman et al.[21] (2005) Clobetasol lotion applied BID for two weeks	AC, MC, PC, RCT, SB Patients with moderate to severe AD	N=229 4 weeks	Primary: Success rate (derived from global severity scale) Secondary:	Primary: At the end of the two-week treatment period (last observation carried forward) the proportion of subjects who achieved "success" was significantly higher in the lotion group compared to the placebo group (72.9 vs 36.4%; P=0.001). There was no difference between the active treatments (72.9 vs 74.0%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs clobetasol cream applied BID for two weeks vs placebo			Global severity scale (full-scale); individual disease scores of erythema, excoriation, induration/ papulation, lichenification, oozing/crusting, and dryness/ scaling; pruritus, global improvement	At all other time points, success rates for the lotion group were significantly higher than for the placebo group (P<0.05), and were non-inferior to the emollient cream group (P>0.05). After the two-week treatment-free period, success rates for both the lotion and cream groups remained significantly higher relative to those observed in the lotion placebo group. Success rates decreased by 14.5% in the clobetasol propionate lotion group as compared to an 18.0% decrease in the cream group. Secondary: At week two, the full-scale global severity scale for the lotion group was significantly lower than that for the placebo group (P=0.001); there was no difference between the two clobetasol propionate formulations. The number of subjects with reduced severity in individual disease scores was significantly higher (P<0.05) in the lotion group as compared to the placebo group; no significant differences were observed between the lotion group and the emollient cream group. Pruritus scores in both active groups were comparable. However, after two weeks of a treatment-free follow-up period, pruritus scores in the lotion group were significantly lower compared to that in the emollient cream group (P=0.014) and placebo group (P=0.002). Global improvement at the two week endpoint demonstrated that the lotion group was more effective that the placebo group (P=0.001); however, the lotion group was not significantly different from the emollient cream group. The majority of subjects in both active treatment groups showed improvement, whereas the majority of subjects in the placebo group showed no changes.
Kircik et al.[22] (2013) Clobetasol 0.05% spray applied BID for 15 days	DB, MC, PG, RCT, VC Patients ≥12 years of age with moderate to severe	N=125 15 days	Primary: Proportion of patients achieving treatment success (defined as improvement from	Primary: The treatment success at day 15 did not differ significantly between treatment groups. Adverse events were reports in 18% of patients treated with clobetasol propionate foam and 8% of patients in the placebo group. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	chronic hand dermatitis with an Investigator's Static Global Assessment score of 3 or 4 at baseline		baseline ≥2 Investigator's Static Global Assessment grades for the target hand at day 15) Secondary: Not reported	Not reported
Wolkerstorfer et al.[23] (1998) Clobetasone 0.05% cream applied BID vs fluticasone 0.05% cream applied daily	DB, RCT Children 3 to 8 years of age with moderately active AD	N=21 4 weeks	Primary: Modified scoring of atopic dermatitis system Secondary: Not reported	Primary: There were no significant differences between the fluticasone and the clobetasone treatment groups in scoring of atopic dermatitis system improvements (P=0.8). Secondary: Not reported
Jorizzo et al.[24] (1995) Desonide 0.05% ointment applied BID vs hydrocortisone 1% ointment applied BID	MC, PG, RCT, SB Children ≤12 years of age with mild to moderate AD	N=111 5 weeks	Primary: Global improvement, erythema, lichenification, excoriations, oozing or crusting, pruritus, induration Secondary: Not reported	Primary: The investigator's global assessment favored desonide over hydrocortisone. In the desonide group, 69% of patients showed clearing or marked improvement, compared to 41% of patients in the hydrocortisone group (P=0.003). There was a greater improvement in erythema, excoriations, oozing/crusting, and pruritus in the desonide group compared to the hydrocortisone group with improvements of 52.7 and 33.9% for erythema, 76.4 and 57.1% for excoriations, 78.2 and 60.7% for oozing/crusting, and 58.2 and 39.3% for pruritus, respectively (P<0.05). There was no significant difference between the treatment groups in lichenification and induration/papules.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Lucky et al.[25] (1997) Desonide 0.05% ointment applied BID vs hydrocortisone 2.5% ointment applied BID	RCT Pediatric patients with AD	N=15 28 days	Primary: Hypothalamic-pituitary-adrenal axis suppression Secondary: Not reported	Primary: No significant differences were seen in either early morning cortisol levels or adrenocorticotropic hormone-stimulated mean cortisol values from baseline to endpoint. Secondary: Not reported
Ashton et al.[26] (1987) Desoximetasone 0.25% cream applied BID vs desoximetasone 0.05% cream applied BID vs betamethasone valerate 0.1% cream applied BID vs hydrocortisone 1% cream applied BID	DB, MC, PG Patients ≥2 years of age with eczema	N=96 3 weeks	Primary: Erythema/redness, scaling, itching, extent of area affected Secondary: Not reported	Primary: Based on final clinician assessment scores, the difference in erythema was most significant between the desoximetasone 0.25% and hydrocortisone (P=0.006; mean P value for all treatments was P<0.05). There was no statistically significant difference in improvement from baseline to endpoint for any of the treatments. The only difference in scaling that was significant was between desoximetasone 0.25% and hydrocortisone (P=0.014). There was a greater decrease in the extent of area affected final mean score for desoximetasone 0.25% (mean, 1.5) and betamethasone (mean, 1.6) compared to hydrocortisone (mean, 3.2; P=0.02). The differences in mean change from baseline between desoximetasone 0.25% (4.3) and betamethasone (2.5) was significant (P=0.047). The difference between desoximetasone 0.25% when compared to hydrocortisone at week three was also significant (P=0.001). The mean scores for scaling were 0.8 for desoximetasone 0.25%, 1.5 for desoximetasone 0.05%, 0.8 for betamethasone, and 3.0 for hydrocortisone (P=0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The patient mean scores for extent of affected area were 1.5 for desoximetasone 0.25%, 2.6 for desoximetasone 0.05%, 2.0 for betamethasone, and 3.8 for hydrocortisone (P=0.08). The patient mean scores for itching were 1.2 for desoximetasone 0.25%, 2.5 for desoximetasone 0.05%, 1.9 for betamethasone, and 4.1 for hydrocortisone (P=0.014). There was no significant difference in patient mean scores for redness between the treatment groups (P=0.13). Secondary: Not reported
Delescluse et al.[27] (1996) Fluticasone 0.005% ointment applied BID vs betamethasone dipropionate 0.05% ointment applied BID	DB, MC, PG, RCT Patients with moderate to severe eczema	N=92 4 weeks	Primary: Physician assessment of clinical response, sign and symptom severity, patient assessment of treatment Secondary: Not reported	Primary: Improvement in signs and symptoms was seen in both treatment groups at two and four weeks. There was no significant difference in efficacy variables between fluticasone and betamethasone. Secondary: Not reported
Friedlander et al.[28] (2002) Fluticasone 0.05% cream applied BID	MC, OL Patients 3 months to 6 years of age with moderate to severe AD	N=51 4 weeks	Primary: Serum cortisol response, fluticasone levels Secondary: Not reported	Primary: Mean stimulated and unstimulated cortisol levels were similar before and after treatment (13.76 µg/dL pre-stimulation and 30.53 µg/dL post-stimulation vs 12.32 µg/dL pre-stimulation and 28.84 µg/dL post-stimulation). Two patients had endpoint post-stimulation results less than 18.0 µg/dL. Post-stimulation cortisol results were affected by the ratio of the amount of fluticasone used to total body surface area treated (P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Eichenfield et al.[29] (2006) Fluticasone 0.05% lotion applied daily vs placebo	DB, PC, PG, RCT Patients ≥3 months of age with moderate to severe AD	N=438 4 weeks	Primary: Treatment success Secondary: Physician's global assessment, sign/symptom severity, and subject/parent assessment	Primary: In study A, 75% of fluticasone-treated patients were considered to have a treatment success compared to 31% of placebo-treated patients (P<0.001). In study B, 66% of fluticasone-treated patients were considered to have a treatment success compared to 26% of placebo-treated patients (P<0.001). For subjects aged three to 12 months, there were 13 (76%) treatment successes on fluticasone compared to 4 (36%) on placebo. Secondary: Physician's Global Assessment of lesional clearance was 75 and 66% in the fluticasone-treated patients compared to 31 and 26% in the placebo-treated patients (study A and study B, respectively; P<0.001 for both comparisons). Stable/improved in uncleared lesions was 85 and 62% in the fluticasone-treated patients compared to 47 and 47% of placebo-treated patients (study A and study B, respectively; P<0.001 and P=0.018, respectively). Subject assessment of excellent response to therapy was 51 and 50% in the fluticasone-treated patients compared to 15 and 7% of placebo-treated patients (study A and study B, respectively; P<0.001 for both comparisons).
Sears et al.[30] (1997) Hydrocortisone buteprate 0.1% cream applied daily vs placebo	DB, MC, PC, RCT Patients with AD	N=168 14 days	Primary: Severity of dermatitis signs based on the mean lesion score for: infiltration, scaling, erythema, lichenification, vesicles, papules, excoriation, pruritus	Primary: At day three evaluations, there was a decrease of 3.10 in the mean lesion score for the hydrocortisone group compared to a decrease of 1.71 for the placebo group (P=0.0027). The mean reductions in mean lesion score at day seven evaluations for the hydrocortisone group compared to placebo were 4.65 and 2.93, respectively (P=0.0061). At endpoint (day 14), the mean decrease was 6.38 for the hydrocortisone group and 3.39 for placebo (P=0.0001). Secondary: On day three, the investigators gave a rating of cleared, excellent, or good,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Overall improvement; overall treatment efficacy; cosmetic acceptability	in terms of overall improvement, to a total of 36 of 98 patients in the hydrocortisone group, compared to six of 58 patients in the placebo group (P=0.0004). The same ratings were given to 65 of 103 hydrocortisone patients and 17 of 60 in the placebo group on day seven (P=0.0001); and, at endpoint, there were 72 of 93 in the hydrocortisone group compared to 19 of 54 in the placebo group assessed as cleared, excellent, or good (P=0.0001). Investigator assessment of treatment efficacy at endpoint was noted as excellent or good for 69% (N=73) of the hydrocortisone patients compared to 26% (N=16) in the placebo group. Patient assessment had 69% (N=73) in the hydrocortisone group compared to 32% (N=20) of placebo patients (P<0.001). The only statistically significant difference in cosmetic acceptability was the response to "pleasant feeling on the skin", in which hydrocortisone was favored (P=0.02).
Fowler et al.[31] (2005) Hydrocortisone butyrate 0.1% cream vs fluticasone propionate 0.05% cream, prednicarbate 0.1% cream, or mometasone furoate 0.1% cream	DB, MC, PG, RCT Patients 18 to 65 years of age with moderate hand dermatitis or AD	N=89 2 weeks	Primary: Investigator and subject ratings of signs and symptoms: erythema, cracking/fissuring, scaling, papules/ vesicles Secondary: Not reported	Primary: Based on the investigators' observations, the rate of improvement of cracking/fissuring was greater in the hydrocortisone butyrate (43%) group compared to the prednicarbate (21%) group (P<0.05). There were no other values that reached statistical significance for the investigators' observations. Based on the subjects' observations, the rate of improvement of erythema was greater in the hydrocortisone butyrate (50%) group compared to the fluticasone propionate (35%) group (P<0.05). There were no other values that reached statistical significance for the investigators' observations. In terms of resolution from baseline, all treatment groups showed improvement (P<0.02). The differences between treatment groups were not statistically significant (P>0.06). Secondary: Not reported
Abramovits et al.[32] (2010)	DB, MC, PC, RCT	N=264	Primary: Treatment success	Primary: In the hydrocortisone group, 63% of patients were considered a "success,"

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hydrocortisone butyrate 0.1% cream applied BID vs placebo	Patients ≥3 months to 18 years of age with mild to moderate AD	4 weeks	(defined as a final physicians global assessment score of 0 or 1, with ≥2-point reduction) Secondary: Change in pruritus score, change in eczema area and severity index, total percent body surface area affected, safety	compared to 28% of patients in the placebo group (P<0.001). Secondary: In the intent-to-treat population, the change in pruritus ranged from –1 to 3 in the hydrocortisone group and –2 to 3 in the placebo group (P<0.001). In the hydrocortisone group, pruritus worsened by 1 grade in 2% of patients, showed no change in 18% of patients, showed a 1-grade improvement in 37% of patients, showed a 2-grade improvement in 36% of patients, and showed a 3-grade improvement in 7% of patients. In the placebo group, pruritus worsened by 2 grades in 2% of patients, worsened by 1 grade in 5% of patients, showed no change in 39% of patients, showed a 1-grade improvement in 34% of patients, showed a 2-grade improvement in 19% of patients, and showed a 3-grade improvement in 2% of patients. In the hydrocortisone group, the mean change in eczema area and severity index scores was 84.2% compared to 45.3% in the placebo group (P<0.001). In the hydrocortisone group, total percent body surface area affected decreased 82.1% compared to 43.6% in the placebo group. In the hydrocortisone group, 22% of patients reported at least 1 adverse events compared 21% of patients in the placebo group (P=0.319). The majority of adverse events were described as mild, and none of the adverse events related to study drug were reported as severe.
Mandelin et al.[33] (2010) Hydrocortisone acetate 1% ointment applied BID (head and neck) and hydrocortisone butyrate 0.1%	DB, RCT Adults with moderate to severe AD	N=80 1 year	Primary: Affected body surface area, and eczema area and severity index Secondary: Adverse events	Primary: At six months, tacrolimus was significantly more effective than the corticosteroid regimen as measured by affected body surface area: 5.4 and 15.5%, respectively (P<0.05). At six months, tacrolimus was significantly more effective than the corticosteroid regimen as measured by the eczema area and severity index score: 3.2 and 7.1, respectively (P<0.05). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ointment applied BID (trunk and limbs) vs tacrolimus 0.1% ointment applied BID				Adverse events occurred in 100% of patients in the tacrolimus group and in 85.0% of patients in the corticosteroid arm (P=0.03). This was primarily due to the higher incidence of application-site skin burning sensation with tacrolimus.
Roth et al.[34] (1978) Hydrocortisone valerate 0.2% cream applied TID vs hydrocortisone 0.1% cream applied TID vs betamethasone valerate 0.1% cream applied TID vs placebo	DB, RCT Patients 2 to 75 years of age with chronic AD	N=68 2 to 4 weeks	Primary: Overall response, pruritus, erythema, scaling, excoriation, lichenification, overall judgment of response Secondary: Not reported	Primary: Overall response was in favor of the hydrocortisone valerate group compared to the hydrocortisone group, with 11 patients showing a better response compared to three patients, respectively (P<0.05). A consistently greater improvement in signs and symptoms was seen in the hydrocortisone valerate group compared to the hydrocortisone group at days five to nine, 12 to 16 and 26 to 35 (there was insufficient data for days 17 to 25). The only instances that were not proven to be significant were erythema at days five to nine (P<0.10) and lichenification at days five to nine and days 12 to 16 (P>0.10 and P<0.10, respectively). Patients in the hydrocortisone valerate and betamethasone valerate groups had moderate improvement in clearing, which was not significantly different between the two groups. More patients in the hydrocortisone valerate treatment group demonstrated excellent improvement or better compared to placebo, a difference that was significant. Secondary: Not reported
Williamson[35] (1987) Hydrocortisone 1% and urea 10% cream applied BID	RCT, SB Patients ≥12 years of age with eczema of the limbs or trunk	N=32 3 weeks	Primary: Assessment of eczema severity; severity of erythema, dryness/scaling,	Primary: Overall severity scores showed a steady improvement in the patients' eczema over the three weeks of the study, this being the same for both preparations. The results of the six individual measures also showed equivalent results.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to lesions on the left side of the body vs betamethasone valerate 0.1% applied BID to lesions on the right side of the body			papules, itching and excoriation Secondary: Patient self-assessment questionnaire	Secondary: Thirty-one of the thirty-two patients in the study completed the questionnaire. There was no statistically significant difference in the results obtained with either preparation. Overall, a total of 15 patients preferred the hydrocortisone and urea cream, and 16 preferred the betamethasone cream.
Pei et al.[36] (2001) Mometasone 0.1% ointment applied daily vs fluticasone 0.005% ointment applied daily One treatment group applied medication without wet wrap dressings (Group I [fluticasone] and II [mometasone]); the other had two weeks without wet wrap dressings followed by two weeks of medication	RCT, SB Patients with refractory AD	N=27 4 weeks	Primary: Disease extent and severity Secondary: Not reported	Primary: The difference in efficacy between the mometasone and fluticasone treatments was not statistically significant in terms of the extent of disease score (P=0.846) and the severity score (P=0.068). There was improvement in disease severity score for both study medications when all patients were not using any wet wrap dressing (P=0.043). Patients who used wet wrap dressings in weeks two to four of treatment had a greater improvement in disease severity compared to those who did not use wet wraps. Groups II, III, and IV had statistically significant improvements in disease severity score during week three with P values of 0.043, 0.008 and 0.011, respectively (P=0.116 for Group I). During week four, only the patients who received wet wraps continued to have statistically significant improvement in their disease severity score. The P value for groups III and IV were 0.018 and 0.050, respectively (P=0.091 for Group I and P=0.078 for group II). The extent of disease did not change significantly between group III and IV, with P values of 0.028 and 0.025, respectively (only patients who were using wet wrap dressings completed the study with less extensive disease). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
application under a wet wrap (Group III [fluticasone] and IV [mometasone]).				
Lebwohl[37] (1999) Mometasone 0.1% cream applied daily vs hydrocortisone valerate 0.2% cream applied BID	MC, RCT Patients 2 to 12 years of age with AD who had failed hydrocortisone	N=219 3 weeks	Primary: Total sign and symptom score, physician assessment of global clinical response Secondary: Not reported	Primary: The mean percentage improvement in total sign/symptom score was greater for the mometasone group (87.2%) compared to the hydrocortisone group (78.6%; P=0.011). Based on the physician's assessment of global clinical response, mometasone was found to be more efficacious than hydrocortisone (P=0.003). Secondary: Not reported
Moshang[38] (2001) Prednicarbate 0.1% cream applied BID	MC, OL Patients 4 months to 12 years of age with AD	N=55 3 weeks	Primary: Global evaluations, sign/symptom scores, cosmetic acceptability Secondary: Not reported	Primary: The percentage of patients who had greater than or equal to 75% clearance of their atopic dermatitis was 33% of patients on day eight evaluations and 78% on day 22. The mean global score decreased over the course of the study, with a mean score value of 1.9 on day eight, 1.5 on day 15, and 1.1 on day 22. Total sign and symptom score improved by 85% at endpoint. Cosmetic acceptability was rated as excellent by 71% of the patients' parents or guardians. Secondary: Not reported
Korting et al.[39] (1992) Prednicarbate 0.25% cream	DB, RCT Patients with atopic eczema	N=24 6 weeks	Primary: Skin thickness Secondary: Not reported	Primary: Clobetasol and betamethasone were found to decrease skin thickness greater than either prednicarbate or its placebo. The decrease in skin thickness was greater with betamethasone compared

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs betamethasone valerate 0.1% cream or clobetasol 0.05% cream				to clobetasol, but this was statistically insignificant. The decrease in skin thickness was greater with prednicarbate compared to its placebo, but this was statistically insignificant. Secondary: Not reported
Berberian et al.[40] (1999) Doxepin 5% and hydrocortisone 2.5% cream applied QID vs doxepin 5% and triamcinolone 0.1% cream applied QID vs hydrocortisone 2.5% cream applied QID vs triamcinolone 0.1% cream applied QID	DB, MC, PG, RCT Patients with pruritic AD who experienced moderate to severe pruritus associated with their eczematous lesions daily for at least 1 week, family history of atopy and/or a personal history of atopic dermatitis, ≤25% body surface area affected by atopic dermatitis, and good general health	N=349 8 days	Primary: Pruritus severity and pruritus relief Secondary: Not reported	Primary: Patients who received doxepin in addition to a steroid achieved significant reductions in pruritus than those treated with a steroid cream alone. The physician's global evaluations for pruritus relief demonstrated that the addition of doxepin to either hydrocortisone or triamcinolone treatment significantly improved itch relief over that of the topical corticosteroid alone. On day two, the doxepin 5% and hydrocortisone 2.5% combination was significantly better for pruritus relief than the hydrocortisone treatment alone (P=0.01) as was the doxepin 5% and triamcinolone 0.1% combination than the triamcinolone alone (P=0.027). By day eight, statistical significance was reached in favor of the doxepin 5% and hydrocortisone 2.5% combination over the steroid alone, but not for the doxepin 5% and triamcinolone 0.1% over triamcinolone alone. A faster improvement in the eczematous condition was noted by the physicians over the first couple of days of the study in those in the combination doxepin doxepin/steroid treatment groups vs steroid treatment alone. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Doss et al.[41] (2010) Tacrolimus 0.03% ointment applied BID vs fluticasone 0.005% ointment applied BID	DB, MC, RCT Patients 2 to 15 years of age with moderate to severe AD who had responded inadequately to topical corticosteroids	N=473 (ITT) N=371 (PP) 6 weeks	Primary: Response rate at week three Secondary: Changes in the mEASI score, global assessment of clinical response by investigators and patients, pruritus, sleep quality	Primary: In the PP analysis, response rates were 86.3% with tacrolimus and 91.5% with fluticasone (95% CI, -11.8 to 1.2). Tacrolimus was found to be non-inferior to fluticasone. In the ITT analysis, response rates were 84.3% with tacrolimus and 89.5% with fluticasone (P=0.0012). Secondary: The overall mean percentage change in total mEASI score was -79.5% in the tacrolimus group and -82.3% in the fluticasone group. Moderate or better improvement on the physicians' global assessment occurred in 93.6 and 92.4% of patients in the tacrolimus and fluticasone groups, respectively (ITT; P=0.05). Patients/parents considered global condition to have improved or greatly improved in 86.9% of patients receiving tacrolimus and 88.6% of those receiving fluticasone (ITT; P=0.047, PP; P=NS). Patients' assessment of pruritus improved in those receiving tacrolimus, with median change at day 21 of -84.0% compared to -91.5% in those receiving fluticasone (P=0.008). There was no significant difference in quality of sleep between the treatment groups (median change: tacrolimus, -91.5%; fluticasone, 92.6%). The incidence of adverse events was similar among the treatment groups. Application site burning occurred more frequently with tacrolimus.
Doss et al.[42] (2009) Tacrolimus 0.1% ointment applied to facial lesions BID vs	DB, MC, RCT Patients ≥16 years of age with moderate to severe AD of the face	N=468 3 weeks	Primary: Change in the mLEASI score Secondary: Facial erythema and pruritus, global clinical response	Primary: After three weeks, the response rate was 93.3% with tacrolimus and 87.8% with fluticasone as assessed by mLEASI (ITT; P=0.026, PP; P=0.046). Secondary: After three weeks, median changes in facial pruritus scores were -89.3% with tacrolimus compared to -88.3% with fluticasone (P=NS). Facial erythema improved in both treatment groups (P=NS).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluticasone 0.005% ointment applied to facial lesions BID				The physicians' global assessment of clinical response for the facial region was significantly different between the two groups. A total of 88% of patients in the tacrolimus group and 79% of patients in the fluticasone group showed marked or excellent improvement, or clearance of lesions (P=0.043). The patients' global assessment of clinical response for the facial region was significantly different between the two treatment groups. A total of 64% of patients in the tacrolimus group and 55% of patients in the fluticasone group considering their condition to have 'greatly improved' (P=0.014).
Reitamo et al.[43] (2005) Tacrolimus 0.1% ointment applied BID until clear and then for seven additional days vs hydrocortisone butyrate 0.1% ointment applied BID (trunk and extremities) and hydrocortisone acetate 1% ointment applied BID (head and neck)	DB, MC, RCT Patients ≥18 years of age with moderate to severe AD	N=972 6 months	Primary: Response rate at month three (improvement in mEASI) Secondary: Response rate at other time points, mEASI, EASI, physician's global evaluation of clinical response, patient's assessment of global response, physician's assessment of individual signs, affected BSA, patient's assessment of itch and quality of sleep, and the number of days on treatment as a	Primary: At month three, 72.6% of patients in the tacrolimus group responded to treatment compared to 52.3% of patients in the corticosteroid group (P<0.001). Secondary: The tacrolimus group had a higher response rate at all other time points throughout the six months compared to the corticosteroid group (P<0.001). A significant improvement in mEASI was observed as early as day eight in both treatment groups and increased up to the six-month point. At month six, the median percentage change in mEASI was -87.7% in the tacrolimus group and -82.5% in the corticosteroid group (P<0.008). The improvement in EASI and affected BSA followed the same trend. For EASI, the median percentage change was -85.0% in the tacrolimus group and -81.5% in the corticosteroid group (P=0.01). For the BSA, the median percentage change was -88.2% for the tacrolimus group and -80.3% in the corticosteroid group (P=0.001). Physicians' global assessments of clinical response was higher in the tacrolimus group compared to the corticosteroid group (P<0.001). There was a greater reduction in individual signs of AD in the tacrolimus group compared to the corticosteroid group and more patients in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			percentage of days in the study	tacrolimus group experienced clearance or excellent improvement (at month six, 61.3% of tacrolimus patients and 46.4% of corticosteroid patients had clearance or excellent improvement, P<0.001). Patients' assessments were significantly higher in the tacrolimus group compared to the corticosteroid group. At six months, 86.6% of patients in the tacrolimus group rated their AD as much better or better compared to 71.8% of patients in the corticosteroid group (P<0.001). Itch and quality of sleep improved significantly in both treatment groups. Patients in the tacrolimus group remained in the study longer compared to the corticosteroid group and had a lower number of treatment days as a percentage of days in the study.
Poole et al.[44] (2010) Tacrolimus 0.1% ointment applied BID until clear and then for seven additional days vs hydrocortisone butyrate 0.1% ointment applied BID (trunk and extremities) and hydrocortisone acetate 1% ointment applied BID (head and neck)	DB, MC, RCT Patients ≥18 years of age with moderate to severe AD	N=972 6 months	Primary: Quality of life (SF-36) assessed using a physical component summary and a mental component summary Secondary: Not reported	Primary: For the physical component summary, patients receiving tacrolimus gained 3.3 points on average compared to 2.3 points in the corticosteroid group (P=0.033). For the mental component summary, patients receiving tacrolimus improved by an average 6.0 points compared to 3.4 points in the corticosteroid group (P<0.001). For the eight SF-36 domains, all except 'Physical Functioning' (P=0.106) showed significant differences in favor of tacrolimus. Secondary: Not reported
Ashcroft et al.[45] (2005)	MA	N=6,897	Primary: For pimecrolimus:	Primary: <u>For pimecrolimus:</u>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tacrolimus or pimecrolimus vs topical corticosteroids or placebo	Patients with AD	1 week to 12 months	proportion of patients rated by the investigator as clear or almost clear For tacrolimus: proportion of patients achieving at least 90% improvement from baseline Secondary: Patients' global assessments of feeling better or much better, proportion of patients with flares of atopic dermatitis, improvements in quality of life, tolerability assessed by overall rates of withdrawal, withdrawal due to adverse effects, proportion of patients with burning of the skin and skin infections	In five trials evaluating pimecrolimus vs placebo, pimecrolimus was significantly more effective than placebo at three weeks (P<0.0001), and three of these found that pimecrolimus retained this efficacy at six weeks (P<0.0001). Another trial found no significant difference at six months between pimecrolimus and placebo. In three placebo-controlled trials, there were significantly fewer flares at six months in the pimecrolimus group compared to the placebo group, and remained more effective at preventing flares at 12 months. One trial evaluated pimecrolimus and a potent corticosteroid and found that betamethasone valerate 0.1% was significantly more effective than pimecrolimus after three weeks treatment when evaluating the proportion of patients who were clear or almost clear (P=0.0008). One study evaluated pimecrolimus vs a potent corticosteroid on the trunk and a mild corticosteroid on the face and found that the combination of corticosteroids was significantly more effective than pimecrolimus (when evaluating the proportion of patients moderately clear or better) at one week, three weeks, and six months but found no difference at 12 months. One direct comparison of pimecrolimus 1% cream and tacrolimus 0.03% ointment found no difference in the proportion of patients (children) who were clear or almost clear at six weeks (P=0.15). One study evaluating pimecrolimus four times daily compared to pimecrolimus two times daily found no difference in the proportion of patients clear or almost clear at the end of three weeks. <u>For tacrolimus:</u> One trial compared tacrolimus 0.03%, tacrolimus 0.1%, and placebo and found that the 0.03% strength was significantly more effective compared to placebo when evaluating the proportion of patients clear or achieving excellent improvement (P=0.006), but that the 0.1% strength did not differ from placebo (P=0.13) at three weeks. When evaluating patients' assessments of improvement as better or much better, both strengths proved significantly better than placebo. Three other trials reported the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				same outcomes as described above after 12 weeks and found both strengths to be significantly more effective than placebo (P<0.0001). Two trials compared tacrolimus 0.03% and 0.1% vs hydrocortisone 1% and found that tacrolimus was significantly more effective than hydrocortisone when evaluating the proportion of patients clear or achieving excellent improvement at three weeks (P<0.0001). One trial compared tacrolimus 0.1% and alclometasone 0.1% and found that tacrolimus was significantly more effective than alclometasone for treating facial dermatitis. One trial compared tacrolimus 0.03 and 0.1% and hydrocortisone butyrate 0.1% (a potent corticosteroid) and found that the 0.03% tacrolimus was significantly less effective than the hydrocortisone butyrate judged by the proportion of patients clear or achieving excellent improvement at three weeks (P=0.008); but no significant difference was seen between the 0.1% strength of tacrolimus and the hydrocortisone butyrate (P=0.65). Two trials compared tacrolimus 0.1% with betamethasone valerate 0.1% or hydrocortisone butyrate 0.1% and found that the tacrolimus was as effective as the corticosteroids in the proportion of patients achieving at least marked improvement. One trial compared tacrolimus 0.1% with a regimen of hydrocortisone butyrate 0.1% on the trunk and extremities and hydrocortisone acetate 1% on the head and neck. It found that tacrolimus was significantly more effective than the combined corticosteroid regimen when evaluating the proportion of patients clear or achieving excellent improvement at 12 weeks (P<0.0001). Six trials compared tacrolimus 0.1% and 0.03%. Three trials found no difference in proportion of patients clear or achieving excellent response at three weeks between the two strengths (P=0.44) and the remaining three found tacrolimus 0.1% to be significantly more effective than the 0.03% strength (P=0.04) at 12 weeks. Secondary: Significantly more patients withdrew from treatment in the placebo groups

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				than with either pimecrolimus or tacrolimus (P<0.05). Rates of withdrawal due to adverse effects did not differ significantly in the pimecrolimus group compared to the placebo group but was significantly higher in the tacrolimus group compared to the placebo group. Rates of withdrawal due to adverse effects did not differ significantly in the pimecrolimus or tacrolimus groups compared to topical corticosteroids, nor did rates when comparing tacrolimus 0.03 to 0.1%. Skin irritation and skin burning did not differ significantly between pimecrolimus groups and placebo (P=0.257), but the rate was significantly higher with pimecrolimus compared to betamethasone valerate 0.1% or a combined regimen of triamcinolone acetonide 0.1% and hydrocortisone acetate 1%. Both strengths of tacrolimus were more likely to cause skin burning compared to placebo (P=0.010) and were more likely to cause skin burning compared to mild or potent corticosteroids. Quality of life was difficult to measure and different outcome measures were used in the studies. In two studies, parents judged quality of life to be improved in patients taking pimecrolimus compared to placebo, and three trials showed increases in quality of life in patients taking tacrolimus 0.03and 0.1% compared to placebo. Tacrolimus 0.1% was found to have a significantly greater improvement on quality of life in adults compared to the 0.03% strength, but no significant differences were found in infants and children. No quality of life assessments were found comparing pimecrolimus and tacrolimus to topical corticosteroids.
El-Batawy et al.[46] (2009) Tacrolimus or	MA Patients with AD	N=7,378 (19 trials) Variable	Primary: Efficacy Secondary:	Primary: Pimecrolimus and tacrolimus were significantly more effective than placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
pimecrolimus vs topical corticosteroids or placebo		duration	Not reported	Compared to topical corticosteroids, tacrolimus 0.1% and 0.03% ointment was as effective as moderate potency topical corticosteroids, and more effective than a combined steroid regimen. Tacrolimus was more effective than mild potency topical corticosteroids. Secondary: Not reported
Chen et al.[47] (2010) Tacrolimus or pimecrolimus vs topical corticosteroids or placebo	MA Pediatric patients with AD	N=6,288 (20 trials) Variable duration	Primary: Efficacy and safety Secondary: Not reported	Primary: More patients using tacrolimus had a good response than those in control groups including placebo, 1% hydrocortisone acetate and 1% pimecrolimus. The corresponding OR were 4.56 (95% CI, 2.80 to 7.44), 3.92 (95% CI, 2.96 to 5.20) and 1.58 (95% CI, 1.18 to 2.12). The effect difference between 0.03% and 0.1% tacrolimus ointments was not statistically significant (OR, 0.90; 95% CI, 0.55 to 1.48). The incidence of adverse events of tacrolimus ointment or pimecrolimus cream was similar to the placebo. The major adverse events were burning and pruritus. Secondary: Not reported
Psoriasis				
Katz et al.[48] (1995) Betamethasone dipropionate 0.05% lotion applied BID vs clobetasol 0.05% solution applied BID	MC, PG, RCT, SB Patients ≥18 years of age with moderate to severe scalp psoriasis	N=193 2 weeks	Primary: Scaling, induration, erythema, pruritus, complied into a total sign and symptom score Secondary: Not reported	Primary: At day four, the mean percent improvement for the betamethasone group was 39.1% compared to 31.8% in the clobetasol group, respectively (P=0.010). The percent improvement was greater in the betamethasone group at day eight, with a 66.0% improvement compared to a 57% improvement for the clobetasol group, respectively (P≤0.005). Evaluations at day 15 showed an 82.8% improvement in the sign/symptom score for the betamethasone group compared to 74.9% improvement in the clobetasol group, respectively (P≤0.015). Erythema was the only individual sign that was significantly different between the two treatment groups at 14 days (P=0.023).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The mean sign/symptom score was 1.5 in the betamethasone group, compared to 2.3 in the clobetasol group, respectively (P≤0.009). Secondary: Not reported
Jacobson et al.[49] (1986) Betamethasone dipropionate 0.05% ointment applied BID vs clobetasol 0.05% ointment applied BID	DB, MC Patients with moderate-to-severe psoriasis	N=130 2 weeks	Primary: Treatment preference, assessment of efficacy of one side compared to the other (erythema, scaling, skin thickening), overall magnitude of response Secondary: Not reported	Primary: At the end of the two-week treatment period, 41% of investigators preferred the response obtained from clobetasol compared to the 8% of investigators who favored the response from betamethasone (P≤0.001). Overall magnitude of response (or at least a 75% reduction in erythema, scaling, and skin thickening) was greater on the clobetasol side (27 patients [22%]) compared to betamethasone (three patients [2 %]; P<0.001). Both treatment sides had an improvement in lesion severity in 59 patients (48%), and neither treatment side showed improvement in 35 patients (28%; P<0.001). Secondary: Not reported
Shupack et al.[50] (1993) Betamethasone dipropionate 0.05% ointment vs diflorasone 0.05% ointment	DB, PG, RCT Patients ≥18 years of age with moderate to severe plaque-type psoriasis for at least 6 months	N=44 2 weeks	Primary: Erythema, scaling, induration, investigator's evaluation Secondary: Patient satisfaction	Primary: No statistically significant differences were found between the treatment groups in erythema, scaling, and induration. At the week one physician evaluation, 18 of 21 patients in both the betamethasone and diflorasone treatment groups were rated as either cleared or improved, with these results remaining virtually unchanged for week two. Secondary: Patient satisfaction was considered high within both treatment groups.
Barsky et al.[51] (1976) Betamethasone	DB, MC, RCT Patients ≥2 years of age with psoriasis	N=263 3 weeks	Primary: Physician evaluation of therapeutic	Primary: A greater number of patients in the fluocinonide group had complete clearing or an excellent response compared to the betamethasone group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
0.025% gel applied TID vs fluocinonide 0.05% gel applied TID			response Secondary: Physician and patient preference	Fifty-five patients in the fluocinonide group demonstrated moderate improvement compared to 86 in the betamethasone group. Secondary: The mean physician preference score was 0.912, and the mean patient preference score was 0.908 (P<0.0001).
Pacifico et al.[52] (2006) Betamethasone valerate 0.12% cream applied daily vs betamethasone valerate 0.1% tape applied daily	PRO, RCT, SB Patients with mild to moderate psoriasis	N=42 30 days	Primary: PASI scores; hydration based on cutaneous trophism evaluation Secondary: Patient quality-of-life questionnaire	Primary: Lesions treated with betamethasone tape had a greater reduction in the PASI score compared to the betamethasone cream with a mean percentage reduction of 59.3 and 38.4%, respectively (P<0.001). The self-administered PASI score had a greater percentage reduction on the tape side (61.8%) compared to the cream side (34.0%), respectively (P<0.001). The mean percentage of skin hydration was increased with the betamethasone tape treatment area (38.8%) compared to the cream treatment area (11.1%, P<0.001). Secondary: Patients had a higher cosmetic acceptability and tolerability for the tape compared to the cream, citing that tape application was easier and that the cream was too greasy.
Reygagne et al.[53] (2005) Calcipotriol 0.005% solution applied BID vs clobetasol 0.05% shampoo applied QD	MC, PG, RCT, SB Patients ≥12 years of age with moderate to severe scalp psoriasis	N=151 4 weeks	Primary: GSS and theTSS Secondary: Pruritus, surface area of scalp affected by psoriasis	Primary: Clobetasol propionate was shown to be significantly more efficacious compared to calcipotriol in TSS measures (P<0.001 at week two and P=0.028 at week four) and GSS measures (P<0.001 at week two and P=0.016 at week four). Secondary: Erythema, plaque thickening, adherent desquamation, and pruritus improved in both treatments groups but a greater improvement was observed in the clobetasol group. The percentage of scalp surface area affected showed significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				difference in favor of clobetasol (P=0.02).
Menter et al.[54] (2013) Calcipotriene 50 µg/g and betamethasone dipropionate 0.5 mg/g suspension vs betamethasone dipropionate 0.5 mg/g suspension vs calcipotriene 50 µg/g suspension vs vehicle suspension	DB, MC, RCT Patients ≥18 years of age with mild to moderate psoriasis for ≥6 months involving ≥10% of the arms, legs or trunk and amenable to treatment with ≤100 g of medication per week	N=1,152 8 weeks	Primary: Proportion of patients achieving controlled disease (IGA score of clear or almost clear and ≥2 point change from baseline) at weeks four and eight Secondary: Change from baseline in PASI at weeks four and eight	Primary: At week four, there was a significantly greater proportion of patients achieving controlled disease in the calcipotriene and betamethasone group (13.3%) compared to calcipotriene groups (5.2%; P=0.019) and vehicle (2.1%; P=0.001). There was no significant difference in achievement of controlled disease between the calcipotriene and betamethasone and betamethasone groups (12.5%; P=0.82). At week eight, the calcipotriene and betamethasone group had a significantly greater proportion of patients achieving controlled disease (29%) compared to the betamethasone (21.5%), calcipotriene (14.6%) and vehicle groups (6.3%; P≤0.008 for all comparisons). Secondary: At week four, the calcipotriene and betamethasone group had a significantly greater mean reduction in PASI (46.4%) compared to the betamethasone (42.7%), calcipotriene (32.2%) and vehicle groups (17.4%; P≤0.038 for all comparisons). At week eight, the calcipotriene and betamethasone group had a significantly greater mean reduction in PASI (55.8%) compared to the betamethasone (48.6%), calcipotriene (43.6%) and vehicle groups (20.9%; P<0.001) for all comparisons).
Douglas et al.[55] (2002) Calcipotriene and betamethasone ointment applied BID (CB) vs betamethasone ointment applied BID (B)	DB, PRO, RCT Patients ≥18 years of age with a diagnosis of psoriasis vulgaris	N=1,106 4 weeks of treatment and an additional 4 weeks of OL treatment with calcipotriene	Primary: Mean percent change in PASI from baseline after four weeks Secondary: Speed of response as assessed from percent change in PASI after one week, mean percentage	Primary: There was a significant reduction in mean percent change in PASI from baseline to week four in the CB group compared to the B group and the C group (74.4, 61.3, and 55.3% respectively; P<0.001). Secondary: There was a significant reduction in mean percent change in PASI after week one in the CB group compared to the B group and the C group (47.4, 39.8, and 31% respectively; P<0.001). There was a significant reduction in the mean percent change in thickness of the psoriatic lesion from baseline to week four in the CB group compared to the B group and the C group (79.4, 61.7, and 63%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs calcipotriene ointment applied BID (C)			decrease in the thickness of psoriatic lesion from baseline after four weeks	respectively; P<0.001). There was no significant difference in the percent of patients reporting adverse effects in any of the treatment groups.
Kaufmann et al.[56] (2002) Calcipotriene and betamethasone ointment applied QD (CB) vs betamethasone ointment applied QD (B) vs calcipotriene ointment applied QD (C) vs vehicle ointment QD (V)	DB, PC, PRO, RCT Patients ≥18 years of age with a diagnosis of psoriasis vulgaris affecting at least 10% of one or more body regions	N=1,603 4 weeks	Primary: PASI score, IGA score, PGA score assessing patients with treatment success (defined as marked improvement or clearance of disease) Secondary: Not reported	Primary: There was a significant decrease in PASI score in the CB group compared to the B, C, and V groups (-71.3, -57.2, -46.1, and -22.7% respectively; P<0.001). There was a significantly larger number of patients assessed as having controlled disease according to the IGA score in the CB group compared to the B, C, and V groups (276, 176, 107, and 16 respectively; P<0.001). There was a significantly larger number of patients assessed as having treatment success according to the PGA scores after four weeks in the CB group compared to the B, C, and V groups (316, 216, 137, and 15 respectively; P<0.001). Secondary: Not reported
Papp et al.[57] (2003) Calcipotriene and betamethasone ointment applied BID (CB)	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of psoriasis vulgaris affecting at least	N=1,028 4 weeks	Primary: Mean percent reduction in PASI from baseline to the end of treatment	Primary: There was a significant percent reduction in PASI at the end of treatment in the CB group compared to the B, C, V groups (73.2, 48.8, 63.1, and 28.8% respectively; P<0.001). Secondary: There was a significant reduction in the mean percent change in PASI

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs betamethasone ointment applied BID (B) vs calcipotriene ointment applied BID (C) vs vehicle ointment BID (V)	10% of one or more body areas		Secondary: Speed of response assessed as the mean percent change in PASI from baseline after one week of treatment	from baseline to after one week of treatment in the CB group compared to the B, C, and V groups (48.1, 28.4, 41.4, and 21.5% respectively; P<0.001).
Luger et al.[58] (2008) Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g vs calcipotriol 50 µg/g	DB, MC, RCT Patients with moderate to severe scalp psoriasis	N=869 52 weeks	Primary: Efficacy and safety Secondary: Not reported	Primary: Disease was satisfactorily controlled in 92.3% of visits in the calcipotriol-betamethasone group vs 80.0% in the calcipotriol group (P<0.001). Adverse drug reactions were less frequent in the calcipotriol-betamethasone group compared to the calcipotriol group (17.2 vs 29.5%; P<0.001). Incidences of adverse events possibly associated with long-term corticosteroid use were low in both the calcipotriol-betamethasone (2.6%) and the calcipotriol (3.0%) groups. Secondary: Not reported
van de Kerkhof et al.[59] (2009) Calcipotriol 50 µg/g and	DB, MC, PG, RCT Patients with scalp psoriasis involving >10% of the scalp	N=1417 8 weeks	Primary: Proportion of patients with 'absence of disease' or 'very mild disease' according	Primary: The proportion of patients with 'absence of disease' or 'very mild disease' at week eight was significantly higher in the calcipotriol and betamethasone group (68.4%) than the betamethasone dipropionate (61.0%; P=0.0079) or calcipotriol (43.4%; P<0.0001) groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
betamethasone dipropionate 0.5 mg/g vs betamethasone dipropionate 0.5 mg/g vs calcipotriol 50 µg/g			to investigators' assessments Secondary: Patient ratings of scalp psoriasis and adverse events	Secondary: The proportion of patients rating their scalp psoriasis as 'clear' or 'almost clear' was significantly higher in the calcipotriol and betamethasone group (69.6%) than for betamethasone dipropionate (59.9%; P=0.0006) or calcipotriol (44.7%; P<0.0001). The incidence of lesional/perilesional adverse events was lower in the calcipotriol and betamethasone and betamethasone dipropionate groups than the calcipotriol group.
Jemec et al.[60] (2008) Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g applied QD vs betamethasone dipropionate 0.5 mg/g applied QD vs calcipotriol 50 µg/g applied QD vs placebo	DB, MC, RCT Patients with scalp psoriasis	N=1505 8 weeks	Primary: Patients with ‘‘absence of disease’’ or ‘‘very mild disease’’ according to IGA of disease severity at week eight Secondary: Total Sign Score at week eight, proportion of patients who were ‘‘almost clear’’ or ‘cleared’’ by patients’ assessment	Primary: The proportion of patients who achieved ‘‘absent’’ or ‘‘very mild’’ disease at week eight was significantly greater in the calcipotriol and betamethasone group (71.2%) compared to the betamethasone dipropionate group (64.0%; P=0.011), the calcipotriene group (36.8%; P<0.0001), and the placebo group (22.8%; P<0.0001). Secondary: At week eight, the percentage change in Total Sign Score was significantly larger for the calcipotriol and betamethasone group (-70.8%) than for calcipotriene (-49.0%; P<0.0001) and for placebo (-35.6%; P<0.001). The difference vs betamethasone dipropionate, (-67.7%) was not statistically significant (P=0.12). The proportion of patients who rated their scalp psoriasis as ‘‘cleared’’ or ‘‘almost clear’’ at week eight was 68.6% for the calcipotriol and betamethasone group, 62.5% for betamethasone dipropionate, 38.3% for calcipotriene, and 20.7% for the placebo alone. The calcipotriol-betamethasone group was significantly more effective than calcipotriene (P<0.0001) and the placebo alone (P<0.0001). The difference vs betamethasone dipropionate was not statistically significant (P=0.2).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Camarasa et al.[61] (2003) Calcitriol 3 µg/g ointment applied BID vs betamethasone dipropionate 0.05% ointment applied BID	DB, MC, RCT Adults with chronic plaque-type psoriasis of at least moderate severity	N=258 Treatment: 6 weeks Follow-up: 8 weeks	Primary: Global improvement of treated psoriatic lesions; PASI; relapse Secondary: Not reported	Primary: After six weeks, both calcitriol and betamethasone were found to be efficacious. Similar proportions of patients (79% in the calcitriol group and 82% in the betamethasone group) showed definite or considerable improvement in their psoriasis, or total clearance of lesions by treatment endpoint. The mean of the global improvement scores at endpoint were similar (2.31 for calcitriol and 2.55 betamethasone; P<0.05). Both treatment groups showed a clinically relevant decrease in the mean GSS which, at endpoint, was 1.58 for the calcitriol group and 1.36 for the betamethasone group (P<0.05). Each treatment also resulted in a marked improvement in the PASI from baseline to endpoint, with the absolute reduction in the mean PASI at endpoint being comparable between the groups (P>0.05). Relapse warranting new treatment within eight weeks of the study endpoint was required in 52% of patients who had been receiving calcitriol, at a mean of 25.3 days post-treatment. In the betamethasone group, relapse was required for 75% of patients at a mean of 23.4 days post-treatment. The proportion of responders remaining in remission at eight weeks post-treatment (48 and 25% for the calcitriol and betamethasone groups, respectively; P<0.01). The two study ointments were similar in terms of cosmetic acceptability. The overall opinion of the ointments by the majority of patients was generally 'good' or 'acceptable' (91 and 92%, for the calcitriol and betamethasone groups, respectively). Secondary: Not reported
Bergstrom et al.[62] (2003)	RCT, SB	N=32	Primary: Patient quality of	Primary: Improvement in psoriasis severity was greater in the clobetasol foam

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Clobetasol 0.05% foam applied to the skin and scalp vs clobetasol cream 0.05% applied to the skin and clobetasol 0.05% solution applied to the scalp	Patients with psoriasis	14 days	life; effectiveness, user satisfaction; severity based on the PASI and self-administered PASI Secondary: Not reported	group compared to the clobetasol cream and solution combination group (P=0.05). There was a greater improvement in scalp psoriasis for the foam group compared to the solution group (P=0.03). Global QOL was greater for the foam group compared to cream (P=0.05) and solution (P=0.02). Secondary: Not reported
Jegasothy et al.[63] (1990) Clobetasol 0.05% ointment applied BID vs diflorasone 0.05% ointment applied BID	DB, RCT Patients with mild to severe psoriasis	N=60 2 weeks	Primary: Physician and patient preferences Secondary: Assessment of sign and symptom severity	Primary: At two weeks post treatment 75% of physicians and 68% of patients favored clobetasol treatment compared to 9% of physicians and 11% of patients who favored diflorasone, respectively (P<0.05). Secondary: At day 15, lesion clearing was greater with clobetasol in 21% of the patients compared to 9% of patients who had greater clearing with diflorasone (P<0.05). Clobetasol was more efficacious in terms of relieving erythema, scaling, and skin thickening on day eight, day 15 and at follow-up when compared to diflorasone (P<0.05).
Decroix et al.[64] (2004) Clobetasol lotion applied BID vs clobetasol cream applied BID	MC, PC, PG, RCT, SB Patients ≥18 years of age with moderate to severe plaque type psoriasis	N=213 4 weeks	Primary: Dermatologic sum score, global severity score Secondary: Patient cosmetic acceptability survey	Primary: Both the dermatologic sum score and the global severity score had a greater improvement in the lotion and cream groups when compared to the placebo group (P<0.001). Overall improvement was seen in 74% in the lotion group and 78% in the cream group compared to 15% in the placebo group (P<0.001). Secondary: Patients favored the lotion over the cream in terms of satisfactory penetration time (P=0.043), drying quickly (P=0.002), feeling greasy

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				(P<0.001), possessing a pleasing aspect and perfume (P=0.001), and leaving a film on the skin (P<0.017).
Lowe et al.[65] (2005) Clobetasol lotion applied BID vs clobetasol cream applied BID vs placebo	MC, PC, RCT, SB Patients with moderate to severe plaque-type psoriasis	N=192 4 weeks	Primary: Erythema, plaque elevation, scaling, dermatological sum score, pruritus, global improvement global severity Secondary: Not reported	Primary: The difference in dermatologic sum score between clobetasol lotion and its placebo was statistically significant, with values of 2.21 and 5.93, respectively (P<0.001). When compared to the cream, the lotion resulted in no significant difference in dermatologic sum score improvement. The number of patients that had mild or no signs and symptoms was greater in the lotion group compared to its placebo (P<0.001). The difference in sign and symptom severity was not statistically significant between the lotion and the emollient cream group (0.168≤P≤0.868). Secondary: Not reported
Sofen et al.[66] (2011) Clobetasol 0.05% spray applied BID for up to four weeks vs placebo	DB, MC, RCT, VC Patients with moderate-to-severe (global severity score=3 or 4) plaque psoriasis of the scalp	N=81 4 weeks	Primary: Global severity score of psoriasis of the scalp after four weeks Secondary: Safety	Primary: At week four, 85% of patients in the clobetasol group achieve treatment success (global severity score clear or almost clear) compared to 13% of patients in the placebo group (P<0.001). The proportion of patients in the clobetasol group who achieved a global severity score of 0 after two weeks and at the end of treatment was 12 and 51%, respectively. Secondary: Clobetasol spray was well-tolerated and there were no serious adverse events or reports of folliculitis or Cushing's syndrome.
Menter et al.[67] (2009) Clobetasol 0.05% spray applied BID	MC, RCT Patients 18 to 80 years of age with stable plaque	N=122 8 weeks	Primary: Efficacy as assessed by overall disease severity, investigator global	Primary: After two weeks, 41% of patients receiving clobetasol had treatment success (clear or almost clear) compared to 27% of patients receiving calcipotriene and betamethasone dipropionate. After four weeks, 75% of patients receiving clobetasol were clear or almost clear compared to 45%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
for four weeks vs calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment applied daily for four weeks	psoriasis involving 3 to 20% of the body surface area		assessment, PQOL-12 Secondary: Not reported	of patients receiving calcipotriene and betamethasone dipropionate (P=0.003). After eight weeks, 14% of patients receiving clobetasol were clear or almost clear compared to 8% of calcipotriene and betamethasone dipropionate patients. After four weeks, there was no significant difference in treatment success (clear or mild as assessed using the investigator global assessment scale) among the treatment groups (73% for clobetasol vs 65% for calcipotriene and betamethasone dipropionate). After two weeks, 52% of patients receiving clobetasol were clear or mild compared to 33% of patients receiving calcipotriene and betamethasone dipropionate (P=0.054). After eight weeks, 41% of patients receiving clobetasol were clear or mild compared to 24% of patients receiving calcipotriene and betamethasone dipropionate. After four weeks, PQOL-12 scores decreased by 36.1 points with clobetasol and by 30.8 points with calcipotriene and betamethasone dipropionate. After two weeks, PQOL-12 scores decreased by 24.4 points with clobetasol and by 21.4 points with calcipotriene and betamethasone dipropionate. After eight weeks, PQOL-12 scores decreased by 15.9 points with clobetasol and by 10.1 points with calcipotriene and betamethasone dipropionate. Patient satisfaction surveys indicate that more patients were satisfied with clobetasol than with calcipotriene and betamethasone dipropionate. Compliance was similar in both treatment groups (100% for clobetasol and 97% for calcipotriene and betamethasone dipropionate). Erythema, scaling and dryness were similar in both treatment groups. More patients experienced stinging/burning with clobetasol. Secondary: Not reported
Tan et al.[68] (2009)	MC, OL Patients ≥18 years	N=288 4 weeks	Primary: Patient-administered	Primary: For skin-related quality of life, the mean dermatology life quality index score decreased significantly from 7.0 at baseline to 3.2 at week four

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Clobetasol 0.05% shampoo applied daily	of age with moderate or severe scalp psoriasis (global severity score of 3 or 4 on a 0 to 5 scale)		questionnaires assessing effect of treatment on skin-related quality of life (using dermatology life quality index); patient satisfaction and treatment preference; efficacy (global severity scale); adverse events Secondary: Not reported	(P<0.001). After four weeks of treatment, 81.7% of patients indicated that scalp psoriasis had a small effect or no effect on their quality of life compared to 45.6% of patients at baseline (P<0.001). The percentage of patients who considered the disease to have a very large effect or extremely large effect on their life decreased from 19.4 to 3.4% (P<0.001). At week four, most patients reported that the disorder had no effect on their daily activities or symptoms/feelings (85.8 and 61.2%, respectively) compared to 54.8 and 14.5% at baseline, respectively. The percentage of patients considering the disease as having no effect on their leisure, work/school, personal relationships, and treatment increased from 83.0%, 91.5, 86.2 and 87.6%, respectively, to 95.1, 98.1, 93.7 and 93.7%, respectively. The percentage of patients who had none or mild pruritus increased from 24.6% at baseline to 83.0% at week four. The percentage of patients who experienced none or mild scaling increased from 0.7% at baseline to 64.9% at week four. The percentage of patients with moderate or severe pruritus decreased from 75.4% at baseline to 17.0% at week four. The percentage of patients with severe or very severe scaling decreased from 57.3% at baseline to 4.5% at week four. Most patients (>90%) were highly satisfied with the cosmetic acceptability of clobetasol: 92.8% of patients considered it pleasant to use, and 91.7% agreed that they could easily incorporate it into their daily routine. According to 95.1% of patients, clobetasol lathered and cleansed hair as well as regular shampoo. Overall, 90.2% of patients were satisfied with the efficacy of the treatment, while 86.4% were unaffected by adverse events. At week four, 78.1% of patients achieved the score of mild, very mild, or clear on the Global Severity Scale. The percentage of patients having severe psoriasis decreased from 41.7% to 3.5%. Only 2.1% of patients reported treatment-related adverse events, which

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				were considered mild or moderate in severity. A total of 80.7% of patients considered clobetasol to be better than prior treatments, with 57.3% indicating it was much better. Overall, 86.5% of patients indicated that they would use clobetasol again. Secondary: Not reported
Poulin et al.[69] (2010) Clobetasol 0.05% shampoo applied twice weekly for up to 6 months vs placebo All patients were enrolled in an initial four-week OL trial. Patients with a global severity scale ≤2 (clear, very mild or mild) were then randomized into the maintenance phase of the study.	DB, PC, RCT Patients with moderate scalp psoriasis (global severity scale of 3 on a 0 to 5 scale)	N=136 6 months	Primary: Relapse rate, safety; patient satisfaction Secondary: Not reported	Primary: The percentage of patients who had no relapse was significantly greater with clobetasol than with placebo (P<0.01) at all time points. After one month, 44% of patients in the placebo group had no relapse; whereas this rate was observed approximately four months later in the clobetasol group. After six months of maintenance treatment, the percentage of patients who had no relapse was 40.3% with clobetasol compared to 11.6% with placebo. The median time to first relapse was 30.5 days with placebo and 141.0 days with clobetasol (P<0.0001). Among the patients who had relapse and entered the alternate treatment regimen, a significantly greater percentage of those in the clobetasol group (73.2%) experienced only one relapse over six months compared to those in the placebo group (34.1%; P<0.001). More patients in the placebo group had two or three relapses (38.3 and 27.6%, respectively) during the maintenance phase than in the clobetasol group (16.8 and 10.0%, respectively; P<0.001). More adverse events occurred in the placebo group (50 events) than in the clobetasol shampoo group (34 events). At the end of treatment, 72.7% of patients in the clobetasol group preferred the twice-weekly treatment for a long period, compared to a daily treatment in case of relapse. There were 86.0% of patients in the clobetasol group willing to continue the treatment in the same way, and 57.1% reported that they could adopt such a regimen for as long as one year. Significantly more patients in the clobetasol group than the placebo group agreed that the treatment was enough to control their disease (73.7 vs 39.7%; P<0.001), considered themselves not bothered at all by side

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				effects (93 vs 79.7%; P<0.05), and were satisfied or very satisfied with the overall treatment (84.2 vs 59.7%; P<0.01). Secondary: Not reported
Bovenschen et al.[70] (2010) Clobetasol 0.05% shampoo applied daily for 15 minutes .	PRO Patients ≥18 years of age with scalp psoriasis	N=56 4 weeks	Primary: Questionnaire assessing treatment satisfaction, user convenience, safety and effectiveness Secondary: Not reported	Primary: A total of 66% of patients judged the treatment as satisfactory after four weeks. A total of 79% of patients reported a positive user convenience with clobetasol. The severity of symptoms decreased as follows after four weeks of treatment (all, P<0.05): pruritus, -46%; pain, -44%; desquamation, -43%; social impairment (-39%). Treatment was generally well-tolerated and there were no major adverse events other than a mild skin irritation in two patients (5%). One patient had mild hair loss (3%). Secondary: Not reported
Mraz et al.[71] (2008) Clobetasol 0.05% spray applied BID for up to four weeks vs clobetasol 0.05% foam applied BID for two weeks	RCT Patients with moderate to severe plaque psoriasis	N=77 4 weeks	Primary: Efficacy Secondary: Quality of life (as determined by the dermatology life quality index) and adverse events	Primary: Patients treated with clobetasol spray had a median 64% reduction in affected body surface area compared to a median 25% reduction in patients treated with the clobetasol foam (P=0.004). At the end of the treatment period, 22% of clobetasol spray-treated patients were completely clear compared to 5% of clobetasol foam-treated patients (P=0.04). Secondary: Improvements in quality of life as determined by the dermatology life quality index were statistically significantly greater at all time points for patients treated with clobetasol spray compared to patients treated with clobetasol foam (P<0.04).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The majority of adverse events for both products were mild in severity.
Saleem et al.[72] (2018) Desoximetasone 0.25% topical spray applied BID vs placebo	DB, MC, RCT Patients ≥18 years of age with moderate to severe plaque psoriasis	N=120 28 days	Primary: Proportion of subjects in each group that achieved clinical success (PGA of 0 or 1) and/or treatment success at (target lesion score of 0 or 1) day 28 Secondary: Mean change from baseline in PGA, mean change from baseline in Total Lesion Severity Scale, mean change from baseline in percent BSA affected	Primary: Clinical success in the intent-to treat and placebo group was 30 and 5% (P=0.0003), respectively; treatment success was 39 and 7% (P<0.0001), respectively. Secondary: Mean change from baseline in PGA (1.14 vs 0.50) and Total Lesion Severity Scale (4.73 vs 1.93) were both improved with desoximetasone as compared to placebo, respectively (both P<0.0001). The mean change from baseline in percent BSA affected was 2.24% in the desoximetasone spray group and 0.37% in the placebo group (P=0.0011).
Willis et al.[73] (1986) Desoximetasone 0.05% gel applied BID vs fluocinonide 0.05% gel applied BID	DB, MC, PG, RCT Patients with scalp psoriasis	N=123 2 weeks	Primary: Mean sign and symptom score based on severity of erythema, scaling, thickening, and pruritus Secondary: Patient cosmetic acceptability	Primary: There was an insignificant difference in the mean overall evaluation scores between the desoximetasone group and the fluocinonide group. Eighty-nine percent (54 of 61) of patients in the desoximetasone group and 82% (49 of 60) in the fluocinonide group achieved either good or excellent improvement. Secondary: No significant difference was found between the treatment groups in terms of cosmetic acceptability.
Zachariae et al.[74] (1976)	DB, RCT	N=27	Primary: Erythema,	Primary: After two weeks of treatment, there was a greater improvement of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Desoximetasone 0.25% applied BID vs hydrocortisone butyrate 0.1% applied BID	Patients with psoriasis	2 weeks	induration, scaling, pruritus, pustulation Secondary: Patient preference	symptoms in the desoximetasone treatment group compared to the hydrocortisone group. Desoximetasone was more efficacious when compared to hydrocortisone in improving erythema, scaling, and induration (P<0.05). Secondary: Thirteen patients preferred desoximetasone and three patients preferred hydrocortisone (P<0.05).
Anonymous[75] (1985) Desoximetasone 0.25% ointment applied BID vs fluocinonide 0.05% ointment applied BID	MC, PG, RCT, SB Patients ≥3 years of age with stable or exacerbating psoriasis	N=121 14 days	Primary: Assessment of sign and symptom severity scores (based on pruritus, erythema, scaling, and thickening), clinical improvement Secondary: Patients' evaluation of cosmetic attributes	Primary: There was a greater improvement in the overall sign and symptom severity score in the desoximetasone group compared to the fluocinonide group. The mean sign and symptom scores for desoximetasone and fluocinonide were 2.47 and 2.66, respectively, at day four (P=0.065); 2.00 and 2.28, respectively at day seven (P=0.080); and, 1.75 and 2.07, respectively at day 14 (P=0.014). These results were statistically significant at day 14. Patient response to treatment was greater in the desoximetasone group compared to the fluocinonide group at day 14 (P≤0.029). Secondary: The percentage of patients with an excellent improvement was greater in the desoximetasone group compared to the fluocinonide group at day four and 14 (day four, 32 vs 18%, respectively; P=0.046, day 14, 42 vs 25%, respectively; P=0.028).
Lee et al.[76] (2009) Fluocinonide 0.1% cream vs clobetasol 0.05% cream	PC, SB, SC Patients ≥18 years of age with clinically diagnosed plaque-type psoriasis	N=5 12 days	Primary: Reduction of erythema, scaling and induration Secondary: Not reported	Primary: After three days, a reduction of erythema, scaling and induration (mild to moderate improvement) was seen in all of the treatment sites. Moderate improvement was seen in 40% of test sites treated with fluocinonide and 20% of sites treated with halobetasol and clobetasol. After five days, moderate improvement or clear or almost clear was seen in 80% of test sites treated with fluocinonide and 60% of sites treated with halobetasol or clobetasol. After seven days, 80% of all active-treated sites were assessed as moderate

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs halobetasol 0.05% cream vs placebo				or clear or almost clear. There was no significant difference among the active treatment groups. The best response was reached by day seven in 10 of 15 (67%) of active-treated sites. The other five sites reached their best response in the second week of treatment. The best response was maintained at each site until the end of the 12-day test period. The active treatments were well tolerated. Secondary: Not reported
Krueger et al.[77] (1987) Flurandrenolide tape 4 mg/cm^2 applied daily for up to 16 hours vs diflorasone 0.05% ointment applied BID	RCT, SB Patients ≥18 years of age with stable psoriasis	N=30 4 weeks	Primary: Erythema, scaling, and induration individually and in aggregate erythema, scaling, and infiltration scores Secondary: Not reported	Primary: At baseline, the erythema, scaling, and infiltration scores values for both groups were 5.8 (P=0.68). At the week two evaluations, the erythema, scaling, and infiltration scores score was less in the flurandrenolide group compared to the diflorasone group at values of 1.9 and 3.3, respectively; also, these scores were decreased from the values obtained at baseline by 67 and 43%, respectively (P<0.01). At the week four evaluation, the erythema, scaling, and infiltration scores was also less for the flurandrenolide tape group vs the diflorasone group, with values of 1.6 and 2.7, respectively. Compared to baseline, the erythema, scaling, and infiltration scores score for the flurandrenolide tape group decreased by 72%, and the diflorasone ointment group decreased by 53% (P<0.01). Flurandrenolide-tape-treated psoriatic plaques showed more positive results in overall treatment success with a rate of 60% at week two and 64% at week four. The overall treatment success rates for diflorasone ointment at week two and week four were 22 and 33%, respectively (P<0.01). Secondary: Not reported
Green et al.[78] (Abstract only)	DB, MC, RCT (two studies)	N=430	Primary: Treatment success,	Primary: By week eight, 36.5% (Study 1) and 38.4% (Study 2) of subjects were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2018) Halobetasol propionate 0.01% lotion QD vs vehicle QD	Patients with moderate-to-severe plaque psoriasis	12 weeks (8 weeks treatment and 4 weeks follow-up)	defined as at least a 2-grade improvement from baseline in IGA score and 'clear' or 'almost clear', at week eight Secondary: Psoriasis signs and symptoms, BSA, QOL, safety and treatment emergent adverse events	treatment successes compared with 8.1% and 12.0% on vehicle (P<0.001). Secondary: Halobetasol propionate 0.01% lotion was also superior in reducing psoriasis signs and symptoms, BSA and improving QOL. Halobetasol propionate 0.01% lotion was well-tolerated with no treatment-related adverse events greater than 1%.
Bhatia et al.[79] (Abstract only) (2019) Halobetasol propionate 0.05% foam BID vs vehicle BID	DB, RCT (two studies) Adult patients with moderate to severe plaque psoriasis	N=560 14 days	Primary: Proportion of subjects with treatment success, defined as those subjects that achieved a score of 0 or 1 and at least a two-grade improvement compared to baseline for the IGA and for the clinical signs of psoriasis as well as pruritus Secondary: Safety, including adverse events and local skin reactions in the treatment area	Primary: Halobetasol propionate 0.05% foam was statistically superior to vehicle in achieving treatment success in 25.3% and 30.7% vs 3.9% and 7.4% (P<0.001) in Studies 1 and 2, respectively. Pruritus scores statistically improved by over 30% in halobetasol propionate 0.05% foam treated subjects. In addition, these subjects experienced a significant reduction in the clinical signs of psoriasis (plaque elevation, scaling, and erythema). In contrast, in the vehicle groups the decrease in psoriasis-related signs was generally not observed. Secondary: Safety outcomes were unremarkable and similar in both the halobetasol propionate 0.05% foam and vehicle treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Swinehart et al.[80] (1989) Mometasone 0.1% lotion applied daily vs triamcinolone 0.1% lotion applied BID	MC, PG, RCT Patients with scalp psoriasis	N=202 21 days	Primary: Changes in disease sign and symptom scores for erythema, scaling, induration, pruritus Secondary: Patient evaluation of efficacy and cosmetic acceptability of treatment	Primary: There was a greater improvement in the sign and symptom scores in the mometasone group compared to the triamcinolone group. Seventy-seven percent of patients in the mometasone group and 62% in the triamcinolone group showed improvement or clearing of disease (P≤0.05). Secondary: Patients considered mometasone the better treatment in terms of efficacy and cosmetic acceptability. Eight-eight percent of patients in the mometasone group and 80% in the triamcinolone group rated their response as either good or excellent (P<0.01).
Medansky et al.[81] (1988) Mometasone 0.1% ointment or cream applied daily vs fluocinolone 0.025% ointment or cream applied TID and mometasone 0.1% ointment or cream applied daily vs triamcinolone 0.1% ointment or cream applied BID	MC, PG, RCT, SB Patients with chronic moderate to severe psoriasis vulgaris	N=764 21days	Primary: Evaluation of individual disease signs in the target areas and change in disease sign score; change in overall disease status Secondary: Not reported	Primary: The mean disease sign score showed a greater percentage improvement in the mometasone ointment patients compared to the fluocinolone ointment group (58 vs 41%; P<0.01). There was a greater percentage improvement in the mometasone ointment group compared to the triamcinolone ointment group with disease sign score improvements of 60 and 37%, respectively (P<0.01). There was a greater percentage improvement in the mean disease sign score in the mometasone cream group compared to the fluocinolone cream group (51 vs 29%; P<0.001). The mometasone cream group had a slight increase in percentage improvement compared to the triamcinolone cream group, but the results were not statistically significant (54 vs 51%). A moderate improvement was found in the mometasone group compared to a slight improvement in the fluocinolone and triamcinolone group (P<0.01). Patients in the mometasone cream group were determined to have

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				moderate improvements in overall disease status, as compared to the fluocinolone cream group with slight improvements (P<0.001). Secondary: Not reported
Rigopoulos et al.[82] (2007) Tazarotene 0.1 % cream applied QHS for 12 weeks vs clobetasol 0.05% cream applied QHS for 12 weeks	DB, RCT Patients with psoriasis including nail involvement	N=23 24 weeks	Primary: Assessment of pitting, onycholysis, subungual hyperkeratosis and salmon patches using the NAPSI Secondary: Not reported	Primary: There was no significant difference in pitting, onycholysis, subungual hyperkeratosis, or salmon patches between tazarotene and clobetasol after 12 weeks of treatment. Post hoc analysis at the end of the follow-up period (24 weeks) demonstrated clinical improvement for hyperkeratosis with tazarotene compared to clobetasol (P<0.001). All adverse events reported were mild, with the symptoms ameliorating after a few days. All patients in both groups declared satisfaction with the results at the end of the treatment period. Secondary: Not reported
Angelo et al.[83] (2007) Tazarotene 0.1% cream applied on one side of the body for 12 weeks vs clobetasol 0.05% cream applied on the other side of the body for 12 weeks	RCT, SB Patients with psoriasis and bilateral symmetrical lesions	N=36 16 weeks	Primary: Assessment of erythema, scaling and induration on a 4-point scale; investigators' overall assessment of psoriasis including extent and severity; treatment success Secondary: Not reported	Primary: During the 12-week treatment period, both tazarotene cream and clobetasol cream were associated with reduction in erythema scores from the baseline except at week two where tazarotene showed no improvement. Clobetasol cream was better than tazarotene cream in reducing the erythema throughout the treatment period with statistically significant differences favoring clobetasol over tazarotene at weeks two, four, six and eight. During the 12-week treatment period, both tazarotene and clobetasol creams were associated with reduction in induration scores from baseline. Tazarotene was better than clobetasol in reducing the induration at weeks two, four, 10 and 12. The difference was statistically significant at week two. Both were equally effective at weeks six and eight. During the 12-week treatment period both tazarotene and clobetasol creams were associated with reduction in desquamation scores from

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				baseline except at week two where tazarotene showed no reduction. Clobetasol cream was better than tazarotene cream in reducing the scaling throughout the treatment period with statistically significant differences favoring clobetasol over tazarotene over the entire 12-week treatment period. The overall improvement at weeks two, four six, eight, 10 and 12 for tazarotene was ~20, ~33, ~43, ~53, ~55 and ~58% respectively and for clobetasol was ~33, ~55, ~73, ~78, ~95 and ~95% respectively. Statistically significant differences favored clobetasol cream over tazarotene cream over the entire 12-week treatment period. Clobetasol produced higher success rates than tazarotene over the 12-week treatment period. Statistically significant differences favored clobetasol over tazarotene at weeks two and four. Treatment success rate was 100% at week six with clobetasol and was 73% with tazarotene. At week 12, it was 100% with clobetasol and 88% with tazarotene. Secondary: Not reported
Choonhakarn et al.[84] (2010) Triamcinolone 0.1% cream applied BID vs aloe vera cream applied BID	DB, RCT Patients ≥18 years of age with a clinical diagnosis of psoriasis	N=80 8 weeks	Primary: Change in PASI score Secondary: Quality of life assessed using the dermatology life quality index	Primary: After eight weeks, no patients experienced complete clearance of psoriasis in either group. Six patients (16.2%) in the aloe vera group and four patients (10.5%) in the triamcinolone group achieved a PASI 75 (‘marked’ response) by week eight. Twenty patients (54.1%) in the aloe vera group achieved a PASI 50 (‘moderate’ response) compared to 25 patients (65.8%) in the triamcinolone group. Ten patients (27%) in the aloe vera group and nine patients (23.7%) in the triamcinolone group experienced a ‘slight’ improvement in their lesions (PASI scores decreased <50% from baseline) by week eight. There was no change observed in the lesion in one patient (2.7%) receiving aloe vera. After eight weeks, the mean PASI score was 3.9 in the aloe vera group and 4.3 in the triamcinolone group (95% CI –0.37 to 1.28; P=0.2783). The between-group difference in the adjusted means was 1.1 in favor of aloe vera (95% CI, -2.13 to -0.16; P=0.0237).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: The mean dermatology life quality index scores decreased in both treatment groups; however, there was no significant difference between the groups after eight weeks of therapy. Patients in the aloe vera group had a mean dermatology life quality index score of 8.6 at baseline, decreasing to 2.5 after eight weeks of treatment. The triamcinolone group showed a dermatology life quality index score decrease from 8.1 at baseline to 2.3 at week eight. The between-group difference in adjusted means was 0.3 (95% CI, -1.18 to -0.64; P=0.5497). There were no serious adverse events reported in either group. Six patients receiving aloe vera cream experienced stinging and itching at the lesions.
Multiple Dermatoses				
Rocha et al.[85] (1976) Amcinonide 0.1% cream applied BID vs betamethasone valerate 0.1% cream applied BID	DB Patients with atopic dermatitis, contact dermatitis, and eczema	N=60 3 weeks	Primary: Investigator assessment of clinical response, patient assessment of clinical response Secondary: Cosmetic acceptability	Primary: Amcinonide and betamethasone treatment groups demonstrated improvement in objective and subjective parameters over the course of three weeks. Investigator's overall ratings of efficacy was comparable for the two treatment groups (P=0.38). All 30 amcinonide patients rated its efficacy as excellent compared to 27 of 30 betamethasone patients (the remaining three gave a rating of good; P=0.24). Secondary: No significant difference was found between treatment groups (P≤1.00).
Rosenberg et al.[86] (1979) Amcinonide 0.1% cream applied BID vs betamethasone	DB, PG, RCT Patients with eczematous dermatitis, including contact dermatitis, atopic dermatitis, nummular eczema,	N=35 2 weeks	Primary: Mean overall improvement rating of disease status and symptoms Secondary: Not reported	Primary: Both treatment groups demonstrated a decrease in pruritus, lichenification, erythema, crust, scaling, papules and excoriation. The amcinonide treatment group had a greater improvement compared to the betamethasone group in pruritus, lichenification, erythema, crust, scaling and excoriation. The betamethasone treatment group had a greater improvement compared to the amcinonide group in papules. None of these differences were found to be statistically significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
valerate 0.1% cream applied BID	seborrheic dermatitis, and eczema			Mean percent improvement was greater for the amcinonide group compared to the betamethasone group (P<0.5). Secondary: Not reported
Rhodes et al.[87] (1983) Betamethasone dipropionate 0.05% cream applied BID vs betamethasone valerate 0.1% cream applied BID	DB, MC Patients with dermatoses, predominantly eczema	N=75 3 weeks	Primary: Signs and symptoms of erythema, scaling, induration, crusting, pruritus, excoriation, pain; patient and investigator overall response to therapy Secondary: Not reported	Primary: An "excellent" response to treatment was reported in 42.9% patients in the Diprosone® group and 10.3% of patients in the betamethasone valerate (P<0.01). Greater than 50% clearing was observed in 78.6% of patients in the Diprosone® group, and 41.4% of patients in the betamethasone valerate group (P<0.01). Secondary: Not reported
Levy et al.[88] (1977) Betamethasone dipropionate 0.05% cream applied BID vs halcinonide 0.1% applied daily	RCT Patients with acute and chronic dermatoses, including psoriasis, lichen chronicus simplex, eczema, contact dermatitis, neurodermatitis, and atopic dermatitis	N=53 4 weeks	Primary: Psoriasis: removal of scales with a decrease in number of plaques; lichen chronicus simplex: decrease in excoriation, pruritus, and infiltration and remission of chronic inflammation; acute dermatoses at the exacerbation stage (eczema, contact dermatitis, neurodermatitis):	Primary: Psoriasis: There was a greater improvement in the four patients with psoriasis treated with betamethasone compared to those treated with halcinonide. There was no significant difference between either treatment groups in the treatment of psoriasis. Lichen chronicus simplex: There was no significant difference between treatment groups. Eczema: Six of eight patients had a greater improvement when using halcinonide treatment compared to treatment with betamethasone. Contact dermatitis: Halcinonide was shown to be more effective when compared to betamethasone in the 10 patients with contact dermatitis.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			relief of acute inflammation, pruritus Secondary: Not reported	Atopic dermatitis: There was no significant difference found between the two treatment groups. Neurodermatitis: There was no significant difference between the two treatment groups. Secondary: Not reported
Bluefarb et al.[89] (1972) Betamethasone valerate 0.1% cream vs desonide 0.05% cream	DB, RCT Patients with dermatological conditions, including atopic eczema, contact dermatitis, lichen simplex, nummular eczema, psoriasis, seborrheic dermatitis	N=117 4 weeks	Primary: Pruritus, erythema, induration, scaling; global response Secondary: Not reported	Primary: Dermatitides: Desonide cleared a greater percent of dermatitides (70.4%) compared to betamethasone (56.5%). Eczematous conditions: There was a greater rate of clearance for the betamethasone group (62.5%) compared to the desonide group (45.5%). Psoriasis: A greater percentage of patients had their psoriasis rated as either clear or excellent in the desonide group (48%) compared to the betamethasone group (35%). Secondary: Not reported
Vollum et al.[90] (1979) Betamethasone valerate 0.1% ointment applied to one side of the face vs halcinonide 0.1%	DB, RCT Patients with lesions of bilateral eczema or psoriasis	N=38	Primary: Improvement in lesions on one side of the patient's face compared to the other Secondary: Not reported	Primary: There were ten clinicians who chose betamethasone valerate, zero that preferred halcinonide and five that found no difference ($P<0.05$). Among patients with eczema, there was no statistical difference between the two medications. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
applied to the other side of the face				
Wishart et al.[91] (1993) Betamethasone valerate 0.1% cream applied BID vs mometasone 0.1% cream applied daily	MC, PG, RCT Patients with a variety of dermatoses, including atopic dermatitis, eczema, seborrheic dermatitis, psoriasis, and allergic dermatitis	N=58 4 weeks	Primary: Scoring of target lesion Secondary: Not reported	Primary: At four weeks, disease improvement was seen in 93% of patients in the mometasone group and in 90% of patients in the betamethasone group. The difference in the number of patients with improvement in their disease in the mometasone group compared to the betamethasone group was not statistically significant at any endpoint. Secondary: Not reported
Jegasothy et al.[92] (1985) Clobetasol 0.05% cream applied TID vs fluocinonide 0.05% cream applied TID	DB, MC, PG Patients 13 to 75 years of age with psoriasis or chronic eczema	N=227 2 weeks	Primary: Physician global assessment, sign and symptom severity, patient evaluation of improvement Secondary: Not reported	Primary: After two weeks, 82% of the psoriasis patients treated with clobetasol had clearance of their lesions compared to 46% of the fluocinonide group (P<0.001). Mild or absent signs and symptoms among the psoriasis patients was found in 91% of patients in the clobetasol group and 55% of patients in the fluocinonide group (P<0.001). Eight-six percent of patients in the clobetasol group had either excellent or good improvement in their psoriasis compared to 61% in the fluocinonide group, respectively (P<0.01). After two weeks, 89% of eczema patients treated with clobetasol had clearance of their lesions compared to 70% of the patients in the fluocinonide group (P<0.05). There was a significant difference in the signs and symptoms among eczema patients in the two treatment groups. Secondary: Not reported
Bleeker et al.[93]	DB	N=100	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1975) Clobetasol 0.05% cream applied BID vs halcinonide 0.1% applied BID	Patients with psoriasis, atopic dermatitis or eczema	14 days	Decrease in erythema, edema, transudation, lichenification, scaling, pruritus and pain, overall therapeutic response Secondary: Not reported	Psoriasis: Among the 53 patients with psoriasis, 15 had either marked or slight improvement with halcinonide, compared to 13 with clobetasol. The remaining 25 patients had an equal response to both treatments. Atopic dermatitis: Of the 27 patients with atopic dermatitis, seven had either marked or slight improvement with halcinonide, compared to six with clobetasol. The remaining 14 patients had an equal response to both treatments. Eczema: Among the 20 patients with atopic dermatitis, one had either marked or slight improvement with halcinonide, compared to five with clobetasol. The remaining 14 patients had an equal response to both treatments. Secondary: Not reported
Barsky et al.[94] (1976) Desonide 0.05% cream applied BID vs fluocinonide 0.05% cream applied BID	DB, RCT Patients with dermatologic disorders, including eczema, seborrheic dermatitis, contact dermatitis, and lichen simplex	N=78 2 weeks	Primary: Erythema, scaling, pruritus, palpable induration Secondary: Physician's scoring of improvement	Primary: The desonide group had a greater improvement in erythema and scaling compared to the fluocinonide group in week one (P<0.05); however, the difference was not statistically significant in week two. There was no significant difference between the treatment groups in all other signs and symptoms (all P values >0.25 or more). Secondary: There was no significant difference in the overall physician evaluation between treatment groups at week one or endpoint (P>0.20 and P>0.60, respectively).
Kelly et al.[95] (1991) Mometasone furoate 0.1% cream applied daily	MC, PG, RCT, SB Patients ≥15 years of age with a variety of dermatoses, including psoriasis, atopic dermatitis, and eczema	N=67 12 weeks	Primary: Erythema, induration, scaling, crusting, pruritus, excoriation, pain Secondary: Mean plasma	Primary: There were 15 of 33 patients in the mometasone furoate group who left the study prior to day 85 due to the fact that their lesions were cleared. This corresponds to 18 of 32 patients in the betamethasone dipropionate patients. The difference in mean sign and symptom scores at end point was not statistically significant between the two treatment groups (mometasone

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vs betamethasone dipropionate 0.05% cream applied BID			cortisol levels	furoate mean=3.0; betamethasone dipropionate mean=2.5; P=0.68). The mean percent improvement was not statistically significant; there was a 74.4% improvement for the mometasone furoate group and an 80.1% improvement in the betamethasone dipropionate side (P=0.51). Secondary: The only instance in which the mean plasma cortisol levels between the two groups reached statistical significance was at day eight. The change in mean plasma cortisol level for the mometasone furoate group at day eight was 6.1, and for the betamethasone dipropionate group the change was -86.0 (P=0.02).
Miscellaneous				
Barikbin et al.[96] (2009) Betamethasone valerate 0.1% cream applied BID vs pimecrolimus 1% cream applied BID	DB, RCT Patients 20 to 53 years of age with moderate to severe discoid lupus erythematosus of the face	N=10 8 weeks	Primary: Clinical severity score Secondary: Not reported	Primary: Before treatment, mean disease severity was 4.2 in the pimecrolimus group and 4.4 in the betamethasone group. Following eight weeks of therapy, the mean disease severity was 0.67 and 1.2 in the pimecrolimus and betamethasone groups, respectively. The mean clinical severity scores decreased 86% and 73% in the pimecrolimus and betamethasone groups, respectively (both, P=0.043). There was no significant difference between the groups in terms of therapeutic efficacy (P=0.1). There were no recurrences at the eight-week follow-up. Secondary: Not reported
Rigopoulos et al.[97] (2009) Betamethasone valerate 0.1% ointment applied BID vs	OL, RCT Patients with chronic paronychia	N=45 Treatment: 3 weeks Follow-up: 6 weeks	Primary: Treatment response Secondary: Not reported	Primary: Eight patients in the betamethasone group were considered as cured, two as improved and four as nonresponders at the end of the treatment period. Thirteen patients in the tacrolimus group were considered as cured and one as improved at the end of the treatment period. Nine patients in the placebo group were considered as stable and six failed to respond.

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tacrolimus 0.1% ointment applied BID vs placebo				Patients in the betamethasone and tacrolimus groups had greater cure or improvement rates compared to patients in the placebo group (P<0.001). Secondary: Not reported
Corazza et al.[98] (2016) Clobetasol propionate 0.05% ointment twice weekly vs mometasone furoate 0.1% ointment twice weekly	OL, RCT Patients with vulvar lichen sclerosus previously stabilized with a topical corticosteroid course	N=48 52 weeks	Primary: Relapse rate at 52-weeks; mean time to relapse (defined by a score ≥5 for at least one evaluable symptom and/or a score = 3 for any of the 4 signs considered reversible); change in symptom and sign severity from baseline to the end of the study Secondary: Patient adherence and satisfaction	Primary: The RR of relapse in the clobetasol group compared with mometasone group was two (95% CI, 0.1940 to 20.6149). The difference between the rate of relapse in the two treatment groups was not statistically significant (P=1, Fisher's test). The mean time to relapse was 30 weeks (range, 20 to 38, median 32 weeks), without differences between the two groups (P=0.794, Mann–Whitney U-test). Comparing clobetasol and mometasone treatment groups with respect to the changes in mean symptom and objective scores across the study period, no significant differences were found. Secondary: Among the 44 patients who completed the study, 40 (90.91%) were considered adherent to maintenance therapy while four (two in clobetasol group and two in mometasone group) were not. Referred adherence was not significantly different between clobetasol and mometasone patients. All patients but three (93.18%) referred being satisfied with treatment. The patients dissatisfied with treatment (6.82%) were the relapsing ones (OR, 581.00; 95% CI, 9.93 to 33986.78).
Goldstein et al.[99] (2011) Clobetasol 0.05% cream daily vs pimecrolimus 1%	DB, RCT Female patients ≥18 years of age with biopsy-proven active vulvar lichen sclerosus	N=38 12 weeks	Primary: Change in inflammation as assessed by biopsy Secondary: Change in pruritus and burning/pain as assessed by	Primary: The improvement in inflammation was significant both for the clobetasol and pimecrolimus groups (P=0.001 and P=0.008, respectively). Clobetasol was found to be more effective in improving inflammation compared to pimecrolimus (P=0.015). There were nine nonresponders (i.e., no improvement in inflammation), one in the clobetasol group and eight in the pimecrolimus group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cream applied BID			patients using a visual analog scale, clinical evaluation of an investigator global assessment of the severity of the disease, clinical evaluation of lichenification, and clinical evaluation of ulceration/fissuring	Secondary: The mean change in the visual analog scale-pruritus score in the clobetasol and pimecrolimus groups were 4.5 and 3.5, respectively (P=0.319). The mean change in visual analog scale-burning/pain score in the clobetasol and pimecrolimus groups was 3.7 and 3.8, respectively (P=0.932). Clobetasol and pimecrolimus were found to be effective in decreasing both the total score on the investigator global assessment (P=0.001) and all three subscales (severity of disease, P=0.001; lichenification, P=0.001; and ulceration, P=0.025). No adverse events were reported and no herpetic events occurred.
Greer et al.[100] (1984) Hydrocortisone 1% and pramoxine 1% applied QID vs placebo	DB, PC, RCT Female patients entering the postnatal ward complaining of episiotomy pain	N=40 5 days	Primary: Edema, erythema, pain, impairment of mobility and analgesic requirements graded by the treating physicians on a scale of 1 to 4 Secondary: Healing and overall subjective response to treatment at day five	Primary: No significant difference was found between mean total daily scores on days one or three, but a significant difference in favor of placebo was seen on day five. Secondary: Subjective response to treatment showed no difference between groups (P>0.1) although healing was better with placebo (P<0.05). Mean individual criterion scores were also compared, but showed no difference except in edema on day five, mobility on day three, and analgesic requirements on days three and five, when placebo was more effective.
Köse et al.[101] (2010) Mometasone 0.1% cream applied daily	OL, SC Patients with stable vitiligo	N=50 12 weeks	Primary: Response to treatment Secondary: Not reported	Primary: Patients receiving mometasone had a better response to treatment than patients in the pimecrolimus group (P=0.008 in the per protocol population). Lesion size decreased from 19.20 to 16.85 cm^2 in the pimecrolimus group (P=0.002) and from 18.65 to 10.45 cm^2 in the mometasone group (P<0.001). There was no significant difference between the treatment groups (P=0.154).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs pimecrolimus 1% cream applied BID				Complete remission occurred in three patients (15%) receiving mometasone. There were no patients who achieved complete remission in the pimecrolimus group (P=0.018 in the per protocol population). Moderate and marked responses were recorded in 11 patients (55%) in the mometasone group and in seven patients (35%) in the pimecrolimus group. No change and minimal responses were observed in six patients (30%) in the mometasone group, and in 13 patients (65%) in the pimecrolimus group. After six months, three patients (15%) in the pimecrolimus group and four patients (20%) in the mometasone group showed some areas of depigmentation over re-pigmented vitiliginous lesions. Initial repigmentation started after 9.25 weeks in the mometasone group and after 11.25 weeks in the pimecrolimus group (P=0.064 in the per protocol population). The mean repigmentation rate was 65% in the mometasone group and 42% in the pimecrolimus group at the end of therapy. Both agents were well tolerated. The reported adverse events with mometasone were atrophy, telangiectasia, and erythema. Patients receiving pimecrolimus reported a burning sensation and pruritus. Secondary: Not reported

Drug regimen abbreviations: BID=twice daily, QD=daily, QHS=at bedtime, QID=four times daily, TID=three times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, ITT=intent to treat, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PP=per protocol, PRO=prospective, RCT=randomized controlled trial, SB=single-blind, SC=single center, VC=vehicle controlled
Miscellaneous abbreviations: AD=atopic dermatitis, BSA=body surface area, GSS=Global Severity Score, IGA=Investigator Global Assessment, ITT=intent to treat, mEASI=Modified Eczema Area and Severity Index, mLEASI=Modified Local Eczema Area and Severity Index, PASI=Psoriasis Area and Severity Index, PGA=Physician Global Assessment, PP=per protocol, PQOL-12=Psoriasis Quality of Life Questionnaire, SF-36=short form 36, TSS=Total Severity Score

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Skin and Mucous Membrane Corticosteroids

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Alclometasone	cream, ointment	N/A	N/A	$$
Amcinonide	cream	N/A	N/A	$$$$
Betamethasone dipropionate	cream*, gel*, lotion*, ointment*	N/A	N/A	$$$
Betamethasone valerate	cream, foam, lotion, ointment	Luxiq®*	$$$$-$$$$$	$$$
Clobetasol	cream, foam, gel, lotion, ointment, shampoo, solution, spray	Clodan®*, Impeklo®, Olux®*, Olux-E®*, Temovate®*, Tovet®*	$$$$$	$$$
Clocortolone	cream	Cloderm®*	$$$$$	$$$$$
Desonide	cream, lotion, ointment	N/A	N/A	$$
Desoximetasone	cream, gel, ointment, spray	Topicort®*	$$$$$	$$$
Diflorasone	cream, ointment	N/A	N/A	$$$$$
Fluocinolone	cream, oil, ointment, solution	Derma-Smoothe/FS®*, Synalar®*	$$$	$$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Fluocinonide	cream, gel, ointment, solution	Vanos®*	$$$$-$$$$$	$
Flurandrenolide	cream*, lotion*, ointment*	N/A	N/A	$$$$$
Fluticasone	cream, lotion, ointment	Beser®*	$$-$$$$$	$$$
Halcinonide	cream*, ointment, solution	Halog®*	$$$-$$$$	$$$$$
Halobetasol	cream*, foam*, lotion, ointment*	Bryhali®, Lexette®*, Ultravate®	$$$$-$$$$$	$$$$
Hydrocortisone	cream, lotion, ointment, rectal cream, rectal enema, solution	Anusol-HC®*, Cortenema®*, Texacort®	$$$$$	$
Hydrocortisone acetate	rectal foam	Cortifoam®	$-$$$$$	$
Hydrocortisone butyrate	cream, lotion, ointment, solution	Locoid®*, Locoid Lipocream®*	N/A	$$$$
Hydrocortisone probutate	cream	Pandel®	$$$-$$$$$	N/A
Hydrocortisone valerate	cream, ointment	N/A	N/A	$$$
Mometasone	cream, ointment, solution	N/A	N/A	$$$
Prednicarbate	cream, ointment	N/A	N/A	$$
Triamcinolone	aerosol, cream, dental paste, lotion, ointment	Kenalog®*, Oralone®*	$$$$	$
Combination Products				
Betamethasone dipropionate and propylene glycol	cream, lotion, ointment	Diprolene®*	$$$-$$$$	$-$$$
Hydrocortisone acetate and pramoxine	rectal foam	ProctoFoam-HC®	$$$$	$-$$$

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
N/A=Not available

X. Conclusions

The skin and mucous membrane corticosteroids are approved for the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. The topical corticosteroids are classified based on their relative potency: super high potency (Class I), high potency (Classes II to III), medium potency (Classes IV to V) and low potency (Classes VI to VII).[5] They are available in a variety of vehicles, including cream, foam, gel, lotion, ointment, paste, shampoo, solution, spray, and tape. There is at least one topical corticosteroid available in a generic formulation in each potency category. Hydrocortisone is also available over-the-counter.

For the treatment of atopic dermatitis, emollients are considered the standard of care.[6-11] They are steroid-sparing and are useful for both prevention and maintenance therapy. Topical corticosteroids provide symptomatic relief and are safe to use in the short term. The selection of therapy should take into consideration the disease severity, location of the lesions, patient's age, and anticipated duration of therapy.[6,7,9,11] Guidelines do not give preference to one topical corticosteroid over another.[6-11] Clinical trials have demonstrated similar efficacy among the various topical corticosteroids for the treatment of atopic dermatitis.[17-20,23,25,27,31,35,36] While some studies have

demonstrated greater efficacy with one agent over another, they were often comparing corticosteroids with different potencies.[24,26,34,37,39]

There are numerous topical and systemic therapies available for the treatment of psoriasis. The selection of therapy should take into consideration the disease severity, location of the lesions, and patient preference. Patients with mild to moderate disease can often be treated with a topical agent; while those with moderate to severe disease may need systemic therapy.[13] Topical preparations that are effective include corticosteroids, tar-based products, dithranol preparations, vitamin A analogs, and vitamin D analogs. Emollients should also be used to soften scaling and reduce irritation. Guidelines do not give preference to one topical agent over another.[13] Clinical trials have demonstrated similar efficacy among the various topical corticosteroids for the treatment of psoriasis.[50,73,76,78,79] Some studies have demonstrated greater efficacy with one agent over another; however, these studies were often comparing corticosteroids with different potencies.[48,49,51,63,74,80,81]

For the treatment of seborrheic dermatitis, the Finnish Medical Society Duodecim guidelines recommend the use of salicylic acid to soften scales.[14] Topical corticosteroids, antifungal agents and moisturizing emollients are also frequently prescribed to decrease fungal growth and control symptoms. Clinical trials in patients with multiple dermatoses, including seborrheic dermatitis, have demonstrated similar efficacy among the various topical corticosteroids.[86,91,94]

For the treatment of hemorrhoids, adequate fiber intake and water is the cornerstone of therapy.[15,16] Topical corticosteroids and analgesics are useful for managing perianal skin irritation due to poor hygiene, mucus discharge, or fecal seepage. Although topical corticosteroids may relieve local perianal inflammation, there is no data to suggest that they actually reduce hemorrhoidal swelling, bleeding or protrusion.[16] Over-the-counter preparations are often used in the empirical treatment of hemorrhoids; however, data supporting their use is lacking.[16] A literature search did not reveal any published studies evaluating the use of the various hydrocortisone rectal preparations for the treatment of hemorrhoids.

There is insufficient evidence to support that one brand skin and mucous membrane corticosteroid is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand skin and mucous membrane corticosteroids within the class reviewed are comparable to each other and to the generics products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand skin and mucous membrane corticosteroid is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Nonsteroidal Anti-inflammatory Agents
AHFS Class 840620
February 8, 2023

I. Overview

Currently there are no prescription medications classified by American Hospital Formulary Service (AHFS) as Skin and Mucous Membrane Nonsteroidal Anti-inflammatory Agents.

II. Conclusions

There are no prescription medications available in the skin and mucous membrane nonsteroidal anti-inflammatory agents class (AHFS Class 840620).

III. Recommendations

No brand skin and mucous membrane nonsteroidal anti-inflammatory agent is recommended for preferred status. Alabama Medicaid should continue to include AHFS Class 840620 in the Preferred Drug List (PDL) screening process. If new prescription skin and mucous membrane nonsteroidal anti-inflammatory agents are added, it is recommended that this class be re-reviewed.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Anti-inflammatory Agents, Miscellaneous
AHFS Class 840692
February 8, 2023

I. Overview

Crisaborole (Eucrisa®) is a topical phosphodiesterase 4 (PDE4) inhibitor Food and Drug Administration (FDA)-approved for the treatment of mild-to-moderate atopic dermatitis in patients three months of age and older. Crisaborole inhibits PDE4, suppressing the release of inflammatory cytokines and preventing inflammation.[1-3]

Atopic dermatitis (AD) is a common dermatologic disorder with symptoms including pruritus and eczematous skin lesions which can relapse and remit. Treatment goals are limited to alleviating pruritic flares, preventing exacerbations, and reducing duration and intensity of symptoms.[4] Mainstays of treatment include topical corticosteroids and topical calcineurin inhibitors, which each have noteworthy safety concerns. Adverse effects associated with topical corticosteroid use include adrenal suppression, skin thinning, telangiectasias, folliculitis, and contact urticaria, especially in patients using potent or superpotent formulations, and/or with disease extending over large body surfaces.[5] Although topical calcineurin inhibitors do not have the same adverse effects as topical corticosteroids, there is a black box warning linking topical calcineurin inhibitors to an increased risk of cancer.[4]

The miscellaneous skin and mucous membrane anti-inflammatory agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Crisaborole is not available in a generic formulation. This class was last reviewed in February 2021.

Table 1. Skin and Mucous Membrane Anti-Inflammatory Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Crisaborole	ointment	Eucrisa®	Eucrisa®CC

*Generic is available in at least one dosage form or strength.
N/A=Not available
PDL=Preferred Drug List
CCDenotes agent is preferred with clinical criteria in place.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the skin and mucous membrane anti-inflammatory agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the Skin and Mucous Membrane Anti-Inflammatory Agents

Clinical Guideline	Recommendation(s)
Scottish Intercollegiate Guidelines Network: **Management of Atopic Eczema in Primary Care (2011)[6]**	<u>Emollient therapy</u> • Patients with atopic eczema should receive ongoing treatment with emollients. <u>Topical corticosteroid therapy</u> • Patients should continue with emollient therapy during treatment with topical corticosteroids. • Patients with atopic eczema should be advised to apply topical corticosteroids once daily. • Twice weekly maintenance therapy with a topical corticosteroid should be considered in patients with moderate to severe atopic eczema experiencing frequent relapses. • There is no good quality evidence to assist in the choice of topical corticosteroid potency in the treatment of atopic eczema. • The choice of topical corticosteroid potency should be tailored to the age of the patient, the body region being treated, and the degree to which the skin is inflamed.

Clinical Guideline	Recommendation(s)
	For delicate areas of skin, such as the face and flexures, only mild or moderately potent preparations should be used. On the face, especially in children, it is reasonable to start with a mildly potent topical corticosteroid. • Topical corticosteroids should be used with caution in the periocular region. <u>Topical calcineurin inhibitors</u> • Tacrolimus should be considered for short-term, intermittent treatment of moderate to severe atopic eczema that has not been controlled by topical corticosteroids, or if there is a serious risk of important adverse effects from further topical corticosteroid use (e.g., skin atrophy). • Topical calcineurin inhibitors should not be applied to skin which appears actively infected. • Due to long-term safety issues, topical calcineurin inhibitors should not be used as first-line treatment unless there is a specific reason to avoid or reduce the use of topical corticosteroids. <u>Antihistamines</u> • Short-term bedtime use of sedating antihistamines should be considered in patients with atopic eczema when there is sleep disturbance.

Primary Care Dermatology Society: **Clinical Guidance for Eczema: Atopic Eczema (2019)**[7]
 	
Reaffirmed June 2022
	<u>Emollients</u>
	• Emollients are the mainstay of therapy and without them it is not possible to manage eczema effectively.
	• Good evidence shows that the more emollients are used, the less topical steroids are needed.
	• Compliance is essential and so always review patients to check they are happy with what has been prescribed - it may be necessary to try a range of emollients before the patient settles on the best combination.
	
	<u>Topical Steroids</u>
	• Use the lowest appropriate potency and only apply thinly to inflamed skin.
	• Allow moisturizers to dry into skin for 20 minutes before applying the steroid.
	• Avoid using combined steroid-antibiotic preparations on a regular basis as it will increase the risk of antibiotic resistance.
	• Amount of steroid needed can be determined by the Finger Tip Unit method.
	• Strength of steroid to be determined by the age of patient, site and severity:
	  ○ Child face: mild potency (e.g., 1% hydrocortisone).
	  ○ Child trunk and limbs: moderate potency (e.g., clobetasone butyrate 0.05% or betamethasone valerate 0.025%).
	  ○ Adult face: mild or moderate potency (e.g., clobetasone butyrate 0.05%)
	  ○ Adult trunk and limbs: potent (e.g., betamethasone valerate 0.1%, mometasone).
	  ○ Palms and soles: potent or very potent (e.g., clobetasol propionate 0.05%).
	• If used appropriately it is uncommon to develop steroid atrophy, however extra care needs to be taken in the following sites:
	  ○ Around the eyes - unless used very infrequently topical steroid preparations should be avoided due to the risks of glaucoma.
	  ○ The face - the regular use of topical steroids should be avoided.
	  ○ Lower legs in older patients / others at risk of leg ulcers - the regular use of topical steroids should be avoided.
	
	<u>Immunomodulatory treatments</u>
	• Immunomodulatory agents (e.g., tacrolimus or pimecrolimus) are calcineurin inhibitors.
	• Their main benefit is that they are not steroid based and so do not cause skin atrophy.

Clinical Guideline	Recommendation(s)

	• Formulations include tacrolimus 0.03% ointment and pimecrolimus approved for ages two years and above and tacrolimus 0.1% ointment is approved for 16 years of age and above.
	• Local adverse effects include stinging, burning, itch, irritation and slight photosensitivity - appropriate sun protection is recommended. Adverse effects are more common with tacrolimus but in many patients are transient. Immunomodulators should be temporarily discontinued when the skin is infected.
	• When to consider immunomodulators:
	  o Eczema involving the eyelids and peri-orbital skin.
	  o Patients regularly using topical steroids on the face.
	  o Patients regularly using topical steroids on the lower legs in elderly patients and others at risk of leg ulcers.
	  o Any signs of skin atrophy.
	• In milder cases use pimecrolimus cream, although if this is ineffective or in the first instance the eczema is of a greater severity consider tacrolimus ointment.
	• While short-term data has showed no serious adverse effects, the possible long-term adverse effects of immunomodulators are not yet known - however the risks are likely to be minimal especially when the treatments are used in the ways described above.
	
	<u>Other treatments</u>
	• There is almost no role for non-sedating antihistamines in the management of eczema; the only exception is patients needing treatment for co-existent hay fever.
	• For the management of scalp eczema, wash with a mild tar-based shampoo. In young children (e.g., 18 months and under) it is often better to use an emollient bath oil to wash the hair rather than using a specific scalp treatment.

European Academy of Dermatology and Venereology: **Consensus-based European Guidelines for Treatment of Atopic Eczema (Atopic Dermatitis) in Adults and Children (2018)[8]**	• Emollients should be prescribed in adequate amounts, and these should be used liberally and frequently, in a minimum amount of 250 g per week for adults. • Emollient bath oils and soap substitutes should also be used. Emollients with a higher lipid content are preferable in winter time. • A regular use of emollient has a short- and long-term steroid sparing effect in mild-to-moderate atopic eczema. An induction of remission with topical corticosteroids or topical calcineurin inhibitors is required first. • Topical corticosteroids are important anti-inflammatory drugs to be used in atopic eczema, especially in the acute phase. • Topical corticosteroids with an improved risk/benefit ratio are recommended in atopic eczema. • Diluted topical corticosteroids may be used under wet wraps for short-term periods in acute atopic eczema to increase their efficacy. • Proactive therapy, e.g., twice-weekly application in the long-term follow-up, may help to reduce relapses. • Proactive therapy with topical corticosteroids may be used safely for at least 20 weeks, which is the longest duration of trials. • Patient fear of side-effects of corticosteroids should be recognized and adequately addressed to improve adherence and avoid undertreatment. • Topical calcineurin inhibitors are important anti-inflammatory drugs to be used in atopic eczema. Instead of treating acute flares with topical calcineurin inhibitors, initial treatment with topical corticosteroids before switching to topical calcineurin inhibitors should be considered. • Topical calcineurin inhibitors are especially indicated in sensitive skin areas (face, intertriginous sites, anogenital area). • Proactive therapy with twice-weekly application of tacrolimus ointment may reduce relapses. • Effective sun protection should be recommended inpatients treated with topical calcineurin inhibitors.

Clinical Guideline	Recommendation(s)
	• Topical corticosteroids are recommended to control pruritus in the initial phase of atopic eczema exacerbation. • Topical calcineurin inhibitors are recommended to control pruritus in atopic eczema until clearance of eczema. • Topical polidocanol may be used to reduce pruritus in atopic eczema patients. • Routine clinical use of topical antihistamines including doxepin, topical cannabinoid receptor agonists, topical μ-opioid receptor antagonists or topical anaesthetics cannot be recommended as an adjuvant antipruritic therapy in atopic eczema. • There is not enough data available to recommend the use of capsaicin in management of itch in atopic eczema patients. • If emollients and anti-inflammatory topical preparations must be applied to the same location, the cream formulation should be applied first and only 15 minutes later the ointment formulation. • For routine treatment of flares once daily application of a potent topical corticosteroid is sufficient, usually for three to six days. • With mild disease activity, a small amount of topical corticosteroids two to three times weekly, associated with a liberal use of emollients, generally allows a good maintenance with SCORAD values below 15 to 20 (indicating mild disease). • The most constructive way to spare topical corticosteroids and avoid steroid-related side-effects is not to spare them during acute flares, but through consequent baseline emollient skin care combined with early anti-inflammatory intervention in order to stabilize the disease, and prevent treatment-intensive flares. • The two steroid-free topical calcineurin inhibitors, tacrolimus ointment and pimecrolimus cream, have demonstrated efficacy against placebo in clinical trials for short-term and long-term use. • Proactive tacrolimus ointment therapy has been shown to be safe and effective for up to one year in reducing the number of flares and improving the quality of life in adult patients and children. • The anti-inflammatory potency of 0.1% tacrolimus ointment is similar to a topical corticosteroid with intermediate activity, while the latter is clearly more active than 1.0% pimecrolimus cream. • The topical calcineurin inhibitors do not induce skin atrophy like corticosteroids, which favors their use on delicate skin areas like the eyelids, perioral skin, genital areas, inguinal fold, and for topical long-term management. • Clinical and preclinical data do not indicate an increased risk of the induction of lymphoma or other types of malignancies, or photocarcinogenicity for topical calcineurin inhibitors, but since the continuous oral administration of the calcineurin inhibitor cyclosporine is associated with an increased photocarcinogenicity risk in solid organ transplant patients, UV protection, (e.g., with sunscreens) is recommended.

National Institute for Health and Clinical Excellence: **Management of Atopic Eczema in Children From Birth Up to the Age of 12 Years (2007)**[9]
 	
Reaffirmed March 2021
	<u>General considerations</u>
	• A stepped approach should be used for managing atopic eczema in children. Treatment should be tailored based on the severity of the atopic eczema.
	• Emollients should always be used, even when the atopic eczema is clear. Treatment can be stepped up or down, according to the severity of symptoms, with the addition of the other treatments as necessary as follows:
	  ○ Mild atopic eczema: emollients and mild potency topical corticosteroids.
	  ○ Moderate atopic eczema: emollients, moderate potency topical corticosteroids, topical calcineurin inhibitors, and bandages.
	  ○ Severe atopic eczema: emollients, potent topical corticosteroids, topical calcineurin inhibitors, bandages, phototherapy, and systemic therapy.
	
	<u>Emollients</u>
	• Emollients should be used on the whole body when the atopic eczema is clear and while using all other treatments.

Clinical Guideline	Recommendation(s)
	Topical corticosteroids • Use mild potency topical corticosteroids on the face and neck, except for short-term (three to five days) use of moderate potency agents for severe flares. • Use moderate or potent topical corticosteroids for short periods only (seven to 14 days) for flares in sites such as axillae and groin. • Do not use very potent preparations in children without specialist dermatological advice. • Topical corticosteroids for atopic eczema should be prescribed for application only once or twice daily. • In children ≥12 months of age, potent topical corticosteroids should be used for the shortest amount of time as possible; no longer than 14 days. They should not be used on the face or neck. Potent topical corticosteroids should not be used in children <12 months of age without specialist dermatological supervision. • Consider treating problem areas with topical corticosteroids for two consecutive days per week to prevent flares, rather than treating flares as they arise, in children with frequent flares (two or three per month), once the eczema has been controlled. • A different topical corticosteroid of the same potency should be considered as an alternative to stepping up treatment if tachyphylaxis to a topical corticosteroid is suspected. Topical calcineurin inhibitors • Topical tacrolimus and pimecrolimus are not recommended for the treatment of mild atopic eczema or as first-line treatments for atopic eczema of any severity. • Topical tacrolimus is recommended as an option for the second-line treatment of moderate to severe atopic eczema in adults and children aged two years and older that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy. • Pimecrolimus is recommended as an option for the second-line treatment of moderate atopic eczema on the face and neck in children aged two to 16 years that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy. • Treatment with tacrolimus or pimecrolimus should only be initiated by physicians (including general practitioners) with a special interest and experience in dermatology. • For facial atopic eczema in children that requires long-term or frequent use of mild topical corticosteroids, consider stepping up treatment to topical calcineurin inhibitors. Antihistamines • Oral antihistamines should not be used routinely in the management of atopic eczema in children. • A one-month trial of a nonsedating antihistamine should be offered to children with severe atopic eczema or children with mild or moderate atopic eczema where there is severe itching or urticaria. Treatment can be continued, if successful, while symptoms persist, and should be reviewed every three months. • A seven to 14 day trial of an age-appropriate sedating antihistamine should be offered to children aged six months or over during an acute flare of atopic eczema if sleep disturbance has a significant impact on the child or parents or carers. This treatment can be repeated during subsequent flares if successful. Phototherapy and systemic treatments • Phototherapy or systemic treatments should be considered for the treatment of

Clinical Guideline	Recommendation(s)
	severe atopic eczema in children when other management options have failed or are inappropriate and where there is a significant negative impact on quality of life.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma and Immunology/ Joint Council on Allergy, Asthma and Immunology: **Disease Management of Atopic Dermatitis: An Updated Practice Parameter (2012)**[10]	General considerations • The intensity of management and treatment of atopic dermatitis is dictated by the severity of illness, which relates to the effect of atopic dermatitis on the quality of life on the patient and his or her family. • The management of atopic dermatitis requires multiple therapeutic approaches including antipruritic therapy, skin hydration, topical anti-inflammatory medications, antibacterial measures, and the identification/elimination of exacerbating factors. Skin hydration • Hydration with warm soaking baths for at least 10 minutes followed by the application of a moisturizer is recommended. • Moisturizers should be recommended as first-line therapy. Topical corticosteroids • Topical corticosteroids are an effective treatment option for atopic dermatitis. If atopic dermatitis is not controlled by moisturizers alone, then the clinician should recommend a topical corticosteroid. • Low-potency corticosteroids are recommended for maintenance therapy, whereas intermediate-and high-potency corticosteroids should be used for the treatment of exacerbation and applied to affected areas over short periods of time. • Potent fluorinated corticosteroids should not be used on the face, eyelids, genitalia, and intertriginous areas or in young infants. • Ultrahigh-potency corticosteroids should be used only for very short periods of time (several days) and in nonfacial non-skinfold areas. • The degree of corticosteroid absorption through the skin and the potential for systemic adverse effects are directly dependent on the surface area of the skin involved, thickness of the skin, the use of occlusive dressing, and the potency of the corticosteroid preparation. Topical calcineurin inhibitors • Tacrolimus ointment has been shown to be effective and safe in both adults and children older than two years of age, with most patients experiencing a reduction of pruritus within three days of initiating therapy. • Tacrolimus ointment does not cause atrophy for eczema on the face, eyelid, and skin folds that is unresponsive to low-potency topical steroids. • Once a flare is controlled, tacrolimus ointment twice daily, twice weekly to eczema-prone areas may prevent future flares. • Pimecrolimus cream decreases the number of flares of atopic dermatitis, reduces the need for corticosteroids, and controls pruritus. Tar preparations • There are no randomized studies that have demonstrated the efficacy of tar preparations, despite their widespread use for the treatment of atopic dermatitis. • Newer coal tar products have been developed that are more cosmetically acceptable than older products. • Coal preparations should not be recommended for acutely inflamed skin because this might result in additional skin irritation. Antihistamines • Patients may benefit from the use of oral antihistamines for the relief of pruritus associated with atopic dermatitis. Treatment of atopic dermatitis with topical antihistamines is generally not recommended because of potential cutaneous

Clinical Guideline	Recommendation(s)
	sensitization. Vitamin D • Patients with atopic dermatitis might benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake. Dilute bleach baths • The addition of dilute bleach baths twice weekly may reduce the severity of atopic dermatitis, especially in patients with recurrent skin infections. Microbes • Skin infections with *Staphylococcus aureus* are a recurrent problem in patients with atopic dermatitis, and patients with moderate-to-severe atopic dermatitis have been found to make IgE antibodies against staphylococcal toxins present in their skin. • A short course of an appropriate systemic antibiotic for patients who are clinically infected with *Staphylococcus aureus* should be prescribed. In areas with high levels of methicillin-resistant *Staphylococcus aureus*, treatment with clindamycin, doxycycline, or sulfamethoxazole-trimethoprim may be initiated while awaiting skin culture results. • Atopic dermatitis can be complicated by recurrent viral skin infections, such as herpes simplex, warts, and molluscum contagiosum. Herpes simplex or eczema herpeticum should be diagnosed and promptly treated with systemic antiviral agents. • Fungal infections can complicate atopic dermatitis and might contribute to exacerbations. Systemic Immunomodulating Agents • Immunosuppressive agents such as cyclosporine, interferon gamma, mycophenolate mofetil, azathioprine, and corticosteroids have been shown to provide benefit for certain cases of severe refractory atopic dermatitis, but potential benefits should be weighed against their potentially serious adverse effects. Phototherapy • Ultraviolet therapy can be a useful treatment for recalcitrant atopic dermatitis. Allergen immunotherapy • Select patients with atopic dermatitis with aeroallergen sensitivity may benefit from allergen immunotherapy.
American Academy of Dermatology: **Guidelines of Care for the Management of Atopic Dermatitis (2014)[5]**	Topical corticosteroids • Topical corticosteroids are the mainstay of anti-inflammatory therapy for the management of atopic dermatitis. • They are typically introduced into the treatment regimen after failure of lesions to respond to good skin care and regular use of moisturizers alone. • Comparative trials are limited in duration and scope (i.e., they mainly involve two, and occasionally three, agents), and as a result, there are no data to support one or a few specific agents as being more efficacious than others. • A variety of factors should be considered when choosing a particular topical corticosteroid for the treatment of atopic dermatitis, including patient age, areas of the body to which the medication will be applied, and other patient factors such as degree of xerosis, patient preference, and cost of medication. • Twice-daily application of corticosteroids is generally recommended for the treatment of atopic dermatitis; however, evidence suggests that once-daily application of some corticosteroids may be sufficient. • Proactive, intermittent use of topical corticosteroids as maintenance therapy (one to two times/week) on areas that commonly flare is recommended to help prevent relapses and is more effective than use of emollients alone.

Clinical Guideline	Recommendation(s)
	• The potential for both topical and systemic side effects, including possible hypothalamic-pituitary-adrenal axis suppression, should be considered, particularly in children with atopic dermatitis in whom corticosteroids are used. • Monitoring by physical examination for cutaneous side effects during long-term, potent steroid use is recommended. • No specific monitoring for systemic side effects is routinely recommended for patients with atopic dermatitis. • Patient fears of side effects associated with the use of topical corticosteroids for atopic dermatitis should be recognized and addressed to improve adherence and avoid undertreatment. <u>Topical calcineurin inhibitors</u> • Topical calcineurin inhibitors are recommended and effective for acute and chronic treatment, along with maintenance, in both adults and children with atopic dermatitis, and are particularly useful in selected clinical situations, including recalcitrance to steroids, use on sensitive areas (e.g., face, anogenital, skin folds), steroid-induced atrophy, and long-term uninterrupted topical steroid use. • Topical calcineurin inhibitors are recommended for use on actively affected areas as a steroid-sparing agent for the treatment of atopic dermatitis. • For patients with atopic dermatitis <2 years of age with mild to severe disease, off-label use of 0.03% tacrolimus or 1% pimecrolimus ointment can be recommended. • Pimecrolimus cream and tacrolimus ointment may cause skin burning and pruritus, especially when applied to acutely inflamed skin. Initial treatment of patients with atopic dermatitis using topical corticosteroids should be considered to minimize topical calcineurin inhibitor application site reactions. Patients with atopic dermatitis should be counseled about the possibility of these reactions. • Proactive, intermittent use of topical calcineurin inhibitor as maintenance therapy (two to three times per week) on areas that commonly flare is recommended to help prevent relapses while reducing the need for topical corticosteroids, and is more effective than the use of emollients alone. • The concomitant use of a topical corticosteroid with a topical calcineurin inhibitor may be recommended for the treatment of atopic dermatitis. • No consistent increases in the prevalence of cutaneous viral infections have been seen with continuous or intermittent use of topical calcineurin inhibitor for up to five years; however, physicians should inform their patients of these theoretical cutaneous risks, given the lack of safety data for longer periods of time. • Clinicians should be aware of the black-box warning on the use of topical calcineurin inhibitor for patients with atopic dermatitis and discuss as warranted. • Routine blood monitoring of tacrolimus and pimecrolimus levels in patients with atopic dermatitis who are applying these agents is not recommended at this time. <u>Topical antimicrobials and antiseptics</u> • Except for bleach baths with intranasal mupirocin, no topical antistaphylococcal treatment has been shown to be clinically helpful in patients with atopic dermatitis, and is not routinely recommended. • In patients with moderate to severe atopic dermatitis and clinical signs of secondary bacterial infection, bleach baths and intranasal mupirocin may be recommended to reduce disease severity. <u>Other topical agents</u> • Topical antihistamines have been tried for the treatment of atopic dermatitis but have demonstrated little utility and are not recommended. • There are not adequate data to make a recommendation regarding the use of coal tar topical agents.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous skin and mucous membrane anti-inflammatory agents are noted in Table 3.

Table 3. FDA-Approved Indications for the Skin and Mucous Membrane Anti-Inflammatory Agents[3]

Indication	Crisaborole
Topical treatment of mild to moderate atopic dermatitis in patients three months of age and older	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous skin and mucous membrane anti-inflammatory agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Skin and Mucous Membrane Anti-Inflammatory Agents[1-3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Crisaborole	Not reported	97	Hydrolysis, oxidation	Renal	Not reported

V. Drug Interactions

Due to limited systemic absorption with the skin and mucous membrane anti-inflammatory agents, no major drug interactions have been reported.[2]

VI. Adverse Drug Events

The most common adverse drug events reported with the skin and mucous membrane anti-inflammatory agents are listed in Table 5. Adverse drug events of the combination products not listed in the tables below would be in line with the properties of their individual components listed in the table below.

Table 5. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Anti-Inflammatory Agents[1-3]

Adverse Events	Crisaborole
Application site pain	✔
Contact urticaria	✔

✔ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the skin and mucous membrane anti-inflammatory agents are listed in Table 6.

Table 6. Usual Dosing Regimens for the Skin and Mucous Membrane Anti-Inflammatory Agents[1-3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Crisaborole	Atopic dermatitis: Ointment: apply a thin layer to affected areas twice daily	Atopic dermatitis in patients ≥3 months of age: Ointment: apply a thin layer to affected areas twice daily	Ointment: 2%

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the skin and mucous membrane anti-inflammatory agents are summarized in Table 7.

Table 7. Comparative Clinical Trials with the Skin and Mucous Membrane Anti-Inflammatory Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Paller et al.[11] Study AD-301 (2016) Crisaborole 2% topical ointment applied twice daily vs vehicle applied twice daily	MC, DB, VC, RCT Patients two years of age and older with mild-to-moderate AD (IGSA of 2 to 3) and ≥5% treatable BSA	N=759 28 days	Primary: Proportion of patients with success in ISGA score at Day 29 (ISGA of 0 or 1 with a ≥2-grade improvement from baseline) Secondary: ISGA grade of clear (0) or almost clear (1) at Day 29, time to success	Primary: A greater proportion of patients treated with crisaborole demonstrated success in ISGA compared to vehicle (32.8 vs 25.4%, respectively; P=0.038). Secondary: A greater proportion of patients treated with crisaborole attained an ISGA of clear (0) or almost clear (1) compared to placebo (51.7 vs 40.6%, respectively; P=0.005). Median time to success could not be calculated as <50% of patients reached success in ISGA.
Paller et al.[12] Study AD-302 (2016) Crisaborole 2% topical ointment applied twice daily vs vehicle applied twice daily	MC, DB, VC, RCT Patients two years of age and older with mild-to-moderate AD (IGSA of 2 to 3) and ≥5% treatable BSA	N=763 28 days	Primary: Proportion of patients with success in ISGA score at Day 29 (ISGA of 0 or 1 with a ≥2-grade improvement from baseline) Secondary: ISGA grade of clear (0) or almost clear (1) at Day 29, time to success	Primary: A greater proportion of patients treated with crisaborole demonstrated success in ISGA compared to vehicle (31.4 vs 18.0%, respectively; P<0.001). Secondary: A greater proportion of patients treated with crisaborole attained an ISGA of clear (0) or almost clear (1) compared to placebo (48.5 vs 29.7%, respectively; P<0.001). Median time to success could not be calculated as <50% of patients reached success in ISGA.

Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, ITT=intent to treat, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PP=per protocol, PRO=prospective, RCT=randomized controlled trial, SB=single-blind, SC=single center, VC=vehicle controlled

Miscellaneous abbreviations: AD=atopic dermatitis, BSA=body surface area, GSS=Global Severity Score, IGA=Investigator Global Assessment, ISGA=Investigator's Static Global Assessment, ITT=intent to treat, mEASI=Modified Eczema Area and Severity Index, mLEASI=Modified Local Eczema Area and Severity Index, PASI=Psoriasis Area and Severity Index, PGA=Physician Global Assessment, PP=per protocol, PQOL-12=Psoriasis Quality of Life Questionnaire, SF-36=short form 36, TSS=Total Severity Score

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 8. Relative Cost of the Skin and Mucous Membrane Anti-Inflammatory Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Crisaborole	ointment	Eucrisa®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

Crisaborole (Eucrisa®) is the only miscellaneous skin and mucous membrane anti-inflammatory agent. It is indicated for topical treatment of mild to moderate atopic dermatitis in patients three months of age and older. Crisaborole is not available in a generic formulation.[3]

Clinical guidelines support a multipronged approach to optimal management of atopic dermatitis based upon disease severity. Proper skin hydration with emollients and patient education on reducing exacerbating factors are integral strategies to the treatment of all atopic dermatitis patients.[5-10] Topical corticosteroids are the first-line of pharmacological treatment in atopic dermatitis.[5-10] Varying potencies and formulations are used depending on disease severity and site of application.[5-10] Topical calcineurin inhibitors are a second-line alternative to topical corticosteroids for treatment of moderate-to-severe disease in patients two years of age and older who are unresponsive, intolerant, or have a contraindication to conventional therapy.[5-10] In severe disease, systemic therapy or phototherapy may be appropriate to achieve adequate disease control.[5]

Crisaborole (Eucrisa®) introduces a novel nonsteroidal, anti-inflammatory mechanism for treating atopic dermatitis. In phase III clinical trials, treatment with crisaborole has demonstrated efficacy in reducing physical and psychosocial symptoms of atopic dermatitis compared to vehicle.[11-12] Crisaborole has not been evaluated in patients with severe atopic dermatitis or in head-to-head trials with other alternative therapies such as topical corticosteroids or topical calcineurin inhibitors. Clinical guidelines have not yet included the place of therapy of crisaborole topical ointment. Given the significant adverse event profile of other therapeutic agents such as topical corticosteroids and topical calcineurin inhibitors, crisaborole provides an alternative to patients with contraindications to or who are intolerant of standard of care therapy, due to its limited systemic exposure and well-tolerated safety profile.[1-3]

There is insufficient evidence to support that one brand miscellaneous skin and mucous membrane anti-inflammatory agent is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand miscellaneous skin and mucous membrane anti-inflammatory agents within the class reviewed are comparable to each other and to the generics products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand miscellaneous skin and mucous membrane anti-inflammatory agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Antipruritics and Local Anesthetics
AHFS Class 840800
February 8, 2023

I. Overview

The skin and mucous membrane antipruritics and local anesthetics have a variety of uses, including relief of itching and pain caused by insect bites, minor burns and sunburns, atopic dermatitis, lichen simplex chronicus, and hemorrhoids.[1-6] They are also used to prevent and treat pain due to postherpetic neuralgia, venipuncture, intravenous cannulation, minor operative/dermatological procedures, endoscopic/diagnostic procedures, as well as other procedures.

The local anesthetics (lidocaine, prilocaine, and tetracaine) inhibit the conduction of nerve impulses from sensory nerves.[1,2] The topical anesthetics are poorly absorbed through intact skin and are readily absorbed through mucous membranes. When skin permeability increases (such as with abrasions and ulcers), there is an increase in absorption. Systemic absorption may also occur if topical anesthetics are applied over a large area of the skin, if a large amount is applied, or if the skin temperature increases. Increased absorption may lead to serious adverse events.[1-6]

Doxepin is a tricyclic antidepressant which blocks histamine receptors; however, the exact mechanism by which it exerts its antipruritic effect is unknown.[1-3]

The skin and mucous membrane antipruritics and local anesthetics that are included in this review are listed in Table 1. This review encompasses all topical dosage forms and strengths. Several of the products are available in a generic formulation. This class was last reviewed in February 2021.

Table 1. Skin and Mucous Membrane Antipruritics and Local Anesthetics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Doxepin	cream	Prudoxin®*, Zonalon®*	doxepin
Lidocaine	cream, ointment, solution, transdermal patch	Lidoderm®*, ZTLido®	lidocaine
Combination Products			
Lidocaine and prilocaine	cream	N/A	lidocaine and prilocaine
Lidocaine and tetracaine	transdermal patch	Synera®	none

*Generic is available in at least one dosage form or strength.
†Generic product requires prior authorization.
N/A=Not available
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the skin and mucous membrane antipruritics and local anesthetics are summarized in Table 2.

Table 2. Treatment Guidelines Using the Skin and Mucous Membrane Antipruritics and Local Anesthetics

Clinical Guideline	Recommendation(s)
Scottish Intercollegiate Guidelines Network: **Management of Atopic Eczema in Primary Care (2011)**[7]	Emollient therapy • Patients with atopic eczema should receive ongoing treatment with emollients. Topical corticosteroid therapy • Patients should continue with emollient therapy during treatment with topical corticosteroids. • Patients with atopic eczema should be advised to apply topical corticosteroids once daily. • Twice weekly maintenance therapy with a topical corticosteroid should be considered in patients with moderate to severe atopic eczema experiencing frequent relapses. • There is no good quality evidence to assist in the choice of topical corticosteroid potency in the treatment of atopic eczema. • The choice of topical corticosteroid potency should be tailored to the age of the patient, the body region being treated, and the degree to which the skin is inflamed. For delicate areas of skin, such as the face and flexures, only mild or moderately potent preparations should be used. On the face, especially in children, it is reasonable to start with a mildly potent topical corticosteroid. • Topical corticosteroids should be used with caution in the periocular region. Topical calcineurin inhibitors • Tacrolimus should be considered for short-term, intermittent treatment of moderate to severe atopic eczema that has not been controlled by topical corticosteroids, or if there is a serious risk of important adverse effects from further topical corticosteroid use (e.g., skin atrophy). • Topical calcineurin inhibitors should not be applied to skin which appears actively infected. • Due to long-term safety issues, topical calcineurin inhibitors should not be used as first-line treatment unless there is a specific reason to avoid or reduce the use of topical corticosteroids. Antihistamines • Short-term bedtime use of sedating antihistamines should be considered in patients with atopic eczema when there is sleep disturbance.
Primary Care Dermatology Society: **Clinical Guidance for Eczema: Atopic Eczema (2019)**[8] Reaffirmed June 2022	Emollients • Emollients are the mainstay of therapy and without them it is not possible to manage eczema effectively. • Good evidence shows that the more emollients are used, the less topical steroids are needed. • Compliance is essential and so always review patients to check they are happy with what has been prescribed - it may be necessary to try a range of emollients before the patient settles on the best combination. Topical Steroids • Use the lowest appropriate potency and only apply thinly to inflamed skin. • Allow moisturizers to dry into skin for 20 minutes before applying the steroid. • Avoid using combined steroid-antibiotic preparations on a regular basis as it will increase the risk of antibiotic resistance. • Amount of steroid needed can be determined by the Finger Tip Unit method.

Clinical Guideline	Recommendation(s)

	• Strength of steroid to be determined by the age of patient, site and severity:
	  o Child face: mild potency (e.g., 1% hydrocortisone).
	  o Child trunk and limbs: moderate potency (e.g., clobetasone butyrate 0.05% or betamethasone valerate 0.025%).
	  o Adult face: mild or moderate potency (e.g., clobetasone butyrate 0.05%)
	  o Adult trunk and limbs: potent (e.g., betamethasone valerate 0.1%, mometasone).
	  o Palms and soles: potent or very potent (e.g., clobetasol propionate 0.05%)
	• If used appropriately it is uncommon to develop steroid atrophy; however, extra care needs to be taken in the following sites:
	  o Around the eyes: unless used very infrequently topical steroid preparations should be avoided due to the risks of glaucoma.
	  o The face - the regular use of topical steroids should be avoided.
	  o Lower legs in older patients / others at risk of leg ulcers - the regular use of topical steroids should be avoided.
	
	<u>Immunomodulatory treatments</u>
	• Immunomodulatory agents (e.g., tacrolimus or pimecrolimus) are calcineurin inhibitors.
	• Their main benefit is that they are not steroid based and so do not cause skin atrophy.
	• Formulations include tacrolimus 0.03% ointment and pimecrolimus approved for ages two years and above and tacrolimus 0.1% ointment is approved for 16 years of age and above.
	• Local adverse effects include stinging, burning, itch, irritation and slight photosensitivity - appropriate sun protection is recommended. Adverse effects are more common with tacrolimus but in many patients are transient. Immunomodulators should be temporarily discontinued when the skin is infected.
	• When to consider immunomodulators:
	  o Eczema involving the eyelids and peri-orbital skin.
	  o Patients regularly using topical steroids on the face.
	  o Patients regularly using topical steroids on the lower legs in elderly patients and others at risk of leg ulcers.
	  o Any signs of skin atrophy.
	• In milder cases, use pimecrolimus cream; although, if this is ineffective or in the first instance the eczema is of a greater severity, consider tacrolimus ointment.
	• While short-term data has showed no serious adverse effects, the possible long-term adverse effects of immunomodulators are not yet known; however, the risks are likely to be minimal especially when the treatments are used in the ways described above.
	
	<u>Other treatments</u>
	• There is almost no role for non-sedating antihistamines in the management of eczema; the only exception is patients needing treatment for co-existent hay fever.
	• For the management of scalp eczema, wash with a mild tar-based shampoo. In young children (e.g., 18 months and under) it is often better to use an emollient bath oil to wash the hair rather than using a specific scalp treatment.

European Academy of Dermatology and Venereology: **Consensus-based European Guidelines for Treatment of Atopic Eczema**	• Emollients should be prescribed in adequate amounts, and these should be used liberally and frequently, in a minimum amount of 250 g per week for adults. • Emollient bath oils and soap substitutes should also be used. Emollients with a higher lipid content are prefer-able in winter time. • A regular use of emollient has a short- and long-term steroid sparing effect in mild-to-moderate atopic eczema. An induction of remission with topical corticosteroids or topical calcineurin inhibitors is required first. • Topical corticosteroids are important anti-inflammatory drugs to be used in atopic

Clinical Guideline	Recommendation(s)
(Atopic Dermatitis) in Adults and Children (2018)[9]	eczema, especially in the acute phase. • Topical corticosteroids with an improved risk/benefit ratio are recommended in atopic eczema. • Diluted topical corticosteroids may be used under wet wraps for short-term periods in acute atopic eczema to increase their efficacy. • Proactive therapy (e.g., twice-weekly application in the long-term follow-up) may help to reduce relapses. • Proactive therapy with topical corticosteroids may be used safely for at least 20 weeks, which is the longest duration of trials. • Patient fear of side-effects of corticosteroids should be recognized and adequately addressed to improve adherence and avoid undertreatment. • Topical calcineurin inhibitors are important anti-inflammatory drugs to be used in atopic eczema. Instead of treating acute flares with topical calcineurin inhibitors, initial treatment with topical corticosteroids before switching to topical calcineurin inhibitors should be considered. • Topical calcineurin inhibitors are especially indicated in sensitive skin areas (face, intertriginous sites, anogenital area). • Proactive therapy with twice-weekly application of tacrolimus ointment may reduce relapses. • Effective sun protection should be recommended in patients treated with topical calcineurin inhibitors. • Topical corticosteroids are recommended to control pruritus in the initial phase of atopic eczema exacerbation. • Topical calcineurin inhibitors are recommended to control pruritus in atopic eczema until clearance of eczema. • Topical polidocanol may be used to reduce pruritus in atopic eczema patients. • Routine clinical use of topical antihistamines including doxepin, topical cannabinoid receptor agonists, topical μ-opioid receptor antagonists or topical anaesthetics cannot be recommended as an adjuvant antipruritic therapy in atopic eczema. • There is not enough data available to recommend the use of capsaicin in management of itch in atopic eczema patients. • If emollients and anti-inflammatory topical preparations must be applied to the same location, the cream formulation should be applied first and only 15 minutes later the ointment formulation. • For routine treatment of flares once daily application of a potent topical corticosteroid is sufficient, usually for three to six days. • With mild disease activity, a small amount of topical corticosteroids two to three times weekly, associated with a liberal use of emollients, generally allows a good maintenance with SCORAD values below 15 to 20 (indicating mild disease). • The most constructive way to spare topical corticosteroids and avoid steroid-related side-effects is not to spare them during acute flares, but through consequent baseline emollient skin care combined with early anti-inflammatory intervention in order to stabilize the disease, and prevent treatment-intensive flares. • The two steroid-free topical calcineurin inhibitors, tacrolimus ointment and pimecrolimus cream, have demonstrated efficacy against placebo in clinical trials for short-term and long-term use. • Proactive tacrolimus ointment therapy has been shown to be safe and effective for up to one year in reducing the number of flares and improving the quality of life in adult patients and children. • The anti-inflammatory potency of 0.1% tacrolimus ointment is similar to a topical corticosteroid with intermediate activity, while the latter is clearly more active than 1.0% pimecrolimus cream. • The topical calcineurin inhibitors do not induce skin atrophy like corticosteroids, which favors their use on delicate skin areas like the eyelids, perioral skin, genital

Clinical Guideline	Recommendation(s)
	areas, inguinal fold, and for topical long-term management. • Clinical and preclinical data do not indicate an increased risk of the induction of lymphoma or other types of malignancies, or photocarcinogenicity for topical calcineurin inhibitors, but since the continuous oral administration of the calcineurin inhibitor cyclosporine is associated with an increased photocarcinogenicity risk in solid organ transplant patients, UV protection, (e.g., with sunscreens) is recommended.
National Institute for Health and Clinical Excellence: **Management of Atopic Eczema in Children From Birth Up to the Age of 12 Years (2007)**[10] Reaffirmed March 2021	General considerations • A stepped approach should be used for managing atopic eczema in children. Treatment should be tailored based on the severity of the atopic eczema. • Emollients should always be used, even when the atopic eczema is clear. Treatment can be stepped up or down, according to the severity of symptoms, with the addition of the other treatments as necessary as follows: o Mild atopic eczema: emollients and mild potency topical corticosteroids. o Moderate atopic eczema: emollients, moderate potency topical corticosteroids, topical calcineurin inhibitors, and bandages. o Severe atopic eczema: emollients, potent topical corticosteroids, topical calcineurin inhibitors, bandages, phototherapy, and systemic therapy. Emollients • Emollients should be used on the whole body when the atopic eczema is clear and while using all other treatments. Topical corticosteroids • Use mild potency topical corticosteroids on the face and neck, except for short-term (three to five days) use of moderate potency agents for severe flares. • Use moderate or potent topical corticosteroids for short periods only (seven to 14 days) for flares in sites such as axillae and groin. • Do not use very potent preparations in children without specialist dermatological advice. • Topical corticosteroids for atopic eczema should be prescribed for application only once or twice daily. • In children ≥12 months of age, potent topical corticosteroids should be used for the shortest amount of time as possible; no longer than 14 days. They should not be used on the face or neck. Potent topical corticosteroids should not be used in children <12 months of age without specialist dermatological supervision. • Consider treating problem areas with topical corticosteroids for two consecutive days per week to prevent flares, rather than treating flares as they arise, in children with frequent flares (two or three per month), once the eczema has been controlled. • A different topical corticosteroid of the same potency should be considered as an alternative to stepping up treatment if tachyphylaxis to a topical corticosteroid is suspected. Topical calcineurin inhibitors • Topical tacrolimus and pimecrolimus are not recommended for the treatment of mild atopic eczema or as first-line treatments for atopic eczema of any severity. • Topical tacrolimus is recommended as an option for the second-line treatment of moderate to severe atopic eczema in adults and children aged two years and older that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy. • Pimecrolimus is recommended as an option for the second-line treatment of moderate atopic eczema on the face and neck in children aged two to 16 years that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly

Clinical Guideline	Recommendation(s)
	irreversible skin atrophy. • Treatment with tacrolimus or pimecrolimus should only be initiated by physicians (including general practitioners) with a special interest and experience in dermatology. • For facial atopic eczema in children that requires long-term or frequent use of mild topical corticosteroids, consider stepping up treatment to topical calcineurin inhibitors. <u>Antihistamines</u> • Oral antihistamines should not be used routinely in the management of atopic eczema in children. • A one-month trial of a nonsedating antihistamine should be offered to children with severe atopic eczema or children with mild or moderate atopic eczema where there is severe itching or urticaria. Treatment can be continued, if successful, while symptoms persist, and should be reviewed every three months. • A seven to 14 day trial of an age-appropriate sedating antihistamine should be offered to children aged six months or over during an acute flare of atopic eczema if sleep disturbance has a significant impact on the child or parents or carers. This treatment can be repeated during subsequent flares if successful. <u>Phototherapy and systemic treatments</u> • Phototherapy or systemic treatments should be considered for the treatment of severe atopic eczema in children when other management options have failed or are inappropriate and where there is a significant negative impact on quality of life.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma and Immunology/ Joint Council on Allergy, Asthma and Immunology: **Disease Management of Atopic Dermatitis: An Updated Practice Parameter (2012)**[11]	<u>General considerations</u> • The intensity of management and treatment of atopic dermatitis is dictated by the severity of illness, which relates to the effect of atopic dermatitis on the quality of life on the patient and his or her family. • The management of atopic dermatitis requires multiple therapeutic approaches including antipruritic therapy, skin hydration, topical anti-inflammatory medications, antibacterial measures, and the identification/elimination of exacerbating factors. <u>Skin hydration</u> • Hydration with warm soaking baths for at least 10 minutes followed by the application of a moisturizer is recommended. • Moisturizers should be recommended as first-line therapy. <u>Topical corticosteroids</u> • Topical corticosteroids are an effective treatment option for atopic dermatitis. If atopic dermatitis is not controlled by moisturizers alone, then the clinician should recommend a topical corticosteroid. • Low-potency corticosteroids are recommended for maintenance therapy, whereas intermediate-and high-potency corticosteroids should be used for the treatment of exacerbation and applied to affected areas over short periods of time. • Potent fluorinated corticosteroids should not be used on the face, eyelids, genitalia, and intertriginous areas or in young infants. • Ultrahigh-potency corticosteroids should be used only for very short periods of time (several days) and in nonfacial non-skinfold areas. • The degree of corticosteroid absorption through the skin and the potential for systemic adverse effects are directly dependent on the surface area of the skin involved, thickness of the skin, the use of occlusive dressing, and the potency of the corticosteroid preparation. <u>Topical calcineurin inhibitors</u>

Clinical Guideline	Recommendation(s)
	• Tacrolimus ointment has been shown to be effective and safe in both adults and children older than two years of age, with most patients experiencing a reduction of pruritus within three days of initiating therapy. • Tacrolimus ointment does not cause atrophy for eczema on the face, eyelid, and skin folds that is unresponsive to low-potency topical steroids. • Once a flare is controlled, tacrolimus ointment twice daily, twice weekly to eczema-prone areas may prevent future flares. • Pimecrolimus cream decreases the number of flares of atopic dermatitis, reduces the need for corticosteroids, and controls pruritus. <u>Tar preparations</u> • There are no randomized studies that have demonstrated the efficacy of tar preparations, despite their widespread use for the treatment of atopic dermatitis. • Newer coal tar products have been developed that are more cosmetically acceptable than older products. • Coal preparations should not be recommended for acutely inflamed skin because this might result in additional skin irritation. <u>Antihistamines</u> • Patients may benefit from the use of oral antihistamines for the relief of pruritus associated with atopic dermatitis. Treatment of atopic dermatitis with topical antihistamines is generally not recommended because of potential cutaneous sensitization. <u>Vitamin D</u> • Patients with atopic dermatitis might benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake. <u>Dilute bleach baths</u> • The addition of dilute bleach baths twice weekly may reduce the severity of atopic dermatitis, especially in patients with recurrent skin infections. <u>Microbes</u> • Skin infections with *Staphylococcus aureus* are a recurrent problem in patients with atopic dermatitis, and patients with moderate-to-severe atopic dermatitis have been found to make IgE antibodies against staphylococcal toxins present in their skin. • A short course of an appropriate systemic antibiotic for patients who are clinically infected with *Staphylococcus aureus* should be prescribed. In areas with high levels of methicillin-resistant *Staphylococcus aureus*, treatment with clindamycin, doxycycline, or sulfamethoxazole-trimethoprim may be initiated while awaiting skin culture results. • Atopic dermatitis can be complicated by recurrent viral skin infections, such as herpes simplex, warts, and molluscum contagiosum. Herpes simplex or eczema herpeticum should be diagnosed and promptly treated with systemic antiviral agents. • Fungal infections can complicate atopic dermatitis and might contribute to exacerbations. <u>Systemic Immunomodulating Agents</u> • Immunosuppressive agents such as cyclosporine, interferon gamma, mycophenolate mofetil, azathioprine, and corticosteroids have been shown to provide benefit for certain cases of severe refractory atopic dermatitis, but potential benefits should be weighed against their potentially serious adverse effects. <u>Phototherapy</u>

Clinical Guideline	Recommendation(s)
	• Ultraviolet therapy can be a useful treatment for recalcitrant atopic dermatitis. Allergen immunotherapy • Select patients with atopic dermatitis with aeroallergen sensitivity may benefit from allergen immunotherapy.
American Academy of Dermatology: **Guidelines of Care for the Management of Atopic Dermatitis (2014)**[12]	Topical corticosteroids • Topical corticosteroids are the mainstay of anti-inflammatory therapy for the management of atopic dermatitis. • They are typically introduced into the treatment regimen after failure of lesions to respond to good skin care and regular use of moisturizers alone. • Comparative trials are limited in duration and scope (i.e., they mainly involve two, and occasionally three, agents), and as a result, there are no data to support one or a few specific agents as being more efficacious than others. • A variety of factors should be considered when choosing a particular topical corticosteroid for the treatment of atopic dermatitis, including patient age, areas of the body to which the medication will be applied, and other patient factors such as degree of xerosis, patient preference, and cost of medication. • Twice-daily application of corticosteroids is generally recommended for the treatment of atopic dermatitis; however, evidence suggests that once-daily application of some corticosteroids may be sufficient. • Proactive, intermittent use of topical corticosteroids as maintenance therapy (one to two times/week) on areas that commonly flare is recommended to help prevent relapses and is more effective than use of emollients alone. • The potential for both topical and systemic side effects, including possible hypothalamic-pituitary-adrenal axis suppression, should be considered, particularly in children with atopic dermatitis in whom corticosteroids are used. • Monitoring by physical examination for cutaneous side effects during long-term, potent steroid use is recommended. • No specific monitoring for systemic side effects is routinely recommended for patients with atopic dermatitis. • Patient fears of side effects associated with the use of topical corticosteroids for atopic dermatitis should be recognized and addressed to improve adherence and avoid undertreatment. Topical calcineurin inhibitors • Topical calcineurin inhibitors are recommended and effective for acute and chronic treatment, along with maintenance, in both adults and children with atopic dermatitis, and are particularly useful in selected clinical situations, including recalcitrance to steroids, use on sensitive areas (e.g., face, anogenital, skin folds), steroid-induced atrophy, and long-term uninterrupted topical steroid use. • Topical calcineurin inhibitors are recommended for use on actively affected areas as a steroid-sparing agent for the treatment of atopic dermatitis. • For patients with atopic dermatitis <2 years of age with mild to severe disease, off-label use of 0.03% tacrolimus or 1% pimecrolimus ointment can be recommended. • Pimecrolimus cream and tacrolimus ointment may cause skin burning and pruritus, especially when applied to acutely inflamed skin. Initial treatment of patients with atopic dermatitis using topical corticosteroids should be considered to minimize topical calcineurin inhibitor application site reactions. Patients with atopic dermatitis should be counseled about the possibility of these reactions. • Proactive, intermittent use of topical calcineurin inhibitor as maintenance therapy (two to three times per week) on areas that commonly flare is recommended to help prevent relapses while reducing the need for topical corticosteroids, and is more effective than the use of emollients alone. • The concomitant use of a topical corticosteroid with a topical calcineurin inhibitor may be recommended for the treatment of atopic dermatitis.

Clinical Guideline	Recommendation(s)
	• No consistent increases in the prevalence of cutaneous viral infections have been seen with continuous or intermittent use of topical calcineurin inhibitor for up to five years; however, physicians should inform their patients of these theoretical cutaneous risks, given the lack of safety data for longer periods of time. • Clinicians should be aware of the black-box warning on the use of topical calcineurin inhibitor for patients with atopic dermatitis and discuss as warranted. • Routine blood monitoring of tacrolimus and pimecrolimus levels in patients with atopic dermatitis who are applying these agents is not recommended at this time. <u>Topical antimicrobials and antiseptics</u> • Except for bleach baths with intranasal mupirocin, no topical antistaphylococcal treatment has been shown to be clinically helpful in patients with atopic dermatitis, and is not routinely recommended. In patients with moderate to severe atopic dermatitis and clinical signs of secondary bacterial infection, bleach baths and intranasal mupirocin may be recommended to reduce disease severity. <u>Other topical agents</u> • Topical antihistamines have been tried for the treatment of atopic dermatitis but have demonstrated little utility and are not recommended. • There are not adequate data to make a recommendation regarding the use of coal tar topical agents.
British Association of Dermatologists: **Guidelines for the Management of Contact Dermatitis (2017)**[13]	• Avoidance of allergens and irritants is the cornerstone of the management of occupational skin disease. • Personal protective equipment such as clothing or gloves may be an adequate solution, although less likely to be effective with potent sensitizers and airborne allergens/irritants. • Replacement of soaps and detergents with emollients is useful, even if they are not the cause of the dermatitis, as they are irritants which will compound the situation. • Therapy for contact dermatitis persisting despite allergen/irritant removal and skin protection largely follows the management of atopic/endogenous dermatitis. • Studies support the efficacy of topical steroids and topical tacrolimus in the treatment of contact dermatitis. • Second-line treatment includes phototherapy and systemic immunomodulators such as methotrexate and mycophenolate mofetil. • Psoralen plus UVA, ciclosporin and alitretinoin have been demonstrated to be useful in chronic hand dermatitis, and azathioprine in chronic actinic dermatitis, but none has been assessed specifically in the treatment of contact dermatitis.
American Gastroenterological Association: **Medical Position Statement: Diagnosis and Treatment of Hemorrhoids (2004)**[14]	• Treatment of hemorrhoids depends on their severity. • The cornerstone of medical therapy is fiber and water. • Topical corticosteroids and analgesics are useful for managing perianal skin irritation due to poor hygiene, mucus discharge, or fecal seepage. • Prolonged use of potent corticosteroid preparations may be harmful and should be avoided.
American Gastroenterological Association: **Technical Review on the Diagnosis and Treatment of Hemorrhoids (2004)**[15]	• Add dietary fiber and avoid straining at stool. • Over-the-counter topical agents and suppositories have become equally ubiquitous in the empirical treatment of hemorrhoidal symptoms, but data supporting their use are lacking. • Topical analgesics may bring relief of local pain and itching. • Corticosteroid creams may ameliorate local perianal inflammation, but no data suggest that they actually reduce hemorrhoidal swelling, bleeding, or protrusion. • Long-term use of high-potency corticosteroid creams is deleterious and should be

Clinical Guideline	Recommendation(s)
	avoided.
European Federation of Neurological Societies: **Guidelines on the Pharmacological Treatment of Neuropathic Pain (2010)**[16]	<u>Postherpetic neuralgia</u> • Tricyclic antidepressants or gabapentin/pregabalin are recommended as first-line therapy of postherpetic neuralgia. • Topical lidocaine may be considered as first-line therapy in the elderly, especially if there are concerns regarding the central nervous system side effects of oral medications. A two to four week trial is recommended before starting other therapy. • Strong opioids and capsaicin cream are recommended as second-line therapy. • Capsaicin patches are promising, but the long-term effects of repeated applications particularly on sensation are not clarified.
National Institute for Health and Clinical Excellence: **Neuropathic pain in adults: pharmacological management in non-specialist settings (2013)**[17] Last updated: July 2019	• Consider referring the person to a specialist pain service and/or a condition-specific service at any stage, including at initial presentation and at the regular clinical reviews if they have severe pain, the pain significantly limits their lifestyle, daily activities and participation or their underlying health condition has deteriorated. • Continue existing treatments for people whose neuropathic pain is already effectively managed, taking into account the need for regular clinical reviews. • When introducing a new treatment, take into account any overlap with the old treatments to avoid deterioration in pain control. • After starting or changing a treatment, carry out an early clinical review of dosage titration, tolerability and adverse effects to assess the suitability of the chosen treatment. • Carry out regular clinical reviews to assess and monitor the effectiveness of the treatment. Each review should include an assessment of: o Pain control. o Impact on lifestyle, daily activities (including sleep disturbance), and participation. o Physical and psychological wellbeing. o Adverse effects. o Continued need for treatment. • When withdrawing or switching treatment, taper the withdrawal regimen to take account of dosage and any discontinuation symptoms. • Treatment of all neuropathic pain (except trigeminal neuralgia): o Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain. o If the initial treatment is not effective or is not tolerated, offer one of the remaining three drugs, and consider switching again if the second and third drugs tried are also not effective or not tolerated. o Consider tramadol only if acute rescue therapy is needed. o Consider capsaicin cream for people with localized neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments. • Treatments that should not be used (unless advised by a specialist to do so): o Cannabis sativa extract. o Capsaicin patch. o Lacosamide. o Lamotrigine. o Levetiracetam. o Morphine. o Oxcarbazepine. o Topiramate. o Tramadol (for long-term use). o Venlafaxine. o Sodium valproate • Treatment of trigeminal neuralgia: o Offer carbamazepine as initial treatment for trigeminal neuralgia.

Clinical Guideline	Recommendation(s)
	○ If initial treatment with carbamazepine is not effective, is not tolerated or is contraindicated, consider seeking expert advice from a specialist and consider early referral to a specialist pain service or a condition-specific service.
International Association for the Study of Pain: **Pharmacologic Management of Neuropathic Pain: Evidence-Based Recommendations (2010)**[18]	<u>General treatment considerations</u> • Medication selection should be individualized, considering side effects, comorbidities, and onset of pain relief. • Recommended first-line treatments include tricyclic antidepressants (nortriptyline, desipramine) and selective serotonin and norepinephrine reuptake inhibitors (duloxetine, venlafaxine), calcium channel α2-δ ligand (gabapentin and pregabalin), and topical lidocaine. • Opioid analgesics and tramadol are recommended as second-line treatments that can be considered for first-line use in select clinical circumstances. • Other medications that would be used as third-line treatments include certain antiepileptic (carbamazepine, lamotrigine, oxcarbazepine, topiramate, valproic acid) and antidepressant (bupropion, citalopram, paroxetine) medications, mexiletine, N-methyl-D-aspartate receptor antagonists, and topical capsaicin. <u>Stepwise pharmacologic management of neuropathic pain</u> Step 1: • Assess pain and establish the diagnosis of neuropathic pain. • Establish and treat the cause of neuropathic pain. • Identify comorbidities that might be relieved or exacerbated by neuropathic pain treatment, or that might require dosage adjustment or additional monitoring of therapy. Step 2: • Initiate therapy of the disease causing neuropathic pain, if applicable. • Initiate symptom treatment with one or more of the following: ○ Tricyclic antidepressant (nortriptyline, desipramine) or a selective serotonin and norepinephrine reuptake inhibitor (duloxetine, venlafaxine). ○ Calcium channel α2-δ ligand (gabapentin or pregabalin). ○ Topical lidocaine used alone or in combination with one of the other first-line therapies for patients with localized peripheral neuropathic pain. ○ Opioid analgesics or tramadol alone or in combination with one of the first-line therapies for patients with acute neuropathic pain, neuropathic cancer pain, or exacerbations of severe pain. Step 3: • Reassess pain and quality of life frequently. • If substantial pain relief (average pain reduced to ≤3/10) and tolerable side effects, continue treatment. • If partial pain relief (average pain remains ≥4/10) after an adequate trial, add one of the other first-line medications. • If no or inadequate pain relief (<30% reduction) at target dosage after an adequate trial, switch to an alternative first-line medication. Step 4: • If trials of first-line medications alone and in combination fail, consider second- and third-line medications or referral to a pain specialist or multidisciplinary pain center.
European Dermatology Forum/ European Academy of Dermatology and Venereology: **Guideline on the Management of**	<u>Antiviral medication</u> • It is recommended to treat the following patient subgroups with an antiviral medication: ○ Herpes zoster of any localization in patients ≥50 years of age. ○ Herpes zoster of the head and/or neck area. ○ Herpes zoster of any localization with: ▪ Moderate to severe zoster-associated pain. ▪ Hemorrhagic or necrotizing lesions.

Clinical Guideline	Recommendation(s)
Herpes Zoster (2016)[19]	▪ More than one segment involved. ▪ Aberrant vesicles/satellite lesions. ▪ Involvement of mucous membranes. o Herpes zoster in immunocompromised patients. o Herpes zoster in patients with severe predisposing skin diseases (e.g., atopic dermatitis). o Herpes zoster in children and adolescents under long-term treatment with salicylic acid or corticosteroids. • In patients <50 years of age who present with herpes zoster of the trunk or extremities, without being at risk of or displaying signs of a complicated course, initiating an antiviral medication is suggested. • Using intravenous acyclovir is suggested in patients who present with complicated herpes zoster or who are at risk of a complicated course. This includes the following patient groups: o Herpes zoster of the head and/or neck area, particularly in elderly patients. o Herpes zoster with hemorrhagic/necrotizing lesions, >1 segment involved, aberrant vesicles/ satellite lesions, involvement of mucous membranes or generalized zoster. o Herpes zoster in immunocompromised patients. o Herpes zoster with signs of visceral or central nervous system involvement (dosage escalation up to 15 mg/kg bodyweight 3x/d possible, treatment for up to 21 days). • In patients who do not present with an indication to initiate an intravenous treatment with acyclovir, shared decision-making with respect to using oral acyclovir, valaciclovir, famciclovir or brivudin, taking practicability (dosage frequency), costs, contraindications, comorbidity and drug interactions into consideration is suggested. • Checking creatinine in patients with known or suspected renal insufficiency is suggested at the time of initiation of an antiviral medication with acyclovir, famciclovir or valaciclovir. • Initiating antiviral medication as early as possible, within 72 hours after the onset of symptoms, or at a later time, is suggested: o As long as new vesicles appear in patients at risk of a complicated course or with manifest complications. o In patients with signs of cutaneous, visceral or neurological dissemination. o In the case of herpes zoster ophthalmicus or herpes zoster oticus. o In all immunocompromised patients. • Initiating an antiviral medication is NOT suggested in patients who have 'uncomplicated' herpes zoster (classical, unilateral thoracic or lumbar herpes zoster in patients younger than 50 years of age, without signs of a complicated course) who present >72 hours after the onset of skin symptoms. <u>Acute pain management</u> • Early initiation of acute zoster-associated pain treatment is recommended, using systemic analgesics. • Analgesic treatment of herpes zoster pain according to the World Health Organization pain ladder is recommended and, if pain severity at baseline is moderate-to-severe or other risk factors for post-herpetic neuralgia are present, consider supplementing with an anti-depressant (e.g., amitriptyline) or anti-epileptic (e.g., gabapentin, pregabalin) drug. • In situations of mild pain intensity, NSAIDs or other non-opioids are appropriate; with moderate pain, non-opioids in combination with weak opioid analgetics might be sufficient; with severe pain, non-opioids combined with strong opioids may be required. <u>Local therapy</u>

Clinical Guideline	Recommendation(s)
	• Selecting a topical treatment according to the current status of the skin lesions is suggested. • Some experts suggest applying sterile saline 0.9% solution or mild antiseptics such as polyhexanide 20% solution to the affected area for 20 to 30 min four to six times daily. The application of local zinc oxide lotion is common practice at some centers. Some experts recommend to refrain from any topical treatment but to keep the lesions clean and dry. • A recommendation cannot be made with respect to the application of local antiviral preparations for cutaneous herpes zoster. • The application of local anaesthetic agents or capsaicin is NOT recommended for acute herpes zoster. • A systematic review of topical lidocaine for the treatment of neuropathic pain concluded that there is no evidence from high quality studies to support its use.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the skin and mucous membrane antipruritics and local anesthetics are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Skin and Mucous Membrane Antipruritics and Local Anesthetics[1-6]

Indications	Single Entity Agents		Combination Products	
	Doxepin	Lidocaine	Lidocaine and Prilocaine	Lidocaine and Tetracaine
Anesthetic lubricant for intubation		✔ †		
For use on intact skin to provide local dermal analgesia for superficial venous access and superficial dermatologic procedures such as excision, electrodesiccation, and shave biopsy of skin lesions				✔
Production of anesthesia of the mucous membranes of the oropharynx		✔ †		
Production of anesthesia of the mucous membranes of the respiratory tract		✔ §		
Pruritus, pruritic eczemas, abrasions, minor burns, insect bites, pain, soreness and discomfort due to pruritus ani, pruritus vulvae, hemorrhoids, anal fissures, and similar conditions of the skin and mucous membranes		✔ ‖		
Relief of pain and itching due to sunburn, minor burns, cuts, scrapes, insect bites or minor skin irritation		✔ ‖†		
Relief of pain associated with post-herpetic neuralgia		✔ ‡		
Short-term (up to eight days) management of moderate pruritus in adults with atopic dermatitis or lichen simplex chronicus	✔			
Topical anesthetic for use on normal intact skin for local analgesia or genital mucous membranes for superficial minor surgery and as pretreatment for infiltration anesthesia.			✔	

‖Cream formulations.
†Ointment formulation.
§Solution formulation.
‡Transdermal patch formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the skin and mucous membrane antipruritics and local anesthetics are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Skin and Mucous Membrane Antipruritics and Local Anesthetics[1-6]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Doxepin	Not reported	Not reported	Hepatic	Renal	Not reported
Lidocaine	Patch: 3	33 to 80	Hepatic	Renal	Not reported
Combination Products					
Lidocaine and prilocaine	Variable	L: 70 P: 40 to 55	L: Hepatic P: Hepatic, Renal	L: Renal (98)	L: 1 to 2.5 P: 10 to 150 minutes
Lidocaine and tetracaine	Variable	75	L: Hepatic T: Plasma	L: Renal (98)	Not reported

L=lidocaine, P=prilocaine, T=tetracaine

V. Drug Interactions

Major drug interactions with the skin and mucous membrane antipruritics and local anesthetics are listed in Table 5. Studies have not been performed examining drug interactions with doxepin cream. However, since plasma levels of doxepin following topical application the cream can reach levels obtained with oral doxepin HCl therapy, the drug interactions listed in Table 5 are possible following topical application.[2-3]

Table 5. Major Drug Interactions with the Skin and Mucous Membrane Antipruritics and Local Anesthetics[2]

Generic Name(s)	Interaction	Mechanism
Doxepin	Monoamine oxidase inhibitors	Altered catecholamine uptake and metabolism may occur when doxepin and monoamine oxidase inhibitors are taken concurrently. This may result in hyperpyrexia, convulsions, and death.
Doxepin	Anticoagulants	The hypoprothrombinemic effect of anticoagulants may be increased by doxepin.
Doxepin	Carbamazepine	Carbamazepine may alter the parent drug-hydroxylated metabolite ratio resulting in increase of toxicity or loss of efficacy of doxepin.
Doxepin	Cimetidine	Concurrent administration of doxepin and cimetidine may cause fluctuations, specifically elevations, in serum doxepin concentrations. Elevated serum doxepin concentrations may result in anticholinergic side effects.
Doxepin	Clonidine	The antihypertensive effects of clonidine may be decreased by doxepin.
Doxepin	Fluconazole	Plasma concentrations and toxic effects of doxepin may be increased by fluconazole.
Doxepin	Fluoxetine	Plasma concentrations and toxic effects of doxepin may be increased by fluoxetine.
Doxepin	Fluvoxamine	Plasma concentrations and pharmacologic effects of doxepin may be increased by fluvoxamine.
Doxepin	Guanethidine	Antihypertensive effects of guanethidine may be decreased by doxepin.
Doxepin	Guanfacine	The antihypertensive effect of guanfacine may be decreased by doxepin.

Generic Name(s)	Interaction	Mechanism
Doxepin	Linezolid	Concurrent use of doxepin and linezolid may result in increased risk of serotonin syndrome (hyperthermia, hyperreflexia, myoclonus, mental status changes).
Doxepin	Methylene blue	Concurrent use of doxepin and methylene blue may result in an increased risk of serotonin syndrome (labile blood pressure, hyperthermia, neuromuscular abnormalities, mental status changes, gastrointestinal symptoms).
Doxepin	Paroxetine	Paroxetine may increase pharmacologic effects and plasma concentrations of doxepin.
Doxepin	Sympathomimetics	The alpha-adrenergic effects of sympathomimetics may be increased or decreased by doxepin.
Doxepin	Tramadol	Increased risk of seizures is a possibility when tramadol and doxepin are coadministered.

VI. Adverse Drug Events

The most common adverse drug events reported with the skin and mucous membrane antipruritics and local anesthetics are listed in Table 6. The Food and Drug Administration (FDA) issued a public health advisory about potentially serious hazards of using topical anesthetics for relieving pain from medical tests and conditions. The FDA remains concerned about the potential for topical anesthetics to cause serious and life-threatening adverse effects when applied to a large area of skin or when the area of application is covered. Skin temperature can increase during exercise, by covering the skin with a wrap, or with use of a heating pad. Under these circumstances, the amount of topical anesthetic that reaches the systemic circulation is unpredictable and may be high enough to cause life-threatening adverse effects such as arrhythmias, seizures, respiratory difficulties, coma, and death.[20]

Table 6. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Antipruritics and Local Anesthetics[1-6]

Adverse Events	Single Entity Agents		Combination Products	
	Doxepin	Lidocaine	Lidocaine and Prilocaine	Lidocaine and Tetracaine
Cardiovascular				
Cyanosis	-	✔	-	-
Hypotension	-	-	✔	<1
Shock	-	-	✔	-
Tachycardia	-	✔	-	-
Central Nervous System				
Anxiety	<1	✔	-	-
Confusion	-	✔	✔	✔
Convulsions	-	-	✔	✔
Dizziness	2	✔	✔	✔
Drowsiness	22	-	✔	✔
Emotional changes	2	-	-	-
Lethargy	-	✔	-	-
Lightheadedness	-	✔	✔	-
Nervousness	-	-	✔	-
Paresthesia	-	✔	-	✔
Somnolence	-	✔	-	-
Stupor	-	-	-	<1
Syncope	-	-	-	<1
Dermatological				
Alteration in temperature sensations	-	-	-	-
Blanching	-	-	-	12 to 16
Bruising	-	✔ †	-	-
Burning sensation	23	-	✔	✔
Contact dermatitis	<1	✔	-	✔
Edema	1	✔	✔	12 to 14
Erythema	-	-	✔	47 to 71

Adverse Events	Single Entity Agents		Combination Products	
	Doxepin	Lidocaine	Lidocaine and Prilocaine	Lidocaine and Tetracaine
Irritation	-	✔ †	-	-
Itching	-	-	-	
Petechia	-	✔ †	-	-
Pruritus	-	✔	✔	✔
Rash	-	✔	✔	✔
Skin pigment alteration	-	✔ †	✔	<4
Stinging	23	-	✔	-
Urticaria	-	✔	✔	✔
Gastrointestinal				
Nausea	-	-	-	✔
Taste alteration	2	-	-	-
Vomiting	-	-	-	✔
Xerostomia	10	-	-	-
Respiratory				
Bronchospasm	-	-	✔	<1
Hypoxia	-	✔	-	-
Other				
Allergic reaction/anaphylaxis	-	-	✔	<1
Alteration in temperature sensation	-	-	✔	-
Angioedema	-	✔	✔	<1
Hypersensitivity	-	-	✔	-
Infection	-	-	-	<1
Methemoglobinemia	-	✔	-	-
Pain	-	✔ †	-	-
Tinnitus	-	-	✔	-
Tongue numbness	<1	-	-	-
Weakness	-	✔	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.
† Transdermal patch.

VII. Dosing and Administration

The usual dosing regimens for the skin and mucous membrane antipruritics and local anesthetics are listed in Table 7.

Table 7. Usual Dosing Regimens for the Skin and Mucous Membrane Antipruritics and Local Anesthetics[1-6]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Doxepin	Short-term (up to eight days) management of moderate pruritus in adults with atopic dermatitis or lichen simplex chronicus: Cream: apply a thin film to affected area four times per day with at least three to four hours between applications; do not use for more than eight days	Safety and efficacy in children have not been established.	Cream: 5%
Lidocaine	Pruritus, pruritic eczemas, abrasions, minor burns, insect bites, pain, soreness and discomfort due to pruritus ani, pruritus vulvae, hemorrhoids, anal fissures, and similar conditions of the skin and mucous membranes: Cream: apply to the affected area two to three times per day Ointment: apply topically for adequate control of symptoms Anesthetic lubricant for intubation, production of anesthesia of the mucous membranes of the oropharynx, relief of pain and itching due to sunburn, minor burns, cuts, scrapes, insect bites or minor skin irritation: Ointment: apply to the external surface of the tube prior to intubation Relief of pain associated with post-herpetic neuralgia: Patch: apply up to three patches to the most painful area, for up to 12 hours within a 24-hour period Production of anesthesia of the mucous membranes of the respiratory tract: Solution: spray 1 to 5 mL (40 to 200 mg lidocaine) to the affected area; maximum, 300 mg or 4.5 mg/kg	Pruritus, pruritic eczemas, abrasions, minor burns, insect bites, pain, soreness and discomfort due to pruritus ani, pruritus vulvae, hemorrhoids, anal fissures, and similar conditions of the skin and mucous membranes: Cream: apply to the affected area two to three times per day; dosages in children should be reduced, commensurate with age and body weight Ointment: apply topically for adequate control of symptoms maximum, 250 mg per single dose or 4.5 mg/kg; dosages in children should be reduced, commensurate with age and body weight Anesthetic lubricant for intubation, production of anesthesia of the mucous membranes of the oropharynx, relief of pain and itching due to sunburn, minor burns, cuts, scrapes, insect bites or minor skin irritation: Ointment: apply ≤5 g (250 mg lidocaine) to the external surface of the tube prior to intubation; maximum, 4.5 mg/kg lidocaine base Production of anesthesia of the mucous membranes of the respiratory tract:	Cream: 3% Ointment: 5% Patch: 1.8% 5% (700 mg) Solution: 4%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		Solution: spray 1 to 5 mL (40 to 200 mg lidocaine) to the affected area; maximum, 300 mg or 4.5 mg/kg; dosages in children should be reduced, commensurate with age and body weight	
Combination Products			
Lidocaine and prilocaine	Topical anesthetic for use on normal intact skin for local analgesia or genital mucous membranes for superficial minor surgery and as pretreatment for infiltration anesthesia: Cream: for minor dermal procedures*, apply 2.5 g (1/2 of the 5 g tube) over 20 to 25 cm^2 of skin surface for at least one hour and cover with an occlusive dressing; for major dermal procedures†, apply 2 g per 10 cm^2 of skin and leave on for at least two hours and cover with an occlusive dressing; for adult male genital skin, apply a thick layer (1 g /10 cm^2) to skin for 15 minutes and cover with an occlusive dressing, perform procedure immediately following removal of the cream; for adult female genital mucous membranes, apply a thick layer (5 to 10 g) to mucous membranes for 5 to 10 minutes and perform procedure immediately following removal of the cream (occlusion is not necessary)	Topical anesthetic for use on normal intact skin for local analgesia or genital mucous membranes for superficial minor surgery and as pretreatment for infiltration anesthesia: Cream: for intact skin, 0 to three months of age (<5 kg), 1 g/dose applied to a maximum area of 10 cm^2 for up to one hour; for three to 12 months of age (>5 kg), 2 g/dose applied to a maximum area of 20 cm^2 for up to four hours; for one to six years of age (10 kg), 10 g/dose applied to a maximum area of 100 cm^2 for up to four hours; for seven to 12 years of age (>20 kg), 20 g/dose applied to a maximum area of 200 cm^2 for up to four hours; do not use in neonates <37 weeks gestational age or in infants less than 12 months who are being treated with other agents associated with methemoglobinemia	Cream: 2.5%-2.5%
Lidocaine and tetracaine	For use on intact skin to provide local dermal analgesia for superficial venous access and superficial dermatologic procedures such as excision, electrodesiccation, and shave biopsy of skin lesions: Transdermal patch: apply to intact skin for 20 to 30 minutes	For use on intact skin to provide local dermal analgesia for superficial venous access and superficial dermatologic procedures such as excision, electrodesiccation, and shave biopsy of skin lesions >3 years of age: Transdermal patch: apply to intact skin for 20 to 30 minutes	Transdermal patch: 70 mg-70 mg

*Venipuncture or intravenous cannulation.
†Split thickness skin graft harvesting.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the skin and mucous membrane antipruritics and local anesthetics are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Skin and Mucous Membrane Antipruritics and Local Anesthetics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Drake et al.[21] (1994) Doxepin 5% cream applied QID vs placebo	DB, MC, PC, RCT Patients with atopic dermatitis who had daily moderate to severe pruritus for at least 1 week	N=270 7 days	Primary: Relief of pruritus, pruritus severity, and adverse events Secondary: Not reported	Primary: Relief of pruritus was achieved in 85% of patients receiving doxepin and 57% of patients receiving placebo. Pruritus severity scores demonstrated significantly greater improvement with doxepin at each study visit (P<0.01). Using visual analog scales, pruritus severity and pruritus relief showed similar improvement in patients receiving doxepin. The physician's global evaluation for relief of pruritus showed significant improvement in the doxepin treatment group (P<0.01). The physician's global evaluations of eczema significantly favored topical doxepin (P<0.01). The most commonly reported adverse events were localized stinging or burning and drowsiness, which decreased in frequency and severity over time. Secondary: Not reported
Drake et al.[22] (1995) Doxepin 5% cream applied QID vs placebo	DB, PC, RCT Patients 12 to 65 years of age diagnosed with lichen simplex chronicus, nummular eczema, or contact dermatitis experiencing	N=309 7 days	Primary: Pruritus severity rating scale, physician's global evaluation for pruritus relief, patient's assessment of pruritus relief on a visual analog scale	Primary: Significantly more patients in the doxepin group experienced pruritus relief in the first 24 hours compared to placebo patients in all forms of eczema included in the study (P<0.04). After seven days, the response to doxepin ranged from 76 to 89%, and there were significant differences favoring doxepin cream in patients with contact dermatitis and lichen simplex chronicus (P<0.05). In the first 24 hours of treatment, patients in the doxepin group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	moderate to severe pruritus on a daily basis for ≥1 week		Secondary: Not reported	experienced at least a 50% reduction in pruritus for all forms of eczema studied. Significant differences were only observed in the lichen simplex chronicus group compared to placebo (visual analog scale; P=0.001). At day seven, patients in the doxepin group experienced at least a 70% reduction in pruritus for all forms of eczema studied. Significant differences were only observed in the lichen simplex chronicus group compared to placebo (visual analog scale; P=0.001). In the first 24 hours, a greater percentage of patients in the doxepin group experienced pruritus relief compared to the placebo group. Significant differences were only observed in lichen simplex chronicus and nummular eczema (physician's global evaluation; P<0.02). At day seven, a greater percentage of patients in the doxepin group experienced pruritus relief compared to the placebo group. Significant differences were only observed in lichen simplex chronicus and nummular eczema (physician's global evaluation; P<0.02). Secondary: Not reported
Breneman et al.[23] (1997) SB Phase Doxepin 5% cream applied QID for 7 days DB Phase Doxepin 5% cream applied QID for 7 days vs	DB, RCT, SB Patients with atopic dermatitis or lichen simplex chronicus with moderate to severe pruritus	N=120 14 days	Primary: Pruritus severity, pruritus relief, eczema severity Secondary: Not reported	Primary: Fifteen minutes following application of doxepin cream, there was a significant improvement in antipruritic activity as measured by visual analog scales of pruritus severity (P<0.001) and pruritus relief (P<0.001). A total of 75% of patients reported reductions in pruritus severity in just 15 minutes and 84% reported reductions by 120 minutes following doxepin cream application. Decreasing pruritus severity and increasing pruritus relief continued significantly through day seven. A significant improvement in pruritus severity rating and physician's global evaluation of pruritus relief was present on day seven and continued to day 14 compared to baseline in both treatment groups (P<0.001). Eczema severity was significantly improved on both days seven and 14 in all treatment groups compared to baseline (P<0.001), with significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo for 7 days				continued improvement in the doxepin group on day 14 compared to day seven (P=0.011). Adverse events were mild to moderate in severity and decreased throughout the study. Secondary: Not reported
Berberian et al.[24] (1999) Doxepin 5% and hydrocortisone 2.5% cream applied QID vs doxepin 5% and triamcinolone 0.1% cream applied QID vs hydrocortisone 2.5% cream applied QID vs triamcinolone 0.1% cream applied QID	DB, MC, PG, RCT Patients with pruritic atopic dermatitis who experienced moderate to severe pruritus associated with their eczematous lesions daily for at least 1 week, family history of atopy and/or a personal history of atopic dermatitis, ≤25% body surface area affected by atopic dermatitis, and good general health	N=349 8 days	Primary: Pruritus severity and pruritus relief Secondary: Not reported	Primary: Patients who received doxepin in addition to a steroid achieved significant reductions in pruritus than those treated with a steroid cream alone. The physician's global evaluations for pruritus relief demonstrated that the addition of doxepin to either hydrocortisone or triamcinolone treatment significantly improved itch relief over that of the topical corticosteroid alone. On day two, the doxepin 5% and hydrocortisone 2.5% combination was significantly better for pruritus relief than the hydrocortisone treatment alone (P=0.01) as was the doxepin 5% and triamcinolone 0.1% combination than the triamcinolone alone (P=0.027). By day eight, statistical significance was reached in favor of the doxepin 5% and hydrocortisone 2.5% combination over the steroid alone, but not for the doxepin 5% and triamcinolone 0.1% over triamcinolone alone. A faster improvement in the eczematous condition was noted by the physicians over the first couple of days of the study in those in the combination doxepin and steroid treatment groups vs steroid treatment alone. Secondary: Not reported
Ramsook et al.[25] (2001)	DB, PC, RCT Patients 3 to 18	N=222 1 day	Primary: Results of the Faces Pain Scale	Primary: Pain scores reported by the patients did not differ between groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ethyl chloride spray vs isopropyl alcohol spray	years of age who presented to the emergency department requiring intravenous cannulation for fluids or medication administration, or venipuncture for diagnostic tests		(used for patients three to 10 years of age) and the Numeric Pain Score (used for patients 10 to 18 years of age) Secondary: Not reported	There was no significant difference in pain scores between groups when stratified for age (<6 years, six to 12 years, and >12 years). Significantly more procedures in the ethyl chloride group were rated as difficult compared to the isopropyl alcohol group (P<0.05). Secondary: Not reported
Davies et al.[26] (2006) Ethyl chloride spray applied to the site of the venipuncture no more than 45 seconds prior to procedure vs tetracaine cream applied to site of the venipuncture, covered with an occlusive dressing, and left in place for 30 to 45 minutes	XO Patients admitted for measurement of glomerular filtration rate which involved a series of 3 venipunctures in a 4 hour period. The first 2 venipunctures constituted the XO and children could choose their own treatment for the third venipuncture	N=77 1 day	Primary: Children's self-reported pain measured by the Wong-Baker faces scale Secondary: Not reported	Primary: The pain scores were higher on the second venipuncture compared to the first for both groups. Ethyl chloride was associated with lower pain scores compared to tetracaine cream on the first and second venipuncture. Both ethyl chloride and tetracaine cream were associated with lower pain scores for the third venipuncture compared to the first two, with ethyl chloride being lower. Secondary: Not reported
Robinson et al.[27] (2007) Ethyl chloride sprayed for 5 to 10	RCT Patient ≥15 years of age requiring intravenous	N=300 1 day	Primary: Pain from intravenous cannulation using a visual analog scale	Primary: Lidocaine, ethyl chloride and nitrous oxide reduced the pain of intravenous cannulation. Lidocaine was significantly more effective than all other groups (P≤0.001). Patients cannulated without analgesia reported the most pain.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
seconds 15 to 20 cm from intended site of cannulation vs nitrous oxide inhaled for 1 minute prior to and during cannulation vs lidocaine 1% injected with a 26-gauge needle vs immediate cannulation with no anesthesia	cannulation		Secondary: Not reported	Lidocaine provided the greatest reduction in the pain of cannulation (median visual analog scale 1 mm vs control visual analog scale 20 mm, P≤0.0001). The ethyl chloride and nitrous oxide groups were not significantly different (P=0.3). Ethyl chloride reduced the pain of cannulation compared to control (median visual analog scale 11 mm, vs control visual analog scale 20 mm; P≤0.003), but this did not reach clinical significance. Nitrous oxide reduced the pain of cannulation compared to control (median visual analog scale 13 mm vs control visual analog scale 20 mm, P=0.047), but this did not reach clinical significance. Neither pain from presenting symptoms (P=0.3), nor size of cannula (P=0.8) affected pain scores. Cannulation success was not affected by either the choice of analgesia or cannulation site. Secondary: Not reported
Celik et al.[28] (2011) Ethyl chloride sprayed for 2 seconds 10 cm from intended site vs lidocaine-prilocaine cream 2 mL applied to	PC, RCT, XO Patients ≥18 years of age undergoing conventional hemodialysis three times a week	N=41 3 dialysis sessions	Primary: Pain caused by venipuncture of arteriovenous fissula Secondary: Not reported	Primary: Lidocaine-prilocaine application resulted in significantly lower total pain scores compared to control and all other interventions (P<0.05). Patients reported less moderate and severe pain with lidocaine-prilocaine, and ethyl chloride spray compared placebo. Moderate and severe pain scores were similar between lidocaine-prilocaine and ethyl chloride spray (P>0.05). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
puncture site under occlusive dressing for 45 to 60 minutes vs placebo cream				
Kokinsky et al.[29] (1999) Lidocaine 10% aerosol vs placebo vs control group	DB, PC, RCT Patients 9 months to 11 years of age undergoing unilateral inguinal hernia repair	N=44 12 hours	Primary: Pain scores assessed by nurse or patient (depending on age) upon arrival to the recovery room, one, four, and 12 hours postoperatively, and reaction scores after gentle palpation of the wound by the nurse Secondary: Plasma concentrations of lidocaine	Primary: At one hour after arrival in the recovery room, pain scores were significantly lower in the lidocaine group compared to the placebo group for nurse and patient assessments (P<0.05). There were no significant differences between the lidocaine group and the placebo group or the lidocaine and the control groups one, four, or 12 hours postoperatively. At one hour postoperatively, reaction scores to palpation were lower in the lidocaine group compared to the placebo and control groups (P<0.05). The number of patients not reacting to wound palpation was significantly higher in the lidocaine group compared to the placebo and control groups (P<0.01 and P<0.05 respectively). There were no significant differences between groups in this endpoint at 0, four, or 12 hours. Secondary: The mean peak lidocaine plasma concentration was 0.40 µg/mL.
Corkill et al.[30] (2001) Lidocaine 2% gel applied up to every 4 hours vs	DB, PC, RCT Female patients who had a normal delivery of a healthy baby and sustained a first or second degree perineal tear	N=149 2 days	Primary: Perineal pain at 24 hours post-delivery Secondary: Perineal pain 48 hours post-delivery, the consumption of	Primary: There were no significant differences between the lidocaine and placebo groups at 24 hours according to the 101-point Numerical Rating Scale (P=0.5). Secondary: At 48 hours, the lidocaine group reported significantly less pain compared to the placebo group according to the 101-point Numerical Rating Scale (P=0.023).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			additional analgesia, maternal satisfaction	There was no significant difference observed in the amount of additional analgesia used between the two groups (P<0.227). Women in the placebo group applied significantly more study gel compared to women in the lidocaine group (P=0.015). There were no significant differences between groups in the satisfaction with analgesia received.
Minassian et al.[31] (2002) Lidocaine 5% ointment applied up to every 4 hours vs placebo	DB, PC, RCT Female patients 21 to 23 years of age with an episiotomy or a first, second, third, or fourth degree perineal laceration during their peripartum period	N=200 2 days	Primary: Pain relief Secondary: Results of a pain questionnaire administered on the first and second day postpartum	Primary: There was no significant difference in the amount of lidocaine or placebo used on postpartum day one or two (P=0.13 and P=0.08, respectively). There was no significant difference in the amount of pain pills taken in the lidocaine group and the placebo group (P=0.53). There was no significant difference in the satisfaction from the ointment in the lidocaine group compared to the placebo group (P=0.99). Patients who received an episiotomy used more pain medications compared to those with lacerations (P=0.003). Patients with minor lacerations used fewer pain pills and less ointment on the first postpartum day (P<0.001 and P=0.02, respectively). Secondary: There was no significant difference in subjective pain parameters from the pain questionnaire between the lidocaine group and the placebo group (P=0.36).
Habib et al.[32] (2009) Lidocaine 5% patch applied on each side of the wound	DB, RCT Patients undergoing radical retropubic prostatectomy under general anesthesia	N=71 24 hours	Primary: Verbal rating score for pain at rest and after coughing Secondary: Postoperative morphine	Primary: Observed mean pain scores were reduced by 17 to 32% at rest up to 12 hours and by 19 to 33% on coughing up to 24 hours after surgery in the lidocaine group. The pain scores were significantly lower on coughing at all times (P<0.0001) and at rest up to six hours (P=0.0003) compared to placebo, after accounting for morphine consumption. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			consumption, sedation scores, pruritus, and nausea scores	There was no significant difference in the amount of cumulative morphine consumed at any of the time points. There was no difference in the incidence or severity of postoperative nausea/vomiting, pruritus, or duration of post-anesthesia care unit and hospital stays among the treatment groups. Patients in the lidocaine group rated the quality of postoperative pain control significantly better than patients in the placebo group (P=0.037). Patients who received the lidocaine patch reported that pain interfered with their walking, deep breathing, and mood significantly less than patients in the placebo group (P=0.05).
Ingalls et al.[33] (2010) Lidocaine 5% patch applied for 12 hours daily directly over the rib fractures vs placebo	DB, PC, RCT Adult patients with rib fractures admitted to the trauma service	N=48 Up to 72 hours	Primary: Total narcotic use Secondary: Non-narcotic pain medication, average pain score, pulmonary complications, and length of stay	Primary: There was no difference between the lidocaine and placebo groups in the amount of total intravenous narcotics used (0.23 vs 0.26 units; P=0.56) or total oral narcotics used (4 vs 7 units; P=0.11). Secondary: There was no difference in pain scores (5.6 vs 6.0; P=0.39), pulmonary complications (72.7 vs 72%; P=0.95), or length of stay (7.8 vs 6.2 days; P=0.28) with lidocaine compared to placebo.
Cheville et al.[34] (2009) Lidocaine 5% patch applied for 18 hours daily for 4 weeks (up to 3 patches could be applied at once) vs placebo	DB, MC, RCT, XO Patients ≥18 years of age with persistent pain (with neuropathic features) associated with a surgical procedure as part of cancer treatment	N=28 8 weeks	Primary: Pain intensity rating Secondary: Brief pain inventory interference scores	Primary: Average weekly pain intensity ratings were not significantly reduced with the lidocaine patch compared to placebo (4.1 vs 3.8; P=0.36). There was no significant difference during period one between the lidocaine and placebo groups in the proportion of patients experiencing 10% relief (64 vs 71%, respectively; P=0.69) or in week four minus baseline change (mean −0.9 vs −0.6, respectively; P=0.91). Secondary: All period one brief pain inventory interference scores improved to a greater degree in the lidocaine group compared to placebo. Significant improvements in both physical (general activity; P=0.02, and work; P=0.04) and psycho-emotional (mood; P=0.06; and relations with others;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P=0.02) domains were demonstrated. Few other endpoints were significantly different when patients used the lidocaine patch compared to placebo.
Galer et al.[35] (1999) Lidocaine 5% patch applied for 12 hours daily (up to 4 patches could be applied at once) vs placebo	PC, RCT, XO Patients 62 to 96 years of age with postherpetic neuralgia already enrolled in the OL protocol and using lidocaine patches on a regular basis for at least 1 month	N=33 28 days	Primary: Time to exit the study Secondary: Not reported	Primary: The median time to exit was >14 days in the lidocaine group compared to 3.8 days in the placebo group (P<0.001). Significantly more patients (78.1%) preferred treatment with lidocaine compared to 9.4% who preferred treatment with placebo (P<0.001). The number of patients reporting moderate or greater pain relief was 29 in the lidocaine group compared to 13 in the placebo group. A total of seven patients used rescue pain relief medications throughout the study (three in the lidocaine group and four in the placebo group). Secondary: Not reported
Meier et al.[36] (2003) Lidocaine 5% patch applied for 12 hours daily (up to 4 patches could be applied at once) vs placebo	DB, PC, PRO, RCT, XO Patients ≥21 years of age suffering from chronic painful peripheral focal neuropathic syndromes that were superficial and localized to a limited skin zone	N=58 28 days	Primary: Ongoing pain intensity, allodynia, quality of neuropathic symptoms, and quality of sleep Secondary: Not reported	Primary: Ongoing pain intensity decreased in both the lidocaine and placebo groups (P<0.001 and P<0.05). The differences between groups were significant at two hours (P=0.003), four hours (P=0.004), day four (P=0.03), day five (P=0.02), and day seven (P=0.002). Lidocaine was more effective during the first eight hours and over the course of the treatment week compared to placebo (P=0.017 and P=0.018, respectively). At all time points, allodynia decreased compared to pretreatment values in both the lidocaine and placebo groups (P<0.001 and P<0.05). The differences between groups were significant at two hours (P=0.005), four hours (P=0.009), six hours (P=0.017) after the first patch application and at day five (P=0.035). Treatment with lidocaine led to better allodynia relief compared to placebo during the first 8 hours (P=0.023) and for the remainder of the treatment period (P=0.03). There was a significant reduction in neuropathic symptoms in the lidocaine group compared to baseline (P=0.032), but no significant differences were observed between the lidocaine and placebo groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				No significant differences were observed between the lidocaine and placebo groups in quality of sleep. Secondary: Not reported
Galer et al.[37] (2002) Lidocaine 5% patch applied for 12 hours daily vs placebo	DB, PC, PG, RCT Adults diagnosed with postherpetic neuralgia involving the torso area for at least 1 month and in whom allodynia was observed on physical examination	N=150 3 weeks	Primary: Change from baseline to week three in neuropathic pain scale Secondary: Not reported	Primary: The reduction in pain scores for all four composite endpoints was consistently greater in the lidocaine patch group compared to the placebo group (P=0.043, P=0.042, P=0.022, and P=0.013 respectively). Secondary: Not reported
Lin et al.[38] (2008) Lidocaine 5% patch applied at 12-hour intervals vs placebo	DB, PC, PG, RCT Patients suffering from moderate to severe pain caused by acute herpes zoster infection	N=46 48 hours	Primary: Analgesic efficacy and adverse events Secondary: Not reported	Primary: Both groups of patients experienced significant pain relief during rest and movement. The difference in the mean reduction of pain intensity during rest was 14 mm for patients wearing the lidocaine patch compared to the vehicle patch (P=0.005). The difference in the mean reduction of pain intensity during movement was 11 mm for patients wearing the lidocaine patch compared to the vehicle patch (P=0.007). The lidocaine patch produced a greater percentage change in a patient's global impression than the vehicle patch. The incidence and severity of adverse events were low with both treatments. Secondary: Not reported
Li et al.[39] (2016) Lidocaine topical	DB, PRO, RCT Children 6 months to 12 years of age	N=322 1 day	Primary: Incidence of perioperative respiratory adverse	Primary: The incidence of perioperative respiratory adverse events was lower in the lidocaine group as compared with that in the saline group (12.89 vs 38.13%, respectively; P<0.001). Patients who received topical airway

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
spray vs placebo (saline topical spray) administered over the supraglottic, glottis and subglottic areas under direct vision before tracheal intubation	(median age of 5 years) who were scheduled for an elective surgical procedure under general anesthesia with endotracheal intubation		events (laryngospasm, excessive coughing, and <95% desaturation) Secondary: Not reported	lidocaine spray experienced less laryngospasm (1.7 vs 8.1%; P=0.01); excessive coughing (4.3 vs 13.2%; P=0.005); and desaturation <95% (6.8 vs 16.9%; P=0.005), as compared with that experienced in children who received topical airway saline spray. Use of lidocaine was associated with longer tracheal extubation time as compared with that associated with use of saline (18.6 ± 7.7 min vs 21.3 ± 8.9 min; P=0.03). Secondary: Not reported
Katz et al.[40] (2002) Lidocaine 5% patch applied for 12 hours daily (up to 3 patches could be applied at once)	OL Patients 20 to 99 years of age diagnosed with postherpetic neuralgia	N=332 28 days	Primary: Changes in pain intensity, pain interference in quality of life, pain relief, and patient and physician global assessments Secondary: Not reported	Primary: Mean scores for all measures of pain intensity were significantly lower than baseline scores at all evaluations (P=0.0001). At the end of the study 40% of patients experienced a ≥50% reduction in average daily pain intensity. Mean pain interference with quality of life scores were significantly lower compared to baseline at all evaluations (P=0.0001). The majority of patients responded to lidocaine treatment within the first week. There was a significant improvement from baseline in pain relief at all evaluations (P=0.0001). Overall, 58% of patients reported moderate to complete pain relief at day 28. The results of the physician global assessments and patient global assessments were similar. Approximately 60% of patients were judged to have complete improvement or moderate (“a lot of”) improvement at day 28, slight improvement was reported in approximately 15% of patients, and no change was reported in 20% of patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Devers et al.[41] (2000) Lidocaine 5% patch applied for 12 hours daily (up to 3 patches could be applied at once)	OL Patients 23 to 85 years of age diagnosed with peripheral neuropathic pain	N=16 12 weeks	Primary: Degree of pain relief Secondary: Not reported	Primary: Thirteen patients (81%) reported either “moderate relief”, “a lot of relief”, or “complete relief” from the lidocaine patch. Of these 13 patients, all noted a reduction in brush-evoked mechanical allodynia. All patients who responded to medication continued to experience relief throughout the duration of the study. Secondary: Not reported
Fleming et al.[42] (2009) Lidocaine 5% patch	RETRO Inpatients and outpatients prescribed lidocaine 5% patch	N=97 Up to 1 year	Primary: Analgesic efficacy Secondary: Not reported	Primary: For the treatment of neuropathic pain syndromes, lidocaine had a ‘potent analgesic effect’ in 25% of patients and a ‘partial analgesic effect’ in 24% of patients. There was no analgesic effect in 47% of patients. The lidocaine patch made pain worse in 3.2% of patients. A ‘potent analgesic effect was seen in patients treated for postherpetic neuralgia (38%), persistent postsurgical pain (35%), pain due to other or multiple treatments for cancer (27%), mixed neuropathic pain syndromes (13%) and neuropathic pain directly attributed to cancer (12%). Secondary: Not reported
Affaitati et al.[43] (2009) Lidocaine 5% patch applied at 12-hour intervals for 4 days vs bupivacaine 0.5%, 2 injections given	DB, RCT (patch), SB (injection) Patients 18 to 80 years of age with a history of recurrent or chronic regional musculoskeletal pain caused by trigger points and a diagnosis of myofascial pain	N=60 9 days	Primary: Number of pain attacks, pain intensity at rest, pain intensity on movement, pressure and electrical pain thresholds of the skin, subcutis, and muscle in the	Primary: In the placebo group, there were no significant changes in any of the subjective symptoms at days five or nine compared to baseline. In the lidocaine and infiltration groups, all subjective symptoms decreased significantly (P<0.001) at days five and nine compared to baseline. There were no significant differences in pain symptoms among the active treatment groups at any time point. The difference between the placebo group and the active treatment groups was significant at days five and nine (both, P<0.001). The visual analog scale score for the discomfort caused by therapy (day

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
2 days apart vs placebo patch applied at 12-hour intervals for 4 days	syndrome		trigger point Secondary: Not reported	five) was significantly higher for patients who underwent infiltration than for those who received a lidocaine or placebo patch (both, P<0.001). Mean scores were 0.91 mm for the placebo patch, 0.87 mm for the lidocaine patch, and 51.45 mm for infiltration. At day nine, 90% of the patients in the placebo group asked for bupivacaine infiltration because of the persistence of pain symptoms. None of the patients in the other two groups requested infiltration (both, P<0.001). Pain thresholds did not vary with the placebo patch from baseline to end, but increased significantly with the lidocaine patch and injection (all, P<0.001). The comparison of thresholds between the placebo group and each of the active-treatment groups showed significant differences at day five and day nine (both, P<0.001). The comparison of the two groups that received active treatments showed no significant differences except for electrical pain thresholds in muscles (greater increase in the infiltration group), at the level of the trigger point (day five and day nine; both, P<0.001) and target area (day five, P<0.03; day nine, P<0.007). No systemic or local adverse events were reported by the patients in any treatment group. Secondary: Not reported
Luhmann et al.[44] (2004) Lidocaine 5% cream applied 30 minutes before intravenous insertion vs	RCT, SB Patients 4 to 17 years of age requiring peripheral intravenous insertion	N=69 1 day	Primary: Pain ratings, anxiety, technical difficulty, and treatment satisfaction Secondary: Not reported	Primary: No significant differences were observed in mean pain ratings between treatment groups reported by children (P=0.19), parents (P=0.17), and blinded observer (P=0.2). No significant differences were observed in anxiety between treatment groups reported by children (P=0.18), parents (P=0.50), and blinded observer (P=0.96). No significant differences were observed between the treatment groups in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
lidocaine injected subcutaneously 5 minutes before intravenous insertion				technical difficulty (P=1.0) or overall satisfaction (P=0.19) according to nurses self-report. Secondary: Not reported
Gursoy et al.[45] (2007) Lidocaine-prilocaine cream applied 60 minutes before biopsy vs placebo	DB, PC Patients with nodular thyroid disease undergoing fine-needle aspiration biopsy	N=99 1 day	Primary: Patient-rated pain using a 100-mm visual analog scale, an 11-point numeric rating scale, and a four-category verbal rating scale; adverse events Secondary: Not reported	Primary: For patients receiving lidocaine-prilocaine, the mean visual analog scale score was 25.0 vs 40.0 mm in the placebo group (P=0.006). For patients receiving lidocaine-prilocaine, the mean numeric rating scale score was 2.9 vs 4.0 points in the placebo group (P=0.02). The absolute numbers according to verbal rating scale score in each group was also significantly different (P=0.01). Secondary: Not reported
Shaikh et al.[46] (2009) Lidocaine-prilocaine cream applied for 30 to 60 minutes before surgery vs placebo	DB, PC, PG, RCT Patients scheduled for elective minor surgical procedures under local anesthesia	N=72 1 day	Primary: Patient's perception of pain on needle insertion for local anesthetic infiltration and pain during the minor surgical procedure Secondary: Not reported	Primary: The mean needle-stick pain score in the lidocaine-prilocaine group was significantly lower than in the placebo group (2.7 vs 5.7; P<0.001). There was significantly less procedure pain in the lidocaine-prilocaine group than in the placebo group (0.83 vs 1.86; P=0.009). There were no complications associated with the use of lidocaine-prilocaine. There was less pain when lidocaine-prilocaine cream was applied for 60 minutes than for 30 minutes. The site of application of lidocaine-prilocaine cream and procedure resulted in a difference in pain. Secondary: Not reported
McCluskey et al.[47] (2003)	DB, PC, RCT	N=90	Primary: Pain severity	Primary: There was a significant reduction in the incidence of pain associated with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Lidocaine-prilocaine cream applied 60 minutes prior to cannulation and induction of anesthesia with propofol vs placebo cream applied 60 minutes prior to cannulation and induction of anesthesia with propofol mixed with saline vs placebo cream applied 60 minutes prior to cannulation and induction of anesthesia with propofol mixed with lidocaine	Patients 18 to 70 years of age presenting for gynecological day surgery	1 day	scores for insertion of cannula, pain severity scores during injection of propofol Secondary: Not reported	insertion of the cannula in the lidocaine-prilocaine group compared to the other two groups (P=0.015). There was no significant difference in the frequency of pain associated with injection of propofol between the lidocaine-prilocaine group and the placebo group. Significantly greater pain frequency was seen in the lidocaine-prilocaine group compared to the lidocaine and propofol mixed injection group (P=0.002). Secondary: Not reported
Abbas et al.[48] (2017) Lidocaine-prilocaine cream placed into cervix	DB, PRO, RCT Women 18 to 49 years of age who were parous, menstruating,	N=120 1 day	Primary: Difference in pain visual analog scale scores during IUD insertion	Primary: The mean visual analog scale score at IUD insertion was two in the lidocaine-prilocaine group and four in the placebo group (P=0.001). Secondary: Lidocaine-prilocaine cream reduces the median visual analog scale pain

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
prior to insertion vs placebo cream	nonpregnant, and undergoing IUD insertion		Secondary: Difference in pain scores during tenaculum application, insertion of sound, and 5 min after insertion; the ease of IUD insertion; the number of women who needed analgesics after insertion; and the side effects of the medication	scores during tenaculum placement (2 vs 4), sound insertion (3 vs 6) and five minutes after insertion (2.0 vs 3.5) with P=0.0001 at all steps. A lower ease of insertion score was also determined among lidocaine-prilocaine treated women (2.5±0.98 vs 4.5±2.7, P=0.001). Six women asked for additional analgesics in the placebo group versus one in the lidocaine-prilocaine group (P=0.114). Participants reported no side effects.
Koh et al.[49] (2004) Lidocaine-prilocaine cream applied to the skin for 60 minutes vs lidocaine 4% cream applied to the skin for 30 minutes	DB, RCT Patients 8 to 17 years of age having an intravenous inserted prior to surgery	N=60 1 day	Primary: Pain scores according to the visual analog scale and difficulty of placing the intravenous according to the investigator Secondary: Not reported	Primary: There was no significant difference in pain ratings according to the visual analog scale scores between the groups (P=0.87). There was no significant difference in the investigator ratings of difficulty of the procedure between the groups (P=0.73). There was significantly more blanching in the lidocaine-prilocaine group compared to the lidocaine group (P=0.04). Secondary: Not reported
Kuvaki et al.[50] (2003) Lidocaine-prilocaine cream applied to the outer half of the inferior orbital margin at	DB, RCT Patients presenting for cataract surgery under local anesthesia	N=103 1 day	Primary: Subjective pain intensity on a 10-point scale Secondary: Not reported	Primary: There were no significant differences in pain scores reported between the lidocaine-prilocaine treatment group and the lidocaine treatment group (P=0.67). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
least 45 minutes prior to retrobulbar injection vs lidocaine 5% ointment applied to the outer half of the inferior orbital margin at least 45 minutes prior to retrobulbar injection				
Mu et al.[51] (2017) Lidocaine-prilocaine cream applied to the urethral mucosal surfaces, and on the surface of the urinary catheter vs control group (urinary catheter lubricated with lidocaine 2% gel)	Case-controlled, PRO, RCT Male patients 23 to 83 years of age with American Society of Anesthesiologists physical status I–III and scheduled to undergo a urinary catheterization after anesthesia induction	N=146 60 minutes post-op	Primary: Differences in the incidence and severity of catheter-related bladder discomfort (CRBD) 15, 30, 45, and 60 minutes postoperatively Secondary: Incidence of postoperative nausea and vomiting, sedation, respiratory depression, and dizziness, as well as use of propofol and tramadol	Primary: Lidocaine-prilocaine decreased moderate and severe CRBD (OR, 0.055; 95% CI, 0.021 to 0.144; P=0.01). Lidocaine-prilocaine also decreased the CRBD incidence at 15, 30, 45, and 60 minutes from 43 to 14%, 70 to 21%, 45 to 7%, and 27 to 4%, respectively. In total, CRBD including mild, moderate, and severe CRBD occurred in 15 patients (20.8%) in the lidocaine-prilocaine group, which was significantly lower than the 52 patients (70.3%) in the control group at the 30-minute time point (P=0.000). Moderate and severe CRBD occurred in the lidocaine-prilocaine group for six patients (8.3%) and no patients (0%) respectively, which was lower than the 10 patients (13.5%) and 13 patients (17.6%) in the control group (P=0.000). Secondary: No patient required treatment with propofol for sedation in the lidocaine-prilocaine group, while 13 patients (18%) were administered 30 to 50 mg propofol to control agitation in the control group (P=0.000). Six patients in the lidocaine-prilocaine group and 10 patients in control group were administered 1 mg/kg tramadol (P=0.316). After treatment, the incidences of moderate CRBD were 14% at 45 minutes and 12% at 60 minutes in the control group, respectively (P=0.001 and P=0.003). Adverse effects, such as postoperative sedation, respiratory depression, and drowsiness, were not different between groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Usmani et al.[52] (2009) Lidocaine-prilocaine cream applied to the incision site 2 hours before surgery vs lidocaine 1% injected into the incision site 3 minutes before surgery vs placebo Fentanyl was a rescue analgesic in the immediate postoperative period and acetaminophen was a rescue analgesic in the surgical ward.	DB, PC, RCT Children 4 to 12 years of age undergoing elective inguinal hernia repair under general anesthesia	N=90 1 day	Primary: Time to the first dose of rescue analgesic, number of patients requiring fentanyl in the recovery room Secondary: Not reported	Primary: The time to the first dose of rescue analgesic was significantly shorter in the placebo group (71 minutes) compared to the study groups (lidocaine-prilocaine, 143 minutes; lidocaine, 148 minutes; P<0.05). The number of patients requiring fentanyl in the recovery room was significantly less in the study groups (five in the lidocaine-prilocaine group and six in the lidocaine group) as compared to the placebo group (20 patients; P<0.05). In the placebo group, 17 patients required both fentanyl and acetaminophen compared to four patients each in the lidocaine-prilocaine and lidocaine groups (P<0.05). Sixty-seven percent of patients in the placebo group required more than one dose of acetaminophen in the first six hours compared to 23% of patients receiving lidocaine-prilocaine and 20% of patients receiving lidocaine. Two patients in the lidocaine group and one patient each of the lidocaine-prilocaine and placebo groups had a subcutaneous infection at the site of incision between the 10th and 15th postoperative day. Secondary: Not reported
Berman et al.[53] (2005) Lidocaine-tetracaine patch applied 30 minutes	DB, PC, PRO, RCT Patients 20 to 80 years of age presenting for minor dermatological	N=49 1 day	Primary: Pain intensity according to the visual analog scale, patients' overall assessment of the	Primary: Median visual analog scale scores were significantly lower in the lidocaine and tetracaine group compared to the placebo group (P<0.001). Median visual analog scale scores were significantly lower in the lidocaine and tetracaine group compared to the placebo group in patients undergoing

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
prior to procedure vs placebo	procedures not requiring sutures		effectiveness of the patch, the need for rescue medication, investigator ratings of patients' pain intensity and anesthetic efficacy Secondary: Not reported	excision, electrodessication, keloid injection, cryotherapy, and skin tag removal (P<0.05). Injected lidocaine as rescue medication was administered to 22% of patients in the lidocaine and tetracaine group compared to 49% of patients in the placebo group (P=0.008). Adequate anesthetic effect was reported in 73% of patients in the lidocaine and tetracaine group compared to 37% in the placebo group (P<0.001). Adequate anesthetic effect was reported by the investigator in 71% of patients in the lidocaine and tetracaine group compared to 39% in the placebo group (P=0.004). A significantly higher number of patients in the lidocaine and tetracaine group were assessed by the investigators and independent witnesses as being pain-free during the procedure compared to the placebo group (P<0.004 and P<0.001 respectively). Secondary: Not reported
Schecter et al.[54] (2005) Lidocaine-tetracaine patch applied 30 minutes prior to minor dermatological procedures vs placebo	DB, PC, RCT Patients ≥65 years of age presenting for minor dermatological procedures	N=79 1 day	Primary: Pain rating according to the visual analog scale Secondary: Patient's assessment of anesthesia, investigator's assessment of the degree of anesthesia	Primary: The visual analog scale scores were significantly lower in the lidocaine-tetracaine group compared to the placebo group in patients undergoing excisions (P=0.020) and procedures on the head and neck (P=0.043). Scores for shave biopsies and procedures on the arm/shoulder, chest/abdomen, back, hip/leg, or penis did not show any statistically significant differences (P≥0.092). Secondary: There were no significant differences between groups in patients reporting adequate pain relief (P=0.767) or in the percentage of patients saying they would use the patch again (P=0.726). There were no significant differences between groups in the investigator's assessments of patient pain or impression of whether or not the local anesthetic provided adequate anesthesia (P=0.461 and P=0.838,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				respectively).
Sethna et al.[55] (2005) Lidocaine-tetracaine patch applied for 20 minutes prior to the procedure vs placebo	DB, PC, PRO, RCT Patients 3 to 17 years of age requiring intravenous access or blood sampling	N=64 1 day	Primary: Pain intensity according to the Oucher Pain Scale, investigator and independent observer assessments of the degree of analgesia provided on a four4-point scale Secondary: Not reported	Primary: Significantly lower pain scores were reported in patients in the lidocaine-tetracaine group compared to the placebo group (P<0.001). No pain was reported in 59% of patients in the lidocaine-tetracaine group compared to 20% in the placebo group (P<0.001). Investigator and independent observer evaluations show significant pain relief in the lidocaine-tetracaine group compared to the placebo group (P<0.001). Secondary: Not reported
Singer et al.[56] (2008) Lidocaine-tetracaine patch applied for 20 minutes prior to intravenous cannulation vs placebo	DB, PC, RCT Patients 3 to 17 years of age who required non-emergency IV cannulation	N=40 1 day	Primary: Pain of cannulation measured using a validated 100-mm visual analog scale or Wong Baker scale Secondary: Not reported	Primary: The median pain of intravenous cannulation in the lidocaine-tetracaine treatment group (18 mm) was significantly lower than in the placebo group (35 mm; P=0.04). Adequate pain relief was more common in the lidocaine-tetracaine group (75%; 95% CI, 53 to 89) vs the placebo group (35%; 95% CI, 18 to 57). The number of successful intravenous cannulations after the first attempt was similar in the lidocaine-tetracaine group (90%; 95% CI, 70 to 97) and the placebo group (85%; 95% CI, 64 to 95). Secondary: Not reported
Curry et al.[57] (2007) Lidocaine-tetracaine patch applied for 20 minutes prior to vascular access	DB, PC, RCT Adults undergoing a vascular access procedure	N=40 1 day	Primary: Pain intensity using a 100 mm visual analog scale, patient perception of pain relief, investigator and independent	Primary: The median patient visual analog scale score was lower for lidocaine-tetracaine compared to placebo (5 vs 28 mm). Forty-nine percent of patients had lower visual analog scale scores with lidocaine-tetracaine than placebo, and 17% had lower visual analog scale scores with the placebo (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
procedure vs placebo			observer rating of patients' pain, investigator's perception of pain relief Secondary: Not reported	More patients reported adequate anesthesia following lidocaine-tetracaine compared to placebo (73 vs 31%). Fifty-nine percent of patients indicated adequate pain relief with lidocaine-tetracaine and not the placebo, and 15% reported adequate pain relief with the placebo and not lidocaine-tetracaine (P=0.002). More patients indicated they would use lidocaine-tetracaine again compared to placebo (70 vs 33%). Fifty-one percent of patients reported that they would use lidocaine-tetracaine again but not the placebo, and 15% reported that they would use the placebo again but not lidocaine-tetracaine (P=0.006). Investigators rated 63% of patients as having no pain with lidocaine-tetracaine treatment compared to 33% of patients with the placebo treatment. Investigators considered 46% of patients to have less pain with lidocaine-tetracaine than placebo, and 15% of patients to have less pain with the placebo than lidocaine-tetracaine (P=0.021). Independent observers rated 68% of patients having no pain with lidocaine-tetracaine compared to 38% with the placebo. The independent observers considered 46% of patients to have less pain with lidocaine-tetracaine than placebo, and 15% of patients to have less pain with the placebo than lidocaine-tetracaine (P=0.015). For the overall rating, the investigators considered more patients to have adequate anesthesia with lidocaine-tetracaine compared to placebo (60 vs 23%). They considered 54% of patients to have adequate anesthesia with lidocaine-tetracaine and not the placebo, and considered 15% of patient to have adequate anesthesia with the placebo and not lidocaine-tetracaine (P=0.004). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
George et al.[58] (2008) Lidocaine-tetracaine patch applied for 20 minutes followed by saline infiltration vs placebo patch applied for 20 minutes followed by infiltration with lidocaine 2%	RCT Women ≥18 years of age who were considering labor epidural analgesia	N=33 1 day	Primary: Provider and patient assessment of discomfort with epidural needle insertion (using a verbal rating scale); ease of epidural insertion Secondary: Not reported	Primary: The patients' recorded verbal rating scale, with epidural placement, was significantly higher in the lidocaine-tetracaine group (P<0.001), as was the anesthesia providers' verbal rating scale of perceived pain (P<0.01) compared to placebo. A greater number of lidocaine-tetracaine patients required additional deep infiltration (P=0.02). The four-point scale, used to subjectively estimate the quality of patient cooperation during epidural placement, was not significantly different between groups. The patients' recorded verbal rating scale and the anesthesiologists' verbal rating scale rating scores were similar in the two groups. Secondary: Not reported
Masud et al.[59] (2010) Lidocaine-tetracaine patch with controlled heat applied 20 minutes before intravenous cannulation vs lidocaine-tetracaine patch applied 20 minutes before intravenous cannulation (with no heat)	DB, MC, RCT Healthy adult volunteers undergoing venipuncture	N=250 1 day	Primary: Patient-reported pain intensity using a visual analog scale, skin reactions and adverse events Secondary: Not reported	Primary: The mean pain intensity scores for patients who received the heated patch was significantly lower than patients who received the unheated patch (14.7 and 23.5 mm, respectively; P=0.04). More patients who received the heated patch reported adequate anesthesia compared to those who received unheated patches (71 vs 53%; P=0.004). The percentage of patients who responded positively to the questions, ''Did the local anesthetic provide adequate pain relief for the vascular access procedure?'' and ''Would you have this form of local anesthesia administered again if given the option?'' did not differ significantly when compared by heated vs unheated patch. Five patients who received the heated patch and two who received the unheated patch experienced an adverse reaction. Six of these seven events were mild skin reactions (erythema) that resolved within a day without treatment. One patient reported a purple-green discoloration during the 24 to 48 hour follow-up conversation that, on investigator evaluation, was noted as an ecchymosis of mild severity, unrelated to the study. No

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				arrhythmias, seizures, or respiratory difficulties were reported. Secondary: Not reported
Sawyer et al.[60] (2009) Lidocaine-tetracaine patch applied for 10, 20, 30, or 60 minutes before intravenous cannulation vs lidocaine-prilocaine cream applied for 10, 20, 30, or 60 minutes before intravenous cannulation All patients received both treatments.	DB, RCT Healthy adult volunteers undergoing venipuncture	N=82 1 day	Primary: Patient-reported pain intensity using a 100 mm visual analog scale Secondary: Patient evaluation of effectiveness, investigator evaluation of the patient's pain intensity and overall impression, and adverse events	Primary: Median visual analog scale scores were significantly lower for the lidocaine-tetracaine patch than for lidocaine-prilocaine cream in the 10 minute (P=0.010), 20 minute (P=0.042), and 30 minute (P=0.001) application groups. There was no difference between treatments in the 60 minute group (P=0.887). Secondary: Significantly more patients using the lidocaine-tetracaine patch said they would use the product again compared to lidocaine-prilocaine cream at 10 minutes (80 vs 47%; P=0.008), 20 minutes (95 vs 70%; P=0.025), and 30 minutes (100 vs 64%; P=0.005). There was no difference among the treatment groups at 60 minutes (90 vs 95%; P=0.317). For those patients who reported no pain associated with the vascular access procedure, significantly more patients in the 20 and 30 minute groups reported that the lidocaine-tetracaine patch eliminated pain compared to lidocaine-prilocaine cream (P=0.014 and P=0.020, respectively). After the 10 minute application of the lidocaine-tetracaine patch, 65% of patients reported no pain, but the difference compared to the lidocaine-prilocaine cream was not significant (P=0.059). There was no difference between treatments in the 60 minute group. Investigator ratings of patient pain intensity were significantly lower for lidocaine-tetracaine patch applications in the 10 minute group (P=0.046). The pain intensity ratings for the remaining groups and the investigator's evaluation of the general effectiveness of the treatments were not significantly different between the lidocaine-tetracaine patch and lidocaine-prilocaine cream. Secondary: The lidocaine-tetracaine patch was associated with significantly more erythema than lidocaine-prilocaine cream at 20, 30, and 60 minutes,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				whereas lidocaine-prilocaine cream produced more blanching than the lidocaine-tetracaine patch at 30 and 60 min. No arrhythmias, seizures, or respiratory difficulties were reported.
Bourolias et al.[61] (2010) Tetracaine 2% solution applied locally vs lidocaine 10% spray applied locally	RCT Patients undergoing transnasal fiber-optic laryngoscopy of the inferior turbinate	N=48 Single dose	Primary: Severity of pain Secondary: Not reported	Primary: There was a significantly lower mean nasal discomfort score in favor of the tetracaine group (2.29 vs 3.04; P<0.001). No complications or side effects regarding the intranasal use of tetracaine or lidocaine were observed. Secondary: Not reported

Drug regimen abbreviations: QID=four times daily
Study abbreviations: CI=confidence interval, DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single blind, XO=crossover

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Skin and Mucous Membrane Antipruritics and Local Anesthetics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Doxepin	cream	Prudoxin®*, Zonalon®*	$$$$	$$$$$
Lidocaine	cream, ointment, solution, transdermal patch	Lidoderm®*, ZTLido®	$$$$	$$$
Combination Products				
Lidocaine and prilocaine	cream	N/A	N/A	$
Lidocaine and tetracaine	transdermal patch	Synera®	$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The skin and mucous membrane antipruritics and local anesthetics have a variety of uses, including relief of itching and pain caused by insect bites, minor burns and sunburns, atopic dermatitis, lichen simplex chronicus, and hemorrhoids.[1-6] They are also used to prevent and treat pain due to postherpetic neuralgia, venipuncture, intravenous cannulation, minor operative/dermatological procedures, endoscopic/diagnostic procedures, as well as other procedures.[1-6] Due to the variety of products, dosage forms, and Food and Drug Administration (FDA)-approved indications, direct comparisons of agents within this class is difficult. There are also few clinical guidelines available that provide recommendations regarding the use of these agents. Several of the products are available in a generic formulation.

When used appropriately, the topical anesthetics can effectively relieve pain. Clinical trials have demonstrated that lidocaine, lidocaine and prilocaine, and lidocaine and tetracaine are more effective at relieving pain than placebo.[29,32,35-38,43,46-48,52-58] There are relatively few studies that directly compare the topical anesthetics. There was no difference in pain relief with lidocaine and prilocaine cream compared to lidocaine (cream, ointment, and transdermal injection).[44,49-50] In one study, pain intensity associated with venipuncture was lower following the use of a lidocaine and tetracaine patch compared to lidocaine and prilocaine cream.[60] The FDA remains concerned about the potential for topical anesthetics to cause life-threatening adverse events such as arrhythmias, seizures, respiratory difficulties, coma and death.[20] If a topical anesthetic is prescribed, patients should use the least amount that will relieve the pain, apply the product sparingly to the area where pain exists or is expected to occur, and do not apply the product to broken or irritated skin. If wrapping or covering the skin is being considered, this can increase the chance of serious adverse events, as can applying heat to the treated area while the medication is still present.[20]

Doxepin cream is approved for the short-term management of moderate pruritus in patients with atopic dermatitis and lichen simplex chronicus. For the treatment of atopic dermatitis, emollients are considered the standard of care.[7-12] They are steroid-sparing and are useful for both prevention and maintenance therapy. Topical corticosteroids provide symptomatic relief and are safe to use in the short term. Although the short-term use of topical doxepin relieves pruritus, adverse events may limit its usefulness.[12] In clinical trials, doxepin was found to be more effective than placebo at controlling pruritus.[21-23]

For the treatment of hemorrhoids, adequate fiber and water intake is the cornerstone of therapy.[14-15] Topical corticosteroids and analgesics are useful for managing perianal skin irritation due to poor hygiene, mucus discharge, or fecal seepage.

There is insufficient evidence to support that one brand skin and mucous membrane antipruritic or local anesthetic is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand skin and mucous membrane antipruritics and local anesthetics within the class reviewed are comparable to each other and to the generics products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand skin and mucous membrane antipruritic or local anesthetic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Astringents
AHFS Class 841200
February 8, 2023

I. Overview

Currently there are no prescription medications classified by American Hospital Formulary Service (AHFS) as Skin and Mucous Membrane Astringents.

II. Conclusions

There are no prescription medications available in the skin and mucous membrane astringents class (AHFS Class 841200).

III. Recommendations

No brand skin and mucous membrane astringent is recommended for preferred status. Alabama Medicaid should continue to include AHFS Class 841200 in the Preferred Drug List (PDL) screening process. If new prescription astringent agents are added, it is recommended that this class be re-reviewed.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Keratolytic Agents
AHFS Class 842800
February 8, 2023

I. Overview

The skin and mucous membrane keratolytic agents are approved for the treatment of a variety of hyperkeratotic skin conditions, including calluses, corns, cutaneous warts, eczema, ichthyosis, psoriasis, xerosis, as well as others.[1-3] Some of the agents are also approved for the treatment of damaged, ingrown, and devitalized nails.[1-3] Cutaneous warts are caused by the human papilloma virus (HPV) and have a variable clinical presentation based on the skin surface location and morphology.[4] Eczema is a chronic inflammatory skin condition characterized by redness, edema, pruritus, dryness, crusting, flaking, blistering, cracking, oozing, and bleeding.[5] Ichthyosis is a genetic hyperkeratotic skin disorder characterized by dry and scaly skin.[6-7] Psoriasis is a chronic, immune-mediated disorder which results in hyperproliferation and abnormal differentiation of the epidermis.[8] It is characterized by erythematous plaques which appear as silvery scales. Xerosis, or excessive dryness of the skin, is characterized by redness, scaling, and fissures.[6]

The stratum corneum is the outermost layer of the epidermis. It is composed of stacked layers of corneocytes, which are held together by a lipid-based intercellular matrix that serves as a tough, yet flexible, protective barrier against excessive water loss.[6] Normal skin contains more than 10% hydration.[6] When the water content is less than 10%, disruption in the stratum corneum can occur, leading to scaling, cracking, and irritation. Salicylic acid and urea hydrate and dissolve the intracellular matrix of the stratum corneum, which causes the cornified tissue to swell, soften, macerate, and desquamate.[1-3] Urea also hydrates and dissolves the intercellular matrix of the nail plate, which can result in the softening and debridement of the nail plate.[1-3]

The skin and mucous membrane keratolytic agents that are included in this review are listed in Table 1. This review encompasses all topical dosage forms and strengths. Products solely indicated for the treatment of acne and/or rosacea are not covered by Alabama Medicaid. Therefore, these products are not included in this review. Urea is available in a generic formulation. This class was last reviewed in February 2021.

Table 1. Skin and Mucous Membrane Keratolytic Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Salicylic acid	ointment	Bensal HP®	none
Urea	cream*, foam, lotion*	Uramaxin®	urea

*Generic is available in at least one dosage form or strength.
N/A=not available
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the skin and mucous membrane keratolytic agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the Skin and Mucous Membrane Keratolytic Agents

Clinical Guideline	Recommendation(s)
American Academy of Dermatology/ National Psoriasis Foundation: **Guidelines of Care for the Management and Treatment of Psoriasis with Topical Therapy and Alternative Medicine Modalities for Psoriasis Severity Measures (2020)**[9]	• Topical corticosteroids, which provide high efficacy and good safety, play a key role in the treatment of psoriasis, especially for localized disease. • Choosing a corticosteroid with appropriate potency plus the appropriate vehicle should be based on the disease severity, disease location, patient preference, as well as the age of the patient. • Lower potency corticosteroids should be used on the face, intertriginous areas, and areas that are susceptible to steroid atrophy (e.g., forearms) and other adverse effects. • The use of class 1, class 2, and class 3 to 5 topical steroids for up to four weeks is recommended for the treatment of plaque psoriasis not involving intertriginous areas. • The use of class 1 to 7 topical steroids for a minimum of up to four weeks is recommended as initial and maintenance treatment of scalp psoriasis. • The use of topical corticosteroids for > 12 weeks can be considered if done under the careful supervision of a physician. • While not FDA approved for psoriasis, the topical calcineurin inhibitors tacrolimus and pimecrolimus are often employed in the treatment of psoriasis. They are especially helpful on thinner skin such as facial and intertriginous areas and used as steroid-sparing agents for prolonged use (> 4 weeks). The majority of the data regarding these medications are derived from their extensive use in atopic dermatitis. • The off-label use of 0.1% tacrolimus for psoriasis involving the face as well as inverse psoriasis for up to eight weeks can be considered. • The off-label use of pimecrolimus for inverse psoriasis for four to eight weeks is recommended. • Long term use of tacrolimus or pimecrolimus can be considered for inverse psoriasis treatment as off-label use. • The off-label combination of tacrolimus and 6% salicylic acid for 12 weeks may be used for the treatment of plaque psoriasis. • The long-term use of topical vitamin D analogues (up to 52 weeks) including calcipotriene/calcipotriene, calcitriol, tacalcitol, and maxacalcitol is recommended for the treatment of mild to moderate psoriasis. • Use of calcipotriene foam and calcipotriene plus betamethasone dipropionate gel is recommended for 4 to 12 weeks for the treatment of mild to moderate scalp psoriasis. • Topical tacalcitol ointment or calcipotriene combined with hydrocortisone for eight weeks can be used for the treatment of facial psoriasis. • Use of combination treatments with vitamin D analogues and potent Class II and Class III topical steroids up to 52 weeks is recommended for the treatment of psoriasis. • Use of combination products with calcipotriol and corticosteroids is recommended for the treatment of psoriasis. • The application of vitamin D analogues twice daily on weekdays in conjunction with high potency topical steroids twice daily on weekends can be considered for maintenance treatment for psoriasis. • The application of morning high potency topical steroids and evening topical vitamin D analogues is an effective treatment regimen that can be considered for the treatment of psoriasis. • Topical tazarotene can be used for the treatment of mild to moderate psoriasis and

Clinical Guideline	Recommendation(s)
	nail psoriasis. • The combination of topical tazarotene and NB-UVB has been shown to be effective and allow a reduction in total usage of NB-UVB. • The use of mid-potency or high potency topical steroid in combination with tazarotene for 8 to 16 weeks is more effective than monotherapy with tazarotene and is recommended for the treatment of mild to moderate psoriasis. • The use of topical steroids along with tazarotene is recommended to decrease the duration of treatment as well as increase the length of remission. • The use of an emollient in conjunction with topical corticosteroids for four to eight weeks can be used to help reduce itching, desquamation, and total body surface area and prevent quick relapse of psoriasis when topical corticosteroids are discontinued. • Topical salicylic acid can be used for 8 to 16 weeks for the treatment of mild to moderate psoriasis. • The combination of salicylic acid with topical corticosteroids can be used for the treatment of moderate to severe psoriasis (BSA ≤ 20%). • Topical anthralin for 8 to 12 weeks can be used for the treatment of mild to moderate psoriasis. Short contact (up to two hours per day) anthralin is recommended to limit side effects. • Coal tar preparations are recommended for the treatment of mild to moderate psoriasis. • The addition of an ultra-high potency (Class 1) topical corticosteroid to standard dose etanercept for 12 weeks is recommended for the treatment of moderate to severe psoriasis. • The addition of calcipotriene/betamethasone to standard dose adalimumab for 16 weeks is recommended for the treatment of moderate to severe psoriasis to accelerate clearance of psoriatic plaques. • All topical steroids can be used in combination with any biologics for the treatment of moderate to severe psoriasis. • The addition of topical calcipotriene to standard dose methotrexate therapy is recommended for the treatment of moderate to severe psoriasis. It may lead to lower cumulative doses of methotrexate and increased time to relapse following methotrexate discontinuation. • The addition of calcipotriene/betamethasone dipropionate ointment to low dose (2 mg/kg/day) cyclosporine can be used for the treatment of moderate to severe psoriasis. • The addition of calcipotriene to standard dose acitretin is recommended for the treatment of moderate to severe psoriasis.
American Academy of Dermatology/ National Psoriasis Foundation: **Guidelines of Care for the Management and Treatment of Psoriasis in Pediatric Patients (2019)**[10]	• A standard way to measure body surface area (BSA) in children is the "rule of 9s," with adjustment of regional relative proportions based on age. (Computer BSA models are available for children but not widely used). BSA should not be the sole predictor of disease severity. • Psoriasis can have a significant negative impact on QOL, including physical, emotional, social, and psychological functioning, and these features should be strongly considered along with clinical and patient-reported assessments. • Body surface area measurement of involved skin is recommended as a useful measure of psoriasis severity in children. • Disease location on the body and impact on physical, social, and psychological quality of life and/or activities of daily living are recommended as measures of psoriasis severity and should be taken into consideration when determining psoriasis severity in children. • Pediatric patients with psoriasis should be educated about the risk of PSA and its clinical manifestations. • Pediatric patients with psoriasis should be routinely screened for PSA via a thorough history and physical examination.

Clinical Guideline	Recommendation(s)
	• Pediatric patients with psoriasis who show signs and symptoms of inflammatory arthritis should be referred to a rheumatologist with pediatric expertise, if available, for further evaluation and management. • Pediatric psoriasis patients with PSA should be routinely screened for uveitis by history and physical examination. • Pediatric patients with psoriasis who show signs and symptoms of uveitis should be referred to an ophthalmology specialist for further evaluation and management. • Topical corticosteroids are recommended for the treatment of pediatric psoriasis as an off-label therapy. • Use of topical steroids is frequently practiced and widely considered for localized disease. • The use of ultra-high-potency topical corticosteroids as monotherapy is effective for short-term treatment of localized psoriasis in pediatric patients. • Selection of a therapeutic routine (potency, delivery vehicle, frequency of application) should take into account sites of involvement, type and thickness of psoriasis, age of the patient, total BSA of application, anticipated occlusion, and disease acuity, among other patient-, disease-, and drug-related factors. • A popular routine is dual topical therapy with a high or ultra-high-potency topical steroid and topical vitamin D analogue. Although this simultaneous or serial use improves adherence by making it simpler for the patient, studies addressing the efficacy of compounded versus separate, simultaneous treatments are lacking. • It is advisable to avoid the use of ultra-high-potency topical corticosteroids in the face, fold, and genitalia of infants and children. • High-potency or ultra-high-potency topical corticosteroids should be used with caution, and patients should be followed closely by a dermatologist to ensure proper use and to monitor for overuse and adverse effects. • Providers and caregivers should be aware of the potential for rebound flare if high-potency corticosteroids are abruptly discontinued without transition to an appropriate alternative treatment. • Tacrolimus 0.1% ointment is recommended for off-label use as monotherapy for pediatric psoriasis of the face and genital region. • Burning, stinging, pruritus, and irritation have been reported as adverse effects of topical calcineurin inhibitors (TCI) use in children. • An important advantage of the vitamin D analogues, especially for pediatric use, is their corticosteroid-sparing function. Treatment with vitamin D analogues is safe, effective, and relatively well tolerated in children of all ages. • Calcipotriene/calcipotriol is recommended as a treatment option for childhood plaque psoriasis. • Because of the theoretical risk of increased calcium absorption and systemic effects of hypercalcemia, occlusion of calcipotriene/calcipotriol applied to large body surface areas is not recommended. • Monitoring of vitamin D metabolites may be considered during calcipotriene/calcipotriol therapy when applied to a large body surface area. • In practice, vitamin D analogues may be used in combination with other topical therapies to enhance efficacy and limit possible adverse effects. • The combination of calcipotriol/betamethasone dipropionate ointment applied once daily for up to four weeks at a time is recommended as a safe and effective treatment for children ages 12 years and older with mild to moderate plaque psoriasis. • The combination of calcipotriol/betamethasone dipropionate suspension applied once daily for up to eight weeks at a time is recommended as a safe and effective treatment for children ages 12 years and older with mild to moderate plaque psoriasis of the scalp. • The use of emollients (at the same time or different time of day) with topical calcipotriene may be considered to reduce irritation and enhance the efficacy of

Clinical Guideline	Recommendation(s)
	calcipotriene. • Rotational therapy with topical vitamin D analogues, topical calcineurin inhibitors, emollients, tar-based therapies, and topical corticosteroids may be considered in children as steroid-sparing regimens that may reduce potential adverse effects from overreliance on topical steroid therapy. • The off-label use of topical tazarotene may be recommended as monotherapy or in combination with topical corticosteroids for the treatment of localized pediatric skin or nail psoriasis. • Long-term use (12 weeks or longer) of topical anthralin (dithranol) is recommended for the treatment of mild to moderate psoriasis. Short-contact anthralin protocols are recommended to limit adverse effects. • Anthralin application is usually limited by poor tolerability and cosmetic concerns and is rarely used on the face and intertriginous areas. Because there are more cosmetically elegant treatments, anthralin is typically an alternative treatment for localized areas of psoriasis. • Coal tar preparations can be used as a monotherapy or combined with other topical therapies for the treatment of pediatric psoriasis. • The use of coal tar preparations in conjunction with phototherapy is effective for the treatment of psoriasis in children but may be limited by the theoretical long-term risk of carcinogenesis. • If coal tar/phototherapy combination therapy is an effective treatment for a particular patient with pediatric psoriasis, this risk may be decreased by alternating this treatment method with other modalities and should be considered on an individual basis. • Narrowband ultraviolet B (NB-UVB) is recommended as a treatment option for moderate to severe pediatric plaque and guttate psoriasis. • The use of excimer laser or psoralen plus ultraviolet A (PUVA) therapy in children with psoriasis may be efficacious and well tolerated but has limited supporting evidence. • Methotrexate is recommended as an effective systemic therapy for moderate to severe plaque psoriasis and other psoriasis subtypes in children. • Methotrexate is recommended as an effective systemic therapy for pustular psoriasis in children. • Methotrexate weight-based dosing is recommended in younger children, ranging from 0.2 to 0.7 mg/kg/wk (maximum, 25 mg/wk). • Folic acid supplementation daily or 6 times weekly during treatment with methotrexate is recommended. • Routine clinical and laboratory monitoring is recommended before and during treatment with methotrexate. • Cyclosporine is recommended as an effective systemic therapy for moderate to severe plaque psoriasis in children. • Cyclosporine is recommended as an effective systemic therapy for moderate to severe pustular psoriasis in children. • Cyclosporine is recommended for short-term crisis management of severe or unstable plaque, erythrodermic, or pustular psoriasis until the patient can be transitioned to a medication appropriate for long-term use. • Routine blood pressure clinical and laboratory monitoring is recommended during therapy with cyclosporine. • Modified cyclosporine (for microemulsion in capsules or solution) is recommended for use and is not interchangeable with unmodified forms of cyclosporine. • Acitretin is recommended as an effective, non-immunosuppressive systemic therapy for children with extensive guttate or moderate to severe (ideally thin plaque) psoriasis vulgaris at a dosage of 0.1 to 1 mg/kg/d. • Acitretin is recommended as an effective systemic therapy for pustular psoriasis in

Clinical Guideline	Recommendation(s)
	children. • Acitretin combined with NB-UVB therapy may be synergistic for plaque and pustular psoriasis in childhood and allows for a reduction in dosing of both agents. • Acitretin may be combined with other systemic therapies such as methotrexate or cyclosporine, or biologics, depending on the individual clinical situation. • Routine clinical and laboratory monitoring is recommended during therapy with acitretin. • Fumaric acid esters may be considered as a potentially effective alternative therapy for pediatric patients with moderate to severe psoriasis who are candidates for systemic therapy. • Clinical and laboratory monitoring is recommended during treatment with fumaric acid esters. • Etanercept is recommended as an effective therapy for moderate to severe psoriasis in children six years of age and older. • Etanercept dosing is typically once weekly and is dosed subcutaneously at 0.8 mg/kg with a maximum of 50 mg weekly. • Adalimumab is recommended for off-label use as an effective therapy in children and adolescents with moderate to severe psoriasis. • The dose of adalimumab is 0.8 mg/kg (maximum, 40 mg) at weeks 0 and 1 and then is given every other week. Adalimumab administered at a dose of 0.8 mg/kg is more efficacious than at a dose of 0.4 mg/kg. • Infliximab can be recommended as monotherapy or in combination with methotrexate for use in pediatric patients with severe plaque or pustular psoriasis that is unresponsive to other systemic medications, rapidly progressive, unstable, and/or life threatening. • The starting dose of infliximab is an infusion of 5 mg/kg administered on weeks 0, 2, and 6 and then every 8 weeks. • Ustekinumab is recommended as an effective therapy for adolescents 12 years and older with moderate to severe plaque psoriasis. • Ustekinumab can be used as an effective therapy for pediatric patients younger than 12 years old with moderate to severe plaque psoriasis. • Ustekinumab is given at weeks 0, 4, and 16 and then every 12 weeks with weight-based dosing as follows: 0.75 mg/kg if <60 kg, 45 mg if 60 to ≤100 kg, and 90 mg if >100 kg. • Biologics may be safely combined with topical corticosteroids, with or without a vitamin D analogue, to augment effectiveness for the treatment of moderate to severe plaque psoriasis. • The major risk for biologics in children is injection site reaction, but patients should be monitored for their increased risk of infection.
Finnish Medical Society Duodecim: **Seborrheic Dermatitis in the Adult (2020)**[11]	General considerations • No permanent results are usually achieved with treatment, which is symptomatic and needs to be repeated from time to time (a course lasting for one to two weeks) when symptoms worsen. • Maintenance therapy, perhaps once or twice weekly, should be continued in order to reduce the frequency of exacerbations. Reduction of dandruff and sebo-suppression • Seborrheic areas should be washed more often than normally (daily). • Basic topical ointments in gel form (e.g., products containing propylene glycol) to wash with, or basic topical ointments may be applied after washing. Face and body • Topical mild to moderately potent glucocorticoid creams. • Creams containing a combination of a glucocorticoid and an azole antifungal. • Glucocorticoid creams are used periodically, e.g., during periods of exacerbation

Clinical Guideline	Recommendation(s)
	once or twice daily in courses of one to two weeks. • Tacrolimus ointment or pimecrolimus cream as a periodical therapy one to two times daily for a period of three to four weeks or as maintenance therapy e.g., once or twice a week. • Creams, gels or shampoos containing topical antifungals (ketoconazole, clotrimazole, miconazole, tioconazole) or terbinafine ointment. • Antifungals may be used in acute exacerbations once or twice daily for one to two weeks, and they are suitable for prophylactic maintenance therapy once or twice a week. • Metronidazole or azelaic acid either as gel or cream in courses of three to four weeks and, if needed, as maintenance therapy one to two times a week. <u>Scalp</u> • Scalp plaques can be softened with 3 to 5% salicylic acid ointment in the evenings and washed away in the mornings. • Scalp may be washed with ketoconazole shampoo or selenium sulfide shampoo. • Corticosteroid solutions (equivalent doses) to the scalp (Class I–III). • In treatment-resistant cases, a sequential treatment schedule using a glucocorticoid shampoo in courses of three to four weeks may be tried. <u>Ears and ear canals</u> • Mild to moderately potent glucocorticoid ointments or solutions one to two times daily in courses of one to two weeks. <u>Flexural areas</u> • Mild to moderately potent glucocorticoid ointments. • A combination ointment of a glucocorticoid and an azole group antifungal. • Tacrolimus ointment or pimecrolimus cream periodically one to two times daily in courses of three to four weeks, or as maintenance therapy, e.g., one to two times a week. • The effect of the warm and moist environment can be reduced by application of talc or azole-containing powder after wash in the mornings and zinc paste after wash in the evenings. • Flexural areas can be painted with antiseptic solutions, many of which stain the skin (rarely used). • An application of a powder containing, for example, an azole antifungal in the morning and a corticosteroid ointment after washing at night for one to two weeks. • Systemic antifungals may be indicated in serious cases, for example fluconazole 50 mg once daily or 150 mg once weekly (for two to four weeks) or itraconazole 100 mg twice daily (for one to two weeks). <u>Severe and treatment-resistant cases</u> • A course of an oral antifungal drug may be combined with topical therapy, itraconazole 200 mg once daily for seven days, for example. Interactions with other medications must be checked. • Also oral fluconazole or terbinafine have been used as courses.
British Association of Dermatologists: **Guidelines for the Management of Cutaneous Warts (2014)**[12]	• There are numerous treatments for warts, and whether used singly or in combination they often have little evidence base for their use. • Salicylic acid formulations are the most common preparation used in the treatment of viral warts. • There are many commercially available preparations, but there is limited information to enable comparisons to be made between products. • Comparisons between salicylic acid-containing paints, monotherapy with glutaraldehyde, fluorouracil, podophyllin, benzalkonium or liquid nitrogen cryotherapy, failed to find any preparation more effective than salicylic acid.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the skin and mucous membrane keratolytic agents are noted in Table 3.

Table 3. FDA-Approved Indications for the Skin and Mucous Membrane Keratolytic Agents[1-3]

Indication	Salicylic Acid	Urea
Dermatitis		
Treatment of inflammation and irritation associated with dermatitis, including eczematoid conditions and complications associated with pyodermas; treatment of insect bites, burns, and fungal infections	✔ *	
Hyperkeratotic Skin Disorders		
Removal of excess keratin in various hyperkeratotic skin disorders and psoriasis (including affected areas of scalp, skin, and feet)	✔	
Treatment and removal of common and plantar warts	✔	
Debridement and promotion of normal healing of hyperkeratotic surface lesions, particularly where healing is retarded by local infection, necrotic tissue, fibrinous or purulent debris, or eschar; urea is useful for the treatment of hyperkeratotic conditions, such as dry, rough skin; dermatitis; psoriasis; xerosis; ichthyosis; eczema; keratosis; keratoderma; and corns and calluses; as well as damaged, ingrown, and devitalized nails		✔

*Ointment.

IV. Pharmacokinetics

The pharmacokinetic parameters of the skin and mucous membrane keratolytic agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Skin and Mucous Membrane Keratolytic Agents[1-3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Salicylic acid	Not reported	50 to 80	Not reported	Urine	Not reported
Urea	Not reported	Not reported	Not reported	Not reported	Not reported

V. Drug Interactions

Due to limited systemic absorption with the skin and mucous membrane keratolytic agents, no major drug interactions have been reported.[2]

VI. Adverse Drug Events

The most common adverse drug events reported with the skin and mucous membrane keratolytic agents are listed in Table 5.

Table 5. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Keratolytic Agents[1-3]

Adverse Events	Salicylic Acid	Urea
Central Nervous System		
Dizziness	✔	-
Headache	✔	-
Mental confusion	✔	-
Dermatological		
Burning	✔	✔
Itching	-	✔

Adverse Events	Salicylic Acid	Urea
Irritation	✔	✔
Peeling	✔	-
Scaling	✔	-
Stinging	-	✔
Other		
Hyperventilation	✔	-
Tinnitus	✔	-

✔ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the skin and mucous membrane keratolytic agents are listed in Table 6.

Table 6. Usual Dosing Regimens for the Skin and Mucous Membrane Keratolytic Agents[1-3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Salicylic acid	Dermatitis: Ointment: Apply once or twice daily. Reevaluate if improvement is not seen in seven days Hyperkeratotic skin disorders: Shampoo: massage into wet hair or affected area; leave in place for several minutes; rinse thoroughly; labeled for over the counter use two to three times a week, or as directed by healthcare provider; some products may be left in place overnight	Hyperkeratotic skin disorders: Shampoo: massage into wet hair or affected area; leave in place for several minutes; rinse thoroughly; labeled for over the counter use two to three times a week, or as directed by healthcare provider; some products may be left in place overnight	Ointment: 3% Shampoo: 6%
Urea	Hyperkeratotic skin disorders: All formulations: apply to the affected area one to three times daily	Hyperkeratotic skin disorders: All formulations: apply to the affected area one to three times daily	Cream: 39% Foam: 20% Lotion: 40%

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the skin and mucous membrane keratolytic agents are summarized in Table 7. Although the keratolytic agents have been available for many years, there are limited clinical trials evaluating their use.

Table 7. Comparative Clinical Trials with the Skin and Mucous Membrane Keratolytic Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hyperkeratotic Skin Disorders				
Carroll et al.[13] (2005) Salicylic acid 6% gel applied twice daily on half of the body for 8 weeks vs salicylic acid 6% gel and tacrolimus 0.1% ointment applied on the other half of the body for 8 weeks	RCT Adult patients with symmetrical plaque-type psoriasis	N=30 12 weeks	Primary: Difference in the sum of the erythema, scale, and thickness scores from baseline to end of treatment Secondary: Global assessments and pruritus	Primary: There were significant differences between the two treatment groups at weeks one, two, and eight, with the tacrolimus plus salicylic acid–treated side of the body showing greater improvement in the target lesions than the vehicle plus salicylic acid–treated side (P<0.05). At week eight, there was greater improvement on the tacrolimus-treated side than on the placebo-treated side in erythema, scaling, and pruritus (P=0.04, P=0.04, and P=0.02, respectively). Thickness improved more on the tacrolimus plus salicylic acid–treated side, but the difference was not significant (P=0.07). Secondary: The tacrolimus plus salicylic acid treatment resulted in greater improvement according to the investigators' global evaluation of scaling and thickness (P=0.01 and P=0.02, respectively). The subjects' global evaluations showed a trend toward decreased severity of disease on the tacrolimus-treated side of the body, but the differences were not significant (P=0.19).
Ademola et al.[14] (2002) Urea 40% cream applied twice daily for 14 days vs	DB, PG, RCT Patients 18 to 65 years of age with a clinical diagnosis of dry skin of at least grade 2 (moderate to severe) on the plantar surface of	N=25 28 days	Primary: Investigators' clinical observations, instrumental measurements, and subjects' self-assessment	Primary: At the end of the second week of treatment, ammonium lactate lotion decreased skin roughness, scaling, fissures, thickness and dryness by 0.2, 0.7, 0.3, 0.4 and 0.6 units from baseline, respectively. These parameters were decreased from baseline by 0.3, 0.5, 0.5, 0.7, and 0.9, respectively by urea cream during the same treatment period. After the second week of treatment, urea cream was associated with statistically significant improvement (P<0.05) in skin roughness, fissures,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ammonium lactate 12% lotion applied twice daily for 14 days	both feet		Secondary: Not reported	thickness and dryness compared to ammonium lactate lotion. At the end of the two week treatment period, there was no significant difference in transepidermal water loss between the two treatment groups. Changes in skin hydration (as measured by corneometer) were significantly higher in the urea treatment arm compared to ammonium lactate (P<0.05). Urea cream treated surfaces demonstrated a significant (P<0.05) increased desquamation index over baseline at the second week of treatment, compared to the ammonium lactate lotion plantar surfaces. There was no significant difference between ammonium lactate lotion or urea cream by patient self-assessment. A preference questionnaire completed by the patients at the end of the 14th day indicated that patients significantly preferred ammonium lactate over urea cream, primarily for its effect on skin texture (P<0.05). Both therapies showed sustaining benefit between day 14 and day 28 were associated with similar scores for roughness, scaling, fissure, thickness and skin dryness and at levels that remained lower than baseline (P<0.05). Patient self-assessments also indicated that by day 28, therapeutic differences disappeared. Secondary: Not reported
Goldstein et al.[15] (2008) Urea 30% emollient foam	OL, OS, PRO, SC Patients ≥18 years of age with hyperkeratosis with a specified symptom skin score ≥5 and not receiving	N=10 28 days	Primary: Clinical assessment of specified symptom skin score from baseline to day 14 and day 28	Primary: Significant improvements in clinicians' specified symptom skin score scores were noted at the day 14 and day 28 visits compared to baseline (P=0.007 and <0.001, respectively). Secondary: There was a 64.3% improvement in aggregate quality of life scores with comparable improvements noted for symptoms (63.4%), emotions

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	any other treatments		Secondary: Frequency and types of adverse events, patient quality of life assessments, patients' subjective ratings of their skin condition recorded on the Likert scale (5-point), patient/clinician ratings of satisfaction with the product on the Liker scale (5-point)	(65.0%), and functioning (63.8%) at day 28. Patients' reported noticeable improvements in their skin condition with a mean score of 3.2 on day 14 and 4.0 on day 28. The use of urea 30% resulted in no adverse events at any point during the study and all patients completed the 28-day treatment course. Patient satisfaction ratings for urea 30% at day 28 were favorable with mean ratings of 4.9 for odor, 4.7 for ease of application, 4.6 for product feel, 4.3 for overall product satisfaction, and 4.2 for absence of sticky residue. Mean clinician satisfaction rating for urea 30% at day 28 was 4.0.
Kwok et al.[16] (2011) Topical treatment of cutaneous warts (salicylic acid, cryotherapy, duct tape, bleomycin, 5-flurourocil, dinitrochlorobenzene, interferon or photodynamic therapy)	MA Studies evaluating the topical treatment of cutaneous warts	N=77 trials Duration varied	Primary: Cure rate Secondary: Not reported	Primary: Salicylic acid was more efficacious compared to placebo. Cryotherapy was not statistically better than placebo but aggressive cryotherapy was significantly better than gentle cryotherapy. Combined therapy of salicylic acid and cryotherapy had a higher cure rate than either agent alone. The results of the pooled analysis found a cure rate of 23% (5 to 73%) in placebo trials, 52% (0 to 87%) in salicylic acid trials, 49% (0 to 69%) in cryotherapy trials, 54% (45 to 75%) in aggressive cryotherapy trials and 58% (38 to 78%) in the combined cryotherapy and SA trials. Secondary: Not reported

Study abbreviations: DB=double-blind, MA=meta-analysis, OL=open-label, OS=observational, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, SC=single center

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 8. Relative Cost of the Skin and Mucous Membrane Keratolytic Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Salicylic acid	ointment	Bensal HP®	$$$$	N/A
Urea	cream, foam, lotion	Uramaxin®	$	$$$

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

Salicylic acid and urea are used to treat a variety of hyperkeratotic skin conditions, including psoriasis, xerosis, ichthyosis, eczema, corns, and calluses.[1-3] Salicylic acid is also approved for the treatment of cutaneous warts. Urea is approved for the treatment of damaged, ingrown, and devitalized nails. Urea is available in a generic formulation.

There are numerous topical and systemic therapies available for the treatment of psoriasis. The selection of therapy should take into consideration the disease severity, location of the lesions, and patient preference. Patients with mild to moderate disease can often be treated with a topical agent, while those with moderate to severe disease may need systemic therapy.[9-11] Topical preparations that are effective include corticosteroids, tar-based products, dithranol preparations, vitamin A analogs, and vitamin D analogs. Salicylic acid may be combined with other topical therapies, including corticosteroids and topical immunomodulators. Emollients should also be used to soften scaling and reduce irritation. Guidelines do not give preference to one topical agent over another.[9-11] For the

treatment of seborrheic dermatitis, the Finnish Medical Society Duodecim guidelines recommend the use of salicylic acid to soften scales.[12] Topical corticosteroids, antifungal agents, and moisturizing emollients are also frequently prescribed to decrease fungal growth and control symptoms. For the management of cutaneous warts, salicylic acid is recommended as one of several initial treatment options.[13] There are no recommendations regarding the use of urea in the guidelines.[9-12]

Although the keratolytic agents have been available for many years, there are relatively few studies evaluating the efficacy of these agents.[14-16] There were no studies found in the medical literature that directly compared salicylic acid and urea.

There is insufficient evidence to support that one brand skin and mucous membrane keratolytic agent is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand skin and mucous membrane keratolytic agents within the class reviewed are comparable to each other and to the generics products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand skin and mucous membrane keratolytic agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Keratoplastic Agents
AHFS Class 843200
February 8, 2023

I. Overview

Currently there are no prescription medications classified by American Hospital Formulary Service (AHFS) as keratoplastic agents.

II. Conclusions

There are no prescription medications available in the keratoplastic agents class (AHFS Class 843200).

III. Recommendations

No brand skin and mucous membrane keratoplastic agent is recommended for preferred status. Alabama Medicaid should continue to include AHFS Class 843200 in the Preferred Drug List (PDL) screening process. If new prescription keratoplastic agents are added, it is recommended that this class be re-reviewed.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Agents, Miscellaneous
AHFS Class 849200
February 8, 2023

I. Overview

The miscellaneous skin and mucous membrane class includes a diverse group of products used to treat many skin conditions, including actinic keratoses, atopic dermatitis, basal cell carcinoma, erythropoietic protoporphyria, facial angiofibroma, nonsegmental vitiligo, pain associated with anal fissure, psoriasis, warts, and wounds.[1-24] The wide variety of products, as well as the range of Food and Drug Administration (FDA)-approved indications, makes direct comparisons difficult. It is important to analyze current treatment guidelines and published studies when making therapeutic decisions about the miscellaneous skin and mucous membrane agents.

Acitretin and tazarotene bind to retinoid receptors, which control cellular differentiation and proliferation.[3,16] Afamelanotide is a melanocortin receptor agonist that mainly binds to MC1-R and increases production of eumelanin in the skin without the need for exposure to sunlight or artificial UV light.[22] Calcipotriene and calcitriol are vitamin D analogs, which regulate skin cell production and proliferation.[4-6,17,18] Collagenase can digest collagen in necrotic tissue, which contributes to the formation of granulation tissue and epithelialization.[7] Imiquimod is an immune response modifier, which induces cytokines, including interferon-alpha and others.[8,9] Nitroglycerin stimulates guanylate cyclase causing an increase in cyclic guanosine 3'5' monophosphate, regulating the contractile state in smooth muscle and leading to vasodilation and analgesia.[10] Pimecrolimus and tacrolimus bind to the intracellular protein FKBP-12, inhibiting calcineurin, which blocks cytokine transcription and inhibits T-cell activation.[11,15] Podophyllin resin is a cytotoxic agent that arrests mitosis in metaphase.[13] Podofilox is an active component of podophyllin resin.[12] Ruxolitinib is a Janus kinase (JAK) inhibitor of JAK1 and JAK2, which mediate the signaling of several cytokines and growth factors and involve the recruitment of signal transducers and activators of transcription (STATs). The mechanism in which the inhibition of specific JAK enzymes contributes to therapeutic effectiveness of ruxolitinib is unknown.[23] Although the mechanism of action of sirolimus in the treatment of angiofibroma associated with tuberous sclerosis is unknown, it is thought to be related to the inhibition of mTOR activation.[24] The thrombin-fibrinogen-aprotinin-calcium chloride product is a two-component fibrin sealant made from pooled human plasma, which mimics the final stage of the blood coagulation cascade and is used in patients undergoing surgery.[19,20] Levulan Kerastick® (aminolevulinic acid) photodynamic therapy is a two-stage process for administration by a health care provider for the treatment of actinic keratoses.[1-2]

The miscellaneous skin and mucous membrane agents that are included in this review are listed in Table 1. Products indicated solely for the treatment of acne and/or rosacea are not covered by Alabama Medicaid. Therefore, these products are not included in this review. This review encompasses all dosage forms and strengths. Several of the agents are available in a generic formulation. This class was last reviewed in February 2021.

Table 1. Skin and Mucous Membrane Agents, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Acitretin	oral capsule	Soriatane®*	acitretin
Afamelanotide	implant	Scenesse®	none
Aminolevulinic acid^	gel, solution	Ameluz®, Levulan Kerastick®	none
Calcipotriene	cream, foam, ointment, solution	Dovonex®*, Sorilux®*	calcipotriene
Calcitriol	ointment	Vectical®*	calcitriol
Collagenase	ointment	Santyl®	none
Imiquimod	cream	Zyclara®*	imiquimod
Nitroglycerin	rectal ointment	Rectiv®	none

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Pimecrolimus	cream	Elidel®*	Elidel®*
Podofilox	gel, solution*	Condylox®	podofilox
Podophyllum resin	liquid	Podocon-25®	none
Ruxolitinib	cream	Opzelura®	none
Sirolimus	gel	Hyftor®	none
Tacrolimus	ointment	Protopic®*	tacrolimus
Tazarotene	cream*, foam*	N/A	tazarotene
Combination Products			
Calcipotriene and betamethasone	foam, ointment*, suspension*	Enstilar®, Taclonex®*	calcipotriene and betamethasone
Halobetasol propionate and tazarotene	lotion	Duobrii®	none
Thrombin, fibrinogen, aprotinin, and calcium chloride^	syringe	Artiss®, Tisseel®	none

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution and will be included in Table 1 only.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous skin and mucous membrane agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the Skin and Mucous Membrane Agents, Miscellaneous

Clinical Guideline	Recommendation(s)
American Academy of Dermatologists: **Guidelines of Care for the Management of Actinic Keratoses (2021)**[25] American Academy of Dermatology: **Focused Update Guidelines of Care for the Management of Actinic Keratosis (2022)**[26]	General management • Treatment options available for actinic keratoses include topically applied creams, gels, and solutions; cryosurgery; and photodynamic therapy. • Selection of treatment is based on actinic keratoses features, treatment-related factors, and patient characteristics and preferences. • The primary patient-focused considerations for the treatment of actinic keratoses are the associated symptoms, the risk of progression to keratinocyte carcinoma, tolerability, burden of treatment, and the cosmetic appearance of the actinic keratoses before, during, and after treatment. • For patients with limited life expectancy or for whom the morbidity of treatment outweighs the potential benefits, observation may be considered. • Field directed treatments, such as topical agents or photodynamic therapy, can be used to manage multiple actinic keratoses and keratinocyte changes in a contiguous area and may provide benefits in reducing the risk of developing new actinic keratoses, limiting actinic keratoses recurrence, and mitigating subclinical damage. • Lesion-directed treatments, such as liquid nitrogen cryosurgery or curettage, are used to manage few or isolated actinic keratoses with a single office visit and require only that the patient participate in post-procedural skincare. • There are practical limitations to the absolute number of individual actinic keratoses lesions that can be treated using lesion-directed treatments before patient discomfort, potential adverse events, and clinician time may make a field directed treatment a better option. UV protection • Randomized controlled trials have demonstrated that the use of sunscreen to

Clinical Guideline	Recommendation(s)
	prevent UV exposure is associated with a small reduction in the incidence of actinic keratosis and in the development of new actinic keratoses. • It is strongly recommended as a measure of good practice that patients with actinic keratoses minimize their exposure to UV. • This avoidance be multifaceted, including avoiding exposure to both natural and artificial sources of UV and the use of sun-protective clothing and sunscreen that can block both UVA and UVB. Topical agents • Topical agents can be used focally or in broad areas and are particularly advantageous when actinic keratoses occur in areas of high density or areas with indistinct clinical borders • Recommended topical agents all have the potential for generating skin reactions which can result in the termination of treatment without reaching the desired therapeutic outcome • The literature on actinic keratosis treatment supports a strong recommendation for field treatment with either 5-fluorouracil or imiquimod. • Due to the various commercial preparations of these drugs, the treatment regimens studied often vary in terms of the concentration, dosing interval, and duration. • Diclofenac is conditionally recommended based on lower quality of evidence compared to the supporting evidence for 5-fluorouracil or imiquimod. • The benefits of 5-FU treatment for AK were assessed as moderate or large, based on moderate-to high quality efficacy data from five identified studies. • Local irritation was the primary source of harm to patients using 5-fluorouracil and often the primary reason for the discontinuation of treatment. • The use of 5-fluorouracil with calcipotriene is an emerging topical treatment option with findings suggesting greater efficacy compared to 5-fluorouracil monotherapy. • The combination of 5-flourouracil and calcipotriene is not a currently available treatment option and therefore they did not make a recommendation for this treatment • Topical application of imiquimod in various concentrations over a range of application frequencies showed moderate to large benefits for the management of actinic keratosis in various anatomic locations. • Harms of imiquimod treatment primarily consisted of localized skin irritation or influenza-like symptoms. • Unpublished safety data reviewed by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee is reported to show that at three years the incidence of skin cancer in skin areas treated with ingenol mebutate is more than three times higher than that observed with imiquimod. • Ingenol mebutate is expected to be completely removed from the market in the US by the end of 2020, and as such no recommendation is provided on the use of ingenol mebutate. • Based on a review of studies of diclofenac gel (in a 2.5% hyaluronic acid vehicle) compared to vehicle, the benefits and potential harms, primarily local skin reactions, of diclofenac treatment were assessed as small, based on efficacy and safety data of low to moderate quality. • Use of nonsteroidal anti-inflammatory drugs, including topical diclofenac, is accompanied by a boxed warning of increased risk of cardiovascular thrombotic events as well as gastrointestinal complications, including gastrointestinal bleeding, ulceration, and perforation. • Tirbanibulin 1% ointment is strongly recommended for field treatment of actinic keratosis based on high certainty of evidence supporting substantial clinical potential (clearance of treated actinic keratoses) in the short term

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	while not substantially increasing the potential for undesirable consequences. • Although cost may be prohibitive with this agent compared to other strongly recommended treatments for actinic keratosis, tirbanibulin provides an abbreviated treatment duration compared to those other treatments. • There is significant evidence from prospective studies and comparative trials to support the use of cryosurgery as a readily available, rapid, and effective lesion-directed treatment for actinic keratoses. • Cryosurgery has been reported to cure between 57% and 98.8% of AKs followed up over three months to 8.5 years. • Discomfort during treatment and dyschromia after treatment constitute the major risks of the procedure and these tend to be minimized with shorter freezing times, although this may also reduce the overall rate of complete responses to treatment. • Laser ablation of actinic keratoses is another destructive therapeutic modality but it is not as widely available as cryosurgery in dermatology offices. • Cryosurgery is conditionally recommended over CO2 laser ablation due to more favorable outcomes and higher patient satisfaction ratings supported by moderate quality evidence. • Photodynamic therapy protocols and duration vary as photosensitizing compound incubation time can range from overnight to less than an hour before the application of a light source. • Methyl aminolevulinate has substantial literature to support its use as a photosensitizing compound for the treatment of actinic keratosis with photodynamic therapy but is unavailable in the United States and therefore is excluded from recommended treatments. • The primary sensitizing agent for photodynamic therapy in the United States is 5-aminolevulinic acid which is conditionally recommended as a treatment for actinic keratosis based on low overall summed quality of evidence. • Longer 5-aminolevulinic acid application times (one hour to four hours) over shorter application times were favored to enhance complete clearance of actinic keratoses and are conditionally recommended based on low quality evidence. • Daylight photodynamic therapy protocols involve the use of natural sunlight as the energy source to activate the sensitizing chemical and are conditionally recommended as less painful, but equally as effective as 5-aminolevulinic acid-red light photodynamic therapy. • 5-aminolevulinic acid-red light photodynamic therapy is conditionally recommended over chemical peeling using 35% trichloroacetic acid • 5-aminolevulinic acid-blue light photodynamic therapy is conditionally recommended as a treatment for actinic keratosis based on moderate quality evidence. • There is some evidence that heating the skin with a heating pad during ALA treatment may improve AK reduction; however, the specific thermal parameters need to be better defined and the study repeated before a specific recommendation on warming the skin can be made. • Pretreatment with alpha hydroxy acid solution before 5-aminolevulinic acid-blue light photodynamic therapy is conditionally recommended against based on very low-quality evidence. • Photodynamic therapy with 5-aminolevulinic acid is conditionally recommended over cryosurgery for the treatment of actinic keratoses based on low quality supporting evidence. • Photodynamic therapy with 5-aminolevulinic acid was shown to have moderate improvements over cryosurgery in actinic keratosis reduction and complete clearance, but also more skin irritation on the day of and the day after treatment.

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	• Combination of 5-fluorouracil cream and cryosurgery is conditionally recommended over cryosurgery based on moderate quality evidence suggesting enhanced lesion reduction without increased adverse events. • Combination of imiquimod 3.75% or 5% cream and cryosurgery is conditionally recommended over cryosurgery alone based on low quality evidence supporting improved outcomes likely outweigh a moderate increase in adverse reactions. • Combination of 3% diclofenac gel with cryosurgery is conditionally recommended against, favoring cryosurgery alone based on low quality evidence supporting increased treatment discontinuation rates with this combination treatment. • The use of adapalene gel in addition to cryosurgery is conditionally recommended against based on low quality evidence showing lack of perceived benefit with combination therapy over cryosurgery alone. • The use of topical imiquimod after 5-aminolevulinic acid-blue light photodynamic therapy is conditionally recommended against due to moderate quality data supporting lack of increased efficacy and added expense and burden to the patient.
Scottish Intercollegiate Guidelines Network: **Management of Atopic Eczema in Primary Care (2011)**[27]	<u>Emollient therapy</u> • Patients with atopic eczema should receive ongoing treatment with emollients. <u>Topical corticosteroid therapy</u> • Patients should continue with emollient therapy during treatment with topical corticosteroids. • Patients with atopic eczema should be advised to apply topical corticosteroids once daily. • Twice weekly maintenance therapy with a topical corticosteroid should be considered in patients with moderate to severe atopic eczema experiencing frequent relapses. • There is no good quality evidence to assist in the choice of topical corticosteroid potency in the treatment of atopic eczema. • The choice of topical corticosteroid potency should be tailored to the age of the patient, the body region being treated, and the degree to which the skin is inflamed. For delicate areas of skin, such as the face and flexures, only mild or moderately potent preparations should be used. On the face, especially in children, it is reasonable to start with a mildly potent topical corticosteroid. • Topical corticosteroids should be used with caution in the periocular region. <u>Topical calcineurin inhibitors</u> • Tacrolimus should be considered for short-term, intermittent treatment of moderate to severe atopic eczema that has not been controlled by topical corticosteroids, or if there is a serious risk of important adverse effects from further topical corticosteroid use (e.g., skin atrophy). • Topical calcineurin inhibitors should not be applied to skin which appears actively infected. • Due to long-term safety issues, topical calcineurin inhibitors should not be used as first-line treatment unless there is a specific reason to avoid or reduce the use of topical corticosteroids. <u>Antihistamines</u> • Short-term bedtime use of sedating antihistamines should be considered in patients with atopic eczema when there is sleep disturbance.
Primary Care Dermatology Society: **Clinical Guidance**	<u>Emollients</u> • Emollients are the mainstay of therapy and without them it is not possible to manage eczema effectively.

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for Eczema: Atopic Eczema (2019)[28] Reaffirmed June 2022	• Good evidence shows that the more emollients are used, the less topical steroids are needed. • Compliance is essential and so always review patients to check they are happy with what has been prescribed - it may be necessary to try a range of emollients before the patient settles on the best combination. • There is no good evidence to support the use of specific products to use in the bath or shower <u>Topical Steroids</u> • Use the lowest appropriate potency and only apply thinly to inflamed skin. • Allow moisturizers to dry into skin for 20 minutes before applying the steroid. • Avoid using combined steroid-antibiotic preparations on a regular basis as it will increase the risk of antibiotic resistance. • Amount of steroid needed can be determined by the Finger Tip Unit method. • Strength of steroid to be determined by the age of patient, site, and severity: o Child face: mild potency (e.g., 1% hydrocortisone). o Child trunk and limbs: moderate potency (e.g., clobetasone butyrate 0.05% or betamethasone valerate 0.025%). o Adult face: mild or moderate potency (e.g., clobetasone butyrate 0.05%) o Adult trunk and limbs: potent (e.g., betamethasone valerate 0.1%, mometasone). o Palms and soles: potent or very potent (e.g., clobetasol propionate 0.05%) • If used appropriately it is uncommon to develop steroid atrophy, however extra care needs to be taken in the following sites: o Around the eyes: unless used very infrequently topical steroid preparations should be avoided due to the risks of glaucoma. o The face - the regular use of topical steroids should be avoided. o Lower legs in older patients / others at risk of leg ulcers - the regular use of topical steroids should be avoided. <u>Immunomodulatory treatments</u> • Immunomodulatory agents (e.g., tacrolimus or pimecrolimus) are calcineurin inhibitors. • Their main benefit is that they are not steroid based and so do not cause skin atrophy. • Formulations include tacrolimus 0.03% ointment and pimecrolimus approved for ages two years and above and tacrolimus 0.1% ointment is approved for 16 years of age and above. • Local adverse effects include stinging, burning, itch, irritation, and slight photosensitivity - appropriate sun protection is recommended. Adverse effects are more common with tacrolimus but in many patients are transient. Immunomodulators should be temporarily discontinued when the skin is infected. • When to consider immunomodulators: o Eczema involving the eyelids and peri-orbital skin. o Patients regularly using topical steroids on the face. o Patients regularly using topical steroids on the lower legs in elderly patients and others at risk of leg ulcers. o Any signs of skin atrophy. • In milder cases, use pimecrolimus cream; although, if this is ineffective or in the first instance the eczema is of a greater severity, consider tacrolimus ointment. • While short-term data has showed no serious adverse effects, the possible long-term adverse effects of immunomodulators are not yet known; however, the risks are likely to be minimal especially when the treatments are used in the ways described above.

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	Other treatments • There is almost no role for non-sedating antihistamines in the management of eczema; the only exception is patients needing treatment for co-existent hay fever. • For the management of scalp eczema, wash with a mild tar-based shampoo. In young children (e.g., 18 months and under) it is often better to use an emollient bath oil to wash the hair rather than using a specific scalp treatment.
European Academy of Dermatology and Venereology: **Consensus-based European Guidelines for Treatment of Atopic Eczema (Atopic Dermatitis) in Adults and Children (2018)[29]**	• Emollients should be prescribed in adequate amounts, and these should be used liberally and frequently, in a minimum amount of 250 g per week for adults. • Emollient bath oils and soap substitutes should also be used. Emollients with a higher lipid content are preferable in wintertime. • A regular use of emollient has a short- and long-term steroid sparing effect in mild-to-moderate atopic eczema. An induction of remission with topical corticosteroids or topical calcineurin inhibitors is required first. • Topical corticosteroids are important anti-inflammatory drugs to be used in atopic eczema, especially in the acute phase. • Topical corticosteroids with an improved risk/benefit ratio are recommended in atopic eczema. • Diluted topical corticosteroids may be used under wet wraps for short-term periods in acute atopic eczema to increase their efficacy. • Proactive therapy (e.g., twice-weekly application in the long-term follow-up) may help to reduce relapses. • Proactive therapy with topical corticosteroids may be used safely for at least 20 weeks, which is the longest duration of trials. • Patient fear of side-effects of corticosteroids should be recognized and adequately addressed to improve adherence and avoid undertreatment. • Topical calcineurin inhibitors are important anti-inflammatory drugs to be used in atopic eczema. Instead of treating acute flares with topical calcineurin inhibitors, initial treatment with topical corticosteroids before switching to topical calcineurin inhibitors should be considered. • Topical calcineurin inhibitors are especially indicated in sensitive skin areas (face, intertriginous sites, anogenital area). • Proactive therapy with twice-weekly application of tacrolimus ointment may reduce relapses. • Effective sun protection should be recommended inpatients treated with topical calcineurin inhibitors. • Topical corticosteroids are recommended to control pruritus in the initial phase of atopic eczema exacerbation. • Topical calcineurin inhibitors are recommended to control pruritus in atopic eczema until clearance of eczema. • Topical polidocanol may be used to reduce pruritus in atopic eczema patients. • Routine clinical use of topical antihistamines including doxepin, topical cannabinoid receptor agonists, topical μ-opioid receptor antagonists or topical anaesthetics cannot be recommended as an adjuvant antipruritic therapy in atopic eczema. • There is not enough data available to recommend the use of capsaicin in management of itch in atopic eczema patients. • If emollients and anti-inflammatory topical preparations must be applied to the same location, the cream formulation should be applied first and only 15 minutes later the ointment formulation. • For routine treatment of flares once daily application of a potent topical corticosteroid is sufficient, usually for three to six days. • With mild disease activity, a small amount of topical corticosteroids two to three times weekly, associated with a liberal use of emollients, generally allows a good maintenance with SCORAD values below 15 to 20 (indicating mild disease). • The most constructive way to spare topical corticosteroids and avoid steroid-

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	related side-effects is not to spare them during acute flares, but through consequent baseline emollient skin care combined with early anti-inflammatory intervention in order to stabilize the disease, and prevent treatment-intensive flares. • The two steroid-free topical calcineurin inhibitors, tacrolimus ointment and pimecrolimus cream, have demonstrated efficacy against placebo in clinical trials for short-term and long-term use. • Proactive tacrolimus ointment therapy has been shown to be safe and effective for up to one year in reducing the number of flares and improving the quality of life in adult patients and children. • The anti-inflammatory potency of 0.1% tacrolimus ointment is similar to a topical corticosteroid with intermediate activity, while the latter is clearly more active than 1.0% pimecrolimus cream. • The topical calcineurin inhibitors do not induce skin atrophy like corticosteroids, which favors their use on delicate skin areas like the eyelids, perioral skin, genital areas, inguinal fold, and for topical long-term management. • Clinical and preclinical data do not indicate an increased risk of the induction of lymphoma or other types of malignancies, or photocarcinogenicity for topical calcineurin inhibitors, but since the continuous oral administration of the calcineurin inhibitor cyclosporine is associated with an increased photocarcinogenicity risk in solid organ transplant patients, UV protection, (e.g., with sunscreens) is recommended.
National Institute for Health and Clinical Excellence: **Management of Atopic Eczema in Children From Birth Up to the Age of 12 Years (2007)**[30] Reaffirmed March 2021	<u>General considerations</u> • A stepped approach should be used for managing atopic eczema in children. Treatment should be tailored based on the severity of the atopic eczema. • Emollients should always be used, even when the atopic eczema is clear. Treatment can be stepped up or down, according to the severity of symptoms, with the addition of the other treatments as necessary as follows: o Mild atopic eczema: emollients and mild potency topical corticosteroids. o Moderate atopic eczema: emollients, moderate potency topical corticosteroids, topical calcineurin inhibitors, and bandages. o Severe atopic eczema: emollients, potent topical corticosteroids, topical calcineurin inhibitors, bandages, phototherapy, and systemic therapy. <u>Emollients</u> • Emollients should be used on the whole body when the atopic eczema is clear and while using all other treatments. <u>Topical corticosteroids</u> • Use mild potency topical corticosteroids on the face and neck, except for short-term (three to five days) use of moderate potency agents for severe flares. • Use moderate or potent topical corticosteroids for short periods only (seven to 14 days) for flares in sites such as axillae and groin. • Do not use very potent preparations in children without specialist dermatological advice. • Topical corticosteroids for atopic eczema should be prescribed for application only once or twice daily. • In children ≥12 months of age, potent topical corticosteroids should be used for the shortest amount of time as possible; no longer than 14 days. They should not be used on the face or neck. Potent topical corticosteroids should not be used in children <12 months of age without specialist dermatological supervision. • Consider treating problem areas with topical corticosteroids for two consecutive days per week to prevent flares, rather than treating flares as they arise, in children with frequent flares (two or three per month), once the eczema has been controlled.

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	• A different topical corticosteroid of the same potency should be considered as an alternative to stepping up treatment if tachyphylaxis to a topical corticosteroid is suspected. <u>Topical calcineurin inhibitors</u> • Topical tacrolimus and pimecrolimus are not recommended for the treatment of mild atopic eczema or as first-line treatments for atopic eczema of any severity. • Topical tacrolimus is recommended as an option for the second-line treatment of moderate to severe atopic eczema in adults and children aged two years and older that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy. • Pimecrolimus is recommended as an option for the second-line treatment of moderate atopic eczema on the face and neck in children aged two to 16 years that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy. • Treatment with tacrolimus or pimecrolimus should only be initiated by physicians (including general practitioners) with a special interest and experience in dermatology. • For facial atopic eczema in children that requires long-term or frequent use of mild topical corticosteroids, consider stepping up treatment to topical calcineurin inhibitors. <u>Antihistamines</u> • Oral antihistamines should not be used routinely in the management of atopic eczema in children. • A one-month trial of a nonsedating antihistamine should be offered to children with severe atopic eczema or children with mild or moderate atopic eczema where there is severe itching or urticaria. Treatment can be continued, if successful, while symptoms persist, and should be reviewed every three months. • A seven to 14 day trial of an age-appropriate sedating antihistamine should be offered to children aged six months or over during an acute flare of atopic eczema if sleep disturbance has a significant impact on the child or parents or carers. This treatment can be repeated during subsequent flares if successful. <u>Phototherapy and systemic treatments</u> • Phototherapy or systemic treatments should be considered for the treatment of severe atopic eczema in children when other management options have failed or are inappropriate and where there is a significant negative impact on quality of life.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/Joint Council on Allergy, Asthma, and Immunology: **Disease Management of Atopic Dermatitis: An Updated Practice Parameter (2012)**[31]	<u>General considerations</u> • The intensity of management and treatment of atopic dermatitis is dictated by the severity of illness, which relates to the effect of atopic dermatitis on the quality of life on the patient and his or her family. • The management of atopic dermatitis requires multiple therapeutic approaches including antipruritic therapy, skin hydration, topical anti-inflammatory medications, antibacterial measures, and the identification/elimination of exacerbating factors. <u>Skin hydration</u> • Hydration with warm soaking baths for at least 10 minutes followed by the application of a moisturizer is recommended. • Moisturizers should be recommended as first-line therapy.

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	Topical corticosteroids • Topical corticosteroids are an effective treatment option for atopic dermatitis. If atopic dermatitis is not controlled by moisturizers alone, then the clinician should recommend a topical corticosteroid. • Low-potency corticosteroids are recommended for maintenance therapy, whereas intermediate-and high-potency corticosteroids should be used for the treatment of exacerbation and applied to affected areas over short periods of time. • Potent fluorinated corticosteroids should not be used on the face, eyelids, genitalia, and intertriginous areas or in young infants. • Ultrahigh-potency corticosteroids should be used only for very short periods of time (several days) and in nonfacial non-skinfold areas. • The degree of corticosteroid absorption through the skin and the potential for systemic adverse effects are directly dependent on the surface area of the skin involved, thickness of the skin, the use of occlusive dressing, and the potency of the corticosteroid preparation. Topical calcineurin inhibitors • Tacrolimus ointment has been shown to be effective and safe in both adults and children older than two years of age, with most patients experiencing a reduction of pruritus within three days of initiating therapy. • Tacrolimus ointment does not cause atrophy for eczema on the face, eyelid, and skin folds that is unresponsive to low-potency topical steroids. • Once a flare is controlled, tacrolimus ointment twice daily, twice weekly to eczema-prone areas may prevent future flares. • Pimecrolimus cream decreases the number of flares of atopic dermatitis, reduces the need for corticosteroids, and controls pruritus. Tar preparations • There are no randomized studies that have demonstrated the efficacy of tar preparations, despite their widespread use for the treatment of atopic dermatitis. • Newer coal tar products have been developed that are more cosmetically acceptable than older products. • Coal preparations should not be recommended for acutely inflamed skin because this might result in additional skin irritation. Antihistamines • Patients may benefit from the use of oral antihistamines for the relief of pruritus associated with atopic dermatitis. Treatment of atopic dermatitis with topical antihistamines is generally not recommended because of potential cutaneous sensitization. Vitamin D • Patients with atopic dermatitis might benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake. Dilute bleach baths • The addition of dilute bleach baths twice weekly may reduce the severity of atopic dermatitis, especially in patients with recurrent skin infections. Microbes • Skin infections with *Staphylococcus aureus* are a recurrent problem in patients with atopic dermatitis, and patients with moderate-to-severe atopic dermatitis have been found to make IgE antibodies against staphylococcal toxins present in their skin. • A short course of an appropriate systemic antibiotic for patients who are clinically

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	infected with *Staphylococcus aureus* should be prescribed. In areas with high levels of methicillin-resistant *Staphylococcus aureus*, treatment with clindamycin, doxycycline, or sulfamethoxazole-trimethoprim may be initiated while awaiting skin culture results. • Atopic dermatitis can be complicated by recurrent viral skin infections, such as herpes simplex, warts, and molluscum contagiosum. Herpes simplex or eczema herpeticum should be diagnosed and promptly treated with systemic antiviral agents. • Fungal infections can complicate atopic dermatitis and might contribute to exacerbations. <u>Systemic Immunomodulating Agents</u> • Immunosuppressive agents such as cyclosporine, interferon gamma, mycophenolate mofetil, azathioprine, and corticosteroids have been shown to provide benefit for certain cases of severe refractory atopic dermatitis, but potential benefits should be weighed against their potentially serious adverse effects. <u>Phototherapy</u> • Ultraviolet therapy can be a useful treatment for recalcitrant atopic dermatitis. <u>Allergen immunotherapy</u> • Select patients with atopic dermatitis with aeroallergen sensitivity may benefit from allergen immunotherapy.
American Academy of Dermatology: **Guidelines of Care for the Management of Atopic Dermatitis (2014)**[32]	<u>Topical corticosteroids</u> • Topical corticosteroids are the mainstay of anti-inflammatory therapy for the management of atopic dermatitis. • They are typically introduced into the treatment regimen after failure of lesions to respond to good skin care and regular use of moisturizers alone. • Comparative trials are limited in duration and scope (i.e., they mainly involve two, and occasionally three, agents), and as a result, there are no data to support one or a few specific agents as being more efficacious than others. • A variety of factors should be considered when choosing a particular topical corticosteroid for the treatment of atopic dermatitis, including patient age, areas of the body to which the medication will be applied, and other patient factors such as degree of xerosis, patient preference, and cost of medication. • Twice-daily application of corticosteroids is generally recommended for the treatment of atopic dermatitis; however, evidence suggests that once-daily application of some corticosteroids may be sufficient. • Proactive, intermittent use of topical corticosteroids as maintenance therapy (one to two times/week) on areas that commonly flare is recommended to help prevent relapses and is more effective than use of emollients alone. • The potential for both topical and systemic side effects, including possible hypothalamic-pituitary-adrenal axis suppression, should be considered, particularly in children with atopic dermatitis in whom corticosteroids are used. • Monitoring by physical examination for cutaneous side effects during long-term, potent steroid use is recommended. • No specific monitoring for systemic side effects is routinely recommended for patients with atopic dermatitis. • Patient fears of side effects associated with the use of topical corticosteroids for atopic dermatitis should be recognized and addressed to improve adherence and avoid undertreatment. <u>Topical calcineurin inhibitors</u> • Topical calcineurin inhibitors are recommended and effective for acute and

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	chronic treatment, along with maintenance, in both adults and children with atopic dermatitis, and are particularly useful in selected clinical situations, including recalcitrance to steroids, use on sensitive areas (e.g., face, anogenital, skin folds), steroid-induced atrophy, and long-term uninterrupted topical steroid use. • Topical calcineurin inhibitors are recommended for use on actively affected areas as a steroid-sparing agent for the treatment of atopic dermatitis. • For patients with atopic dermatitis <2 years of age with mild to severe disease, off-label use of 0.03% tacrolimus or 1% pimecrolimus ointment can be recommended. • Pimecrolimus cream and tacrolimus ointment may cause skin burning and pruritus, especially when applied to acutely inflamed skin. Initial treatment of patients with atopic dermatitis using topical corticosteroids should be considered to minimize topical calcineurin inhibitor application site reactions. Patients with atopic dermatitis should be counseled about the possibility of these reactions. • Proactive, intermittent use of topical calcineurin inhibitor as maintenance therapy (two to three times per week) on areas that commonly flare is recommended to help prevent relapses while reducing the need for topical corticosteroids and is more effective than the use of emollients alone. • The concomitant use of a topical corticosteroid with a topical calcineurin inhibitor may be recommended for the treatment of atopic dermatitis. • No consistent increases in the prevalence of cutaneous viral infections have been seen with continuous or intermittent use of topical calcineurin inhibitor for up to five years; however, physicians should inform their patients of these theoretical cutaneous risks, given the lack of safety data for longer periods of time. • Clinicians should be aware of the black-box warning on the use of topical calcineurin inhibitor for patients with atopic dermatitis and discuss as warranted. • Routine blood monitoring of tacrolimus and pimecrolimus levels in patients with atopic dermatitis who are applying these agents is not recommended at this time. <u>Topical antimicrobials and antiseptics</u> • Except for bleach baths with intranasal mupirocin, no topical antistaphylococcal treatment has been shown to be clinically helpful in patients with atopic dermatitis and is not routinely recommended. In patients with moderate to severe atopic dermatitis and clinical signs of secondary bacterial infection, bleach baths and intranasal mupirocin may be recommended to reduce disease severity. <u>Other topical agents</u> • Topical antihistamines have been tried for the treatment of atopic dermatitis but have demonstrated little utility and are not recommended. • There are not adequate data to make a recommendation regarding the use of coal tar topical agents.
National Comprehensive Cancer Network: **Basal Cell Skin Cancer (2022)**[33]	• The primary goal of treatment of basal cell skin cancer is the complete removal of the tumor and the maximal preservation of function and cosmesis. All treatment decisions should be customized to account for the particular factors present in the individual case and for the patient's preference. • Surgical approaches often offer the most efficient means for accomplishing cure, but considerations of function, cosmesis, patient preference and performance status may lead to choosing radiation therapy as primary treatment in order to achieve optimal overall results. • In certain patients at high risk for multiple primary tumors, increased surveillance and consideration of prophylactic measures may be indicated. • In patients with superficial basal cell skin cancer, therapies such as topical imiquimod, topical 5-fluorouracil, photodynamic therapy with aminolevulinic acid (ALA) or porfimer sodium, or cryotherapy may be considered, even though the

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	cure rates are approximately 10% lower than with surgical treatment modalities. • Use of nicotinamide may be effective in reducing the development of basal cell skin cancers. • Photodynamic therapy (PDT) has similar efficacy as cryotherapy but better cosmetic outcomes. • Systemic therapy may be considered for complicated cases of locally advanced disease if curative surgery and curative radiation therapy are not feasible. • PDT, imiquimod, and fluorouracil have similar efficacy and cosmetic outcomes, although risk of recurrence may be somewhat higher with PDT vs imiquimod. • Imiquimod was found to be effective for treating nodular and superficial basal cell skin cancer in randomized studies. • A meta-analysis of 23 randomized and non-randomized trials found no significant difference in efficacy for photodynamic therapy versus imiquimod, however, a more recent randomized trial showed that treatment success was more likely with imiquimod. • This study also demonstrated superior imiquimod outcomes compared to 5-fluorouracil cream. Sub-analyses found that treatment success rates were significantly higher with imiquimod for tumors that are large or truncal, while photodynamic therapy provided significantly better outcomes in elderly patients with lesions on the lower extremities. • Imiquimod and 5-fluorouracil are more likely to cause moderate to severe local swelling, erosion, crust formation, itching and wound infections compared to photodynamic therapy, which is more likely to cause moderate to severe pain during treatment administration.
National Comprehensive Cancer Network: **Squamous Cell Skin Cancer (2022)**[34]	• The primary goals of treatment of squamous cell skin cancer are the complete removal of the tumor and maximal preservation of function and cosmesis. All treatment decisions should be customized to account for the particular factors present in the individual case and for the patient's preference. • Surgical approaches often offer the most effective and efficient means for accomplishing cure, but considerations of function, cosmesis, and patient preference may lead to choosing radiation therapy as primary treatment in order to achieve optimal overall results. • In certain patients at high risk for multiple primary tumors, increased surveillance and consideration of prophylactic measures may be indicated. • In patients with squamous cell carcinoma in situ (Bowen's disease), alternative therapies such as 5-fluorouracil, topical imiquimod, photodynamic therapy, or vigorous cryotherapy may be considered, even though the cure rates may be lower than with surgical treatments. • Use of nicotinamide may be effective in reducing the development of squamous cell skin cancers. • Actinic keratoses are considered precancerous and should be treated at first development. • Accepted treatment modalities include cryotherapy, topical 5-fluorouracil (5-FU) (preferred) with or without calcipotriol (calcipotriene), topical imiquimod, topical tirbanibulin, photodynamic therapy (e.g., aminolevulinic acid [ALA], porfimer sodium), and C&E. • For hyperkeratotic actinic keratoses, pretreatment with topical tazarotene, curettage, or topical keratolytics (topical urea, lactic acid, and salicylic acid) prior to above therapies may be considered. • In patients who develop multiple adjacent tumors in close proximity, surgical excision of invasive disease sometimes does not include surrounding in situ disease, and tissue rearrangement should be minimized. In situ disease may then be treated with topical approaches similar to actinic keratoses/field cancerization. • In patients with cutaneous squamous cell carcinoma (CSCC) in situ (Bowen disease), alternative therapies such as topical 5-fluorouracil, topical imiquimod,

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	photodynamic therapy (e.g., ALA, porfimer sodium), or vigorous cryotherapy may be considered even though cure rates may be lower than with surgical treatment modalities. • Results from randomized trials showed fewer treatments required for complete clearance and higher durable complete response rates with PDT versus cryotherapy. • Compared to 5-fluorouracil, PDT was also associated with higher rates of initial complete clearance and higher durable complete response rates. • Cryotherapy may be associated with poorer cosmetic outcomes compared with topical 5-fluorouracil. • The NCCN guidelines do not recommend topical retinoids as prophylactic treatment for patients at high risk for multiple AKs or CSCCs
British Association of Dermatologists: **Guidelines for the Management of Basal Cell Carcinoma (2021)**[35]	Surgical treatment • Standard surgical excision is a first-line treatment option to adults with low-risk basal cell carcinoma (BCC). • Standard surgical excision with immediate reconstruction is a first-line treatment option to adults with primary BCC with a high-risk factor, if the BCC has well-defined clinical margins under bright lighting and magnification or dermoscopy. • Standard surgical excision with delayed definitive reconstruction, or Mohs micrographic surgery, is the first-line treatment option to adults with high-risk BCC within a high-risk anatomical site if the BCC has poorly defined clinical margins under bright lighting and magnification or dermoscopy. • Consider Mohs micrographic surgery in adults with primary BCC with at least one high-risk factor. • Mohs micrographic surgery is a first-line treatment option to adults with recurrent BCC with at least one other high-risk factor, especially if the tumor is at a high-risk site. • Standard surgical excision or radiotherapy is a treatment option to adults with advanced BCC. • Mohs micrographic surgery is a treatment option to adults with advanced BCC. Systemic therapy • Vismodegib, subject to availability, is a treatment option to adults with advanced BCC who are unsuitable for Mohs micrographic surgery, standard surgical excision or radiotherapy, including patients with Gorlin syndrome, following discussion with multidisciplinary team (MDT). Radiotherapy • Radiotherapy is a treatment option to adults (suggested age ≥ 60 years) with low-risk and high-risk BCC who are unsuitable for or decline Mohs micrographic surgery or standard surgical excision and who express a preference for radiotherapy, and in whom the lesion is a nodular BCC, an infiltrative subtype of BCC, provided a sufficient planning margin is used, or an excised BCC with involved margins. • Do not offer radiotherapy as a treatment option to adults with BCC who are unsuitable for or decline Mohs micrographic surgery or standard surgical excision, and in whom the lesion is a recurrent BCC following previous radiotherapy or associated with certain genetic syndromes predisposing to skin cancers, for example Gorlin syndrome or xeroderma pigmentosum. • Do not routinely offer radiotherapy as a treatment option to adults with BCC who are unsuitable for or decline Mohs micrographic surgery or standard surgical excision, and in whom the lesion is on areas of poor blood supply

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	(e.g., the lower limbs), in younger patients in whom the late effects of radiotherapy could be an issue (suggested age < 60 years), or a BCC invading bone or cartilage. Other treatment options • Topical imiquimod, topical 5-fluorouracil, cryosurgery or topical PDT is a treatment options to adults with low-risk BCC who are unsuitable for or decline standard surgical excision. • Do not offer topical imiquimod, topical 5-fluorouracil, cryosurgery, curettage and cautery, or topical PDT as treatment options to adults with high-risk BCC who are unsuitable for or decline Mohs micrographic surgery or standard surgical excision. • Do not offer topical imiquimod, topical 5-fluorouracil, cryosurgery, or topical PDT as a treatment option to adults with advanced BCC unless for palliation of symptoms, following discussion at an MDT. • In adults with BCC who decline all treatments, the risk of significant progression of the tumor is at least 25% over 2–5 years. • There is insufficient evidence to support any recommendation for Mohs micrographic surgery or vismodegib for low-risk (including recurrent, low-risk) BCC. • There is insufficient evidence to support any recommendation for topical ingenol mebutate gel, topical Curaderm-BEC5 cream, electrochemotherapy (ECT), CO_2 laser, or pulsed-dye laser for BCC. • There is insufficient evidence to support any recommendation for combinations of topical diclofenac and calcitriol, topical imiquimod and Mohs micrographic surgery, intralesional interferon-α and standard surgical excision, topical PDT and Mohs micrographic surgery, or laser therapy and topical PDT for BCC. • There is insufficient evidence to recommend 'no treatment' as an option for adults with recurrent BCC with at least one other high-risk factor or advanced BCC who are not suitable for or decline Mohs micrographic surgery or standard surgical excision. Management following primary treatment • Following discussion at an MDT, further standard surgical re-excision may be a treatment option for adults with excised high-risk BCC with involved histological margin unless there is a contraindication. • All adults with excised high-risk BCC with a close histological margin (< 1 mm) should be referred for MDT discussion of management options. These may include surgical re-excision, Mohs micrographic surgery, radiotherapy, or monitoring. Patient choice should especially be factored into the decision-making process in such a situation. • Adults adequately treated for BCC should receive a postoperative review by an appropriate healthcare professional, in either secondary or primary care if possible. • Adults with a history of multiple BCCs who are likely to develop further tumors or recurrence within 12 months should have at least yearly follow-up if possible.

British Association of Dermatologists: **Guidelines on the Efficacy and Use of Acitretin in Dermatology (2010)**[36]	In which conditions should acitretin be used?
	• Severe psoriasis, or psoriasis with severe effects on quality of life, meriting systemic therapy, which is resistant to topical therapy, phototherapy or is unsuitable for these treatments.
	  ○ Acitretin is recommended as a combination with psoralen combined with ultraviolet A therapy or narrowband phototherapy.
	  ○ Acitretin is recommended with hydroxycarbamide.

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	○ Acitretin is recommended in combination with calcipotriol ointment. ○ The following combinations are not recommended: 1) acitretin with cyclosporine; and 2) acitretin with methotrexate. • Palmoplantar pustular psoriasis. • Hyperkeratotic hand eczema. • Severe Darier disease (keratosis follicularis). • Severe congenital ichthyosis. • Keratoderma. • There is evidence that patients with lichen planus benefit from acitretin.
American Academy of Dermatology/ National Psoriasis Foundation: **Guidelines of Care for the Management and Treatment of Psoriasis with Topical Therapy and Alternative Medicine Modalities for Psoriasis Severity Measures (2020)**[37]	• Topical corticosteroids, which provide high efficacy and good safety, play a key role in the treatment of psoriasis, especially for localized disease. • Choosing a corticosteroid with appropriate potency plus the appropriate vehicle should be based on the disease severity, disease location, patient preference, as well as the age of the patient. • Lower potency corticosteroids should be used on the face, intertriginous areas, and areas that are susceptible to steroid atrophy (e.g., forearms) and other adverse effects. • The use of class 1, class 2, and class 3 to 5 topical steroids for up to four weeks is recommended for the treatment of plaque psoriasis not involving intertriginous areas. • The use of class 1 to 7 topical steroids for a minimum of up to four weeks is recommended as initial and maintenance treatment of scalp psoriasis. • The use of topical corticosteroids for > 12 weeks can be considered if done under the careful supervision of a physician. • While not FDA approved for psoriasis, the topical calcineurin inhibitors tacrolimus and pimecrolimus are often employed in the treatment of psoriasis. They are especially helpful on thinner skin such as facial and intertriginous areas and used as steroid-sparing agents for prolonged use (>4 weeks). The majority of the data regarding these medications are derived from their extensive use in atopic dermatitis. • The off-label use of 0.1% tacrolimus for psoriasis involving the face as well as inverse psoriasis for up to eight weeks can be considered. • The off-label use of pimecrolimus for inverse psoriasis for four to eight weeks is recommended. • Long term use of tacrolimus or pimecrolimus can be considered for inverse psoriasis treatment as off-label use. • The off-label combination of tacrolimus and 6% salicylic acid for 12 weeks may be used for the treatment of plaque psoriasis. • The long-term use of topical vitamin D analogues (up to 52 weeks) including calcipotriene-calcipotriene, calcitriol, tacalcitol, and maxacalcitol is recommended for the treatment of mild to moderate psoriasis. • Use of calcipotriene foam and calcipotriene plus betamethasone dipropionate gel is recommended for four to 12 weeks for the treatment of mild to moderate scalp psoriasis. • Topical tacalcitol ointment or calcipotriene combined with hydrocortisone for eight weeks can be used for the treatment of facial psoriasis. • Use of combination treatments with vitamin D analogues and potent Class II and Class III topical steroids up to 52 weeks is recommended for the treatment of psoriasis. • Use of combination products with calcipotriol and corticosteroids is recommended for the treatment of psoriasis. • The application of vitamin D analogues twice daily on weekdays in conjunction with high potency topical steroids twice daily on weekends can be considered for maintenance treatment for psoriasis. • The application of morning high potency topical steroids and evening topical

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	vitamin D analogues is an effective treatment regimen that can be considered for the treatment of psoriasis. • Topical tazarotene can be used for the treatment of mild to moderate psoriasis and nail psoriasis. • The combination of topical tazarotene and NB-UVB has been shown to be effective and allow a reduction in total usage of NB-UVB. • The use of mid-potency or high potency topical steroid in combination with tazarotene for eight to 16 weeks is more effective than monotherapy with tazarotene and is recommended for the treatment of mild to moderate psoriasis. • The use of topical steroids along with tazarotene is recommended to decrease the duration of treatment as well as increase the length of remission. • The use of an emollient in conjunction with topical corticosteroids for four to eight weeks can be used to help reduce itching, desquamation, and total body surface area and prevent quick relapse of psoriasis when topical corticosteroids are discontinued. • Topical salicylic acid can be used for eight to 16 weeks for the treatment of mild to moderate psoriasis. • The combination of salicylic acid with topical corticosteroids can be used for the treatment of moderate to severe psoriasis (BSA ≤ 20%). • Topical anthralin for eight to 12 weeks can be used for the treatment of mild to moderate psoriasis. Short contact (up to two hours per day) anthralin is recommended to limit side effects. • Coal tar preparations are recommended for the treatment of mild to moderate psoriasis. • The addition of an ultra-high potency (Class 1) topical corticosteroid to standard dose etanercept for 12 weeks is recommended for the treatment of moderate to severe psoriasis. • The addition of calcipotriene/betamethasone to standard dose adalimumab for 16 weeks is recommended for the treatment of moderate to severe psoriasis to accelerate clearance of psoriatic plaques. • All topical steroids can be used in combination with any biologics for the treatment of moderate to severe psoriasis. • The addition of topical calcipotriene to standard dose methotrexate therapy is recommended for the treatment of moderate to severe psoriasis. It may lead to lower cumulative doses of methotrexate and increased time to relapse following methotrexate discontinuation. • The addition of calcipotriene/betamethasone dipropionate ointment to low dose (2 mg/kg/day) cyclosporine can be used for the treatment of moderate to severe psoriasis. • The addition of calcipotriene to standard dose acitretin is recommended for the treatment of moderate to severe psoriasis.
American Academy of Dermatology/ National Psoriasis Foundation: **Guidelines of Care for the Management and Treatment of Psoriasis in Pediatric Patients (2019)**[38]	• A standard way to measure body surface area (BSA) in children is the "rule of 9s," with adjustment of regional relative proportions based on age. (Computer BSA models are available for children but not widely used). BSA should not be the sole predictor of disease severity. • Psoriasis can have a significant negative impact on QOL, including physical, emotional, social, and psychological functioning, and these features should be strongly considered along with clinical and patient-reported assessments. • Body surface area measurement of involved skin is recommended as a useful measure of psoriasis severity in children. • Disease location on the body and impact on physical, social, and psychological quality of life and/or activities of daily living are recommended as measures of psoriasis severity and should be taken into consideration when determining psoriasis severity in children. • Pediatric patients with psoriasis should be educated about the risk of PSA and its

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	clinical manifestations. • Pediatric patients with psoriasis should be routinely screened for PSA via a thorough history and physical examination. • Pediatric patients with psoriasis who show signs and symptoms of inflammatory arthritis should be referred to a rheumatologist with pediatric expertise, if available, for further evaluation and management. • Pediatric psoriasis patients with PSA should be routinely screened for uveitis by history and physical examination. • Pediatric patients with psoriasis who show signs and symptoms of uveitis should be referred to an ophthalmology specialist for further evaluation and management. • Topical corticosteroids are recommended for the treatment of pediatric psoriasis as an off-label therapy. • Use of topical steroids is frequently practiced and widely considered for localized disease. • The use of ultra-high-potency topical corticosteroids as monotherapy is effective for short-term treatment of localized psoriasis in pediatric patients. • Selection of a therapeutic routine (potency, delivery vehicle, frequency of application) should take into account sites of involvement, type and thickness of psoriasis, age of the patient, total BSA of application, anticipated occlusion, and disease acuity, among other patient-, disease-, and drug-related factors. • A popular routine is dual topical therapy with a high or ultra-high-potency topical steroid and topical vitamin D analogue. Although this simultaneous or serial use improves adherence by making it simpler for the patient, studies addressing the efficacy of compounded versus separate, simultaneous treatments are lacking. • It is advisable to avoid the use of ultra-high-potency topical corticosteroids in the face, fold, and genitalia of infants and children. • High-potency or ultra-high-potency topical corticosteroids should be used with caution, and patients should be followed closely by a dermatologist to ensure proper use and to monitor for overuse and adverse effects. • Providers and caregivers should be aware of the potential for rebound flare if high-potency corticosteroids are abruptly discontinued without transition to an appropriate alternative treatment. • Tacrolimus 0.1% ointment is recommended for off-label use as monotherapy for pediatric psoriasis of the face and genital region. • Burning, stinging, pruritus, and irritation have been reported as adverse effects of topical calcineurin inhibitors (TCI) use in children. • An important advantage of the vitamin D analogues, especially for pediatric use, is their corticosteroid-sparing function. Treatment with vitamin D analogues is safe, effective, and relatively well tolerated in children of all ages. • Calcipotriene/calcipotriol is recommended as a treatment option for childhood plaque psoriasis. • Because of the theoretical risk of increased calcium absorption and systemic effects of hypercalcemia, occlusion of calcipotriene/calcipotriol applied to large body surface areas is not recommended. • Monitoring of vitamin D metabolites may be considered during calcipotriene/calcipotriol therapy when applied to a large body surface area. • In practice, vitamin D analogues may be used in combination with other topical therapies to enhance efficacy and limit possible adverse effects. • The combination of calcipotriol/betamethasone dipropionate ointment applied once daily for up to four weeks at a time is recommended as a safe and effective treatment for children ages 12 years and older with mild to moderate plaque psoriasis. • The combination of calcipotriol/betamethasone dipropionate suspension applied once daily for up to eight weeks at a time is recommended as a safe and effective treatment for children ages 12 years and older with mild to moderate plaque

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	psoriasis of the scalp. • The use of emollients (at the same time or different time of day) with topical calcipotriene may be considered to reduce irritation and enhance the efficacy of calcipotriene. • Rotational therapy with topical vitamin D analogues, topical calcineurin inhibitors, emollients, tar-based therapies, and topical corticosteroids may be considered in children as steroid-sparing regimens that may reduce potential adverse effects from overreliance on topical steroid therapy. • The off-label use of topical tazarotene may be recommended as monotherapy or in combination with topical corticosteroids for the treatment of localized pediatric skin or nail psoriasis. • Long-term use (12 weeks or longer) of topical anthralin (dithranol) is recommended for the treatment of mild to moderate psoriasis. Short-contact anthralin protocols are recommended to limit adverse effects. • Anthralin application is usually limited by poor tolerability and cosmetic concerns and is rarely used on the face and intertriginous areas. Because there are more cosmetically elegant treatments, anthralin is typically an alternative treatment for localized areas of psoriasis. • Coal tar preparations can be used as a monotherapy or combined with other topical therapies for the treatment of pediatric psoriasis. • The use of coal tar preparations in conjunction with phototherapy is effective for the treatment of psoriasis in children but may be limited by the theoretical long-term risk of carcinogenesis. • If coal tar/phototherapy combination therapy is an effective treatment for a particular patient with pediatric psoriasis, this risk may be decreased by alternating this treatment method with other modalities and should be considered on an individual basis. • Narrowband ultraviolet B (NB-UVB) is recommended as a treatment option for moderate to severe pediatric plaque and guttate psoriasis. • The use of excimer laser or psoralen plus ultraviolet A (PUVA) therapy in children with psoriasis may be efficacious and well tolerated but has limited supporting evidence. • Methotrexate is recommended as an effective systemic therapy for moderate to severe plaque psoriasis and other psoriasis subtypes in children. • Methotrexate is recommended as an effective systemic therapy for pustular psoriasis in children. • Methotrexate weight-based dosing is recommended in younger children, ranging from 0.2 to 0.7 mg/kg/wk (maximum, 25 mg/wk). • Folic acid supplementation daily or 6 times weekly during treatment with methotrexate is recommended. • Routine clinical and laboratory monitoring is recommended before and during treatment with methotrexate. • Cyclosporine is recommended as an effective systemic therapy for moderate to severe plaque psoriasis in children. • Cyclosporine is recommended as an effective systemic therapy for moderate to severe pustular psoriasis in children. • Cyclosporine is recommended for short-term crisis management of severe or unstable plaque, erythrodermic, or pustular psoriasis until the patient can be transitioned to a medication appropriate for long-term use. • Routine blood pressure clinical and laboratory monitoring is recommended during therapy with cyclosporine. • Modified cyclosporine (for microemulsion in capsules or solution) is recommended for use and is not interchangeable with unmodified forms of cyclosporine. • Acitretin is recommended as an effective, non-immunosuppressive systemic

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	therapy for children with extensive guttate or moderate to severe (ideally thin plaque) psoriasis vulgaris at a dosage of 0.1 to 1 mg/kg/d. • Acitretin is recommended as an effective systemic therapy for pustular psoriasis in children. • Acitretin combined with NB-UVB therapy may be synergistic for plaque and pustular psoriasis in childhood and allows for a reduction in dosing of both agents. • Acitretin may be combined with other systemic therapies such as methotrexate or cyclosporine, or biologics, depending on the individual clinical situation. • Routine clinical and laboratory monitoring is recommended during therapy with acitretin. • Fumaric acid esters may be considered as a potentially effective alternative therapy for pediatric patients with moderate to severe psoriasis who are candidates for systemic therapy. • Clinical and laboratory monitoring is recommended during treatment with fumaric acid esters. • Etanercept is recommended as an effective therapy for moderate to severe psoriasis in children six years of age and older. • Etanercept dosing is typically once weekly and is dosed subcutaneously at 0.8 mg/kg with a maximum of 50 mg weekly. • Adalimumab is recommended for off-label use as an effective therapy in children and adolescents with moderate to severe psoriasis. • The dose of adalimumab is 0.8 mg/kg (maximum, 40 mg) at weeks 0 and 1 and then is given every other week. Adalimumab administered at a dose of 0.8 mg/kg is more efficacious than at a dose of 0.4 mg/kg. • Infliximab can be recommended as monotherapy or in combination with methotrexate for use in pediatric patients with severe plaque or pustular psoriasis that is unresponsive to other systemic medications, rapidly progressive, unstable, and/or life threatening. • The starting dose of infliximab is an infusion of 5 mg/kg administered on weeks 0, 2, and 6 and then every 8 weeks. • Ustekinumab is recommended as an effective therapy for adolescents 12 years and older with moderate to severe plaque psoriasis. • Ustekinumab can be used as an effective therapy for pediatric patients younger than 12 years old with moderate to severe plaque psoriasis. • Ustekinumab is given at weeks 0, 4, and 16 and then every 12 weeks with weight-based dosing as follows: 0.75 mg/kg if <60 kg, 45 mg if 60 to ≤100 kg, and 90 mg if >100 kg. • Biologics may be safely combined with topical corticosteroids, with or without a vitamin D analogue, to augment effectiveness for the treatment of moderate to severe plaque psoriasis. • The major risk for biologics in children is injection site reaction, but patients should be monitored for their increased risk of infection.
Centers for Disease Control and Prevention: **Sexually Transmitted Diseases Treatment Guidelines (2022)**[39-41]	Genital herpes • Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management. • Systemic antiviral drugs can partially control the signs and symptoms of herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy. • Systemic antiviral drugs do not eradicate latent virus or affect the risk, frequency, or severity of recurrences after the drug is discontinued. • Randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes. • Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability. • Topical therapy with antiviral drugs provides minimal clinical benefit, and

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	use is discouraged. • Newly acquired genital herpes can cause prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even patients with first episode herpes who have mild clinical manifestations initially can develop severe or prolonged symptoms. Therefore, all patients with first episodes of genital herpes should receive antiviral therapy. • Recommended regimens for first episodes of genital herpes: o acyclovir 400 mg orally three times daily for seven to 10 days o famciclovir 250 mg orally three times daily for seven to 10 days o valacyclovir 1,000 mg orally twice daily for seven to 10 days. • Treatment can be extended if healing is incomplete after 10 days of therapy. • Acyclovir 200 mg orally five times daily is also effective but is not recommended because of frequency of dosing. • Almost all patients with symptomatic first episode genital herpes simplex virus (HSV)-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection. • Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Suppressive therapy may be preferred because of the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners. • Long-term safety and efficacy have been documented among patients receiving daily acyclovir, valacyclovir, and famciclovir. • Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment. • Providers should discuss with patients on an annual basis whether they want to continue suppressive therapy because frequency of genital HSV-2 recurrence diminishes over time for many persons. • Discordant heterosexual couples in which a partner has a history of genital HSV-2 infection should be encouraged to consider suppressive antiviral therapy as part of a strategy for preventing transmission, in addition to consistent condom use and avoidance of sexual activity during recurrences. Suppressive antiviral therapy for persons with a history of symptomatic genital herpes also is likely to reduce transmission when used by those who have multiple partners. • Recommended regimens for suppressive therapy of genital herpes: o acyclovir 400 mg orally twice daily o famciclovir 250 mg orally twice daily o valacyclovir 500 mg orally once daily o valacyclovir 1,000 mg orally once daily. • Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens for persons who have frequent recurrences (i.e., ≥10 episodes/year). • Acyclovir, famciclovir and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding. Ease of administration and cost also are important to consider when deciding on prolonged treatment. • Because of the decreased risk for recurrences and shedding, suppressive therapy for HSV-1 genital herpes should be reserved for those with frequent recurrences through shared clinical decision-making between the patient and the provider. • Episodic treatment of recurrent herpes is most effective if initiation of therapy within one day of lesion onset or during the prodrome that precedes some outbreaks. Patients should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when

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	symptoms begin. • Recommended regimens for episodic treatment of recurrent HSV-2 genital herpes: o acyclovir 800 mg orally twice daily for five days o acyclovir 800 mg orally three times daily for two days o famciclovir 1,000 mg orally twice daily for one day o famciclovir 500 mg orally once; followed by 250 mg orally twice daily for two days o famciclovir 125 mg orally twice daily for five days o valacyclovir 500 mg orally twice daily for three days o valacyclovir 1,000 mg orally once daily for five days. • Acyclovir 400 mg orally three times daily is also effective but is not recommended because of frequency of dosing. • Intravenous acyclovir should be provided to patients with severe HSV disease or complications that necessitate hospitalization or central nervous system complications. • HSV-2 meningitis is characterized clinically by signs of headache, photophobia, fever, meningismus, and cerebrospinal fluid (CSF) lymphocytic pleocytosis, accompanied by mildly elevated protein and normal glucose. • Optimal therapies for HSV-2 meningitis have not been well studied; however, acyclovir 5 to 10 mg/kg body weight IV every 8 hours until clinical improvement is observed, followed by high-dose oral antiviral therapy (valacyclovir 1 g 3 times/day) to complete a 10- to 14-day course of total therapy, is recommended. • Hepatitis is a rare manifestation of disseminated HSV infection, often reported among pregnant women who acquire HSV during pregnancy. Among pregnant women with fever and unexplained severe hepatitis, disseminated HSV infection should be considered, and empiric IV acyclovir should be initiated pending confirmation. • Consistent and correct condom use has been reported in multiple studies to decrease, but not eliminate, the risk for HSV-2 transmission from men to women. Condoms are less effective for preventing transmission from women to men. • Randomized clinical trials have demonstrated that PrEP with daily oral tenofovir disoproxil fumarate/emtricitabine decreases the risk for HSV-2 acquisition by 30% in heterosexual partnerships. Pericoital intravaginal tenofovir 1% gel also decreases the risk for HSV-2 acquisition among heterosexual women. • The patients who have genital herpes and their sex partners can benefit from evaluation and counseling to help them cope with the infection and prevent sexual and perinatal transmission. • Lesions caused by HSV are common among persons with human immunodeficiency virus (HIV) infection and might be severe, painful, and atypical. HSV shedding is increased among persons with HIV infection. • Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV infection among persons with HIV. • Recommended regimens for daily suppressive therapy of genital herpes in patients infected with HIV: o acyclovir 400 to 800 mg orally two to three times daily o famciclovir 500 mg orally twice daily o valacyclovir 500 mg orally twice daily • Recommended regimens for episodic treatment of genital herpes in patients infected with HIV: o acyclovir 400 mg orally three times daily for five to 10 days

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	○ famciclovir 500 mg orally twice daily for five to 10 days ○ valacyclovir 1,000 mg orally twice daily for five to 10 days • If lesions persist or recur in a patient receiving antiviral treatment, acyclovir resistance should be suspected, and a viral culture obtained for phenotypic sensitivity testing. • Foscarnet (40 to 80 mg/kg body weight IV every 8 hours until clinical resolution is attained) is the treatment of choice for acyclovir-resistant genital herpes. Intravenous cidofovir 5 mg/kg body weight once weekly might also be effective. • Imiquimod 5% applied to the lesion for 8 hours 3 times/week until clinical resolution is an alternative that has been reported to be effective. • Acyclovir can be administered orally to pregnant women with first-episode genital herpes or recurrent herpes and should be administered IV to pregnant women with severe HSV. • Suppressive acyclovir treatment starting at 36 weeks' gestation reduces the frequency of cesarean delivery among women who have recurrent genital herpes by diminishing the frequency of recurrences at term. However, such treatment might not protect against transmission to neonates in all cases. • Recommended regimen for suppression of recurrent genital herpes among pregnant women: ○ acyclovir 400 mg orally three times daily ○ valacyclovir 500 mg orally twice daily • Treatment recommended starting at 36 weeks' gestation. • Infants exposed to HSV during birth should be followed in consultation with a pediatric infectious disease specialist. • All newborn infants who have neonatal herpes should be promptly evaluated and treated with systemic acyclovir. The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 14 days if disease is limited to the skin and mucous membranes, or for 21 days for disseminated disease and disease involving the CNS. <u>Bacterial vaginosis</u> • Bacterial vaginosis (BV) is a highly prevalent condition and the most common cause of vaginal discharge worldwide. However, in a nationally representative survey, the majority of women with BV were asymptomatic. • Treatment for BV is recommended for women with symptoms. • Established benefits of therapy among nonpregnant women are to relieve vaginal symptoms and signs of infection and reduce the risk for acquiring *C. trachomatis, N. gonorrhoeae*, *T. vaginalis*, *M. genitalium*, HIV, HPV, and HSV-2. • Recommended regimens for bacterial vaginosis include: ○ Metronidazole 500 mg orally twice daily for seven days. ○ Metronidazole 0.75% gel 5 g intravaginally once daily for five days. ○ Clindamycin 2% cream 5 g intravaginally at bedtime for seven days. • Alternative regimens include: ○ Tinidazole 2 g orally once daily for two days. ○ Tinidazole 1 g orally once daily for five days. ○ Clindamycin 300 mg orally twice daily for seven days. ○ Clindamycin 100 mg ovules intravaginally once at bedtime for three days. ○ Secnidazole 2 g oral granules in a single dose • Clindamycin ovules use an oleaginous base that might weaken latex or rubber products (e.g., condoms and diaphragms). Use of such products within 72 hours after treatment with clindamycin ovules is not recommended.

Clinical Guideline	Recommendation(s)
	• Oral granules should be sprinkled onto unsweetened applesauce, yogurt, or pudding before ingestion. A glass of water can be taken after administration to aid in swallowing. • Using a different recommended treatment regimen can be considered for women who have a recurrence; however, retreatment with the same recommended regimen is an acceptable approach for treating persistent or recurrent BV after the first occurrence. • BV treatment is recommended for all symptomatic pregnant women because symptomatic BV has been associated with adverse pregnancy outcomes, including premature rupture of membranes, preterm birth, intra-amniotic infection, and postpartum endometritis. <u>Uncomplicated vulvovaginal candidiasis</u> • Uncomplicated vulvovaginal candidiasis is defined as sporadic or infrequent vulvovaginal candidiasis, mild to moderate vulvovaginal candidiasis, candidiasis likely to be *Candida albicans*, or candidiasis in non-immunocompromised women. • Short-course topical formulations (i.e., single dose and regimens of one to three days) effectively treat uncomplicated vulvovaginal candidiasis. • Treatment with azoles results in relief of symptoms and negative cultures in 80 to 90% of patients who complete therapy. • Recommended regimens include: o Butoconazole 2% cream 5 g single intravaginal application. o Clotrimazole 1% cream 5 g intravaginally daily for seven to 14 days. o Clotrimazole 2% cream 5 g intravaginally daily for three days. o Miconazole 2% cream 5 g intravaginally daily for seven days. o Miconazole 4% cream 5 g intravaginally daily for three days. o Miconazole 100 mg vaginal suppository one suppository daily for seven days. o Miconazole 200 mg vaginal suppository one suppository for three days. o Miconazole 1,200 mg vaginal suppository one suppository for one day. o Tioconazole 6.5% ointment 5 g single intravaginal application. o Terconazole 0.4% cream 5 g intravaginally daily for seven days. o Terconazole 0.8% cream 5 g intravaginally daily for three days. o Terconazole 80 mg vaginal suppository one suppository daily for three days. o Fluconazole 150 mg oral tablet in single dose. <u>Complicated vulvovaginal candidiasis</u> • Complicated vulvovaginal candidiasis is defined as recurrent vulvovaginal candidiasis, severe vulvovaginal candidiasis, non-albicans candidiasis, or candidiasis in women with diabetes, immunocompromising conditions, underlying immunodeficiency, or immunosuppressive therapy. • Most episodes of recurrent vulvovaginal candidiasis caused by *Candida albicans* respond well to short duration oral or topical azole therapy. • However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., seven to 14 days of topical therapy or a 100, 150, or 200 mg oral dose of fluconazole every third day for a total of three doses (day one, four, and seven) to attempt mycologic remission before initiating a maintenance antifungal regimen. • Recommended maintenance regimen is oral fluconazole (i.e., a 100-mg, 150-mg, or 200-mg dose) weekly for six months. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be

Clinical Guideline	Recommendation(s)
	considered. Severe vulvovaginal candidiasis • Severe vulvovaginal candidiasis is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy. • Either seven to 14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended. Non-albicans vulvovaginal candidiasis • The optimal treatment of non-albicans vulvovaginal candidiasis remains unknown. However, a longer duration of therapy (seven to 14 days) with a non-fluconazole azole drug (oral or topical) is recommended. • If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for three weeks. Genital warts • Treatment of anogenital warts should be guided by wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and provider experience. • There is no definitive evidence to suggest that any of the available treatments are superior to any other and no single treatment is ideal for all patients or all warts. • Because of uncertainty regarding the effect of treatment on future transmission of human papilloma virus and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution. • Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy. • In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment. • The treatment modality should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe. • Most genital warts respond within three months of therapy. • Recommended regimens for external anogenital warts (patient-applied): o Podofilox 0.5% solution or gel. o Imiquimod 3.75% or 5% cream. o Sinecatechins 15% ointment. • Recommended regimens (provider administered): o Cryotherapy with liquid nitrogen or cryoprobe. o Trichloroacetic acid or bichloracetic acid 80 to 90% solution o Surgical removal • Fewer data are available regarding the efficacy of alternative regimens for treating anogenital warts, which include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir. Shared clinical decision-making between the patient and provider regarding benefits and risks of these regimens should be provided. • Podophyllin resin is no longer a recommended regimen because of the number of safer regimens available, and severe systemic toxicity has been reported when podophyllin resin was applied to large areas of friable tissue and was not washed off within 4 hours. Cervical warts • For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade squamous intraepithelial lesion must be performed before

Clinical Guideline	Recommendation(s)

	treatment is initiated.
	• Management of exophytic cervical warts should include consultation with a specialist.
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution
	
	Vaginal warts
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution
	
	Urethral meatus warts
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal
	
	Intra-Anal warts
	• Management of intra-anal warts should include consultation with a colorectal specialist.
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal.
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution.

British Association for Sexual Health and Human Immunodeficiency Virus: **United Kingdom National Guideline on the Management of Anogenital Warts (2015)**[42]	Genital warts • Treatment choice depends on the morphology, number, and distribution of warts and patient preference. • Treatment decisions should be made after discussing the appropriate options with the patient, taking into account their preference and convenience. • The evidence base to direct first and second line treatments is not strong. • All treatments have significant failure and relapse rates. • Soft non-keratinized warts respond well to podophyllotoxin and trichloroacetic acid. • Keratinized lesions are better treated with physical ablative methods such as cryotherapy, excision, or electrocautery. • Imiquimod may be suitable for both keratinized and non-keratinized warts. • People with a small number of low volume warts, irrespective of type, can be treated with ablative therapy or topical treatment with podophyllotoxin from the outset. • Podophyllotoxin or Imiquimod are suitable for home treatment by patients. The patient should be given a demonstration on lesion finding and treatment application. • No treatment may be an option, as about 30% of patients will experience spontaneous clearance of warts over a period of up to six months. However, most patients seek treatment for the discomfort, anxiety, distress or the social unacceptability that warts cause. Intravaginal warts • Cryotherapy, electrosurgery and trichloroacetic acid are recommended treatments. Cervical warts • Cryotherapy, electrosurgery, trichloroacetic acid, laser ablation and excision are recommended treatments.

Clinical Guideline	Recommendation(s)
	Urethral meatus warts • If base of lesions seen, treatment with cryotherapy, electrosurgery, laser ablation, podophyllotoxin or imiquimod. • Lesions deeper in the urethra should be surgically ablated under direct vision. Intra-anal warts • Treatment options include trichloroacetic acid, cryotherapy, electrosurgery, and laser ablation.
British Association of Dermatologists: **Guidelines for the Management of Cutaneous Warts (2014)**[43]	• There are numerous treatments for warts, and whether used singly or in combination they often have little evidence base for their use. • Salicylic acid formulations are the most common preparation used in the treatment of viral warts. • There are many commercially available preparations, but there is limited information to enable comparisons to be made between products. • Comparisons between salicylic acid-containing paints, monotherapy with glutaraldehyde, fluorouracil, podophyllin, benzalkonium or liquid nitrogen cryotherapy, failed to find any preparation more effective than salicylic acid.

International Working Group on the Diabetic Foot: **Practical Guidelines on the Prevention and Management of Diabetic Foot Disease (2019)**[44]	Principles of ulcer treatment
	• Relief of pressure and protection of the ulcer.
	• Restoration of skin perfusion.
	• Treatment of infection.
	• Metabolic control and treatment of comorbidity.
	• Local ulcer care.
	  ○ Frequent wound inspection.
	  ○ Frequent wound debridement with scalpel.
	  ○ Control of exudate and maintenance of moist environment.
	  ○ Consideration of negative pressure therapy in postoperative wounds.
	  ○ Avoiding soaking feet as this may induce skin maceration.
	  ○ Consideration of systemic oxygen treatment as adjunctive treatment in ischemic ulcers that do not heal after four to six weeks despite revascularization.
	• The following treatments are not established in routine management:
	  ○ Biological active products (collagen, growth factors, bioengineered tissue) in neuropathic ulcers.
	  ○ Silver or other anti-microbial agents containing dressings.

Infectious Diseases Society of America: **Clinical Practice Guideline for the Diagnosis and Treatment of Diabetic Foot Infections (2012)**[45]	Wound care techniques and dressings
	• Diabetic patients with a foot wound should receive appropriate wound care, which usually consists of the following:
	  ○ Debridement, aimed at removing debris, eschar, and surrounding callus. Sharp (or surgical) methods are generally best, but mechanical, autolytic, or larval debridement techniques may be appropriate for some wounds.
	  ○ Redistribution of pressure off the wound to the entire weight-bearing surface of the foot ("off-loading"). While particularly important for plantar wounds, this is also necessary to relieve pressure caused by dressings, footwear, or ambulation to any surface of the wound.
	  ○ Selection of dressings that allow for moist wound healing and control excess exudation. The choice of dressing should be based on the size, depth, and nature of the ulcer (e.g., dry, exudative, purulent).
	• Using topical antimicrobials is not recommended for treating most clinically uninfected wounds.
	• No adjunctive therapy has been proven to improve resolution of infection, but for selected diabetic foot wounds that are slow to heal, clinicians might consider using bioengineered skin equivalents, growth factors, granulocyte colony-stimulating factors, hyperbaric oxygen therapy, or negative pressure wound therapy.

Clinical Guideline	Recommendation(s)
	• Platelet-derived growth factors (e.g., becaplermin): Although an initial study demonstrated benefit, subsequent investigations have not shown these treatments to improve healing, or they have been conducted in a fashion where the data cannot be interpreted in the context of routine care.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous skin and mucous membrane agents are noted in Tables 3 to 5. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Skin and Mucous Membrane Agents, Miscellaneous Single Entity Agents (Drugs A-C)[1-24]

Indication	Acitretin	Afamelanotide	Calcipotriene	Calcitriol	Collagenase
Psoriasis					
Treatment of plaque psoriasis			✔ *		
Treatment of mild to moderate plaque psoriasis				✔	
Treatment of severe psoriasis	✔				
Treatment of moderate to severe psoriasis of the scalp			✔ †		
Treatment of plaque psoriasis of the scalp and body			✔ ‡		
Wound Care					
Debriding chronic dermal ulcers and severely burned areas					✔
Increasing pain free light exposure in adult patients with a history of phototoxic reactions from erythropoietic protoporphyria		✔			

*Cream/ointment formulations.
†Solution formulation.
‡Foam formulation.

Table 4. FDA-Approved Indications for the Skin and Mucous Membrane Agents, Miscellaneous Single Entity Agents (Drugs I-P)[1-24]

Indication	Imiquimod	Nitroglycerin	Pimecrolimus	Podofilox	Podophyllum	Ruxolitinib	Sirolimus	Tacrolimus	Tazarotene
Cutaneous Lesions									
Treatment of actinic keratoses of the face and scalp	✔ *†								
Treatment of biopsy-confirmed, superficial basal cell carcinoma with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate	✔ *								
Dermatitis									
Second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in patients who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable			✔						

Indication	Imiquimod	Nitroglycerin	Pimecrolimus	Podofilox	Podophyllum	Ruxolitinib	Sirolimus	Tacrolimus	Tazarotene
Second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in patients who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable								✔	
Short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable						✔			
Warts									
Treatment of external genital and perianal warts	✔ *†			✔ ‡					
Removal of soft genital warts					✔				
Treatment of external genital warts				✔ §					
Miscellaneous									
Treatment of facial angiofibroma associated with tuberous sclerosis in adults and pediatric patients six years of age and older							✔		
Treatment of moderate to severe pain associated with chronic anal fissure		✔							
Treatment of plaque psoriasis									✔ ‖¶
Treatment of acne vulgaris									✔ ¶
Treatment of nonsegmental vitiligo						✔			

*5% formulation.
†3.75% formulation.
‡Gel formulation.
§Solution formulation.
‖0.05% formulation.
¶0.1% formulation.

Table 5. FDA-Approved Indications for the Skin and Mucous Membrane Agents, Miscellaneous Combination Agents[1-24]

Indication	Calcipotriene and Betamethasone	Halobetasol Propionate and Tazarotene
Psoriasis		
Treatment of plaque psoriasis	✔ *	✔
Treatment of plaque psoriasis of the scalp and body	✔ †	

*Ointment formulations.
†Suspension formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous skin and mucous membrane agents are listed in Table 6.

Table 6. Pharmacokinetic Parameters of the Skin and Mucous Membrane Agents, Miscellaneous[2,22]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life
Single Entity Agents					
Acitretin	59	>99	Liver	Feces (16 to 53), Renal (34 to 54)	49 hours
Afamelanotide	Not reported	Not reported	Not reported	Not reported	15 hours
Calcipotriene	Minimal to 6	Not reported	Liver	Bile	Not reported
Calcitriol	Not reported	Not reported	Kidney	Renal	5 to 8 hours
Collagenase	Not reported	Not reported	Not reported	Not reported	Not reported
Imiquimod	Minimal	Not reported	Not reported	Renal (0.08 to 2.41)	20 to 24 hours
Nitroglycerin	50	60	Liver	Not reported	3 minutes
Pimecrolimus	Minimal	Not reported	Liver	Feces (79)	Not reported
Podofilox	Not reported	Not reported	Not reported	Not reported	1 to 5 hours
Podophyllum resin	Not reported	Not reported	Not reported	Not reported	Not reported
Ruxolitinib	Not reported	97	Liver	Renal (74), Feces (22)	116 hours
Sirolimus	Not reported	Not reported	Not reported	Fecal (91), Renal (2.2)	Not reported
Tacrolimus	Minimal	99	Liver	Renal, Bile	71 to 112 hours
Tazarotene	2 to 3	>99	Liver	Bile	18 hours
Combination Products					
Calcipotriene and betamethasone	Minimal	Not reported	Liver	Not reported	Not reported
Halobetasol propionate and tazarotene	Not reported	Not reported	Not reported	Not reported	Not reported

V. Drug Interactions

Major drug interactions with the miscellaneous skin and mucous membrane agents are listed in Table 7.

Table 7. Major Drug Interactions with the Skin and Mucous Membrane Agents, Miscellaneous[2]

Generic Name(s)	Interaction	Mechanism
Acitretin	Tetracyclines	Concurrent administration may increase the risk for development of pseudotumor cerebri (benign intracranial hypertension).
Nitroglycerin	Phosphodiesterase-5 Inhibitors	Concurrent administration may result in potentiation of hypotensive effects.
Sirolimus	CYP3A4 inhibitors	Concomitant use of sirolimus topical gel with inhibitors of CYP3A4 has the potential to increase the systemic exposure of sirolimus and increase the risk of sirolimus topical gel adverse reactions.

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous skin and mucous membrane agents are listed in Tables 8 to 10. The boxed warnings for the miscellaneous skin and mucous membrane agents are listed in Tables 11 to 16.

Table 8. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Agents, Miscellaneous Single Entity Agents (Drugs A-C)[1]

Adverse Events	Acitretin	Afamelanotide	Calcipotriene	Calcitriol	Collagenase
Cardiovascular					
Capillary leak syndrome	<1	-	-	-	-
Chest pain	<1	-	-	-	-
Cyanosis	<1	-	-	-	-
Flushing	1 to 10	-	-	-	-
Increased bleeding time	<1	-	-	-	-
Myocardial infarction	<1	-	-	-	-
Peripheral ischemia	<1	-	-	-	-
Thromboembolism	<1	-	-	-	-
Central Nervous System					
Abnormal gait	<1	-	-	-	-
Aggressive behavior	<1	-	-	-	-
Anxiety	<1	-	-	-	-
Bell's palsy	1 to 10	-	-	-	-
Cerebrovascular accident	<1	-	-	-	-
Depression	1 to 10	-	-	-	-
Dizziness	<1	4	-	-	-
Drowsiness	1 to 10	2	-	-	-
Fatigue	1 to 10	6	-	-	-
Fever	<1	-	-	-	-
Headache	1 to 10	-	-	-	-
Hyperesthesia	10 to 25	-	-	-	-
Hypertonia	1 to 10	-	-	-	-
Insomnia	1 to 10	-	-	-	-
Intermittent claudication	<1	-	-	-	-
Migraine	<1	-	-	-	-
Nervousness	<1	-	-	-	-
Neuritis	<1	-	-	-	-
Pain	1 to 10	-	-	-	-
Paresthesia	10 to 25	-	-	-	-
Pseudotumor cerebri	<1	-	-	-	-
Rigors	10 to 25	-	-	-	-

Adverse Events	Acitretin	Afamelanotide	Calcipotriene	Calcitriol	Collagenase
Somnolence	<1	2	-	-	-
Suicidal ideation	<1	-	-	-	-
Dermatological					
Abnormal hair texture	1 to 10	-	-	-	-
Abnormal skin odor	1 to 10	-	-	-	-
Acne	<1	-	-	-	-
Acquired cutaneous adherence	10 to 25	-	-	-	-
Alopecia	50 to 75	-	-	-	-
Bullous eruption	1 to 10	-	-	-	-
Burning	-	-	≤23	✔	-
Cheilitis	>75	-	-	-	-
Cold/clammy skin	1 to 10	-	-	-	✔
Dermatitis	1 to 10	-	1 to 10	✔	-
Dry skin	25 to 50	-	1 to 10	-	-
Eczema	<1	-	-	-	-
Edema	1 to 10	-	-	-	-
Epidermal thinning	<1	-	-	-	-
Erythema	10 to 25	-	1 to 10	✔	-
Erythroderma	<1	-	-	-	-
Exfoliation	50 to 75	-	✔	-	-
Exfoliative dermatitis	<1	-	-	-	-
Fissure	1 to 10	-	-	-	-
Folliculitis	-	-	<1	-	-
Fragile skin	<1	-	-	-	-
Fungal dermatitis	<1	-	-	-	-
Furunculosis	<1	-	-	-	-
Hair discoloration	<1	-	-	-	-
Herpes simplex	<1	-	-	-	-
Hyperesthesia	10 to 25	-	-	-	-
Hyperkeratosis	<1	-	-	-	-
Hyperpigmentation	-	4	<1	-	-
Hypertrichosis	<1	-	-	-	-
Hypoesthesia	<1	-	-	-	-
Impaired healing	<1	-	-	-	-
Implant site reaction	-	21	-	-	-
Irritation	-	2	1 to 15	-	✔
Madarosis	1 to 10	-	-	-	-
Mastalgia	<1	-	-	-	-
Melanocytic nevus	-	4	-	-	-
Nail disorder	25 to 50	-	-	-	-

Adverse Events	Acitretin	Afamelanotide	Calcipotriene	Calcitriol	Collagenase
Pain (local)	-	-	3	-	✔
Paronychia	10 to 25	-	-	-	-
Peeling	50 to 75	-	1 to 10	-	-
Photosensitivity	<1	-	✔	-	-
Pruritus	25 to 50	-	1 to 15	1 to 3	-
Psoriasis form rash	1 to 10	-	-	-	-
Purpura	1 to 10	-	-	-	-
Pyogenic granuloma	1 to 10	-	-	-	-
Rash	1 to 10	-	1 to 11	-	-
Scleroderma	<1	-	-	-	-
Seborrhea	1 to 10	-	-	-	-
Skin atrophy	10 to 25	-	<1	-	-
Skin discoloration	-	10	-	-	-
Skin discomfort	-	2	-	3	-
Skin disorder	1 to 10	-	-	-	-
Skin hypertrophy	<1	-	-	-	-
Skin inflammation	<1	-	-	-	-
Skin nodule	<1	-	-	-	-
Skin papilloma (warts)	<1	-	-	-	-
Skin stickiness	10 to 25	-	-	-	-
Stinging	-	-	≤23	-	-
Sunburn	1 to 10	-	-	-	-
Sweat gland disorder	<1	-	-	-	-
Sweating	1 to 10	-	-	-	-
Tingling	-	-	≤23	-	-
Urticaria	<1	-	✔	-	-
Verrucae	<1	-	-	-	-
Worsening of psoriasis	<1	-	1 to 10	-	-
Endocrine and Metabolic					
Acetonuria	10 to 25	-	-	-	-
Breast pain	<1	-	-	-	-
Decreased high-density lipoprotein	25 to 50	-	-	-	-
Decreased serum albumin	1 to 10	-	-	-	-
Decreased serum calcium	1 to 10	-	-	-	-
Decreased serum glucose	10 to 25	-	-	-	-
Decreased serum iron	1 to 10	-	-	-	-
Decreased serum magnesium	10 to 25	-	-	-	-
Decreased serum potassium	1 to 10	-	-	-	-
Decreased serum sodium	1 to 10	-	-	-	-
Glycosuria	1 to 10	-	-	-	-
Hot flashes	1 to 10	-	-	-	-

Adverse Events	Acitretin	Afamelanotide	Calcipotriene	Calcitriol	Collagenase
Hypercalcemia	1 to 10	-	<1	≤24	-
Hyperchloremia	1 to 10	-	-	-	-
Hypermagnesemia	10 to 25	-	-	-	-
Hyperphosphatemia	10 to 25	-	-	-	-
Hypochloremia	1 to 10	-	-	-	-
Hypophosphatemia	1 to 10	-	-	-	-
Increased cholesterol	25 to 50	-	-	-	-
Increased serum albumin	1 to 10	-	-	-	-
Increased serum calcium	1 to 10	-	-	-	-
Increased serum glucose	25 to 50	-	-	-	-
Increased serum iron	1 to 10	-	-	-	-
Increased serum potassium	10 to 25	-	-	-	-
Increased serum sodium	10 to 25	-	-	-	-
Increased triglycerides	50 to 75	-	-	-	-
Increased uric acid	10 to 25	-	-	-	-
Jaundice	<1	-	-	-	-
Pancreatitis	<1	-	-	-	-
Polydipsia	1 to 10	-	-	-	-
Porphyria	-	2	-	-	-
Weight gain	<1	-	-	-	-
Gastrointestinal					
Abdominal pain	1 to 10	-	-	-	-
Altered saliva	<1	-	-	-	-
Anal disorder	<1	-	-	-	-
Anorexia	1 to 10	-	-	-	-
Constipation	<1	-	-	-	-
Diarrhea	1 to 10	-	-	-	-
Dyspepsia	<1	-	-	-	-
Esophagitis	<1	-	-	-	-
Gastritis	<1	-	-	-	-
Gastroenteritis	<1	-	-	-	-
Gingival bleeding	1 to 10	-	-	-	-
Gingivitis	1 to 10	-	-	-	-
Glossitis	<1	-	-	-	-
Gum hyperplasia	<1	-	-	-	-
Hemorrhoids	<1	-	-	-	-
Increased appetite	1 to 10	-	-	-	-
Melena	<1	-	-	-	-
Nausea	1 to 10	19	-	-	-
Stomatitis	1 to 10	-	-	-	-
Taste loss/perversion	1 to 10	-	-	-	-

Adverse Events	Acitretin	Afamelanotide	Calcipotriene	Calcitriol	Collagenase
Tenesmus	<1	-	-	-	-
Tongue disorder	1 to 10	-	-	-	-
Tongue ulceration	<1	-	-	-	-
Ulcerative stomatitis	1 to 10	-	-	-	-
Xerostomia	10 to 25	-	-	-	-
Genitourinary					
Abnormal urine	<1	-	-	-	-
Atrophic vaginitis	<1	-	-	-	-
Dysuria	<1	-	-	-	-
Erythrocyturia	10 to 25	-	-	-	-
Hematuria	10 to 25	-	-	-	-
Hypercalciuria	-	-	-	3	-
Kidney stones	-	-	-	✔	-
Leukorrhea	<1	-	-	-	-
Libido alterations	<1	-	-	-	-
Proteinuria	1 to 10	-	-	-	-
Urine abnormality	-	-	-	4	-
Vaginal moniliasis	<1	-	-	-	-
Vulvovaginitis	<1	-	-	-	-
Hematologic					
Change in RBC count	1 to 10	-	-	-	-
Change in WBC count	10 to 25	-	-	-	-
Decreased haptoglobin	1 to 10	-	-	-	-
Decreased hematocrit	10 to 25	-	-	-	-
Decreased hemoglobin	10 to 25	-	-	-	-
Increased blood urea nitrogen	1 to 10	-	-	-	-
Increased haptoglobin	10 to 25	-	-	-	-
Increased hematocrit	1 to 10	-	-	-	-
Increased hemoglobin	1 to 10	-	-	-	-
Increased serum creatinine	1 to 10	-	-	-	-
Leukocyturia	25 to 50	-	-	-	-
Neutropenia	1 to 10	-	-	-	-
Neutrophilia	10 to 25	-	-	-	-
Reticulocytopenia	1 to 10	-	-	-	-
Reticulocytosis	25 to 50	-	-	-	-
Thrombocytosis	✔	-	-	-	-
Hepatic					
Cirrhosis	<1	-	-	-	-
Hepatitis	<1	-	-	-	-
Increased alanine aminotransferase	25 to 50	-	-	-	-

Adverse Events	Acitretin	Afamelanotide	Calcipotriene	Calcitriol	Collagenase
Increased alkaline phosphatase	10 to 25	-	-	-	-
Increased aspartate aminotransferase	25 to 50	-	-	-	-
Increased direct serum bilirubin	1 to 25	-	-	-	-
Increased gamma-glutamyltransferase	10 to 25	-	-	-	-
Increased lactate dehydrogenase	✔	-	-	-	-
Musculoskeletal					
Arthralgia	10 to 25	-	-	-	-
Arthritis	1 to 10	-	-	-	-
Arthrosis	1 to 10	-	-	-	-
Back pain	1 to 10	-	-	-	-
Bone disorder	<1	-	-	-	-
Bursitis	<1	-	-	-	-
Hypertonia	1 to 10	-	-	-	-
Increased creatine phosphokinase	25 to 50	-	-	-	-
Myalgia	1 to 10	-	-	-	-
Myasthenia	<1	-	-	-	-
Myopathy	<1	-	-	-	-
Osteoarthritis	1 to 10	-	-	-	-
Osteodynia	1 to 10	-	-	-	-
Spinal/peripheral joint hyperostosis	1 to 25	-	-	-	-
Tendonitis	<1	-	-	-	-
Respiratory					
Cough	<1	6	-	-	-
Increased bronchial secretions	<1	-	-	-	-
Laryngitis	<1	-	-	-	-
Pharyngitis	<1	7	-	-	-
Rhinitis	25 to 50	-	-	-	-
Sinusitis	1 to 10	-	-	-	-
Special Senses					
Abnormal vision	1 to 10	-	-	-	-
Blepharitis	1 to 10	-	-	-	-
Cataract	1 to 10	-	-	-	-
Conjunctival hemorrhage	<1	-	-	-	-
Conjunctivitis	1 to 10	-	-	-	-
Corneal epithelial abnormality	1 to 10	-	-	-	-
Corneal lesion	<1	-	-	-	-
Corneal ulceration	<1	-	-	-	-
Deafness	<1	-	-	-	-
Decreased night vision/ blindness	1 to 10	-	-	-	-
Diplopia	<1	-	-	-	-
Ear pain	1 to 10	-	-	-	-

Adverse Events	Acitretin	Afamelanotide	Calcipotriene	Calcitriol	Collagenase
Ectropion	<1	-	-	-	-
Epithelial keratopathy	1 to 10	-	-	-	-
Eye pain	1 to 10	-	-	-	-
Eye pruritus	<1	-	-	-	-
Hordeolum	<1	-	-	-	-
Increased cerumen production	<1	-	-	-	-
Lacrimation	<1	-	-	-	-
Nocturnal amblyopia	1 to 10	-	-	-	-
Otitis media	<1	-	-	-	-
Papilledema	<1	-	-	-	-
Photophobia	1 to 10	-	-	-	-
Tinnitus	1 to 10	-	-	-	-
Xerophthalmia	10 to 25	-	-	-	-
Other					
Alcohol intolerance	<1	-	-	-	-
Angioedema	<1	-	-	-	-
Birth defect	✔	-	-	-	-
Candidiasis	<1	-	-	-	-
Ceruminosis	<1	-	-	-	-
Chalazion	<1	-	-	-	-
Cheilitis	>75	-	-	-	-
Cyst	<1	-	-	-	-
Epistaxis	10 to 25	-	-	-	-
Fatigue	1 to 10	-	-	-	-
Flu symptoms	<1	-	-	-	-
Fungal infection	<1	-	-	-	-
Hemorrhage	<1	-	-	-	-
Hot flashes	1 to 10	-	-	-	-
Hypersensitivity	<1	-	✔	-	<1
Infection	1 to 10	4	-	-	-
Increased saliva	1 to 10	-	-	-	-
Malaise	<1	-	-	-	-
Thirst	1 to 10	-	-	-	-
Voice disorder	<1	-	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 9. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Agents, Miscellaneous Single Entity Agents (Drugs I-T)[1]

Adverse Events	Imiquimod	Nitroglycerin	Pimecrolimus	Podofilox	Podophyllum Resin	Ruxolitinib	Sirolimus	Tacrolimus	Tazarotene
Cardiovascular									
Arrhythmias	✔	-	-	-	-	-	-	-	-
Atrial fibrillation	1	-	-	-	-	-	-	-	-
Bradycardia	-	✔	-	-	-	-	-	-	-
Capillary leak syndrome	✔	-	-	-	-	-	-	-	-
Cardiac failure	✔	-	-	-	-	-	-	-	-
Cardiomyopathy	✔	-	-	-	-	-	-	-	-
Chest pain	1 to 10	-	-	-	-	-	-	<1	-
Hypertension	-	-	-	-	-	-	-	1	-
Hypotension	-	≤4	-	-	-	-	-	-	-
Ischemia	✔	-	-	-	-	-	-	-	-
Myocardial infarction	✔	-	-	-	-	✔	-	-	-
Orthostatic hypotension	-	✔	-	-	-	-	-	-	-
Palpitations	✔		-	-	-	-	-	-	-
Peripheral edema	-	-	-	-	-	-	-	3 to 4	1 to 10
Pulmonary edema	✔	-	-	-	-	-	-	-	-
Syncope	✔	≤4	-	-	-	-	-	<1	-
Tachycardia	✔	-	-	-	-	-	-	<1	-
Thrombosis	-	-	-	-	-	✔	-	-	-
Valvular heart disease	-	-	-	-	-	-	-	<1	-
Vasodilation	-	-	-	-	-	-	-	<1	-
Central Nervous System									
Abnormal thinking	-	-	-	-	-	-	-	<1	-
Agitation	✔	-	-	-	-	-	-	-	-
Anxiety	1 to 10	-	-	-	-	-	-	<1	-
Asthenia	-	-	-	-	-	-	-	1 to 3	-
Cerebrovascular accident	✔	-	-	-	-	✔	-	-	-
Chills	✔	-	-	-	-	-	-	<1	-
Coma	-	-	-	-	✔	-	-	-	-
Convulsions	✔	-	-	-	-	-	-	-	-
Depression	✔	-	-	-	-	-	-	1 to 2	-
Dizziness	<1 to 3	>2 to 6	-	<1	-	-	-	<1	-
Fatigue	1 to 4	-	-	-	-	-	-	-	-
Fever	≤3	-	1 to 13	-	✔	<1	-	1 to 21	-
Headache	2 to 6	50 to 64	7 to 25	7	-	-	-	1 to 20	-
Hyperesthesia	-	-	-	-	-	-	-	1 to 7	-

Adverse Events	Imiquimod	Nitroglycerin	Pimecrolimus	Podofilox	Podophyllum Resin	Ruxolitinib	Sirolimus	Tacrolimus	Tazarotene
Hypertonia	-	-	-	-	-	-	-	<1	-
Insomnia	✔	-	-	<1	-	-	-	1 to 4	-
Malaise	-	-	-	-	-	-	-	<1	-
Migraine	-	-	-	-	-	-	-	<1	-
Multiple sclerosis aggravation	✔	-	-	-	-	-	-	-	-
Paresthesia	-	>2	-	-	✔	-	-	1 to 3	-
Polyneuritis	-	-	-	-	✔	-	-	-	-
Rigors	1	-	-	-	-	-	-	-	-
Seizure	-	-	-	-	-	-	-	<1	-
Suicide	✔	-	-	-	-	-	-	-	-
Vertigo	-	-	-	-	-	-	-	<1	-
Dermatological									
Acne	-	-	≤2	-	-	<1	7	2 to 7	-
Acneiform dermatitis	-	-	-	-	-	-	3	-	-
Alopecia	✔	-	-	-	-	-	-	1	-
Bleeding	2 to 3	-	-	<1 to 19	-	-	-	-	1 to 10
Blistering	-	-	-	<1	-	-	-	-	<1
Burning	9 to 26	-	2 to 26	12 to 78	-	-	-	43 to 58	26
Cellulitis	✔	-	-	-	-	-	-	1	-
Chafing	-	-	-	<5	-	-	-	-	-
Cheilitis	-	-	-	-	-	-	-	-	1
Contact dermatitis	✔	<1	-	-	-	-	-	3 to 4	8
Cutaneous moniliasis	-	-	-	-	-	-	-	<1	-
Crusting	4 to 93	-	-	<1	-	-	-	-	-
Cyst	-	-	-	-	-	-	-	1 to 3	-
Desquamation	-	-	-	<1	-	-	-	-	<1 to 40
Discharge	22 to 51	-	-	-	-	-	-	-	-
Dry skin	-	-	-	<1	-	-	40	1	7 to 16
Ecchymosis	-	-	-	-	-	-	-	<1	-
Eczema	2	-	-	-	-	-	-	1 to 2	1 to 10
Eczema herpeticum	-	-	<1	-	-	-	-	1 to 2	-
Edema	1 to 78	-	-	<1	-	-	-	<1	<1
Erosion	30 to 66	-	-	9 to 67	-	-	-	-	-
Erythema	2 to 100	-	≤2	5	-	-	-	25 to 28	<1 to 34
Excoriation	18 to 26	-	-	-	-	-	-	-	-
Exfoliative dermatitis	✔	<1	-	-	-	-	-	1 to 3	<1
Facial edema	-	-	<1	-	-	-	-	1 to 2	-
Fissure	-	-	-	<1	-	-	-	-	1 to 10

Adverse Events	Imiquimod	Nitroglycerin	Pimecrolimus	Podofilox	Podophyllum Resin	Ruxolitinib	Sirolimus	Tacrolimus	Tazarotene
Flaking	1 to 93	-	-	-	-	-	-	-	-
Flushing	-	✔	<1	-	-	-	-	3 to 7	-
Folliculitis	-	-	1 to 6	-	-	1	-	2 to 6	-
Fungal dermatitis	-	-	-	-	-	-	-	1 to 2	-
Furunculosis	-	-	-	-	-	-	-	<1	-
Herpes simplex	≤3	-	≤4	-	-	-	-	3 to 4	-
Hyperesthesia	-	-	-	-	-	-	-	1 to 7	-
Hyperkeratosis	1 to 8	-	-	-	-	-	-	-	-
Hyperpigmentation	✔	-	-	-	-	-	-	-	-
Hypopigmentation	>1	-	-	-	-	-	-	-	-
Impetigo	-	-	4	-	-	-	-	<1	<1
Induration	2 to 84	-	-	-	-	-	-	-	-
Inflammation	-	-	-	9 to 71	-	-	-	-	1 to 10
Irritation	3 to 6	-	<1 to 6	-	-	-	37	-	10 to 14
Leukoderma	-	-	-	-	-	-	-	<1	-
Molluscum contagiosum	-	-	≤2	-	-	-	-	-	-
Nail disorder	-	-	-	-	-	-	-	<1	-
Necrosis	-	-	-	-	-	-	-	-	-
Pain	1 to 8	-	-	12 to 72	-	-	-	1 to 2	>10
Papules	2	-	-	-	-	-	-	-	-
Peeling	-	-	-	<5	-	-	-	-	-
Photosensitivity	1	-	-	-	-	-	-	<1	1
Pruritus	3 to 32	-	1 to 6	8 to 65	-	-	17	41 to 46	<1 to 10
Pustular vasculitis	44 to 56	-	-	-	-	-	-	-	-
Rash	>1	✔	-	<1	-	-	-	1 to 5	≤3
Rosacea	-	-	-	-	-	-	-	<1	-
Scabbing	4 to 86	-	-	✔	-	-	-	-	-
Scaling	84 to 93	-	-	-	-	-	-	-	-
Scarring	-	-	-	<5	-	-	-	-	-
Seborrhea	-	-	-	-	-	-	-	<1	-
Skin carcinoma	-	-	-	-	-	-	-	<1	-
Skin discoloration	-	-	<1	<1	-	-	-	<1	1 to 10
Skin disorder	-	-	-	-	-	-	-	1 to 4	-
Skin hemorrhage	-	-	-	-	-	-	3	-	-
Skin hypertrophy	-	-	-	-	-	-	-	<1	-
Skin infection	-	-	5 to 6	-	-	-	-	1 to 12	-
Skin papilloma (warts)	-	-	≤3	-	-	-	-	-	-
Skin sclerosis	5 to 84	-	-	-	-	-	-		
Skin ulcer	-	-	-	-	-	-	-	<1	-
Soreness	<3	-	-	✔	-	-	-	-	-

Adverse Events	Imiquimod	Nitroglycerin	Pimecrolimus	Podofilox	Podophyllum Resin	Ruxolitinib	Sirolimus	Tacrolimus	Tazarotene
Squamous carcinoma	4	-	-	-	-	-	-	-	-
Stinging	3	-	-	7	-	-	-	2 to 8	3
Sunburn	-	-	-	-	-	-	-	1 to 2	-
Sweating	-	✔	-	-	-	-	-	<1	-
Tenderness	1 to 2	-	-	<1	-	-	-	-	-
Tinea cruris	>1	-	-	-	-	-	-	-	-
Tingling	1 to 10	-	-	<1	-	-	-	1 to 8	-
Ulceration	4 to 62	-	-	<1		-		<1	-
Urticaria	✔	-	≤1	-	-	1	-	1 to 6	-
Vesicles	2 to 31	-	-	<5	-	-	-	-	-
Vesiculobullous dermatitis	-	-	-	-	-	-	-	1 to 4	-
Weeping/exudate	22	-	-	-	-	-	-	-	-
Worsening of psoriasis	✔	-	-	-	-	-	-	-	>10
Endocrine/Metabolic									
Dehydration	-	-	-	-	-	-	-	<1	-
Hypertriglyceridemia	-	-	-	-	-	-	-	-	1 to 10
Hypothyroidism	-	-	-	-	-	-	-	<1	-
Increased serum glucose	1 to 10	-	-	-	-	-	-	-	-
Thyroiditis	✔	-	-	-	-	-	-	-	-
Gastrointestinal									
Anorexia	≤3	-	-	-	-	-	-	<1	-
Abdominal pain	✔	-	≤3	-	-	-	-	1 to 3	-
Colitis	-	-	-	-	-	-	-	<1	-
Constipation	-	-	≤4	-	-	-	-	<1	-
Cramps	-	-	-	-	-	-	-	<1	-
Diarrhea	1 to 3	-	1 to 8	-	-	1	-	3 to 5	-
Dyspepsia	2 to 3	-	-	-	-	-	-	1 to 4	-
Gastritis	-	-	-	-	-	-	-	<1	-
Gastroenteritis	-	-	2 to ≤7	-	-	-	-	1 to 2	-
Hernia	-	-	-	-	-	-	-	<1	-
Mouth ulceration	-	-	-	-	-	-	-	<1	-
Oral moniliasis	-	-	-	-	-	-	-	<1	-
Nausea	1 to 4	-	1 to 2	-	-	-	-	1	-
Paralytic ileus	-	-	-	-	✔	-	-	-	-
Periodontal abscess	-	-	-	-	-	-	-	<1	-
Stomatitis	-	-	-	-	-	-	-	<1	-
Taste perversion	-	-	-	-	-	-	-	<1	-
Toothache	-	-	≤3	-	-	-	-	-	-
Tooth disorder	-	-	-	-	-	-	-	1 to 2	-
Vomiting	1	✔	1 to 4	<1	-	-	-	1	-

Adverse Events	Imiquimod	Nitroglycerin	Pimecrolimus	Podofilox	Podophyllum Resin	Ruxolitinib	Sirolimus	Tacrolimus	Tazarotene
Worsening of ulcerative colitis	✔	-	-	-	-	-	-	-	-
Genitourinary									
Acute renal failure	-	-	-	-	-	-	-	<1	-
Bacterial vaginosis	3	-	-	-	-	-	-	-	
Cystitis	-	-	-	-	-	-	-	<1	-
Dysmenorrhea	-	-	1 to 2	-	-	-	-	1 to 4	-
Dysuria	✔	-	-	-	-	-	-	-	-
Foreskin retraction	-	-	-	<5	-	-	-	-	-
Hematuria	-	-	-	<1	-	-	-	-	-
Moniliasis	-	-	-	-	-	-	-	<1	-
Pain with intercourse	-	-	-	<5	-	-	-	-	-
Proteinuria	✔	-	-	-	-	-	-	-	-
Urinary retention	✔	-	-	-	-	-	-	-	-
Urinary tract infection	1	-	-	-	-	-	-	1	-
Vaginal moniliasis	-	-	-	-	-	-	-	<1	-
Vaginitis	-	-	-	-	-	-	-	<1	-
Hematologic									
Anemia	✔	-	-	-	-	✔	-	<1	-
Bilirubinemia	-	-	-	-	-	-	-	<1	-
Ecchymosis	-	-	-	-	-	-	-	<1	-
Eosinophil count raised	-	-	-	-	-	1	-	-	-
Erythropenia	✔	-	-	-	-	-	-	-	-
Hyperbilirubinemia	-	-	-	-	-	-	-	<1	-
Hypercholesterolemia	-	-	-	-	-	-	-	<1	-
Leukopenia	✔	-	-	-	✔	-	-	-	-
Lymphadenopathy	2 to 3	-	-	-	-	-	-	1 to 3	-
Methemoglobinemia	-	✔	-	-	-	-	-	-	-
Pancytopenia	✔	-	-	-	-	-	-	-	-
Thrombocytopenia	✔	-	-	-	✔	✔	-	-	-
Musculoskeletal									
Arthralgia	1 to 3	-	≤2	-	-	-	-	1 to 3	-
Arthritis	-	-	-	-	-	-	-	<1	-
Arthrosis	-	-	-	-	-	-	-	<1	-
Back pain	1 to 4	-	≤2	-	-	-	-	1 to 2	-
Bone disorder	-	-	-	-	-	-	-	<1	-
Bursitis	-	-	-	-	-	-	-	<1	-
Joint disorder	-	-	-	-	-	-	-	<1	-
Myalgia	≥1	-	-	-	-	-	-	1 to 3	-
Neck disorder	-	-	-	-	-	-	-	<1	-
Tendon disorder	-	-	-	-	-	-	-	<1	-

Adverse Events	Imiquimod	Nitroglycerin	Pimecrolimus	Podofilox	Podophyllum Resin	Ruxolitinib	Sirolimus	Tacrolimus	Tazarotene
Vertebral disk disease	✔	-	-	-	-	-	-	-	-
Weakness	✔	-	-	-	-	-	-	1 to 3	-
Respiratory									
Asthma	-	-	3 to 4	-	-	-	-	1 to 6	-
Bronchitis	-	-	≤11	-	-	1	-	1 to 2	-
Cough	1 to 3	-	2 to 16	-	-	-	-	1 to 18	-
Dry mouth/nose	-	-	-	-	-	-	-	<1	-
Dyspnea	✔	≤2	≤2	-	-	-	-	<1	-
Epistaxis	-	-	≤3	-	-	-	-	<1	-
Laryngitis	-	-	-	-	-	-	-	<1	-
Lower respiratory infection	-	-	-	-	-	✔	-	-	-
Lung disorder	-	-	-	-	-	-	-	<1	-
Nasal congestion	-	-	1 to 3	-	-	-	-	-	-
Nasopharyngitis	-	-	8 to 27	-	-	3	-	-	-
Oral candidiasis	-	-	-	-	-	-	-	<1	-
Oral mucosa ulcer	-	-	-	-	-	-	-	<1	-
Pharyngitis	1 to 10	-	1 to 8	-	-	-	-	1 to 4	-
Pneumonia	-	-	≤2	-	-	-	-	1	-
Rhinitis	2 to 3	-	≤2	-	-	-	-	1 to 6	-
Rhinorrhea	-	-	≤2	-	-	1	-	-	-
Sinusitis	7	-	1 to 3	-	-	-	-	1 to 4	-
Upper respiratory infection	15 to 33	-	4 to 19	-	-	-	-	-	-
Wheezing	-	-	≤1	-	-	-	-	-	-
Special Senses									
Abnormal vision	-	-	-	-	-	-	-	<1	-
Blepharitis	-	-	-	-	-	-	-	<1	-
Cataract	-	-	-	-	-	-	-	<1	-
Conjunctival edema	-	-	-	-	-	-	-	<1	4
Conjunctivitis	3	-	≤2 to 3	-	-	<1	-	1 to 2	4
Dry eyes	-	-	-	-	-	-	-	<1	-
Ear disorder	-	-	-	-	-	-	-	<1	-
Ear infection	-	-	1 to 6	-	-	1	-	-	-
Ear pain	-	-	-	-	-	-	-	1	-
Eye infection	-	-	≤1	-	-	-	-	-	-
Eye irritation	-	-	<1	-	-	-	-	-	4
Eye pain	-	-	-	-	-	-	-	<1	-
Ocular hyperemia	-	-	-	-	-	-	3	-	-
Otitis externa	-	-	-	-	-	<1	-	<1	-
Otitis media	-	-	1 to 3	-	-	-	-	1 to 12	-
Seasonal allergy	-	-	-	-	-	<1	-	-	-

Adverse Events	Imiquimod	Nitroglycerin	Pimecrolimus	Podofilox	Podophyllum Resin	Ruxolitinib	Sirolimus	Tacrolimus	Tazarotene
Other									
Abscess	-	-	-	-	-	-	-	<1	-
Abnormal liver function	✔	-	-	-	-	-	-	-	-
Active tuberculosis	-	-	-	-	-	✔	-	-	-
Alcohol intolerance	-	-	-	-	-	-	-	3 to 7	-
Aggravated tooth caries	-	-	-	-	-	-	-	<1	-
Allergic reaction	-	-	-	-	-	-	-	4 to 12	-
Anaphylaxis	-	-	<1	-	-	-	-	<1	-
Angioedema	✔	-	-	-	-	-	-	-	-
Angioneurotic edema	-	-	<1	-	-	-	-	-	-
Bacterial infection	-	-	1 to 2	-	-	✔	-	-	-
Basal cell carcinoma	-	-	<1	-	-	✔	-	<1	-
Breast neoplasm benign	-	-	-	-	-	-	-	<1	-
Death	-	-	-	-	✔	-	-	-	-
Fixed drug eruption	-	<1	-	-	-	-	-	-	-
Flu symptoms	<1 to 4	-	≤2	-	-	-	-	23 to 31	-
Fungal infection	2 to 11	-	-	-	-	✔	-	<1	-
Hypersensitivity	-	<1	3 to 5	-	-	-	-	1 to 12	✔
Infection	1	-	-	-	-	✔	-	1 to 2	-
Influenza	-	-	3 to 11	-	-	-	-	-	-
Laceration	-	-	≤2	-	-	-	-	-	-
Lymphadenopathy	-	-	<1	-	-	-	-	1 to 3	-
Lymphoma	✔	-	<1	-	-	✔	-	<1	-
Malignant melanoma	-	-	<1	-	-	-	-	<1	-
Malignant neoplasm	-	-	-	-	-	✔	-	✔	-
Malodor	-	-	-	<1	-	-	-	-	-
Osteomyelitis	-	-	-	-	-	-	-	<1	-
Septicemia	-	-	-	-	-	-	-	<1	-
Skin neoplasm benign	-	-	-	-	-	-	-	1 to 2	-
Squamous cell carcinoma	4	-	<1	-	-	✔	-	<1	-
Tonsillitis	-	-	≤6	-	-	1	-	-	-
Varicella/herpes zoster	-	-	≤1	-	-	<1	-	1 to 5	-
Viral infection	1	-	≤7	-	-	✔	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 10. Adverse Drug Events (%) Reported with the Skin and Mucous Membrane Agents, Miscellaneous Combination Products[1]

Adverse Events	Calcipotriene and Betamethasone	Halobetasol Propionate and Tazarotene
Central Nervous System		
Headache	2	-
Dermatological		
Acne	<1	-
Application site pain	-	3
Atrophic striae	-	✔
Burning	1	-
Contact dermatitis	<1	7
Dermatitis	<1	-
Dry skin	<1	-
Ecchymoses	1	-
Erythema	≤2	-
Excoriation	-	2
Exfoliation	-	1
Exfoliative dermatitis	1	-
Facial edema	<1	-
Folliculitis	≤1	2
Hand dermatosis	1	-
Hyperpigmentation	<1	-
Hypopigmentation	<1	-
Irritation	≤1	-
Pain	<1	3
Photosensitivity	-	✔
Pruritus	4 to 7	-
Psoriasis	2 to 3	-
Rash	<1	1
Skin abrasion	-	1
Skin atrophy	<2	2
Skin pain	<1	-
Telangiectasia	<1	✔
Urticaria	<1	-
Worsening of psoriasis	<1	-
Endocrine/Metabolic		
HPA-axis suppression	3 to 23	✔
Hypercalcemia	<1	-
Genitourinary		
Hypercalciuria	<1	-
Respiratory		
Upper respiratory infection	7	-

Adverse Events	Calcipotriene and Betamethasone	Halobetasol Propionate and Tazarotene
Special Senses		
Eye irritation	<1	-
Otitis externa	<1	-

- Event not reported or incidence <1%.

Table 11. Boxed Warning for Acitretin[3]

WARNING

Acitretin causes birth defects. Female patients must not get pregnant.

Acitretin must not be used by females who are pregnant, or who intend to become pregnant during therapy or at any time for at least three years following discontinuation of therapy. Acitretin also must not be used by females who may not use reliable contraception while undergoing treatment or for at least three years following discontinuation of treatment. Acitretin is a metabolite of etretinate, and major human fetal abnormalities have been reported with the administration of etretinate and acitretin. Potentially, any fetus exposed can be affected.

Clinical evidence has shown that concurrent ingestion of acitretin and ethanol has been associated with the formation of etretinate, which has a longer elimination half-life than acitretin. Because the longer elimination half-life of etretinate would increase the duration of teratogenic potential for female patients, ethanol must not be ingested by female patients either during treatment with acitretin or for two months after cessation of therapy. This allows for elimination of acitretin, thus removing the substrate for transesterification to etretinate. The mechanism of the metabolic process for conversion of acitretin to etretinate has not been fully defined. It is not known whether substances other than ethanol are associated with transesterification.

Acitretin has been shown to be embryotoxic or teratogenic in rabbits, mice, and rats at doses of 0.6, 3.0, and 15.0 mg/kg, respectively. These doses are approximately 0.2, 0.3, and 3.0 times the maximum recommended therapeutic dose, respectively, based on a mg/m^2 comparison.

Major human fetal abnormalities associated with acitretin or etretinate administration have been reported including meningomyelocele, meningoencephalocele, multiple synostoses, facial dysmorphia, syndactylies, absence of terminal phalanges, malformations of hip, ankle and forearm, low set ears, high palate, decreased cranial volume, cardiovascular malformation, and alterations of the skull and cervical vertebrae.

Acitretin should be prescribed only by those who have special competence in the diagnosis and treatment of severe psoriasis, are experienced in the use of systemic retinoids, and understand the risk of teratogenicity.

Important information for women of childbearing potential:
Acitretin should be considered only for women with severe psoriasis unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments.

Females of reproductive potential must not be given a prescription for acitretin until pregnancy is excluded. Acitretin is contraindicated in females of reproductive potential unless the patient meets all of the following conditions:

- Must have had two negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial acitretin prescription. The

WARNING

first test (a screening test) is obtained by the prescriber when the decision is made to pursue acitretin therapy. The second pregnancy test (a confirmation test) should be done during the first five days of the menstrual period immediately preceding the beginning of acitretin therapy. For patients with amenorrhea, the second test should be done at least 11 days after the last act of unprotected sexual intercourse (without using two effective forms of contraception [birth control] simultaneously). Timing of pregnancy testing throughout the treatment course should be monthly or individualized based on the prescriber's clinical judgment.

- Must have selected and have committed to use two effective forms of contraception (birth control) simultaneously, at least one of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy or is clearly postmenopausal.
- Patients must use two effective forms of contraception (birth control) simultaneously for at least one month prior to initiation of acitretin therapy, during acitretin therapy, and for at least three years after discontinuing acitretin therapy. An acitretin patient referral form is available so that patients can receive an initial free contraceptive counseling session and pregnancy testing. Counseling about contraception and behaviors associated with an increased risk of pregnancy must be repeated on a regular basis by the prescriber. To encourage compliance with this recommendation, a limited supply of the drug should be prescribed. Effective forms of contraception include both primary and secondary forms of contraception. Primary forms of contraception include the following: Tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, and injectable/implantable/insertable/topical hormonal birth control products. Secondary forms of contraception include diaphragms, latex condoms, and cervical caps; each secondary form must be used with a spermicide. Any birth control method can fail. Therefore, it is critically important that women of childbearing potential use two effective forms of contraception (birth control) simultaneously. It has not been established if there is a pharmacokinetic interaction between acitretin and combined oral contraceptives. However, it has been established that acitretin interferes with the contraceptive effect of microdosed progestin preparations. Microdosed "minipill" progestin preparations are not recommended for use with acitretin. It is not known whether other progestational contraceptives, such as implants and injectables, are adequate methods of contraception during acitretin therapy. Prescribers are advised to consult the package insert of any medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products. Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's wort.
- Must have signed a Patient Agreement/Informed Consent for Female Patients that contains warnings about the risk of potential birth defects if the fetus is exposed to acitretin, about contraceptive failure, and about the fact that they must not ingest beverages or products containing ethanol while taking acitretin and for two months after acitretin treatment has been discontinued.

If pregnancy does occur during acitretin therapy or at any time for at least three years following discontinuation of acitretin therapy, the prescriber and patient should discuss the possible effects on the pregnancy. The available information is as follows:

Acitretin, the active metabolite of etretinate, is teratogenic and is contraindicated during pregnancy. The risk of severe fetal malformations is well established when systemic retinoids are taken during pregnancy. Pregnancy must also be prevented after stopping acitretin therapy, while the drug is being eliminated to below a threshold blood concentration that would be associated with an increased incidence of birth defects. Because this threshold has not been established for acitretin in humans and because elimination rates vary among patients, the duration of posttherapy contraception to achieve adequate elimination cannot be calculated precisely. It is strongly recommended that contraception be continued for at least three years after stopping treatment with acitretin, based on the following considerations:

- In the absence of transesterification to form etretinate, greater than 98% of the acitretin would be eliminated within two months, assuming a mean elimination half-life of 49 hours.

WARNING

- In cases where etretinate is formed, as has been demonstrated with concomitant administration of acitretin and ethanol, greater than 98% of the etretinate formed would be eliminated in two years, assuming a mean elimination half-life of 120 days, and greater than 98% of the etretinate formed would be eliminated in three years, based on the longest demonstrated elimination half-life of 168 days. However, etretinate was found in plasma and subcutaneous fat in one patient reported to have had sporadic alcohol intake, 52 months after she stopped acitretin therapy.
- Severe birth defects have been reported where conception occurred during the time interval when the patient was being treated with acitretin and/or etretinate. In addition, severe birth defects have also been reported when conception occurred after the mother completed therapy. These cases have been reported both prospectively (before the outcome was known) and retrospectively (after the outcome was known). The events below are listed without distinction as to whether the reported birth defects are consistent with retinoid-induced embryopathy or not.
- There have been 318 prospectively reported cases involving pregnancies and the use of etretinate, acitretin or both. In 238 of these cases, the conception occurred after the last dose of etretinate (103 cases), acitretin (126) or both (nine). Fetal outcome remained unknown in approximately one-half of these cases, of which 62 were terminated and 14 were spontaneous abortions. Fetal outcome is known for the other 118 cases and 15 of the outcomes were abnormal (including cases of absent hand/wrist, clubfoot, gastrointestinal malformation, hypocalcemia, hypotonia, limb malformation, neonatal apnea/anemia, neonatal ichthyosis, placental disorder/death, undescended testicle and five cases of premature birth). In the 126 prospectively reported cases where conception occurred after the last dose of acitretin only, 43 cases involved conception at least one year but less than two years after the last dose. There were three reports of abnormal outcomes out of these 43 cases (involving limb malformation, gastrointestinal tract malformations and premature birth). There were only four cases where conception occurred at least two years after the last dose but there were no reports of birth defects in these cases.
- There is also a total of 35 retrospectively reported cases where conception occurred at least one year after the last dose of etretinate, acitretin or both. From these cases there are three reports of birth defects when the conception occurred at least one year but less than two years after the last dose of acitretin (including heart malformations, Turner's Syndrome, and unspecified congenital malformations) and four reports of birth defects when conception occurred two or more years after the last dose of acitretin (including foot malformation, cardiac malformations [two cases] and unspecified neonatal and infancy disorder). There were three additional abnormal outcomes in cases where conception occurred two or more years after the last dose of etretinate (including chromosome disorder, forearm aplasia, and stillbirth).
- Females who have taken etretinate must continue to follow the contraceptive recommendations for etretinate. Etretinate is no longer marketed in the United States; for information, call the manufacturer at 1-800-526-6367.
- Patients should not donate blood during and for at least three years following the completion of acitretin therapy because women of childbearing potential must not receive blood from patients being treated with acitretin.

Important information for males taking acitretin:
Patients should not donate blood during and for at least three years following acitretin therapy because women of childbearing potential must not receive blood from patients being treated with acitretin.

Samples of seminal fluid from three male patients treated with acitretin and 6 male patients treated with etretinate have been assayed for the presence of acitretin. The maximum concentration of acitretin observed in the seminal fluid of these men was 12.5 ng/mL. Assuming an ejaculate volume of 10 mL, the amount of drug transferred in semen would be 125 ng, which is 1/200,000 of a single 25 mg capsule. Thus, although it appears that residual acitretin in seminal fluid poses little, if any, risk to a fetus while a male patient is taking the drug or after it is discontinued, the no-effect limit for teratogenicity is unknown and there is no registry for birth defects associated with acitretin. The available data are as follows:

There have been 25 cases of reported conception when the male partner was taking acitretin. The pregnancy outcome is known in 13 of these 25 cases. Of these,

WARNING
nine reports were retrospective and four were prospective (meaning the pregnancy was reported prior to knowledge of the outcome). • When acitretin treatment was given at time of conception, there were five deliveries of healthy neonates (four of five cases were prospective), five spontaneous abortions, and one induced abortion. • When acitretin was discontinued approximately four weeks prior to conception, there was one induced abortion (with malformation pattern not typical of retinoid embryopathy [bilateral cystic hygromas of neck, hypoplasia of lungs bilateral, pulmonary atresia, VSD with overriding truncus arteriosus]). • When acitretin was discontinued approximately six to eight months prior to conception, there was one spontaneous abortion. **For all patients:** An acitretin medication guide must be given to the patient each time acitretin is dispensed, as required by law. **Hepatotoxicity:** Of the 525 patients treated in United States clinical trials, two had clinical jaundice with elevated serum bilirubin and transaminases considered related to acitretin treatment. Liver function test results in these patients returned to normal after acitretin was discontinued. Two of the 1,289 patients treated in European clinical trials developed biopsy-confirmed toxic hepatitis. A second biopsy in one of these patients revealed nodule formation suggestive of cirrhosis. One patient in a Canadian clinical trial of 63 patients developed a three-fold increase of transaminases. A liver biopsy of this patient showed mild lobular disarray, multifocal hepatocyte loss and mild triaditis of the portal tracts compatible with acute reversible hepatic injury. The patient's transaminase levels returned to normal two months after acitretin was discontinued. The potential of acitretin therapy to induce hepatotoxicity was prospectively evaluated using liver biopsies in an open-label study of 128 patients. Pretreatment and posttreatment biopsies were available for 87 patients. A comparison of liver biopsy findings before and after therapy revealed 49 (58%) patients showed no change, 21 (25%) improved and 14 (17%) patients had a worsening of their liver biopsy status. For six patients, the classification changed from class 0 (no pathology) to class I (normal fatty infiltration; nuclear variability and portal inflammation; both mild); for seven patients, the change was from class I to class II (fatty infiltration, nuclear variability, portal inflammation and focal necrosis; all moderate to severe); and for one patient, the change was from class II to class IIIb (fibrosis, moderate to severe). No correlation could be found between liver function test result abnormalities and the change in liver biopsy status, and no cumulative dose relationship was found. Elevations of aspartate aminotransferase, alanine transaminase, gamma-glutamyl transpeptidase (gamma-glutamyl transpeptidase) or lactate dehydrogenase have occurred in approximately one in three patients treated with acitretin. Of the 525 patients treated in clinical trials in the United States, treatment was discontinued in 20 (3.8%) due to elevated liver function test results. If hepatotoxicity is suspected during treatment with acitretin, the drug should be discontinued and the etiology further investigated. Ten of 652 patients treated in United States clinical trials of etretinate, of which acitretin is the active metabolite, had clinical or histologic hepatitis considered to be possibly or probably related to etretinate treatment. There have been reports of hepatitis-related deaths worldwide; a few of these patients had received etretinate for one month or less before presenting with hepatic symptoms or signs.

Table 14. Boxed Warning for Ruxolitinib[23]

WARNING

WARNING
Serious Infections: Patients treated with oral Janus kinase inhibitors for inflammatory conditions are at risk for developing serious infections that may lead to hospitalization or death. Reported infections include: • Active tuberculosis, which may present with pulmonary or extrapulmonary disease. • Invasive fungal infections, including cryptococcosis, and pneumocystosis. • Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens. Avoid use of ruxolitinib in patients with an active, serious infection, including localized infections. If a serious infection develops, interrupt ruxolitinib until the infection is controlled. The risks and benefits of treatment with ruxolitinib should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with ruxolitinib. **Mortality:** In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing an oral JAK inhibitor to tumor necrosis factor (TNF) blocker treatment, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with the JAK inhibitor. **Malignancies:** Malignancies were reported in patients treated with ruxolitinib. Lymphoma and other malignancies have been observed in patients receiving JAK inhibitors used to treat inflammatory conditions. In RA patients treated with an oral JAK inhibitor, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC) was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. **Major Adverse Cardiovascular Events (MACE):** In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with an oral JAK inhibitor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue ruxolitinib in patients who have experienced a myocardial infarction or stroke. **Thrombosis:** Thromboembolic events were observed in trials with ruxolitinib. Thrombosis, including pulmonary embolism (PE), deep venous thrombosis (DVT), and arterial thrombosis have been reported in patients receiving JAK inhibitors used to treat inflammatory conditions. Many of these adverse reactions were serious and some resulted in death. In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with an oral JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid ruxolitinib in patients at risk. If symptoms of thrombosis occur, discontinue ruxolitinib and treat appropriately.

Table 15. Boxed Warning for Pimecrolimus[11]

WARNING
Long-term safety of topical calcineurin inhibitors has not been established.

WARNING
Although a causal relationship has not been established, rare cases of malignancy (e.g., skin malignancy, lymphoma) have been reported in patients treated with topical calcineurin inhibitors including pimecrolimus. Therefore, • Avoid continuous, long-term use of topical calcineurin inhibitors, including pimecrolimus, in any age group, and limit application to areas of involvement with atopic dermatitis. • Pimecrolimus is not indicated for use in children younger than two years of age.

Table 16. Boxed Warning for Tacrolimus[15]

WARNING
Long-term safety of topical calcineurin inhibitors has not been established. Although a causal relationship has not been established, rare cases of malignancy (i.e., skin cancer and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including tacrolimus ointment. Therefore: • Avoid continuous long-term use of topical calcineurin inhibitors, including tacrolimus ointment, in any age group, and limit application to areas of involvement with atopic dermatitis. • Tacrolimus ointment is not indicated for use in children younger than two years of age. Only tacrolimus 0.03% ointment is indicated for use in children two to 15 years of age.

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous skin and mucous membrane agents are listed in Table 17.

Table 17. Usual Dosing Regimens for the Skin and Mucous Membrane Agents, Miscellaneous[1-24]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Acitretin	Severe psoriasis: Capsule: 25 to 50 mg per day, given as a single dose with the main meal	Safety and efficacy in children have not been established.	Capsule: 10 mg 17.5 mg 25 mg
Afamelanotide	Erythropoietic protoporphyria – phototoxic dermatitis prophylaxis: Implant: 16 mg subcutaneously implanted above the anterior supra-iliac crest every two months	Safety and efficacy in children have not been established.	Implant: 16 mg
Calcipotriene	Plaque psoriasis: Cream: apply to the affected area twice daily Ointment: apply to the affected area one to two times daily Moderate to severe psoriasis of the scalp: Solution: apply to the affected scalp area twice daily Plaque psoriasis of the scalp and body: Foam: apply to the affected area twice daily	Plaque psoriasis of the scalp and body ≥12 years of age: Foam: apply to the affected area twice daily	Cream: 0.005% Foam: 0.005% Ointment: 0.005% Solution: 0.005%
Calcitriol	Mild to moderate plaque psoriasis: Ointment: apply to the affected area twice daily	Mild to moderate plaque psoriasis for individuals ≥2 years of age: Ointment: apply to the affected area twice daily	Ointment: 3 µg/g
Collagenase	Debriding chronic dermal ulcers and severely burned areas: Ointment: apply to the affected area once daily	Safety and efficacy in children have not been established.	Ointment: 250 units/g
Imiquimod	Actinic keratosis of the face and scalp: Cream 2.5 and 3.75%: apply up to two packets or full pump actuations to the affected area once daily before bedtime Cream 5%: apply to the affected area twice weekly before bedtime External genital and perianal warts: Cream 3.75%: apply up to one packet or pump actuation to the affected area once daily before bedtime Cream 5%: apply to the affected area three times per week before bedtime	External genital and perianal warts for individuals ≥12 years of age: Cream 3.75%: apply to the affected area once daily before bedtime Cream 5%: apply to the affected area before bedtime three times per week	Cream: 2.5% 3.75% 5%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Treatment of biopsy-confirmed, superficial basal cell carcinoma with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate: Cream 5%: apply to the affected area before bedtime five times per week		
Nitroglycerin	Moderate to severe pain associated with chronic anal fissure: Ointment: apply one inch of ointment every 12 hours	Safety and efficacy in children have not been established.	Rectal ointment: 0.4%
Pimecrolimus	Second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in patients who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable: Cream: apply to the affected area twice daily	Second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in patients who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable for individuals ≥2 years of age: Cream: apply to the affected area twice daily	Cream: 1%
Podofilox	External genital/perianal warts: Gel: apply twice daily for three consecutive days, then discontinue for four consecutive days; this one-week cycle of treatment may be repeated until there is no visible wart tissue or for a maximum of four cycles External genital warts: Solution: apply twice daily for three consecutive days, then discontinue for four consecutive days; this one-week cycle of treatment may be repeated until there is no visible wart tissue or for a maximum of four cycles	Safety and efficacy in children have not been established.	Gel: 0.5% Solution: 0.5%
Podophyllum resin	Removal of soft genital warts: Liquid: apply to the affected area for not more than one to four hours	Safety and efficacy in children have not been established.	Liquid: 25%
Ruxolitinib	Second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable: Cream: Apply twice daily to affected areas up to 20% of body surface area	Second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients who have failed to respond adequately to other topical prescription	Cream: 1.5%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Nonsegmental vitiligo: Cream: Apply twice daily to affected areas up to 10% of body surface area	treatments, or when those treatments are not advisable in individuals ≥12 years of age: Cream: Apply twice daily to affected areas up to 20% of body surface area Nonsegmental vitiligo in individuals ≥12 years of age: Cream: Apply twice daily to affected areas up to 10% of body surface area	
Sirolimus	Treatment of facial angiofibroma associated with tuberous sclerosis: Gel: Apply to the skin of the face affected with angiofibroma twice daily in the morning and at bedtime; maximum daily dose, 800 mg (2.5 cm)	Treatment of facial angiofibroma associated with tuberous sclerosis in pediatric patients 6 years of age and older: Gel: Apply to the skin of the face affected with angiofibroma twice daily in the morning and at bedtime; maximum daily dose, 600 mg (2 cm) for pediatric patients 6 to 11 years of age, 800 mg (2.5 cm) for pediatric patients 12 years of age and older	Gel: 0.2%
Tacrolimus	Second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in patients who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable: Ointment: apply to the affected area twice daily	Second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in patients who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable for individuals ≥2 years of age: Ointment (0.1% for patients ≥16 years of age, 0.03% for patients two to 15 years of age): apply to the affected area twice daily	Ointment: 0.03% 0.1%
Tazarotene	Acne vulgaris: 0.1% formulations: apply to the affected area once daily in the evening Plaque psoriasis: 0.05 and 0.1% formulations: apply to the affected area once daily in the evening	Acne vulgaris in individuals ≥12 years of age: 0.1% formulations: apply to the affected area once daily in the evening Plaque psoriasis in individuals ≥12 years of	Cream: 0.1% Foam: 0.1% Gel: 0.05% 0.1%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		age: Gel: apply to the affected area once daily in the evening	
Combination Products			
Calcipotriene and betamethasone	Plaque psoriasis: Foam, ointment: apply to the affected area once daily Plaque psoriasis of the scalp and body: Suspension: apply to the affected area once daily	Plaque psoriasis in individuals 12 to 17 years of age: Foam, ointment: apply to the affected area once daily Plaque psoriasis of the scalp in individuals 12 to 17 years of age: Suspension: apply to the affected area once daily	Foam: 0.005%-0.064% Ointment: 0.005%-0.064% Suspension: 0.005%-0.064%
Halobetasol propionate and tazarotene	Plaque psoriasis: Lotion: apply thin layer to the affected area once daily	Safety and efficacy in children have not been established.	Lotion: 0.01%-0.045%

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous skin and mucous membrane agents are summarized in Table 18.

Table 18. Comparative Clinical Trials with the Skin and Mucous Membrane Agents, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Actinic Keratosis				
Kose et al.[46] (2008) Imiquimod 5% cream applied three times per week vs diclofenac 3% gel applied QD	OL, RCT Patients with AK	N=49 12 weeks	Primary: Complete response according to IGII and PGII Secondary: Not reported	Primary: According to the IGII results, a complete response was observed in 12% of the diclofenac group and 22% of the imiquimod group (P>0.05). According to the PGII scores, a complete response was observed in 28% of the diclofenac group and 23% of the imiquimod group (P>0.05). Both treatments were well tolerated, with most adverse events related to skin. Secondary: Not reported
Tanghetti et al.[47] (2007) Imiquimod 5% cream applied two times per week for 16 weeks vs fluorouracil 5% cream applied BID for two to four weeks (5-FU)	MC, RCT, SB Patients >21 years of age with at least four AK lesions on the face, forehead, or scalp	N=39 24 weeks	Primary: Change in AK count, complete clearance, physician's global assessment, patient perception of efficacy, physician's assessment of erythema, and patient perception of discomfort associated with the treatment Secondary: Not reported	Primary: At week 24, the total AK count was reduced by 94% from baseline with 5-FU compared to 66% with imiquimod (P<0.05). Complete clearance of AKs was attained in a significantly greater proportion of patients in the 5-FU group than the imiquimod group by week 24 (84 vs 24%; P<0.01). Mean scores for the physician's global assessment showed that 5-FU resulted in significantly greater efficacy than imiquimod from week four through week 24. Patient ratings were similar and revealed consistently greater efficacy with 5-FU than with imiquimod. Physician assessments of erythema showed that mean levels were moderate in the 5-FU group at week four and decreased post-treatment to less than mild from week eight onward.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Mean levels of erythema in the imiquimod group remained at mild levels throughout the 16-week duration of treatment and did not decrease substantially until week 24. The patients' mean ratings of discomfort associated with treatment were less than "slightly painful" in both groups throughout the study. Secondary: Not reported
Jorizzo et al.[48] (2010) Imiquimod 3.75% cream applied QD for 2 two-week cycles vs placebo	DB, RCT Patients with ≥5 AKs on the face following cryosurgery	N=247 26 weeks	Primary: Complete clearance rates; adverse events Secondary: Not reported	Primary: Medial total AK reductions were 86.5% in the imiquimod group compared to 50% in the placebo group (P<0.0001). The proportion of patients with complete clearance was 30.2% in the imiquimod group compared to 3.3% in the placebo group (P<0.0001). One patient discontinued therapy for a treatment-related adverse event in the imiquimod group. Secondary: Not reported
Swanson et al.[49] (2010) Imiquimod 2.5% cream applied QD for 2 two-week cycles vs imiquimod 3.75% cream applied QD for 2 two-week cycles vs	MC, RCT (2 trials) Adults with 5 to 20 AK in an area >25 cm^2 on either the face or the balding scalp, but not both	N=479 Treatment: 2 two-week cycles Follow-up: 8 weeks	Primary: Complete clearance rate, partial clearance rates, percent change in AK number, IGIP score, safety Secondary: Not reported	Primary: Complete clearance rates, partial clearance rates, and percent reduction in AK lesions from baseline were all significant for imiquimod 2.5% and 3.75% compared to placebo. Efficacy for imiquimod 3.75% was numerically greater than that of imiquimod 2.5% for these outcomes, and statistically different at the visit for both partial clearance (P=0.047) and percent change in AK lesions from baseline (P=0.048). Complete clearance rates were 2.5% (95% CI, 0.3 to 8.7) and 10.1% (95% CI, 4.5 to 19.0) for placebo, 23.5% (95% CI, 14.8 to 34.2) and 38.0% (95% CI, 27.3 to 49.0%) for imiquimod 2.5%, and 25.9% (95% CI, 16.8 to 36.9) and 45.6% (95% CI, 34.3 to 57.2) for imiquimod 3.75%, respectively (P<0.001 for all vs placebo). There was a greater increase in mean IGIP scores, and a greater proportion of patients who were considered significantly or much improved, for both

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				imiquimod groups compared to placebo group, and for imiquimod 3.75% compared to 2.5%. There were 15 serious adverse events reported in 12 patients (two placebo, five imiquimod 2.5%, five imiquimod 3.75%). Only one serious adverse event, severe diarrhea in a patient in the imiquimod 3.75% group, was considered by the investigator to be probably related to study cream. Secondary: Not reported
Shaffelburg.[50] (2009) Imiquimod 5% cream applied two times per week vs placebo All patients were treated with PDT with aminolevulinic acid 20% at baseline and at month 1.	PC, RCT Adults with ≥10 AKs on the face	N=25 12 months	Primary: Clearance rates, adverse events Secondary: Not reported	Primary: At month 12, median lesion reductions were 89.9% with imiquimod compared to 74.5% with placebo (P=0.0023). No patient discontinued for an adverse event. Severe local skin reactions occurring in the most patients were erythema (17%) and flaking/scaling/dryness (13%). Secondary: Not reported
Lebwohl et al.[51] (2004) Imiquimod 5% cream applied QD two times per week vs	DB, MC, PC, RCT Patients ≥18 years of age with four to eight AK lesions with a contiguous 25 cm^2 treatment area on the face or balding scalp, but	N=436 Treatment: 16 weeks Follow-up: 8 weeks	Primary: Complete clearance rate Secondary: Partial clearance rate	Primary: The complete clearance rate was significantly higher in the imiquimod group (45.1%) compared to the placebo group (3.2%; P<0.001). Secondary: The partial clearance rate was significantly better in the imiquimod group compared to the placebo group (59.1 vs 11.8%, respectively; P<0.001). At the eight-week post-treatment visit, the median percent reduction in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	not both			number if AK lesions was 83.3% for the imiquimod group compared to 0% for the placebo group (half of the patients in the imiquimod group had at least an 83.3% reduction in the number of AK lesions). During the treatment period 48% of patients in the imiquimod group and 33% of patients in the placebo group had an increase in AK lesion count at one or more of the treatment visits. This was positively correlated with complete clearance rates- patients in the imiquimod group who experienced complete clearance had a higher rate of AK lesion counts during the treatment period. Complete clearance rates increased as the severity of erythema, edema, erosion/ulceration, weeping/exudate, and scabbing/crusting increased (P<0.05).
Stockfleth et al.[52] (2002) Imiquimod 5% cream applied QD three times per week vs placebo	DB, PC, RCT Patients 45 to 85 years of age with AK in a treatment area that did not exceed 20 cm^2	N=36 Treatment: 12 weeks Follow-up: 1 year	Primary: Clearance rates at the end of treatment and at 14 weeks, recurrence of AK lesions in patients treated with imiquimod one-year posttreatment Secondary: Not reported	Primary: In the imiquimod group, 84% of patients were recorded as having complete clearance of lesions (95% CI, 64 to 95; P<0.001compared to placebo group). In the imiquimod group, 8% (two patients) were recorded as having partial clearance (one had a reduction in 50% of AK lesion size and the other had a 75% reduction). No change in size or number of lesions was recorded in the remaining two patients (P<0.001 compared to placebo group). No changes in the size or number of lesions in the placebo group were recorded (P<0.001 compared to imiquimod group). One year after treatment, the clinical recurrence rate in patients treated with imiquimod was 10%. Patients in the placebo group were not assessed at one year. Secondary: Not reported
Stockfleth et al.[53] (2004) Imiquimod 5%	DB, PC, RCT Patients 45 to 85 years of age with	N=25 Treatment: 12 weeks	Primary: Recurrence of AK lesions in patients treated with	Primary: At 18 months, 16% of patients developed new AK lesions or were lost to follow-up and at 24 months, 20% had developed new AK lesions or were lost to follow-up. None of these patients had developed SCC after

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cream applied BID three times week vs placebo	AK in a treatment area that did not exceed 20 cm^2	Follow-up: 2 years	imiquimod up to two years post-treatment Secondary: Not reported	treatment with imiquimod. Ten placebo-treated patients were observed for one year. In those patients, spontaneous remission of AK lesions was reported in one patient; all of the remaining nine developed new AKs and one developed SCC. Secondary: Not reported
Zeichner et al.[54] (2009) Imiquimod 5% cream applied QD once weekly for 24 weeks vs placebo	DB, PC, RCT, SC Patients ≥18 years of age with ≥6 AKs on the face, head, and scalp	N=20 6 months	Primary: Efficacy using an IAS, adverse events Secondary: Not reported	Primary: At the posttreatment visit, 46.7% of patients had marked improvement or better with imiquimod compared to 6.7% of patients receiving placebo. All patients had some improvement with imiquimod, whereas six patients had no improvement and seven had slight worsening with placebo. The average change in IAS score was 12.20 for imiquimod compared to -0.27 for placebo (P=0.0002). Skin reactions were minimal or nonexistent in most patients. Secondary: Not reported
Lee at al.[55] (2005) Imiquimod 5% cream applied QD two or three times per week for 16 weeks vs placebo This study followed patients	OS Patients 45 to 86 years of age with AK who demonstrated complete clearance of AK lesions at eight weeks post-treatment in four phase III clinical trials of imiquimod vs placebo cream	N=146 Single visit (12 to 18 months post-original treatment)	Primary: AK recurrence rate Secondary: Not reported	Primary: The recurrence rate of AK lesions was lower in patients who had previously received imiquimod three times/week (24.7%) compared to those who had received it two times/week (42.6%). Patients with fair skin had a higher recurrence of AK lesions compared to patients with Fitzpatrick type III-V skin (in the three times/week group: 29 vs 14%, and in the two times/week group: 50 vs 33%). The recurrence rate of AK lesions in the placebo-treated patients was 46.7%. Statistical comparisons between groups were not reported. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
who had showed complete clearance of AK lesions at 8 weeks post-treatment in four phase III studies, and invited them back for a 1-time evaluation at 12-18 months post-original treatment.				Not reported
Korman et al.[56] (2005) Imiquimod 5% cream applied QD three times per week for 16 weeks vs placebo	MA Patients ≥18 years of age with four to eight AK lesions with a contiguous 25 cm^2 treatment area on the face or balding scalp	N=492 Treatment: 16 weeks Follow-up: 8 weeks	Primary: Complete clearance rate Secondary: Partial clearance rate, median percentage of reduction of baseline AK lesions at the eight-week post-treatment visit	Primary: Complete clearance was observed in 48.3% of patients in the imiquimod group and 7.2% of patients in the placebo group (P<0.001). Secondary: Partial clearance was observed in 64% of patients in the imiquimod group and in 13.6% of patients in the placebo group (P<0.001). The median percentage of reduction in AK-lesion count was 86.6% in the imiquimod group and 14.3% in the placebo group. Stated another way, half of the patients in the imiquimod group had at least an 86.6% reduction in the number of baseline AK lesions. There was a difference noted in complete and partial clearance rates between the two studies: complete clearance rates were 56.4 vs 40.8% and partial clearance rates were 71.8 vs 56.8%.
Krawtchenko et al.[57] (2007) Imiquimod 5% cream applied QD three times per week for 4 weeks vs	RCT Patients with a minimum of five typical, visible, and histologically proven AK lesions in one anatomical area of up to 50 cm^2 at head or neck	N=75 Treatment: 4 weeks Follow-up: 12 months	Primary: Complete clearance at the TOC, sustained clearance at 12 months, cosmetic outcome Secondary: Not reported	Primary: Complete clearance at the TOC was observed in 68% of the cryosurgery group, in 96% of the 5-FU group, and in 85% of the imiquimod group, respectively (P=0.03). Total clearance of AK at TOC was histologically confirmed in 32% of the cryotherapy group, 67% of the 5-FU group (P=0.03) and 73% of the imiquimod group (P=0.008). The 12-month sustained clearance rate of initially cleared individual

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluorouracil (5-FU) 5% ointment applied BID for four weeks vs cryosurgery (one or two courses of therapy)				lesions was 28% for cryosurgery, 54% for 5-FU and 73% for imiquimod (P<0.01). The 12-month sustained clearance of the total treatment field was 4, 33, and 73% of patients after cryosurgery, 5-FU, and imiquimod, respectively (P<0.01). Based on the investigator's assessments, 4% of patients in the 5-FU group and the cryosurgery group, but 81% of patients in the imiquimod group showed an excellent cosmetic outcome (P<0.002). Similar results were obtained from the patients' assessments. Secondary: Not reported
Sotiriou et al.[58] (2009) Imiquimod 5% cream applied QD three times per week for four weeks (course 1) vs 5-aminolevulinic acid PDT Patients who had not cleared all of their lesions in the imiquimod group participated in a second 4-week treatment cycle (course 2).	RCT Patients with non-hyperkeratotic grade I (mild) and grade II (moderate) AKs on the dorsa of hands and forearms	N=30 6 months	Primary: Clearance rate, patient preference, adverse events Secondary: Not reported	Primary: After one month, the overall lesion complete response rate was 70.16% for PDT and 18.26% for imiquimod cream (P<0.05). At month six, the overall lesion complete response rate was 65.32% for PDT (95% CI, 56.9 to 73.7) compared to 55.65% for imiquimod (95% CI, 46.6 to 64.7; P>0.05). At month six, 80% of the lesions in the PDT group had an excellent cosmetic outcome compared to 75% of those treated with imiquimod. Good, fair and poor outcome was observed in 19.1 and 0% lesions treated with PDT and in 20.5 and 0% lesions treated with imiquimod, respectively (P=0.065). Results from patient questionnaire showed that patients preferred PDT regarding the procedure (69 vs 31%). Only 55% of the patients favored PDT in terms of efficacy compared to 45% who favored imiquimod. If they had to be treated again, 70% of patients would prefer PDT compared to 30% of patients who would prefer imiquimod cream. The most commonly reported adverse events were expected, were related to the type of therapeutic procedure and were mild to moderate and transient in nature. No patient discontinued the study due to adverse

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				events. Secondary: Not reported
Jansen et al.[59] (2019) Fluorouracil cream 5% vs imiquimod cream 5% vs methyl aminolevulinate photodynamic therapy (MAL-PDT) vs ingenol mebutate gel 0.015%	MC, RCT, SB Patients ≥18 years of age with a clinical diagnosis of five or more AK lesions in one continuous area of skin measuring 25 to 100 cm^2 in the head and neck	N=624 12 months (after end of treatment)	Primary: Proportion of patients with a reduction of 75% or more in the number of AK lesions from baseline to 12 months after the end of treatment Secondary: Adverse events, adherence, patient satisfaction with treatment, health-related quality of life, and cosmetic results	Primary: At 12 months after the end of treatment, the cumulative probability of remaining free from treatment failure was higher among patients who received fluorouracil (74.7%; 95% CI, 66.8 to 81.0) than among those who received imiquimod (53.9%; 95% CI, 45.4 to 61.6), MAL-PDT (37.7%; 95% CI, 30.0 to 45.3), or ingenol mebutate (28.9%; 95% CI, 21.8 to 36.3). As compared with fluorouracil, the hazard ratio for treatment failure was 2.03 (95% CI, 1.36 to 3.04) with imiquimod, 2.73 (95% CI, 1.87 to 3.99) with MAL-PDT, and 3.33 (95% CI, 2.29 to 4.85) with ingenol mebutate (P≤0.001 for all comparisons). Secondary: There were no serious adverse events that were considered by the investigators and the medical ethics committee to be related to the trial treatment. The percentage of patients with 100% adherence was higher in the ingenol mebutate group (98.7%) and the MAL-PDT group (96.8%) than in the fluorouracil group (88.7%) and the imiquimod group (88.2%). Patient satisfaction with treatment and increase in health-related quality of life were highest in the fluorouracil group. Good-to-excellent cosmetic outcome was more often observed in the MAL-PDT group (96.6%) and the ingenol mebutate group (95.1%) than in the fluorouracil group (90.3%) and the imiquimod group (89.7%).
Cortelazzi et al.[60] (2021) Imiquimod 3.75% vs	Randomized, intraindividual right-left pilot study Male bald patients ≥18 years of age with multiple AK	N=9 12 months	Primary: Overall clearance rate Secondary: Not reported	Primary: Imiquimod ultimately had a slightly greater overall clearance rate than MAP-PDT (68.1% vs 56.5%). Based on AK degree of severity, clearance rates for degree I, II and III with imiquimod were 68.8%, 64.5%, and 75%. Clearance rates for degree I, II and III with MAL-PDT were 48%, 69.8%, and 66.7% for MAL-PDT.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Photodynamic therapy with 5-aminolaevulinic acid (MAL-PDT) Patients were treated with imiquimod on one side of the scalp and treated with MAL-PDT on the opposite side of the scalp 14 days apart.				After 12 months, there was a slightly higher total recurrence rate for imiquimod compared to MAL-PDT (9.9% vs. 8.6%). Patients reported moderate to severe pain for both treatments. Common adverse effects that were noted included erythema, burning sensation, appearance of edema, erosions, scabs, and systemic flu-like symptoms, with MAL-PDT appearing to be the less tolerable treatment option. An excellent aesthetic result was obtained with both treatments. Secondary: Not reported
Atopic Dermatitis				
Gollnick et al.[61] (2008) Pimecrolimus 1% cream applied BID at the first sign or symptom of a relapse vs placebo Patients were also allowed to use moderately potent corticosteroids to treat flares.	DB, MC, PC, PG, RCT Adults ≥18 years of age with mild to moderate AD who were clear/almost clear of disease	N=543 26 weeks	Primary: Number of days without topical corticosteroid use for disease worsening, flares requiring topical corticosteroid use, physician office visits Secondary: Not reported	Primary: The mean number of topical corticosteroid-free days was significantly higher in the pimecrolimus cream group than in the placebo cream group (152 vs 138.7 days, respectively; P<0.001). Treatment with pimecrolimus cream reduced the mean number of flares requiring topical corticosteroid use from 1.39 to 0.97 compared to placebo cream (P=0.0014). Patients on pimecrolimus cream made 30% fewer unscheduled visits to their physician's office than patients on placebo cream (156 vs 223, respectively). Secondary: Not reported
Sigurgeirsson et al.[62] (2008)	DB, MC, PC, RCT Children and adolescents 2 to 17	N=521 26 weeks	Primary: Number of days without topical corticosteroid use	Primary: The mean number of topical corticosteroid-free days was significantly higher in the pimecrolimus cream group than in the control group (160.2 vs 137.7 days, respectively; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Pimecrolimus 1% cream applied BID at the first sign or symptom of recurring AD vs placebo Patients were allowed to use moderately potent corticosteroids to treat flares.	years of age with a history of mild or moderate AD who were clear/almost clear of disease		for disease worsening, flares requiring topical corticosteroid use, physician office visits Secondary: Not reported	Patients on pimecrolimus cream experienced 50% fewer flares requiring topical corticosteroids than patients on placebo cream (0.84 vs 1.68, respectively; P<0.0001). Patients on pimecrolimus cream had fewer unscheduled visits to their physician's office than patients on placebo cream (87 vs 246, respectively). Secondary: Not reported
Zuberbier et al.[63] (2007) Pimecrolimus 1% cream applied BID vs placebo Patients were allowed to use prednicarbate 0.25% cream if a flare occurred that was not controlled by study medication.	RCT Children and adolescents 2 to 17 years of age with a history of severe AD	N=184 24 weeks	Primary: Percentage of days patients used prednicarbate instead of study medication Secondary: Not reported	Primary: Patients on pimecrolimus required topical corticosteroids on a mean of 29% of study days compared to 35% of patients on placebo (P=0.1841). On the head and neck only, patients on pimecrolimus required topical corticosteroids on a mean of 10% of study days compared to 19% of patients on placebo (P=0.0009). In patients with acute severe disease (IGA > or=4), topical corticosteroids were used on 28% of the days in the pimecrolimus group compared to 45% in the placebo group (P= 0.0024). In patients with acute severe disease (IGA > or=4) on the head and neck, topical corticosteroids were used on 10% of study days with pimecrolimus vs 30% with placebo (P<0.0001). Secondary: Not reported
Zuberbier et al.[64] (2008) Pimecrolimus 1%	DB, MC, RCT Children and adolescents 2 to 17	N=140 24 weeks	Primary: Percentage of days patients used prednicarbate	Primary: Patients in the pimecrolimus group needed prednicarbate treatment on the face on 11.7% of the study days compared to 20.7% of the study days in the placebo group (P=0.0024).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cream applied BID vs placebo Patients were allowed to use prednicarbate 0.25% cream if a flare occurred that was not controlled by study medication.	years of age with facial AD and mild to moderate disease after treatment of the initial flare with prednicarbate 0.25% cream		instead of study medication Secondary: Not reported	Fifty percent of patients in the pimecrolimus group had no flare on the face during the treatment period compared to 37.5% of patients in the placebo group (P=0.012). The median time to first flare in pimecrolimus-treated patients was twice as long as in patients receiving placebo (138 vs 68 days, respectively; P=0.01). Primary: Percentage of days patients used prednicarbate instead of study medication Secondary: Not reported
Murrell et al.[65] (2007) Pimecrolimus 1% cream applied BID vs placebo	DB, PC, RCT Patients 12 years of age or older with mild to moderate head and neck AD who were intolerant of, or dependent on, topical corticosteroids	N=200 12 weeks (6-week RCT followed by 6-week OL phase)	Primary: Facial investigator's global assessment score at six weeks Secondary: Head and neck EASI, pruritus score, eyelid dermatitis, facial skin atrophy and telangiectasia	Primary: A significantly higher percentage of patients treated with pimecrolimus was cleared or almost cleared of facial AD compared to placebo (47 vs 16%, respectively). Secondary: A statistically significant difference was also seen on head and neck EASI and pruritus score. Significantly more pimecrolimus-treated patients than placebo-treated patients achieved clearance of eyelid dermatitis (45 vs 19%, respectively). Among the 77 patients with skin atrophy at baseline, treatment with pimecrolimus was associated with a reversal in skin thinning. Of the 112 patients with telangiectasia at baseline, no statistically significant difference was seen between treatment groups. Adverse events occurred with similar frequency in both groups.
Kapp et al.[66] (2002) Pimecrolimus 1%	DB, MC, PC, PG, RCT Infants 3 to 23	N=251 12 months	Primary: Incidence of flares of AD at six months	Primary: There was a significantly lower number of flares in the pimecrolimus group compared to the placebo group (67.6% of patients in the pimecrolimus group had no flare at six months vs 30.4% in the placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cream applied BID at the first sign of a flare until complete clearance of signs and symptoms vs placebo Patients were also allowed to use moderately potent corticosteroids to treat flares.	months of age with a clinical diagnosis of AD		Secondary: Investigator's IGA score, (EAS), and caregiver's assessments of pruritus and overall level of disease control (pruritus was assessed by the caregiver for 24 hours prior to study visits and ranked on a scale of 0 [none] to 3 [severe], and were asked to assess the level of control over the preceding seven days on a 4-point scale. The IGA score, pruritus assessment, and caregiver assessments were dichotomized into treatment success [score of 0 or 1] or treatment failure [all other scores]).	group; P<0.001). At 12 months, 56.9% of patients in the pimecrolimus group had no flares compared to 28.3% of patients in the placebo group. Baseline severity of AD did not affect the trend towards a lower incidence of flares in the pimecrolimus group. Patients in the pimecrolimus group had a significantly longer flare-free period compared to patients in the placebo group (P<0.001) and the mean number of flares was lower in the pimecrolimus group compared to the control group (P<0.001). In the pimecrolimus group, 63.7% of patients did not require a corticosteroid during the study period, compared to 34.8% in the placebo group and the proportion of study days on a corticosteroid was 3.2% in the pimecrolimus group compared to 6.2% in the placebo group. Secondary: An IGA score of 0 or 1 (clear or almost clear) was achieved in 44.6% of patients in the pimecrolimus group compared to 8.7% in the placebo group (P<0.001). The maximum benefit of therapy was achieved by day 22 in the pimecrolimus group compared to three months in the placebo group and the magnitude of effect was greater in the pimecrolimus group (54.9% had achieved an IGA score of 0 or 1 by day 22 compared to 39.1% in the placebo group (P=0.034). At month six, a significantly greater proportion of patients in the pimecrolimus group had clear or nearly clear skin compared to those in the placebo group (52.9 vs 37.0%; P=0.03). At month 12, a higher number of patients in the pimecrolimus group had clear or nearly clear skin compared to the placebo group, though this difference was not statistically significant (53.9 vs 47.8%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				EASI mean total scores were significantly lower for patients in the pimecrolimus group compared to the placebo group at day 43 (P<0.0001) but were not significantly different at month six, nine, or 12 (P>0.076). Pruritus scores were significantly lower for patients in the pimecrolimus group compared to the placebo group at day 43, month six and month nine (P<0.016) but were not significantly different at month 12 (P=0.074). A significantly higher number of patients in the pimecrolimus group had a caregiver assessment of 0 or 1 (complete or good disease control) compared to the placebo group at day 43 and month six (P<0.016), but the differences were not significant at month nine or 12 (P>0.058).
Staab et al.[67] (2005) Pimecrolimus 1% cream applied BID vs placebo	DB, MC, PC, PG, RCT Patients 3 to 23 months of age diagnosed with atopic eczema affecting some part of face and affecting ≥5% of BSA, and having a baseline IGA score of mild severity or greater	N=196 4 weeks	Primary: Parents' quality of as measured by the questionnaire for PQoL-AD, pruritus, and sleep loss, using the SCOR-AD, severity of disease, using IGA, and degree of disease control as measured by the EASI Secondary: Not reported	Primary: Significant improvements were seen in all domains of the PQoL-AD in favor of pimecrolimus (P<0.05). The most significant differences were seen in the domains of "psychosomatic well-being", "emotional coping", and "acceptance of disease". There was a significant pruritus treatment effect observed in favor of pimecrolimus by day two (P=0.018) and a significant improvement in sleep observed by day three (P=0.002). By day 29, the mean percentage change in the SCOR-AD index was -55.2% for pimecrolimus and 1.13% for the placebo group (P=0.002). Treatment success (IGA=0 [clear] or IGA=1 [almost clear]) was observed in 53.5% of patients in the pimecrolimus group at day 29 compared to 10.6% of patients in the placebo group (P<0.001). The mean EASI decreased by 71.5% in the pimecrolimus group compared to 19.4% in the placebo group by the end of the four-week treatment phase (P<0.001). The reduction in EASI was observed as early as day four in the pimecrolimus group and it decreased by 38.5% compared to a decrease of 17.6% in the placebo group on day four (P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Kaufman et al.[68] (2006) Pimecrolimus 1% cream applied BID for 7 days vs placebo	DB, MC, PC, PG, RCT Patients 18 to 81 years of age with mild to moderate AD affecting ≥5% of total BSA	N=198 7 days of treatment with optional 5-week extension	Primary: Time taken to achieve pruritus improvement of ≥1 point on a 4-point pruritus severity scale compared to baseline Secondary: Percentage of patients achieving pruritus improvement of ≥1 point compared to baseline within 48 and/or 72 hours, percentage of patients with a pruritus response within four, five, six, and seven days of treatment, the percentage of patients with a pruritus severity score of 0 (absent) or 1 (mild) for treatment days two, three, four, five, six, and seven regardless of baseline scores, and the percentage of patients with an IGA score	Primary: There was a significant improvement in pruritus (≥1 point) in the pimecrolimus group compared to the placebo group over the seven-day treatment period (P=0.001). The median time to pruritus improvement (≥1 point) was two days in the pimecrolimus group compared to four days in the placebo group. Secondary: Improvements in pruritus scores (≥1 point) were seen by day two (within 48 hours) in 56% if pimecrolimus patients compared to 34% of patients in the placebo group (P=0.003). By day three (within 72 hours), 72% of pimecrolimus patients reported improvements in pruritus severity compared to 45% of placebo patients (P<0.001). In the pimecrolimus group, 81% of patients sustained their pruritus relief on days four to seven compared to 63% in the placebo group who showed improvement by day seven (P<0.001). For days two to seven: 42% of pimecrolimus patients recorded “mild” or “absent” pruritus scores compared to 27% in the placebo group by day two (P=0.04), 55% of pimecrolimus patients recorded “mild” or “absent” pruritus scores compared to 31% in the placebo group by day three (P=0.002), and 63% of pimecrolimus patients recorded “mild” or “absent” pruritus scores compared to 36% in the placebo group by day seven (P<0.001). Significant improvements in IGA score (≥1 point reduction) were seen in 53% of the pimecrolimus patients compared to 20% of the placebo patients by day 7 (P<0.001). During the open label extension period (146 patients), pruritus and IGA score improvements were maintained or improved in 92% of patients previously treated with placebo and 76% of patients previously treated with pimecrolimus.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			improvement of ≥1 point at study completion compared to baseline	During the extension, 83% of patients overall improved or maintained their condition, and 45% scored their pruritus as "mild" and 25% scored their pruritus as "absent" at the end of the extension.
Hoeger et al.[69] (2009) Pimecrolimus 1% cream BID vs placebo Completion of the DB phase occurred on day 43 or at the time a patient achieved a facial IGA of 0. During the OL phase patients were treated intermittently with pimecrolimus BID; treatment was discontinued when clearance occurred and was resumed upon recurrence of first signs and symptoms of AD. Use of other medications that	DB, MC, OL, PC, RCT Patients 2 to 11 years of age with mild to moderate facial AD who were dependent on, or intolerant of topical corticosteroids	N=200 12 weeks (6 weeks DB followed by 6 weeks OL)	Primary: Efficacy (assessed by facial IGA score) Secondary: Head and neck EASI, overall EASI, pruritus severity score, time to clearance of facial AD, the amount of study drug used, safety and tolerability	Primary: A significantly greater proportion of patients treated with pimecrolimus became clear/almost clear of facial AD lesions at day 43 compared to patients in the placebo group (74.5 vs 51.0%, respectively; P<0.001). Statistically significant differences between groups were apparent at day 22, with 57.1% of pimecrolimus-treated patients experiencing clearance or almost clearance of their facial AD compared to 36.0% of placebo-treated patients (P=0.004). Improvements in facial IGA continued into the OL phase for the pimecrolimus group (87.6% at day 64 and 90.3% at day 85). A substantial improvement was also seen in patients who switched from placebo to pimecrolimus in the OL phase, of whom 79.5% at day 64 and 88.6% at day 85 achieved facial IGA scores of 0/1. Secondary: A significantly greater proportion of pimecrolimus-treated patients at day eight were EASI responders (defined as patients achieving ≥60% improvement in head and neck EASI compared to baseline) compared to placebo (37.8 vs 18.0%, respectively; P<0.003), rising to 77.6 vs 55.0%, respectively, at day 43 (P<0.001). Improvement continued into the OL phase for the pimecrolimus group and for those who switched to pimecrolimus. Overall EASI scores showed a similar trend to those for the head and neck, with significantly more overall EASI responders in the pimecrolimus group than the placebo group at day 22 (51.0 vs 27.0%, respectively; P<0.001) and at day 43 (71.4 vs 38.0%, respectively; P<0.001). At day eight, 89.8 and 60.0% of pimecrolimus- and placebo-treated patients had no or mild pruritus of the head and neck (P<0.001), increasing

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
could potentially have an effect on AD (topical or systemic corticosteroids, phototherapy, topical antibiotics or oral immunosuppressants) was not permitted.				to 93.9 vs 68.0%, respectively, at day 43 (P<0.001). This improvement continued into the OL phase in the pimecrolimus group, and in those who switched to pimecrolimus. Facial AD cleared twice as rapidly in patients treated with pimecrolimus compared to placebo (median time to clearance [facial IGA 0/1]: 22 vs 43 days, respectively; P value not reported). A higher proportion of pimecrolimus-treated patients was cleared of eyelid dermatitis at six weeks compared to placebo-treated patients (41.8 vs 31.0%, respectively; P=0.140). This improvement continued into the OL phase, and a marked improvement was seen in those patients who switched to pimecrolimus. Drug usage, by weight, for the head and neck was similar in the pimecrolimus and placebo groups in both the DB and OL phases. The mean±SD of total usage during the DB phase in the pimecrolimus and placebo groups were 24.2±19.5 g vs 26.9±21.9 g (P value not reported). In the OL phase drug usage was 19.0±15.5 g vs 21.6±18.4 g (P value not reported). Drug usage for the rest of the body was slightly lower in the pimecrolimus group than in the placebo group (DB phase, 45.5±28.7 vs 50.7±39.0 g; OL phase, 35.6±25.4 vs 39.0±28.5 g; P values not reported). Most treatment-emergent adverse events were mild to moderate in both phases of the study. Forty out of 99 (40.4%) pimecrolimus-treated patients and 34/101 (33.7%) placebo-treated patients experienced at least one adverse event during the DB phase. During the DB phase the most commonly reported adverse events were nasopharyngitis, application site irritation and pyrexia. Fewer adverse events were reported during the OL phase with the frequency of application site reactions being comparable between the two groups.
Papp et al.[70] (2005) Pimecrolimus 1% cream applied BID at the first sign of	ES, OL Infants 3 to 23 months of age with a clinical diagnosis of AD	N=91 12 months	Primary: Proportion of patients with no flares, treatment success rates (proportion of	Primary: The median number of days of pimecrolimus use during the 12 months of the present study was 99.0, and 27.5% of these patients required corticosteroids during this time. Seventy-six patients used pimecrolimus for two years (original study by

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
flare until complete clearance of signs and symptoms Patients were also allowed the use of moderately potent corticosteroids to help treat flares.			patients with clear or almost clear skin as indicated by an IGA of 0 or 1), EASI, percentage of total BSA affected by AD, course of disease (proportion of disease-free days without the use of any medication), adverse effects Secondary: Not reported	Kapp et al, and present study combined) and there was a progressive reduction in the mean proportion of pimecrolimus treatment days from 73.7% during the first three months of the second year to 42.3% during the last three months of the second year. The proportion of patients in this study who did not use topical corticosteroids during the first year was 71.1% and this increased to 72.4% during the second year. Overall, 57.9% of patients in the pimecrolimus group did not use corticosteroids at all during the two years. The percentage of patients experiencing no flares during the second year was 76.9% and 8.8% had only a single flare. In patients on pimecrolimus for two years, the proportion experiencing no flares increased from 77.6% during the first year to 85.5% during the second year. The proportion of patients who were clear or almost clear of signs of AD increased from 36.3% at the beginning of the second year to 71.4% at the end of the second year. The mean EASI score decreased from 5.8 to 2.9 and the mean percentage of total BSA affected by AD decreased from 11.3% to 6.6%. At the beginning of the first, DB year, 75% of patients treated with pimecrolimus for two years had moderate or severe disease. At the end of the second year, the percentage of patients with minimal residual activity or were clear of signs of AD was 69.7%. Only 13.2% had an IGA of >2. In this same group of patients, an improvement in EASI scores was already evident at 3 months and persisted for the remaining 21months. The mean percentage of total BSA affected by AD decreased from 28.4% at the beginning of the first year to 7.3% at the end of the second year. The proportion of disease-free days increased from 30% during the first six months of the second year to 50.9% during the last two months. The majority of adverse effects reported were conditions commonly seen in childhood such as nasopharyngitis, pyrexia, cough, diarrhea, ear

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				infection, bronchitis, rhinitis, vomiting, and gastroenteritis. There were no reports of application site reactions. Secondary: Not reported
Meurer et al.[71] (2010) Pimecrolimus 1% cream applied BID and fluticasone 0.05% cream applied BID vs fluticasone 0.05% cream applied BID (TCS)	DB, MC, PC, RCT Patients 2 to 17 years of age with severe AD	N=376 Treatment: 4 weeks Observation: 12 weeks	Primary: Incidence of predefined adverse events associated with the topical use of corticosteroids Secondary: Incidence of all other adverse events, time to relapse of AD, time to AD treatment success, QOL	Primary: With the exception of erythematous rash, seen more often in the combination group, there were no differences in the frequency of adverse events of clinical interest (e.g., folliculitis, infected eczema, or herpes simplex infection) between the combination and monotherapy groups. Secondary: The overall incidence of adverse events was comparable between the combination and TCS monotherapy groups. The most frequently reported adverse events in both treatment groups were infections and infestations in 25 to 30% of patients. The overall proportion of patients with severe adverse events was 2.6% in the combination group and 1.6% in the TCS monotherapy group. The proportion of patients with adverse events related to the study drug was higher in the combination group (6.3%) compared to the TCS monotherapy group (4.4%). There was no significant difference in the time to relapse of AD in the observational period between the combination and TCS monotherapy treatment groups (P=0.754). There was no significant difference between the treatment groups with respect to treatment success for whole body IGA or facial IGA (P=0.790 and P=0.085, respectively). There was no significant difference between the two treatment arms for change in overall EASI from baseline during the treatment period (P=0.827).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference between the combination group and TCS monotherapy group with respect to pruritus treatment success (P=0.528). The mean percentage decrease in PQoL-AD total score from baseline was higher in the TCS monotherapy group (54.4%) compared to the combination group (35.7%).
Kempers et al.[72] (2004) Pimecrolimus 1% cream applied BID until clearing or for 6 weeks vs tacrolimus 0.03% ointment applied BID until clearing or for 6 weeks	MC, PG, RCT, SB Patients 2 to 17 years of age with moderate AD	N=141 6 weeks	Primary: Incidence of local application-site reactions Secondary: Formulation attributes, safety, and efficacy (measured by IGA and patient assessment)	Primary: The incidence of application-site reactions decreased with time in both groups, but this was more pronounced in the pimecrolimus group. Application-site reactions were experienced by 24% of patients in the pimecrolimus group and 26% in the tacrolimus group. Erythema/irritation was reported in 8% of the pimecrolimus patients compared to 19% in the tacrolimus patients (P=0.039). Itching was reported in 8% of the pimecrolimus patients compared to 20% in the tacrolimus patients though this difference was not statistically significant (P=0.073). Warmth/stinging/burning was reported in 20% of the pimecrolimus patients compared to 17% in the tacrolimus patients though this difference was not statistically significant (P=0.931). The duration of application-site reactions tended to be shorter in the pimecrolimus group compared to the tacrolimus group. None of the patients in the pimecrolimus group who experienced erythema/irritation reported that it lasted longer than 30 minutes, compared to 85% of patients in the tacrolimus group who reported that this application-site reaction lasted between 30 minutes and 12 hours (P<0.001). None of the patients in the pimecrolimus group who experienced warmth/burning/stinging reported that it lasted longer than 30 minutes, compared to 67% of patients in the tacrolimus group who reported that this application-site reaction lasted between 30 minutes and 12 hours (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The difference between the two treatment groups in the duration of itching was not significant (P=0.559). Secondary: A significantly higher proportion of patients/caregivers in the tacrolimus group reported that their skin felt oily compared to the pimecrolimus group (P<0.001). There was no significant difference in the proportion of patients who reported that their skin felt dry during treatment (P=0.308). At day 43, a significantly higher proportion of patients reported that pimecrolimus was suitable for use on sensitive facial skin, had a non-sticky feel, and was easy to apply and rub in compared to tacrolimus (P<0.020). There was no significant difference in the spreadability of either product (P=0.06). The overall incidence of adverse effects was similar between the treatment groups: 86% of patients in the pimecrolimus group reported adverse effects compared to 845 in the tacrolimus group. There was no significant difference in IGA scores of clear/almost clear between treatment groups at any visit, though both increased compared to baseline values (P>0.05). On day 22, significantly more patients in the tacrolimus group reported absent or mild pruritus compared to the pimecrolimus group (P=0.042), though differences on all other days were not significant. On day 43, there were no significant differences between treatment groups in the proportion of patients achieving IGA or pruritus scores of 0 or 1 (P=0.493). IGA response rates were slightly higher in the tacrolimus group compared

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				to the pimecrolimus group from day eight to 43, though these differences were not statistically significant (except for day 22 as mentioned above). More than 60% of patients in both groups reported absent or mild pruritus. The change from baseline in BSA affected by AD was similar in both treatment groups, though pimecrolimus tended to have a greater effect on the head and neck compared to tacrolimus which tended to have a greater effect on the legs.
Bissonnette et al.[73] (2022) Ruxolitinib 1.5% cream applied to all atopic dermatitis lesions twice daily for 28 days Patients with no safety concerns were allowed to continue to apply ruxolitinib 1.5% cream twice daily to active lesions for an additional 28 days	OL, MC, SG Patients 12 to 65 years of age, diagnosed with atopic dermatitis defined by Hanifin and Rajka criteria, disease duration of at least two years, Investigator's Global Assessment (IGA) score of ≥2 and body surface area involvement of ≥25% at screening and baseline	N=41 127 days	Primary: Number of treatment-emergent adverse events Secondary: Plasma concentration, maximum measured plasma concentration, time to achieve the observed maximum plasma concentration, area under the concentration-time curve from 0 to 12 hours	Primary: The number of patients who experienced treatment-emergent adverse events was 13 (31.7%). There were four patients with treatment-related adverse events (9.8%) and one patient with a serious treatment-emergent adverse event (2.4%). Secondary: The mean (standard-deviation) steady-state plasma concentration was 104 (309) nM during the first 28 days. The mean (standard deviation) maximum measured plasma at day one was 271 (650) nM compared to 137 (377) nM at day 28. The mean time to achieve the observed maximum plasma concentration at was 4.0 hours on both day one and at day 28. The mean (standard deviation) area under the concentration-time curve from 0 to 12 hours was 1950 (4610) h*nM on day one compared to 1120 (2930) h*nM on day 28.
Kim et al.[74] (2020) Ruxolitinib 1.5% cream applied twice daily vs	DB, PG, RCT Patients 18 to 70 years of age, diagnosed with atopic dermatitis defined by Hanifin and Rajka criteria, disease duration of	N=307 8 weeks	Primary: Mean percentage change in EASI score from baseline to week 4 Secondary: Mean percentage change in EASI	Primary: The mean percentage change in EASI score from baseline to week for was 15.5% in the placebo group compared to 71.6% in the ruxolitinib 1.5% twice daily group (P<0.0001). Secondary: There was no statistically significant difference between the mean percentage change in EASI score from baseline to week four between the ruxolitinib 1.5% group and the triamcinolone 0.1% group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
triamcinolone 0.1% applied twice daily followed by placebo vs placebo After the eight-week blinded trial period, patients without safety concerns who were adherent to the study protocol were eligible to receive an additional four weeks of open-label treatment.	at least two years, IGA score of 2 to 3 and body surface area involvement excluding face and intertriginous areas of 3% to 20% at screening and baseline		score from baseline to week 4 compared to triamcinolone 0.1% followed by placebo, percentage of patients achieving an IGA score of 0 to 1 who had an improvement ≥2 points from baseline to week 4, mean change from baseline in itch numerical rating scale score at weeks 2, 4, and 8, and proportion of patients who achieved ≥50%, ≥75%, and ≥90% EASI scores.	The percentage of patients achieving an IGA score of 0 to 1 who had an improvement ≥2 points from baseline to week 4 was 7.7% in the placebo group compared to 38.0% in the ruxolitinib 1.5% twice daily group (P<0.001). The mean change in itch numerical rating scale score was observed as early as within 36 hours of initiation of treatment where placebo was a 0.2% reduction compared to a 1.8% reduction in the ruxolitinib 1.5% twice daily group (P<0.001). This reduction was observed over the remainder of the 12 weeks of treatment. The proportion of patients who achieved ≥50%, ≥75%, and ≥90% EASI scores was 23.1%, 17.3%, and 5.8% respectively in the placebo group compared to 78.0%, 56.0%, and 26.0% respectively in the ruxolitinib 1.5% twice daily group.
Papp et al.[75] (2021) Ruxolitinib 1.5% cream applied twice daily vs placebo	DB, MC, PG, RCT Patients 12 years of age and older, diagnosed with atopic dermatitis defined by Hanifin and Rajka criteria, disease duration of at least two years, IGA score of 2 to 3 at screening and baseline and 0 to 4 at week 8, body	N=631 in Study 1 N=577 in Study 2 Eight weeks	Primary: Proportion of patients achieving IGA score of 0 or 1 at week 8 with improvement of ≥2 points from baseline Secondary: Proportion of patients achieving ≥75% improvement in	Primary: The proportion of patients achieving IGA score of 0 or 1 at week 8 with ≥2 points of improvement from baseline in the placebo group was 15.1% compared to 53.8% in the ruxolitinib 1.5% group (OR 7.5; 95% CI, 4.2 to 14.0). Secondary: The proportion of patients achieving ≥75% improvement in EASI-75 score from baseline to week 8 was 5.6% in the placebo group compared to 36.0% in the ruxolitinib 1.5% group (OR 5.2; 95% CI, 3.1 to 8.8). The proportion of patients achieving ≥4-point reduction in Itch Numerical Rating Scale score at weeks 2, 4, and 8 was in the placebo group was 5.1%, 11.5%, and 15.4% respectively compared to 33.5%, 51.6%, and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	surface area involvement excluding scalp of 3% to 20% at screening and baseline and 0% to 20% at week 8, one target lesion measuring 10 cm^2 or more at screening and baseline not located on the hands, feet, or genitalia		EASI-75 score from baseline to week 8, proportion of patients with a ≥4-point reduction in Itch Numerical Rating Scale score from baseline to week 8, proportion of patients with a ≥6-point improvement in Patient-Reported Outcomes Measurement Information System 8b from baseline to week 8	52.2% respectively in the ruxolitinib 1.5% group (OR 6.0; 95% CI, 2.9 to 13.2). The proportion of patients with ≥6-point improvement in Patient-Reported Outcomes Measurement Information System 8b at weeks 2, 4, and 8 in the placebo group was 5.2%, 6.9%, and 9.5% respectively compared to 14.7%, 21.0%, and 22.3% respectively in the ruxolitinib 1.5% treatment group (OR 2.7; 95% CI, 5.3 to 20.3).
Doss et al.[76] (2010) Tacrolimus 0.03% ointment applied BID vs fluticasone 0.005% ointment applied BID	DB, MC, RCT Patients 2 to 15 years of age with moderate to severe AD who had responded inadequately to topical corticosteroids	N=239 6 weeks	Primary: Response rate at week three Secondary: Changes in the mEASI score, global assessment of clinical response by investigators and patients, pruritus, sleep quality	Primary: In the PP analysis, response rates were 86.3% with tacrolimus and 91.5% with fluticasone (95% CI, -11.8 to 1.2). Tacrolimus was found to be non-inferior to fluticasone. In the ITT analysis, response rates were 84.3% with tacrolimus and 89.5% with fluticasone (P=0.0012). Secondary: The overall mean percentage change in total mEASI score was -79.5% in the tacrolimus group and -82.3% in the fluticasone group. Moderate or better improvement on the physicians' global assessment occurred in 93.6 and 92.4% of patients in the tacrolimus and fluticasone groups, respectively (ITT; P=0.05). Patients/parents considered global condition to have improved or greatly improved in 86.9% of patients receiving tacrolimus and 88.6% of those receiving fluticasone (ITT; P=0.047, PP; P=NS). Patients' assessment of pruritus improved in those receiving tacrolimus,

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				with median change at day 21 of -84.0% compared to -91.5% in those receiving fluticasone (P=0.008). There was no significant difference in quality of sleep between the treatment groups (median change: tacrolimus, -91.5%; fluticasone, 92.6%). The incidence of adverse events was similar among the treatment groups. Application site burning occurred more frequently with tacrolimus.
Doss et al.[77] (2009) Tacrolimus 0.1% ointment applied to facial lesions BID vs fluticasone 0.005% ointment applied to facial lesions BID	DB, MC, RCT Patients ≥16 years of age with moderate to severe AD of the face	N=468 3 weeks	Primary: Change in the mLEASI score Secondary: Facial erythema and pruritus, global clinical response	Primary: After three weeks, the response rate was 93.3% with tacrolimus and 87.8% with fluticasone as assessed by mLEASI (ITT; P=0.026, PP; P=0.046). Secondary: After three weeks, median changes in facial pruritus scores were -89.3% with tacrolimus compared to -88.3% with fluticasone (P=NS). Facial erythema improved in both treatment groups (P=NS). The physicians' global assessment of clinical response for the facial region was significantly different between the two groups. A total of 88% of patients in the tacrolimus group and 79% of patients in the fluticasone group showed marked or excellent improvement, or clearance of lesions (P=0.043). The patients' global assessment of clinical response for the facial region was significantly different between the two treatment groups. A total of 64% of patients in the tacrolimus group and 55% of patients in the fluticasone group considering their condition to have 'greatly improved' (P=0.014).
Reitamo et al.[78] (2005) Tacrolimus 0.1% ointment applied BID until clear and then for seven additional days	DB, MC, RCT Patients ≥18 years of age with moderate to severe AD	N=972 6 months	Primary: Response rate at month three (improvement in mEASI) Secondary: Response rate at	Primary: At month three, 72.6% of patients in the tacrolimus group responded to treatment compared to 52.3% of patients in the corticosteroid group (P<0.001). Secondary: The tacrolimus group had a higher response rate at all other time points throughout the six months compared to the corticosteroid group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs hydrocortisone butyrate 0.1% ointment applied BID (trunk and extremities) and hydrocortisone acetate 1% ointment applied BID (head and neck)			other time points, mEASI, EASI, physician's global evaluation of clinical response, patient's assessment of global response, physician's assessment of individual signs, affected BSA, patient's assessment of itch and quality of sleep, and the number of days on treatment as a percentage of days in the study	(P<0.001). A significant improvement in mEASI was observed as early as day eight in both treatment groups and increased up to the six-month point. At month six, the median percentage change in mEASI was -87.7% in the tacrolimus group and -82.5% in the corticosteroid group (P<0.008). The improvement in EASI and affected BSA followed the same trend. For EASI, the median percentage change was -85.0% in the tacrolimus group and -81.5% in the corticosteroid group (P=0.01). For the BSA, the median percentage change was -88.2% for the tacrolimus group and -80.3% in the corticosteroid group (P=0.001). Physicians' global assessments of clinical response was higher in the tacrolimus group compared to the corticosteroid group (P<0.001). There was a greater reduction in individual signs of AD in the tacrolimus group compared to the corticosteroid group and more patients in the tacrolimus group experienced clearance or excellent improvement (at month six, 61.3% of tacrolimus patients and 46.4% of corticosteroid patients had clearance or excellent improvement, P<0.001). Patients' assessments were significantly higher in the tacrolimus group compared to the corticosteroid group. At six months, 86.6% of patients in the tacrolimus group rated their AD as much better or better compared to 71.8% of patients in the corticosteroid group (P<0.001). Itch and quality of sleep improved significantly in both treatment groups. Patients in the tacrolimus group remained in the study longer compared to the corticosteroid group and had a lower number of treatment days as a percentage of days in the study.
Poole et al.[79] (2010) Tacrolimus 0.1% ointment applied	DB, MC, RCT Patients ≥18 years of age with moderate to severe	N=972 6 months	Primary: QOL (SF-36) assessed using a physical component	Primary: For the physical component summary, patients receiving tacrolimus gained 3.3 points on average compared to 2.3 points in the corticosteroid group (P=0.033).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID until clear and then for seven additional days vs hydrocortisone butyrate 0.1% ointment applied BID (trunk and extremities) and hydrocortisone acetate 1% ointment applied BID (head and neck)	AD		summary and a mental component summary Secondary: Not reported	For the mental component summary, patients receiving tacrolimus improved by an average 6.0 points compared to 3.4 points in the corticosteroid group (P<0.001). For the eight SF-36 domains, all except 'Physical Functioning' (P=0.106) showed significant differences in favor of tacrolimus. Secondary: Not reported
Mandelin et al.[80] (2010) Tacrolimus 0.1% ointment applied BID vs hydrocortisone acetate 1% ointment applied BID (head and neck) and hydrocortisone butyrate 0.1% ointment applied BID (trunk and extremities) Flares were treated	DB, RCT, SC Patients ≥18 years of age with moderate to severe AD	N=80 1 year	Primary: Response rate as measured by affected BSA, improvement in EASI and mEASI, adverse events Secondary: Not reported	Primary: After three months, the proportion of patients with > 60% improvement in mEASI was similar for both groups (tacrolimus, 77.5%; hydrocortisone, 72.5%). After six months, tacrolimus was significantly more effective than the corticosteroid regimen as measured by affected BSA: 5.4% (95% CI, 1.5 to 28.4) and 15.5% (95% CI, 5.6 to 48.8), respectively (P<0.05). After six months, tacrolimus was significantly more effective than the corticosteroid regimen as measured by the EASI score: 3.2 (95% CI, 1.4 to 9.1) and 7.1 (95% CI, 3.0 to 17.9), respectively (P<0.05). After 12 months, 57.5% of patients receiving tacrolimus were rated by their physician as having a response of "cleared or excellent" for the global evaluation of clinical response compared to 42.5% of patients receiving the corticosteroid regimen (P=0.26). When the head and neck region was considered separately, 60.0% of the patients receiving tacrolimus and 30.0% of the patients receiving the corticosteroid regimen were rated as "cleared or excellent" by the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID until 7 days after clearance, and treatment resumed in the event of a recurrence or new flare.				physician (P=0.01). Adverse events occurred in 40 patients (100%) in the tacrolimus group and in 34 patients (85.0%) in the corticosteroid group (P=0.03), which was primarily due to the higher incidence of application-site skin burning sensation with tacrolimus. Secondary: Not reported
Kubota et al.[81] (2009) <u>Phase 1</u> Tacrolimus 0.03% ointment applied in the morning and a strong- or weak-potency corticosteroid ointment in the evening applied for 2 weeks <u>Phase 2</u> Tacrolimus 0.03% ointment applied BID on weekdays and a strong- or weak-potency corticosteroid ointment applied on weekends for 2 weeks <u>Phase 3</u> Tacrolimus 0.03% ointment applied	OL Pediatric patients with AD	N=28 12 weeks	Primary: EASI score, IGA, severity of pruritus, sleep disturbance, and CDLQI or IDQOL questionnaires Secondary: Not reported	Primary: After the sequential therapy, mean EASI scores significantly decreased from 12.87 at baseline to 1.43 at six weeks, and continuous improvement was observed throughout the following six-week period (1.39 at 12 weeks). The patient assessment of pruritus score decreased during the initial two weeks, from 2.35 at baseline to 1.03, and this improvement was maintained throughout the study (1.00 at 12 weeks). Sleep disturbance score decreased from 1.00 at baseline to 0.03 at six weeks and to 0.04 at 12 weeks. Investigators' Global Assessment at six weeks showed 3% clear, 48% excellent, 39% marked, and 10% moderate improvement, and 7, 46, 42%, and 4% at 12 weeks, respectively. On the CDLQI survey, the mean QOL score significantly improved, from 5.14 at baseline to 2.33 at six weeks and to 2.63 at 12 weeks. On the IDQOL survey, the mean QOL score also significantly improved, from 6.40 at baseline to 2.20 at six weeks and 2.75 at 12 weeks. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD for 2 weeks, then emollient applied for 6 weeks (with use of tacrolimus for flares)				
Fleischer et al.[82] (2007) Tacrolimus 0.1% ointment applied BID vs pimecrolimus 1% cream applied BID	MC, RCT, SB Patients ≥18 years of age with moderate to very severe AD	N=281 6 weeks	Primary: Response rate as measured by the EASI, treatment success rate Secondary: Not reported	Primary: Tacrolimus-treated patients had significantly greater reduction in the EASI score compared to pimecrolimus-treated patients (57 vs 39%, respectively; P=0.0002). Treatment success was significantly greater among the tacrolimus-treated patients compared to pimecrolimus-treated patients (40 vs 22%, respectively; P=0.001). Improvement in percentage of total BSA affected was significantly greater among the tacrolimus-treated patients compared to pimecrolimus-treated patients (49 vs 34%, respectively; P=0.01). Both treatment groups had similar improvements in patient assessment of itch. Significantly more pimecrolimus-treated patients than tacrolimus-treated patients withdrew from the study due to lack of efficacy (10 vs 1, respectively; P=0.005). There were no significant differences in the incidences of adverse events between the two treatment groups. Secondary: Not reported
Abramovits et al.[83] (2008) Tacrolimus 0.1% ointment applied BID	MC, RCT, SB Patients ≥16 years of age with moderate AD	N=188 6 weeks	Primary: Response rate as measured by the EASI, Investigators' global AD	Primary: Tacrolimus ointment-treated patients had significantly greater reduction in EASI score compared to pimecrolimus cream-treated patients (59 vs 43%, respectively; P=0.01). Significantly more tacrolimus ointment-treated patients than pimecrolimus

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs pimecrolimus 1% cream applied BID			assessment Secondary: Not reported	cream-treated patients improved by 1 or more grades on the investigators' global AD assessment (P<0.02). A total of five pimecrolimus cream-treated patients discontinued the study early due to lack of efficacy compared to no tacrolimus ointment-treated patients (P=0.02). Adverse events occurred at a similar frequency for both treatment groups. Secondary: Not reported
Paller et al.[84] (2005) Tacrolimus 0.03% or 0.1% ointment applied BID for up to 6 weeks or until 7 days after clearance vs pimecrolimus 1% cream applied BID for up to 6 weeks or until 7 days after clearance	Pooled analysis (3 trials) Patients ≥2 years of age with mild to severe AD	N=1,065 6 weeks	Primary: Change in EASI score at week six Secondary: IGADA where success means clear or almost clear, percent of BSA affected, patient's assessment of itch, and safety	Primary: The change in baseline in EASI score at week six was significantly greater in the tacrolimus groups compared to the pimecrolimus groups in adults (54.1 and 34.9%, respectively; P<0.0001), children with moderate to severe disease (67.2 and 56.4%, respectively; P=0.04), and in the combined analysis (52.8 and 39.1%, respectively; P<0.0001). In the study evaluating pediatric patients with mild AD, there was a significant difference in EASI score favoring tacrolimus at week one (P=0.04), and a trend toward advantage with tacrolimus at week six, but this difference was not significant (P=0.07). In all patients with moderate disease, the percentage reduction in EASI score at week six was significantly higher in the tacrolimus group compared to the pimecrolimus group (P=0.003). In patients with head and neck involvement, the percentage reduction in EASI score at week six was greater in the tacrolimus group compared to the pimecrolimus group (57 and 42%, respectively; P=0.01). Secondary: IGADA scores were significantly better at six weeks for tacrolimus compared to pimecrolimus in the adult patient group, in the children with moderate to very severe disease, and in the combined analysis (all P<0.01) but this difference was not significant in the pediatric patients with mild disease.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				At six weeks, there was a significantly greater reduction with tacrolimus compared to pimecrolimus in percentage of BSA affected for the adult patients, for the pediatric patients with moderate to very severe disease, and in the combined analysis (all P<0.001), and this difference was observed as early as week three (P<0.01). In pediatric patients with mild disease, a significant difference in favor of tacrolimus was observed at week one (P=0.02) but this difference was not significant at week six (P=0.15). At week six in all three studies, the reduction in itch score was significantly greater in all the tacrolimus groups compared to the pimecrolimus groups (P<0.01) and significant differences in favor of tacrolimus were observed as early as week one in both pediatric studies (P<0.05). The most common adverse effects in all studies were local application site reactions including burning and stinging. In both pediatric studies, there were no significant differences observed in adverse effects between tacrolimus and pimecrolimus groups. In the adult study, application site burning occurred more frequently in the tacrolimus group compared to the pimecrolimus group (P=0.02) early in treatment, but by week one there were no significant differences observed between the groups. In the pediatric study of patients with mild AD, significantly more patients withdrew from the study due to an adverse effect in the pimecrolimus group compared to the tacrolimus group (P=0.002).
Kirsner et al.[85] (2010) Tacrolimus 0.03% or 0.1% ointment applied BID for up to 6 weeks or until	MA (subgroup analysis of pooled data from Paller et al.) Patients ≥2 years of age with mild to	N=347 6 weeks	Primary: Change in EASI score at week six Secondary: IGADA where success means	Primary: At week six, the mean percentage improvement in EASI score was significantly greater for patients treated with tacrolimus compared to patients treated with pimecrolimus (53.2 vs 33.7%, respectively; P=0.0002). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
7 days after clearance vs pimecrolimus 1% cream applied BID for up to 6 weeks or until 7 days after clearance	severe AD who were treated with corticosteroids within the 30 days prior to enrollment		clear or almost clear, percent of BSA affected, patient's assessment of itch, and safety	At week six, significantly more patients treated with tacrolimus achieved treatment success ("Clear" or "Almost Clear" by IGADA score) than patients treated with pimecrolimus (P=0.0007). Significantly more of the patients (with mild, moderate or severe/very severe AD at baseline) treated with tacrolimus than with pimecrolimus improved by one or more grades on the IGADA (P=0.0006). Relative to baseline, the improvement in the percent of BSA affected was significantly greater with tacrolimus than with pimecrolimus at week six (P=0.002). Itch was significantly improved among patients treated with tacrolimus compared to those treated with pimecrolimus (P=0.002). Adverse events were similar with both treatments (24.0% for tacrolimus vs 25.6% for pimecrolimus). The most common adverse events were application-site burning (9.9% with tacrolimus vs 14.2% with pimecrolimus; P=0.3) and application-site itching (7.0% with tacrolimus vs 10.2% with pimecrolimus; P=0.3).
Yin et al.[86] (2011) Tacrolimus 0.03% ointment or 0.1% ointment BID for six weeks or until seven days after clearance vs pimecrolimus 1% cream BID for six weeks or until seven days after clearance	MA Patients adult and pediatric patients with mild to severe AD	N=1,834 6 weeks or until seven days after clearance	Primary: IGADA at week one, three and six or end of study (success means clear or almost clear) for pediatric and adult patients based on severity of AD Secondary: Safety endpoints (overall incidences of all adverse events) and withdrawals due adverse events and	Primary: IGADA scores were significantly better at six weeks for tacrolimus 0.1% compared to pimecrolimus 1% in the adult patient group at week three (RR, 0.55; 95% CI, 0.42 to 0.73) and week six/end of study (RR, 0.58; 95% CI, 0.46 to 0.72). In the children with moderate to very severe disease, IGADA scores were significantly better at six weeks/end of study (RR, 0.55; 95% CI, 0.34 to 0.88). The combined analysis of efficacy show that tacrolimus was more effective than pimecrolimus at week three and at week six/end of study (three weeks RR, 0.67; 95% CI, 0.56 to 0.80; six weeks RR, 0.65; 95% CI, 0.57 to 0.75). There was no significant difference in IGADA scores for pediatric patients with mild disease taking 0.03% tacrolimus or 1% pimecrolimus.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			lack of efficacy	Secondary: In adults, incidence of adverse events (most often reported as application site reactions) occurred more frequently in the tacrolimus 0.1% group compared to the pimecrolimus group (RR, 1.30; 95% CI, 1.02 to 1.66). In pediatric patients with mild-moderate AD, there were no significant differences observed in adverse effects between the tacrolimus 0.3% and pimecrolimus. In pediatric patients with moderate-very severe AD, there were no significant differences observed in adverse effects between the tacrolimus 0.1% and pimecrolimus. Fewer pediatric patients with mild AD treated with 0.03% tacrolimus withdrew due to lack of efficacy than 1% pimecrolimus (RR, 0.05; 95% CI, 0.00 to 0.84). There was no difference in withdrawals between 0.03% tacrolimus and 1% pimecrolimus in pediatric patients with moderate AD. There was no difference in withdrawals between 0.1% tacrolimus and1% pimecrolimus in the treatment of adult patients or moderate to very severe pediatric patients. Combined analyses of withdrawal showed that fewer tacrolimus-treated patients withdrew because of a lack of efficacy (RR, 0.32; 95% CI, 0.19 to 0.53) or adverse event (RR, 0.43; 95% CI, 0.24 to 0.75), compared to pimecrolimus-treated patients.
Bieber et al.[87] (2007) Tacrolimus 0.03% ointment BID to all affected BSA vs	CS, DB, MC, RCT Patients 2 to 15 years of age with a history of moderate to severe AD for at least 1 year experiencing acute flare of AD	N=265 3 weeks	Primary: Treatment success (defined as a score of clear or almost clear in the static IGA score) Secondary: The percentage	Primary: In both groups, treatment was successful in the majority of patients by the end of treatment: MPA, 66.6%; tacrolimus, 66.9%. The difference between treatment groups was not statistically significant (P=0.9314). At day 14 the success rate was 50.3% for MPA vs 41.1% for tacrolimus. The number of patients cleared at the end of treatment was 37.2% for MPA and 29.4% for tacrolimus. All patients in the MPA groups and 97.1% in the tacrolimus group reported an improved IGA score at the end of treatment (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
methyl-prednisolone aceponate (MPA) 0.1% ointment in the evening (vehicle ointment was applied in the morning)	according to IGA (≥4) with at least 5% of total BSA involvement		change in EASI and patient's assessment of itch and sleep, children's DLQI, patient's assessment of global response, affected BSA and medication costs	Secondary: Substantial improvement in EASI was noted at days four and seven for both treatment groups. However, there was a greater mean percentage change from baseline for EASI with MPA compared to tacrolimus during the study. At the end of treatment, the mean percentage change from baseline for EASI was 89.7% in the MPA group compared to 85.3% in the tacrolimus group. The difference between the two groups was significant after seven days of treatment (P=0.0352) and after 14 days of treatment (P=0.0214) but not at day 21 (P=0.0667). The percentage of affected BSA decreased from approximately 29.0% at baseline for both treatment groups to 6.8% in the MPA group compared to 7.7% in the tacrolimus group at the end of the study. The mean intensity of itching declined substantially from baseline to end of treatment and was particularly pronounced in the MPA group. The change in assessment of itch was statistically significant for MPA by day four (day four; P=0.026; day seven; P=0.0006; day 14; P=0.0007; day 21; P=0.0004). The improvement in quality of sleep with MPA was significantly better than tacrolimus at day 14 (P=0.0409) and at the end of treatment (P=0.0094). Medication cost comparison between MPA and tacrolimus were significant for MPA (P=0.0001). Six patients in the tacrolimus group and none from the MPA group experienced adverse reactions including pruritus, erythema, skin burning and hot flushes that were attributed to treatment. A total of four patients (all in the tacrolimus group) discontinued the study due to adverse events. No patients in the MPA group and two patients in the tacrolimus group reported a worsening of the disease compared to baseline.
Ashcroft et al.[88] (2005)	MA Patients with AD	N=6,897 1 week to 12	Primary: For pimecrolimus: proportion of	Primary: <u>For pimecrolimus:</u> In five trials evaluating pimecrolimus vs placebo, pimecrolimus was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tacrolimus or pimecrolimus vs topical corticosteroids or placebo		months	patients rated by the investigator as clear or almost clear For tacrolimus: proportion of patients achieving at least 90% improvement from baseline Secondary: Patients' global assessments of feeling better or much better, proportion of patients with flares of AD, improvements in QOL, tolerability assessed by overall rates of withdrawal, withdrawal due to adverse effects, proportion of patients with burning of the skin and skin infections	significantly more effective than placebo at three weeks (P<0.0001), and three of these found that pimecrolimus retained this efficacy at six weeks (P<0.0001). Another trial found no significant difference at six months between pimecrolimus and placebo. In three PC trials, there were significantly fewer flares at six months in the pimecrolimus group compared to the placebo group and remained more effective at preventing flares at 12 months. One trial evaluated pimecrolimus and a potent corticosteroid and found that betamethasone valerate 0.1% was significantly more effective than pimecrolimus after three weeks treatment when evaluating the proportion of patients who were clear or almost clear (P=0.0008). One study evaluated pimecrolimus vs a potent corticosteroid on the trunk and a mild corticosteroid on the face and found that the combination of corticosteroids was significantly more effective than pimecrolimus (when evaluating the proportion of patients moderately clear or better) at one week, three weeks, and six months but found no difference at 12 months. One direct comparison of pimecrolimus 1% cream and tacrolimus 0.03% ointment found no difference in the proportion of patients (children) who were clear or almost clear at six weeks (P=0.15). One study evaluating pimecrolimus QID compared to pimecrolimus two times daily found no difference in the proportion of patients clear or almost clear at the end of three weeks. <u>For tacrolimus:</u> One trial compared tacrolimus 0.03%, tacrolimus 0.1%, and placebo and found that the 0.03% strength was significantly more effective compared to placebo when evaluating the proportion of patients clear or achieving excellent improvement (P=0.006), but that the 0.1% strength did not differ from placebo (P=0.13) at three weeks. When evaluating patients' assessments of improvement as better or much better, both strengths proved significantly better than placebo. Three other trials reported the same outcomes as described above after 12 weeks and found both

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				strengths to be significantly more effective than placebo (P<0.0001). Two trials compared tacrolimus 0.03% and 0.1% vs hydrocortisone 1% and found that tacrolimus was significantly more effective than hydrocortisone when evaluating the proportion of patients clear or achieving excellent improvement at three weeks (P<0.0001). One trial compared tacrolimus 0.1% and alclometasone 0.1% and found that tacrolimus was significantly more effective than alclometasone for treating facial dermatitis. One trial compared tacrolimus 0.03 and 0.1% and hydrocortisone butyrate 0.1% (a potent corticosteroid) and found that the 0.03% tacrolimus was significantly less effective than the hydrocortisone butyrate judged by the proportion of patients clear or achieving excellent improvement at three weeks (P=0.008); but no significant difference was seen between the 0.1% strength of tacrolimus and the hydrocortisone butyrate (P=0.65). Two trials compared tacrolimus 0.1% with betamethasone valerate 0.1% or hydrocortisone butyrate 0.1% and found that the tacrolimus was as effective as the corticosteroids in the proportion of patients achieving at least marked improvement. One trial compared tacrolimus 0.1% with a regimen of hydrocortisone butyrate 0.1% on the trunk and extremities and hydrocortisone acetate 1% on the head and neck. It found that tacrolimus was significantly more effective than the combined corticosteroid regimen when evaluating the proportion of patients clear or achieving excellent improvement at 12 weeks (P<0.0001). Six trials compared tacrolimus 0.1% and 0.03%. Three trials found no difference in proportion of patients clear or achieving excellent response at three weeks between the two strengths (P=0.44) and the remaining three found tacrolimus 0.1% to be significantly more effective than the 0.03% strength (P=0.04) at 12 weeks. Secondary: Significantly more patients withdrew from treatment in the placebo groups than with either pimecrolimus or tacrolimus (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Rates of withdrawal due to adverse effects did not differ significantly in the pimecrolimus group compared to the placebo group but was significantly higher in the tacrolimus group compared to the placebo group. Rates of withdrawal due to adverse effects did not differ significantly in the pimecrolimus or tacrolimus groups compared to topical corticosteroids, nor did rates when comparing tacrolimus 0.03 to 0.1%. Skin irritation and skin burning did not differ significantly between pimecrolimus groups and placebo (P=0.257), but the rate was significantly higher with pimecrolimus compared to betamethasone valerate 0.1% or a combined regimen of triamcinolone acetonide 0.1% and hydrocortisone acetate 1%. Both strengths of tacrolimus were more likely to cause skin burning compared to placebo (P=0.010) and were more likely to cause skin burning compared to mild or potent corticosteroids. QOL was difficult to measure, and different outcome measures were used in the studies. In two studies, parents judged QOL to be improved in patients taking pimecrolimus compared to placebo, and three trials showed increases in QOL in patients taking tacrolimus 0.03and 0.1% compared to placebo. Tacrolimus 0.1% was found to have a significantly greater improvement on QOL in adults compared to the 0.03% strength, but no significant differences were found in infants and children. No QOL assessments were found comparing pimecrolimus and tacrolimus to topical corticosteroids.
El-Batawy et al.[89] (2009) Tacrolimus or pimecrolimus	MA Patients with AD	N=7,378 (19 trials) Variable duration	Primary: Efficacy Secondary: Not reported	Primary: Pimecrolimus and tacrolimus were significantly more effective than placebo. Compared to topical corticosteroids, tacrolimus 0.1% and 0.03% ointment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs topical corticosteroids or placebo				was as effective as moderate potency topical corticosteroids, and more effective than a combined steroid regimen. Tacrolimus was more effective than mild potency topical corticosteroids. Secondary: Not reported
Chen et al.[90] (2010) Tacrolimus or pimecrolimus vs topical corticosteroids or placebo	MA Pediatric patients with AD	N=6,288 (20 trials) Variable duration	Primary: Efficacy and safety Secondary: Not reported	Primary: More patients using tacrolimus had a good response than those in control groups including placebo, 1% hydrocortisone acetate and 1% pimecrolimus. The corresponding OR were 4.56 (95% CI, 2.80 to 7.44), 3.92 (95% CI, 2.96 to 5.20) and 1.58 (95% CI, 1.18 to 2.12). The effect difference between 0.03% and 0.1% tacrolimus ointments was not statistically significant (OR, 0.90; 95% CI, 0.55 to 1.48). The incidence of adverse events of tacrolimus ointment or pimecrolimus cream was similar to the placebo. The major adverse events were burning and pruritus. Secondary: Not reported
Hui et al.[91] (2009) Tacrolimus or pimecrolimus vs no exposure to topical calcineurin inhibitors	RETRO Patients >6 months of age with AD	N=953,064 Variable duration	Primary: Risk of cancer Secondary: Not reported	Primary: The age- and sex-adjusted HR for all cancers were 0.93 (95% CI, 0.81 to 1.07; P=0.306) for tacrolimus-exposed vs -unexposed patients and 1.15 (95% CI, 0.99 to 1.31; P=0.054) for pimecrolimus-exposed vs -unexposed patients. T-cell lymphoma was the only cancer associated with a significantly increased risk among patients exposed to tacrolimus (HR, 5.04; 95% CI, 2.39 to 10.63; P<0.001) or pimecrolimus (HR, 3.76; 95% CI, 1.71 to 8.28; P=0.01). Secondary: Not reported
Basal Cell Carcinoma				
Schulze et al.[92] (2005)	DB, MC, PC, RCT Patients ≥18 years	N=166 Treatment:	Primary: Composite clearance rate	Primary: Composite clearance rates were 77% for the imiquimod group compared to 6% for the placebo group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Imiquimod 5% cream applied QD for 6 weeks vs placebo	of age with a histologically confirmed primary sBCC located on the trunk, limbs, neck, or head	6 weeks Follow-up: 12 weeks	Secondary: Histological clearance rate	Secondary: Histological clearance rates were 80% in the imiquimod group compared to 6% for the placebo group (P<0.001). The prevalence of sBCC in post-treatment excision histology in the imiquimod group was 16%.
Giesse et al.[93] (2004) Imiquimod 5% cream applied QD 5 times per week vs imiquimod 5% cream applied QD 7 times per week vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with a histologically confirmed sBCC on the limbs, trunk, neck, or head	N=724 Treatment: 6 weeks Follow-up: 12 weeks	Primary: Composite clearance rate, adverse events Secondary: Not reported	Primary: The composite clearance rates for the five times per week and seven times per week imiquimod groups were 75% (95% CI, 68 to 81) and 73% (95% CI, 66 to 79), respectively. Clearance rates based on histological data only for the five times per week and seven times per week groups were 82% (95% CI, 76 to 87) and 79% (95% CI, 73 to 85), respectively. Composite and histological clearance rates for the placebo groups were 2 to 3% (P<0.001). The percentage of patients who experienced ≥1 adverse event during the treatment phase in the five times per week, seven times per week, and placebo groups were 58, 64, and 36%, respectively. The percentage of patients who experienced ≥1 adverse event during the post-treatment period in the five times per week and seven times per week groups was 33 and 31%, respectively. Influenza symptoms, myalgia, malaise, fatigue, and fever were reported in <3% in any treatment group. Adverse effects seen in ≥3% in any treatment group include application site reactions, headache, upper respiratory tract infection, sinusitis, back pain, and pain. The incidence of headache was statistically higher in the five times per week group compared to its corresponding placebo group (P=0.027). Application site reactions possibly or probably related to treatment occurred in 29% of patients in the imiquimod five times per week group,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and in 43% of the seven times per week group, compared to 2.8% and 6.6% of patients in the respective placebo groups. Less than 10% of patients experienced a severe adverse effect. Local skin reactions were more intense in the active treatment groups compared to the placebo groups. Local skin reactions were most intense at three weeks and fell back to at or below baseline by week 12. Local skin reactions had significantly higher severity ratings in the imiquimod groups compared to their respective placebo groups (P<0.001). Erythema was the most commonly observed local skin reactions. Erythema, vesicles, edema, erosion, and scabbing/crusting were all significantly more severe in the imiquimod seven times per week group compared to the five times per week group (P<0.05). There was a significant correlation observed between the intensity of the local skin reactions and clearance rates in both imiquimod groups (P<0.05). Secondary: Not reported
Marks et al.[94] (2004) Imiquimod 5% cream applied QD 5 times per week vs imiquimod 5% cream applied QD 7 times per week	OS Patients with a histologically confirmed sBCC on their trunk, limbs, or neck	N=67 (208 tumors) 18 weeks	Primary: Presence of residual tumor upon clinical and histological evaluation 12 weeks after treatment, tolerability of treatment Secondary: Not reported	Primary: Histological clearance occurred in 161 tumors (77%). In the five times per week group, 100% of patients had clearance of at least one tumor compared to 93% in the seven times per week regimen. Tumors cleared in 47% of patients in the five times per week regimen and in 58% of patients in the seven times per week regimen. In the five times per week regimen, 89% of patients had 50% or more of their tumors clear compared to 84% in the seven times per week regimen. Local skin reactions were common, but well tolerated and there was a correlation to the intensity of local inflammatory reactions and the histological clearance of tumors. Lower histological clearance was noted on the lower extremities accompanied by a lower incidence of local

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				inflammatory reactions. Secondary: Not reported
Gollnick et al.[95] (2005) Imiquimod 5% cream applied QD 5 times per week on consecutive days for 6 weeks	OL, OS Patients 21 to 89 years of age with a histologically confirmed sBCC on the limbs, trunk, neck, or head	N=182 Treatment: 6 weeks Follow-up: 24 months	Primary: Non-recurrence rate Secondary: Not reported	Primary: The initial clearance rate for the ITT population was 89.6% at the 12-week post-treatment visit. Fourteen patients who were clinically clear of their treated tumor at the 12-week visit had clinical evidence of recurrence at the 24-month follow-up. Of these patients, histological data was available for 13 patients, of whom two had no histological evidence of recurrence. The estimated proportion of patients who were clinically clear of their treated tumor after a single six-week treatment at five times per week declined from 87.3% at month three to 79.4% at month 24. Secondary: Not reported
Gollnick et al.[96] (2008) Imiquimod 5% cream applied QD 5 times per week on consecutive days for 6 weeks	OL, OS Patients 21 to 89 years of age with a histologically confirmed sBCC on the limbs, trunk, neck, or head	N=182 Treatment: 6 weeks Follow-up: 5 years	Primary: Non-recurrence rate Secondary: Not reported	Primary: The initial clearance rate for the ITT population was 89.6% at the 12-week post-treatment visit. During the five-year follow-up period, 18 clinical recurrences occurred at the target tumor site, eight and 10 of which occurred during the first six and 12 months of follow-up, respectively. The five-year Kaplan-Meier and life-table estimates for sustained clinical clearance of those patients initially cleared were 84.5 and 86.9%, respectively, and 90.3% considering histology. The estimate of overall treatment success for all treated patients at the end of follow-up was 77.9%. Secondary: Not reported
Quirk et al.[97]	MC, OL	N=169	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2010) Imiquimod 5% cream applied QD 7 times per week for 6 weeks	Patients ≥18 years of age with a histologically confirmed sBCC on the limbs, trunk, neck, or head	Treatment: 6 weeks Follow-up: 60 months	Initial clearance, tumor recurrence, adverse events Secondary: Not reported	The initial clearance rate at the 12-week posttreatment visit was 94.1%. Of 157 patients who entered the long-term follow-up period, 20 had a clinical recurrence of their target sBCC, occurring within the first 24 months for 14 patients. The overall estimate of treatment success was 80.4% at 60 months (95% CI, 74.4 to 86.4). Local skin reactions and application site reactions occurred predominantly during the treatment period and resolved posttreatment. Secondary: Not reported
Peris et al.[98] (2005) Imiquimod 5% cream applied QD 3 times per week for 12 weeks	OL, OS Patients 45 to 83 years of age with a superficial or a nodular BCC with multiple or recurrent lesions where surgery is not an option or if treatment other than surgery was requested	N=49 (94 tumors) Treatment: 12 weeks Follow-up: 12 months	Primary: Clinical remission at the end of treatment and recurrences during the post-treatment observational period Secondary: Adverse effects	Primary: Overall, complete response was seen in 85.1% of the lesions. Partial remission was seen in 11.7% of lesions. None of the patients experienced a total lack of response, or had worsening of the lesions. A complete response was observed in 93.3% of superficial BCCs in 26 patients. Of these, 37.1% regressed after six weeks of treatment, 42.9% after two more weeks of treatment, and 20% after the full 12 weeks of treatment. A PR was observed in 5.3% of superficial BCCs in four patients. A complete response was observed in 52.6% of nodular BCCs in 10 patients after the full 12 weeks of treatment. A PR was seen in the remaining 36.8% of lesions. Two of the seven patients with PR were treated for an additional four weeks without further improvement. Recurrence was observed in 2.9% of successfully treated sBCCs six to eight months after treatment discontinuation. No recurrence was observed in the remaining 68 sBCCs and in 10 successfully treated nodular BCCs after 12 to 34 months of follow-up. Secondary: Local adverse effects were observed in 67.3% of patients, and no patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				experienced systemic adverse effects. Erythema was observed in 63.3% of patients, erosion in 53.1%, ulceration in 24.5%, vesicle formation in 14.3%, edema in 6.1%, pruritus in 67.3%, and burning in 24.5%. Hyperpigmentation and hypopigmentation were each observed in one and 15 patients respectively six months after treatment discontinuation. All skin reactions were rated as mild to moderate by the patients, with the exception of one patient who experienced a severe local reaction on the nose.
Garcia-Martin et al.[99] (2010) Imiquimod 5% cream applied QD 5 times per week for 6 weeks	OL Adults with a nodular BCC on the eyelid	N=15 24 to 28 months	Primary: Complete clinical clearance, adverse events Secondary: Not reported	Primary: All tumors showed histopathological remission within three months of starting imiquimod, and sustained clinical remission was documented in each patient after 24 to 28 months' follow-up. Adverse effects during treatment with imiquimod were almost exclusively local in nature (conjunctival irritation and discomfort with blinking). Overall tolerability was rated as excellent (n=1), good (n=7), or bad (n=7). Secondary: Not reported
Williams et al.[100] SINS (2017) Imiquimod 5% cream once daily vs excisional surgery	5-year follow up of a MC, NI, RCT Patients of any age with low-risk superficial and nodular BCC	N=383 patients with data at year 5 5 years	Primary: Five-year success (defined as 3-year success plus absence of recurrences identified through hospital, histopathology, and general practitioner records) Secondary:	Primary: Five-year success rate for imiquimod was 82.5% compared with 97.7% for surgery (RR of imiquimod success, 0.84; 95% CI, 0.77 to 0.91; P<0.001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	
Roozeboom et al.[101] (2016) Imiquimod cream (once daily, five times a week for 6 weeks) vs fluorouracil cream (twice daily for 4 weeks) vs methyl aminolevulinate photodynamic therapy (MAL-PDT; two sessions with an interval of 1 week)	3-year follow up of a MC, NI, RCT, SB Patients with a histologically proven superficial basal-cell carcinoma	N=417 patients with data at year 3 3 years	Primary: Probability of tumor-free survival Secondary: Treatment failure	Primary: According to the intention-to-treat analysis, the probability of tumor-free survival at three years was 58.0% for MAL-PDT (95% CI, 47.8 to 66.9), 79.7% for imiquimod (95% CI, 71.6 to 85.7), and 68.2% for fluorouracil (95% CI, 58.1 to 76.3). According to these results at three years post-treatment, imiquimod is superior and fluorouracil not inferior to MAL-PDT in treatment of superficial basal cell carcinoma. Secondary: At three years post-treatment, the HR for treatment failure comparing imiquimod with MAL-PDT was 0.50 (95% CI, 0.33 to 0.76; P=0.001). Comparison of fluorouracil with MAL-PDT resulted in an HR of 0.73 (95% CI, 0.51 to 1.05; P=0.092), and comparison of fluorouracil with imiquimod in an HR of 0.68 (95% CI, 0.44 to 1.06; P=0.091).
Burke et al.[102] (2022) Imiquimod 5% cream five days per week vs Ascorbic acid 30% solution twice daily seven days	RCT Patients with histologically confirmed primary nodular or superficial basal cell carcinoma, previously untreated, and not arising at sites of high risk for sub-	N=25 8 weeks or until lesion cleared	Primary: Presence or absence of residual tumor at conclusion of study, confirmed by 2 mm punch biopsy Secondary: Not reported	Primary: After eight weeks of treatment, the 2 mm punch biopsy showed complete resolution of 13/15 (86.7%) in the ascorbic acid group and complete resolution of 8/14 (57.1%) in the imiquimod group (P<0.05 Chi Square). Six nodular lesions in the imiquimod group did not completely resolve after eight weeks, so they were treated for an additional four weeks. After the treatment extension, three additional lesions resolved. Hence, 11/14 (78.6%) lesions in the imiquimod group had resolved at 12 weeks. This result is not different from the ascorbic acid group at eight weeks (P>0.1). Local skin irritation occurred at most of the treatment sites in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
per week	clinical tumor spread.			both groups, although superficial erosion was more evident in the imiquimod group. There were no patients who discontinued treatment due to adverse reaction in either group, but six patients in the imiquimod group developed enough pain that it required them to pause treatment for several days before continuing after symptoms improved. Secondary: Not reported
Erythropoietic Protoporphyria				
Biolcati et al.[103] (2021) Afamelanotide 16mg implant administered subcutaneously every second month Treatment continued as tolerated by patients throughout the follow-up period of the trial.	OL, MC, SG Patients diagnosed with EPP who were previously enrolled in phase II/III clinical trials for afamelanotide in Switzerland and Italy	N=115 8 years	Primary: Endpoints were not defined in advance of study completion. Data were primarily collected to document effectiveness and safety for individual patients Secondary: Not reported	Primary: The mean quality of life score participants in Switzerland before treatment was 31% ± 24% of the maximum score, which increased to 74% ± 17% in the first six months of treatment and remained between 66% and 84% during the whole six-year observation period. Mean quality of life scores were not assessed at baseline from participants in Italy, but was reported to be stable between 74% and 80% of the maximum score until year 5 where it increased to 83%. Patients who discontinued treatment reported a slightly lower score (70.3% ± 16.3%), but statistically insignificant difference compared to those on continuous treatment (76.4% ± 10.3%, P=0.17) Melanin density rose about 0.4 units during the first two months and by about 0.7 units during the third and fourth months compared to baseline. Melanin density remained stable between 0.7 and 1.0 units between the fifth month and sixth year. Secondary: Not reported
Langendock et al.[104] (2015) Afamelanotide 16 mg SC every 60 days vs	DB, MC, PG, RCT Patients ≥18 years of age and biochemically confirmed EPP	N=168 270 days in the European Union study 180 days in the United State study	Primary: Number of hours in direct sunlight between 10 am and 3 pm without pain in the European Union study	Primary: In the European Union study, the median total number of hours on days for which “most of the day” was spent in direct sunlight between 10 am and 3 pm with no pain was 6.0 hours for patients receiving afamelanotide and 0.8 hours for patients receiving placebo (P=0.005). In the United States study, the median total number of hours spent in direct sunlight between 10 am and 6 pm on days with no pain was 69.4 hours for patients receiving afamelanotide and 40.8 hours for patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo SC every 60 days			Number of hours in direct sunlight between 10 am and 6 pm without pain in the United States study Secondary: Number of phototoxic reactions, duration of longest phototoxic reaction, sum of Likert score for severity of phototoxic reactions for both studies Number of hours in direct sunlight between 10 am and 3 pm without pain in the United States study	receiving placebo over the 180-day study period (P=0.04). Secondary: In the European Union study, the number of phototoxic reactions during study was lower in the afamelanotide group compared to placebo (77 versus 146; P=0.04). In the United States study, there were no significant differences observed in the number of phototoxic reactions (46 vs 43; P=0.60). In the European Union study, the median duration of phototoxicity was one day in the afamelanotide group compared to three days in the placebo group (P=0.04). In the United States study, there were no significant differences in the median duration of phototoxic reactions (one day vs one day; P=0.50). In the European Union study, the median sum of Likert score for severity of phototoxic reactions during the study was 5.0 for patients receiving afamelanotide and 17.5 for patients receiving placebo (P=0.02). In the United States study, the median sum was 4.0 for patients receiving afamelanotide and 6.0 for patients receiving placebo (P=0.44). In the United States study. the median total number of hours spent in direct sunlight between 10 am and 3 pm on days with no pain was 39.6 hours for patients receiving afamelanotide and 31.8 hours for patients receiving placebo (P=0.09).
Facial Angiofibromas				
Wataya-Kaneda et al.[105] (2018) Sirolimus gel 0.2% topically twice daily for 12 weeks vs placebo topically	DB, MC, PC, RCT Patients ≥3 years of age with a definitive diagnosis of tuberous sclerosis complex, displayed three or more reddish papules of facial angiofibromas (≥2 mm in	N=62 12 weeks	Primary: Composite improvement in the size and color of angiofibromas in photographs at week 12 of treatment Secondary: Safety	Primary: For the primary end point of composite improvements in angiofibromas at week 12, none of the 31 assessable patients in the placebo group were rated improved or better, and 26 of them (84%) were rated unchanged. In contrast, five (17%) and 13 (43%) patients in the sirolimus group were rated markedly improved and improved, respectively (P<0.001). Secondary: Adverse events were mild to moderate and were observed in 27 (90%) and 22 (69%) patients in the sirolimus and placebo groups, respectively; however, none of the trial participants discontinued treatment. Acute

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
twice daily for 12 weeks	diameter), and had difficulty or did not desire to undergo laser therapy and/or surgery			pancreatitis developed as a serious adverse event in one patient in the sirolimus group, and the patient recovered soon after hospitalization without discontinuing treatment.
Psoriasis				
Tosti et al.[106] (2009) Acitretin 0.2 to 0.3 mg/kg/day	OL Patients 28 to 67 years of age with moderate to severe nail psoriasis	N=36 6 months	Primary: Clinical evaluation, and NAPSI before therapy, during therapy, and 6 months after treatment Secondary: Not reported	Primary: The mean percentage reduction of the NAPSI score and modified NAPSI score were 41 and 50%, respectively. Clinical evaluation at six months showed complete or almost complete clearing of the nail lesions in nine patients (25%), moderate improvement in nine (25%), mild improvement in 12 (33%), and no improvement in six (11%). Patients' perception of treatment efficacy was high in 11 patients, moderate in 10, low in three, and absent in eight cases. Secondary: Not reported
Rim et al.[107] (2003) Acitretin 10 to 20 mg/day titrated up to a maximum dose of 40mg/day vs acitretin 10 to 20 mg/day titrated up to a maximum dose of 40 mg/day and calcipotriol ointment 50 µg/g	RCT Patients with chronic plaque type psoriasis with over 5% involvement of total BSA	N=60 4 to 52 weeks	Primary: Efficacy using the PASI Secondary: Not reported	Primary: After 12 weeks, 40% of patients in the calcipotriol plus acitretin group achieved complete clearance and 15% of patients in the acitretin monotherapy group achieved complete clearance (P<0.05). No significant differences were observed with regards to the degree of reduction of PASI scores after 12 weeks in both groups, however patients in the calcipotriol plus acitretin group showed faster remission at an early stage of therapy. After 52 weeks, 60% of patients in the calcipotriol plus acitretin group and 40% of patients in the acitretin monotherapy group achieved complete clearance (P<0.05). The duration of treatment and total dose of retinoid required to achieve clearance were slightly lower in the calcipotriol+acitretin combination group; however, this was not statistically significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
applied BID up to a maximum of 60 mg/week				With the exception of liver enzyme elevation, adverse effects were not significantly different between the two treatment groups. Secondary: Not reported
van de Kerkhof et al.[108] (1998) Acitretin 20 mg QD (maximum of 70 mg/day or 1 mg/kg/day) vs acitretin 20 mg QD (maximum of 70 mg/day or 1mg/kg/day) and calcipotriol ointment (50 µg/g) applied BID (maximum of 120 mg/week)	DB, MC, PC, RCT Patients ≥18 years of age with a clinical diagnosis of severe/extensive psoriasis vulgaris which was not deemed responsive to topical treatment alone	N=135 12 weeks	Primary: Investigator assessment of the extent and severity of the patient's psoriasis, using the PASI scoring system; patient assessment of overall response to treatment considering both the extent and the severity of the psoriasis Secondary: Not reported	Primary: In the calcipotriol group, the mean change in PASI from baseline to the end of the DB treatment was -13.2 (P<0.001). In the placebo group, the mean change in PASI from baseline to the end of the DB treatment was -8.8 (P<0.001). Comparing the two treatment groups at the end of the treatment, there was a statistically significant difference, favoring calcipotriol treatment (P=0.007). Comparing the mean whole-body scores for redness, thickness and scaliness at the end of the DB treatment, there was a statistically significant difference between the two treatment groups, favoring calcipotriol treatment (P=0.0001, P=0.002 and P=0.03, respectively). The patients' overall assessments revealed that comparing the two treatment groups at the end of the treatment, there was a trend which appeared to favor calcipotriol therapy (P=0.05). Secondary: Not reported
Mittal et al.[109] (2009) Acitretin 25 mg QD vs acitretin 25 mg QD	DB, RCT Patients 18 to 65 years of age with moderate to severe chronic plaque-type psoriasis	N=41 12 weeks	Primary: Change in PASI score, adverse events Secondary: Not reported	Primary: The percent reduction in the PASI score from baseline to 12 weeks of treatment was 64.2% (95% CI, 49.2 to 79.3) in the acitretin and pioglitazone group compared to 51.7% (95% CI, 38.7 to 64.7) in the acitretin plus placebo group (P=0.04). Overall, the lesions cleared or almost cleared in seven patients (37%) in the acitretin plus pioglitazone group compared to two patients (9%) in the acitretin plus placebo group (P=0.06).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
and pioglitazone 15 mg QD				At 12 weeks, PASI75 was achieved in eight patients (42%) in the acitretin plus pioglitazone group compared to five patients (23%) in the acitretin plus placebo group (P=0.31). PASI75 was attained earlier (by week eight in two patients (11%) in the acitretin plus pioglitazone group compared to one patient (4%) in the acitretin plus placebo group (P=0.59). Most of the adverse events observed were mild and tolerable. Common adverse events involved mucocutaneous and musculoskeletal complaints. There were no abnormalities in laboratory parameters, including serum lipid levels, liver function test results, and fasting blood glucose levels, in either group. Secondary: Not reported
Veronikis et al.[110] (1999) Calcipotriene applied BID vs coal tar 1% emulsion applied BID	CS, SB Patients 18 to 75 years of age with plaque-type psoriasis	N=20 12 to 125 days	Primary: Erythema, scaling, and plaque thickness Secondary: Not reported	Primary: The scores for erythema, scaling, and plaque thickness significantly decreased in both the calcipotriene group and the coal tar group (P<0.05), though there were no significant differences observed between treatment groups. Secondary: Not reported
Alora-Palli et al.[111] (2010) Calcipotriene 0.005% cream applied BID vs liquor carbonis distillate (LCD)	RCT Patients ≥18 years of age with moderate, chronic plaque psoriasis	N=60 Treatment: 12 weeks Follow-up: 6 weeks	Primary: Change in PASI Secondary: Change in PGA scale score, Pruritus Scale score, DLQI, and patient-reported psoriasis symptoms score	Primary: After 12 weeks, mean PASI scores improved by 58% in the LCD group and by 37% in the calcipotriene group (P<0.05). Significantly more patients in the LCD group achieved PASI 50 than in the calcipotriene group (P<0.05). Secondary: The LCD group had more patients (14/27) with absent or minimal psoriasis on the PGA scale than the calcipotriene group (6/28) by the end of treatment (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
15% solution (equivalent to 2.3% coal tar) applied BID			Secondary: Not reported	Patients' DLQI scores, Pruritus Scale scores, and patient's scores for flaking/scaling, itch, redness/irritation, burning sensation, roughness/texture, and overall discomfort improved with both treatments (P<0.05 vs baseline). Improvement in redness/irritation was more pronounced in the LCD group (52%) than in the calcipotriene group (29%; P<0.05). Significantly fewer patients in the LCD group than in the calcipotriene group lost their PASI 50 response at week 18 after six weeks without treatment (P<0.05) or had PGA scores at week 18 worsen to pre-treatment severity (P<0.01). Between week 12 and week 18, PASI scores and PGA scores worsened after stopping calcipotriene therapy (P<0.05), but not after stopping LCD therapy. Patients' Pruritus Scale scores worsened after stopping calcipotriene therapy (P=0.006) but not after stopping LCD therapy (P=0.28). This difference was significant between treatment groups (P=0.003). Patients' DLQI scores improved after stopping LCD therapy (P=0.03) but worsened directionally after stopping calcipotriene therapy (P=0.13). This difference was significant between treatment groups (P=0.009). Patients scores for scaling/flaking, redness/irritation, itch, and roughness/texture worsened after stopping calcipotriene therapy (P<0.05), but not after stopping LCD therapy. More LCD- than calcipotriene-treated patients considered their psoriasis to be stabilized or improved after 6 weeks without treatment. Patients' assessments of convenience, tolerability, and overall opinion of LCD solution and calcipotriene cream were comparable and favorable for both products. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Feldman et al.[112] (2012) Calcipotriene 0.005% foam BID vs vehicle foam (Two studies reported of identical design).	DB, MC, PG, RCT Patients ≥12 years of age with plaque psoriasis involving 2 to 20% of BSA	N=529 8 weeks	Primary: Treatment success defined as change from baseline at week eight of at least two grades and an ISGA score of 0 or 1 Secondary: Change from baseline in ISGA score, ISGA score of 0 or 1, target lesion score of 0 or 1 for erythema and at least a 2-grade improvement from baseline, target lesion score of 0 or 1 for scaling and at least a 2-grade improvement from baseline, a target lesion score of 0 for plaque psoriasis, and adverse effects	Primary: In Study 1, 14% of the calcipotriene group achieved treatment success compared to 7% in the vehicle group (P=0.058). In Study 2, there was a significantly greater proportion of patients that achieved treatment success in the calcipotriene group compared to placebo (P=0.016). Secondary: In Study 1, there was no significant difference in the proportion of patients with mild severity (ISGA scores of 2) who achieved treatment success between the two groups (3 vs 9%; P=0.167). For patients with moderate disease severity (ISGA score of 3), the treatment success rate was significantly higher in the calcipotriene group compared to vehicle (19 vs 6%; P=0.009). In Study 2, there was no significant difference in the proportion of patients with mild severity (ISGA scores of 2) who achieved treatment success between the two groups (14% vs 13%; P=0.859). For patients with moderate disease severity (ISGA score of 3), the treatment success rate was significantly higher in the calcipotriene group compared to vehicle (32 vs 17%; P=0.015). For Study 1, the secondary endpoints for IGSA score of 0 or 1, target lesion score for erythema, scaling, and psoriasis were not considered significant because the primary endpoint failed to reach significance. For Study 2, the proportion of patients with target lesion score of 0 or 1 and grade-2 improvement in the calcipotriene group compared to vehicle was significantly greater for erythema (P=0.034), scaling (P=0.004), but not plaque thickness (P=0.052). A similar proportion of patients in the calcipotriene group experienced adverse effects compared to the vehicle group (16 vs 18%).
Feldman et al.[113] (2013) Calcipotriene 0.005% foam BID	DB, MC, PG, RCT Patients ≥12 years of age with plaque psoriasis involving	N=363 8 weeks	Primary: Proportion of patients with ISGA score of 0 or 1 for scalp involvement	Primary: A significantly greater proportion of patients in the calcipotriene group had an ISGA score of 0 or 1 for scalp involvement compared to vehicle (40.9 vs 24.2%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs vehicle foam	3 to 10% of total BSA (excluding scalp and face), with an ISGA of 3 at baseline, target lesion of >2 cm^2 on the trunk or extremities with a score of 2 or 3 for erythema, scaling and plaque thickness and plaque psoriasis on ≥10% of the total scalp surface area with an ISGA score of 3 at baseline		at week eight Secondary: Proportion of patients with ISGA score of 0 or 1 for body involvement at week eight; target lesion score of 0 or 1 for erythema, sling and plaque thickness; and an improvement of ≥2 grades; primary and secondary endpoints at weeks two and four	Secondary: At week eight, there was no significant difference in the proportion of patients with an ISGA score of 0 or 1 for total body involvement between the groups (P=0.544). At week eight, there was no significant difference in the proportion of patients that achieved an ISGA score of 0 or 1 and an improvement of ≥2 grades for target lesion erythema (P=0.112), scaling (P=0.059) or plaque thickness (P=0.116). At weeks two and four, there were a significantly greater proportions of patients in the calcipotriene group that achieved an ISGA score of 0 or 1 for scalp psoriasis compared to vehicle (P=0.41 and P<0.001, respectively), scaling (P=0.02 and P=0.015, respectively). At week four, there was a significantly greater proportion of patients in the calcipotriene group that achieved an ISGA score of 0 or 1 and an improvement of ≥2 grades for target lesion erythema (P<0.001) and plaque thickness (P=0.036), but not at week two (P=0.895 and P=0.268, respectively). The mean percent reduction in the percent of scalp affected by psoriasis was significantly greater in the calcipotriene patients compared to vehicle at week four (P=0.017) and eight (P=0.002), but not at week two (P=0.159). There was a higher incidence of treatment related adverse events with calcipotriene compared to vehicle (17 vs 7%). The most common adverse event was application site reactions.
Sharma et al.[114] (2003) Calcipotriol 0.005% ointment applied BID vs	RCT, SB Patients 16 to 60 years of age with nearly bilaterally symmetrical lesions of stable plaque psoriasis	N=36 12 weeks	Primary: Improvements in the ESI of psoriatic lesions, relapse rates, and self-assessment by patient of efficacy and acceptability	Primary: At four weeks, there was a significant improvement (>50% reduction in ESI score) in 60% of patients on the calcipotriol side compared to 23.3% of patients on the coal tar side (P<0.01). At eight weeks, there was a significant improvement (>505 reduction in ESI score) in 73.3% of patients on the calcipotriol side compared to 33.3% of patients on the coal tar side (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
coal tar 5% ointment applied QHS			Secondary: Not reported	At eight weeks, there was a marked improvement (>75% reduction in ESI score) in 26.6% of patients on the calcipotriol side compared to 0% of patients on the coal tar side. At 12 weeks, there was a marked improvement (>75% reduction in ESI score) in 53.3% of patients on the calcipotriol side compared to 33.3% of patients on the coal tar side (P<0.01). At 12 weeks, there was a significant improvement observed in 86.7% of patients for both calcipotriol and coal tar. The median time for attaining a >50% reduction in ESI score for calcipotriol was 6.1±1.9 weeks and 9.6±1.8 weeks for coal tar (P<0.01). During the eight-week follow-up period, relapse was observed in 10% of patients on the calcipotriol side compared to 16.7% of patients on the coal tar side, though this difference was not significant (P>0.05). There was no significant difference between the physician and patient assessments of degree of improvement at any time during the study. There was a preference for calcipotriol ointment for visual presentability, lack of staining, and cosmetic elegance compared to coal tar. Secondary: Not reported
Thaci et al.[115] (2001) Calcipotriol 50 µg/mL solution applied BID as monotherapy or in combination with other treatments	OS, PRO Patients 30 to 62 years of age with scalp psoriasis	N=3,396 8 weeks	Primary: Investigator assessment of psoriasis severity based on the PSSI at each visit, investigators' global assessments of changes in psoriasis, tolerance, and	Primary: There was a significant decrease in mean PSSI after eight weeks of therapy in the group treated only with calcipotriol solution from 16.0 to 4.9 and in the patients treated with calcipotriol solution in combination with other agents from 20.7 to 6.2 (P<0.001). There was an additional therapeutic effect noted in patients treated with calcipotriol solution in combination with selective ultraviolet phototherapy and topical corticosteroids (P<0.001 and P<0.01 respectively). Investigators rated the improvements to be very good or good in 79.8% of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			cosmetic acceptance of the treatment, and investigator and patient comparison of this therapy to previous therapies Secondary: Not reported	patients. Among patients, 75.7% rated the improvements to be very good or good, 91.7% rated the treatment to be very well or well tolerated, and 95.8% rated the cosmetic acceptance to be very good or good. Investigators rated calcipotriol solution to be more effective than past treatments in 45.1% of patients. Safety was rated as improved by 32.4% of patients compared to past treatments. Application of the product was rated easier by 36.8% of patients. Calcipotriol was rated cosmetically more acceptable than previous treatments by 45.1% of patients. There were no major differences between investigator and patient global assessments. Secondary: Not reported
Reygagne et al.[116] (2005) Calcipotriol 0.005% solution applied BID vs clobetasol 0.05% shampoo applied QD	MC, PG, RCT, SB Patients ≥12 years of age with moderate to severe scalp psoriasis	N=151 4 weeks	Primary: GSS and TSS Secondary: Pruritus, surface area of scalp affected by psoriasis	Primary: Clobetasol propionate was shown to be significantly more efficacious compared to calcipotriol in TSS measures (P<0.001 at week two and P=0.028 at week four) and GSS measures (P<0.001 at week two and P=0.016 at week four). Secondary: Erythema, plaque thickening, adherent desquamation, and pruritus improved in both treatment groups, but a greater improvement was observed in the clobetasol group. The percentage of scalp surface area affected showed significant difference in favor of clobetasol (P=0.02).
Tosti et al.[117] (1998)	DB, RCT	N=58	Primary: Nail thickness	Primary: For fingernail psoriasis, subungual hyperkeratosis was reduced by 26.5%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Calcipotriol 50 µg/g ointment applied BID vs betamethasone 64 mg/g ointment and salicylic acid 0.03 g/g ointment applied BID	Patients ≥18 years of age with a diagnosis of nail bed psoriasis with severe subungual hyperkeratosis	3 months with an optional additional 2 months of treatment for responders	expressed in millimeters using a micrometer caliper, patient assessment of acceptability of treatment Secondary: Not reported	in the calcipotriol group and by 30.4% in the betamethasone and salicylic acid group after three months and the difference between groups was not significant. Eight patients in the calcipotriol group and 10 patients in the betamethasone and salicylic acid group were considered responders (>50% reduction in subungual hyperkeratosis in at least one nail). At five months, responders showed a 49.2% reduction in hyperkeratosis in the calcipotriol group and 51.7% reduction in the betamethasone and salicylic acid group (P<0.001). For toenail psoriasis, hyperkeratosis was reduced by 20.1% in the calcipotriol group and 22.9% in the betamethasone plus salicylic acid group at three months (P<0.001 from baseline), but the differences between groups were not significant. Seven patients in the calcipotriol group were considered responders and 12 in the betamethasone and salicylic acid group (>50% reduction in subungual hyperkeratosis in at least one nail). At five months, there was a further reduction in hyperkeratosis in the calcipotriol group (40.7%) and in the betamethasone and salicylic acid group (51.9%) from baseline (P<0.0001 for both groups, between-group differences not reported). Differences in patient assessment of the acceptability of their treatment at three and five months were not significant between groups. Secondary: Not reported
Crosti et al.[118] (1997) Calcipotriol 50 µg/g ointment applied BID vs	RCT Patients ≥18 years of age with mild stable psoriasis	N=160 Treatment: 6 weeks Follow-up 1 month	Primary: Improvement in PASI scores, investigator assessments of efficacy Secondary: Not reported	Primary: At the end of the study period, trunk lesions had disappeared in 21.3% of calcipotriol patients and 16.3% of betamethasone and salicylic acid patients, lesions on the arms had disappeared in 21.3% of calcipotriol patients and 15.0% of betamethasone and salicylic acid patients, and lesions on the legs had disappeared in 13.8% of calcipotriol patients and 10.0% of betamethasone and salicylic acid patients. These differences were significant compared to baseline (P<0.05), but not significant between groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
betamethasone dipropionate ointment and salicylic acid ointment applied BID				Erythema of the trunk disappeared in 21.3% of calcipotriol patients and 17.5% of betamethasone and salicylic acid patients, erythema of the arms disappeared in 25.0% of calcipotriol patients and 16.3% of betamethasone and salicylic acid patients, and erythema of the legs disappeared in 20.0% of calcipotriol patients and 12.5% of betamethasone and salicylic acid patients. These differences were significant compared to baseline (P<0.01), but not significant between groups. Skin infiltration on the trunk disappeared in 30.0% of calcipotriol and betamethasone and salicylic acid patients, skin infiltration on the arms disappeared in 55.0% of calcipotriol patients and 56.2% of betamethasone and salicylic acid patients, and infiltration on the legs disappeared in 42.5% of calcipotriol patients and 36.3% of betamethasone and salicylic acid patients. These differences were significant compared to baseline (P<0.01), but not significant between groups. Exfoliation on the trunk disappeared in 48.8% of calcipotriol patients and 41.3% of betamethasone and salicylic acid patients, scales on the arms disappeared in 61.3% of calcipotriol patients and 55.0% of betamethasone and salicylic acid patients, and scales on the legs disappeared in 23.8% of calcipotriol patients and 37.5% of betamethasone and salicylic acid patients. These differences were significant compared to baseline (P<0.01), but not significant between groups. By 6 weeks of treatment, PASI scored decreased 66.8% in the calcipotriol patients and 60.8% of betamethasone and salicylic acid patients compared to baseline (P<0.001). Significance for the between-group differences was not reported. Investigators assessed 79% of patients in the calcipotriol group and 89.4% of patients in the betamethasone and salicylic acid group as improved or healed. Treatment acceptability was assessed as “good” or “excellent” by 83.8% of patients in the calcipotriol group and 76.3% of the betamethasone and salicylic acid group. Significance for the between-group differences was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				not reported. Secondary: Not reported
Parslew et al.[119] (2005) Calcipotriene and betamethasone dipropionate applied QD vs placebo	MA Patients ≥18 years of age with a diagnosis of psoriasis vulgaris	N=1,534 (4 trials) Up to 4 weeks of treatment	Primary: Percent change in PASI Secondary: PASI after one week of treatment (assessed in three of the four studies), IGA	Primary: The mean PASI at baseline was 10.2 in patients <60 and 9.7 in patients ≥60. The mean reduction in PASI was 67.8% in patients <60 and 72.6% in patients ≥60. Secondary: More than half of the treatment response was seen after the first week of treatment with a 39% reduction in PASI in patients <60 and a 40.75 reduction in patients ≥60. In the two studies assessing IGA of Disease Severity, 52.1% of patients <60 and 52.8% of those ≥60 had controlled disease after up to four weeks of treatment. A total of 59% of patients <60 and 64.4% of those ≥60 judged themselves as having attained treatment success. A similar portion of patients <60 and ≥60 experienced lesional or perilesional adverse reactions during the study.
Tyring et al.[120] (2010) Calcipotriene 50 µg/g and betamethasone dipropionate 0.5 mg/g scalp formulation applied QD vs placebo	DB, RCT Patients ≥18 years of age with scalp psoriasis who were Hispanic or Latino and/or Black or African American	N=177 8 weeks	Primary: Proportion of patients with cleared or minimal disease Secondary: Investigator's assessment of clinical signs of scalp psoriasis; patient's global assessment of severity of scalp	Primary: In the calcipotriene and betamethasone group, 71.9% of patients had cleared or minimal disease at week eight by the IGA compared to 40.5% in the placebo group (OR, 3.30; 95% CI, 1.62 to 6.72; P<0.001). Secondary: For total sign score ≤1, thickness of scalp psoriasis absent and patient's global assessment of cleared/very mild), calcipotriene and betamethasone was significantly more effective than placebo (P=0.004, P=0.002 and P=0.004, respectively). For absence of redness and scaliness of scalp psoriasis, the response rate was greater with calcipotriene and betamethasone than placebo (P=0.010 and

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			psoriasis	P=0.017, respectively). There were 7.0% of patients in the calcipotriene and betamethasone group with 11 adverse events, compared to 7.9% of patients with four adverse events in the placebo group (OR, 0.88; 95% CI, 0.23 to 3.44; P=1.00).
Menter et al.[121] (2013) Calcipotriene 50 µg/g and betamethasone dipropionate 0.5 mg/g suspension vs betamethasone dipropionate 0.5 mg/g suspension vs calcipotriene 50 µg/g suspension vs vehicle suspension	DB, MC, RCT Patients ≥18 years of age with mild to moderate psoriasis for ≥6 months involving ≥10% of the arms, legs or trunk and amenable to treatment with ≤100 g of medication per week	N=1,152 8 weeks	Primary: Proportion of patients achieving controlled disease (IGA score of clear or almost clear and ≥2 point change from baseline) at weeks four and eight Secondary: Change from baseline in PASI at weeks four and eight	Primary: At week four, there was a significantly greater proportion of patients achieving controlled disease in the calcipotriene and betamethasone group (13.3%) compared to calcipotriene groups (5.2%; P=0.019) and vehicle (2.1%; P=0.001). There was no significant difference in achievement of controlled disease between the calcipotriene and betamethasone and betamethasone groups (12.5%; P=0.82). At week eight, the calcipotriene and betamethasone group had a significantly greater proportion of patients achieving controlled disease (29%) compared to the betamethasone (21.5%), calcipotriene (14.6%) and vehicle groups (6.3%; P≤0.008 for all comparisons). Secondary: At week four, the calcipotriene and betamethasone group had a significantly greater mean reduction in PASI (46.4%) compared to the betamethasone (42.7%), calcipotriene (32.2%) and vehicle groups (17.4%; P≤0.038 for all comparisons). At week eight, the calcipotriene and betamethasone group had a significantly greater mean reduction in PASI (55.8%) compared to the betamethasone (48.6%), calcipotriene (43.6%) and vehicle groups (20.9%; P<0.001) for all comparisons).
Singh et al.[122] (2000) Calcipotriene 0.005% ointment applied BID on weeks 2 and 4 and augmented betamethasone	PG, RCT, SB Patients 20 to 50 years of age with stable plaque psoriasis	N=52 4 weeks	Primary: Proportion of patients having at least 90% reduction in baseline PASI scores at the end of the four-week study period	Primary: In the betamethasone group, 18.5% of patients had a 90% or greater reduction in baseline PASI scores after four weeks of therapy compared to 68% of patients in the calcipotriene and betamethasone group (P<0.001). Secondary: PASI scores were significantly lower in the calcipotriene and betamethasone group compared to the betamethasone group at different points of time except on days 0 and seven.

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0.05% cream applied QD on weeks 1 and 3 vs augmented betamethasone 0.05% cream applied QD for 4 weeks			Secondary: PASI scores on a weekly basis, reduction in PASI scores after two to four weeks, patients with marked improvement or almost clear at the end of treatment	The percentage reduction in PASI scores after two and four weeks of treatment was significantly higher in the calcipotriene and betamethasone group compared to the betamethasone group. The proportion of patients with marked improvement or who were almost completely cleared at the end of treatment was significantly higher in the calcipotriene and betamethasone group compared to the betamethasone group in both investigator and patient assessments.
Douglas et al.[123] (2002) Calcipotriene and betamethasone ointment applied BID (CB) vs betamethasone ointment applied BID (B) vs calcipotriene ointment applied BID (C)	DB, PRO, RCT Patients ≥18 years of age with a diagnosis of psoriasis vulgaris	N=1,106 4 weeks of treatment and an additional 4 weeks of OL treatment with calcipotriene	Primary: Mean percent change in PASI from baseline after four weeks Secondary: Speed of response as assessed from percent change in PASI after one-week, mean percentage decrease in the thickness of psoriatic lesion from baseline after four weeks	Primary: There was a significant reduction in mean percent change in PASI from baseline to week four in the CB group compared to the B group and the C group (74.4, 61.3, and 55.3% respectively; P<0.001). Secondary: There was a significant reduction in mean percent change in PASI after week one in the CB group compared to the B group and the C group (47.4, 39.8, and 31% respectively; P<0.001). There was a significant reduction in the mean percent change in thickness of the psoriatic lesion from baseline to week four in the CB group compared to the B group and the C group (79.4, 61.7, and 63% respectively; P<0.001). There was no significant difference in the percent of patients reporting adverse effects in any of the treatment groups.
Kaufman et al.[124] (2002) Calcipotriene and betamethasone ointment applied	DB, PC, PRO, RCT Patients ≥18 years of age with a diagnosis of psoriasis vulgaris	N=1,603 4 weeks	Primary: PASI score, IGA score, PGA score assessing patients with treatment success (defined as	Primary: There was a significant decrease in PASI score in the CB group compared to the B, C, and V groups (-71.3, -57.2, -46.1, and -22.7% respectively; P<0.001). There was a significantly larger number of patients assessed as having

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QD (CB) vs betamethasone ointment applied QD (B) vs calcipotriene ointment applied QD (C) vs vehicle ointment QD (V)	affecting at least 10% of one or more body regions		marked improvement or clearance of disease) Secondary: Not reported	controlled disease according to the IGA score in the CB group compared to the B, C, and V groups (276, 176, 107, and 16 respectively; P<0.001). There was a significantly larger number of patients assessed as having treatment success according to the PGA scores after four weeks in the CB group compared to the B, C, and V groups (316, 216, 137, and 15 respectively; P<0.001). Secondary: Not reported
Papp et al.[125] (2003) Calcipotriene and betamethasone ointment applied BID (CB) vs betamethasone ointment applied BID (B) vs calcipotriene ointment applied BID (C)	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of psoriasis vulgaris affecting at least 10% of one or more body areas	N=1,028 4 weeks	Primary: Mean percent reduction in PASI from baseline to the end of treatment Secondary: Speed of response assessed as the mean percent change in PASI from baseline after one week of treatment	Primary: There was a significant percent reduction in PASI at the end of treatment in the CB group compared to the B, C, V groups (73.2, 48.8, 63.1, and 28.8% respectively; P<0.001). Secondary: There was a significant reduction in the mean percent change in PASI from baseline to after one week of treatment in the CB group compared to the B, C, and V groups (48.1, 28.4, 41.4, and 21.5% respectively; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs vehicle ointment BID (V)				
Guenther et al.[126] (2002) Calcipotriene and betamethasone ointment applied QD vs calcipotriene and betamethasone ointment applied BID vs calcipotriene ointment applied BID vs placebo	DB, MC, PC, PG, PRO, RCT Patients 18 to 86 years of age with a diagnosis of psoriasis vulgaris involving at least 10% of one or more body regions	N=828 4 weeks	Primary: Percentage change in PASI from baseline to week four Secondary: Percentage change in thickness score of a target psoriatic lesion from baseline to each treatment visit, speed of response assessed by change in PASI from baseline to week two, investigator's overall assessment of treatment efficacy, adverse effects	Primary: The difference in PASI from baseline to week four in the combination treatment groups of once and BID was not significant (5.4%; P=0.052). The once-daily combined-medication group had a significantly reduced PASI compared to the calcipotriol group (68.6 vs 58.8%; P<0.001) and the placebo group (68.6 vs 26.6%; P<0.001). The twice-daily combined-medication group had a significantly reduced PASI compared to the calcipotriene group and the placebo group (P<0.001). Secondary: No significant difference was observed between the QD combined-medication group and the calcipotriene group or the once vs BID combined-medication groups in lesion thickness. There was a significant difference in lesion thickness in the once and BID combination-medication groups compared to the placebo group at the end of treatment (P<0.001). After one week of treatment, the change in PASI was greater in the combined-medication groups (45.5% for QD and 47.6% for BID) compared to the calcipotriene group (33.6%) and the placebo group (20%); (P<0.001). There was no significant difference observed in the speed of response between the QD and BID combination groups (P=0.30). For the investigators' and patients' assessment of efficacy, there was a higher percentage of responders (those achieving marked improvement or clearing) in the QD and BID combination groups (QD: 63.3%

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				investigators, 65.3% patients, BID: 73.5% investigators, 70.1% patients) compared to the calcipotriene group (50.7% investigators, 51.5% patients), and the placebo group (9.2% investigators, 12.6% patients; P<0.033). According to investigators' assessments, 14% of patients receiving the QD and 20.1% of patients receiving the BID combination products achieved clearance compared to 9.7% in the calcipotriene group and 0% in the placebo group. A significantly lower proportion of patients experienced adverse effects in both combination groups compared to the calcipotriene group (P<0.01). The percentage of patients with lesional or perilesional adverse reactions was less in the combination groups and the placebo group compared to the calcipotriene group (9.9% QD combination group, 10.6% BID combination group, 19.8% calcipotriene group, 12.5% placebo Group).
van de Kerkhof[127] (2004) Calcipotriene and betamethasone ointment applied QD vs calcipotriene and betamethasone ointment applied BID vs calcipotriene ointment applied BID	DB, MC, PC, RCT Patients 18 to 86 years of age with a diagnosis of psoriasis vulgaris involving at least 10% of one or more body regions	N=828 4 weeks	Primary: Changes in the PDI, EuroQOL 5D, VAS, and the EuroQOL 5D-VAS score from baseline to the end of the study (each of these tools measure overall QOL) Secondary: Not reported	Primary: Results of the PDI scores indicate that patients' QOL improved significantly in both combination groups and the calcipotriene group compared to baseline (P<0.001). No significant effect was seen in the placebo group (P>0.1). No statistical difference was found in QOL based on PDI score between the combination groups and the calcipotriene group (P>0.1), though a significant difference was noted in favor of the combination groups when compared to the placebo group (P<0.001). At baseline, pain/discomfort and anxiety/depression were the most significant problems reported by psoriasis patients. Parameters for pain/discomfort and anxiety/depression improved to a greater extent in the combination groups than in the calcipotriene and placebo groups. The VAS scores from baseline to the end of the study showed a significant improvement in QOL in both combination groups and the calcipotriene group (P<0.001), and no significant difference was seen in the placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				group from baseline (P>0.1). There was a significant improvement observed in the EuroQOL 5D-VAS score between both combination groups compared to the placebo group (P<0.001), as well as the QD combination group compared to the calcipotriene group (P<0.05). PASI reduction in both combination groups was significantly greater compared to the calcipotriene group and the placebo group after one week (P<0.001). Secondary: Not reported
Kragballe et al.[128] (2004) Calcipotriene and betamethasone ointment applied QD for 8 weeks followed by calcipotriene ointment applied QD for 4 weeks (Group 1) vs calcipotriene and betamethasone ointment applied QD for 4 weeks followed by calcipotriene ointment applied QD on weekdays and calcipotriene	DB, PG, PRO, RCT Patients ≥18 years of age with a diagnosis of psoriasis	N=971 12 weeks	Primary: Mean percent change in PASI from baseline to week eight, proportion of patients with absent or very mild disease according to the IGA at the end of eight weeks Secondary: Mean percent change in PASI from baseline to each visit and at 12 weeks, proportion of patients with absent/very mild disease according to IGA severity at each visit and at 12 weeks	Primary: There was a significant reduction in the mean percent change in PASI from baseline to week eight in group 1 compared to groups 2 and 3 (73.3, 68.2, and 64.1% respectively; P<0.001). There was a significantly greater percentage of patients with absent or very mild disease in group 1 compared to groups 2 and 3 (55.3, 47.7, and 40.7% respectively; P<0.001). Secondary: There were no significant differences between the three groups with respect to reduction in PASI scores at week 12. At week 12, significantly more patients in group 2 were assessed as having absent or very mild disease compared to group 3 (P=0.026).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
and betamethasone ointment applied QD on weekends for 8 weeks (Group 2) vs calcipotriene ointment applied BID for 12 weeks (Group 3)				
Paul et al.[129] PSO-ABLE (2016) Calcipotriol 50 µg/g (Cal)-betamethasone 0.5 mg/g (BD) foam vs Cal-BD gel vs foam vehicle vs gel vehicle	IB, PG, RCT Patients ≥18 years of age with mild-to-severe psoriasis	N=463 Up to 12 weeks	Primary: Proportion of patients with treatment success ('clear' or 'almost clear' with a ≥2 grade improvement in PGA-assessed disease severity) at week four in the foam group and week eight in the gel group Secondary: Changes from baseline in modified (excluding the head, which was not treated) PASI score; proportion of patients achieving modified PASI75;	Primary: A larger proportion of Cal-BD foam-treated patients achieved treatment success, compared with Cal-BD gel-treated patients (38.3 vs 22.5%; OR, 2.55; 95% CI, 1.46 to 4.46; P<0.001). Secondary: Adjusted mean modified PASI was significantly lower with Cal-BD foam than Cal-BD gel (4.50 vs 5.20; adjusted difference, −0.70; 95% CI, −1.05 to −0.35; P<0.001) at week one. The significant difference was maintained at week four for Cal-BD aerosol foam vs week 8eight for Cal-BD gel (2.18 vs 2.77; adjusted difference, −0.59; 95% CI, −1.11 to −0.06; P=0.028). The proportion of patients achieving modified PASI75 was greater with Cal-BD aerosol foam than Cal-BD gel throughout the study. Modified PASI75 was achieved by significantly more Cal-BD aerosol foam-treated patients (52.1%) at week four than Cal-BD gel-treated patients (34.6%) at week eight (OR, 2.18; 95% CI, 1.37 to 3.47; P<0.001). Modified PASI90 results with Cal-BD aerosol foam at week four vs Cal-BD gel at week eight were 22.2 vs 10.7% (OR, 2.43; 95% CI, 1.22 to 4.82; P=0.009); at weeks eight and 12 in the Cal-BD aerosol foam group, mPASI90 scores were 29.0 and 22.9%, respectively. Median time to achieving treatment success with Cal-BD aerosol foam was six weeks; time to achieving treatment success could not be

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			proportion of patients achieving modified PASI90; and time to achieving treatment success	determined for Cal-BD gel, as 50% treatment success was not achieved by 12 weeks (HR, 1.97; 95% CI, 1.46 to 2.65; P<0.001).
van de Kerkhof et al.[130] (2005) Calcipotriene and betamethasone ointment applied QD	MA Patients ≥18 years of age with a diagnosis of psoriasis vulgaris involving at least 10% of one or more body areas	N=1,534 Up to 4 weeks	Primary: Percent change in PASI from baseline Secondary: Rate of disease response assessed by the mean reduction in PASI (after week one), patients who achieved treatment success (marked improvement or clearance), and patients with controlled disease (absent or very mild disease) according to IGA and PASI	Primary: Among patients with severe disease at baseline, there was a 71.6% mean reduction in PASI at week four, 68.9% in patients with moderate disease, and 67.2% in patients with mild disease. Secondary: Among patients with severe disease at baseline, there was a 41.2% mean reduction in PASI after week one, 39.3% in patients with moderate disease, and 38.5% in patients with mild disease. Among patients with severe disease at baseline, 44.4% of patients achieved treatment success after four weeks according to IGA, 60.7% in patients with moderate disease, and 63.8% in patients with mild disease. Among patients with severe disease at baseline, 54.2% of patients achieved treatment success after four weeks according to patient's assessments, 60.9% in patients with moderate disease, and 61.2% in patients with mild disease. According to PASI-defined baseline disease severity, 38.7% of patients had controlled disease after four weeks, 52.9% in patients with moderate disease, and 66.1% in patients with mild disease. According to IGA-defined baseline disease severity, 44.1% of patients had controlled disease after four weeks, 53.0% in patients with moderate disease, and 69.3% in patients with mild disease.
Eichenfield et al.[131] (2015) Calcipotriene and	OL Patients 12 to 17 years of age with a clinical diagnosis of	N=31 8 weeks	Primary: Safety Secondary: Investigator- and	Primary: Sixteen patients (52%) experienced a total of 20 adverse events; 14 were mild in severity and none were serious or lesional/perilesional on the scalp. The most common adverse events were cough (n=3; 10%), oropharyngeal pain (n=3; 10%), nasopharyngitis (n=2; 7%), and upper

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betamethasone suspension applied QD	scalp psoriasis vulgaris involving ≥20% of the scalp		patient-assessed efficacy	respiratory tract infection (n=2; 7%). The investigator considered only one adverse event to be possibly related to study treatment—a patient with laboratory signs of adrenal suppression at week four. This adverse drug reaction was judged to be mild. The patient discontinued treatment and a normal ACTH challenge test was reported at the follow-up visit four weeks after the end of study treatment. No other patients showed signs of adrenal suppression. Secondary: Treatment success according to IGA was reported in 17 patients (55%) by the end of treatment, including three patients who achieved clear disease status at week four and completed the study at this time point according to the protocol. The mean TSS improved from 6.9 at baseline to 2.9 at the end of treatment (59% improvement). The proportion of patients with TSS success was 39% (n=12) at the end of treatment, compared with 0% at baseline. Changes in disease severity as evaluated by patients demonstrated similar results to the investigator assessments, with the number of patients reporting treatment success increasing from three (10%) at baseline to 18 (58%) at the end of treatment.
Menter et al.[132] (2009) Clobetasol 0.05% spray applied BID for four weeks vs calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment applied daily for four weeks	MC, RCT Patients 18 to 80 years of age with stable plaque psoriasis involving 3 to 20% of the BSA	N=122 8 weeks	Primary: Efficacy as assessed by ODS, investigator global assessment, PQOL-12 Secondary: Not reported	Primary: After two weeks, 41% of patients receiving clobetasol had treatment success (clear or almost clear) compared to 27% of patients receiving calcipotriene and betamethasone dipropionate. After four weeks, 75% of patients receiving clobetasol were clear or almost clear compared to 45% of patients receiving calcipotriene and betamethasone dipropionate (P=0.003). After eight weeks, 14% of patients receiving clobetasol were clear or almost clear compared to 8% of calcipotriene and betamethasone dipropionate patients. After four weeks, there was no significant difference in treatment success (clear or mild as assessed using the investigator global assessment scale) among the treatment groups (73% for clobetasol vs 65% for calcipotriene and betamethasone dipropionate). After two weeks, 52% of patients receiving clobetasol were clear or mild compared to 33% of patients receiving calcipotriene and betamethasone dipropionate (P=0.054). After eight weeks, 41% of patients receiving clobetasol were clear or mild compared to 24% of patients receiving calcipotriene and betamethasone

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				dipropionate. After four weeks, PQOL-12 scores decreased by 36.1 points with clobetasol and by 30.8 points with calcipotriene and betamethasone dipropionate. After two weeks, PQOL-12 scores decreased by 24.4 points with clobetasol and by 21.4 points with calcipotriene and betamethasone dipropionate. After eight weeks, PQOL-12 scores decreased by 15.9 points with clobetasol and by 10.1 points with calcipotriene and betamethasone dipropionate. Patient satisfaction surveys indicate that more patients were satisfied with clobetasol than with calcipotriene and betamethasone dipropionate. Compliance was similar in both treatment groups (100% for clobetasol and 97% for calcipotriene and betamethasone dipropionate). Erythema, scaling and dryness were similar in both treatment groups. More patients experienced stinging/burning with clobetasol. Secondary: Not reported
Luger et al.[133] (2008) Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g vs calcipotriol 50 µg/g	DB, MC, RCT Patients with moderate to severe scalp psoriasis	N=869 52 weeks	Primary: Efficacy and safety Secondary: Not reported	Primary: Disease was satisfactorily controlled in 92.3% of visits in the calcipotriol-betamethasone group vs 80.0% in the calcipotriol group (P<0.001). Adverse drug reactions were less frequent in the calcipotriol-betamethasone group compared to the calcipotriol group (17.2 vs 29.5%; P<0.001). Incidences of adverse events possibly associated with long-term corticosteroid use were low in both the calcipotriol-betamethasone (2.6%) and the calcipotriol (3.0%) groups. Secondary: Not reported
Saraceno et al.[134] (2007)	MC, RCT	N=150	Primary: Changes	Primary: A significant improvement of PASI score was demonstrated in patients

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Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g applied QD for 4 weeks, followed by calcipotriol 50 µg/g cream applied BID for 8 weeks vs calcipotriol 50 µg/g cream applied BID for 12 weeks	Patients >18 years of age with mild to moderate plaque psoriasis	12 weeks	in the PASI after four weeks of treatment Secondary: Maintenance of the PASI score with calcipotriol as a sequential therapy in the following eight weeks; safety of the study drugs; patients' QOL, as assessed by the Skindex-29	receiving QD treatment with calcipotriol and betamethasone dipropionate compared to BID treatment with calcipotriol at week two (P<0.001). These results were confirmed and maintained at week four (P<0.001). Secondary: Treatment with calcipotriol from week five to week 12 was associated with a further clinical improvement and treatment with calcipotriol and betamethasone dipropionate was associated with maintenance of the results. At week 12, no significant differences of PASI score were seen between the two groups. The QOL assessment showed a marked improvement in terms of Skindex-29 in both groups at weeks two and four as compared to baseline. Similarly to the clinical improvement, the QOL results were significantly superior in the calcipotriol and betamethasone dipropionate group compared to the calcipotriol group (P<0.001). Treatments were well tolerated. Common side effects included erythema, burning, exacerbation of psoriasis, vesicles, lesional or perilesional irritation, itching.
van de Kerkhof et al.[135] (2009) Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g vs betamethasone dipropionate 0.5 mg/g vs	DB, MC, PG, RCT Patients with scalp psoriasis involving >10% of the scalp	N=1417 8 weeks	Primary: Proportion of patients with 'absence of disease' or 'very mild disease' according to investigators' assessments Secondary: Patient ratings of scalp psoriasis and adverse events	Primary: The proportion of patients with 'absence of disease' or 'very mild disease' at week eight was significantly higher in the calcipotriol and betamethasone group (68.4%) than the betamethasone dipropionate (61.0%; P=0.0079) or calcipotriol (43.4%; P<0.0001) groups. Secondary: The proportion of patients rating their scalp psoriasis as 'clear' or 'almost clear' was significantly higher in the calcipotriol and betamethasone group (69.6%) than for betamethasone dipropionate (59.9%; P=0.0006) or calcipotriol (44.7%; P<0.0001). The incidence of lesional/perilesional adverse events was lower in the calcipotriol and betamethasone and betamethasone dipropionate groups than the calcipotriol group.

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calcipotriol 50 µg/g				
Jemec et al.[136] (2008) Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g applied QD vs betamethasone dipropionate 0.5 mg/g applied QD vs calcipotriol 50 µg/g applied QD vs placebo	DB, MC, RCT Patients with scalp psoriasis	N=1505 8 weeks	Primary: Patients with ‘‘absence of disease’’ or ‘‘very mild disease’’ according to IGA of disease severity at week eight Secondary: Total Sign Score at week eight, proportion of patients who were ‘‘almost clear’’ or ‘cleared’’ by patients’ assessment	Primary: The proportion of patients who achieved ‘‘absent’’ or ‘‘very mild’’ disease at week eight was significantly greater in the calcipotriol and betamethasone group (71.2%) compared to the betamethasone dipropionate group (64.0%; P=0.011), the calcipotriene group (36.8%; P<0.0001), and the placebo group (22.8%; P<0.0001). Secondary: At week eight, the percentage change in Total Sign Score was significantly larger for the calcipotriol and betamethasone group (-70.8%) than for calcipotriene (-49.0%; P<0.0001) and for placebo (-35.6%; P<0.001). The difference vs betamethasone dipropionate, (-67.7%) was not statistically significant (P=0.12). The proportion of patients who rated their scalp psoriasis as ‘‘cleared’’ or ‘‘almost clear’’ at week eight was 68.6% for the calcipotriol and betamethasone group, 62.5% for betamethasone dipropionate, 38.3% for calcipotriene, and 20.7% for the placebo alone. The calcipotriol-betamethasone group was significantly more effective than calcipotriene (P<0.0001) and the placebo alone (P<0.0001). The difference vs betamethasone dipropionate was not statistically significant (P=0.2).
White et al.[137] (2006) Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g ointment for 4 weeks followed by calcipotriol cream 50 µg/g for	RCT, SB (4 weeks), DB (8 weeks) Patients ≥18 years of age with a clinical diagnosis of psoriasis vulgaris affecting at least 10% of the arms and/or 10% of the trunk and/or 10% of	N=1136 12 weeks	Primary: Assessment of the PASI, investigators’ global assessment of disease severity on a six-point scale (disease absent, very mild, mild, moderate, severe, or very severe),	Primary: The mean percentage change in the PASI from baseline to the end of the trial was -44.5% in the calcipotriene cream group, -58.4% in the alternating group, and -33.1% in the vehicle group. The mean difference between the calcipotriene cream and vehicle groups was -11.7% (P<0.001), and the mean difference between the alternating and vehicle groups was -24.7% (P<0.001). For the investigators' global assessment of disease severity at the end of the trial, the differences between the calcipotriene cream and vehicle groups, and between the alternating and vehicle groups demonstrated

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8 weeks (cream group) vs calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g ointment for 4 weeks followed by calcipotriol cream 50 µg/g on weekdays and calcipotriol and betamethasone on weekends for 8 weeks (alternating group) vs calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g ointment for 4 weeks followed by vehicle cream for 8 weeks (vehicle group)	the legs		and adverse events Secondary: Not reported	greater efficacy in the non-vehicle groups (P<0.001). The patients' global assessment of disease severity demonstrated similar results (P<0.001). There were no statistically significant differences in the incidence of adverse drug reactions in the calcipotriene cream group relative to the vehicle group (P=0.21), or in the alternating group relative to the vehicle group (P=0.61). Secondary: Not reported
Kragballe et al.[138] (2006) Calcipotriol 50 µg/g and betamethasone	DB, RCT Patients ≥18 years of age with a clinical diagnosis of psoriasis vulgaris of	N=634 52 weeks	Primary: Adverse events Secondary: Not reported	Primary: Adverse drug reactions occurred in 21.7% of patients in the calcipotriol and betamethasone group, 29.6% in the alternating group and 37.9% in the calcipotriol group (P<0.001). The OR for an adverse drug reaction in the calcipotriol and betamethasone

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dipropionate 0.5 mg/g for 52 weeks vs calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g for 4 weeks followed by calcipotriol 50 µg/g for 4 weeks (alternating for 52 weeks) vs calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g for 4 weeks followed by calcipotriol 50 µg/g for 48 weeks	the trunk and/or limbs			group relative to the calcipotriol group was 0.46 (95% CI, 0.3 to 0.7; P<0.001). The OR for the alternating group relative to the calcipotriol group was 0.69 (95% CI, 0.46 to 1.04; P=0.073), and for the calcipotriol and betamethasone group relative to the alternating group 0.66 (95% CI, 0.42 to 1.03; P=0.066). Adverse drug reaction of concern associated with long-term topical corticosteroid use occurred in 4.8% of patients in the calcipotriol and betamethasone group, 2.8% of patients in the alternating group and 2.9% of patients in the calcipotriol group. Those adverse drug reactions with the highest incidence were skin atrophy and folliculitis. Secondary: Not reported
De Jong et al.[139] (2003) Calcipotriol 50 µg/g ointment applied BID and MTX vs MTX	DB, MC, PC, PG, RCT Patients ≥18 years of age with chronic plaque psoriasis who had been treated with MTX with or without topical treatment during the last 6	N=98 54 weeks	Phase I: Relapse-free interval [relapse measured by the MPSS] Phase II: MTX-sparing effect of calcipotriol (measured by the	Phases I and III: There was a statistically significant difference in favor of calcipotriol in MPSS scores (P=0.031). The median time to relapse was 113 days in the calcipotriol group compared to 35 days in the placebo group (P<0.001). There was no psoriasis relapse in 41.2% of patients in the calcipotriol group compared to 17.4%of patients in the placebo group. Phase II:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Phase I: Cessation of MTX and treatment initiation of blinded topical treatment with either calcipotriol or placebo for total of 30 weeks or until relapse occurs. Phase II: MTX titration phase with open MTX treatment and continuation of blinded topical therapy for 18 weeks or until target MPSS reached. Phase III: Follow-up phase for patients reaching the target MPSS for a maximum of 6 weeks.	months and whose psoriasis had been stable for at least 3 months		dose of MTX needed) Phase III: Maintenance of the target MPSS on topical treatment plus the MTX dose used at the end of phase II (measured by the occurrence of relapse)	The group treated with calcipotriol required a significantly reduced dose of MTX compared to the placebo group (3.3 compared to 6.3 mg/week [P<0.001]). At the end of phase II, the calcipotriol group required less MTX, 6.5 mg/week, than the placebo group, who required 9.9 mg/week of MTX (P=0.002). Investigator assessments of efficacy in the intent-to-treat population showed a non-significant trend in favor of calcipotriol (P=0.068).
Torras et al.[140] (2004) Calcipotriol 50 µg/g cream applied BID and PUVA 3	MC, PC, PG, RCT Patients ≥18 years of age with skin type II or III and a diagnosis of	N=120 12 weeks	Primary: PASI scores, overall patient assessment of skin lesions, and the total UVA dosage	Primary: Statistically significant decreases in PASI scores were observed form week two to week 10 with the decrease being greater in the calcipotriol group (P<0.0063). At the end of treatment, the PASI score was significantly lower in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
times per week vs PUVA 3 times per week	extensive psoriasis vulgaris covering 20 to 50% of BSA, and who were scheduled to receive PUVA therapy on the trunk and the limbs Phase I: Two-week washout period during which patients received an emollient only, or a shorter wash out if patients had received no previous treatment and did not need the full 2 weeks Phase II: Patients received either calcipotriol 50 µg/g or placebo BID for at least 10 weeks Phase III: Within 1 week of randomization, patients received PUVA therapy 3 times per week in addition to topical therapy (methopsoralen was administered 2		needed Secondary: Not reported	calcipotriol group compared to the placebo group (-87.5 vs -49.6; P<0.001). In the calcipotriol group, 87.9% of patients achieved reductions of at least 75% in PASI scores and 69% achieved reductions of 90% in PASI scores compared to 47.3% and 36.4% respectively in the placebo group (P<0.001 between groups). The median duration of treatment needed to achieve these decreases was significantly shorter in the calcipotriol group compared to the placebo group (42 and 56 days vs 77 and 79 days, respectively; P<0.004). At the end of Phase III, overall patient assessment of lesions was rated moderately improved or totally cleared in 79.3% of patients in the calcipotriol group compared to 60% of patients in the placebo group (P<0.01). The total UVA dose needed in the calcipotriol group was significantly lower compared to the placebo group (P=0.016). The average number of irradiations needed was significantly lower in the calcipotriol group compared to the placebo group (P<0.01). The mean cumulative PUVA dose needed to achieve at least 90% reduction in PASI score was lower in the calcipotriol group compared to the placebo group (P=0.03). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	hours prior to UVA treatment)			
Lebwohl et al.[141] (2007) Calcitriol 3 µg/g ointment applied BID vs placebo	DB, RCT Patients with mild to moderate chronic plaque psoriasis	N=839 8 weeks	Primary: GSS; safety Secondary: Not reported	Primary: Calcitriol 3 µg/g ointment was significantly more effective than placebo, with onset of therapeutic effect seen as early as week two and sustained at all subsequent visits. Calcitriol 3 µg/g ointment demonstrated good systemic and local safety profile comparable to its placebo with no effect on calcium homeostasis. Secondary: Not reported
Lebwohl et al.[142] (2009) Calcitriol 3 µg/g ointment applied BID	MC, OL Patients ≥12 years of age with mild to moderate chronic plaque psoriasis	N=324 26 to 52 weeks	Primary: Safety Secondary: Global assessment of improvement	Primary: Adverse events were reported for 40% of patients. The most common adverse events were abnormal laboratory test results, which included elevated blood calcitriol levels (7%), pathological blood PTH and calcitriol levels (0.3%), and elevated blood PTH levels (0.3%). Adverse events thought to be related to study treatment were noted for 45 patients (13.9%). Eight patients (2.5%) had adverse events leading to study discontinuation, and adverse events for four of these patients (1.2%) were considered related to treatment. These events included irritant dermatitis, pruritus, kidney pain, and urine abnormality (one patient each). Six patients experienced severe adverse events; none were related to calcitriol treatment. Secondary: At least marked improvement was reported by 131 of 249 patients (52.6%) at week 26 and 83 of 130 patients (63.8%) at week 52. Approximately 21% (52/249) of patients rated themselves as clear or almost clear at week 26 and 30% (39/130) at week 52. Mean percentage BSA decreased over time from 16.1% at baseline to 10.7% at end point.
Langner et al.[143] (1996)	MC, OL Patients ≥18 years	N=253 78 weeks	Primary: Overall improvement of	Primary: Ninety-six (40.1%) patients showed definite or considerable improvement at endpoint compared to baseline, and clearance of psoriasis was reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Calcitriol 3 µg/g ointment applied BID	of age with chronic plaque-type psoriasis		the treated lesions; PASI score Secondary: Not reported	in 39 (16.3%) patients. Forty-six patients who showed clearing or considerable improvement of psoriasis were withdrawn from the study due to this outcome. Eleven (23%) of these patients relapsed within three months and subsequently re-entered the study. From the remaining group of 36 patients, a relapse after 3 months was reported in six patients. The number of patients with severe or very severe psoriasis fell from 120 (47.4%) at baseline to 54 (21.4%) at endpoint. The number with none or slight psoriasis increased from 19 (7.5%) to 98 (38.8%). Pruritus showed a significant improvement over the course of the study. At baseline, 4.3% of the patients complained of severe, distressing pruritus, which had fallen to 1.2% at the three- and 12-month assessments. At the start of the study, only 17% of patients had no specific complaint of pruritus, but this had improved to 48.4% at the three-month assessment and 38.7% at endpoint. The PASI score showed a marked improvement after three months treatment (53.2% reduction in score), which was maintained over the whole course of the study. Secondary: Not reported
Bourke et al.[144] (1997) Calcitriol 3 µg/g ointment vs calcipotriol 50 µg/g ointment	DB, RCT Patients with moderately extensive chronic plaque psoriasis	N=24 8 weeks	Primary: Change in the PASI scores Secondary: Not reported	Primary: Mean PASI in patients receiving calcitriol decreased from 13.0 to 8.8 ($P<0.05$). Mean PASI in patients receiving calcipotriol decreased from 14.9 to 4.7 ($P<0.005$). The reduction in PASI was significantly greater in the calcipotriol-treated group than in the calcitriol group ($P<0.05$). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Zhu et al.[145] (2007) Calcitriol 3 µg/g ointment applied BID vs calcipotriol 50 µg/g ointment applied BID	RCT, SB Patients 18 to 65 years of age with mild to moderate chronic plaque-type psoriasis involving up to 35% of the BSA	N=250 12 weeks	Primary: Global assessment of improvement assessed by the investigator Secondary: Global assessment of improvement assessed by the patient; safety	Primary: At week 12, the mean global improvement score rated by the investigator was 2.27 for calcitriol and 2.22 for calcipotriol (P=NS). Secondary: At week 12, the mean global improvement score rated by the patient was 2.12 for calcitriol and 2.09 for calcipotriol. There was no significant different in the percentage of patients with at least marked improvement with calcitriol (95.7%) compared to calcipotriol (85%; P=NS). The three clinical signs of the disease, plaque elevation, erythema, and scaling, were significantly reduced in all treatment groups. Mean DSS decreased from 8.14 at baseline to 1.87 over the 12-week treatment with calcipotriol and from 8.10 to 2.54 with calcitriol (P<0.01). The cutaneous safety score as assessed by the investigator was higher with calcipotriol than with calcitriol (mean scores 0.3 vs 0.1), showing a better local tolerance of calcitriol. A total of 11 (8.9%) patients had a score of 2 or 3, corresponding to 'moderate' or 'severe' local reaction with calcipotriol, whereas only one (0.8%) patient had a 'moderate' reaction with calcitriol (P=0.0035).
Ortonne et al.[146] (2003) Calcitriol 3 µg/g ointment applied BID vs calcipotriol 50 µg/g ointment applied BID	RCT, SB Patients 18 to 70 years of age with mild to moderate chronic plaque psoriasis localized in facial, hairline, retroauricular or flexural areas	N=75 6 weeks	Primary: Perilesional erythema and edema; Global assessment of improvement Secondary: Not reported	Primary: Perilesional erythema (P<0.001), perilesional edema (P<0.02) and stinging/burning (P<0.001) were all less severe with calcitriol than with calcipotriol. The IGA of local safety showed that calcitriol was better tolerated than calcipotriol. More patients considered calcitriol better or much better tolerated than calcipotriol (49.3 vs 10.7%, respectively; P<0.0001). Global assessment of improvement from baseline by the investigators was significantly greater for the calcitriol-treated lesions (P<0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				A total of 44% of patients considered efficacy to be greater on the calcitriol-treated side than on the calcipotriol-treated side, whereas 29% of patients reported the opposite. The patient's global preference showed a significant difference in favor of calcitriol (P <0.02), with 57% of the patients rating calcitriol as being better or much better than calcipotriol. Secondary: Not reported
Camarasa et al.[147] (2003) Calcitriol 3 µg/g ointment applied BID vs betamethasone dipropionate 0.05% ointment applied BID	DB, MC, RCT Adults with chronic plaque-type psoriasis of at least moderate severity	N=258 Treatment: 6 weeks Follow-up: 8 weeks	Primary: Global improvement of treated psoriatic lesions; PASI; relapse Secondary: Not reported	Primary: After six weeks, both calcitriol and betamethasone were found to be efficacious. Similar proportions of patients (79% in the calcitriol group and 82% in the betamethasone group) showed definite or considerable improvement in their psoriasis, or total clearance of lesions by treatment endpoint. The mean of the global improvement scores at endpoint were similar (2.31 for calcitriol and 2.55 betamethasone; P<0.05). Both treatment groups showed a clinically relevant decrease in the mean GSS which, at endpoint, was 1.58 for the calcitriol group and 1.36 for the betamethasone group (P<0.05). Each treatment also resulted in a marked improvement in the PASI from baseline to endpoint, with the absolute reduction in the mean PASI at endpoint being comparable between the groups (P>0.05). Relapse warranting new treatment within eight weeks of the study endpoint was required in 52% of patients who had been receiving calcitriol, at a mean of 25.3 days post-treatment. In the betamethasone group, relapse was required for 75% of patients at a mean of 23.4 days post-treatment. The proportion of responders remaining in remission at eight weeks post-treatment (48 and 25% for the calcitriol and betamethasone groups, respectively; P<0.01). The two study ointments were similar in terms of cosmetic acceptability.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The overall opinion of the ointments by the majority of patients was generally 'good' or 'acceptable' (91 and 92%, for the calcitriol and betamethasone groups, respectively). Secondary: Not reported
Liao et al.[148] (2007) Calcitriol 3 µg/g ointment applied BID vs tacrolimus 0.3 mg/g ointment applied BID	DB, RCT, SC Patients 18 to 70 years of age with chronic plaque psoriasis affecting face or genitofemoral regions	N=50 6 weeks	Primary: Mean reduction of the TAS Secondary: Percent of patients with complete or almost complete clearance based on the PGA score	Primary: The mean TAS significantly decreased by 51.4% for calcitriol, and 63.8% for tacrolimus. Tacrolimus was significantly more effective than calcitriol at week four and at the end of the six-week treatment period (P<0.05). Secondary: During the treatment period, there was no significant difference in the mean global improvement scores for tacrolimus or calcitriol (3.48 vs 2.67; P=0.066). At the end of the study, more patients achieved complete or almost complete clearance in the tacrolimus group compared to the calcitriol group (60 vs 33%; P<0.05).
Lahfa et al.[149] (2003) Calcitriol 3 µg/g ointment applied QPM and clobetasol 0.05% cream applied QAM vs calcipotriol 50 µg/g ointment applied QPM and clobetasol 0.05% cream applied QAM	MC, RCT, SB Patients with mild to moderate chronic plaque-type psoriasis	N=125 12 weeks	Primary: Investigator's assessment of global improvement Secondary: Patients' assessments of global improvement, PASI, proportion of the BSA affected by psoriasis	Primary: No significant differences between the two regimen groups in the IGA of improvement were detected at any of the study time points (all, P>0.05). The global assessment by investigators at endpoint revealed a successful clinical response (marked improvement, almost clear or clear) for 79% of patients receiving calcitriol compared to 88% of patients receiving calcipotriol. Secondary: At study endpoint, there was complete clearing of psoriasis lesions in 26% of patients in the calcitriol group and in 25% of patients in the calcipotriol group. In each of the treatment groups, the beneficial effect of treatment on the severity of psoriasis was detected by a marked decrease in PASI. No significant differences between the two regimen groups were detected at any of the study time points.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
When the patient's skin had cleared or improved, the steroid was discontinued and monotherapy with calcitriol or calcipotriol started.				
Gold et al.[150] (2018) Halobetasol propionate 0.01% /tazarotene 0.045% (HP/TAZ) lotion once daily vs vehicle once daily	DB, MC, RCT (two trials) Patients ≥18 years of age and have moderate-to-severe plaque psoriasis with an IGA score of 3 or 4 and affected BSA of 3% to 12%	N=418 (N=203 in study 1 and N=215 in study 2) 12 weeks (8 weeks of treatment and 4 weeks after treatment)	Primary: Percentage of subjects who were treatment successes at week eight (those with at least a 2-grade improvement from baseline IGA score and a score of clear or almost clear) Secondary: Percentage of subjects who were treatment successes at weeks two, four, six, and 12; signs and symptoms of psoriasis and safety	Primary: By week eight, 35.8% (study 1) and 45.3% (study 2) of subjects were treatment successes compared with 7.0% (study 1) and 12.5% (study 2) of those treated with vehicle (P <0.001). Secondary: HP/TAZ lotion was consistently more effective than vehicle in achieving treatment success, demonstrating statistical significance by week two (study 2) and week four (study 1). The majority of subjects maintained treatment success over the four-week post-treatment period. HP/TAZ lotion demonstrated sustained therapeutic success in 33.3% (study 1) and 33.4% (study 2) of subjects (vs 8.5% and 8.8% in those who were receiving vehicle) (both P < .001). HP/TAZ lotion was also "superior" in reducing signs and symptoms of psoriasis and body surface area affected by psoriasis. HP/TAZ lotion was "superior" to vehicle in reducing erythema, plaque elevation, and scaling, with sustained efficacy after treatment. At week eight, treatment success was achieved by 44.2% and 49.6% (erythema in study 1 and study 2, respectively), 59.3% and 59.7% (plaque elevation), and 59.4% and 62.9% (scaling) of subjects treated with HP/TAZ lotion (vs 10.0% and 18.7%, 17.9% and 21.3%, and 20.6% and 21.0% of those receiving vehicle in study 1 and study 2, respectively) (P <0.001). Of the subjects treated with HP/TAZ lotion, 35.9% reported adverse events (compared with 21.4% of those treated with vehicle), with the majority of adverse events (85.6%) being mild or moderate. The most

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				frequently reported treatment-related adverse events were contact dermatitis (6.3%), application site pain (2.6%), and pruritus (2.2%).
Rigopoulos et al.[151] (2007) Tazarotene 0.1 % cream applied QHS for 12 weeks vs clobetasol 0.05% cream applied QHS for 12 weeks	DB, RCT Patients with psoriasis including nail involvement	N=23 24 weeks	Primary: Assessment of pitting, onycholysis, subungual hyperkeratosis and salmon patches using the NAPSI Secondary: Not reported	Primary: There was no significant difference in pitting, onycholysis, subungual hyperkeratosis, or salmon patches between tazarotene and clobetasol after 12 weeks of treatment. Post hoc analysis at the end of the follow-up period (24 weeks) demonstrated clinical improvement for hyperkeratosis with tazarotene compared to clobetasol (P<0.001). All adverse events reported were mild, with the symptoms ameliorating after a few days. All patients in both groups declared satisfaction with the results at the end of the treatment period. Secondary: Not reported
Angelo et al.[152] (2007) Tazarotene 0.1% cream applied on one side of the body for 12 weeks vs clobetasol 0.05% cream applied on the other side of the body for 12 weeks	RCT, SB Patients with psoriasis and bilateral symmetrical lesions	N=36 16 weeks	Primary: Assessment of erythema, scaling and induration on a 4-point scale; investigators' overall assessment of psoriasis including extent and severity; treatment success Secondary: Not reported	Primary: During the 12-week treatment period, both tazarotene cream and clobetasol cream were associated with reduction in erythema scores from the baseline except at week two where tazarotene showed no improvement. Clobetasol cream was better than tazarotene cream in reducing the erythema throughout the treatment period with statistically significant differences favoring clobetasol over tazarotene at weeks two, four, six and eight. During the 12-week treatment period, both tazarotene and clobetasol creams were associated with reduction in induration scores from baseline. Tazarotene was better than clobetasol in reducing the induration at weeks two, four, 10 and 12. The difference was statistically significant at week two. Both were equally effective at weeks six and eight. During the 12-week treatment period both tazarotene and clobetasol creams were associated with reduction in desquamation scores from baseline except at week two where tazarotene showed no reduction. Clobetasol cream was better than tazarotene cream in reducing the scaling throughout the treatment period with statistically significant differences

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				favoring clobetasol over tazarotene over the entire 12-week treatment period. The overall improvement at weeks two, four six, eight, 10 and 12 for tazarotene was ~20, ~33, ~43, ~53, ~55 and ~58% respectively and for clobetasol was ~33, ~55, ~73, ~78, ~95 and ~95% respectively. Statistically significant differences favored clobetasol cream over tazarotene cream over the entire 12-week treatment period. Clobetasol produced higher success rates than tazarotene over the 12-week treatment period. Statistically significant differences favored clobetasol over tazarotene at weeks two and four. Treatment success rate was 100% at week six with clobetasol and was 73% with tazarotene. At week 12, it was 100% with clobetasol and 88% with tazarotene. Secondary: Not reported
Kumar et al.[153] (2010) Tazarotene 0.1% gel applied QHS vs crude coal tar 5% (CCT) ointment applied QHS	RCT Patients with chronic stable plaque psoriasis	N=27 Treatment: 12 weeks Follow-up: 8 weeks	Primary: Severity of psoriatic lesions and response to treatment evaluated by ESI Secondary: Not reported	Primary: In the per-protocol analysis, the mean percentage reduction in ESI score at the end of the treatment period was 74.15 and 77.37% with tazarotene and CCT, respectively (P>0.05). With regard to clinical response, marked, moderate, mild and no response was seen in 0, 3.7, 73.3 and 14.8% of patients, respectively, for both treatments at the end of four weeks of treatment. At the end of eight weeks, the corresponding grades of improvement were 3.7, 70.3, 29.9 and 0% for the tazarotene-treated side, and 3.7, 66.6, 29.6 and 0% for the CCT-treated side. At the end of the 12 weeks of treatment, all 27 patients had moderate to marked improvement on both sides. With tazarotene, marked improvement was seen in 40.7% of lesions, and moderate improvement in 59.2%. With CCT, marked improvement was seen in 59.2% and moderate improvement in 40.7%. Side effects were seen in 48.14% of patients treated with tazarotene: mild irritation (four patients), erythema (four), burning sensation (six), itching (one) and dryness and fissuring (two). No side effects were seen in any of the patients treated with 5% CCT.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Tzung et al.[154] (2005) Tazarotene 0.1% gel applied QHS and petrolatum applied QAM vs calcipotriene 0.005% ointment applied BID	CS, IB, RETRO Patients 12 to 80 years of age with a diagnosis of psoriasis and a total of 50 target lesion pairs	N=19 Treatment: 12 weeks Follow-up 4 weeks	Primary: Severity scores for scaling, plaque elevation, erythema, overall lesion severity, and patient self-reported efficacy Secondary: Not reported	Primary: At the end of the 12-week treatment period, the tazarotene plus petrolatum was as effective as calcipotriol in the reduction of scaling, plaque elevation, erythema, and overall lesion severity. Erythema worsened in the tazarotene plus petrolatum side in week one and reduction of erythema on this side was first observed in week two. The difference in erythema between sides was not significant after eight weeks. Lesion severity scores worsened on both sides during the post-treatment phase, though the tazarotene plus petrolatum side maintained the therapeutic effect significantly better in terms of scaling, plaque elevation, erythema, and overall severity at week 16 ($P<0.001$, $P<0.001$, $P=0.01$, and $P=0.007$ respectively). Patient-assessed success rates were 74% on the tazarotene plus petrolatum side and 85% on the calcipotriol side, though this difference was not significant ($P>0.46$). Secondary: Not reported
Schiener et al.[155] (2000) Tazarotene 0.05% gel applied QD and total body narrowband UVB irradiation QD 4 times per week vs calcipotriene	CS, IB Patients with psoriasis	N=10 ≥4 weeks	Primary: PASI Secondary: Not reported	Primary: PASI scores decreased on both treatment sides and there was no significant difference between treatment regimens. Complete clearance of the skin was observed after a median of 19 treatment sessions for both treatment regimens. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
0.005% ointment applied QD plus total body narrowband UVB irradiation QD 4 times per week				
Guenther et al.[156] (2000) Tazarotene 0.1% gel applied QHS and mometasone 0.1% cream applied QAM vs calcipotriene 0.005% applied BID	IB, MC, PG Patients with chronic, stable plaque psoriasis affecting 5 to 20% of total BSA	N=120 Treatment: 8 weeks Follow-up: 12 weeks	Primary: Physician-rated measures of efficacy including global improvement, plaque elevation, scaling, erythema, and percentage of BSA involvement; patient-rated assessments including efficacy of study treatment compared to previous therapies, comfort of treated skin, outlook for long-term control, and overall impression of treatment Secondary: Not reported	Primary: Physician-rated assessments: After two weeks of treatment, the percentage of patients achieving marked improvement (≥75% global improvement) was significantly higher in the tazarotene and corticosteroid group compared to the calcipotriene group (45 and 25% respectively; P<0.05). There was no significant difference in the percentage of patients achieving complete or almost complete clearance between the two treatment groups at any time. For trunk lesions, the mean percentage of reduction in plaque elevation was not significant between groups during the treatment phase, but was significantly higher in the tazarotene plus corticosteroid group at the end of treatment and week four of the post-treatment phase (P<0.05) For upper or lower limb lesions, no significant between-group differences in plaque elevations were observed at any point. For trunk lesions, the mean percentage of reduction in scaling was significantly greater in the tazarotene plus corticosteroid group compared to the calcipotriene group at week four of treatment and at week four of the post-treatment phase (P<0.05). For upper or lower limb lesions, no significant between-group differences in scaling were observed at any point. For trunk lesions, the mean percentage of reduction in erythema was significantly greater in the tazarotene plus corticosteroid group compared to the calcipotriene group at week four of treatment and at the end of treatment (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				For upper or lower limb lesions, no significant between-group differences in erythema were observed at any point. For trunk lesions, the mean percentage of reduction in BSA involvement was significantly greater in the tazarotene plus corticosteroid group compared to the calcipotriene group after two and four weeks of treatment (P<0.01), though no significant differences were observed between groups in the post-treatment phase. For upper limb lesions, the tazarotene plus corticosteroid group had a significantly higher percentage of reduction in percentage of BSA involvement after two and four weeks of treatment compared to the calcipotriene group (P<0.05 at two weeks and P<0.01 at four weeks). No significant differences were observed during the post-treatment phase between groups. For lower limb lesions, significance was only achieved for patients admitted to the post-treatment phase and only at the end-of-treatment visit (P<0.001). <u>Patient-rated assessments:</u> A significantly greater percentage of patients rated their therapy more effective or much more effective than previously tried therapies in the tazarotene plus corticosteroid group compared to the calcipotriene group (P<0.05). At the end of treatment, 16% of patients in the tazarotene plus corticosteroid group and 9% of patients in the calcipotriene group rated the comfort of their therapy as somewhat comfortable, 42 and 51% rated it as comfortable, and 27 and 25% rated it as very comfortable, respectively (the significance of these findings is not discussed). No significant between-group differences were observed in the percentage of patients who rated their outlook for long-term control as very promising or extremely promising at the end of the 12-week post-treatment phase. Overall impression of treatment favored the tazarotene plus corticosteroid regimen compared to the calcipotriene regimen, however the percentages

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				of patients who rated their impression of therapy as favorable or highly favorable did not differ between groups, except at the 12-week post-treatment visit (P<0.05). Secondary: Not reported
Bowman et al.[157] (2002) Tazarotene 0.05% gel and calcipotriene 0.005% ointment applied QAM and calcipotriene ointment applied QHS vs clobetasol 0.05% ointment applied BID	CS, OL, PRO Patients ≥18 years of age with psoriasis vulgaris that was chronically stable for at least 1 month prior to screening with at least 1 bilateral mirror image plaque on the trunk, arms, or legs	N=15 Treatment: 2 weeks Follow-up 4 weeks	Primary: Severity scores for erythema, scaling, and plaque elevation Secondary: Not reported	Primary: At the end of the two-week treatment period, both the tazarotene plus calcipotriene side and the clobetasol side showed marked reductions in scaling, plaque elevation, and overall lesional severity (P<0.0001). There were no significant differences in the tazarotene plus calcipotriene side compared to the clobetasol side in the reduction in scaling (P=0.93), plaque elevation (P=0.76), and overall lesional severity scores (P=0.29). Erythema improved significantly more in the clobetasol-treated lesions during the treatment period (P<0.01) but there was no significant difference between the sides during the post-treatment period (P=0.20). Lesional severity scores worsened on both sides during the post-treatment phase. Plaque elevation returned more rapidly on the tazarotene plus calcipotriene side (P<0.01), but scaling, erythema, and overall lesional severity were not significantly different between the two treatments (P>0.05). No treatment-related adverse effects were reported on the clobetasol side. Adverse effects in the tazarotene plus calcipotriene side were mild and did not result in alteration of the treatment schedule for any patient. Secondary: Not reported
Yélamos et al.[158] (2021) Calcipotriol/betamethasone dipropionate 50	PRO, OL, RCT Patients with mild to moderate plaque psoriasis who can be treated with	N=36 8 weeks	Primary: Achievement of a Total Clinical Score (TCS) of ≤1 at week four	Primary: After four weeks, more patients in the Cal/BD foam group achieved the primary end point (TCS ≤ 1) than in the clobetasol group (63.2% vs 18.8%, P=0.016). No severe adverse events were noted during the study.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
µg/g + 0.5 mg/g foam (Cal/BD foam) once daily for 4 weeks vs clobetasol 0.5 mg/g cream once daily for two to four weeks	topical treatments [total body surface area (BSA) <10%].		Secondary: Not reported	Patient satisfaction was significantly higher with Cal/BD foam treatment than with clobetasol treatment (P<0.03). Secondary: Not reported
Lebwohl et al.[159] (2021) Halobetasol propionate 0.01%/tazarotene 0.045% (HP/TAZ) lotion once daily for 8 weeks and then intermittently as needed in 4-week intervals for up to one year	MC, OL single group study Adults ≥18 years of age with moderate-to-severe plaque psoriasis and body surface area (BSA) of 3 to 12% at baseline	N=555 52 weeks	Primary: Safety and tolerability after long-term treatment with HP 0.01%/TAZ 0.045% lotion Secondary: Not reported	Primary: In total, 318 participants (57.8%) achieved treatment success at some point during the study, with the majority (54.4%, n=173) achieving treatment success within the first eight weeks. Of the 226 patients who enrolled at least eight weeks in the study and achieved treatment success, more than half (55.3%) did not require retreatment for at least 29 days and 6.6% did not relapse and therefore did not require any retreatment Affected BSA decreased over time and a median BSA of 2.0% was maintained for the full duration of the study. Over half of participants experienced treatment-emergent AEs (TEAEs) during the study such as dermatitis, pruritus, pain, and irritation, mainly during the first 12 weeks. Most TEAEs were mild to moderate in severity and no treatment-related serious AEs were noted. Most local skin reactions that occurred were temporary and did not require interruption of treatment. Secondary: Not reported
Lebwohl et al.[160] (2022) Halobetasol propionate	Post-hoc analysis of three phase 3 studies	N=276 from two pooled phase 3 studies; N=555 from	Primary: Maintenance of treatment success after end of treatment	Primary: Of those who had achieved treatment success at week eight (n=101) in the pooled phase 3 studies, 62.4% maintained treatment success at four weeks post-treatment (week 12). Of those who had not achieved treatment success at week eight (n=133), 18 individuals (13.5%) achieved treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
0.01%/tazarotene 0.045% lotion once daily for 8 weeks	Adults ≥18 years of age with moderate-to-severe plaque psoriasis	long-term OL phase 3 study 12 weeks (pooled phase 3 studies); 52 weeks (long-term OL phase 3 study)	Secondary: Not reported	success at week 12. In the long-term open label study, treatment was deemed successful in patients with clear or almost clear skin. Of the 226 total participants who achieved treatment success, time to retreatment was greater than four weeks for more than half of these participants (55.3%). The participants who did not relapse (6.6%) did not require any retreatment. For the 170 (75.2%) participants who achieved treatment success with almost clear skin, the duration of posttreatment effect was shorter than for participants who achieved treatment success with clear skin. Across all three studies, the majority of participants who achieved treatment success maintained this effect for a minimum of one-month post-treatment. Secondary: Not reported
Vitiligo				
Rosmarin et al.[161] (2020) Ruxolitinib 1.5% cream applied twice daily vs ruxolitinib 1.5% cream applied once daily vs ruxolitinib 0.5% cream applied once daily	DB, MC, RCT Patients 18 to 75 years of age diagnosed with vitiligo who have depigmentation of 0.5% or more of their facial body surface area and 3% or more of their non-facial body surface area	N=157 52 weeks (part 1: 24 weeks; part 2: patients initially randomly assigned to vehicle and to 0.15% once daily who did not achieve at least a 25% improvement from baseline in F-VASI score were randomly	Primary: Proportion of patients achieving a ≥50% improvement in facial Vitiligo Area Scoring Index (F-VASI) from baseline to week 24 Secondary: Proportion of patients achieving a facial PhGVA of clear or almost clear at week 24, proportion of patients achieving	Primary: The proportion of patients achieving ≥50% improvement in F-VASI from baseline to week 24 in the placebo group was 3% compared to 45% in the ruxolitinib 1.5% twice daily group (OR, 24.7; 95% CI, 3.3 to 1121.4; P=0.0001). Secondary: Total-VASI50 at week 52 was reached by patients in the total population in a dose-dependent manner (1.5% twice daily, 36%; 1.5% once daily, 30%; 0.5% once daily, 26%). Among patients who treated all depigmented skin (baseline T-BSA ≤20%), nine (45%) of 20 achieved T-VASI50 response (1.5% twice daily) at week 52. Mean percentage change from baseline in VASI and BSA showed clear separation from vehicle for face and total body starting as early as week eight of treatment with most ruxolitinib cream doses. The additional key secondary endpoint of reaching scores of clear or almost clear in the Facial-PhGVA at week 24 was attained only by patients given ruxolitinib cream (0.15% once daily, 3%; 0.5% once daily,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ruxolitinib 0.15% cream applied once daily vs placebo		assigned to one of three higher dosing groups for 28 weeks)	a 50% or higher improvement from baseline in total VASI at week 52	10%; 1.5% once daily, 13%; 1.5% twice daily, 9%).
Warts				
Arican et al.[162] (2004) Imiquimod 5% cream applied 3 times per week for 12 weeks vs placebo	DB, PC, RCT Patients ≥18 years of age with a diagnosis of external anogenital warts	N=45 Treatment: 12 weeks Follow-up 6 months	Primary: Clearance of anogenital warts Secondary: Not reported	Primary: After treatment, 69.7% of patients in the treatment group (all the female patients and 54.5% of the male patients) had complete clearance of the warts, nine patients had 50 to 90% clearance, and one patient had <50% clearance. After treatment, one patient displayed complete clearance, one patient had 50 to 90% clearance, and the remaining eight patients showed no alteration in lesions. These results are statistically significant in favor of the treatment group (P<0.01). Secondary: Not reported
Haidopoulos et al.[163] (2004) Imiquimod 5% cream applied 3 times per week at bedtime for maximum of 12 weeks or until wart clearing	OL, OS Female patients 16 to 52 years of age with vulvar warts with a median wart area of 55 mm^2	N=73 Treatment: 12 weeks Follow-up 3 months	Primary: Total or partial clearing of the warts Secondary: Not reported	Primary: No improvement was detected in 6% of patients during the 12-week treatment period. Total clearing of the lesions was reported in 71% of patients, 85% of patients reported more than 50% reduction in the size of the lesions, and 8% reported less than 50% reduction in the size of the lesions. In the women experiencing total clearance, 43% reported that the warts were eradicated in the first six weeks of treatment. During the follow-up period, 13% developed recurrent disease and were treated with CO_2 vaporization (17 patients were lost to follow-up during

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				this time). Secondary: Not reported
Stefanaki et al.[164] (2008) Imiquimod 5% cream applied 3 times per week for 12 weeks vs cryotherapy administered once over 3 weeks for 3 consecutive sessions	OL, RCT HIV-negative males with anogenital warts	N=80 12 months	Primary: Clearance of treated warts, recurrence, adverse events Secondary: Not reported	Primary: At the end of three months, irrespective of the type of treatment, 78.8% of the patients demonstrated 100% improvement. Cryotherapy was more effective as 86.7% of the patients showed 100% improvement compared to 68.6% of patients in the imiquimod group. In the imiquimod group, 17.1% of patients did not show any signs of improvement compared to only 2.2% in the cryotherapy group (P=0.019). Patients treated with imiquimod tended to improve earlier than patients on cryotherapy (P=0.012). At the end of the first month, 31.4% of patients on imiquimod demonstrated 100% clearance compared to 20.0% of the patients in the cryotherapy group. At the end of the second month more patients in the imiquimod group (37.1%) were free of the disease compared to the cryotherapy group (22.2%). Initial disease parameters, such as number of warts (P=0.640), color (P=0.053), location (P=0.101) and duration of lesions (P=0.17), were not statistically different between imiquimod or cryotherapy treatments. At 12 months after the initial visit, the recurrence rate was 41% for the imiquimod and 59% for the cryotherapy group (P=0.138). Treatment with imiquimod was less painful than cryotherapy (P=0.034). Secondary: Not reported
Yan et al.[165] (2006) Imiquimod 5% cream applied 3	MA Patients with clinically visible genital warts in	N=473 ≤10 months	Primary: Clearance rate; adverse events Secondary:	Primary: <u>Imiquimod vs placebo</u> Pooled analysis across three studies including 194 patients in the imiquimod group and 168 in the placebo group showed a statistically significant difference between the two groups (OR, 11.65; 95% CI, 6.05 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
times per week until the warts were completely cleared or for a maximum of 16 weeks vs podophyllotoxin 0.5% applied 2-3 times per day for 3 consecutive days followed by a 4-day treatment-free period until the complete shedding of the warts or for a maximum of 4 weeks vs placebo	the genital, anal, perineal, or perianal area		Not reported	22.44). Patients treated with imiquimod had a much higher cure rate than those who were treated with a placebo. The complete clearance rate was 50.34% in the imiquimod group and the recurrence rate was 13% to 19%. <u>Podophyllotoxin vs placebo</u> Pooled analysis across 9 studies including 479 patients in the podophyllotoxin group and 294 patients in the placebo group revealed a statistically significant difference between the two groups (OR, 16.70; 95% CI, 7.06 to 39.48). Patients treated with podophyllotoxin had a much higher cure rate than those who were treated with a placebo. The complete clearance rate was 56.41% in the podophyllotoxin group and the recurrence rate was 2% to 90%. The clinical cure rates of imiquimod and podophyllotoxin were 50.34 and 56.41%, respectively, without statistically significant differences between the two (P>0.05). The most common adverse events of imiquimod were erythema (37%; 70/187), itching (38%; 26/81), erosion (13%; 24/187) and burning (20%; 16/81). Secondary: Not reported
Moresi et al.[166] (2001) Imiquimod 5% cream vs	RETRO Infants and young children diagnosed with anogenital warts	N=25 4 months	Primary: Clearing of lesions, adverse effects, and recurrence of lesions with estimated length of wart-free period	Primary: Seventeen patients were treated with podofilox and of those, parents of 15 patients reported resolution of lesions with no recurrence for periods ranging from four months to two years. Adverse reactions reported in the podofilox group included burning (most common), pain, redness, erosions, and edema.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
podofilox 0.05% gel			Secondary: Not reported	Eight patients were treated with imiquimod and of those, parents of six patients reported clearing of lesions which remained clear six to 12 months after therapy ended. Adverse reactions reported in the imiquimod group included itching, redness, and irritation. Half of the patients reported few or no side effects. Secondary: Not reported
Tyring et al.[167] (1998) Podofilox 0.5% gel applied BID for 3 consecutive days followed by 4 days with no treatment vs placebo	DB, MC, PC, RCT Patients ≥18 years of age who were immunocompetent and had at least 2 distinct external anogenital warts	N=326 Treatment: 8 weeks Follow-up: 8 weeks	Primary: Disappearance of treated warts Secondary: Number of warts, wart surface area, individual wart assessment scores, physician assessment of overall response, patient discontinuation due to insufficient response, and recurrence rate of treated warts	Primary: Podofilox gel was significantly better than placebo at clearing anogenital and external genital warts after four and eight weeks of treatment (P<0.001). With additional podofilox gel therapy (four to eight weeks), the proportion of patients with anogenital warts treated successfully increased from 62 to 81 patients (P<0.001). After four and eight weeks of treatment, complete clearance was observed in 38.4 and 44.6% of patients with anogenital warts, respectively. Secondary: Baseline data were higher in the podofilox group in mean wart surface area so absolute changes in this outcome were obscured slightly. The change on percentage of baseline wart area showed a significant effect of podofilox gel at four and eight weeks in the external and anogenital wart populations (P=0.001) and at eight weeks in patients with perianal warts (P=0.03). At four weeks, 41.5% of baseline number of anogenital warts treated with podofilox remained, compared to 89.5% of warts remaining in the placebo group (P=0.001). At eight weeks, 35.9% of baseline anogenital warts treated with podofilox remained compared to 88.4% of warts in the placebo group (P=0.001). Physician assessment of improvement was significantly better at four

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				weeks in the podofilox group compared to the placebo group (73.8% of patients had either moderate or marked improvement or complete clearance compared to 15.1% in the placebo group; P=0.001). This trend continued at week eight (81.1% of patients in the podofilox group compared to 17.2% in the placebo group; P=0.001). Overall, 61.1% of patients in the placebo group discontinued therapy due to insufficient response compared to 8.6% of patients in the podofilox group (P=0.002). At week four, 37% in the placebo group and 1.5% in the podofilox group had discontinued due to insufficient response. After treatment was completed, 30.9% of patients in the podofilox group had recurrence of at least one wart within 12 weeks, most occurring within the first four weeks. The investigators were not able to compare this to the placebo group since only four patients in this group had their warts clear completely during treatment.
Beutner et al.[168] (1989) Podofilox 0.5% solution applied BID for 3 days followed by 4 days with no treatment vs placebo	DB, MC, PC, RCT Men ≥18 years of age with a diagnosis of genital warts	N=109 16 weeks	Primary: Change in wart count, change in wart area, and number and percentage of patients completely cleared Secondary: Not reported	Primary: At the end of the active treatment phase (week four), 73.6% of warts in the podofilox group were cleared compared to 8.3% in the placebo group and the total wart area was reduced by 82.3% in the podofilox group compared to 4.2% in the placebo group on weeks one to six (P=0.0001 for each). Comparisons could not be made at weeks 12 and 16 because there were no patients left in the placebo group. At week six, 82% of warts in the podofilox group had completely cleared and of these, 34% had some evidence of recurrence compared to 13% of warts in the placebo group achieving complete clearance with one wart having evidence of recurrence. Overall, 44.6% of podofilox patients were completely clear at some point in the study compared to zero patients in the placebo group (P<0.001). In the podofilox group, 40% of patients who completely healed did not have a recurrence. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gilson et al.[169] (2009) Podophyllotoxin 0.15% cream applied BID for 3 days per week for up to 4 weeks vs placebo Patients also received weekly cryotherapy until week 12.	DB, MC, RCT Patients with external anogenital warts	N=140 12 weeks	Primary: Wart clearance at weeks four and 12 Secondary: Not reported	Primary: Clearance rates at week four and week 12 were higher in the imiquimod group (60.0 and 60.0%, respectively) than with cryotherapy alone (45.7 and 45.7%, respectively; RR, 1.31; 95% CI, 0.95 to 1.81). Secondary: Not reported
Baker et al.[170] (1990) Podofilox 0.5% solution applied BID for 3 days followed by 4 days without treatment	OL Women 18 to 46 years of age with a diagnosis of external anogenital warts involving an area of less than 10 cm^2	N=37 10 weeks	Primary: Patients' subjective response to treatment, physicians' objective evaluation of the area, number of warts Secondary: Not reported	Primary: There was an 83% reduction in the mean wart number and a 79% reduction in the maximum number of warts over the 10 weeks. Approximately 75% of the warts had been eliminated by the end of the treatment period. The percentages of patients who achieved complete clearance at weeks one, two, three, four, six, and 10 were 11.1, 25.0, 29.0, 44.4, 50.0, and 50.0% respectively. After complete clearance, 21.6% of women had new occurrences by week 10. Patients' subjective reports of pain, burning, and itching decreased during treatment, as did physicians' objective reports of inflammation and erosion. Other objective observations by investigators occurred during the first three visits and included edema, odor, skin slough, tenderness, and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				stinging and no patients described these as severe. Over 80% of patients had none of these additional objective observations. Secondary: Not reported
Greenberg et al.[171] (1991) Podofilox 0.5% solution applied BID for 3 days followed by no treatment for 4 days vs podofilox 0.5% cream applied BID for 3 days followed by no treatment for 4 days vs placebo	DB, PC, PG, RCT Women ≥18 years of age with a clinical diagnosis of exophytic vulvar condyloma	N=72 10 weeks	Primary: Percentage of warts that were completely healed at any time during the study, investigators' overall assessment of treatment response Secondary: Not reported	Primary: There was a significant difference in the percentage of warts cleared in the podofilox groups compared to the placebo group at every week of the study (P<0.042). There was a slight increase in wart count after the week-four study visit, especially in those patients receiving only two treatment cycles. The relapse rate was 33% in those patients achieving complete response, and time to relapse was one to seven weeks. New warts appeared in untreated areas in nine patients in the placebo group and eight patients in the podofilox groups . The investigators' overall assessment of response demonstrated a statistical difference in favor of podofilox at each week (P<0.038). Secondary: Not reported
Gross et al.[172] (2007) Sinecatechins 15% ointment applied TID vs sinecatechins 10%	DB, MC, RCT Patients ≥18 years of age with 2 to 30 clinically diagnosed external genital warts	N=242 Treatment: 12 weeks Follow-up: 12 weeks	Primary: Clearance of warts; local reactions or adverse effects Secondary: Not reported	Primary: Differences in complete clearance rates between the 10% cream and the placebo groups in male and female patients were not statistically significant (P=0.2693 for males and P=0.6479 for females). When the data for both genders were pooled, the complete clearance rates with the 10% cream were not significantly different from placebo (46.8 vs 37.3%, respectively; P=0.2290). Differences between the 15% ointment and the placebo groups in male and female patients were not statistically significant (P=0.0802 for males and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cream applied TID vs placebo				P=0.0678 for females). The complete clearance rate of the 15% ointment group was significantly higher compared to placebo (P=0.0066). There was no significant difference in the complete clearance of all warts (baseline and new warts occurring during treatment). A total of 56.4 and 45.5% of patients of the 15% ointment and 10% cream groups were completely wart-free after 12 weeks of treatment compared to 37.5 and 37.2% of patients of the placebo ointment and cream groups, respectively. Adverse events were observed in only 7.9% of patients, with no serious adverse events reported. Local skin reactions were generally mild to moderate and resolved with continued treatment. Secondary: Not reported
Stockfleth et al.[173] (2008) Sinecatechins 15% ointment applied TID vs sinecatechins 10% ointment applied TID vs placebo	DB, MC, RCT Patients ≥18 years of age with 2 to 30 clinically diagnosed external genital warts	N=503 Treatment: 16 weeks Follow-up: 12 weeks	Primary: Clearance of warts Secondary: Complete clearance of baseline warts, total wart number, total wart area, partial clearance, and recurrent and new warts	Primary: In the sinecatechins 15 and 10% groups, complete clearance of all warts was established in 52.6% (P=0.0143) and in 50.8% of patients (P=0.0280), respectively compared to 37.3% of patients in the placebo group. Secondary: For complete clearance of baseline warts, significant treatment effects were observed with sinecatechins 15% (54.6%; P=0.0143) and sinecatechins 10% (52.3%; P=0.0376) compared to placebo (39.2%). Median total wart number decreased to zero in the sinecatechins 15% and 10% groups compared to three in the placebo group (P=0.0007 and P=0.0025, respectively). Median total wart area decreased to zero in both sinecatechins 15% and 10% groups compared to 15 in the placebo group (P=0.0011 and P=0.0010, respectively). During the 12-week treatment-free follow-up period, 5.9 and 4.1% of patients in the sinecatechins 15 and 10% groups had a recurrence of anogenital warts, respectively compared to 2.6% of patients in the placebo group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Most local skin reactions were of mild intensity in all three treatment groups. Serious adverse events occurred in two patients only, one patient in each of the active treatment groups. The patient in the sinecatechins 15% group had an application site reaction with severe local symptoms (redness, edema, burning and pain). The second patient (sinecatechins 10% group) had an unrelated limb injury.
Tatti et al.[174] (2008) Sinecatechins 15% ointment applied TID vs sinecatechins 10% ointment applied TID vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with 2 to 30 external genital and perianal warts with a total wart area of 12 to 600 mm^2	N=502 Treatment: 16 weeks Follow-up: 12 weeks	Primary: Clearance of warts Secondary: Not reported	Primary: Complete clearance of all external anogenital warts was achieved in 57.2% of patients in the sinecatechins ointment 15% group, 56.3% of patients in the sinecatechins ointment 10% group, and 33.7% of patients in the placebo group (P<0.001). Both genders in both the sinecatechins ointment 15% (women 64.6%; P<0.0048; men 50.0%; P<0.001) and the sinecatechins ointment 10% (women 64.9%; P<0.003; men 48.0%; P<0.003) groups showed statistically significantly higher complete clearance rates of all warts when compared to placebo (women 45.8%; men 23.2%). Clearance rates of at least 50% were reported for 152 (78.4%) patients and 145 (74.0%) patients in the sinecatechins ointment 15% and 10% groups compared to 53 (51.5%) of the placebo patients (P<0.001). During the 12-week follow-up period, 6.5 and 8.3% of patients treated with sinecatechins ointment 15 and 10%, respectively, had recurrent warts compared to 8.8% of placebo-treated patients. A total of 3.7, 8.3, and 0% developed new warts in the sinecatechins 15%, sinecatechins 10% and placebo groups, respectively. A total of 87.7, 87.3, and 72.1% of patients experienced application site reactions in the sinecatechins 15%, sinecatechins 10% and placebo groups, respectively. Secondary: Not reported
Tatti et al.[175] (2010)	DB, MC, RCT (Pooled analysis of	N=1,004	Primary: Clearance of all	Primary: Complete clearance of all warts was obtained in 53.6% of patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sinecatechins 15% ointment applied TID (G15%) vs sinecatechins 10% ointment applied TID (G10%) vs placebo	2 trials) Patients ≥18 years of age with 2 to 30 clinically diagnosed external genital warts	16 weeks	warts Secondary: Complete clearance of baseline warts, time to complete clearance of both all and baseline warts, partial clearance of both all and baseline warts and incidence of recurrent and new warts	receiving G10% and in 54.9% of patients receiving G15% compared to 35.4% in the placebo group (P<0.001). Secondary: The time to complete clearance of all warts was shorter with G10% and G15% than with placebo (P<0.01). The complete clearance of baseline warts was obtained in significantly more patients receiving G10% and G15% than in the placebo group (P<0.01). Partial clearance of all warts (with clearance levels of at least 50% of all warts) was reached in 76.0 and 77.8% of patients in the G10% and G15% groups compared to 52.2% in the placebo group. The recurrence rates did not differ significantly between groups: 5.8% of patients in the placebo group; 6.5% of patients in the G10% group; 6.8% of patients in the G15% group. Few patients developed new warts during follow-up: 1.4% of patients in the placebo group, 7.0% of patients in the G10% group and 2.4% of patients in the G15% group (P=NS). Very few of the adverse events related to study treatment were classified as serious: one patient in the PE10% group developed pustular vulvovaginitis and two patients in the PE15% group had application-site reactions (erythema, burning and pain).
Wound Care				
Burgos et al.[176] (2000) Collagenase ointment applied at 24-hour intervals vs	MC, OL, PG, RCT Hospitalized or institutionalized patients ≥55 years of age presenting with stage III pressure ulcers for <1 year	N=102 8 weeks	Primary: Ulcer area Secondary: Assessment of ulcer characteristics and adverse events	Primary: Ulcer area in the 24-hour interval group was reduced from 17.7±18.6 to 12.6±17.0cm^2 compared to from 21.4±20.4 to 15.4±19.9cm^2 in the 48-hour interval group (P=0.0005). No statistically significant differences in ulcer area changes were observed between the two treatment groups (P=0.641). Ulcers showed complete healing (closure and epithelization) in 21 (24.4%)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
collagenase ointment applied at 48-hour intervals All patients were entered into an active run-in period with collagenase ointment in order to develop 10 to 30% granulation tissue in the ulcer bed before randomization.				patients (12 in the 24-hour group, nine in the 48-hour group). There were no statistically significant differences between the two treatment groups (P=0.451). The RR of non-healing among the 48-hour interval group as compared to the 24-hour interval group when granulation tissue covered 11 to 30% of the ulcer surface was 1.097 (95% CI, 0.86 to 1.39). Secondary: Analysis of ulcer characteristics by ITT showed a pain intensity decrease in both treatment groups that was statistically significant (P=0.001) only in patients treated at 24-hour intervals. Granulation tissue formation was increased (P<0.0005) and exudate production decreased in both treatment groups (24-hour group, P=0.012; 48-hour group, P=0.04), but differences between treatment groups were not statistically significant. Odor was absent in 70% of ulcers at the time of randomization. Although a reduction in odor intensity was observed in both groups, the difference was not significant. The RR of adverse reaction occurrence was 1.02 (95% CI, 0.21 to 4.80).
Palmieri et al.[177] (1998) Collagenase ointment vs placebo	DB, PC, RCT Patients with chronic ulcers of the lower extremities	N=30 14 days	Primary: Evaluation of wound debridement, granulation, epithelization and inflammation using 5-point scales and by measuring wound size; investigator’s rating of clinical global efficacy	Primary: Collagenase was significantly more effective than placebo for debridement, granulation, epithelization, and inflammation (P<0.01). Differences reached statistical significance after six days of treatment for both debridement and inflammation, and after four, five, and eight days for granulation, epithelization and wound size, respectively. The investigator's rating of clinical global efficacy also demonstrated the greater efficacy with collagenase than placebo (P<0.001). Both treatments were well tolerated. Adverse events were minor and consisted of a burning sensation following ointment application and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	erythema. There were no withdrawals as a result of adverse events in either group. Secondary: Not reported
Ostlie et al.[178] (2012) Collagenase QD for 10 days (mixed with polymyxin for antibacterial coverage) vs silver sulfadiazine QD for 10 days Both groups were treated with silver sulfasalazine for the first days of debridement followed by the study drug.	RCT Patients two months to 18 years of age with partial thickness burns	N=100 12 days	Primary: Need for skin grafting Secondary: None reported	Primary: There was no significant difference in the proportion of patients that required skin grafting between the collagenase and silver sulfasalazine groups (32 vs 36%; P=0.68). Secondary: None reported
Ramundo et al.[179] (2009) Collagenase vs petrolatum-based or other ointment, autolytic debridement via a	SR Patients with pressure ulcers, leg ulcers, or burn wounds	N=376 (11 trials) Variable duration	Primary: Safety and efficacy of collagenase Secondary: Not reported	Primary: Collagenase ointment was more effective than inactive ointment for debridement of necrotic tissue from pressure ulcers, leg ulcers, and partial-thickness burn wounds. Collagenase was more effective as a debriding agent than silver sulfadiazine cream and equal to a fibrinolysin/DNAse ointment. Equivocal results were found in two studies comparing collagenase to autolytic debridement, but the quality of these studies is not sufficient to allow us to reach definitive conclusions.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hydrogel or polyacrylate dressing, surgical excision, silver sulfadiazine, and alternative enzymatic agents (papain-urea and trypsin-chymotrypsin)				Results suggest that collagenase may remove slough more rapidly than a trypsin/chymotrypsin debriding ointment, but another study found that collagenase ointment removed necrotic tissue more slowly than a papain-urea ointment. However, there was no significant difference in wound closure between collagenase ointment and papain-urea ointment. Results of a comparison cohort study suggest that debridement with collagenase is similar to surgical excision alone in children with partial-thickness burns. Treatment with collagenase may reduce the need for excision if the techniques are combined. Only one study reported wound healing outcomes as well as time to complete debridement. Treatment of partial-thickness burns covering less than 25% of total body surface healed more quickly using collagenase compared to silver sulfadiazine. Secondary: Not reported
Tallis et al.[180] (2013) Collagenase ointment vs standard debridement using saline moistened gauze (SMG) and selective sharp debridement	MC, OL, RCT Patients ≥18 years of age with diabetic foot ulcers of ≥1 month's duration between 0.5 and 10 cm^2 in area	N=48 12 weeks	Primary: Change from baseline in wound status total score (modified Bates-Jensen Wound Assessment Tool) Secondary: Percentage of the wound area change from baseline during the 4-week treatment period and at the end of the follow-up period	Primary: Mean wound assessment scores were not significantly different among the collagenase and SMG groups at baseline, at any of the treatment visits (weeks one to four), or at study exit. The decrease in mean (SD) total score at week 12 from baseline was 3.7 (5.2) for the collagenase group and 3.5 (7.1) for the SMG group. Both treatment groups provided a clinically meaningful reduction from baseline in wound assessment total score. Secondary: Ulcers in the collagenase group had a mean percent change from baseline in area of −44.9% at the end of treatment visit and −53.8% at study exit. Both findings were statistically significant (P=0.016; P=0.012). The corresponding changes for the SMG group were 0.8% at end of treatment and 8.1% at study exit; neither was significantly different from baseline.
Miscellaneous				

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Barikbin et al.[181] (2009) Betamethasone valerate 0.1% cream applied BID vs pimecrolimus 1% cream applied BID	DB, RCT Patients 20 to 53 years of age with moderate to severe discoid lupus erythematosus of the face	N=10 8 weeks	Primary: Clinical severity score Secondary: Not reported	Primary: Before treatment, mean disease severity was 4.2 in the pimecrolimus group and 4.4 in the betamethasone group. Following eight weeks of therapy, the mean disease severity was 0.67 and 1.2 in the pimecrolimus and betamethasone groups, respectively. The mean clinical severity scores decreased 86% and 73% in the pimecrolimus and betamethasone groups, respectively (both, P=0.043). There was no significant difference between the groups in terms of therapeutic efficacy (P=0.1). There were no recurrences at the eight-week follow-up. Secondary: Not reported
Goldstein et al.[182] (2011) Clobetasol 0.05% cream daily vs pimecrolimus 1% cream applied BID	DB, RCT Female patients ≥18 years of age with biopsy-proven active vulvar lichen sclerosus	N=38 12 weeks	Primary: Change in inflammation as assessed by biopsy Secondary: Change in pruritus and burning/pain as assessed by patients using a VAS, clinical evaluation of an investigator global assessment of the severity of the disease, clinical evaluation of lichenification, and clinical evaluation of ulceration/fissuring	Primary: The improvement in inflammation was significant both for the clobetasol and pimecrolimus groups (P=0.001 and P=0.008, respectively). Clobetasol was found to be more effective in improving inflammation compared to pimecrolimus (P=0.015). There were nine nonresponders (i.e., no improvement in inflammation), one in the clobetasol group and eight in the pimecrolimus group. Secondary: The mean change in the VAS-pruritus score in the clobetasol and pimecrolimus groups were 4.5 and 3.5, respectively (P=0.319). The mean change in VAS-burning/pain score in the clobetasol and pimecrolimus groups was 3.7 and 3.8, respectively (P=0.932). Clobetasol and pimecrolimus were found to be effective in decreasing both the total score on the investigator global assessment (P=0.001) and all three subscales (severity of disease, P=0.001; lichenification, P=0.001; and ulceration, P=0.025). No adverse events were reported, and no herpetic events occurred.
Koc et al.[183] (2009)	OL, RCT	N=48	Primary: Treatment efficacy	Primary: In both treatment groups, there was a significant decrease in erythema,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ketoconazole 2% cream applied BID vs pimecrolimus 1% cream applied BID	Patients with mild to moderate seborrheic dermatitis	6 weeks	(symptoms of erythema, scaling, and infiltration) Secondary: Not reported	scaling, and infiltration criteria (P<0.05). Clinical improvements were as follows: 81.4 and 78.3% for erythema, 86.1 and 87.2% for scaling, and 93.3 and 94.6% for infiltration in the pimecrolimus and ketoconazole groups, respectively. The mean percentage decrease in the total clinical severity scores was 86.2 and 86.1% in the pimecrolimus and ketoconazole groups, respectively (P>0.05). Adverse events were observed in 12 patients in the pimecrolimus group and four patients in the ketoconazole group. Burning sensation, pruritus, irritation, and erythema were more common in the pimecrolimus group than in the ketoconazole group (P<0.05). Secondary: Not reported
Köse et al.[184] (2010) Mometasone 0.1% cream applied daily vs pimecrolimus 1% cream applied BID	OL, SC Patients with stable vitiligo	N=50 12 weeks	Primary: Response to treatment Secondary: Not reported	Primary: Patients receiving mometasone had a better response to treatment than patients in the pimecrolimus group (P=0.008 in the PP population). Lesion size decreased from 19.20 to 16.85 cm^2 in the pimecrolimus group (P=0.002) and from 18.65 to 10.45 cm^2 in the mometasone group (P<0.001). There was no significant difference between the treatment groups (P=0.154). Complete remission occurred in three patients (15%) receiving mometasone. There were no patients who achieved complete remission in the pimecrolimus group (P=0.018 in the PP population). Moderate and marked responses were recorded in 11 patients (55%) in the mometasone group and in seven patients (35%) in the pimecrolimus group. No change and minimal responses were observed in six patients (30%) in the mometasone group, and in 13 patients (65%) in the pimecrolimus group. After six months, three patients (15%) in the pimecrolimus group and four patients (20%) in the mometasone group showed some areas of depigmentation over re-pigmented vitiliginous lesions.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Initial repigmentation started after 9.25 weeks in the mometasone group and after 11.25 weeks in the pimecrolimus group (P=0.064 in the PP population). The mean repigmentation rate was 65% in the mometasone group and 42% in the pimecrolimus group at the end of therapy. Both agents were well tolerated. The reported adverse events with mometasone were atrophy, telangiectasia, and erythema. Patients receiving pimecrolimus reported a burning sensation and pruritus. Secondary: Not reported
Rigopoulos et al.[185] (2009) Betamethasone valerate 0.1% ointment applied BID vs tacrolimus 0.1% ointment applied BID vs placebo	OL, RCT Patients with chronic paronychia	N=45 Treatment: 3 weeks Follow-up: 6 weeks	Primary: Treatment response Secondary: Not reported	Primary: Eight patients in the betamethasone group were considered as cured, two as improved and four as nonresponders at the end of the treatment period. Thirteen patients in the tacrolimus group were considered as cured and one as improved at the end of the treatment period. Nine patients in the placebo group were considered as stable and six failed to respond. Patients in the betamethasone and tacrolimus groups had greater cure or improvement rates compared to patients in the placebo group (P<0.001). Secondary: Not reported

Drug regimen abbreviations: BID=twice daily, QAM= every morning, QD=once daily, QID=four times daily, QHS=every bedtime, QOD=every other day. QPM=every evening, TID=three times daily
Study abbreviations: CI=confidence interval, CS=comparative study, DB=double-blind, ES=extension study, HR=hazard ratio, IB=investigator-blinded, ITT=intention to treat, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PP=per protocol, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single blind, SG=single group SR=systematic review
Miscellaneous abbreviations: ACTG=AIDS Clinical Trials Group, AD=atopic dermatitis, AK=actinic keratosis, AUC=area under the curve, BCC=basal cell carcinoma, BPI=brief pain inventory, BSA=body surface area, CA=Composite Assessment of Index Lesion Disease Severity, CCR=clinical complete response, CGIC=Investigator-Related Clinical Impression of Change, CLNS=Cumulative Lesion Number Score, CTCL=cutaneous T-cell lymphoma, DLQI=Dermatology Life Quality Index, EASI=Eczema Area and Severity Index, ESI=erythema, scaling, and induration, GII=Global Improvement Indices, GSS=Global Severity Score, HIV=human immunodeficiency virus, HIV-DSP= Human Immunodeficiency Virus Associated Distal Sensory Polyneuropathy, IAS=Investigator Assessment Scale, IDQOLInfants' Dermatitis Quality of Life Index, IGA=Investigator's Global Assessment, IGADA=Investigator Global Atopic Dermatitis Assessment, IGII=Investigators' Global

Improvement Index, IGIP=Investigator Global Integrated Photodamage, ISGA=Investigator Static Global Assessment, KC=keratinocyte carcinomas, KS=Kaposi's Sarcoma, mEASI=Modified Eczema Area and Severity Index, mLEASI=Modified Local Eczema Area and Severity Index, MPSS=Modified Psoriasis Severity Score, MTX=methotrexate, NPRS=Numeric Pain Rating Scale, NAPSI=Nail Psoriases Severity Index, ODS=overall disease severity, PASI=Psoriasis Area and Severity Index, PD=progressive disease, PDI=Psoriasis Disability Index, PDT=photodynamic therapy, PGA=Physicians Global Assessment of Clinical Condition, PGIC=Patient Global Impression of Change, PGII=Patient Global Improvement Index, PhGVA=Physician's Global Vitiligo Assessment, PHN=post-herpetic neuralgia, PR=partial response, PRA=partial response area, PRH=partial response height, PQoL-12=Psoriasis Quality of Life Questionnaire, PQoL-AD=Quality-f-Life Questionnaire for Parents of Children with Atopic Dermatitis, PSSI=Psoriasis Scalp Severity Index, PTH=parathyroid, PUVA=psoralen ultraviolet A, QOL=quality of life, sBCC=superficial basal cell carcinoma, SCC=squamous cell carcinoma, SCOR-AD=Severity Scoring of Atopic Dermatitis, SD=stable disease, SF-MPQ=Short Form McGill Pain Questionnaire, TAS=target area score, TLNS=Target Lesion Number Score, TNM=tumor nodes metastasis, TOC=test of cure, TSS=Total Severity Score, TTS=total thickness score, UVA=ultraviolet A, UVB=ultraviolet B, VAS=visual analog scale, VAS-BP=burning/pain visual analog scale, VAS-PR=pruritics visual analog scale

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 19. Relative Cost of the Skin and Mucous Membrane Agents, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Acitretin	oral capsule	Soriatane®*	$$$$$	$$$$$
Afamelanotide	implant	Scenesse®	$$$$$	N/A
Calcipotriene	cream, foam, ointment, solution	Dovonex®*, Sorilux®*	$$$$$	$$$$
Calcitriol	ointment	Vectical®*	$$$$$	$$$$$
Collagenase	ointment	Santyl®	$$$$$	N/A
Imiquimod	cream	Zyclara®*	$$$$$	$$$
Nitroglycerin	rectal ointment	Rectiv®	$$$$$	N/A
Pimecrolimus	cream	Elidel®	$$$$$	N/A
Podofilox	gel, solution*	Condylox®	$$$$-$$$$$	$$
Podophyllum resin	liquid	Podocon-25®	$$$	N/A
Ruxolitinib	cream	Opzelura®	$$$$$	N/A
Sirolimus	gel	Hyftor®	$$$$$	N/A
Tacrolimus	ointment	Protopic®*	$$$$$	$$$$
Tazarotene	cream*, foam*	N/A	$$$$$	$$$$$
Combination Products				
Calcipotriene and betamethasone	foam, ointment, suspension	Enstilar®*, Taclonex®*	$$$$$	$$$$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Halobetasol propionate and tazarotene	Lotion	Duobrii®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The miscellaneous skin and mucous membrane agents are approved for the treatment of actinic keratoses, atopic dermatitis, basal cell carcinoma, erythropoietic protoporphyria, facial angiofibroma, nonsegmental vitiligo, pain associated with anal fissure, psoriasis, warts, and wounds.[1-24] The wide variety of products, as well as the range of Food and Drug Administration (FDA)-approved indications, makes direct comparisons difficult. Several of the agents are available in a generic formulation.

Imiquimod is approved for the treatment of actinic keratosis. Topical therapies (e.g., cryotherapy, 5-fluorouracil, diclofenac, imiquimod, photodynamic therapy) are all acceptable treatment options for patients with actinic keratosis, with the strongest recommendations supporting treatment with 5-fluorouracil or imiquimod.[25,26] Clinical trials have demonstrated a significant reduction in actinic keratosis lesions with, imiquimod compared to placebo.[48-56,58] In a 12-week comparative study, diclofenac and imiquimod were found to be equally effective.[51] Two studies evaluated the effects of fluorouracil and imiquimod on clinical and histological outcomes. Fluorouracil was found to be more effective than imiquimod in a 24-week study.[46] A second study demonstrated similar initial clearance rates with fluorouracil and imiquimod at the end of the active treatment phase; however, the 12-month sustained clearance rates were significantly higher with imiquimod compared to fluorouracil.[57]

Imiquimod is also approved for the treatment of superficial basal cell carcinoma. The goal of therapy is to eradicate the tumor in a manner that will be the most acceptable to the patient.[33,35] Surgery is often the most effective way to eradicate the tumor.[33,35] The National Comprehensive Cancer Network guidelines recommend the use of topical therapies (e.g., cryotherapy, 5-fluorouracil, imiquimod, photodynamic therapy) in patients with low-risk superficial basal cell carcinoma when surgery or radiation is contraindicated or impractical.[33] There are relatively few studies that compare the different skin cancer treatments. Several trials have demonstrated the efficacy of imiquimod and fluorouracil in the treatment of superficial basal cell carcinoma.[92-98] A study comparing imiquimod cream, fluorouracil cream, and methyl aminolevulinate photodynamic therapy for the treatment of superficial basal-cell carcinoma found the probability of tumor-free survival at three years was 79.7% for imiquimod (95% CI, 71.6 to 85.7), 68.2% for fluorouracil (95% CI, 58.1 to 76.3), and 58.0% for photodynamic therapy (95% CI, 47.8 to 66.9).[101]

Pimecrolimus, ruxolitinib, and tacrolimus are approved for the treatment of atopic dermatitis. Pimecrolimus and ruxolitinib are only indicated for the treatment of mild to moderate disease; whereas, tacrolimus is indicated for the treatment of moderate to severe disease.[11,15] For the treatment of atopic dermatitis, emollients are considered the standard of care.[27-32] They are steroid-sparing and are useful for both prevention and maintenance therapy. Topical corticosteroids provide symptomatic relief and are safe to use in the short term. Topical calcineurin inhibitors are second-line therapy in patients who have failed to respond adequately to other topical treatments, or when those treatments are not advisable. Ruxolitinib is not currently mentioned in consensus guidelines for the treatment of atopic dermatitis, but is only indicated for use in mild to moderate disease not adequately controlled by topical prescription therapies.[11,15,23,27-31] According to the prescribing information, the long-term safety of topical calcineurin inhibitors has not been established.[11,15] Rare cases of malignancy have been reported in patients treated with topical calcineurin inhibitors, although a causal relationship has not been established. Serious infections including active tuberculosis, invasive fungal infections, and other bacterial, viral, and opportunistic pathogens have been reported in patients using JAK inhibitors. Ruxolitinib should be avoided in patients with active, serious infections.[23] Pimecrolimus 1% and tacrolimus 0.03% were found to be equally effective in patients with mild to moderate atopic dermatitis.[72,84,87] Clinical trials have also compared pimecrolimus 1% and tacrolimus 0.1% in patients with moderate to severe disease. Patients receiving tacrolimus had a higher treatment success rate following six weeks of therapy than those receiving pimecrolimus.[82-84] There were no studies found in the medical literature that directly compared pimecrolimus 1% and tacrolimus 0.03% in patients with moderate to severe atopic dermatitis. Clinical trials comparing ruxolitinib 1.5% to placebo showed substantial improvements in EASI

and IGA scores over placebo. Ruxolitinib was found to have no statistically significant difference in the mean percentage change in EASI score compared to triamcinolone 0.1%.[73-75] There were no studies found in the medical literature that directly compared ruxolitinib 1.5% with topical calcineurin inhibitors for any severity of atopic dermatitis.

Ruxolitinib is also approved for the treatment of nonsegmental vitiligo. There are numerous topical and systemic therapies available for the treatment of vitiligo. Selection of therapy should take into consideration the disease severity, disease activity, patient preference, and response to treatment options. Treatment typically includes phototherapy plus systemic or topical corticosteroids, calcineurin inhibitors, or vitamin D analogs. Guidelines recommend topical corticosteroids or calcineurin inhibitors for localized nonsegmental vitiligo involving less than ten percent of the total body surface area. Disseminated disease, recalcitrant disease, or involvement of greater than ten percent of total body surface area warrants the use of narrow-band ultraviolet-b phototherapy as first-line therapy in combination with intermittent use of topical treatment options.[187] Ruxolitinib is not currently mentioned in consensus guidelines for the treatment of nonsegmental vitiligo.[187] Results available from one clinical trial indicate that ruxolitinib may be an effective and safe prophylactic treatment for nonsegmental vitiligo.[161] There were no studies found in the medical literature that compared ruxolitinib to phototherapy, topical corticosteroids, or topical calcineurin inhibitors. Consideration in consensus guidelines and additional clinical literature may be necessary before ruxolitinib use in nonsegmental vitiligo is recommended over alternative topical therapies.

Sirolimus topical gel (Hyftor®) is an mTOR inhibitor immunosuppressant indicated for the treatment of facial angiofibroma associated with tuberous sclerosis in adults and pediatric patients six years of age and older.[1,2,24] In a single, randomized, double-blind, vehicle-controlled, multi-center, Phase 3 trial, the primary end point of composite improvements in angiofibromas at week 12, none of the 31 assessable patients in the placebo group were rated improved or better, and 26 of them (84%) were rated unchanged. In contrast, five (17%) and 13 (43%) patients in the sirolimus group were rated markedly improved and improved, respectively (P<0.001).[105]

Afamelanotide is approved for the prophylaxis of pain from free-light exposure in adult patients with a history of phototoxic reaction caused by erythropoietic protoporphyria. The preferred method of preventing phototoxicity in patients with erythropoietic protoporphyria is the avoidance and protection from UV light. This includes use of protective clothing or broad-spectrum sunscreen preparations while outdoors, or avoidance of exposure to UV light altogether.[186] Afamelanotide is the first FDA-approved treatment option for adult patients with erythropoietic protoporphyria and is administered as a subcutaneous implant every other month.[22,186] As demonstrated in clinical trials, afamelanotide is an effective and safe prophylactic treatment to increase the number of pain-free hours spent in direct sunlight for patients with erythropoietic protoporphyria.[103,104] As afamelanotide is only effective to reduce pain from phototoxicity associated with erythropoietic protoporphyria, it will only benefit patients regularly exposed to direct sunlight and may provide less benefit during seasons with less daylight hours.[186]

Acitretin, calcipotriene, calcipotriene-betamethasone, calcitriol, halobetasol-tazarotene and tazarotene are approved for the treatment of psoriasis. Acitretin is available as an oral capsule, while the other agents are topical formulations. There are numerous topical and systemic therapies available for the treatment of psoriasis.[1] The selection of therapy should take into consideration the disease severity, location of the lesions, and patient preference. Patients with mild to moderate disease can often be treated with a topical agent, while those with moderate to severe disease may need systemic therapy.[37] Topical agents are also used adjunctively for resistant lesions in patients who are being treated with ultraviolet light or systemic medications. Topical preparations that are effective for the treatment of psoriasis include corticosteroids, tar-based products, dithranol preparations, vitamin A analogs, and vitamin D analogs. Emollients should also be used to soften scaling and reduce irritation. Guidelines do not give preference to one topical agent over another.[37] As demonstrated in clinical trials, calcipotriene is an effective and safe treatment for the management of psoriasis.[110,111,114-118,139] The combination of calcipotriene and betamethasone was more effective than monotherapy with either agent alone.[37,122-128] The combination of halobetasol and tazarotene was more effective than vehicle.[150] There were no studies found in the medical literature that directly compared the calcipotriene-betamethasone or halobetasol-tazarotene combination products with the coadministration of the individual agents as separate formulations. Calcitriol has also been shown to be an effective treatment option for patients with psoriasis in several clinical trials.[141-146] It appears to cause less irritation than calcipotriene, especially in sensitive areas of the skin.[37,145,146] Tazarotene has been shown to be as effective as calcipotriene, clobetasol, and coal tar.[152-157] Acitretin is an effective systemic agent for the treatment of severe psoriasis; however, it is teratogenic and its use is limited in female patients of childbearing potential.[3,36,106-109]

Imiquimod, podofilox, and podophyllum resin are approved for the treatment of external anogenital warts. According to the Centers for Disease Control and Prevention and British Association for Sexual Health and human immunodeficiency virus guidelines, there is no evidence to suggest that any of the available treatments are more effective than any other.[39-42] The selection of therapy should be based on the size, number, and location of the warts, patient preference, adverse events, and provider experience. Imiquimod and podofilox are patient-administered treatments, whereas podophyllum resin is applied by health care professionals. Clinical trials have demonstrated that all these agents are effective for the treatment of external anogenital warts.[162-175] Collagenase is approved for debriding chronic dermal ulcers and severely burned areas; however, there are very few published studies comparing its use with other agents or debridement techniques.[176-180]

At this time, there is not a role for the miscellaneous skin and mucous membrane agents in general use. Because these agents have narrow indications with limited usage, they should be available for special needs/circumstances that require medical justification through the prior authorization process. After clinical circumstances are explored, proper medical justification will provide patient access to these agents.

Therefore, all brand miscellaneous skin and mucous membrane agents within the class reviewed are comparable to each other and to the generics in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand miscellaneous skin and mucous membrane agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucous Membrane Cell Stimulants and Proliferants
AHFS Class 841600
February 8, 2023

I. Overview

The skin and mucous membrane cell stimulants and proliferants that are included in this review are listed in Table 1. This review encompasses all topical dosage forms and strengths. This class was previously a part of AHFS class 849200, Skin and Mucous Membrane Miscellaneous Agents. Palifermin is primarily administered in an institution and is included in Table 1 only. These agents were last reviewed in February 2021.

Table 1. Skin and Mucous Membrane Cell Stimulants and Proliferants Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Palifermin^	vial	Kepivance®	none

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution and will be included in Table 1 only.
PDL=Preferred Drug List

II. Conclusions

At this time, there is not a role for the skin and mucous membrane cell stimulants and proliferants in general use.

III. Recommendations

No brand skin and mucous membrane stimulant and proliferant is recommended for preferred status. Alabama Medicaid should continue to include AHFS Class 841600 in the Preferred Drug List (PDL) screening process. If new prescription skin and mucous membrane Cell Stimulants and Proliferants are added, it is recommended that this class be re-reviewed.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Disease-Modifying Antirheumatic Agents
AHFS Class 923600
February 8, 2023

I. Overview

The disease-modifying antirheumatic drugs (DMARDs) are used for a variety of inflammatory and immunologic conditions. These agents achieve their therapeutic effect via several different mechanisms of action. The majority of oral and injectable agents inhibit the effect of proinflammatory cytokines, specifically interleukins or tumor necrosis factor (TNF)-α. Interleukin (IL) inhibitors include anakinra (Kineret®), sarilumab (Kevzara®), secukinumab (Cosentyx®), and tocilizumab (Actemra®); while the TNF-α inhibitors are adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), golimumab (Simponi®, Simponi ARIA®), and infliximab (Remicade®, Inflectra®, Renflexis®, Avsola®). Abatacept (Orencia®) is a T-cell activation inhibitor, apremilast (Otezla®) is a phosohodiesterase-4 (PDE-4) inhibitor, leflunomide (Arava®) is a pyrimidine synthesis inhibitor, and tofacitinib (Xeljanz®), baricitinib (Olumiant®), upadacitinib (Rinvoq®), and abrocitinib (Cibinqo®) are Janus kinase inhibitors. Sulfasalazine (Azulfidine®) is a prodrug composed of 5-aminosalicylic acid linked to sulfapyridine. The mechanism of action is not well defined but may be related to the anti-inflammatory and/or immunomodulatory properties, to its affinity for connective tissue, and/or to the relatively high concentration it reaches in serous fluids, the liver, and intestinal walls.[1-24] Voclosporin is a calcineurin inhibitor immunosuppressant FDA-approved for the treatment of adult patients with active lupus nephritis in combination with a background immunosuppressive therapy regimen. Although the full mechanism of action of calcineurin suppression has not been established, activated lymphocytes cause increased intracellular calcium concentrations and subsequent activation of Nuclear Factor of Activated T-Cell Cytoplasmic. The immunosuppressant activity results in lowered lymphocyte and T-cell proliferation and expression of T-cell activation surface antigens.[21]

The interleukins (ILs) that are targeted by immunomodulator agents are IL-1 (1α and/or 1β), IL-6, IL-12, IL-17A, or IL-23. IL-1 plays an important role in the inflammatory process as a proinflammatory mediator along with TNF-α. IL-1 is also associated with cartilage breakdown as well as stimulation of bone resorption. Anakinra is a recombinant, non-glycosylated form of the naturally occurring human interleukin-1 receptor antagonist (IL-1Ra) and blocks the effect of both IL-1α and IL-1β at its receptor.[4,23,24] IL-6 is a chemical messenger that has been associated with the inflammatory process as well as other diverse processes such as T-cell activation, immunoglobulin secretion induction, hepatic acute phase protein synthesis initiation, and hematopoietic precursor cell proliferation and differentiation stimulation. Sarilumab binds to both soluble and membrane-bound IL-6 receptors and has been shown to inhibit IL-6-mediated signaling through these receptors.[15,23,24] Secukinumab selectively binds to the IL-17A cytokine and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Secukinumab inhibits the release of proinflammatory cytokines and chemokines.[16,23,24] Tocilizumab is a humanized monoclonal antibody that competes with IL-6 for binding to IL-6 receptor which can be found in the serum or membrane-bound.[18,23,24]

TNF-α is another proinflammatory mediator that is released by lymphocytes. Working together with IL-1 and other cytokines and growth factors, they induce certain gene expression and protein synthesis.[23,24] Adalimumab, golimumab, and infliximab are monoclonal antibodies that bind to both membrane-bound TNF-α and soluble TNF-α, preventing its binding to the TNF receptors. Certolizumab pegol, an antibody-binding fragment modified with polyethylene glycol (pegylated), acts in a similar fashion. Certolizumab pegol binds to membrane bound and soluble TNF-α preventing its binding to the TNF receptor. Neither of these drugs have affinity for TNF-β, which utilizes that same receptor.[3,6,8-12,23,24] Etanercept is a fusion protein that that contains the ligand binding site of the p75 TNF receptor. As etanercept mimics the TNF receptor, it has affinity for and binds both TNF-α and TNF-β. These agents have been found to be similar with respect to adverse events and interacting medications.[7,23,24]

Abatacept is the only T-cell activation inhibitor in this class of drugs. Abatacept binds to CD80 and CD86 preventing CD28 activation, which is required for the costimulatory signal necessary for full activation of the T-cell.[1,23,24] Apremilast is an oral small-molecule inhibitor of PDE-4 specific for cyclic adenosine monophosphate (cAMP). Cyclic AMP is an intracellular second messenger that controls a network of pro-inflammatory and anti-inflammatory mediators. PDE-4 inhibition results in increased intracellular cAMP levels, which is thought to

restore a balance of pro- and anti-inflammatory signals.[5,23,24] Leflunomide inhibits dihydroorotate dehydrogenase, leading to antiproliferative activity which includes the inhibition of T-cell proliferation and reduction of production of autoantibodies by B cells.[14,23,24] Tofacitinib, baricitinib, and upadacitinib are oral Janus kinase inhibitors. They are synthetic chemical compound that interfere with specific signal-transduction pathways. Through their broad effect on multiple cytokine pathways, Janus kinas inhibitors may reduce tissue inflammation and joint damage in rheumatoid arthritis.[19-24]

Because many of the DMARDs are biologic agents made from living organisms and are extremely difficult to duplicate, regulations to approve generic versions of these agents have been difficult to create. Congress, through the Biologics Price Competition and Innovation Act (BPCI Act) of 2009, created an abbreviated licensure pathway for biological products that are demonstrated to be biosimilar to or interchangeable with an FDA-approved biological product.[26] A biosimilar product is defined as a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product. Currently, the FDA has approved 39 biosimilar products and three interchangeable biologic products.[26]

The disease-modifying antirheumatic agents that are included in this review are listed in Table 1. Adalimumab, etanercept, and infliximab are available in multiple biosimilar formulations. Secukinumab and sulfasalazine have both been changed to the DMARD AHFS class from other classes in 2022. This class was last reviewed in February 2021.

Table 1. Disease-Modifying Antirheumatic Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Abatacept	injection	Orencia®	none
Abrocitinib	tablet	Cibinqo®	none
Adalimumab	injection	Humira®	Humira®CC
Anakinra	injection	Kineret®	none
Apremilast	tablet	Otezla®	none
Baricitinib	tablet	Olumiant®	none
Certolizumab pegol	injection	Cimzia®	Cimzia®CC
Etanercept	injection	Enbrel®	Enbrel®CC
Golimumab	injection	Simponi®, Simponi Aria®	none
Infliximab	injection	Avsola®^, Inflectra®^, Remicade®*, Renflexis®^	none
Leflunomide	tablet	Arava®*	leflunomide
Sarilumab	injection	Kevzara®	none
Secukinumab	injection	Cosentyx®	none
Sulfasalazine	delayed-release tablet, tablet	Azulfidine®*	sulfasalazine
Tocilizumab	injection	Actemra®	none
Tofacitinib	extended-release tablet, tablet, oral solution	Xeljanz®, Xeljanz XR®	none
Upadacitinib	extended-release tablet	Rinvoq®	none
Voclosporin	capsule	Lupkynis®	none

*Generic is available in at least one dosage form or strength. Unbranded Infliximab was approved under a supplemental biologics license application and is the same product as Remicade®.
PDL=Preferred Drug List
^Biosimilar product.
ccDenotes agent is preferred with clinical criteria in place.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the disease-modifying antirheumatic agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the Disease-Modifying Antirheumatic Agents

Clinical Guideline	Recommendation(s)

Clinical Guideline	Recommendation(s)

Assessment of Spondyloarthritis International Society/European League Against Rheumatism: **2016 Update of the Assessment of Spondyloarthritis International Society/European League Against Rheumatism Recommendations for the Management of Axial Spondyloarthritis (2017)**[27]	• Treatment of axial spondyloarthritis (axSpA) should be tailored according to:
	  o Current manifestations of the disease (axial, peripheral, extra-articular symptoms and signs).
	  o Patient characteristics (comorbidities and psychosocial factors).
	• Disease monitoring of patients with axSpA should include: patient-reported outcomes, clinical findings, laboratory tests, and imaging, all with the appropriate instruments and relevant to the clinical presentation. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity, and treatment.
	• Treatment should be guided according to a predefined treatment target.
	• Patients should be educated about axSpA and encouraged to exercise on a regular basis and stop smoking; physical therapy should be considered.
	• Nonsteroidal anti-inflammatory drugs (NSAIDs) up to the maximum dose, are recommended as first line drug treatment for patients suffering from pain and stiffness, taking risks and benefits into account. Continuous treatment with an NSAID is preferred for patients who respond well to NSAIDs if symptomatic otherwise.
	• Analgesics, such as paracetamol and opioid-(like) drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated, and/or poorly tolerated.
	• Patients with purely axial disease should normally not be treated with conventional synthetic disease-modifying antirheumatic drug (DMARD); sulfasalazine may be considered in patients with peripheral arthritis. Biological DMARDS should be considered in patients with persistently high disease activity despite conventional treatments; current practice is to start with tumor necrosis factor inhibitor (TNFi) therapy.
	• If TNFi therapy fails, switching to another TNFi or interleukin-17 inhibitor therapy should be considered.
	• If a patient is in sustained remission, tapering of a biological DMARD can be considered.
	• Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age. Spinal corrective osteotomy in specialized centers may be considered in patients with severe disabling deformity.
	• If a significant change in the course of the disease occurs, causes other than inflammation, such as a spinal fracture, should be considered and appropriate evaluation, including imaging, should be performed.

American College of Rheumatology/ Spondylitis Association of America/ Spondyloarthritis Research and Treatment Network: **Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis (2019)**[28]	<u>Recommendations for adults with active ankylosing spondylitis (AS)</u>
	• Treatment with NSAIDs is recommended over no treatment with NSAIDs. Continuous treatment with NSAIDs is recommended over on-demand treatment with NSAIDs. No particular NSAID is recommended as a preferred choice.
	• In adults with active AS despite treatment with NSAIDs:
	  o Treatment with sulfasalazine, methotrexate or tofacitinib is recommended over no treatment with these medications. Sulfasalazine or methotrexate should be considered only in patients with prominent peripheral arthritis or when TNFi are not available.
	  o Treatment with TNFi is recommended over treatment with tofacitinib
	  o TNFi treatment is recommended over no treatment with TNFi. No TNF-α inhibitor is recommended as preferred.
	  o Treatment with secukinumab or ixekizumab is recommended over no treatment with secukinumab or ixekizumab.
	  o Treatment with TNFi is recommended over treatment with secukinumab or ixekizumab.
	  o Treatment with secukinumab or ixekizumab is recommended over treatment with tofacitinib.

Clinical Guideline	Recommendation(s)
	○ For those patients who have contraindications to TNFi, treatment with secukinumab or ixekizumab is recommended over treatment with sulfasalazine, methotrexate or tofacitinib. • In adults with active AS despite treatment with the first TNFi used: ○ Treatment with secukinumab or ixekizumab is recommended over treatment with a different TNFi in patients with primary nonresponse to TNFi. ○ Treatment with a different TNFi is recommended over treatment with a non- TNFi biologic agent in patients with secondary nonresponse to TNFi. ○ Switching to treatment with a biosimilar of the first TNFi is strongly not recommended. ○ Addition of sulfasalazine or methotrexate in favor of treatment with a new biologic is not recommended. • In adults with active AS, treatment with systemic glucocorticoids is strongly not recommended. • In adults with AS and isolated active sacroiliitis despite treatment with NSAIDs, treatment with locally administered parenteral glucocorticoids is recommended over no treatment with local glucocorticoids. • In adults with AS with stable axial disease and active enthesitis despite treatment with NSAIDs, treatment with locally administered parenteral glucocorticoids is recommended over no treatment with local glucocorticoids. Peri-tendon injections of Achilles, patellar, and quadriceps tendons should be avoided. • In adults with stable axial disease and active peripheral arthritis despite treatment with NSAIDs, treatment with locally administered parenteral glucocorticoids is recommended over no treatment with local glucocorticoids. • Treatment with physical therapy is recommended over no treatment with physical therapy. Active physical therapy interventions are recommended over passive physical therapy interventions. Land-based physical therapy interventions are recommended over aquatic therapy interventions. <u>Recommendations for adults with stable AS</u> • On-demand treatment with NSAIDS is recommended over continuous treatment with NSAIDs. • In adults receiving treatment with TNFi and NSAIDs, continuing treatment with TNFi alone is recommended compared to continuing both treatments. • In adults receiving treatment with TNFi and conventional synthetic antirheumatic drug, continuing treatment with TNFi alone is recommended over continuing both treatments. • In adults receiving treatment with a biologic, discontinuation of the biologic or tapering of the biologic dose as a standard approach is not recommended. • In adults receiving treatment with an originator TNFi, continuing treatment with the originator TNFi is recommended over mandated switching to its biosimilar. • Treatment with physical therapy over no treatment with physical therapy is recommended. <u>Recommendations for adults with active or stable AS</u> • In adults receiving treatment with TNFi, co-treatment with low-dose methotrexate is not recommended. <u>Recommendations for adults with active nonradiographic axSpA</u> • Treatment with NSAIDs is recommended over no treatment or on-demand treatment with NSAIDs. No particular NSAID is recommended as the preferred choice • In adults with nonradiographic axSpA despite treatment with NSAIDs:

Clinical Guideline	Recommendation(s)
	○ Treatment with sulfasalazine, methotrexate or tofacitinib is recommended over no treatment with these medications. ○ Treatment with TNFi is recommended over no treatment with TNFi. No particular TNFi is recommended as the preferred choice. ○ Treatment with TNFi is recommended over treatment with tofacitinib. ○ Treatment with secukinumab or ixekizumab is recommended over no treatment with secukinumab or ixekizumab. ○ Treatment with TNFi is recommended over treatment with secukinumab or ixekizumab. ○ Treatment with secukinumab or ixekizumab is recommended over treatment with tofacitinib. ○ For those patients who have contraindications to TNFi, treatment with secukinumab or ixekizumab is recommended over treatment with sulfasalazine, methotrexate or tofacitinib. • In adults with primary nonresponse to the first TNFi used, switching to secukinumab or ixekizumab is recommend over switching to a different TNFi. • In adults with secondary nonresponse to the first TNFi used, switching to a different TNFi is recommended over switching to a non-TNFi biologic. • In adults with nonradiographic axSpA despite treatment with the first TNFi used: ○ Switching to treatment with a biosimilar of the first TNFi is strongly not recommended. ○ Addition of sulfasalazine or methotrexate in favor of treatment with a new biologic is not recommended in favor of treatment with a different biologic. • Treatment with systemic glucocorticoids is strongly not recommended. • In adults with isolated active sacroiliitis despite treatment with NSAIDs, treatment with local glucocorticoids is recommended over no treatment with local glucocorticoids. • In adults with active enthesitis despite treatment with NSAIDs, treatment with locally administered parenteral glucocorticoids is recommended over no treatment with local glucocorticoids. Peri-tendon injections of Achilles, patellar, and quadriceps tendons should be avoided. • In adults with active peripheral arthritis despite treatment with NSAIDs, using treatment with locally administered parenteral glucocorticoids is recommended over no treatment with local glucocorticoids. • Treatment with physical therapy is recommended over no treatment with physical therapy. Active physical therapy interventions are recommended over passive physical therapy interventions. Land-based physical therapy interventions are recommended over aquatic therapy interventions. <u>Recommendations for adults with stable nonradiographic axSpA</u> • On-demand treatment with NSAIDS is recommended over continuous treatment with NSAIDs. • In adults receiving treatment with TNFi and NSAIDs, continuing treatment with TNFi alone is recommended compared to continuing both treatments. • In adults receiving treatment with TNFi and conventional synthetic antirheumatic drug, continuing treatment with TNFi alone is recommended over continuing both treatments. • In adults receiving treatment with a biologic, discontinuation of the biologic or tapering of the biologic dose as a standard approach is not recommended. • In adults receiving treatment with an originator TNFi, continuation of treatment with the originator TNFi is recommended over mandated switching to its biosimilar. <u>Recommendations for adults with active or stable nonradiographic axSpA</u>

Clinical Guideline	Recommendation(s)
	• In adults receiving treatment with TNFi, co-treatment with low-dose methotrexate is not recommended.

National Institute for Health and Clinical Excellence: **TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (2016)**[29]
 	
Reaffirmed March 2019
	• Adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab are recommended, within their marketing authorizations, as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs. Infliximab is recommended only if treatment is started with the least expensive infliximab product. People currently receiving infliximab should be able to continue treatment with the same infliximab product until they and their clinician consider it appropriate to stop.
	• Adalimumab, certolizumab pegol, and etanercept are recommended, within their marketing authorizations, as options for treating severe non‑radiographic axial spondyloarthritis in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs.
	• The choice of treatment should be made after discussion between the clinician and the patient about the advantages and disadvantages of the treatments available. This may include considering associated conditions such as extra‑articular manifestations. If more than one treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) should be chosen.
	• The response to adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab treatment should be assessed 12 weeks after the start of treatment. Treatment should only be continued if there is clear evidence of response, defined as:
	  ○ a reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre‑treatment value or by 2 or more units and
	  ○ a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more.
	• Treatment with another TNF-α inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-α inhibitor, or whose disease has stopped responding after an initial response.
	• When using BASDAI and spinal pain VAS scores, healthcare professionals should take into account any physical, sensory, or learning disabilities, or communication difficulties that could affect the responses to the questionnaires and make any adjustments they consider appropriate.

European League Against Rheumatism: **Recommendations for the Management of Behcet's Syndrome: 2018 Update (2018)**[30]	<u>Mucocutaneous involvement</u> • Topical measures such as steroids should be used for the treatment of oral and genital ulcers. Colchicine should be tried first for the prevention of recurrent mucocutaneous lesions especially when the dominant lesion is erythema nodosum or genital ulcer. Papulopustular or acne-like lesions are treated with topical or systemic measures as used in acne vulgaris. • Leg ulcers in Behcet's Syndrome (BS) might be caused by venous stasis or obliterative vasculitis. Treatment should be planned with the help of a dermatologist and vascular surgeon. • Drugs such as azathioprine, thalidomide, interferon-alpha, TNFi or apremilast should be considered in selected cases. <u>Uveitis</u> • Management of uveitis of BS requires close collaboration with ophthalmologists with the ultimate aim of inducing and maintaining remission. • Any patient with BS and inflammatory eye disease affecting the posterior segment should be on a treatment regime such as azathioprine, cyclosporine-A, interferon alpha or monoclonal anti-TNF antibodies. Systemic glucocorticoids should be used only in combination with azathioprine or other systemic

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	immunosuppressives. • Patients presenting with an initial or recurrent episode of acute sight-threatening uveitis should be treated with high-dose glucocorticoids, infliximab or interferon alpha. Intravitreal glucocorticoid injection is an option in patients with unilateral exacerbation as an adjunct to systemic treatment. • In patients with isolated anterior uveitis, systemic immunosuppressives could be considered for those with poor prognostic factors such as young age, male sex and early disease onset. <u>Venous thrombosis</u> • For the management of acute deep vein thrombosis in BS, glucocorticoids and immunosuppressives such as azathioprine, cyclophosphamide or cyclosporine-A are recommended. • Monoclonal anti-TNF antibodies could be considered in refractory patients. • Anticoagulants may be added, provided the risk of bleeding in general is low and coexistent pulmonary artery aneurysms are ruled out. <u>Arterial involvement</u> • For the management of pulmonary artery aneurysms, high-dose glucocorticoids and cyclophosphamide are recommended. Monoclonal anti-TNF antibodies should be considered in refractory cases. For patients who have or who are at high risk of major bleeding, embolization should be preferred to open surgery. • For both aortic and peripheral artery aneurysms, medical treatment with cyclophosphamide and corticosteroids is necessary before intervention to repair. • Surgery or stenting should not be delayed if the patient is symptomatic. <u>Gastrointestinal involvement</u> • Gastrointestinal involvement of BS should be confirmed by endoscopy and/or imaging. NSAID ulcers, inflammatory bowel disease and infections such as tuberculosis should be ruled out. • Urgent surgical consultation is necessary in cases of perforation, major bleeding and obstruction. • Glucocorticoids should be considered during acute exacerbations together with disease-modifying agents such as 5-ASA or azathioprine. For severe and/or refractory patients, monoclonal anti-TNF antibodies and/or thalidomide should be considered. <u>Nervous system involvement</u> • Acute attacks of parenchymal involvement should be treated with high-dose glucocorticoids followed by slow tapering, together with immunosuppressives such as azathioprine. Cyclosporine should be avoided. Monoclonal anti-TNF antibodies should be considered in severe disease as first-line or in refractory patients. • The first episode of cerebral venous thrombosis should be treated with high-dose glucocorticoids followed by tapering. Anticoagulants may be added for a short duration. Screening is needed for vascular disease at an extracranial site. <u>Joint involvement</u> • Colchicine should be the initial treatment in BS patients with acute arthritis. Acute monoarticular disease can be treated with intra-articular glucocorticoids. Azathioprine, interferon-alpha or TNFi should be considered in recurrent and chronic cases.
American College of Gastroenterology: **Management of**	<u>Mild-to-moderately severe disease/low-risk disease</u> • Sulfasalazine is effective for treating symptoms of colonic Crohn's disease that is mild to moderately active (conditional recommendation, low level of

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Crohn's Disease in Adults (2018)[31]	evidence). • Oral mesalamine has not consistently been demonstrated to be effective compared with placebo for induction of remission and achieving mucosal healing in patients with active Crohn's disease and should not be used to treat patients with active Crohn's disease (strong recommendation, moderate level of evidence). • Controlled ileal release budesonide at a dose of 9 mg once daily is effective and should be used for induction of symptomatic remission for patients with mild-to-moderate ileocecal Crohn's disease (strong recommendation, low level of evidence). • Metronidazole is not more effective than placebo as therapy for luminal inflammatory Crohn's disease and should not be used as primary therapy (conditional recommendation, low level of evidence). • Ciprofloxacin has shown similar efficacy to mesalamine in active luminal Crohn's disease but has not been shown to be more effective than placebo to induce remission in Crohn's disease and should not be used as therapy for luminal inflammatory Crohn's disease (conditional recommendation, very low level of evidence). • Antimycobacterial therapy has not been shown to be effective for induction or for maintenance of remission or mucosal healing in patients with Crohn's disease and should not be used as primary therapy (conditional recommendation, low level of evidence). • For patients with low risk of progression, treatment of active symptoms with anti-diarrheals, other non-specific medications, and dietary manipulation, along with careful observation for inadequate symptom relief, worsening inflammation, or disease progression, is acceptable (strong recommendation, very low level of evidence). <u>Moderate-to-severe disease/moderate-to-high-risk disease</u> • Oral corticosteroids are effective and can be used for short-term use in alleviating signs and symptoms of moderate to severely active Crohn's disease (strong recommendation, moderate level of evidence). • Conventional corticosteroids do not consistently achieve mucosal healing and should be used sparingly (weak recommendation, low level of evidence). • Azathioprine (at doses of 1.5 to 2.5 mg/kg/day) and 6-mercaptopurine (at doses of 0.75 to 1.5 mg/kg day) are not more effective than placebo to induce short-term symptomatic remission and should not be used in this manner (strong recommendation, low level of evidence). • Thiopurines (azathioprine, 6-mercaptopurine) are effective and should be considered for use for steroid sparing in Crohn's disease (strong recommendation, low level of evidence). • Azathioprine and 6-mercaptourine are effective therapies and should be considered for treatment of patients with Crohn's disease for maintenance of remission (strong recommendation, moderate level of evidence). • Thiopurine methyltransferase (TPMT) testing should be considered before initial use of azathioprine or 6-mercaptopurine to treat patients with Crohn's disease (strong recommendation, low level of evidence). • Methotrexate (up to 25 mg once weekly IM or SC) is effective and should be considered for use in alleviating signs and symptoms in patients with steroid-dependent Crohn's disease and for maintaining remission (conditional recommendation, low level of evidence). • Anti-TNF agents (infliximab, adalimumab, certolizumab pegol) should be used to treat Crohn's disease that is resistant to treatment with corticosteroids (strong recommendation, moderate level of evidence). • Anti-TNF agents should be given for Crohn's disease refractory to thiopurines

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	or methotrexate (strong recommendation, moderate level of evidence). • Combination therapy of infliximab with immunomodulators (thiopurines) is more effective than treatment with either immunomodulators alone or infliximab alone in patients who are naive to those agents (strong recommendation, high level of evidence). • For patients with moderately to severely active Crohn's disease and objective evidence of active disease, anti-integrin therapy (with vedolizumab) with or without an immunomodulator is more effective than placebo and should be considered to be used for induction of symptomatic remission in patients with Crohn's disease (strong recommendation, high level of evidence). • Natalizumab is more effective than placebo and should be considered to be used for induction of symptomatic response and remission in patients with active Crohn's disease (strong recommendation, high level of evidence). • Natalizumab should be used for maintenance of natalizumab-induced remission of Crohn's disease only if serum antibody to John Cunningham (JC) virus is negative. Testing for anti-JC virus antibody should be repeated every 6 months and treatment stopped if the result is positive. (strong recommendation, moderate level of evidence). • Ustekinumab should be given for moderate-to-severe Crohn's disease patients who failed previous treatment with corticosteroids, thiopurines, methotrexate, or anti-TNF inhibitors or who have had no prior exposure to anti-TNF inhibitors (strong recommendation, high level of evidence). • Cyclosporine, mycophenolate mofetil, and tacrolimus should not be used for Crohn's disease (strong recommendation, moderate level of evidence). <u>Severe/fulminant disease</u> • Intravenous corticosteroids should be used to treat severe or fulminant Crohn's disease (conditional recommendation, moderate level of evidence). • Anti-TNF agents (infliximab, adalimumab, certolizumab pegol) can be considered to treat severely active Crohn's disease (strong recommendation, moderate level of evidence). • Infliximab may be administered to treat fulminant Crohn's disease (conditional recommendation, low level of evidence). <u>Perianal/fistulizing disease</u> • Infliximab is effective and should be considered in treating perianal fistulas in Crohn's disease (strong recommendation, moderate level of evidence). • Infliximab may be effective and should be considered in treating enterocutaneous and rectovaginal fistulas in Crohn's disease (strong recommendation, moderate level of evidence). • Adalimumab and certolizumab pegol may be effective and should be considered in treating perianal fistulas in Crohn's disease (strong recommendation, low level of evidence). • Thiopurines (azathioprine, 6-mercaptopurine) may be effective and should be considered in treating fistulizing Crohn's disease (strong recommendation, low level of evidence). • Tacrolimus can be administered for short-term treatment of perianal and cutaneous fistulas in Crohn's disease (strong recommendation, moderate level of evidence). • Antibiotics (imidazoles) may be effective and should be considered in treating simple perianal fistulas (strong recommendation, moderate level of evidence). • The addition of antibiotics to infliximab is more effective than infliximab alone and should be considered in treating perianal fistulas (strong recommendation, moderate level of evidence). • Drainage of abscesses (surgically or percutaneously) should be undertaken

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	before treatment of fistulizing Crohn's disease with anti-TNF agents (conditional recommendation, very low level of evidence). • Placement of setons increases the efficacy of infliximab and should be considered in treating perianal fistulas (strong recommendation, moderate level of evidence). <u>Maintenance Therapy of Luminal Crohn's Disease</u> • Once remission is induced with corticosteroids, a thiopurine or methotrexate should be considered (strong recommendation, moderate level of evidence). • Patients who are steroid dependent should be started on thiopurines or methotrexate with or without anti-TNF therapy (strong recommendation, moderate level of evidence). • Oral 5-aminosalicylic acid has not been demonstrated to be effective for maintenance of medically induced remission in patients with Crohn's disease, and is not recommended for long-term treatment (strong recommendation, moderate level of evidence). • Corticosteroids are not effective for maintenance of medically induced remission in Crohn's disease and should not be used for long-term treatment (strong recommendation, moderate level of evidence). • Budesonide should not be used to maintain remission of Crohn's disease beyond 4 months (strong recommendation, moderate level of evidence). • Anti-TNF therapy, specifically infliximab, adalimumab, and certolizumab pegol, should be used to maintain remission of anti-TNF-induced remission (strong recommendation, high level of evidence). • Anti-TNF monotherapy is effective at maintaining anti-TNF induced remission, but because of the potential for immunogenicity and loss of response, combination with azathioprine/6-mercaptopurine or methotrexate should be considered (strong recommendation, moderate level of evidence). • Vedolizumab should be used for maintenance of remission of vedolizumab-induced remission of Crohn's disease (conditional recommendation, moderate level of evidence). • Natalizumab should be considered for maintaining remission of natalizumab-induced remission of Crohn's disease patients only if John Cunningham (JC) virus is negative (conditional recommendation, moderate level of evidence). • Ustekinumab should be use for maintenance of remission of ustekinumab-induced response of Crohn's disease (conditional recommendation, moderate level of evidence). <u>Postoperative Crohn's Disease</u> • All patients who have Crohn's disease should quit smoking (conditional recommendation, very low level of evidence). • Mesalamine is of limited benefit in preventing postoperative Crohn's disease, but in addition to no treatment is an option for patients with an isolated ileal resection and no risk factors for recurrence (conditional recommendation, moderate level of evidence). • Imidazole antibiotics (metronidazole and ornidazole) at doses between 1 and 2 g/day can be used after small intestinal resection in Crohn's disease patients to prevent recurrence (conditional recommendation, low level of evidence). • Thiopurines may be used to prevent clinical and endoscopic recurrence and are more effective than mesalamine or placebo. However, they are not effective at preventing severe endoscopic recurrence (strong recommendation, moderate level of evidence). • In high-risk patients, anti-TNF agents should be started within four weeks of surgery in order to prevent postoperative Crohn's disease recurrence (conditional recommendation, low level of evidence).

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	• Although data are lacking in postoperative Crohn's disease, anti-TNF therapy should be combined with an immunomodulator to decrease immunogenicity and decrease loss of response (conditional recommendation, very low level of evidence).
National Institute for Health and Clinical Excellence: **Crohn's Disease Management (2019)**[32]	<u>Monotherapy</u> • Offer monotherapy with a conventional glucocorticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission in people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period. • Consider enteral nutrition as an alternative to a conventional glucocorticosteroid to induce remission for: o Children in whom there is concern about growth or side effects. o Young people in whom there is concern about growth. • In people with one or more of distal ileal, ileocecal or right-sided colonic disease who decline, cannot tolerate or in whom a conventional glucocorticosteroid is contraindicated, consider budesonide for a first presentation or a single inflammatory exacerbation in a 12-month period. • In people who decline, cannot tolerate or in whom glucocorticosteroid treatment is contraindicated, consider 5-aminosalicylate (5-ASA) treatment for a first presentation or a single inflammatory exacerbation in a 12-month period. • Do not offer budesonide or 5-ASA treatment for severe presentations or exacerbations. • Do not offer azathioprine, mercaptopurine or methotrexate as monotherapy to induce remission. <u>Combination therapy</u> • Consider adding azathioprine or mercaptopurine to a conventional glucocorticosteroid or budesonide to induce remission of Crohn's disease if: o There are two or more inflammatory exacerbations in a 12-month period, or o The glucocorticosteroid dose cannot be tapered. • Assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine. Do not offer azathioprine or mercaptopurine if TPMT activity is deficient (very low or absent). Consider azathioprine or mercaptopurine at a lower dose if TPMT activity is below normal but not deficient (according to local laboratory reference values). • Consider adding methotrexate to a conventional glucocorticosteroid or budesonide to induce remission in people who cannot tolerate azathioprine or mercaptopurine, or in whom TPMT activity is deficient, if: o There are two or more inflammatory exacerbations in a 12-month period, or o The glucocorticosteroid dose cannot be tapered. • Monitor the effects of azathioprine, mercaptopurine and methotrexate. Monitor for neutropenia in people taking azathioprine or mercaptopurine even if they have normal TPMT activity. <u>Infliximab and adalimumab</u> • Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active Crohn's disease whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy. • Infliximab or adalimumab should be given as a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter. People should then have their

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	disease reassessed to determine whether ongoing treatment is still clinically appropriate. • Treatment as described should normally be started with the less expensive drug. This may need to be varied for individuals because of differences in the method of administration and treatment schedules. • Options of monotherapy with one of these drugs or combined therapy should be discussed when starting infliximab or adalimumab. • Infliximab is recommended as a treatment option for people with active fistulizing Crohn's disease whose disease has not responded to conventional therapy (including antibiotics, drainage and immunosuppressive treatments), or who are intolerant of or have contraindications to conventional therapy. • Infliximab should be given as a planned course of treatment until treatment failure (including the need for surgery) or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed to determine whether ongoing treatment is still clinically appropriate. • Treatment with infliximab or adalimumab should only be continued if there is clear evidence of ongoing active disease as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. Specialists should discuss the risks and benefits of continued treatment with patients and consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People who continue treatment with infliximab or adalimumab should have their disease reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate. People whose disease relapses after treatment is stopped should have the option to start treatment again. • Infliximab is recommended for the treatment of people aged 6 to 17 years with severe active Crohn's disease whose disease has not responded to conventional therapy (including corticosteroids, immunomodulators and primary nutrition therapy), or who are intolerant of or have contraindications to conventional therapy. The need to continue treatment should be reviewed at least every 12 months. • Treatment with infliximab or adalimumab should only be started and reviewed by clinicians with experience of TNFi and of managing Crohn's disease. <u>Remission maintenance</u> • For patients that choose maintenance therapy, offer azathioprine or mercaptopurine as monotherapy to maintain remission when previously used with a conventional glucocorticosteroid or budesonide to induce remission or to maintain remission in patients not previously treated with these medications. • Consider methotrexate to maintain remission only in patients who: o Needed methotrexate to induce remission. o Did not tolerate azathioprine or mercaptopurine for maintenance. o Contraindicated to azathioprine or mercaptopurine. • Do not offer conventional glucocorticosteroids or budesonide to maintain remission. <u>Remission maintenance following surgery</u> • To maintain remission in people with ileocolonic Crohn’s disease who have had complete macroscopic resection within the last three months, consider azathioprine in combination with up to three months post-operative metronidazole. Azathioprine alone should be considered for patients who cannot tolerate metronidazole. • Effects of azathioprine and metronidazole should be monitored, including neutropenia in patients taking azathioprine even if they have normal TPMT. • Biologics should not be offered to maintain remission after complete

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	macroscopic resection of ileocolonic Crohn's disease. For patients who have had surgery and started taking biologics already, continue with their current treatment until both they and their healthcare professional agree it is appropriate to change.
American College of Rheumatology/ Arthritis Foundation: **Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-systemic Polyarthritis, Sacroiliitis and Enthesitis (2019)**[33]	Recommendations for children and adolescents with JIA and polyarthritis • NSAIDs are recommended as adjunct therapy. • Using methotrexate is recommended over leflunomide or sulfasalazine. • Using subcutaneous methotrexate is recommended over oral methotrexate. • Intraarticular glucocorticoids are recommended as adjunct therapy. • Triamcinolone hexacetonide is strongly recommended over triamcinolone acetonide for intraarticular glucocorticoid injections. • Bridging therapy with a limited course of oral glucocorticoids (<3 months) during initiation or escalation of therapy in patients with high or moderate disease activity is recommended. Bridging therapy with a limited course of oral glucocorticoids is not recommended in patients with low disease activity. • Chronic low-dose glucocorticoid is strongly not recommended, irrespective of risk factors or disease activity. • Initiating treatment with biologic (etanercept, adalimumab, golimumab, abatacept, or tocilizumab) combination therapy with a DMARD is recommended over biologic monotherapy. • Combination therapy with a DMARD is strongly recommended for infliximab. • In all patients with JIA and active polyarthritis, initial therapy with a DMARD is strongly recommended over NSAID monotherapy. Using methotrexate monotherapy as initial therapy is conditionally recommended over triple DMARD therapy. • In patients without risk factors, initial therapy with a DMARD is recommended over a biologic. • In patients with risk factors, initial therapy with a DMARD is recommended over a biologic, recognizing that there are situations where initial therapy that includes a biologic may be preferred. Initial biologic therapy may be considered for patients with risk factors and involvement of high-risk joints (e.g., cervical spine, wrist, or hip), high disease activity, and/or those judged by their physician to be at high risk of disabling joint damage. • For subsequent therapy in patients receiving DMARD and/or biologic with low disease activity, escalating therapy is conditionally recommended over no escalation of therapy. Escalation of therapy may include: Intraarticular glucocorticoid injection(s), optimization of DMARD dose, trial of methotrexate if not done, and adding or changing biologic. • For subsequent therapy in patients receiving DMARD monotherapy with moderate/high disease activity, adding a biologic to original DMARD is recommended over changing to a second DMARD. Adding a biologic is recommended over changing to a triple DMARD therapy. • For subsequent therapy in patients receiving first TNFi with or without DMARD therapy with moderate/high disease activity, switching to a non-TNFi biologic (tocilizumab or abatacept) is recommended over switching to a second TNFi. A second TNFi may be appropriate for patients with good initial response to their first TNFi (i.e., secondary failure). • For subsequent therapy in patients receiving second biologic with moderate/high disease activity, using TNFi, abatacept, or tocilizumab (depending on prior biologics received) is recommended over rituximab.
American College of Rheumatology: **Guideline for the Treatment of Juvenile Idiopathic Arthritis:**	Recommendations for oligoarticular juvenile idiopathic arthritis (JIA) • A trial of nonsteroidal antiinflammatory drugs (NSAIDs) is conditionally recommended as part of initial therapy. • Intra-articular glucocorticoids are strongly recommended as part of initial therapy.

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Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint Arthritis, and Systemic Juvenile Idiopathic Arthritis (2021)[34]	• Triamcinolone hexacetonide is strongly recommended as the preferred agent. • Oral glucocorticoids are conditionally recommended *against* as part of initial therapy. • Conventional synthetic disease-modifying antirheumatic drugs (DMARDs) are strongly recommended if there is inadequate response to scheduled NSAIDs and/or intra-articular glucocorticoids. Methotrexate is conditionally recommended as a preferred agent over leflunomide, sulfasalazine, and hydroxychloroquine (in that order). • Biologic DMARDs are strongly recommended if there is inadequate response to or intolerance of NSAIDs and/or intra-articular glucocorticoids and at least one conventional synthetic DMARD. There is no preferred biologic DMARD. • Consideration of risk factors for poor outcome (e.g., involvement of ankle, wrist, hip, sacroiliac joint, and/or temporomandibular joint, presence of erosive disease or enthesitis, delay in diagnosis, elevated levels of inflammation markers, symmetric disease) is conditionally recommended to guide treatment decisions. • Use of validated disease activity measures is conditionally recommended to guide treatment decisions, especially to facilitate treat-to-target approaches. <u>Recommendations for temporomandibular joint arthritis</u> • A trial of NSAIDs is conditionally recommended as part of initial therapy. • Intra-articular glucocorticoids are conditionally recommended as part of initial therapy. There is no preferred agent. • Oral glucocorticoids are conditionally recommended *against* as part of initial therapy. • Conventional synthetic DMARDs are strongly recommended for inadequate response to or intolerance of NSAIDs and/or intra-articular glucocorticoids. Methotrexate is conditionally recommended as a preferred agent over leflunomide. • Biologic DMARDs are conditionally recommended for inadequate response to or intolerance of NSAIDs and/or intra-articular glucocorticoids and at least one conventional synthetic DMARD. There is no preferred biologic agent. • Consideration of poor prognostic features (e.g., involvement of ankle, wrist, hip, sacroiliac joint, and/or temporomandibular joint, presence of erosive disease or enthesitis, delay in diagnosis, elevated levels of inflammation markers, symmetric disease) is conditionally recommended to guide treatment decisions. <u>Recommendations for systemic juvenile idiopathic arthritis **without** macrophage activation syndrome</u> • NSAIDs are conditionally recommended as initial monotherapy. • Oral glucocorticoids are conditionally recommended *against* as initial monotherapy. • Conventional synthetic DMARDs are strongly recommended against as initial monotherapy. • Biologic DMARDs (IL-1 and IL-6 inhibitors) are conditionally recommended as initial monotherapy. There is no preferred agent. • IL-1 and IL-6 inhibitors are strongly recommended over a single or combination of conventional synthetic DMARDs for inadequate response to or intolerance of NSAIDs and/or glucocorticoids. • Biologic DMARDs or conventional synthetic DMARDs are strongly recommended over long-term glucocorticoids for residual arthritis and incomplete response to IL-1 and/ or IL-6 inhibitors. There is no preferred agent. <u>Recommendations for systemic juvenile idiopathic arthritis **with** macrophage activation syndrome</u>

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	• IL-1 and IL-6 inhibitors are conditionally recommended over calcineurin inhibitors alone to achieve inactive disease and resolution of macrophage activation syndrome. Glucocorticoids are conditionally recommended as part of initial treatment of systemic JIA with macrophage activation syndrome. There is no preferred agent. • Biologic DMARDs or conventional synthetic DMARDs are strongly recommended over long-term glucocorticoids for residual arthritis and incomplete response to IL-1 and/or IL-6 inhibitors. There is no preferred agent. Recommendations for systemic juvenile idiopathic arthritis with inactive disease • Tapering and discontinuing glucocorticoids is strongly recommended after inactive disease has been attained. • Tapering and discontinuing biologic DMARDs is conditionally recommended after inactive disease has been attained.
American College of Rheumatology: **Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Initiation and Safety Monitoring of Therapeutic Agents for the Treatment of Arthritis and Systemic Features (2011)**[35]	General considerations • Recommendations for the treatment of juvenile idiopathic arthritis (JIA) are divided into five treatment groups that were developed by the core expert panel responsible for the literature review in the recommendation development. The treatment groups are as follows: history of arthritis of four or fewer joints, history of arthritis of five or more joints, active sacroiliac arthritis, systemic arthritis with active systemic features (and without active arthritis) and systemic arthritis with active arthritis (and without active systemic features). • Glucocorticoid joint injections for active arthritis are recommended regardless of concurrent therapy (no DMARD, nonbiologic DMARD, biologic DMARD) or JIA treatment group. Due to its "superior" efficacy, triamcinolone hexacetonide should be used. • When initiating a TNF-α inhibitor (etanercept or adalimumab), continuation of methotrexate is recommended for patients that had a partial previous response. History of arthritis in four or fewer joints • For patients with low disease activity, no joint contractures and without features of poor prognosis, initiation of therapy with NSAID monotherapy is recommended as a treatment option. Therapy with an NSAID without additional therapy is not recommended longer than two months. • For all patients regardless of disease activity level, prognostic features or joint contractures, initiation of intra-articular joint injections (with or without additional therapy is recommended. • For patients with high disease activity and poor prognostic features, methotrexate is recommended as initial treatment (without prior therapy). For patients with high disease activity without poor prognostic features or with moderate disease activity and poor prognostic features, methotrexate is recommended after initial joint injection. For patients with low disease activity and poor prognostic features or moderate disease activity without poor prognostic features, methotrexate is recommended after repeated joint injections. • For patients with enthesitis-related arthritis category of JIA with moderate or high disease activity with and without poor prognostic features, sulfasalazine is recommended after glucocorticoid injections or an adequate trial of NSAIDs. • Initiation of a TNF-α inhibitor is recommended for patients with moderate or high disease activity with poor prognostic features after receiving glucocorticoid joint injections and three months of methotrexate at maximum tolerated dose. Initiation of a TNF-α inhibitor is also recommended in patients with high disease activity without poor prognostic features after receiving glucocorticoid joint injections and six months of methotrexate. For patients with

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	enthesitis-related arthritis category of JIA and moderate or high disease activity, regardless of prognostic features, TNF-α inhibitors are recommended after receiving glucocorticoid joint injections and an adequate trial of sulfasalazine (without prior methotrexate). <u>History of arthritis of five or more joints</u> • Initial treatment with methotrexate is recommended in patients with high disease activity with or without poor prognostic features and in patients with moderate disease activity and poor prognostic features. For patients with low disease activity and poor prognostic features, methotrexate therapy is recommended after one month of therapy with NSAIDs. In patients with moderate disease activity without poor prognostic features, methotrexate is recommended after one to two months of therapy with NSAIDs. • Leflunomide is a treatment alternative to methotrexate as initial therapy in patients with high disease activity and poor prognostic features. In patients with high disease activity without poor prognostic features or moderate disease activity with poor prognostic features, leflunomide is a treatment alternative after a brief trial with NSAIDs. • For patients with moderate or high disease activity, regardless of prognostic features, TNF-α inhibitors are recommended after receiving methotrexate or leflunomide for three months at the maximum tolerated typical doses. For patients with low disease activity with or without poor prognostic features, TNF-α inhibitors are recommended after receiving methotrexate or leflunomide for six months. • For patients with moderate or high disease activity regardless of prognostic features, switching from one TNF-α inhibitor to another is recommended as a treatment option after receiving four months of therapy with current TNF-α inhibitor. • Abatacept is recommended as a treatment option after receiving four months of therapy with a TNF-α inhibitor in patients with high disease activity regardless of prognostic features or moderate disease activity and poor prognostic features. For patients with moderate or high disease activity regardless of prognostic features or patients with low disease activity with features of poor prognosis, abatacept is recommended as a treatment option after receiving more than one TNF-α inhibitor sequentially. • Switching to a TNF-α inhibitor is recommended as a treatment option in patients that received abatacept for three months and have high disease activity with poor prognostic features and in patients that received abatacept for six months and have moderate to high disease activity with or without features of poor prognosis. <u>Active sacroiliac arthritis</u> • For patients with high disease activity and features of poor prognosis, TNF-α inhibitors are recommended after receiving an adequate trial of NSAIDs. • A TNF-α inhibitor is recommended in patients with high disease activity regardless of prognostic features or moderate disease activity with features of poor prognosis that have received three months of methotrexate, or in patients with moderate disease without poor prognosis that received six months of methotrexate. • A TNF-α inhibitor is recommended in patients with moderate or high disease activity regardless of prognostic features that have received three months of sulfasalazine, or in patients with low disease with poor prognosis that received six months of sulfasalazine. <u>Systemic arthritis with active systemic features</u> • NSAID monotherapy is appropriate during clinical evaluation for possible

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	systemic arthritis. NSAID monotherapy is not recommended for patients with active fever and physician global assessment of overall disease activity ≥7 of 10. In patients with active fever, continuation of NSAID monotherapy longer than one month is not appropriate. • Initial therapy with systemic glucocorticoids (with or without additional concurrent therapy) is recommended for patients with active fever and physician global assessment of seven or greater. For all patients with active fever, systemic glucocorticoids are recommended following up to two weeks of NSAIDs. • Anakinra is recommended for all patients with active fever and poor prognostic features, regardless of current therapy. For patients that sustain or develop fever while receiving systemic glucocorticoid, anakinra is recommended. <u>Systemic arthritis with active arthritis</u> • NSAID monotherapy (with or without glucocorticoid joint injections) for up to one month is recommended for patients with low disease activity without features of poor prognosis. • For all patients with active arthritis, regardless of prognostic features, methotrexate is recommended after one month or less of NSAID monotherapy (with or without glucocorticoid injections). • After three months of methotrexate, anakinra is recommended for patients with moderate or high disease activity with or without poor prognostic features. Anakinra is recommended for patients with high or moderate disease activity, regardless of prognostic features, and have received methotrexate and a TNF-α inhibitor or methotrexate and abatacept. Initiation of anakinra later in the disease course may be less appropriate compared to nearer to the onset of disease. • For patients with moderate or high disease activity with or without poor prognosis features, TNF-α inhibitors are recommended after receiving three months of methotrexate. Switching from anakinra to TNF-α inhibitors may be appropriate for patients with moderate to high disease activity regardless of prognostic features. • Abatacept is recommended for patients that received methotrexate and a TNF-α inhibitor and have high disease activity regardless of prognostic features or moderate disease activity and poor prognostic features.
American College of Rheumatology: **2013 Update of the 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Recommendations for the Medical Therapy of Children With Systemic Juvenile Idiopathic Arthritis and Tuberculosis Screening Among Children Receiving Biologic Medications (2013)[36]**	<u>Initial treatment of systemic JIA with active systemic features and varying degrees of synovitis</u> • Anakinra is recommended as one initial treatment option for patients with a physician global assessment (MD global) ≥5 irrespective of the active joint count (AJC), or an MD global <5 and an AJC >0. • Systemic glucocorticoid monotherapy (oral or intravenous) is recommended for a maximum period of two weeks for patients with an MD global <5 and an AJC >4 and for all patients with an MD global ≥5 irrespective of the AJC. • Initiating NSAID monotherapy in a patient without prior treatment is recommended as one approach for patients with an MD global <5 irrespective of the AJC. <u>Treatment of systemic JIA with active systemic features and varying degrees of synovitis in patients with continued disease activity</u> • Use of abatacept is recommended only in patients with an MD global ≥5 and an AJC >4 after a trial of both an IL-1 inhibitor and tocilizumab (sequentially). • Use of abatacept for patients with an AJC of zero irrespective of the MD global is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially), in which case it is uncertain. • Use of abatacept for patients with an MD global <5 and an AJC >0 or an MD

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	global ≥5 and an AJC <4 is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or a DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it is uncertain. • Use of abatacept for patients with an MD global ≥5 and an AJC >4 is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially), in which case it is appropriate, or patients who had tried a DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it is uncertain. • Anakinra is recommended for patients with continued disease activity after treatment with glucocorticoid monotherapy or NSAID monotherapy. • Use of a calcineurin inhibitor is recommended only for patients with an MD global ≥5 and an AJC of zero after a trial of both an IL-1 inhibitor and tocilizumab (sequentially). • Use of a calcineurin inhibitor for patients with an MD global <5 and an AJC of zero is inappropriate, with the exception of patients who received either an IL-1 inhibitor or tocilizumab, in which case it is uncertain. • Use of a calcineurin inhibitor for patients with an MD global ≥5 and an AJC of zero is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially), in which case it is appropriate, or patients who had tried an IL-1 inhibitor or tocilizumab, in which case it is uncertain. • Use of a calcineurin inhibitor for patients with an AJC >0 irrespective of the MD global is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or an alternate DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it is uncertain. • Canakinumab is recommended for patients with continued disease activity after treatment with glucocorticoid monotherapy, methotrexate or leflunomide, anakinra, or tocilizumab irrespective of the MD global and AJC. • Canakinumab is also recommended for patients with an MD global ≥5 irrespective of the AJC, despite prior NSAID monotherapy. • Glucocorticoid monotherapy is recommended as a treatment option after failure of NSAID monotherapy for patients with an MD global <5 and an AJC >0 and for patients with an MD global ≥5 irrespective of the AJC. Adjunct glucocorticoid therapy at any point is appropriate to consider. • Intraarticular glucocorticoid injection is recommended as adjunct therapy at any time. • Methotrexate or leflunomide is recommended for patients with an MD global <5 and an AJC >0 after treatment with glucocorticoid monotherapy, an IL-1 inhibitor, or tocilizumab. Methotrexate or leflunomide is recommended for patients with an MD global ≥5 and an AJC >0, only after a trial of an IL-1 inhibitor or tocilizumab. • Initiation of a TNF-α inhibitor is recommended for patients with an AJC >4 irrespective of the MD global after a trial of an IL-1 inhibitor or tocilizumab. Initiation of a TNF-α inhibitor is recommended for patients with an AJC >0 irrespective of the MD global after a trial of both an IL-1 inhibitor and tocilizumab (sequentially). • Use of a TNF-α inhibitor for patients with an MD global <5 and an AJC of zero is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or a DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it is uncertain. • Use of a TNF-α inhibitor for patients with an MD global ≥5 and an AJC of zero is inappropriate, with the exception of patients who had tried an IL-1 inhibitor or tocilizumab, in which case it is uncertain. • Tocilizumab is recommended as a treatment option for patients with continued disease activity following glucocorticoid monotherapy, methotrexate or

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	leflunomide, or anakinra irrespective of the MD global and AJC. • Tocilizumab is also recommended for patients with an MD global ≥5 irrespective of the AJC despite prior NSAID monotherapy. <u>Initial treatment of systemic JIA without active systemic features and varying degrees of synovitis</u> • Intraarticular glucocorticoid injection is recommended as an initial treatment for patients with an AJC ≤4. The utility of repeating injections in the same joint(s) as the only intervention is uncertain. • Initiation of methotrexate or leflunomide is recommended for patients with an AJC >4. • Initiation of NSAID monotherapy in a patient without prior treatment for a maximum period of one month is recommended as one treatment approach for patients with an AJC >0. Continuing NSAID monotherapy for longer than two months for patients with continued disease activity is inappropriate. <u>Treatment of systemic JIA without active systemic features and varying degrees of synovitis in patients with continued disease activity</u> • Use of abatacept is recommended for patients with an AJC >0 after treatment with methotrexate or leflunomide, anakinra, or tocilizumab. • Anakinra is recommended as a treatment option for patients with an AJC >4 following failed intraarticular injection or NSAID monotherapy. Use of anakinra is also recommended for patients with an AJC >0 following treatment with methotrexate or leflunomide. • Initiation of canakinumab is recommended for patients with an AJC >4 only after a trial of a DMARD plus anakinra or tocilizumab, a DMARD plus a TNF-α inhibitor, or abatacept. • Use of methotrexate or leflunomide is recommended as a treatment option for an AJC >0 following treatment with intraarticular injection, NSAID monotherapy, an IL-1 inhibitor, or tocilizumab. • Initiation of a TNF-α inhibitor is recommended for patients with an AJC >0 after treatment with methotrexate or leflunomide, anakinra, or tocilizumab. • Initiation of tocilizumab is recommended for an AJC >0 following treatment with anakinra or methotrexate or leflunomide. <u>Initial treatment of systemic JIA with features concerning for macrophage activation syndrome (MAS)</u> • Use of anakinra is recommended as one treatment option for patients with features concerning for MAS. • Use of a calcineurin inhibitor is recommended as one therapeutic option for patients with features concerning for MAS. • Use of systemic glucocorticoid monotherapy (administered by oral or intravenous route) is also recommended as a therapeutic option for patients with features concerning for MAS. • Continuing glucocorticoid monotherapy for longer than two weeks is inappropriate.
European League Against Rheumatism: **Recommendations for the Management of Psoriatic Arthritis with Pharmacological Therapies (2012)**[37]	<u>Recommendations for treatment</u> • In patients with psoriatic arthritis, NSAIDs may be used to relieve musculoskeletal signs and symptoms. • In patients with active disease (particularly those with many swollen joints, structural damage in the presence of inflammation, high erythrocyte sedimentation rate/C-reactive protein and/or clinically relevant extraarticular manifestations), treatment with DMARDs, such as methotrexate, sulfasalazine, leflunomide, should be considered at an early stage. • In patients with active psoriatic arthritis and clinically relevant psoriasis, a

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	DMARD that also improves psoriasis, such as methotrexate, should be preferred. • Local corticosteroid injections should be considered as adjunctive therapy in psoriatic arthritis; systemic steroids at the lowest effective dose may be used with caution. • In patients with active arthritis and an inadequate response to at least one synthetic DMARD, such as methotrexate, therapy with a TNF-α inhibitor should be commenced. • In patients with active enthesitis and/or dactylitis and insufficient response to NSAIDs or steroid injections, a TNF-α inhibitor may be considered. • In patients with predominantly axial disease that is active and has insufficient response to NSAIDs, a TNF-α inhibitor should be considered. • A TNF-α inhibitor might be considered for a very active patient treatment naïve to DMARDs (particularly those with many swollen joints, structural damage in the presence of inflammation, and/ or clinically relevant extra-articular manifestations, especially extensive skin involvement). • In patients who fail to respond adequately to one TNF-α inhibitor, switching to another TNF-α inhibitor should be considered. • When adjusting therapy, factors apart from disease activity, such as comorbidities and safety issues, should be taken into account.
European League Against Rheumatism: **Recommendations for The Management Of Psoriatic Arthritis With Pharmacological Therapies: 2015 Update (2015)[38]**	• Treatment of patients with psoriatic arthritis should aim at the best care and must be based on a shared decision between the patient and the rheumatologist, considering efficacy, safety and costs. • The primary goal of treating patients with psoriatic arthritis is to maximize health-related quality of life, through control of symptoms, prevention of structural damage, normalization of function and social participation; abrogation of inflammation is an important component to achieve these goals. • Treatment should be aimed at reaching the target of remission or, alternatively, minimal/low disease activity, by regular monitoring and appropriate adjustment of therapy. • In patients with psoriatic arthritis, NSAIDs may be used to relieve musculoskeletal signs and symptoms. • In patients with peripheral arthritis, particularly in those with many swollen joints, structural damage in the presence of inflammation, high ESR/CRP and/or clinically relevant extra-articular manifestations, conventional synthetic DMARDs should be considered at an early stage, with methotrexate preferred in those with relevant skin involvement. • Local injections of glucocorticoids should be considered as adjunctive therapy in psoriatic arthritis; systemic glucocorticoids may be used with caution at the lowest effective dose. • In patients with peripheral arthritis and an inadequate response to at least one conventional synthetic DMARD, therapy with a biological DMARD, usually a TNF-α inhibitor, should be commenced. • In patients with peripheral arthritis and an inadequate response to at least one conventional synthetic DMARD, in whom TNF-α inhibitor are not appropriate, biological DMARDs targeting IL12/23 or IL17 pathways may be considered. • In patients with peripheral arthritis and an inadequate response to at least one conventional synthetic DMARD, in whom biological DMARDs are not appropriate, a targeted synthetic DMARD such as a PDE4-inhibitor may be considered. • In patients with active enthesitis and/or dactylitis and insufficient response to NSAIDs or local glucocorticoid injections, therapy with a biological DMARD should be considered, which according to current practice is a TNF-α inhibitor. • In patients with predominantly axial disease that is active and has insufficient response to NSAIDs, therapy with a biological DMARD should be considered,

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	which according to current practice is a TNF-α inhibitor. • In patients who fail to respond adequately to a biological DMARD, switching to another biological DMARD should be considered, including switching between TNF-α inhibitors.
European League Against Rheumatism: **Recommendations For The Management Of Psoriatic Arthritis With Pharmacological Therapies: 2019 Update (2019)**[39]	• Treatment should be aimed at reaching the target of remission or, alternatively, low disease activity, by regular disease activity assessment and appropriate adjustment of therapy. • NSAIDs may be used to relieve musculoskeletal signs and symptoms. • Local injections of glucocorticoids should be considered as adjunctive therapy in psoriatic arthritis; systemic glucocorticoids may be used with caution at the lowest effective dose. • In patients with polyarthritis, a conventional synthetic DMARD should be initiated rapidly, with methotrexate preferred in those with relevant skin involvement. • In patients with monoarthritis or oligoarthritis, particularly with poor prognostic factors such as structural damage, high erythrocyte sedimentation rate/C reactive protein, dactylitis or nail involvement, a conventional synthetic DMARD should be considered. • In patients with peripheral arthritis and an inadequate response to at least one conventional synthetic DMARD, therapy with a biological DMARD should be commenced; when there is relevant skin involvement, an interleukin-17 inhibitor or interleukin-12/23 inhibitor may be preferred. • In patients with peripheral arthritis and an inadequate response to at least one conventional synthetic DMARD and at least one DMARD, or when a biological DMARD is not appropriate, a JAK inhibitor may be considered. • In patients with mild disease and an inadequate response to at least one conventional synthetic DMARD†, in whom neither a biological DMARD nor a JAK inhibitor is appropriate*, a phosphodiesterase-4 inhibitor may be considered. • In patients with unequivocal enthesitis and insufficient response to NSAIDs or local glucocorticoid injections, therapy with a biological DMARD should be considered. • In patients with predominantly axial disease which is active and has insufficient response to NSAIDs, therapy with a biological DMARD should be considered, which according to current practice is a TNFi; when there is relevant skin involvement, interleukin-17 inhibitor may be preferred. • In patients who fail to respond adequately to, or are intolerant of a biological DMARD, switching to another biological DMARD or targeted synthetic DMARD should be considered, including one switch within a class. • In patients in sustained remission, cautious tapering of DMARDs may be considered.
American Academy of Dermatology/National Psoriasis Foundation: **Joint Guidelines of Care for the Management and Treatment of Psoriasis with Biologics (2019)**[40]	<u>Biologics</u> • Four TNFis are FDA-approved for the treatment of moderate-to-severe psoriasis: adalimumab, etanercept, infliximab, and certolizumab. • Seven interleukin antagonists are FDA-approved for the treatment of moderate-to-severe psoriasis: ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, and risankizumab. • Etanercept and adalimumab are recommended as monotherapy, and can be combined with topical therapies, acitretin, methotrexate, apremilast, cyclosporine, and phototherapy to augment efficacy. • Infliximab is recommended as monotherapy, and can be combined with topical therapies, acitretin, methotrexate, and apremilast to augment efficacy. • Ustekinumab is recommended as monotherapy, and can be combined with topical therapies, acitretin, methotrexate, apremilast, cyclosporine, and phototherapy to augment efficacy. Ustekinumab is less effective than TNF-α

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	inhibitors for psoriatic arthritis. • Secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, and risankizumab are recommended as monotherapy. • All biologics may lose efficacy in patients who initially respond favorably to medication (secondary failure). • The necessity of repeating loading doses depends on disease severity and how many doses were missed. Retreatment after discontinuation may result in a small percentage of patients not being able to recapture previous robust level of response. • If clinically needed, all therapies may be switched with a different biologic agent with the possibility of improved efficacy, safety, and/or tolerability. • Etanercept is the only biologic approved for plaque psoriasis in children aged 4 to 17 years, whereas ustekinumab is approved for plaque psoriasis in adolescents aged 12 to 17 years.
American Academy of Dermatology/National Psoriasis Foundation: **Joint Guidelines of Care for the Management and Treatment of Psoriasis with Systemic Nonbiologic Therapies (2020)**[41]	• Methotrexate is recommended for the treatment of moderate to severe psoriasis in adults. • Methotrexate is less effective than adalimumab and infliximab for cutaneous psoriasis. • Methotrexate is efficacious for treatment of psoriatic arthritis (peripheral arthritis, but not for axial involvement); in psoriatic arthritis, the efficacy of methotrexate is lower than TNFi. • Methotrexate can be administered orally or subcutaneously. • Apremilast is recommended for the treatment of moderate to severe psoriasis in adults. • Cyclosporine is recommended for patients with severe, recalcitrant psoriasis. • Cyclosporine can be recommended for the treatment of erythrodermic, generalized pustular, and/or palmoplantar psoriasis. • Cyclosporine can be recommended as short-term interventional therapy in patients who flare up while on a pre-existing systemic therapy. • Acitretin can be recommended as monotherapy for plaque psoriasis. • Acitretin can be recommended for treatment of erythrodermic, pustular, and palmar plantar psoriasis. • Tofacitinib can be considered for treatment of moderate to severe psoriasis but is not currently FDA approved for that indication. • Dimethyl fumarate is approved in the United States for treatment of relapsing forms of multiple sclerosis. It can be recommended for psoriasis. • Although rarely necessary for psoriasis, systemic immunosuppressants and antimetabolites, including hydroxyurea, mycophenolate mofetil, azathioprine, leflunomide, tacrolimus, and thioguanine, may have value for this disease in certain instances.
American College of Rheumatology: **2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis (2015)**[42]	<u>Recommendations for Early RA Patients</u> • Using a treat-to-target strategy rather than a non-targeted approach, regardless of disease activity level is strongly recommended. The ideal target should be low disease activity or remission, as determined by the clinician and the patient. In some cases, another target may be chosen because risk tolerance by patients or comorbidities may mitigate the usual choices. • For DMARD-naïve patients with early, symptomatic RA, DMARD monotherapy over double or triple DMARD therapy in patients with low disease activity is strongly recommended and DMARD monotherapy over double or triple DMARD therapy in patients with moderate or high disease activity is conditionally recommended. Methotrexate should be the preferred initial therapy for most patients with early RA with active disease. • For patients with moderate or high disease activity despite DMARD therapy (with or without glucocorticoids), treatment with a combination of DMARDs <u>or</u> a TNF-α inhibitor <u>or</u> a non-TNF biologic, with or without methotrexate

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	(MTX) in no particular order of preference, rather than continuing DMARD monotherapy alone is strongly recommend. Biologic therapy should be used in combination with MTX over biologic monotherapy, when possible, due to superior efficacy. • For patients with moderate or high disease activity despite any of the above DMARD or biologic therapies, adding low-dose glucocorticoids (defined as ≤10 mg/day of prednisone or equivalent) is conditionally recommended. Low-dose glucocorticoids may also be used in patients who need a bridge until realizing the benefits of DMARD therapy. The risk/benefit ratio of glucocorticoid therapy is favorable as long as the dose is low and the duration of therapy is short. • For patients experiencing a flare of RA, adding short-term glucocorticoids (less than three months of treatment) at the lowest possible dose for the shortest possible duration, to provide a favorable benefit-risk ratio for the patient is conditionally recommended. <u>Recommendations for Established RA Patients</u> • Using a treat-to-target strategy rather than a non-targeted approach, regardless of disease activity level is strongly recommended. • For DMARD-naïve patients with low disease activity, using DMARD monotherapy over a TNF-α inhibitor is strongly recommended. For DMARD-naïve patients with moderate or high disease activity, DMARD monotherapy over double or triple DMARD therapy and DMARD monotherapy over tofacitinib is conditionally recommend. In general, MTX should be the preferred initial therapy for most patients with established RA with active disease. • For patients with moderate or high disease activity despite DMARD monotherapy including methotrexate, using combination DMARDs <u>or</u> adding a TNF-α inhibitor <u>or</u> a non-TNF biologic <u>or</u> tofacitinib (all choices with or without methotrexate) in no particular order of preference, rather than continuing DMARD monotherapy alone is strongly recommended. Biologic therapy should be used in combination with MTX over biologic monotherapy, when possible, due to its superior efficacy. *For all scenarios for established RA below, treatment may be with or without MTX:* • For moderate or high disease activity despite TNF-α inhibitor therapy in patients currently not on a DMARD, it is strongly recommended that one or two DMARDs be added to TNF-α inhibitor therapy rather than continuing TNF-α inhibitor therapy alone. • If disease activity is moderate or high despite single TNF-α inhibitor biologic therapy, it is conditionally recommended to use a non-TNF biologic. • If disease activity is moderate or high despite non-TNF biologic therapy, using another non-TNF biologic is conditionally recommended. However, if a patient has failed multiple non-TNF biologics and they are TNF-α inhibitor - naïve with moderate or high disease activity, treatment with a TNF-α inhibitor is conditionally recommended. • For patients with moderate or high disease activity despite prior treatment with at least one TNF-α inhibitor and at least one non-TNF-biologic (sequentially, not combined), first treating with another non-TNF biologic is conditionally recommended. However, when a non-TNF biologic is not an option (e.g., patient declines non-TNF biologic therapy due to inefficacy or side effects), treatment with tofacitinib is conditionally recommended. • If disease activity is moderate or high despite the use of multiple (two or more) TNF-α inhibitor therapies (in sequence, not concurrently), non-TNF biologic therapy is conditionally recommended and then conditionally treating with tofacitinib when a non-TNF biologic is not an option. • If disease activity is moderate or high despite any of the above DMARD or

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	biologic therapies, adding low-dose glucocorticoids is conditionally recommended. • If patients with established RA experience an RA flare while on DMARD, TNF-α inhibitor, or non-TNF biologic therapy, it is conditionally recommended to add short-term glucocorticoids (less than three months of treatment) at the lowest possible dose and for shortest possible duration to provide the best benefit-risk ratio for the patient. • In patients with established RA and low disease activity but not remission, continuing DMARD therapy, TNF-α inhibitor, non-TNF biologic or tofacitinib rather than discontinuing respective medication is strongly recommended. • In patients with established RA currently in remission, tapering DMARD therapy, TNF-α inhibitor, non-TNF biologic, or tofacitinib is conditionally recommended. • It is strongly recommended not to discontinue all therapies in patients with established RA in disease remission. Recommendations for RA patients with high-risk comorbidities • In patients with established RA with moderate or high disease activity and New York Heart Association (NYHA) class III or IV congestive heart failure (CHF), using combination DMARD therapy, a non-TNF biologic, or tofacitinib rather than a TNF-α inhibitor is conditionally recommended. If patients in this population are treated with a TNF-α inhibitor and their CHF worsens while on the TNF-α inhibitor, it is conditionally recommended to switch to combination DMARD therapy, a non-TNF biologic, or tofacitinib rather than a different TNF-α inhibitor. • In patients with established RA with moderate or high disease activity and evidence of active hepatitis B infection (hepatitis surface antigen positive > 6 months), who are receiving or have received effective antiviral treatment, treating them the same as patients without this condition is strongly recommended. For patients with chronic hepatitis B who are untreated, referral for antiviral therapy is appropriate prior to immunosuppressive therapy. • In patients with established RA with moderate or high disease activity and evidence of chronic hepatitis C virus (HCV) infection, who are receiving or have received effective antiviral treatment, treating them the same as the patients without this condition is conditionally recommended. If the same patient is not requiring or receiving antiviral treatment for their hepatitis C, using DMARD therapy rather than TNF-α inhibitor is conditionally recommended. • In patients with established RA and moderate or high disease activity and a history of previously treated or untreated skin cancer (melanoma or non-melanoma), the use of DMARD therapy over biologics or tofacitinib is conditionally recommended. • In patients with established RA with moderate or high disease activity and a history of a previously treated lymphoproliferative disorder, using rituximab rather than a TNF-α inhibitor is strongly recommended and using combination DMARD therapy, abatacept, or tocilizumab rather than TNF-α inhibitor is conditionally recommended. • In patients with established RA with moderate or high disease activity and previously treated solid organ cancer, it is conditionally recommended that they be treated for RA just as one would treat an RA patient without a history of solid organ cancer. • In patients with established RA with moderate or high disease activity and previous serious infection(s), using combination DMARD therapy or abatacept rather than TNF-α inhibitor is conditionally recommended.

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	Recommendations for the Use of Vaccines in RA patients on DMARD and/or biologic therapy • In early or established RA patients aged 50 and over, giving the herpes zoster vaccine before the patient receives biologic therapy or tofacitinib for their RA is conditionally recommended. • In early or established RA patients who are currently receiving biologics, it is conditionally recommended that live attenuated vaccines such as the herpes zoster (shingles) vaccine not be given. • In patients with early or established RA who are currently receiving biologics, using appropriately indicated killed/inactivated vaccines is strongly recommended.

American College of Rheumatology: **2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis (2021)[43]**	Guiding principles
	• Rheumatoid arthritis (RA) requires early evaluation, diagnosis, and management.
	• Treatment decisions should follow a shared decision-making process.
	• Treatment decisions should be reevaluated within a minimum of three months based on efficacy and tolerability of the DMARD(s) chosen.
	• Disease activity levels refer to those calculated using RA disease activity measures endorsed by the American College of Rheumatology (ACR).
	• Recommendations are intended for the general RA patient population and assume that patients do not have contraindications to the options under consideration.
	• Recommendations are limited to DMARDs approved by the US FDA for treatment of RA.
	  ○ Conventional (csDMARDs): hydroxychloroquine, sulfasalazine, methotrexate, leflunomide.
	  ○ Biologic (bDMARDs): TNF inhibitors (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), T cell costimulatory inhibitor (abatacept), IL-6 receptor inhibitors (tocilizumab, sarilumab), anti-CD20 antibody (rituximab); Anakinra was not included due to infrequent use for patients with RA.
	  ○ Targeted synthetic (tsDMARDs): JAK inhibitors (tofacitinib, baricitinib, upadacitinib).
	• Triple therapy refers to hydroxychloroquine, sulfasalazine, and either methotrexate or leflunomide.
	• Serious infection refers to an infection requiring intravenous antibiotics or hospitalization.
	• Biosimilars are considered equivalent to FDA-approved originator bDMARDs.
	• Recommendations referring to bDMARDs exclude rituximab unless patients have had an inadequate response to TNF inhibitors (in order to be consistent with FDA approval) or have a history of lymphoproliferative disorder for which rituximab is an approved therapy.
	• Treat-to-target refers to a systematic approach involving frequent monitoring of disease activity using validated instruments and modification of treatment to minimize disease activity with the goal of reaching a predefined target (low disease activity or remission).
	• Target refers to low disease activity or remission.
	• Recommendations specify that patients be at target (low disease activity or remission) for at least six months prior to tapering.
	• Dose reduction refers to lowering the dose or increasing the dosing interval of a DMARD. Gradual discontinuation of a DMARD is defined as gradually lowering the dose of a DMARD and subsequently stopping it.

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	Recommendations for DMARD-naïve patients with moderate-to-high disease activity
	• Initiation of treatment in DMARD-naive patients with moderate-to-high disease activity.
	  ○ Methotrexate monotherapy is strongly recommended over:
	  ▪ Hydroxychloroquine or sulfasalazine
	  ▪ bDMARD or tsDMARD monotherapy
	  ▪ Combination of methotrexate plus a non–TNF inhibitor bDMARD or tsDMARD
	  ○ Methotrexate monotherapy is conditionally recommended over:
	  ▪ Leflunomide
	  ▪ Dual or triple csDMARD therapy
	  ▪ Combination of methotrexate plus a TNF inhibitor
	  ○ Initiation of a csDMARD without short-term (<3 months) glucocorticoids is conditionally recommended over initiation of a csDMARD with short-term glucocorticoids.
	  ○ Initiation of a csDMARD without longer-term (≥3 months) glucocorticoids is strongly recommended over initiation of a csDMARD with longer-term glucocorticoids.
	• Initiation of treatment in DMARD-naïve patients with low disease activity
	  ○ Hydroxychloroquine is conditionally recommended over other csDMARDs.
	  ○ Sulfasalazine is conditionally recommended over methotrexate.
	  ○ Methotrexate is conditionally recommended over leflunomide.
	• Initiation of treatment in csDMARD-treated, but methotrexate-naive, patients with moderate-to-high disease activity
	  ○ Methotrexate monotherapy is conditionally recommended over the combination of methotrexate plus a bDMARD or tsDMARD.
	
	Recommendations for treatment modification in patients treated with DMARDs who are not at target
	• A treat-to-target (TTT) approach is strongly recommended over usual care for patients who have not been previously treated with bDMARDs or tsDMARDs.
	• A TTT approach is conditionally recommended over usual care for patients who have had an inadequate response to bDMARDs or tsDMARDs.
	• A minimal initial treatment goal of low disease activity is conditionally recommended over a goal of remission.
	• Addition of a bDMARD or tsDMARD is conditionally recommended over triple therapy for patients taking maximally tolerated doses of methotrexate who are not at target.
	• Switching to a bDMARD or tsDMARD of a different class is conditionally recommended over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target.
	• Addition of/switching to DMARDs is conditionally recommended over continuation of glucocorticoids for patients taking glucocorticoids to remain at target.
	• Addition of/switching to DMARDs (with or without intraarticular glucocorticoids) is conditionally recommended over the use of intraarticular glucocorticoids alone for patients taking DMARDs who are not at target.

European League Against Rheumatism: **Management Of Rheumatoid Arthritis With Synthetic And Biological Disease-Modifying**	• Treatment of rheumatoid arthritis must be based on a shared decision between the patient and the rheumatologist. • Treatment decisions are based on disease activity and other patient factors, such as progression of structural damage, comorbidities and safety issues. • Patients require access to multiple drugs with different modes of action to address the heterogeneity of rheumatoid arthritis; they may require multiple

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Antirheumatic Drugs: 2019 Update (2020)[44]	successive therapies throughout life. • Rheumatoid arthritis incurs high individual, societal and medical costs, all of which should be considered in its management. • Therapy with DMARDs should be started as soon as the diagnosis of rheumatoid arthritis is made. • Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient. • Monitoring should be frequent in active disease (every one to three months); if there is no improvement by at most three months after the start of treatment or the target has not been reached by six months, therapy should be adjusted. • Methotrexate should be part of the first treatment strategy. • In patients with a contraindication to methotrexate (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy. • Short-term glucocorticoids should be considered when initiating or changing conventional synthetic DMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible. • If the treatment target is not achieved with the first conventional synthetic DMARD strategy, in the absence of poor prognostic factors, other conventional synthetic DMARDs should be considered. • If the treatment target is not achieved with the first conventional synthetic DMARD strategy, when poor prognostic factors are present, addition of a biological DMARD or a targeted synthetic DMARD should be considered. • Biological DMARDs and targeted synthetic DMARDs should be combined with a conventional synthetic DMARD; in patients who cannot use conventional synthetic DMARDs as comedication, IL-6 pathway inhibitors and targeted synthetic DMARDs may have some advantages compared with other biological DMARDs. • If a biological DMARD or targeted synthetic DMARD has failed, treatment with another biological DMARD or a targeted synthetic DMARD should be considered; if one TNF-inhibitor therapy has failed, patients may receive another TNF-inhibitor or an agent with another mode of action. • If a patient is in persistent remission after having tapered glucocorticoids, tapering of biological DMARDs or targeted synthetic DMARDs can be considered, especially if this treatment is combined with a conventional synthetic DMARD. • If a patient is in persistent remission, tapering the csDMARD could be considered. Terminology: conventional synthetic DMARDs (methotrexate, leflunomide, sulfasalazine); biological DMARDs (tumour necrosis factor (TNF)-inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), abatacept, rituximab, tocilizumab, clazakizumab, sarilumab and sirukumab and biosimilar DMARDs) and targeted synthetic DMARDs (Janus kinase inhibitors, tofacitinib, baricitinib).
National Institute for Health and Clinical Excellence: **Rheumatoid Arthritis in Adults: Management (2018)[45]** Updated October 2020	• In people with newly diagnosed active rheumatoid arthritis, conventional DMARD monotherapy using oral methotrexate, leflunomide or sulfasalazine as first-line treatment as soon as possible, ideally within three months of the onset of persistent symptoms. Hydroxychloroquine can be considered as an alternative to oral methotrexate, leflunomide or sulfasalazine for mild or palindromic disease. Dose can be escalated as tolerated. • Short-term bridging treatment with glucocorticoids (oral, intramuscular or intra-articular) can be considered when starting a new conventional DMARD. • Additional conventional DMARDs (oral methotrexate, leflunomide, sulfasalazine or hydroxychloroquine) in combination in a step-up strategy

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	should be offered when the treatment target (remission or low disease activity) has not been achieved despite dose escalation. • Offer short-term treatment with glucocorticoids for managing flares in people with recent onset or established disease, to rapidly decrease inflammation. • In people with established rheumatoid arthritis, only continue long-term treatment with glucocorticoids when the long-term complications of glucocorticoid therapy have been fully discussed, and all other treatment options (including biological drugs and targeted synthetic DMARDs) have been offered. • On the balance of its clinical benefits and cost effectiveness, anakinra is not recommended for the treatment of rheumatoid arthritis, except in the context of a controlled, long-term clinical study. • Patients currently receiving anakinra for rheumatoid arthritis may suffer loss of wellbeing if their treatment were discontinued at a time they did not anticipate. Therefore, patients should continue therapy with anakinra until they and their consultant consider it is appropriate to stop. • Do not offer the combination of TNF-α inhibitor therapy and anakinra for rheumatoid arthritis. • Oral NSAIDs or COX-2 inhibitors should be considered when control of pain or stiffness is inadequate. Potential gastrointestinal, liver and cardio-renal toxicity, and the person's risk factors, including age and pregnancy should be considered. • When treating symptoms of rheumatoid arthritis with oral NSAIDS, offer the lowest effective dose for the shortest possible time, offer a proton pump inhibitor and review risk factors for adverse events regularly. • If a person with rheumatoid arthritis needs to take low-dose aspirin, healthcare professionals should consider other treatments adding an NSAID (with a proton pump inhibitor) if pain relief is ineffective or insufficient.
National Institute for Health and Clinical Excellence: **Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (2016)**[46] Updated June 2021	• Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept, all in combination with methotrexate, are recommended as options for treating rheumatoid arthritis, only if: o disease is severe, that is, a disease activity score (DAS28) greater than 5.1 and o disease has not responded to intensive therapy with a combination of conventional DMARDs and o the companies provide certolizumab pegol, golimumab, abatacept, and tocilizumab as agreed in their patient access schemes. • Adalimumab, etanercept, certolizumab pegol, or tocilizumab can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, when the criteria above are met. • Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at six months after starting therapy. • After initial response within six months, withdraw treatment if a moderate EULAR response is not maintained. • Start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose). This may need to be varied for some people because of differences in the mode of administration and treatment schedules. • Take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the DAS28 and make any appropriate adjustments. • People whose treatment with adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, or abatacept is not recommended in this NICE guidance, but was started before this guidance was published, should be able to continue treatment until they and their clinician consider it appropriate to stop.

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American College of Gastroenterology: **Ulcerative Colitis in Adults (2019)**[47]	Induction of remission in mildly active ulcerative colitis (UC) • In patients with mildly active ulcerative proctitis, rectal 5-ASA therapies are recommended. • In patients with mildly active left-sided colitis, rectal 5-ASA enemas are recommended over rectal steroids for induction of remission • In patients with mildly active left-sided UC, rectal 5-ASA enemas are recommended combined with oral 5-ASA compared with oral 5-ASA therapy alone for induction of remission • In patients with mildly active left-sided UC who are intolerant or nonresponsive to oral and rectal 5-ASA at appropriate doses oral budesonide MMX is recommended for induction of remission • In patients with mildly active extensive colitis, oral 5-ASA is recommended to induce remission. • In patients with UC of any extent who fail to respond to 5-ASA therapy, oral systemic corticosteroids are recommended to induce remission. • In patients with mildly active UC who fail to reach remission with appropriately dosed 5-ASA changing to an alternate 5-ASA formulation to induce remission is not recommended. Alternative therapeutic classes should be considered (conditional recommendation, low quality of evidence). • In patients with mildly active UC of any extent, using a low dose of 5-ASA compared with a higher dose is recommended, as there is no difference in the remission rate. • In patients with mildly to moderately active UC not responding to oral 5-ASA, the addition of budesonide MMX to induce remission is recommended. • In patients with mildly to moderately active UC of any extent using 5-ASA to induce remission, either once-daily or more frequently dosed oral 5-ASA is recommended based on patient preference to optimize adherence. Maintenance of remission in patients with previously mildly active UC • In patients with mildly active ulcerative proctitis, rectal 5-ASA is recommended. • In patients with mildly active left-sided or extensive UC, oral 5-ASA therapy is recommended. • Use of systemic corticosteroids for maintenance of remission in patients with UC is not recommended. Induction of remission in moderately to severely active UC • In patients with moderately active UC, oral budesonide MMX is recommended for induction of remission. • In patients with moderately to severely active UC of any extent, oral systemic corticosteroids are recommended to induce remission. • In patients with moderately to severely active UC, monotherapy with thiopurines or methotrexate is not recommended for induction of remission. • In patients with moderately to severely active UC, anti-TNF therapy using adalimumab, golimumab, or infliximab for induction of remission is recommended. • In patients with moderately to severely active UC who have failed 5-ASA therapy and in whom anti-TNF therapy is used for induction of remission, using 5-ASA for added clinical efficacy is not recommended. • When infliximab is used as induction therapy for patients with moderately to severely active UC, combination therapy with a thiopurine is recommended. • In patients with moderately to severely active UC, vedolizumab is recommended for induction of remission. • In patients with moderately to severely active UC who have previously failed anti-TNF therapy, vedolizumab is recommended for induction of remission.

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	• In patients with moderately to severely active UC, tofacitinib is recommended to induce remission. • In patients with moderately to severely active UC who have previously failed anti-TNF therapy, tofacitinib is recommended for induction of remission. • In patients with moderately to severely active UC who are responders to anti-TNF therapy and now losing response, measuring serum drug levels and antibodies is recommended to assess the reason for loss of response. <u>Maintenance of remission in patients with previously moderately to severely active UC</u> • In patients with previously moderately to severely active UC who have achieved remission but previously failed 5-ASA therapy and are now on anti-TNF therapy, using concomitant 5-ASA for efficacy of maintenance of remission is not recommended • Use of systemic corticosteroids for maintenance of remission in patients with UC is not recommended. • For patients with previously moderately to severely active UC now in remission due to corticosteroid induction, thiopurines for maintenance of remission is recommended compared with no treatment or corticosteroids • In patients with previously moderately to severely active UC now in remission, using methotrexate for maintenance of remission is not recommended. • Continuation of anti-TNF therapy using adalimumab, golimumab, or infliximab is recommended to maintain remission after anti-TNF induction in patients with previously moderately to severely active UC. • Continuation of vedolizumab to maintain remission is recommended in patients with previously moderately to severely active UC now in remission after vedolizumab induction. • Continuation of tofacitinib for maintenance of remission is recommended in patients with previously moderately to severely active UC now in remission after induction with tofacitinib.

European Academy of Dermatology and Venereology: **European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa (2015)**[48]	<u>Adjuvant Therapy</u>
	• It is recommended that adjuvant therapy is offered to patients in the form of general measures and specific help with bandaging lesions in order to improve the patients' quality of life.
	• Cigarette smoking and obesity have to be avoided.
	• Bandages used must be customized due to the anatomical variation, and should be absorbent, nonirritant. They should keep the surface dry and absorb smell. Dedicated hidradenitis suppurativa (HS)-bandages are not currently available.
	• Psychosocial support measures in HS may be of considerable benefit to the patients.
	
	<u>Medical Therapy (non-antibiotic topical therapies)</u>
	• Exfoliants and Peels
	  ○ Topical resorcinol 15% twice daily had good effect compared to previous experience in treating recurrent lesions in patients with Hurley stage I or II HS.
	  ○ Systemic toxicity following topical use of resorcinol is extremely rare, but physicians must be aware of the potential risk.
	• Other Therapies
	  ○ The use of adapalene or azelaic acid may occasionally be beneficial, but must currently be considered experimental. No formal studies have been conducted.
	
	<u>Medical Therapy (topical antibiotics)</u>
	• Clindamycin is the only antibiotic that has been studied as a topical agent.

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	○ Studied in localized Hurley Stage I or mild stage II disease. ○ Clindamycin lotion three times a day for three months (or prolonged if clinically indicated). ○ A significant improvement was observed with clindamycin than to placebo using of a disease score constructed for the study. <u>Medical Therapy (systemic antibiotics)</u> • Systemic treatment is indicated when more severe or widely spread lesions are present. • Tetracycline ○ More widely spread Hurley stage I or mild stage II disease. ○ Tetracycline 500 mg three times a day for four months (or prolonged if clinically indicated). ○ Resulted in an approximately 30% reduction in disease severity. • Clindamycin-Rifampicin ○ Any stage active inflammatory HS. ○ Clindamycin 300 mg three times a day plus rifampicin 600 mg daily for 10 weeks. ○ All [three] studies conclude the treatment to be beneficial. • Other antibiotics ○ Rifampicin-moxifloxacin-metronidazole, either alone or proceeded by systemic ceftriaxone for 12 weeks. Patients had treatment resistant stage II and III disease. Combination therapy was effective in half (28/58) the patients. ▪ Patients who showed response after 12 weeks of initial treatment were treated for an additional 12 weeks using a combination of moxifloxacin and rifampicin. Intensive treatment led to complete response in 16/28 patients. ○ A range of other topical and systemic antibiotics have been suggested in case reports and in expert opinion, but none have been systematically evaluated even at the level of open prospective case-series. <u>Medical Therapy (anti-inflammatory therapy)</u> • Intralesional corticosteroids ○ Rapid reduction in inflammation associated with acute flares and for management of recalcitrant nodules and sinus tracts. ○ Utilized as both monotherapy and an adjunct to systemic therapies. ○ When effective, clinical response (flattening, resolution or spontaneous discharge of nodules) is seen within 48 to 72 hours. ○ Therapy is contraindicated if clinical suspicion of bacterial infection exists. ○ Triamcinolone acetonide 5 to 10 mg/mL is recommended • Systemic corticosteroids ○ There are limited data on the use of corticosteroids in HS. ○ Short and long-term therapy can result in rebound flare on withdrawal. ○ Short-term, rapidly tapering therapy can provide benefit in reduction in inflammation associated with acute flares. ○ In the event of clinical relapse on dose reduction, introduction of a second line anti-inflammatory or immunosuppressive agent is recommended. ○ Routine long-term use is not currently recommended. ○ Systemic corticosteroid dose and duration should be kept to a minimum to limit long-term complications. ○ A dose of 0.5 to 0.7 mg/kg oral prednisolone is recommended for short-term use for acute flares; the dose should be rapidly tapered to

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	stop over weeks. o Limited case reports and one case series describe response to the corticosteroid agents hydrocortisone, dexamethasone and prednisolone, as short-term monotherapy and long-term combination therapy. ▪ Short-term systemic hydrocortisone monotherapy (60 to 80 mg daily; 15 to 56 days) provided sustained remission at 12 months. ▪ Use of prolonged prednisolone monotherapy (60 mg reduced to 25 mg daily; duration not specified) in severe disease resulted in 65% improvement in one case. ▪ Prolonged prednisolone combination therapy (20 mg da to stop over 27 weeks) with antimicrobials followed by isotretinoin resulted in sustained clinical response in one case. • Dapsone o Reserved for patients with mild to moderate disease (Hurley stage I or II) in which standard first or second line agents fail. o Recommended dose is 25 to 200 mg/day. Higher doses are limited by adverse events. o Reported duration and response is variable; the minimum recommended duration of therapy is three months. o When effective, rapid relapse may occur on therapy withdrawal. o There are no data on maximum duration of therapy (reported range three to 48 months). • Ciclosporin A (cyclosporin) o Reserved to cases where failure of response to standard first, second and third line therapies. o Daily doses of two to six mg/kg have been used for variable duration (six weeks to seven months). o Beneficial response to ciclosporin A is reported in four cases. o Combination ciclosporin A (three mg/kg daily for four months) with tapering corticosteroids (two months) resulted in four months of remission in one case. • Hormones o There are indications that antiandrogens, such as cyproterone acetate, and estrogens improve HS, while progestogens induce or worsen a pre-existing HS due to their androgenic properties. o Indication and contraindication: Female patients with menstrual abnormalities, signs of hyperandrogenism or upper normal or high serum levels of dehydroepiandrosterone, androstenedione and/or sexual hormone-binding protein. o All reported patients improved but no evidence-based data exist. <u>Medical Therapy (Biologics)</u> • Used for the treatment of moderate to severe HS. o Improved quality of patient life. o Studied in adalimumab and infliximab, however, adalimumab is considered more tolerable. • Adalimumab o Recommended doses: ▪ To condition for a curative surgical procedure: 160 mg on day zero and possibly 80 mg one week later. ▪ Long-term therapy: 40 mg once weekly. o There are different rates of response to adalimumab reported in case series and in a current, prospective controlled study. • Infliximab o Recommended doses:

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	▪ To condition for a curative surgical procedure: 5 mg/kg. ▪ Long-term therapy: 5 mg/kg on day zero, two and six then every eight weeks. o Response rates are varied. • Etanercept and ustekinumab have also been studied in case reports. <u>Medical Therapy (retinoids)</u> • Isotretinoin o Not recommended in the treatment of HS. o If given early enough in the treatment of HS, isotretinoin may potentially prevent an affected pilosebaceous unit from being occluded by ductal hyper cornification. However, its usage in HS is often disappointing and the literature data are inconsistent. • Acitretin/Etretinate o Acitretin usage in early HS stages (Hurley I or mild II) is reasonable and could also be advocated in the chronic stages of HS with recurrent abscesses with sinus tracts (even interconnected) and/or scarring. o The response rate was high. <u>Medical Therapy (analgesics)</u> • Non-steroidal anti-inflammatory drugs (NSAIDs) o No clinical evidence exists on the use of NSAIDs in the amelioration of pain and inflammation in HS. o Their anecdotal use in the usual dosage schemas may be justified for the amelioration of acute pain related to HS. • Opiates o No clinical evidence exists for the use of opioids in the amelioration of pain in HS. o Their use should be restricted and limited to cases where all other painkillers have failed. o Codeine should be the first treatment option for this drug class. <u>Medical Therapy (miscellaneous and experimental therapies)</u> • Zinc gluconate o Maintenance treatment in Hurley stage I and II disease. o High dose (90 mg/day) is recommended o Response rate in one study of 22 patients resulted in complete remission in eight patients and partial remission in 14 patients. • Intramuscular gamma-globulin o Not recommended due to limited data (one report) • Colchicine o Not recommended due to poor efficacy. • Botulinum toxin o Experimental treatment in Hurley stage I or II disease. o Limited data from two case reports; both had good effect with one case resulting in six months of remission. <u>Therapeutic Conclusion</u> • It is recommended that HS is treated based on the subjective impact and objective severity of the disease. • Locally recurring lesions can be treated surgically, whereas medical treatment either as monotherapy or in combination with surgery is more appropriate for widely spread lesions. • Medical therapy may include antibiotics and immunosuppressants. • HS treatment algorithm:

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	○ Adjuvant therapy should be utilized for all disease severities: ▪ Pain management ▪ Treatment of superinfections ▪ Weight loss and tobacco abstinence ○ As disease severity increases, provide surgical interventions: ▪ Less severe disease: deroofing, LASERs, local excision ▪ More severe disease: wide surgical excision ○ As disease severity increases, medication therapy should include: ▪ Stage I or II (localized): topical clindamycin ▪ More severe: provide systemic treatment with 1) clindamycin + rifampicin/tetracycline or 2) acitretin ▪ Most severe: provide systemic treatment with anti-TNF biologics adalimumab or infliximab
European Academy of Dermatology and Venereology: **Consensus-based European Guidelines for Treatment of Atopic Eczema (Atopic Dermatitis) in Adults and Children (2018)[49]**	• Emollients should be prescribed in adequate amounts, and these should be used liberally and frequently, in a minimum amount of 250 g per week for adults. • Emollient bath oils and soap substitutes should also be used. Emollients with a higher lipid content are preferable in wintertime. • A regular use of emollient has a short- and long-term steroid sparing effect in mild-to-moderate atopic eczema. An induction of remission with topical corticosteroids or topical calcineurin inhibitors is required first. • Topical corticosteroids are important anti-inflammatory drugs to be used in atopic eczema, especially in the acute phase. • Topical corticosteroids with an improved risk/benefit ratio are recommended in atopic eczema. • Diluted topical corticosteroids may be used under wet wraps for short-term periods in acute atopic eczema to increase their efficacy. • Proactive therapy (e.g., twice-weekly application in the long-term follow-up) may help to reduce relapses. • Proactive therapy with topical corticosteroids may be used safely for at least 20 weeks, which is the longest duration of trials. • Patient fear of side-effects of corticosteroids should be recognized and adequately addressed to improve adherence and avoid undertreatment. • Topical calcineurin inhibitors are important anti-inflammatory drugs to be used in atopic eczema. Instead of treating acute flares with topical calcineurin inhibitors, initial treatment with topical corticosteroids before switching to topical calcineurin inhibitors should be considered. • Topical calcineurin inhibitors are especially indicated in sensitive skin areas (face, intertriginous sites, anogenital area). • Proactive therapy with twice-weekly application of tacrolimus ointment may reduce relapses. • Effective sun protection should be recommended inpatients treated with topical calcineurin inhibitors. • Topical corticosteroids are recommended to control pruritus in the initial phase of atopic eczema exacerbation. • Topical calcineurin inhibitors are recommended to control pruritus in atopic eczema until clearance of eczema. • Topical polidocanol may be used to reduce pruritus in atopic eczema patients. • Routine clinical use of topical antihistamines including doxepin, topical cannabinoid receptor agonists, topical μ-opioid receptor antagonists or topical anaesthetics cannot be recommended as an adjuvant antipruritic therapy in atopic eczema. • There is not enough data available to recommend the use of capsaicin in management of itch in atopic eczema patients. • If emollients and anti-inflammatory topical preparations must be applied to the same location, the cream formulation should be applied first and only 15

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	minutes later the ointment formulation. • For routine treatment of flares once daily application of a potent topical corticosteroid is sufficient, usually for three to six days. • With mild disease activity, a small amount of topical corticosteroids two to three times weekly, associated with a liberal use of emollients, generally allows a good maintenance with SCORAD values below 15 to 20 (indicating mild disease). • The most constructive way to spare topical corticosteroids and avoid steroid-related side-effects is not to spare them during acute flares, but through consequent baseline emollient skin care combined with early anti-inflammatory intervention in order to stabilize the disease, and prevent treatment-intensive flares. • The two steroid-free topical calcineurin inhibitors, tacrolimus ointment and pimecrolimus cream, have demonstrated efficacy against placebo in clinical trials for short-term and long-term use. • Proactive tacrolimus ointment therapy has been shown to be safe and effective for up to one year in reducing the number of flares and improving the quality of life in adult patients and children. • The anti-inflammatory potency of 0.1% tacrolimus ointment is similar to a topical corticosteroid with intermediate activity, while the latter is clearly more active than 1.0% pimecrolimus cream. • The topical calcineurin inhibitors do not induce skin atrophy like corticosteroids, which favors their use on delicate skin areas like the eyelids, perioral skin, genital areas, inguinal fold, and for topical long-term management. • Clinical and preclinical data do not indicate an increased risk of the induction of lymphoma or other types of malignancies, or photocarcinogenicity for topical calcineurin inhibitors, but since the continuous oral administration of the calcineurin inhibitor cyclosporine is associated with an increased photocarcinogenicity risk in solid organ transplant patients, UV protection, (e.g., with sunscreens) is recommended.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/Joint Council on Allergy, Asthma, and Immunology: **Disease Management of Atopic Dermatitis: An Updated Practice Parameter (2012)**[50]	<u>General considerations</u> • The intensity of management and treatment of atopic dermatitis is dictated by the severity of illness, which relates to the effect of atopic dermatitis on the quality of life on the patient and his or her family. • The management of atopic dermatitis requires multiple therapeutic approaches including antipruritic therapy, skin hydration, topical anti-inflammatory medications, antibacterial measures, and the identification/elimination of exacerbating factors. <u>Skin hydration</u> • Hydration with warm soaking baths for at least 10 minutes followed by the application of a moisturizer is recommended. • Moisturizers should be recommended as first-line therapy. <u>Topical corticosteroids</u> • Topical corticosteroids are an effective treatment option for atopic dermatitis. If atopic dermatitis is not controlled by moisturizers alone, then the clinician should recommend a topical corticosteroid. • Low-potency corticosteroids are recommended for maintenance therapy, whereas intermediate-and high-potency corticosteroids should be used for the treatment of exacerbation and applied to affected areas over short periods of time. • Potent fluorinated corticosteroids should not be used on the face, eyelids, genitalia, and intertriginous areas or in young infants.

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	• Ultrahigh-potency corticosteroids should be used only for very short periods of time (several days) and in nonfacial non-skinfold areas. • The degree of corticosteroid absorption through the skin and the potential for systemic adverse effects are directly dependent on the surface area of the skin involved, thickness of the skin, the use of occlusive dressing, and the potency of the corticosteroid preparation. <u>Topical calcineurin inhibitors</u> • Tacrolimus ointment has been shown to be effective and safe in both adults and children older than two years of age, with most patients experiencing a reduction of pruritus within three days of initiating therapy. • Tacrolimus ointment does not cause atrophy for eczema on the face, eyelid, and skin folds that is unresponsive to low-potency topical steroids. • Once a flare is controlled, tacrolimus ointment twice daily, twice weekly to eczema-prone areas may prevent future flares. • Pimecrolimus cream decreases the number of flares of atopic dermatitis, reduces the need for corticosteroids, and controls pruritus. <u>Tar preparations</u> • There are no randomized studies that have demonstrated the efficacy of tar preparations, despite their widespread use for the treatment of atopic dermatitis. • Newer coal tar products have been developed that are more cosmetically acceptable than older products. • Coal preparations should not be recommended for acutely inflamed skin because this might result in additional skin irritation. <u>Antihistamines</u> • Patients may benefit from the use of oral antihistamines for the relief of pruritus associated with atopic dermatitis. Treatment of atopic dermatitis with topical antihistamines is generally not recommended because of potential cutaneous sensitization. <u>Vitamin D</u> • Patients with atopic dermatitis might benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake. <u>Dilute bleach baths</u> • The addition of dilute bleach baths twice weekly may reduce the severity of atopic dermatitis, especially in patients with recurrent skin infections. <u>Microbes</u> • Skin infections with *Staphylococcus aureus* are a recurrent problem in patients with atopic dermatitis, and patients with moderate-to-severe atopic dermatitis have been found to make IgE antibodies against staphylococcal toxins present in their skin. • A short course of an appropriate systemic antibiotic for patients who are clinically infected with *Staphylococcus aureus* should be prescribed. In areas with high levels of methicillin-resistant *Staphylococcus aureus*, treatment with clindamycin, doxycycline, or sulfamethoxazole-trimethoprim may be initiated while awaiting skin culture results. • Atopic dermatitis can be complicated by recurrent viral skin infections, such as herpes simplex, warts, and molluscum contagiosum. Herpes simplex or eczema herpeticum should be diagnosed and promptly treated with systemic antiviral agents. • Fungal infections can complicate atopic dermatitis and might contribute to

Clinical Guideline	Recommendation(s)
	exacerbations. Systemic Immunomodulating Agents • Immunosuppressive agents such as cyclosporine, interferon gamma, mycophenolate mofetil, azathioprine, and corticosteroids have been shown to provide benefit for certain cases of severe refractory atopic dermatitis, but potential benefits should be weighed against their potentially serious adverse effects. Phototherapy • Ultraviolet therapy can be a useful treatment for recalcitrant atopic dermatitis. Allergen immunotherapy Select patients with atopic dermatitis with aeroallergen sensitivity may benefit from allergen immunotherapy.
American Academy of Dermatology: **Guidelines of Care for the Management of Atopic Dermatitis (2014)[51]**	Topical corticosteroids • Topical corticosteroids are the mainstay of anti-inflammatory therapy for the management of atopic dermatitis. • They are typically introduced into the treatment regimen after failure of lesions to respond to good skin care and regular use of moisturizers alone. • Comparative trials are limited in duration and scope (i.e., they mainly involve two, and occasionally three, agents), and as a result, there are no data to support one or a few specific agents as being more efficacious than others. • A variety of factors should be considered when choosing a particular topical corticosteroid for the treatment of atopic dermatitis, including patient age, areas of the body to which the medication will be applied, and other patient factors such as degree of xerosis, patient preference, and cost of medication. • Twice-daily application of corticosteroids is generally recommended for the treatment of atopic dermatitis; however, evidence suggests that once-daily application of some corticosteroids may be sufficient. • Proactive, intermittent use of topical corticosteroids as maintenance therapy (one to two times/week) on areas that commonly flare is recommended to help prevent relapses and is more effective than use of emollients alone. • The potential for both topical and systemic side effects, including possible hypothalamic-pituitary-adrenal axis suppression, should be considered, particularly in children with atopic dermatitis in whom corticosteroids are used. • Monitoring by physical examination for cutaneous side effects during long-term, potent steroid use is recommended. • No specific monitoring for systemic side effects is routinely recommended for patients with atopic dermatitis. • Patient fears of side effects associated with the use of topical corticosteroids for atopic dermatitis should be recognized and addressed to improve adherence and avoid undertreatment. Topical calcineurin inhibitors • Topical calcineurin inhibitors are recommended and effective for acute and chronic treatment, along with maintenance, in both adults and children with atopic dermatitis, and are particularly useful in selected clinical situations, including recalcitrance to steroids, use on sensitive areas (e.g., face, anogenital, skin folds), steroid-induced atrophy, and long-term uninterrupted topical steroid use. • Topical calcineurin inhibitors are recommended for use on actively affected areas as a steroid-sparing agent for the treatment of atopic dermatitis. • For patients with atopic dermatitis <2 years of age with mild to severe disease, off-label use of 0.03% tacrolimus or 1% pimecrolimus ointment can be

Clinical Guideline	Recommendation(s)
	recommended. • Pimecrolimus cream and tacrolimus ointment may cause skin burning and pruritus, especially when applied to acutely inflamed skin. Initial treatment of patients with atopic dermatitis using topical corticosteroids should be considered to minimize topical calcineurin inhibitor application site reactions. Patients with atopic dermatitis should be counseled about the possibility of these reactions. • Proactive, intermittent use of topical calcineurin inhibitor as maintenance therapy (two to three times per week) on areas that commonly flare is recommended to help prevent relapses while reducing the need for topical corticosteroids and is more effective than the use of emollients alone. • The concomitant use of a topical corticosteroid with a topical calcineurin inhibitor may be recommended for the treatment of atopic dermatitis. • No consistent increases in the prevalence of cutaneous viral infections have been seen with continuous or intermittent use of topical calcineurin inhibitor for up to five years; however, physicians should inform their patients of these theoretical cutaneous risks, given the lack of safety data for longer periods of time. • Clinicians should be aware of the black-box warning on the use of topical calcineurin inhibitor for patients with atopic dermatitis and discuss as warranted. • Routine blood monitoring of tacrolimus and pimecrolimus levels in patients with atopic dermatitis who are applying these agents is not recommended at this time. Topical antimicrobials and antiseptics • Except for bleach baths with intranasal mupirocin, no topical antistaphylococcal treatment has been shown to be clinically helpful in patients with atopic dermatitis and is not routinely recommended. In patients with moderate to severe atopic dermatitis and clinical signs of secondary bacterial infection, bleach baths and intranasal mupirocin may be recommended to reduce disease severity. Other topical agents • Topical antihistamines have been tried for the treatment of atopic dermatitis but have demonstrated little utility and are not recommended. • There are not adequate data to make a recommendation regarding the use of coal tar topical agents.
Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association: 2019 Update of the recommendations for the management of lupus nephritis (2020)[52]	Overarching principles • Kidney involvement in systemic lupus erythematosus, a major cause of morbidity and mortality that leads to high medical and societal costs, is best managed by interdisciplinary care with shared patient–physician decisions. • Vigilance for symptoms and signs suggestive of kidney involvement, histological assessment by nephropathologists and input from specialized centers ensure optimal outcomes. • Goals of treatment include patient survival, long-term preservation of kidney function, prevention of disease flares, prevention of organ damage, management of comorbidities and improvement in disease-related quality of life. • Management of active phases of lupus nephritis includes an initial period of intense immunosuppressive therapy to control disease activity, followed by a longer period of usually less intensive therapy to consolidate response and prevent relapses. Goals of treatment

Clinical Guideline	Recommendation(s)
	• Treatment aims for optimization (preservation or improvement) of kidney function, accompanied by a reduction in proteinuria of at least 25% by three months, 50% by six months, and a urine protein–creatine ratio target below 500 to 700 mg/g by 12 months (complete clinical response). • Patients with nephrotic-range proteinuria at baseline may require an additional 6 to 12 months to reach complete clinical response; in such cases, prompt switches of therapy are not necessary if proteinuria is improving. Initial treatment • For patients with class III or IV (±V) lupus nephritis, mycophenolate mofetil (target dose: 2 to 3 g/day, or mycophenolic acid at equivalent dose) or low-dose intravenous cyclophosphamide (500 mg every two weeks for a total of six doses) in combination with glucocorticoids, are recommended as they have the best efficacy/toxicity ratio. • Combination of mycophenolate mofetil (target dose: 1 to 2 g/day, or mycophenolic acid at equivalent dose) with a calcineurin inhibitor (especially tacrolimus) is an alternative, particularly in patients with nephrotic-range proteinuria. • Patients at high risk for kidney failure (reduced GFR, histological presence of crescents or fibrinoid necrosis or severe interstitial inflammation) can be treated as above, but high-dose intravenous cyclophosphamide (0.5 to 0.75 g/m^2 monthly for six months) can also be considered. • To reduce cumulative glucocorticoid dose, the use of intravenous pulses methylprednisolone (total dose 500 to 2500 mg, depending on disease severity) is recommended, followed by oral prednisone (0.3 to 0.5 mg/kg/day) for up to four weeks, tapered to ≤7.5 mg/day by three to six months. • In pure class V nephritis, mycophenolate mofetil (target dose 2 to 3 g/day; or mycophenolic acid at equivalent dose), in combination with pulse intravenous methylprednisolone (total dose 500 to 2500 mg, depending on disease severity) followed by oral prednisone (20 mg/day, tapered to ≤5 mg/day by three months) is recommended as initial treatment due to best efficacy/toxicity ratio. • Alternative options for class V nephritis include intravenous cyclophosphamide, or calcineurin inhibitors (especially tacrolimus) in monotherapy or in combination with mycophenolate mofetil/ mycophenolic acid, particularly in patients with nephrotic-range proteinuria. • Hydroxychloroquine should be coadministered, at a dose not to exceed 5 mg/kg/day and adjusted for the GFR. Subsequent treatment • If improvement after initial treatment is achieved, subsequent immunosuppression is recommended with either mycophenolate mofetil/mycophenolic acid (dose: 1 to 2 g/day)—especially if it was used as initial treatment— or azathioprine (2 mg/kg/day)—preferred if pregnancy is contemplated—in combination with low-dose prednisone (2.5 to 5 mg/day) when needed to control disease activity. • Gradual withdrawal of treatment (glucocorticoids first, then immunosuppressive drugs) can be attempted after at least three to five years therapy in complete clinical response. Hydroxychloroquine should be continued long-term. • Continuation, switching to or addition of calcineurin inhibitors (especially tacrolimus) can be considered in pure class V nephritis at the lowest effective dose and after considering nephrotoxicity risks.

Clinical Guideline	Recommendation(s)
	Non-responding/refractory disease • In case of failure to achieve the treatment goals, thorough evaluation of the possible causes is recommended, including assessment of adherence to treatment and therapeutic drug monitoring. • For active non-responding/refractory disease, treatment may be switched to one of the alternative initial therapies mentioned above, or rituximab (1000 mg on days 0 and 14) may be given. Adjunct treatment • Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are recommended for all patients with urine protein–creatine ratio >500 mg/g or arterial hypertension. • Statins are recommended on the basis of lipid levels and estimated 10-year cardiovascular disease risk using the Systematic Coronary Risk Evaluation or other validated tools. • Bone protection (calcium/vitamin D supplementation and/or antiresorptive agents) and immunizations with non-live vaccines may reduce treatment-related and disease-related comorbidities and are recommended. • If antiphospholipid antibodies (defined as in the international consensus statement for definite antiphospholipid syndrome classification criteria) are positive, and based on antiphospholipid antibodies profile, acetyl-salicylic acid (80 to 100 mg/day) may be used after balancing benefits and bleeding risk. • Anticoagulant treatment should be considered in cases of nephrotic syndrome with serum albumin <20 g/L. • Belimumab may be considered as add-on treatment, to facilitate glucocorticoid sparing, control extra-renal lupus activity and decrease the risk for extra-renal flares.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the disease-modifying antirheumatic agents are noted in Tables 3 and 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Disease-Modifying Antirheumatic Agents (A-H)[1-23]

Indications	Abatacept	Abrocitinib	Adalimumab	Anakinra	Apremilast	Baricitinib	Certolizumab pegol	Etanercept	Golimumab
Alopecia Areata						✔			
Ankylosing Spondylitis			✔				✔	✔	✔ *^
Atopic dermatitis		✔							
Crohn's Disease			✔				✔		
COVID-19						✔			
Deficiency of Interleukin-1 Receptor Antagonist				✔					
Hidradenitis Suppurativa			✔						

Indications	Abatacept	Abrocitinib	Adalimumab	Anakinra	Apremilast	Baricitinib	Certolizumab pegol	Etanercept	Golimumab
JIA	✔		✔					✔	✔ *
NOMID				✔					
Non-radiographic axSpA							✔		
Oral Ulcers Associated with Behcet's Disease					✔				
Plaque Psoriasis			✔		✔		✔	✔	
Prophylaxis of acute GVHD	✔								
Psoriatic Arthritis	✔		✔		✔		✔	✔	✔ *^
Rheumatoid Arthritis	✔		✔	✔		✔	✔	✔	✔ *^
Ulcerative Colitis			✔						✔ ^
Uveitis			✔						

axSpA=axial spondyloarthritis, COVID-19=coronavirus disease 2019, CRS=cytokine release syndrome, GVHD=graft versus host disease, JIA=juvenile Idiopathic Arthritis, NOMID=Neonatal-Onset Multisystem Inflammatory Disease
*Infusion (Simponi Aria)
^Subcutaneous injection (Simponi)

Table 4. FDA-Approved Indications for the Disease-Modifying Antirheumatic Agents (I-Z)[1-22]

Indications	Infliximab	Leflunomide	Sarilumab	Secukinumab	Sulfasalazine	Tocilizumab	Tofacitinib	Upadacitinib	Voclosporin
Ankylosing Spondylitis	✔			✔			✔	✔	
Atopic dermatitis								✔	
Crohn's Disease	✔								
CRS						✔			
Enthesitis-Related Arthritis				✔					
Giant Cell Arteritis						✔			
JIA					✔ ±	✔	✔		
Lupus nephritis									✔
Non-radiographic axSpA				✔				✔	
Plaque Psoriasis	✔			✔					
Psoriatic Arthritis	✔			✔			✔	✔	
Rheumatoid Arthritis	✔	✔	✔		✔ ±	✔	✔	✔	
Systemic Sclerosis-Associated Interstitial Lung Disease						✔			
Ulcerative Colitis	✔				✔ #±		✔	✔	

axSpA=axial spondyloarthritis, CRS=cytokine release syndrome, JIA=juvenile Idiopathic Arthritis, NOMID=Neonatal-Onset Multisystem Inflammatory Disease
*Infusion (Simponi Aria)
^Subcutaneous injection (Simponi)
#Immediade-release
±Delayed-release

IV. Pharmacokinetics

The pharmacokinetic parameters of the disease-modifying antirheumatic agents are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Disease-Modifying Antirheumatic Agents[24]

Generic Name(s)	Bioavailability (%)	Time to Peak Concentration	Half-Life
Abatacept	100 (intravenous); 78.6 (subcutaneous)	Not reported	13.0 to 14.3 days
Abrocitinib	60	1 hour	3 to 5 hours
Adalimumab	64	131±56 hours	10 to 20 days
Anakinra	95	3 to 7 hours	4 to 6 hours
Apremilast	73	2.5 hours	6 to 9 hours
Baricitinib	80	1 hour	12 hours
Certolizumab	80	54 to 171 hours	14 days
Etanercept	58	69±34 hours	102±30 hours
Golimumab	100 (intravenous); 53 (subcutaneous)	48 to 144 hours (subcutaneous)	14 days
Infliximab	100	Not reported	8 to 10 days
Leflunomide	80	6 to 12 hours	4 to 28 days
Sarilumab	Not reported	2 to 4 days	2 to 4 days
Secukinumab	55 to 77	6 days	22 to 31 days
Sulfasalazine	<15	3 to 12 hours	7.6 hours
Tocilizumab	100 (intravenous); 80 (subcutaneous)	Not reported	11 to 23 days
Tofacitinib	74	0.5 to 1.0 hour	IR: 3 hours XR: 6 hours
Upadacitinib	Not reported	2 to 4 hours	8 to 14 hours
Voclosporin	Not reported	1 to 4 hours	30 hours

V. Drug Interactions

Major drug interactions with the disease-modifying antirheumatic agents are listed in Table 6.

Table 6. Major Drug Interactions with the Disease-Modifying Antirheumatic Agents[24]

Generic Name(s)	Interaction	Mechanism
Abatacept, adalimumab, anakinra, baricitinib, certolizumab, etanercept, golimumab, infliximab, leflunomide, sarilumab, secukinumab, tocilizumab, tofacitinib, upadacitinib	Live vaccines	Concomitant use may result in an increased risk of secondary transmission of infection by the live vaccine.
Abatacept, adalimumab, anakinra, etanercept, infliximab, golimumab	Other DMARDs	Concurrent use of may result in an increased risk of infections.
Interleukin-receptor blockers	Other biologic immunomodulators	Concurrent use may increase the risk of infections.
Interleukin-receptor blockers	CYP450 substrates with a narrow therapeutic index	Increased cytokine levels (interleukins) suppress the effect of CYP450 and should be normalized with interleukin-receptor blocking agents. Monitor effect of agents that may have metabolism increased.

Generic Name(s)	Interaction	Mechanism
Apremilast	CYP3A strong inducers (e.g., rifampin)	Concurrent use of apremilast and strong CYP3A4 inducers may result in decreased apremilast exposure.
Baricitinib	OAT3 Strong inhibitors (e.g., probenecid)	Concurrent use may increase baricitinib exposure.
Tumor Necrosis Factor Blocking Agents	Other biologic immunomodulators	Concurrent use may increase the risk of infections.
Abrocitinib	Antiplatelet agents	Concurrent use of abrocitinib and antiplatelet agents may result in increased risk of bleeding.
Abrocitinib	Ticlopidine	Concurrent use of abrocitinib and ticlopidine may result in increased risk of bleeding, and increased abrocitinib and active metabolite exposure.
Abrocitinib	Fluconazole	Concurrent use of abrocitinib and dual moderate or strong CYP2C19 and CYP2C9 inhibitors may result in increased abrocitinib and active metabolite exposure.
Abrocitinib	Digoxin	Concurrent use of abrocitinib and p-gp substrates with a narrow therapeutic index may result in increased exposure of P-glycoprotein substrate.
Abrocitinib	Strong CYP2C19 or CYP2C9 inducers	Concurrent use of abrocitinib and strong CYP2C19 or CYP2C9 inducers may result in decreased abrocitinib and active metabolite exposure.
Abrocitinib	Fluvoxamine	Concurrent use of abrocitinib and strong CYP2C19 inhibitors may result in increased abrocitinib and active metabolite exposure.
Etanercept	Cyclophosphamide	Concurrent administration may result in a higher incidence of developing noncutaneous solid malignancies.
Infliximab	Tocilizumab	Concurrent use may increase immunosuppression and the risk of infections.
Leflunomide	Methotrexate	Concurrent use of leflunomide and methotrexate may result in increased risk of hepatotoxicity and bone marrow toxicity.
Leflunomide	Warfarin	Concurrent use of leflunomide and warfarin may result in increased risk of bleeding.
Sulfasalazine	Amoxicillin	Concurrent use of amoxicillin and sulfasalazine may result in an increased risk of drug reaction with eosinophilia and systemic symptoms.
Sulfasalazine	Azathioprine and metabolites	Concurrent use of sulfasalazine and azathioprine and metabolites may result in an increased risk of bone marrow suppression.
Sulfasalazine	Celecoxib	Concurrent use may result in increased risk of bleeding.
Sulfasalazine	Nonsteroidal anti-inflammatory drugs and salicylates	Concurrent use may result in increased risk of bleeding.
Tofacitinib	Biological DMARDs	Concurrent use may increase the risk of serious infections. Coadministration should be avoided.
Tofacitinib	CYP2C19 potent and CYP3A moderate inhibitors (e.g., fluconazole)	Concurrent use may elevate tofacitinib concentrations, increasing the pharmacologic effects and risk of adverse reactions; the dose of tofacitinib should be reduced to 5 mg once daily.
Tofacitinib	CYP3A strong inhibitors (e.g., ketoconazole)	Concurrent use may elevate tofacitinib concentrations, increasing the pharmacologic effects and risk of adverse reactions; the dose of tofacitinib should be reduced to 5 mg once daily.
Tofacitinib	CYP3A strong inducers (e.g., rifampin)	Concurrent use may reduce tofacitinib concentrations, decreasing the clinical response. Coadminister with

Generic Name(s)	Interaction	Mechanism
		caution. Close clinical monitoring is warranted.
Infliximab, tofacitinib	Immunosuppressants (e.g., azathioprine, cyclosporine, tacrolimus)	Concurrent use may increase the risk of added immunosuppression and serious infections. Coadministration of tofacitinib with potent immunosuppressants should be avoided.
Upadacitinib	CYP3A4 strong inhibitors (e.g., ketoconazole)	Concurrent use may increase upadacitinib exposure; upadacitinib should be used with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors.
Upadacitinib	CYP3A4 strong inducers (e.g., rifampin)	Concurrent use may decrease upadacitinib exposure, which may lead to reduced therapeutic effect of upadacitinib. Coadministration is not recommended.
Voclosporin	Strong and Moderate CYP 3A4 Inhibitors	Patients using strong and moderate CYP 3A4 inhibitors alongside voclosporin can increase exposure to voclosporin and increase the risk of acute and/or chronic nephrotoxicity. Strong CYP 3A4 inhibitors may decrease voclosporin elimination by inhibiting its metabolism resulting in increased pharmacologic and toxic effects of voclosporin. Decrease voclosporin dose accordingly; monitor plasma levels, efficacy, and toxicity.
Voclosporin	Strong and Moderate CYP 3A4 Inducers	Strong and moderate CYP 3A4 inducers may increase the clearance of voclosporin through increased metabolism. The dose of voclosporin may need to be increased.
Voclosporin	P-gp Substrates	Voclosporin is a P-gp inhibitor. For certain P-gp substrates with narrow therapeutic windows, dose reduction is recommended in the prescribing information if need.
Voclosporin	OATP1B1 Substrates	Voclosporin is an OATP1B1 inhibitor. Patients should be monitored for adverse reactions when used concomitantly with OATP1B1 substrates.

DMARD=disease-modifying antirheumatic drug

VI. Adverse Drug Events

The most common adverse drug events reported with the disease-modifying antirheumatic agents are listed in Table 7. The boxed warnings for the disease-modifying antirheumatic agents are listed in Tables 8 to 15.

Table 7. Adverse Drug Events (%) Reported with the Disease-Modifying Antirheumatic Agents[1-24]

Adverse Event	Abatacept	Abrocitinib	Adalimumab	Anakinra*	Apremilast	Baricitinib	Certolizumab	Etanercept	Golimumab†	Infliximab	Leflunomide	Sarilumab	Secukinumab	Sulfasalazine	Tocilizumab	Tofacitinib	Upadacitinib	Voclosporin
Gastrointestinal																		
Abdominal pain	-	≤2	7	5	4	-	-	5 to 10	-	12	5 to 6	-	-	8	-	-	-	5
Anorexia	-	-	-	-	-	-	-	-	-	-	-	-	-	33	-	-	-	-
Diarrhea	-	-	-	7	8 to 17	-	-	8 to 16	-	12	17 to 27	-	3 to 4		-	-	-	19
Dyspepsia	6	-	-	-	3	-	-	4 to 11	-	10	5 to 6	-	-	13	-	-	-	6
Gastroenteritis	-	1	-	-	-	-	-	-	-	-	3	-	-	-	-	-	-	-
Gingivitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	≤3
Inflammatory bowel disease	-	-	-	-	-	-	-	-	-	-	-	-	≤1	-	-	-	-	-
Mucocutaneous candidiasis	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-
Nausea	≥10	6 to 15	9	8	7 to 17	3	-	9 to 15	-	21	9 to 13	-	≥2	19 to 33	-	-	4	-
Oral mucosa ulcer	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4
Stomatitis	-	-	-	-	-	-	-	-	-	-	-	-	-	4	-	-	-	-
Vomiting	-	2 to 3	-	14‡	≤4	-	-	3 to 5	-	-	5 to 5	-	-	8 to 33	-	-	-	-
Laboratory Tests																		
Abnormal hepatic test	-	-	8	-	-	-	-	-	-	-	5 to 10	-	-	4	3 to 6	-	-	-
Alkaline phosphatase increased	-	-	5	-	-	-	-	-	-	-	2 to 4	5	-	-	-	-	-	-
Creatinine phosphokinase increased	-	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Mean glomerular filtration rate decreased	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	26
Hematuria	-	-	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hypercholesterolemia	-	-	6	-	-	-	-	-	-	-	-	-	≥2	-	-	-	-	-
Hyperglycemia	-	-	-	-	-	-	-	-	-	-	1 to 3	-	-	-	-	-	-	-

Adverse Event	Abatacept	Abrocitinib	Adalimumab	Anakinra*	Apremilast	Baricitinib	Certolizumab	Etanercept	Golimumab†	Infliximab	Leflunomide	Sarilumab	Secukinumab	Sulfasalazine	Tocilizumab	Tofacitinib	Upadacitinib	Voclosporin
Hyperthyroidism	-	-	-	-	-	-	-	-	-	-	1 to 3	-	-	-	-	-	-	-
Hyperlipidemia	-	-	7	-	-	-	-	-	-	-	1 to 3	-	-	-	-	-	-	-
Hypokalemia	-	-	-	-	-	-	-	-	-	-	1 to 3	-	-	-	-	-	-	-
Leukopenia	-	-	-	-	-	-	-	-	-	-	-	-	-	3	-	-	-	-
Neutropenia	-	-	-	-	-	-	-	-	-	-	-	≤10			-	-	-	-
Thrombocytopenia	-	2	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-
Respiratory																		
Bronchitis	5 to 13	-	-	-	1	-	3	-	-	10	5 to 8	-	-	-	-	-	-	-
Coughing	8	-	-	-	-	-	-	5 to 6	-	12	3 to 5	-	-	-	-	-	2	11
Cyanosis	-	-	-	-	-	-	-	-	-	-	-	-	-	≤3	-	-	-	-
Flu syndrome	-	-	7	-	-	-	-	-	-	14	≤4	-	-	-	-	-	-	-
Nasopharyngitis	12	9 to 12	-	-	3	-	5	-	-	-	-	-	11 to 12	-	4 to 7	-	-	-
Non-upper respiratory infection	-	-	-	-	-	-	-	21 to 54	-	-	-	-	-	-	-	-	-	-
Pharyngitis	-	-	-	11.6‡	-	-	3	6 to 7	-	-	2 to 3	-	1	-	-	-	-	-
Respiratory disorder	-	-	-	-	-	-	-	5	-	-	-	-	-	-	-	-	-	-
Rhinitis	-	-	-	-	-	-	-	12 to 16	-	-	2 to 5	-	1	-	-	-	-	-
Rhinorrhea	-	-	-	-	-	-	-	-	-	-	-	-	≤1	-	-	-	-	-
Sinusitis	5 to 13	-	11	7	1	-	-	3 to 5	-	14	1 to 2	-	-	-	-	-	-	-
Upper respiratory infection	≥10	-	17	14	4 to 9	15 to 16	6	38 to 65	13§ to 16	32	15 to 27	-	3	-	6 to 8	-	14	-
Skin																		
Acne	-	2 to 5	-	-	-	-	-	-	-	-	1 to 3	-	-	-	-	-	-	-
Contact dermatitis	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Eczema	-	-	-	-	-	-	-	-	-	-	2 to 3	-	-	-	-	-	-	-
Folliculitis	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-
Impetigo	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pruritus	-	-	-	-	-	-	-	-	-	7	4 to 6	-	-	≤4	-	-	-	-
Rash	-	-	12	-	-	-	3	3 to 13	-	10	10 to 12	-	-	≤3 to 13	-	-	-	-
Urticaria	-	-	-	-	-	-	-	-	-	-	-	-	≤1	≤3	-	-	-	-
Other																		
Accidental injury	-	-	10	-	-	-	-	-	-	-	5 to 7	-	-	-	-	-	-	-
Acute kidney injury	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3
Alopecia	-	-	-	-	-	-	-	1 to 6	-	-	9 to 17	-	-	-	-	-	-	6

Adverse Event	Abatacept	Abrocitinib	Adalimumab	Anakinra*	Apremilast	Baricitinib	Certolizumab	Etanercept	Golimumab†	Infliximab	Leflunomide	Sarilumab	Secukinumab	Sulfasalazine	Tocilizumab	Tofacitinib	Upadacitinib	Voclosporin
Anemia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	12
Angina pectoris	-	-	-	-	-	-	-	-	-	-	1 to 3	-	-	-	-	-	-	-
Anxiety	-	-	-	-	-	-	-	-	-	-	1 to 3	-	-	-	-	-	-	-
Arthralgia	-	-	-	6, 11.6‡	-	-	-	-	-	-	≤4	-	-	-	-	-	-	-
Asthenia	-	-	-	-	-	-	-	5 to 11	-	-	-	-	-	-	-	-	-	-
Back pain	7	-	6	-	2	-	4	-	-	8	5 to 8	-	-	-	-	-	-	-
Body pain	-	-	-	-	-	-	-	-	-	8	-	-	-	-	-	-	-	-
Chest pain	-	-	-	-	-	-	-	-	-	-	1 to 4	-	-	-	-	-	-	-
Depression	-	-	-	-	-	-	-	-	-	-	1 to 3	-	-	-	-	-	-	-
Dizziness	9	2 to 3	-	-	-	-	-	7 to 8	-	-	-	-	-	4	-	-	-	-
Fatigue	-	1 to 2	-	-	3	-	3	-	-	9	-	-	-	-	-	-	-	4
Fever	-	-	-	11.6‡	-	-	3	2 to 3	-	7	1 to 3	-	-	≤5	-	-	-	-
Flu like symptoms	-	-	-	6	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Headache	18	6 to 8	12	12, 14‡	5 to 6	-	5	17 to 24	-	18	7 to 13	-	≥2	9 to 33	5 to 7	-	-	15
Hemolytic anemia	-	-	-	-	-	-	-	-	-	-	-	-	-	≤3	-	-	-	-
Herpes simplex	-	3 to 4	-	-	-	1 to 2	-	-	-	-	-	-	-	-	-	-	-	-
Herpes zoster	-	≤1	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-
Hypertension	7	1	5	-	-	-	5	-	-	7	9 to 10	-	-	-	4 to 6	-	-	19
Hypertrichosis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	≤3
Immunoglobulin abnormality	-	-	-	-	-	-	-	-	-	-	-	-	-	10	-	-	-	-
Infections (overall)	-	35	-	-	-	-	-	-	-	-	-	-	29 to 48	-	20	-	-	-
Injection site pain	-	-	12	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Injection site reaction	-	-	8	16‡, 71	-	-	-	37 to 43	6	-	-	6 to 7	-	-	7.1‖ to 10.1‖	-	-	-
Insomnia	-	-	-	-	2	-	-	-	-	-	1 to 3	-	-	-	-	-	-	-
Moniliasis	-	-	-	-	-	-	-	-	-	5	-	-	-	-	-	-	-	-
Mouth ulcer	-	-	-	-	-	-	-	2 to 6	-	-	3 to 5	-	-	-	-	-	-	-
Muscle Pain	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Neuralgia	-	-	-	-	-	-	-	-	-	-	1 to 3	-	-	-	-	-	-	-
Oligospermia	-	-	-	-	-	-	-	-	-	-	-	-	-	33	-	-	-	-
Pain	-	-	-	-	-	-	-	-	-	-	1 to 4	-	-	-	-	-	-	-
Palpitations	-	-	-	-	-	-	-	-	-	-	1 to 3	-	-	-	-	-	-	-
Paresthesia	-	-	-	-	-	-	-	-	-	-	2 to 4	-	-	-	-	-	-	-

Adverse Event	Abatacept	Abrocitinib	Adalimumab	Anakinra*	Apremilast	Baricitinib	Certolizumab	Etanercept	Golimumab†	Infliximab	Leflunomide	Sarilumab	Secukinumab	Sulfasalazine	Tocilizumab	Tofacitinib	Upadacitinib	Voclosporin
Peripheral edema	-	-	-	-	-	-	-	2 to 8	-	-	-	-	-	-	-	-	-	-
Pyrexia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-
Renal insufficiency	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6
Synovitis	-	-	-	-	-	-	-	-	-	-	2 to 4	-	-	-	-	-	-	-
Tachycardia	-	-	-	-	-	-	-	-	-	-	1 to 3	-	-	-	-	-	-	-
Tremor	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3
Urinary tract infection	6	2	8	-	-	-	-	-	-	8	5	3	-	-	-	-	-	10
Vasculitis	-	-	-	-	-	-	-	-	-	-	1 to 3	-	-	-	-	-	-	-
Vertigo	-	-	-	-	-	-	-	-	-	-	1 to 3	-	-	-	-	-	-	-
Viral infection	-	-	-	-	-	-	-	-	5	-	-	-	-	-	-	-	-	-
Weight Gain	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Weight Loss	-	-	-	-	10 to 12	-	-	-	-	-	2 to 4	-	-	-	-	-	-	-
Worsening of rheumatoid arthritis	-	-	-	19	-	-	-	-	-	-	-	-	-	-	-	-	-	-

-Event not reported or incidence <1%.
*Unless otherwise specified, adverse reaction observed in patients treated for rheumatoid arthritis.
†With or without disease modifying antirheumatic agents. Unless otherwise specified, adverse reaction observed in patients treated with subcutaneous formulation.
‡Neonatal-onset multisystem inflammatory disease during the first six months of therapy.
§Intravenous formulation (Simponi Aria®) only.
‖Subcutaneous formulation only.

Table 8. Boxed Warning for Leflunomide[23]

WARNING
Embryo-fetal toxicity: Leflunomide is contraindicated for use in pregnant women because of the potential for fetal harm. Teratogenicity and embryo-lethality occurred in animals administered leflunomide at doses lower than the human exposure level. Exclude pregnancy before the start of treatment with leflunomide in females of reproductive potential. Advise females of reproductive potential to use effective contraception during leflunomide treatment and during an accelerated drug elimination procedure after leflunomide treatment. Stop leflunomide and use an accelerated drug elimination procedure if the patient becomes pregnant. Hepatotoxicity: Severe liver injury, including fatal liver failure, has been reported in patients treated with leflunomide. Leflunomide is contraindicated in patients with severe hepatic impairment. Concomitant use of leflunomide with other potentially hepatotoxic drugs may increase the risk of liver injury. Patients with preexisting acute or chronic liver disease, or those with serum ALT greater than 2 times the upper limit of normal (ULN) before initiating treatment, are at increased risk and should not be treated with leflunomide. Monitor ALT levels at least monthly for 6 months after starting leflunomide, and thereafter every 6 to 8 weeks. If leflunomide-induced liver injury is suspected, stop leflunomide treatment, start an accelerated drug elimination procedure, and monitor liver tests weekly until normalized.

Table 9. Boxed Warning for Tocilizumab[23]

WARNING
Serious Infections Patients treated with Actemra® are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. If a serious infection develops, interrupt Actemra® until the infection is controlled. Reported infections include: • Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before Actemra® use and during therapy. Treatment for latent infection should be initiated prior to Actemra® use. • Invasive fungal infections, including candidiasis, aspergillosis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease. • Bacterial, viral and other infections due to opportunistic pathogens. The risks and benefits of treatment with Actemra® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Actemra®, including the possible development of tuberculosis in patients who tested negative for infection prior to initiating therapy.

Table 10. Boxed Warning for adalimumab, certolizumab pegol, etanercept, golimumab, infliximab[23]

WARNING
Serious Infections Patients treated with Cimzia®, Enbrel®, Humira®, Remicade®, Simponi Aria®, or Simponi® are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Cimzia®, Enbrel®, Humira®, Remicade®, Simponi Aria®, and Simponi® should be discontinued if a patient develops a serious infection or sepsis. Reported infections include: • Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before Cimzia®, Enbrel®, Remicade®, Simponi Aria®, or Simponi® use and during therapy. Treatment for latent infection should be initiated prior to Cimzia®, Enbrel®, Humira®, Remicade®, Simponi Aria®, or Simponi® use.

WARNING

- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.

The risks and benefits of treatment with Cimzia®, Enbrel®, Humira®, Remicade®, Simponi Aria®, or Simponi® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Cimzia®, Enbrel®, Humira®, Remicade®, Simponi Aria®, or Simponi®, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Malignancy
Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor blockers, of which Cimzia®, Enbrel®, Humira®, Remicade®, Simponi Aria®, or Simponi® are members.

Table 11. Boxed Warning for Tofacitinib[23]

WARNING

Serious Infections
Patients treated with Xeljanz® are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt Xeljanz® until the infection is controlled.

Reported infections include:

- Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before Xeljanz® use and during therapy. Treatment for latent infection should be initiated prior to Xeljanz® use.
- Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.
- Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.

The risks and benefits of treatment with Xeljanz® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Xeljanz®, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Mortality
In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing Xeljanz® 5 mg twice a day or Xeljanz® 10 mg twice a day to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with Xeljanz® 5 mg twice a day or Xeljanz® 10 mg twice a day. A Xeljanz®/Xeljanz® Oral Solution 10 mg twice daily (or a Xeljanz® XR 22 mg once daily) dosage is not recommended for the treatment of RA or PsA.

Malignancies
Malignancies, including lymphomas and solid tumors, have occurred in patients treated with Xeljanz® and other Janus kinase inhibitors used to treat inflammatory conditions. In RA patients, a higher rate of

WARNING
malignancies (excluding NMSC) was observed in patients treated with Xeljanz® 5 mg twice a day or Xeljanz® 10 mg twice a day compared with TNF blockers. Lymphomas and lung cancers were observed at a higher rate in patients treated with Xeljanz® 5 mg twice a day or Xeljanz® 10 mg twice a day in RA patients compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with Xeljanz® and concomitant immunosuppressive medications. Major Adverse Cardiovascular Events RA patients 50 years of age and older with at least one cardiovascular risk factor, treated with Xeljanz® 5 mg twice daily or Xeljanz® 10 mg twice daily, had a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue Xeljanz®/Xeljanz® XR/Xeljanz® Oral Solution in patients that have experienced a myocardial infarction or stroke. Thrombosis Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis have occurred in patients treated with Xeljanz® and other Janus kinase inhibitors used to treat inflammatory conditions. Many of these events were serious and some resulted in death. RA patients 50 years of age and older with at least one cardiovascular risk factor treated with Xeljanz® 5 mg twice daily or Xeljanz® 10 mg twice daily compared to TNF blockers had an observed increase in incidence of these events. Avoid Xeljanz®/Xeljanz® XR/Xeljanz® Oral Solution in patients at risk. Discontinue Xeljanz®/Xeljanz® XR/Xeljanz® Oral Solution and promptly evaluate patients with symptoms of thrombosis.

Table 12. Boxed Warning for Sarilumab[23]

WARNING
Risk of serious infections Patients treated with sarilumab are at increased risk for developing serious infections that may lead to hospitalization or death. Opportunistic infections have also been reported in patients receiving sarilumab. Most patients who developed infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Avoid use of sarilumab in patients with an active infection. Reported infections include: • Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before sarilumab use and during therapy. Treatment for latent infection should be initiated prior to sarilumab use. • Invasive fungal infections, such as candidiasis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease. • Bacterial, viral and other infections due to opportunistic pathogens. Closely monitor patients for signs and symptoms of infection during treatment with sarilumab. If a serious infection develops, interrupt sarilumab until the infection is controlled. Consider the risks and benefits of treatment with sarilumab prior to initiating therapy in patients with chronic or recurrent infection.

Table 13. Boxed Warning for Baricitinib[23]

WARNING
SERIOUS INFECTIONS

WARNING
Patients treated with baricitinib are at risk for developing serious infections that may lead to hospitalization or death. Most patients with rheumatoid arthritis who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. If a serious infection develops, interrupt baricitinib until the infection is controlled. Reported infections include: • Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Baricitinib should not be given to patients with active tuberculosis. Patients, except those with COVID-19, should be tested for latent tuberculosis before initiating baricitinib and during therapy. If positive, start treatment for latent infection prior to baricitinib use. • Invasive fungal infections, including candidiasis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease. • Bacterial, viral, and other infections due to opportunistic pathogens. The risks and benefits of treatment with baricitinib should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with baricitinib including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. MORTALITY In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing another Janus kinase (JAK) inhibitor to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with the JAK inhibitor. MALIGNANCIES Lymphoma and other malignancies have been observed in patients treated with baricitinib. In RA patients treated with another JAK inhibitor, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. MAJOR ADVERSE CARDIOVASCULAR EVENTS In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke) was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue baricitinib in patients that have experienced a myocardial infarction or stroke. THROMBOSIS Thrombosis, including deep venous thrombosis and pulmonary embolism, has been observed at an increased incidence in patients treated with baricitinib compared to placebo. In addition, there were cases of arterial thrombosis. Many of these adverse events were serious and some resulted in death. In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid baricitinib in patients at risk. Patients with symptoms of thrombosis should discontinue baricitinib and be promptly evaluated.

Table 14. Boxed Warning for Abrocitinib and Upadacitinib[23]

WARNING
SERIOUS INFECTIONS Patients treated with these agents are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. If a serious infection develops, interrupt treatment until the infection is controlled. Reported infections from Janus kinase (JAK) inhibitors used to treat inflammatory conditions:

WARNING
• Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Test for latent TB before and during therapy; treat latent TB prior to use. Monitor all patients for active TB during treatment, even patients with initial negative, latent TB test. • Invasive fungal infections, including cryptococcosis and pneumocystosis. • Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens. The risks and benefits of treatment should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. MORTALITY In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing another Janus kinase (JAK) inhibitor to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with the JAK inhibitor. MALIGNANCIES Lymphoma and other malignancies have been observed in patients receiving JAK inhibitors used to treat inflammatory conditions. In RA patients treated with another JAK inhibitor, a higher rate of malignancies (excluding nonmelanoma skin cancer (NMSC)) was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. MAJOR ADVERSE CARDIOVASCULAR EVENTS In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue treatment in patients that have experienced a myocardial infarction or stroke. THROMBOSIS Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients treated with JAK inhibitors used to treat inflammatory conditions. Many of these adverse events were serious and some resulted in death. In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid treatment in patients at risk. Patients with symptoms of thrombosis should discontinue treatment and be promptly evaluated.

Table 15. Boxed Warning for Voclosporin[23]

WARNING
WARNING: MALIGNANCIES AND SERIOUS INFECTIONS Increased risk for developing malignancies and serious infections with voclosporin or other immunosuppressants that may lead to hospitalization or death

VII. Dosing and Administration

The usual dosing regimens for the disease-modifying antirheumatic agents are listed in Table 16.

Table 16. Usual Dosing Regimens for the Disease-Modifying Antirheumatic Agents[1-24]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Abatacept	Psoriatic arthritis, rheumatoid arthritis: Injections: initial (<60 kg), 500 mg IV over 30 minutes at weeks zero, two and four; (60 to 100 kg), 750 mg IV over 30 minutes at weeks zero, two and four; (>100 kg), 1,000 mg IV over 30 minutes at weeks zero, two and four; maintenance (<60 kg), 500 mg IV over 30 minutes every four weeks; (60 to 100 kg), 750 mg IV over 30 minutes every four weeks; (>100 kg), 1,000 mg IV over 30 minutes every four weeks; or initial (<60 kg), 500 mg IV over 30 minutes followed by 125 mg SC within 24 hours; (60 to 100 kg), 750 mg IV over 30 minutes followed by 125 mg SC within 24 hours; (>100 kg), 1,000 mg IV over 30 minutes followed by 125 mg SC within 24 hours; maintenance, 125 mg SC once weekly Prophylaxis for acute graft versus host disease (in combination with a calcineurin inhibitor and methotrexate): Injection: 10 mg/kg (maximum dose of 1,000 mg) as an intravenous infusion over 60 minutes on the day before transplantation (Day -1), followed by administration on Days 5, 14, and 28 after transplantation	Juvenile idiopathic arthritis (two to 17 years of age): Single use vial: initial, (<75 kg),10 mg/kg IV over 30 minutes at weeks zero, two and four; (≥75 kg), follow adult dosing not to exceed 1,000 mg/dose; maintenance (<75 kg), 10 mg/kg IV over 30 minutes every four weeks; (≥75 kg), follow adult dosing not to exceed 1,000 mg/dose Auto-injector, prefilled syringe: 10 to <25 kg, 50 mg SC once weekly; 25 kg to <50 kg, 87.5 mg SC once weekly; ≥50 kg, 125 mg SC once weekly Prophylaxis for acute graft versus host disease (in combination with a calcineurin inhibitor and methotrexate): Injection: For patients 6 years and older, 10 mg/kg (maximum dose of 1,000 mg) as an intravenous infusion over 60 minutes on the day before transplantation (Day -1), followed by administration on Days 5, 14, and 28 after transplantation; For patients 2 to less than 6 years of age, 15 mg/kg as an intravenous infusion over 60 minutes on the day before transplantation (Day -1), followed by 12 mg/kg as an intravenous infusion over 60 minutes on	Auto-injector: 125 mg/mL Prefilled syringe: 50 mg/0.4 mL 87.5 mg/0.7 mL 125 mg/mL Vial: 250 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
		Days 5, 14, and 28 after transplantation	
Abrocitinib	Atopic dermatitis: Tablet: 100 mg orally once daily; if an adequate response is not achieved with 100 mg orally daily after 12 weeks, consider increasing dosage to 200 mg orally once daily; discontinue therapy if inadequate response is seen after dosage increase to 200 mg once daily.	Safety and efficacy in the pediatric population have not been established.	Tablets: 50 mg 100 mg 200 mg
Adalimumab	Ankylosing spondylitis, psoriatic arthritis: Prefilled pen and syringe, single use vial: initial/maintenance, 40 mg SC every other week Crohn's disease, ulcerative colitis: Prefilled pen and syringe, single use vial: initial, 160 mg SC at week zero (may administer as four injections in one day or two injections daily for two consecutive days), followed by 80 mg SC during week two (day 15); maintenance, 40 mg SC every other week starting at week four (day 29) Hidradenitis Suppurativa: Prefilled pen and syringe, single use vial: 160 mg (four 40 mg injections) on day one, then 80 mg (two 40 mg injections) on day 15, then 40 mg weekly or 80 mg every other week starting on day 29 Plaque psoriasis, uveitis: Prefilled pen and syringe, single use vial: initial, 80 mg SC; maintenance, 40 mg SC every other week starting one week after the initial dose Rheumatoid arthritis: Prefilled pen and syringe, single use vial: initial/maintenance, 40 mg SC every other week; may increase to 40 mg SC every week in patients not receiving concomitant methotrexate	Crohn's disease (six to 17 years of age): 17 to <40 kg, 80 mg on day one, then 40 mg on day 15, then 20 mg every other week; ≥40 kg, 160 mg on day one, then 80 mg on day 15, then 40 mg every other week Hidradenitis Suppurativa (12 to 17 years of age): 30 to <60 kg, 80 mg on day one, then 40 mg on day eight and 40 mg every other week thereafter; ≥60 kg, 160 mg on day one, then 80 mg on day 15, then 40 mg every week or 80 every other week on day 29 and thereafter Juvenile idiopathic arthritis, pediatric uveitis (two to 17 years of age): 10 to <15 kg, 10 mg every other week; 15 to <30 kg, 20 mg SC every other week; ≥30 kg, 40 mg SC every other week (Dose has not been established for patients with a weight of <10 kg) Ulcerative colitis (five to 17 years of age): 20 to <40 kg, 80 mg on day one, then 40 mg on day eight, then	Prefilled pen: 40 mg/0.4 mL 40 mg/0.8 mL 80 mg/0.8 mL Prefilled syringe: 10 mg/0.1 mL 10 mg/0.2 mL 20 mg/0.2 mL 20 mg/0.4 mL 40 mg/0.4 mL 40 mg/0.8 mL 80 mg/0.8 mL

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
		40 mg on day 15, then 40 mg every other week or 20 mg every week; ≥40 kg, 160 mg on day one, then 80 mg on day eight, then 80 mg on day 15, then 80 mg every other week or 40 mg every week	
Anakinra	Deficiency of Interleukin-1 Receptor Antagonist: Prefilled syringe: initial: 1 to 2 mg/kg daily; maintenance, dose can be individually adjusted to a maximum of 8 mg/kg daily NOMID: Prefilled syringe: initial: 1 to 2 mg/kg daily; maintenance, dose can be individually adjusted to a maximum of 8 mg/kg daily Rheumatoid arthritis: Prefilled syringe: initial, 100 mg SC daily; maintenance, 100 mg SC daily	Deficiency of Interleukin-1 Receptor Antagonist: Prefilled syringe: initial: 1 to 2 mg/kg daily; maintenance, dose can be individually adjusted to a maximum of 8 mg/kg daily NOMID: Prefilled syringe: initial: 1 to 2 mg/kg SC daily; maintenance, 3 to 4 mg/kg SC daily	Prefilled syringe: 100 mg/0.67 mL
Apremilast	Oral ulcers associated with Behcet's Disease, plaque psoriasis, psoriatic arthritis: Tablet: initial, 10 mg in the morning on day one; 10 mg twice daily on day two; 10 mg in the morning and 20 mg in the evening on day three; 20 mg twice daily on day four; 20 mg in the morning and 30 mg in the evening on day five; maintenance, 30 mg twice daily starting on day six	Safety and efficacy in the pediatric population have not been established.	Dose pack: 10 mg (4)-20 mg (4)-30 mg (47) Tablet: 30 mg
Baricitinib	Alopecia areata: Tablet: 2 mg by mouth once daily; may increase to 4 mg once daily if inadequate response COVID-19: Tablet: 4 mg once daily for 14 days or until hospital discharge, whichever occurs first Moderate to severe rheumatoid arthritis: Tablet: 2 mg by mouth once daily	Safety and efficacy in the pediatric population have not been established.	Tablet: 1 mg 2 mg
Certolizumab	Ankylosing spondylitis, non-radiographic axial spondyloarthritis, psoriatic arthritis, rheumatoid arthritis: Prefilled syringe and vial: initial, 400 mg SC (as two SC injections of 200 mg) once and then repeat at weeks two and four; maintenance, 200 mg SC once every other week or 400 mg (as two SC injections of 200 mg) every four weeks	Safety and efficacy in the pediatric population have not been established.	Prefilled syringe: 200 mg/mL Vial: 200 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	Crohn's disease: Prefilled syringe and vial: initial, 400 mg SC (as two SC injections of 200 mg) once, repeat at weeks two and four; maintenance, 400 mg SC (as two SC injections of 200 mg) once every four weeks Plaque psoriasis: Prefilled syringe and vial: initial and maintenance, 400 mg SC (as two SC injections of 200 mg) every other week; for some patients (with body weight ≤ 90 kg), 400 mg SC (as two SC injections of 200 mg) once, repeat at weeks two and four; maintenance, 200 mg every other week may be considered		
Etanercept	Ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis: Prefilled autoinjector and syringe and vial: initial/maintenance, 50 mg SC weekly Plaque psoriasis: Prefilled autoinjector and syringe and vial: initial, 50 mg SC twice weekly for three months; maintenance, 50 mg SC weekly	Juvenile idiopathic arthritis, plaque psoriasis (two to 17 years of age): Prefilled autoinjector and syringe and vial: initial and maintenance (<63 kg), 0.8 mg/kg SC weekly; (≥63 kg), 50 mg SC weekly	Prefilled "SureClick" autoinjector: 50 mg/mL Prefilled syringes: 25 mg/0.5 mL 50 mg/mL Vial: 25 mg
Golimumab	Ankylosing spondylitis, psoriatic arthritis: Prefilled autoinjector and syringe: initial, 50 mg SC once monthly; maintenance, 50 mg SC once monthly Vial (Simponi Aria®): initial, 2 mg/kg IV over 30 minutes at weeks zero and four; maintenance, 2 mg/kg IV over 30 minutes every eight weeks; all in combination with methotrexate Rheumatoid arthritis: Prefilled autoinjector and syringe: initial, 50 mg SC once monthly in combination with methotrexate; maintenance, 50 mg SC once monthly in combination with methotrexate Vial (Simponi Aria®): initial, 2 mg/kg IV over 30 minutes at weeks zero and four; maintenance, 2 mg/kg IV over 30 minutes every eight weeks; all in combination with methotrexate Ulcerative colitis: Prefilled autoinjector and syringe: initial, 200 mg SC once, followed by 100 mg SC at week two; maintenance, 100 mg SC once every four weeks	Juvenile idiopathic arthritis, psoriatic arthritis (two to 17 years of age): Vial (Simponi Aria®): 80 mg/m^2 given as an IV infusion over 30 minutes at weeks 0 and 4, and every 8 weeks thereafter	Prefilled "SmartJect" autoinjector: 50 mg/0.5 mL 100 mg/mL Prefilled syringe: 50 mg/0.5 mL 100 mg/mL Single use vial (Simponi Aria®): 50 mg/4 mL

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Infliximab	Ankylosing spondylitis: Vial: initial, 5 mg/kg IV over two hours at weeks zero, two, and six; maintenance, 5 mg/kg IV over two hours every six weeks Crohn's disease: Vial: initial, 5 mg/kg IV over two hours at weeks zero, two, and six; maintenance, 5 mg/kg IV over two hours every eight weeks; may be increased to 10 mg/kg in patients who respond and then lose response Plaque psoriasis, psoriatic arthritis, ulcerative colitis: Vial: initial, 5 mg/kg IV over two hours at weeks zero, two, and six; maintenance, 5 mg/kg IV over two hours every eight weeks Rheumatoid arthritis: Vial: initial, 3 mg/kg IV over two hours at weeks zero, two, and six; maintenance, 3 mg/kg IV over two hours every eight weeks; may be increased to 10 mg/kg IV over two hours every eight weeks or 3 mg/kg IV over two hours every four weeks if incomplete response; all in combination with methotrexate	Crohn's disease, ulcerative colitis (six years of age and older): Vial: initial, 5 mg/kg IV over two hours at weeks zero, two and six; maintenance, 5 mg/kg IV over two hours every eight weeks	Single use vial: 100 mg
Leflunomide	Rheumatoid arthritis: Tablet: Use a loading dose of 100 mg once daily for three days only if the patient is not high risk for leflunomide-associated hepatotoxicity (e.g., taking concomitant methotrexate) or myelosuppression (e.g., taking concomitant immunosuppressants); maintenance, 20 mg once daily	Safety and efficacy in the pediatric population have not been established.	Tablet: 10 mg 20 mg
Sarilumab	Rheumatoid arthritis: Prefilled syringe: initial and maintenance, 200 mg SC every two weeks; do not initiate if ANC is less than 2,000/mm^3, platelets are less than 150,000/mm^3, or if ALT or AST are greater than 1.5 times ULN	Safety and efficacy in the pediatric population have not been established.	Prefilled syringe: 150 mg/1.14 mL 200 mg/1.14 mL
Secukinumab	Ankylosing Spondylitis: Injection: with a loading dosage, 150 mg at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter; without a loading dosage, 150 mg every 4 weeks; if a patient continues to have active AS, consider a dosage of 300 mg every 4 weeks Enthesitis-Related Arthritis: Injection: ≥15 kg and <50 kg, 75 mg; ≥50 kg, 150 mg administered by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by dosing every 4 weeks Non-Radiographic Axial Spondyloarthritis: Injection: with a loading dosage, 150 mg at	Enthesitis-Related Arthritis in patients four years of age and older: Injection: ≥15 kg and <50 kg, 75 mg; ≥50 kg, 150 mg administered by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by dosing every 4 weeks Plaque Psoriasis in patients six years of age and older:	Pen injector: 150 mg/mL Prefilled syringe: 150 mg/mL

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter; without a loading dosage, 150 mg every 4 weeks Plaque Psoriasis, Psoriatic Arthritis: Injection: 300 mg by subcutaneous injection (two injections of 150 mg) at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks; for some patients, a dose of 150 mg may be acceptable	Injection: <50 kg, 75 mg; ≥50 kg, 150 mg administered by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by dosing every 4 weeks Psoriatic Arthritis in patients two years of age and older: Injection: ≥15 kg and <50 kg, 75 mg; ≥50 kg, 150 mg administered by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by dosing every 4 weeks	
Sulfasalazine	Rheumatoid arthritis: Delayed-release tablet: 2 grams daily in two evenly divided doses Ulcerative colitis: Delayed-release tablet, tablet: initial, 3 to 4 grams daily in evenly divided doses with dosage intervals not exceeding eight hours; maintenance, 2 grams daily	Juvenile rheumatoid arthritis in patients ≥6 years of age: Delayed-release tablet: 30 to 50 mg/kg of body weight daily in two evenly divided doses; maximum, 2 grams/day Ulcerative colitis in patients ≥6 years of age: Delayed-release tablet, tablet: initial, 40 to 60 mg/kg body weight in each 24-hour period, divided into 3 to 6 doses; maintenance, 30 mg/kg body weight in each 24-hour period, divided into 4 doses	Delayed-release tablet: 500 mg Tablet: 500 mg
Tocilizumab	Cytokine release syndrome (due to chimeric antigen receptor T-cell therapy): Vial: 8 mg/kg IV for patients ≥30 kg; 12 mg/kg for patients <30 kg; maximum, 800 mg per dose; if clinical improvement does not occur after the first dose, up to three additional doses may be administered (with at least an 8-hour interval between consecutive doses) Giant cell arteritis: Prefilled syringe: 162 mg SC every week (in combination with a tapering course of glucocorticoids)	Cytokine release syndrome (due to chimeric antigen receptor T-cell therapy) in patients two years of age and older: Vial: 8 mg/kg IV for patients ≥30 kg; 12 mg/kg for patients <30 kg; maximum, 800 mg per dose; if clinical improvement does not occur after the first	Prefilled syringe: 162 mg/0.9 mL Single use vial: 80 mg/4 mL 200 mg/10 mL 400 mg/20 mL

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	Vial: 6 mg/kg every four weeks; maximum, 600 mg per infusion (in combination with a tapering course of glucocorticoids) Rheumatoid arthritis: Prefilled syringe: initial and maintenance (<100 kg), 162 mg SC every other week, followed by 162 mg SC every week; (≥100 kg), 162 mg SC every week Vial: initial, 4 mg/kg IV every four weeks as a 60 minute infusion; maintenance, dose may be increased to 8 mg/kg IV every four weeks; maximum, 800 mg/infusion Slowing the rate of decline in pulmonary function in adult patients with Systemic Sclerosis-Associated Interstitial Lung Disease: Prefilled syringe: 162 mg SC every week	dose, up to three additional doses may be administered (with at least an 8-hour interval between consecutive doses) Polyarticular juvenile idiopathic arthritis (two years of age and older): Prefilled syringe: initial and maintenance (<30 kg), 162 mg SC every three weeks; (≥30 kg), 162 mg SC every two weeks Vial: initial and maintenance (<30 kg), 10 mg/kg IV every four weeks as a 60 minute infusion; (≥30 kg), 8 mg/kg IV every four weeks as a 60 minute infusion Systemic juvenile idiopathic arthritis (two years of age and older): Prefilled syringe: initial and maintenance (<30 kg), 162 mg SC every two weeks; (≥30 kg), 162 mg SC every week Vial: initial and maintenance (<30 kg), 12 mg/kg IV every two weeks as a 60 minute infusion; (≥30 kg), 8 mg/kg IV every two weeks as a 60 minute infusion	
Tofacitinib	Ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis: Tablet: 5 mg by mouth twice daily XR tablet: 11 mg once daily Ulcerative colitis: Tablet: 10 mg twice daily for at least eight weeks; followed by 5 or 10 mg twice	Polyarticular juvenile idiopathic arthritis (two years of age and older): Tablet, oral solution: 10 kg ≤ body weight <20 kg, 3.2 mg (3.2 mL oral solution) twice daily; 20 kg ≤	Extended-release tablet: 11 mg 22 mg Tablet: 5 mg 10 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	daily, depending on therapeutic response XR tablet: 22 mg once daily for at least eight weeks; followed by 11 or 22 mg once daily, depending on therapeutic response	body weight <40 kg, 4 mg (4 mL oral solution) twice daily; body weight ≥40 kg, 5 mg (one 5 mg tablet or 5 mL oral solution) twice daily	Oral solution: 1 mg/mL
Upadacitinib	Ankylosing spondylitis, non-radiographic axial spondyloarthritis, psoriatic arthritis, rheumatoid arthritis: XR tablet: 15 mg by mouth once daily Atopic dermatitis: XR tablet: initial, 15 mg by mouth once daily; may increase to a maximum of 30 mg once daily; do not exceed 15 mg once daily in patients ≥65 years of age Ulcerative colitis: XR tablet: initial,45 mg by mouth once daily for eight weeks; maintenance, 15 mg once daily with a maximum of 30 mg once daily	Atopic dermatitis in patients ≥12 years of age weighing ≥40 kg: XR tablet: initial, 15 mg by mouth once daily; may increase to a maximum of 30 mg once daily	Extended-release tablet: 15 mg 30 mg 45 mg
Voclosporin	Lupus nephritis: Capsule: 23.7 mg twice a day (Use in combination with mycophenolate mofetil and corticosteroids)	Safety and efficacy in the pediatric population have not been established.	Capsule: 7.9 mg

IV=intravenously, SC=subcutaneously
JIA=juvenile Idiopathic Arthritis, NOMID=Neonatal-Onset Multisystem Inflammatory Disease

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the disease-modifying antirheumatic agents are summarized in Table 17.

Table 17. Comparative Clinical Trials with the Disease-Modifying Antirheumatic Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Alopecia Areata				
King et al.[53] (2022) BRAVE-AA1 and BRAVE-AA2 Baricitinib 4 mg once daily vs baricitinib 2 mg once daily vs placebo	2 DB, MC, PC, PG, RCTs Adults with severe alopecia areata with a Severity of Alopecia Tool (SALT) score of 50 or higher (range, 0 [no scalp hair loss] to 100 [complete scalp hair loss])	N=654 (AA1) N=546 (AA2) 36 weeks	Primary: SALT score of 20 or less at week 36 Secondary: There were 10 key secondary outcomes analyzed in a graphical scheme	Primary: The estimated percentage of patients with a SALT score of 20 or less at week 36 was 38.8% with 4-mg baricitinib, 22.8% with 2-mg baricitinib, and 6.2% with placebo in BRAVE-AA1 and 35.9%, 19.4%, and 3.3%, respectively, in BRAVE-AA2. In BRAVE-AA1, the difference between 4-mg baricitinib and placebo was 32.6 percentage points (95% CI, 25.6 to 39.5), and the difference between 2-mg baricitinib and placebo was 16.6 percentage points (95% CI, 9.5 to 23.8) (P<0.001 for each dose vs. placebo). In BRAVE-AA2, the corresponding values were 32.6 percentage points (95% CI, 25.6 to 39.6) and 16.1 percentage points (95% CI, 9.1 to 23.2) (P<0.001 for each dose vs. placebo). Secondary: Secondary outcomes for baricitinib at a dose of 4 mg but not at a dose of 2 mg generally favored baricitinib over placebo.
Atopic Dermatitis				
Bieber et al.[54] (2021) JADE COMPARE Abrocitinib 100 mg orally once daily vs abrocitinib 200 mg orally once daily	DB, MC, PC, RCT Adults with moderate-to-severe atopic dermatitis who were receiving background topical therapy	N=838 16 weeks	Primary: IGA response (defined as a score of 0 or 1 on the IGA, with an improvement of ≥2 points from baseline) and an EASI-75 response (defined as ≥75% improvement from baseline in the	Primary: An IGA response at week 12 was observed in 48.4% of patients in the 200 mg abrocitinib group, 36.6% in the 100 mg abrocitinib group, 36.5% in the dupilumab group, and 14.0% in the placebo group (P<0.001 for both abrocitinib doses vs. placebo); an EASI-75 response at week 12 was observed in 70.3%, 58.7%, 58.1%, and 27.1%, respectively (P<0.001 for both abrocitinib doses vs. placebo). Secondary: The weighted difference in the percentage of patients who had an itch response at week two between the 200 mg abrocitinib group and the placebo group was 34.9 percentage points (95% CI, 26.0 to 43.7) and that

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Study Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td>vs

dupilumab 300 mg subcutaneously every other week (after a loading dose of 600 mg)

vs

placebo</td><td></td><td></td><td>score on the EASI) at week 12

Secondary:
Itch response (defined as ≥4-point improvement from baseline in the score on the PP-NRS) at week two and IGA and EASI-75 responses at week 16</td><td>between the 100 mg abrocitinib group and the placebo group was 17.9 percentage points (95% CI, 9.5 to 26.3) (P<0.001 for both comparisons). The weighted difference in the percentage of patients who had an itch response at week two between the 200 mg abrocitinib group and the dupilumab group was 22.1 percentage points favoring this dose of abrocitinib (95% CI, 13.5 to 30.7; P<0.001). The weighted difference between the 100 mg abrocitinib group and the dupilumab group was 5.2 percentage points (95% CI, –2.9 to 13.4; P=0.20), indicating no significant difference between the trial groups for this dose of abrocitinib.

The weighted difference in the percentage of patients who had an IGA response at week 16 between the 200 mg abrocitinib group and the placebo group was 35.0 percentage points (95% CI, 26.3 to 43.7) and that between the 100 mg abrocitinib group and the placebo group was 22.1 percentage points (95% CI, 13.7 to 30.5) (P<0.001 for both comparisons). The weighted difference in the percentage of patients who had an IGA response at week 16 between the 200 mg abrocitinib group and the dupilumab group was 9.4 percentage points (95% CI, 0.4 to 18.5), and the difference between the 100 mg abrocitinib group and the dupilumab group was –3.5 percentage points (95% CI, –12.2 to 5.2).

The weighted difference in the percentage of patients who had an EASI-75 response at week 16 between the 200 mg abrocitinib group and the placebo group was 40.4 percentage points (95% CI, 30.4 to 50.4; P<0.001) and that between the 100 mg abrocitinib group and the placebo group was 29.7 percentage points (95% CI, 19.5 to 39.9; P<0.001). The weighted difference in the percentage of patients who had an EASI-75 response at week 16 between the 200 mg abrocitinib group and the dupilumab group was 5.5 percentage points (95% CI, –3.1 to 14.1), and the difference between the 100 mg group and the dupilumab group was –5.1 percentage points (95% CI, –13.9 to 3.7). Therefore, both doses of abrocitinib were not significantly different from dupilumab with respect to an EASI-75 response at week 16.</td></tr>
<tr><td>Shi et al.[55]
2022
JADE EXTEND</td><td>Extension study

Patients with moderate-to-severe</td><td>N=203

12 weeks</td><td>Primary:
Efficacy response

Secondary:</td><td>Primary:
Efficacy responses with abrocitinib among prior dupilumab responders:<table><tr><td></td><td>Abrocitinib 100 mg</td><td>Abrocitinib 200 mg</td></tr><tr><td>IGA 0/1 responses, n/N</td><td>40/52 (76.9%, 65.5-88.4)</td><td>25/30 (83.3%, 70.0-96.7)</td></tr></table></td></tr>
</table>

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Study Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr>
<td>Abrocitinib 200 mg or 100 mg orally once daily</td>
<td>atopic dermatitis received abrocitinib 200 mg or 100 mg once daily in JADE EXTEND (phase 3 extension) after dupilumab in double-blind, placebo-controlled phase 3 JADE COMPARE</td>
<td></td>
<td>Not reported</td>
<td>
<table>
<tr><td>(%, 95% CI)</td><td></td><td></td></tr>
<tr><td>EASI-75 responses, n/N (%, 95% CI)</td><td>83/92 (90.2%, 84.1-96.3)</td><td>43/46 (93.5%, 86.3-100.0)</td></tr>
<tr><td>EASI-90 responses, n/N (%, 95% CI)</td><td>43/55 (78.2%, 67.3-89.1)</td><td>24/29 (82.8%, 69.0-96.5)</td></tr>
<tr><td>PP-NRS4 responses, n/N (%, 95% CI)</td><td>62/76 (81.6%, 72.9-90.3)</td><td>35/39 (89.7%, 80.2-99.3)</td></tr>
<tr><td>PP-NRS 0/1 responses, n/N (%, 95% CI)</td><td>17/32 (53.1%, 35.8-70.4)</td><td>14/19 (73.7%, 53.9-93.5)</td></tr>
</table>
Efficacy responses with abrocitinib among prior dupilumab nonresponders:
<table>
<tr><td></td><td>Abrocitinib 100 mg</td><td>Abrocitinib 200 mg</td></tr>
<tr><td>IGA 0/1 responses, n/N (%, 95% CI)</td><td>25/71 (35.2%, 24.1-46.3)</td><td>17/36 (47.2%, 30.9-63.5)</td></tr>
<tr><td>EASI-75 responses, n/N (%, 95% CI)</td><td>21/31 (67.7%, 51.3-84.2)</td><td>16/20 (80.0%, 62.5-97.5)</td></tr>
<tr><td>EASI-90 responses, n/N (%, 95% CI)</td><td>27/68 (39.7%, 28.1-51.3)</td><td>22/37 (59.5%, 43.6-75.3)</td></tr>
<tr><td>PP-NRS4 responses, n/N (%, 95% CI)</td><td>17/45 (37.8%, 23.6-51.9)</td><td>17/22 (77.3%, 59.8-94.8)</td></tr>
<tr><td>PP-NRS 0/1 responses, n/N (%, 95% CI)</td><td>23/89 (25.8%, 16.7-34.9)</td><td>18/42 (42.9%, 27.9-57.8)</td></tr>
</table>
Secondary:
Not reported
</td>
</tr>
<tr>
<td>Simpson et al.[56] (2020)
JADE MONO-1

Abrocitinib 100 mg orally once daily

vs

abrocitinib 200 mg orally once daily

vs</td>
<td>DB, MC, PC, RCT

Patients (aged ≥12 years) with moderate-to-severe atopic dermatitis (IGA score ≥3, EASI score ≥16, percentage of BSA affected ≥10%, and Peak Pruritus Numerical Rating Scale score ≥4) with a bodyweight of 40</td>
<td>N=387

12 weeks</td>
<td>Primary:
IGA response (defined as a score of 0 or 1 on the IGA, with an improvement of ≥2 points from baseline) and an EASI-75 response (defined as ≥75% improvement from baseline in the score on the EASI) at week 12</td>
<td>Primary:
Of the patients with available data for the coprimary endpoints at week 12, the proportion of patients who had achieved an IGA response was higher in the abrocitinib 100 mg group than in the placebo group (37 [24%] of 156 patients vs six [8%] of 76 patients; P=0.0037) and in the abrocitinib 200 mg group compared with the placebo group (67 [44%] of 153 patients vs six [8%] of 76 patients; P<0.0001). Of the patients with available data for the coprimary endpoints at week 12, compared with the placebo group, the proportion of patients who had achieved an EASI-75 response was significantly higher in the abrocitinib 100 mg group (62 [40%] of 156 patients vs nine [12%] of 76 patients; P<0.0001) and abrocitinib 200 mg group (96 [63%] of 153 patients vs nine [12%] of 76 patients; P<0.0001).

Secondary:</td>
</tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	kg or more		Secondary: Safety	Adverse events were reported in 108 (69%) of 156 patients in the abrocitinib 100 mg group, 120 (78%) of 154 patients in the abrocitinib 200 mg group, and 44 (57%) of 77 patients in the placebo group. Serious adverse events were reported in five (3%) of 156 patients in the abrocitinib 100 mg group, five (3%) of 154 patients in the abrocitinib 200 mg group, and three (4%) of 77 patients in the placebo group. No treatment-related deaths were reported.
Silverberg et al.[57] (2020) JADE MONO-2 Abrocitinib 100 mg orally once daily vs abrocitinib 200 mg orally once daily vs placebo	DB, MC, PC, RCT Patients (aged ≥12 years) with moderate-to-severe atopic dermatitis (IGA score ≥3, EASI score ≥16, percentage of BSA affected ≥10%, and Peak Pruritus Numerical Rating Scale score ≥4) with a bodyweight of 40 kg or more	N=391 12 weeks	Primary: IGA response (defined as a score of 0 or 1 on the IGA, with an improvement of ≥2 points from baseline) and an EASI-75 response (defined as ≥75% improvement from baseline in the score on the EASI) at week 12 Secondary: Safety	Primary: Among patients with data available at week 12 for the efficacy analysis, 59 of 155 patients in the 200 mg group (38.1%), 44 of 155 in the 100 mg group (28.4%), and 7 of 77 in the placebo group (9.1%) had an IGA response; differences from placebo were 28.7% (95% CI, 18.6% to 38.8%; P<0.001) for the 200 mg group and 19.3% (95% CI, 9.6% to 29.0%; P<0.001) for the 100 mg group. At week 12, 94 of 154 patients in the 200 mg group (61.0%), 69 of 155 in the 100 mg group (44.5%), and 8 of 77 in the placebo group (10.4%) had an EASI-75 response; differences from placebo were 50.5% (95% CI, 40.0% to 60.9%; P<0.001) for the 200 mg group and 33.9% (95% CI, 23.3% to 44.4%; P<0.001) for the 100 mg group. Secondary: Adverse events were reported for 102 patients (65.8%) in the 200 mg group, 99 (62.7%) in the 100 mg group, and 42 (53.8%) in the placebo group; serious adverse events were reported for 2 patients (1.3%) in the 200 mg group, 5 (3.2%) in the 100 mg group, and 1 (1.3%) in the placebo group. Decreases in platelet count (2 [1.3%]) and laboratory values indicating thrombocytopenia (5 [3.2%]) were reported in the 200 mg group.
Reich et al.[58] (2022) JADE DARE Abrocitinib 200 mg by mouth per day vs	AC, DB, MC, RCT Adults with moderate-to-severe atopic dermatitis who required systemic therapy or had inadequate response to topical	N=727 26 weeks	Primary: Response based on achieving a 4 point or higher improvement in Peak Pruritus Numerical Rating Scale (PP-NRS4) at week 2 and a 90%	Primary: The proportion of patients who reached the primary endpoint of PP-NRS4 at week two was higher in the abrocitinib group than in the dupilumab group (172 [48%] of 357; 95% CI, 43.0 to 53.4 vs 93 [26%] of 364; 21.1 to 30.0). The difference between the abrocitinib and dupilumab groups was 22.6% (95% CI, 15.8 to 29.5; P<0.0001). The proportion of patients who reached the other primary endpoint, EASI-90 at week four, was also higher in the abrocitinib group than in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dupilumab 300 mg subcutaneous every 2 weeks	medications		or better improvement in Eczema Area and Severity Index (EASI-90) at week 4 Secondary: Response based on achieving EASI-90 at week 16; safety	dupilumab group (101 [29%] of 354; 95% CI, 23.8 to 33.2 vs 53 [15%] of 364; 10.9% to 18.2%), and the between-group difference was 14.1% (8.2 to 20.0; P<0.0001). Secondary: In addition, 194 (54%) of 357 patients (49.2 to 59.5) treated with abrocitinib reached the key secondary endpoint of EASI-90 at week 16, compared with 151 (42%) of 360 patients (36.8 to 47.0) in the dupilumab group. This resulted in a between-group difference of 12.5% (5.3 to 19.7), which achieved both non-inferiority (lower bound of the 95% CI interval higher than −10%) and superiority (P=0.0008). The 727 patients who made up the safety population had 1417 adverse events (817 with abrocitinib and 600 with dupilumab) during the 26-week treatment period and the 28-day safety follow-up after the last dose of study medication. More patients who received abrocitinib than dupilumab had adverse events (268 [74%] of 362 vs 239 [65%] of 365); the proportions of patients who had adverse events that were serious, severe, or led to study discontinuation were similar between the two treatment groups.
Reich et al.[59] (2021) AD Up Upadacitinib 15 mg once daily vs upadacitinib 30 mg once daily vs placebo once daily All in combination	DB, MC, PC, RCT Adults (18 to 75 years of age) and adolescents (12 to 17 years of age) with chronic atopic dermatitis that was moderate to severe (≥10% of BSA, EASI score of ≥16, validated Investigator's Global Assessment for atopic dermatitis [vIGA-AD] score of ≥3, and weekly	N=901 16 weeks	Primary: Proportion of patients who had EASI-75 and the proportion of patients who had achieved a vIGA-AD response (defined as a vIGA-AD score of 0 [clear] or 1 [almost clear] with ≥2 grades of improvement from baseline) at week 16	Primary: At week 16, the proportion of patients who had achieved EASI-75 was higher in the upadacitinib 15 mg group (194 [65%] of 300 patients) and the upadacitinib 30 mg group (229 [77%] of 297 patients) than the placebo group (80 [26%] of 304 patients; adjusted difference in EASI-75 response rate vs placebo, 38.1%; 95% CI, 30.8 to 45.4 for the upadacitinib 15 mg group and 50.6%; 95% CI, 43.8 to 57.4 for the upadacitinib 30 mg group; P<0.0001 for both doses). The proportion of patients who had achieved a vIGA-AD response at week 16 was higher in the upadacitinib 15 mg group (119 [40%] patients) and upadacitinib 30 mg group (174 [59%] patients) than the placebo group (33 [11%] patients; adjusted difference in vIGA-AD response vs placebo, 28.5%; 95% CI, 22.1 to 34.9 for the upadacitinib 15 mg group and 47.6%; 95% CI, 41.1 to 54.0 for the upadacitinib 30 mg group; P<0.0001 for both doses).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
with topical corticosteroids	average Worst Pruritus Numerical Rating Scale score of ≥4 at baseline)		Secondary: Safety	Secondary: The most frequently reported treatment-emergent adverse events (≥5% in any treatment group) were acne, nasopharyngitis, upper respiratory tract infection, oral herpes, elevation of blood creatine phosphokinase levels, headache, and atopic dermatitis. The incidence of acne was higher in the upadacitinib 15 mg (30 [10%] of 300 patients) and upadacitinib 30 mg (41 [14%] of 297 patients) groups than the placebo group (six [2%] of 304 patients). The incidence of adverse events leading to discontinuation of study drug (four [1%] patients in the upadacitinib 15 mg group, four [1%] patients in the upadacitinib 30 mg group, and seven [2%] patients in the placebo group) and serious adverse events (seven [2%] patients, four [1%] patients, and nine [3%] patients) were similar among treatment groups. No deaths were reported in any treatment group.
Guttman-Yassky et al.[60] (2021) Measure Up 1 and Measure Up 2 Upadacitinib 15 mg once daily vs upadacitinib 30 mg once daily vs placebo once daily	Replicate DB, MC, PC, RCTs Adults (18 to 75 years of age) and adolescents (12 to 17 years of age) with chronic atopic dermatitis that was moderate to severe (≥10% of BSA, EASI score of ≥16, validated Investigator's Global Assessment for atopic dermatitis [vIGA-AD] score of ≥3, and weekly average Worst Pruritus Numerical Rating Scale score of ≥4 at baseline)	N=847 (Measure Up 1) N=836 (Measure Up 2) 16 weeks	Primary: Proportion of patients who had EASI-75 and the proportion of patients who had achieved a vIGA-AD response (defined as a vIGA-AD score of 0 [clear] or 1 [almost clear] with ≥2 grades of improvement from baseline) at week 16 Secondary: Safety	Primary: The proportion of patients who had achieved EASI-75 at week 16 was higher in the upadacitinib 15 mg (196 [70%] of 281 patients) and upadacitinib 30 mg (227 [80%] of 285 patients) groups than the placebo group (46 [16%] of 281 patients) in Measure Up 1 (adjusted difference in EASI-75 response rate vs placebo, 53.3%; 95% CI, 46.4 to 60.2 for the upadacitinib 15 mg group; 63.4%; 95% CI, 57.1 to 69.8 for the upadacitinib 30 mg group) and Measure Up 2 (166 [60%] of 276 patients in the upadacitinib 15 mg group and 206 [73%] of 282 patients in the upadacitinib 30 mg group vs 37 [13%] of 278 patients in the placebo group; adjusted difference in EASI-75 response rate vs placebo, 46.9%; 95% CI, 39.9 to 53.9 for the upadacitinib 15 mg group; 59.6%; 95% CI, 53.1 to 66.2 for the upadacitinib 30 mg group). The proportion of patients who achieved a vIGA-AD response at week 16 was higher in the upadacitinib 15 mg (135 [48%] patients) and upadacitinib 30 mg (177 [62%] patients) groups than the placebo group (24 [8%] patients) in Measure Up 1 (adjusted difference in vIGA-AD response rate vs placebo, 39.8%; 95% CI, 33.2 to 46.4 for the upadacitinib 15 mg group; 53.6%; 95% CI, 47.2 to 60.0 for the upadacitinib 30 mg group) and Measure Up 2 (107 [39%] patients in the upadacitinib 15 mg group and 147 [52%] patients in the upadacitinib 30 mg group vs 13 [5%] patients in the placebo group; adjusted difference in vIGA-AD response rate vs placebo, 34.0%; 95% CI, 27.8 to 40.2 for the upadacitinib 15 mg

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				group; 47.4%; 95% CI, 41.0 to 53.7 for the upadacitinib 30 mg group). Secondary: The most frequently reported treatment-emergent adverse events were acne (19 [7%] of 281 patients in the upadacitinib 15 mg group, 49 [17%] of 285 patients in the upadacitinib 30 mg group, and six [2%] of 281 patients in the placebo group in Measure Up 1; 35 [13%] of 276 patients in the upadacitinib 15 mg group, 41 [15%] of 282 patients in the upadacitinib 30 mg group, and six [2%] of 278 patients in the placebo group in Measure Up 2), upper respiratory tract infection (25 [9%] patients, 38 [13%] patients, and 20 [7%] patients; 19 [7%] patients, 17 [16%] patients, and 12 [4%] patients), nasopharyngitis (22 [8%] patients, 33 [12%] patients, and 16 [6%] patients; 16 [6%] patients, 18 [6%] patients, and 13 [5%] patients), headache (14 [5%] patients, 19 [7%] patients, and 12 [4%] patients; 18 [7%] patients, 20 [7%] patients, and 11 [4%] patients), elevation in creatine phosphokinase levels (16 [6%] patients, 16 [6%] patients, and seven [3%] patients; nine [3%] patients, 12 [4%] patients, and five [2%] patients), and atopic dermatitis (nine [3%] patients, four [1%] patients, and 26 [9%] patients; eight [3%] patients, four [1%] patients, and 26 [9%] patients).
Blauvelt et al.[61] (2021) Heads Up Upadacitinib 30 mg orally once daily vs dupilumab subcutaneous 300 mg every other week	DB, MC, RCT Adults 18 to 75 years of age with moderate-to-severe atopic dermatitis who were candidates for systemic therapy	N=692 24 weeks	Primary: EASI75 at week 16 Secondary: Efficacy endpoints at 16 and 24 weeks	Primary: At week 16, 247 patients receiving upadacitinib (71.0%) and 210 patients receiving dupilumab (61.1%) achieved EASI75 (P=0.006). Secondary: All ranked secondary end points also demonstrated the superiority of upadacitinib vs dupilumab, including improvement in Worst Pruritus NRS as early as week one (mean, 31.4% vs 8.8%; P<0.001), achievement of EASI75 as early as week two (152 vs 60; P<0.001), and achievement of EASI100 at week 16 (97 vs 26; P<0.001). A greater proportion of upadacitinib-treated than dupilumab-treated patients achieved EASI75 (223 of 348 [64.2%] vs 205 of 344 [59.2%]) at week 24. Upadacitinib-treated patients also had greater improvement from baseline in mean Worst Pruritus NRS than dupilumab-treated patients at week 24 (63.1% vs 54.7%).
Axial Spondyloarthritis (Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis)				
van der Heijde et	DB, MC, RCT	N=315	Primary:	Primary:

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al.[62] (2006) Adalimumab 40 mg every other week vs placebo Patients were allowed to continue MTX, NSAIDs, prednisone or prednisone equivalent and SSZ.	Patients ≥18 years of age with a diagnosis of AS based on the modified New York criteria with active disease BASDAI score ≥4, a total back pain score ≥4 by VAS (VAS, 0 to 10 cm) or a duration of morning stiffness ≥1 hour	24 weeks	ASAS 20 response at week 12 Secondary: ASAS 20 response at week 24, measures of disease activity, spinal mobility and function, and ASAS partial remission	An ASAS 20 response was attained in 58% of participants taking adalimumab vs 21% of participants taking placebo at week 12 (P<0.001). Secondary: A significantly greater ASAS 20 response was also noted at week 24 with adalimumab vs placebo (52 vs 18%; P<0.001). Adalimumab, compared to placebo, resulted in a significant improvement in other measures of disease activity such as a 50% improvement in BASDAI at week 12 (45 vs 16%; P<0.001) which was sustained through week 24 (42 vs 15%; P<0.001). ASAS 5/6 and ASAS 40 responses were attained in 49 vs 13% and 40 vs 13% of adalimumab vs placebo patients at week 12 (P<0.001) and 45 vs 12% and 39 vs 13% at week 24 (P<0.001), respectively. Partial remission was achieved in 21 vs 4% at week 12 and 22 vs 6% at week 24 in the adalimumab and placebo groups, respectively (P<0.001).
Landewe et al.[63] (2013) RAPID-axSpA Certolizumab 400 mg at weeks 0, 2, and 4 then 200 mg every 2 weeks (CZP 200 mg) vs certolizumab 400 mg at weeks 0, 2, and 4 then 400 mg every 2 weeks (CZP 400 mg) vs	DB, MC, PC, PG, RCT Patients ≥18 years of age with a diagnosis of AS based on the ASAS criteria, with active disease BASDAI score ≥4, spinal pain ≥4, CRP>7.9 mg/L and/or sacroiliitis on MRI, chronic back pain ≥3 months, inadequate response or intolerance to ≥1 NSAID or ≥2 weeks each for ≥2 NSAIDs in the last ≥30 days	N=325 24 weeks	Primary: ASAS 20 response at week 12 Secondary: ASAS 20 response at week 24, change from baseline in BASFI, BASDAI, and BASMI linear at week 12 and 24	Primary: A greater proportion of patients treated with CZP 200 mg every two weeks (57.7%) and CZP 400 mg every four weeks (63.6%) achieved ASAS 20 response at week 12 compared to placebo (38.3%; P=0.004 and P<0.001, respectively). Secondary: The difference in ASAS 20 response was sustained through week 24 in both CZP treatment groups (P<0.001). Improvements in BASFI scores from baseline were greater in patients treated with CZP 200 mg every two weeks and CZP 400 mg every four weeks compared to placebo at 12 weeks (-2.0 and -2.0 vs -0.5; P<0.001) and at 24 weeks (-2.2 and -2.2 vs -0.4; P<0.001 for both comparisons), respectively. Improvements in BASDAI scores from baseline were greater in patients treated with CZP 200 mg every two weeks and CZP 400 mg every four weeks compared to placebo at 12 weeks (-2.8 and -2.8 vs -1.2; P<0.001)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo Patients receiving placebo who did not achieve an ASAS 20 response at weeks 14 and 16 were randomized to active treatment at week 16. Concurrent DMARDs (SSZ and MTX) were allowed.				and at 24 weeks (-3.1 and -3.0 vs -1.1; P<0.001 for both comparisons), respectively. Improvements in BASMI linear scores from baseline were greater in patients treated with CZP 200 mg every two weeks and CZP 400 mg every four weeks compared to placebo at 12 weeks (-0.6 and -0.5 vs -0.1; P<0.001 and P<0.05, respectively) and at 24 weeks (-0.5 and -0.5 vs -0.1; P<0.001 for both comparisons), respectively.
Van der Heijde et al.[64] (2017) RAPID-axSpA extension study Certolizumab pegol 200 mg every 2 weeks or certolizumab pegol 400 mg every 4 weeks Placebo-controlled to week 24, dose-blind to week 48 and OL to week 204	OL, extension study Patients ≥18 years of age with chronic back pain of ≥3 months and fulfilling the ASAS criteria for axSpA with active disease	N=218 4 years	Primary: ASAS 20, ASAS 40, ASDAS, BASDAI, BASFI and BASMI scores and remission. Secondary: Not reported	Primary: At week 204 of certolizumab pegol-randomized patients, ASAS 20 and ASAS 40 responses were achieved by 54.1 (44.0%) and 83.7 (68.1%), respectively, showing sustained efficacy from week 24. Responses were comparable between the AS and nr-axSpA subpopulations Responses were maintained across the continuous disease activity outcomes BASDAI and ASDAS, and in measures of spinal mobility (BASMI-linear) and function (BASFI). Although AS patients tended to have higher BASFI scores than nr-axSpA patients at baseline (mean at baseline: AS: 5.6; nr-axSpA: 5.0) and week 204 [AS: 3.0; nr-axSpA: 2.2], the mean change from baseline was similar [week 204: AS: -2.6; nr-axSpA: -2.7]. The proportion of certolizumab pegol -randomized patients in remission, as ASDAS-ID and BASDAI <2 with normal CRP (LOCF), was sustained from week 24 (30.3% for both measures) to week 204 (32.1 and 33.0%, respectively. Partial remission, as ASAS-PR, was achieved by 30.3% of certolizumab pegol-randomized patients at week 24 and 23.4% at week 204 (NRI); 32.4 and 36.5%, respectively,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Gorman et al.[65] (2002) Etanercept 25 mg twice a week vs placebo Patients were allowed to continue stable doses of DMARDs, NSAIDs, and oral corticosteroids.	DB, RCT Patients ≥18 years of age with active inflammatory AS based on the modified New York criteria, despite accepted treatments	N=40 4 months	Primary: Measures of morning stiffness, spinal pain, functioning, patient's global assessment of disease activity, and joint swelling Secondary: Physician's global assessment of disease activity, measures of spinal mobility, scores for enthesitis and peripheral-joint tenderness, ESR and CRP levels, and adverse events	Primary: A response to treatment was detected in 80% of individuals receiving etanercept as opposed to 30% of individuals receiving placebo (P=0.004). Primary endpoints were reported as follows for the etanercept and placebo groups, respectively: duration of morning stiffness, 25.0±78.9 vs 60.0±65.0 minutes (P<0.001); scores for nocturnal spinal pain (0=none to 100=most severe), 15.0±24.3 vs 38.0±27.8 (P<0.001); mean swollen joint scores (0=none to 3=severe), 1.6±3.8 vs 3.7±7.6 (P=0.17); patient's global assessment of disease activity (0=none to 5=very severe), 2.0±0.6 vs 3.0±0.9 (P<0.001); and the BASFI scores (0=none to 10=severe limitations), 2.2±2.1 vs 3.1±3.0 (P<0.001). Secondary: Differences in a number of secondary outcomes did reach statistical significance among those taking etanercept compared to those taking placebo including, physician's global assessment of disease activity (23.0±10.6; P<0.001), chest expansion (3.5±1.9 vs 2.9±1.7 cm; P=0.006), Modified Newcastle Enthesis Index, which is a measure of 17 enthesis on a four point pain scale (0.0±3.0 vs 1.5±8.0; P=0.001), ESR level (8.5±12.8 vs 16.5±18.7 mm/hour; P<0.001) and CRP level (0.7±1.1 vs 2.0±2.8 mg/dL; P=0.003). Injection site reactions and minor infections were the most commonly reported adverse events. The incidence in overall adverse events or specific events did not differ significantly.
Calin et al.[66] (2004) Etanercept 25 mg twice a week vs placebo	DB, MC, RCT Patients 18 to 70 years of age with active AS based on the modified New York criteria	N=84 12 weeks	Primary: ASAS 20 response Secondary: ASAS 50 response, ASAS 70 response, individual components of ASAS, BASDAI,	Primary: ASAS 20 response was found in 60.0% of etanercept patients compared to 23.1% of placebo patients at 12 weeks (P<0.001). Secondary: The etanercept group was associated with the higher rates of ASAS 50 and 70 responses (48.9 and 24.4%) compared to placebo (10.3 and 10.3%) at week 12. However, only the differences in ASAS 50 response reached statistical significance at this assessment point (P<0.001). ASAS 70

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients were allowed to continue stable doses of DMARDs (HCQ, MTX, or SSZ) one NSAID, and oral corticosteroids (≤10 mg prednisone).			acute phase reactants, spinal mobility tests, and safety	response was significantly different between groups up until week eight (28.9% with etanercept vs 7.7% with placebo; P<0.05). The changes in the individual ASAS components were reported as follows for etanercept and placebo: spinal inflammation, 43.3 vs 15.9% (P=0.003); nocturnal and total pain, 43.1 vs 6.2% (P=0.000); patient's global assessment, 37.0 vs 12.6% (P=0.11); functional impairment (BASFI), 35.4 vs 3.4% (P=0.000); BASDAI composite score, 43.6 vs 13.6% (P=0.001); and BASDAI fatigue score, 42.6 vs -4.9% (P=0.000). Injection site reactions occurred more frequently with etanercept compared to placebo (33 vs 15%; P<0.05).
Davis et al.[67] (2008) Etanercept 25 mg twice weekly until week 72, then 50 mg once weekly Stable doses of corticosteroids and NSAIDs were required 2 weeks prior to enrollment; stable doses of HCQ, MTX, or SSZ were required if deemed necessary.	ES, OL Patients 18 to 70 years of age with active AS based on the modified New York criteria	N=257 Up to 192 weeks	Primary: Safety (adverse events, serious adverse events, infections, serious infections, and death) and efficacy (ASAS 20 response, ASAS 5/6 response, and partial remission rates) Secondary: Not reported	Primary: After up to 192 weeks of treatment, the most common adverse events were injection site reactions, headache and diarrhea; no deaths were reported. For etanercept treatment the exposure adjusted serious event rate/patient year was 0.08, the exposure adjusted infection rate/patient year was 1.10, and the exposure adjusted serious infection rate/patient year was 0.02. Injection site reactions were reported in 22.2% of patients, which lead to the withdrawal of 0.4% of patients. A total of 71% of patients were considered ASAS 20 responders at week 96 and 81% of patients were considered responders at week 192. ASAS 5/6 response rates were 61% at week 96 and 60% at week 144. Partial remission response rates were 41% at week 96 and 44% at week 192. Placebo patients who switched to etanercept in the OL extension showed similar rates of efficacy maintenance. Secondary: Not reported
Braun et al.[68] (2011)	DB, MC, RCT	N=566	Primary: Proportion of	Primary: At week 16, significantly greater proportion of patients in the etanercept

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ASCEND Etanercept 50 mg once weekly vs SSZ titrated to 3 g daily in divided doses	Patients ≥18 years of age with active AS (diagnosed according to modified New York criteria) who failed treatment with ≥1 NSAID taken for ≥3 months at the maximum recommended dose and were determined to be candidates for SSZ therapy by the investigators	16 weeks	patients achieving ASAS 20 response at week 16 Secondary: Proportion of patients achieving ASAS 20 response at weeks two, four, eight and 12; proportion of patients achieving ASAS 40 response and ASAS 5/6 response at all time points	group achieved ASAS 20 response compared to the SSZ group (75.9 vs 52.9%; P<0.0001). Secondary: Significantly greater proportion of patients in the etanercept group achieved ASAS 20 response at week two compared to patients in the SSZ group; this difference was maintained throughout the time points (P<0.0001 for all). Significantly greater proportion of patients in the etanercept group achieved ASAS 40 and ASAS 5/6 responses compared to patients in the SSZ group at all time points (P<0.0001 for all). At week 16, a greater proportion of patients achieved ASAS 40 and ASAS 5/6 responses in the etanercept group compared to the SSZ group (59.8 vs 32.6%; P<0.0001 and 45.5 vs 21.2%; P<0.0001, respectively). The rates of adverse events and serious adverse events were similar between the two groups.
Inman et al.[69] (2008) Golimumab 50 mg once every 4 weeks vs golimumab 100 mg once every 4 weeks vs placebo Patients who were on stable doses of HCQ, MTX, NSAID, oral	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of AS and no evidence of active TB and/or no evidence of latent TB on screening	N=356 24 weeks	Primary: ASAS 20 response at week 14 Secondary: Not reported	Primary: Treatment with golimumab with or without a DMARD, compared to placebo with or without a DMARD, resulted in a significant improvement in signs and symptoms as demonstrated by ASAS 20 response at week 14 (59 vs 22%; P≤0.001). All individual components of the ASAS response criteria were significantly improved in the golimumab 50 mg group compared to the placebo group at week 14. Secondary: Not reported

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corticosteroid and/or SSZ were permitted in the study.				
Braun et al.[70] (2002) Infliximab 5 mg/kg at weeks 0, 2 and 6 vs placebo Concurrent use of NSAIDs not exceeding the baseline dose was allowed.	DB, MC, PC, RCT Adult patients (mean age of 40) with AS based on the modified New York criteria with BASDAI score ≥4 and spinal pain score ≥4	N=70 12 weeks	Primary: Improvement from baseline in BASDAI by 50% at week 12 Secondary: Improvement from baseline in spinal pain, BASFI, BASMI, SF-36, CRP, and ESR	Primary: A greater proportion of patients achieved a 50% improvement in BASDAI at week 12 in the infliximab group (53%; 95% CI, 37 to 69) compared to the placebo group (9%; 95% CI, 3 to 22). The difference between the groups was significant starting at week two and continuing through until week 12 (P<0.0001). Secondary: At week 12, the infliximab group had a significant mean improvement from baseline in spinal pain (P<0.0001), BASFI (P<0.0023), BASMI (P<0.0001), CRP (P<0.0001), and ESR (P<0.0001); while there was no significant difference in the placebo group. At 12 weeks, there were significant improvements from baseline in the physical component and mental component of the SF-36 in the infliximab group (P<0.0001); however, only the improvement in the physical component was significantly greater compared to the placebo group (P<0.0001). A greater proportion of patients reported infections in the infliximab group (51%) compared to the placebo group (35%; difference, 16%; 95% CI, -7 to 40; P=0.227). A greater proportion of patients in the infliximab group experienced serious adverse events and were withdrawn from the study compared to the placebo group (3 vs 0; P=0.239).
van der Heijde et al.[71] (2005) ASSERT Infliximab 5 mg/kg at weeks 0, 2, 6, 12 and 18 vs placebo	MC, PC, RCT Adult patients (median age of 40) with AS based on the modified New York criteria for at least three months with a BASDAI score ≥4, spinal pain assessment score ≥4 on a VAS and a	N=279 24 weeks	Primary: Proportion of patients with ASAS 20 at week 24 Secondary: ASAS 40 response, ASAS partial remission, ASAS 5/6, disease activity (BASDAI, night pain, patient's	Primary: After 24 weeks, significantly greater proportion of patients were ASAS 20 responders in the infliximab group (61.2%) compared to the placebo group (19.2%; P<0.001). The difference was significant at week two and continued to week 24. Secondary: Over the 24-week study period, significantly greater proportion of patients were ASAS 40 responders in the infliximab group compared to the placebo group (P<0.001). At 24 weeks 47% of patients were ASAS 40 responders in the infliximab group compared to 12% in the placebo group (P<0.001). Significantly greater proportion of patients treated with

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Concurrent NSAIDs, acetaminophen or tramadol were allowed during the study.	normal chest radiograph within three months, and negative TB screening		global assessment and CRP), physical function (BASFI), range of motion (BASMI), other musculoskeletal assessments (swollen joint count and degree of tenderness) and quality of life (SF-36)	infliximab achieved ASAS 5/6 (49%) compared to placebo treated patients (8%; P<0.001). Significantly greater proportion of patients achieved a partial ASAS response in the infliximab group (22.4%) compared to the placebo group (1.3%; P<0.001). The median improvement in all measures of disease activity (BASDAI, night pain, patient's global assessment and CRP) was significantly greater in the infliximab treated patients compared to placebo treated patients (P<0.001). The patients in the infliximab group had a significantly greater median improvement in BASFI compared to patients in the placebo group (P<0.001). There was a significantly greater median improvement in BASMI in the infliximab group compared to the placebo group (P=0.019). The infliximab treated patients had a significantly greater median improvement in swollen joint count compared to the placebo treated patients (P=0.019). There was a significantly greater improvement in the physical component of the SF-36 in the infliximab group compared to the placebo group (P<0.001); there was no significant difference in the mental component (P=0.547). Compared to patients in the placebo group, a greater proportion of patients in the infliximab group experienced at least on adverse event (82.2 vs 72.0%), reported at least one infection (42.6 vs 36.0%) and had severe adverse reactions (3.5 vs 2.7%). Of the adverse events that occurred in at least 5% of patients in either group, the rates of pharyngitis, rhinitis, and increased liver enzymes were greater in the infliximab group.
Machado et al.[72] (2013) Infliximab vs etanercept vs adalimumab	MA RCTs of patients with AS based on the modified New York criteria	N=2,820 (18 trials) 6 to 104 weeks	Primary: Proportion of patients with ASAS 20 at 12- or 14 weeks and at 30 weeks of follow-up Secondary: ASAS 40 response, ASAS 5/6, ASAS partial remission, BASDAI,	Primary: Patients treated with TNF-blockers were more likely to achieve ASAS 20 response after 12 or 14 weeks (RR, 2.21; 95% CI, 1.91 to 2.56) and 24 weeks (RR, 2.68; 95% CI, 2.06 to 3.48) compared to controls. Treatment with golimumab was associated with the highest RR for ASAS 20 response after 12 or 14 weeks (RR, 2.74; 95% CI, 1.78 to 4.22), followed by adalimumab (RR, 2.33; 95% CI, 1.45 to 3.74), etanercept (RR, 2.13; 95% CI, 1.75 to 2.58), and infliximab (RR, 1.82; 95% CI, 1.16 to 2.58) compared to controls. Treatment with infliximab was associated with the highest RR for ASAS

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs golimumab vs certolizumab vs control Concurrent use of stable doses of other medications was allowed.			BASDAI 50, BASFI, and BASMI, withdraws and safety outcomes at 12 or 14 weeks and 30 weeks of follow-up	20 response after 24 weeks (RR, 3.18; 95% CI, 1.99 to 5.08), followed by etanercept (RR, 2.53; 95% CI, 1.80 to 3.57) and adalimumab (RR, 2.15; 95% CI, 0.96 to 4.83) compared to controls. Secondary: Patients treated with TNF-blockers were more likely to achieve ASAS 40 response after 12 or 14 weeks (RR, 2.77; 95% CI, 2.05 to 3.75) and 24 weeks (RR, 3.32; 95% CI, 2.44 to 4.51) compared to controls. Patients treated with TNF-blockers were more likely to achieve ASAS 5/6 response after 12 or 14 weeks (RR, 3.52; 95% CI, 2.17 to 5.71) and 24 weeks (RR, 4.25; 95% CI, 2.80 to 6.46) compared to controls. Patients treated with TNF-blockers were more likely to achieve partial remission after 12 or 14 weeks (RR, 4.79; 95% CI, 2.46 to 9.34) and 24 weeks (RR, 4.43; 95% CI, 2.62 to 7.49) compared to controls. Patients treated with TNF-blockers achieved greater improvements in the disease activity (BASDAI) after 12 weeks (mean difference, -1.64; 95% CI, -2.06 to -1.22) and after 30 weeks (mean difference, -1.79; 95% CI, -2.27 to 1.31) compared to controls. Patients treated with TNF-blockers were more likely to achieve BASDAI 50 response at 12 or 14 weeks (RR, 2.87; 95% CI, 2.23 to 3.69) and at 24 weeks (RR, 3.39; 95% CI, 2.46 to 4.67) compared to controls. Patients treated with TNF-blockers achieved greater improvements in physical function (BASFI) at 12 weeks (mean difference, -1.39; 95% CI, -1.59 to -1.19) and at 24 weeks (mean difference, -1.52; 95% CI, -1.72 to -1.31) compared to controls. Patients treated with TNF-blockers achieved greater improvements in vertebral mobility (BASMI) at 12 weeks (mean difference, -0.53; 95% CI, -0.72 to -0.35) and at 24 weeks (mean difference, -0.60; 95% CI, -0.87 to -0.33) compared to controls. Meta-analysis of safety outcomes and withdraws did not indicate

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				statistically significant differences between treatment and control groups after 12 or 30 weeks (P value not reported).
Deodhar et al.[73] (2019) C-axSpAnd Certolizumab pegol 400 mg at weeks 0, two and four followed by 200 mg every two weeks vs placebo Given in addition to nonbiologic background medication	DB, MC, PC, PG, RCT Patients ≥18 years of age with a diagnosis of adult-onset axSpA, have ≥12 months of symptom duration, have active disease at screening and baseline despite treatment with nonbiologic background medication and have objective signs of inflammation (patients with radiographic sacroiliitis excluded)	N=317 52 weeks	Primary: Proportion of patients achieving major improvement (i.e., a ≥2.0-point decrease in the score from baseline or achievement of the lowest possible score [0.6]) in the ASDAS at week 52 Secondary: Achievement of ASAS 40 at weeks 12 and 52	Primary: At week 52, major improvement in ASDAS was achieved in 47.2% (75/159) of certolizumab pegol plus nonbiologic background medication patients, which was greater (P<0.0001) than the 7.0% (11/158) of placebo plus nonbiologic background medication patients in whom major improvement in ASDAS was achieved. Secondary: At week 12, 47.8% (76/159) of certolizumab pegol plus nonbiologic background medication patients had achieved an ASAS 40 response, compared to 11.4% (18 of 158) of placebo plus nonbiologic background medication patients (P<0.0001). By week 52, 56.6% (90/159) of certolizumab pegol plus nonbiologic background medication patients and 15.8% (25/158) of placebo plus nonbiologic background medication patients had achieved an ASAS 40 response (P<0.0001).
Deodhar et al.[74] (2020) PREVENT secukinumab 150 mg subcutaneous with a loading dose (loading dose [LD] group) vs secukinumab 150 mg without a	DB, MC, PC, RCT Patients with a clinical diagnosis of nonradiographic axial SpA who were age ≥18 years were included if they met the ASAS classification criteria for axial SpA	N=555 52 weeks	Primary: Proportion of patients achieving an ASAS40 response Secondary: ASAS and BASDAI responses	Primary: ASAS40 response in TNFi-naive patients was significantly higher in the secukinumab 150 mg LD group (41.5%) compared with the placebo group (29.2%) at week 16 (P=0.0197) and significantly higher in the secukinumab 150 mg NL group (39.8%) compared with the placebo group (19.9%) at week 52 (P<0.0021). Secondary: The total BASDAI score was significantly improved from baseline in patients treated with 150 mg LD (−2.35) or NL (−2.43) versus placebo (−1.46; P=0.0006 and P=0.0002, respectively), with improvement versus placebo seen as early as week one (−0.87 in the LD group and −0.82 in the NL group versus −0.48 in the placebo group). The proportion of BASDAI50 responders was significantly higher in patients treated with

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loading dose (non-loading dose [NL] group) vs placebo Given weekly and then every 4 weeks starting at week 4; Switch to open-label secukinumab or standard of care was permitted after week 20				150 mg LD (37.3%) or 150 mg NL (37.5%) versus placebo (21.0%; P=0.0001 and P=0.0002, respectively). Secukinumab 150 mg LD and NL regimens significantly reduced the sacroiliac joint edema score on MRI in the overall study population versus placebo (−1.68 and −1.03, respectively, versus −0.39; both P<0.0001).
Deodhar et al.[75] (2021) Tofacitinib 5 mg two times per day for 16 weeks vs placebo two times per day for 16 weeks After week 16, all patients received OL tofacitinib until week 48	DB, PC, RCT Patients aged ≥18 years diagnosed with active AS, meeting the modified New York criteria, with centrally read radiographs, and an inadequate response or intolerance to ≥2 non-steroidal anti-inflammatory drugs	N=269 48 weeks	Primary: ASAS20 at week 16 Secondary: ASAS40 at week 16; safety	Primary: At week 16, the ASAS20 response rate was significantly (P<0.0001) greater with tofacitinib (56.4%, 75 of 133) versus placebo (29.4%, 40 of 136). Secondary: At week 16, the ASAS40 response rate was significantly (P<0.0001) greater with tofacitinib (40.6%, 54 of 133) versus placebo (12.5%, 17 of 136). Up to week 48, with tofacitinib, three of 133 (2.3%) patients had adjudicated hepatic events, three of 133 (2.3%) had non-serious herpes zoster, and one of 133 (0.8%) had a serious infection; with placebo→tofacitinib, two (1.5%) patients had non-serious herpes zoster. There were no deaths, malignancies, major adverse cardiovascular events, thromboembolic events or opportunistic infections.
van der Heijde et al.[76] (2022) SELECT-AXIS 1	DB, MC, RCT followed by OL extension	N=187 N=144 completed	Primary: ASAS40 Secondary:	Primary: Among patients receiving continuous upadacitinib, 85.9% (as-observed) and 65.6% (non-responder imputation) achieved ASAS40 at week 104. Similar magnitude of ASAS40 responses were observed among patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Upadacitinib 15 mg once daily vs placebo Patients who completed the initial 14 weeks were eligible to enter period 2 to receive open-label upadacitinib 15 mg once daily for 90 weeks up to week 104	Patients ≥18 years of age with a clinical diagnosis of AS who met the modified New York criteria, had active disease at screening and baseline (i.e., week 0), and had an inadequate response to ≥2 NSAIDs or intolerance to or contraindication for NSAIDs	104 weeks 2 years	Inflammation, safety	who switched from placebo to upadacitinib (88.7% and 63.8%, respectively). Secondary: The mean change from baseline to week 104 in Spondyloarthritis Research Consortium of Canada MRI spine and sacroiliac joint inflammation scores were -7.3 and -5.3, respectively, in the continuous upadacitinib group and -7.9 and -4.9 in the placebo-to-upadacitinib switch group. The mean change from baseline to week 104 in the modified Stoke Ankylosing Spondylitis Spine Score was 0.7 (95% CI, 0.3 to 1.1) in the total group. Adverse event rate was 242.7/100 patient-years. No serious infections, adjudicated major adverse cardiovascular events, lymphoma, non-melanoma skin cancer, or gastrointestinal perforations were observed.
Deodhar et al.[77] (2022) SELECT-AXIS 2 Upadacitinib 15 mg once daily vs placebo	DB, MC, PC, RCT Adults with active non-radiographic axial spondyloarthritis, with objective signs of inflammation based on MRI or elevated C-reactive protein and an inadequate response to non-steroidal anti-inflammatory drugs	N=314 14 weeks	Primary: ASAS40 response at week 14 Secondary: Additional measures of disease activity, safety	Primary: A higher ASAS40 response rate was achieved with upadacitinib compared with placebo at week 14 (70 [45%] of 156 patients vs 35 [23%] of 157 patients; P<0.0001; treatment difference, 22%; 95% CI 12 to 32). Secondary: Improvements from baseline were seen across the individual ASAS components with upadacitinib versus placebo from week one onwards for patient's global assessment of disease activity (nominal P=0.047) and from week two onwards for patient's assessment of total back pain (nominal P=0.0078), BASFI (nominal P=0.0022), and morning stiffness (nominal P=0.0036). Upadacitinib showed greater improvement in total back pain (P=0.0004) and BASFI (P<0.0001) at week 14 than did placebo. Upadacitinib showed significantly higher response rates versus placebo at week 14 in additional measures of disease activity, including BASDAI50 (P=0.0001), ASDAS inactive disease (P=0.0063), ASDAS low disease activity (P<0.0001), ASAS partial remission (P=0.0035), and ASAS20 (P<0.0001). A greater proportion of patients also achieved ASDAS major

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				improvement (nominal P=0.0001) and ASDAS clinically important improvement (nominal P<0.0001) with upadacitinib than with placebo. The rate of adverse events up to week 14 was similar in the upadacitinib group (75 [48%] of 156 patients) and placebo group (72 [46%] of 157 patients). Serious adverse events and adverse events leading to discontinuation of study drug occurred in four (3%) of 156 patients in the upadacitinib group and two (1%) of 157 patients in the placebo group. Few patients had serious infections or herpes zoster in either treatment group (each event occurred in two [1%] of 156 patients in the upadacitinib group and one [1%] of 157 patients in the placebo group). Five (3%) of 156 patients in the upadacitinib group had neutropenia; no events of neutropenia occurred in the placebo group. No opportunistic infections, malignancies, major adverse cardiovascular events, venous thromboembolic events, or deaths were reported with upadacitinib treatment.
van der Heijde et al.[78] (2022) SELECT-AXIS 2 AS bDMARD-IR Upadacitinib 15 mg once daily vs placebo	DB, RCT Adults with active AS who met modified New York criteria and had an IR to one or two bDMARDs (tumour necrosis factor or interleukin-17 inhibitors)	N=420 14 weeks	Primary: ASAS40 response at week 14 Secondary: Ankylosing Spondylitis Disease Activity score, Spondyloarthritis Research Consortium of Canada MRI spine inflammation score, total back pain, nocturnal back pain, Bath Ankylosing Spondylitis Functional Index, Bath Ankylosing Spondylitis	Primary: More patients achieved the primary endpoint of ASAS40 at week 14 with upadacitinib vs placebo (45% vs 18%; P<0.0001). Secondary: Statistically significant improvements were observed with upadacitinib vs placebo for all multiplicity-controlled secondary endpoints (P<0.0001). Adverse events were reported for 41% of upadacitinib-treated and 37% of placebo-treated patients through week 14.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Metrology Index and Maastricht Ankylosing Spondylitis Enthesitis Score	
COVID-19				
Kalil et al.[79] (2021) ACTT-2 Baricitinib (4 mg daily for 14 days or until hospital discharge) and remdesivir vs placebo and remdesivir	DB, MC, PC, RCT Patients ≥18 years of age hospitalized with moderate to severe laboratory-confirmed SARS-CoV-2 infection	N=1,033 29 days	Primary: Time to recovery Secondary: Clinical status at day 15	Primary: Patients receiving baricitinib had a median time to recovery of seven days (95% CI, 6 to 8), as compared with eight days (95% CI, 7 to 9) with control (rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.32; P=0.03). Secondary: Patients receiving baricitinib had a 30% higher odds of improvement in clinical status at day 15 (odds ratio, 1.3; 95% CI, 1.0 to 1.6). Patients receiving high-flow oxygen or noninvasive ventilation at enrollment had a time to recovery of 10 days with combination treatment and 18 days with control (rate ratio for recovery, 1.51; 95% CI, 1.10 to 2.08). The 28-day mortality was 5.1% in the combination group and 7.8% in the control group (hazard ratio for death, 0.65; 95% CI, 0.39 to 1.09).
Crohn's Disease				
Ma et al.[80] (2009) Adalimumab	SR OL and RCT cohort studies of patients with CD who had either lost response, were intolerant or refractory to infliximab	N=1,810 (15 trials) 8 weeks to 4 years	Primary: Short-term and long-term efficacy Secondary: Adverse events	Primary: Short-term clinical response or remission was evaluated in nine trials. Forty-one to 83% of patients achieved a clinical response at four weeks, while 12 to 67% of participants attained clinical remission. Long-term remission rates ranged from 31 to 82% at six months and 19 to 68% at one year. Secondary: Serious adverse events were reported in 0 to 19% of patients and included sepsis, cellulitis, and fungal pneumonia.
Lofberg et al.[81] (2012) CARE	MC, OL Patients 18 to 75 years of age with a	N=945 20 weeks	Primary: Remission rates, proportion of patients free of	Primary: The proportion of patients in remission who received adalimumab was 43% at week four (95% CI, 40 to 46) and increased to 52% (95% CI, 49 to 55) at week 20. There was a significantly higher remission rate at week 20

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Adalimumab 160 mg at week zero, followed by 80 mg at week two, followed by 40 mg every other week At week 12 or later, patients who experienced a disease flare or did not respond to treatment could increase the adalimumab dose to 40 mg weekly.	radiologic or endoscopic diagnosis of CD for ≥4 months and a HBI >7 points at screening		EIM at week 20 Secondary: Fistula healing, remission rates based on concomitant therapies and adverse events	among adalimumab-treated patients who were also infliximab naïve compared to patients exposed to infliximab (62 vs 42; P<0.001). A shorter disease duration (less than two years and between two and five years) was associated with higher rates of clinical remission at week four compared to a disease duration longer than five years (50, 52, and 38%, respectively; P<0.001); however the remission rates at 20 weeks were not significantly different (58, 56, and 50%, respectively; P=0.136). Overall, 53% of patients had at least one EIM at baseline, compared to 30% at week 20. Of these, 79% had resolution of at least one EIM and 51% were free of EIM signs and symptoms following 20 weeks of adalimumab treatment. The EIM resolution rates were similar across adalimumab-treated patients regardless of prior infliximab use (P=0.100) and prior infliximab response and those who discontinued treatment for other reasons (P=0.625). Secondary: Complete fistula healing occurred in 26% of patients at week 20. Fistula closure rates were numerically higher in the infliximab-naïve group at week 20 (33%) compared to the infliximab-experienced group (22%); however, the difference was not significant (P=0.275). Fistula healing rates were similar in nonresponders to infliximab compared to those who discontinued infliximab for other reasons (19 vs 23%; P=0.973). Of patients taking corticosteroids at baseline, 37% were able to discontinue them by week 20; Eleven percent and 14% of patients achieved a steroid-free remission at weeks 12 and 20, respectively. Seven percent of patients taking immunosuppressants at baseline were able to discontinue them at week 20. There were similar rates of clinical remission at week 20 between patients taking and not taking steroids at baseline (52% in both groups; P=0.976). By week 20, the rates of clinical remission were 55 and 49%, respectively, in patients who were and were not taking immunosuppressants at baseline (P=0.052).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Adverse events occurred in 80% of patients and 11% of patients who discontinued treatment due to adverse events. Serious adverse events were reported in 19% of patients. The adverse events profiles were similar among patients who were exposed to infliximab previously and those who were treatment naïve. The most common adverse event categories were "gastrointestinal disorders" and "CD'' indicating a worsening of patient's underlying disease.
Faubion et al.[82] (2017) IMAgINE 2 Adalimumab 40 mg every week or every other week if ≥40 kg or 20 mg every week or every other week if <40 kg	ES, MC, OL Patients 6 to 17 years of age with a diagnosis of CD who successfully completed IMAgINE 1 through week 52 and achieved clinical response at any time point during the study	N=100 240 weeks	Primary: PDCAI remission (≤10) and response (decrease ≥15 from IMAgINE 1 baseline) Secondary: Corticosteroid-free remission, safety	Primary: Remission and response were achieved by 41% and 48% of patients who entered IMAgINE 2, respectively. Secondary: Corticosteroid-free remission rates in IMAgINE 2 among patients who used corticosteroids at IMAgINE 1 baseline increased from 40.5% (15/37) at enrollment into IMAgINE 2 to 63.2% (12/19, observed analysis) at week 240 of IMAgINE 2. Discontinuation of corticosteroid use increased from week 12 (86.5% [32/37]) through week 240 of IMAgINE 2 (100% [19/19], observed analysis). Serious adverse events (48%) and adverse events leading to discontinuation (32%) of study drug were primarily due to worsening or flare of CD. The most frequently reported adverse events were CD (55%), headache (27%), upper respiratory tract infection (22%), nasopharyngitis (21%), and diarrhea (19%).
Watanabe et al.[83] (2012) (Induction study) Adalimumab 160 mg at week zero, followed by 80 mg at week two (ADA 160/80 group) vs	2 DB, MC, PC, RCT Patients 15 to 75 years of age, with moderate to severely active CD, CDAI score 220 to 450 for >4 months and a diagnosis of ileal, colonic or ileocolonic CD confirmed by	N=90 (induction) N=83 (maintenance) 56 weeks (4 weeks induction study and 52 week maintenance	Primary: Induction study Proportion of patients in clinical remission (CDAI <150) at week four Maintenance Clinical remission (CDAI <150) at week 52	Primary: Induction A greater proportion of patients treated with ADA 160/80 and ADA 80/40 achieved a clinical remission by week four compared to placebo (33 and 18 vs 12%, respectively; P value not reported). Maintenance By week 52, a significantly greater proportion of patients treated with adalimumab 40 mg achieved a clinical remission compared to placebo (P<0.05). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
adalimumab 80 mg at week zero, followed by 40 mg at week two (ADA 80/40 group) vs placebo (Maintenance study) adalimumab 40 mg every other week vs placebo Patients achieving a Clinical Response 70 (decrease from baseline in CDAI ≥70 points at week four) entered the blinded maintenance trial.	endoscopy or radiologic evaluation	study)	Secondary: Induction study Proportion of patients in clinical remission at week two and with CR-100 or CR-70 (CDAI decrease ≥100 or ≥70) at week four, changes from baseline in CDAI and IOIBD at week two and week four and changes in SF-36 MCS and PCS, and IBDQ scores in each treatment group at week four Maintenance Proportion of patients in clinical remission, (CDAI decrease ≥100 or ≥70) every four weeks, changes from baseline of the induction to week 52 in CDAI, IOIBD, SF-36 MCS and PCS scores, and IBDQ	Induction At week two, clinical remission rates were higher with ADA 160/80 and ADA 80/40 compared to placebo (18 and 15 vs 4%, respectively; P value not reported). At week four, significantly greater proportion of patients receiving ADA 160/80 or ADA 80/40 experienced a CR-100 (50 and 46 vs 17%, respectively; P<0.05 for both) compared to placebo. At week four, significantly greater proportion of patients receiving ADA 160/80 experienced a CR-70 (70 vs 30%; P=0.0062); however, the improvement with the ADA 80/40 was not statistically significant. The changes in CDAI from baseline to week two and four, respectively, were, -75.9 and -101.3 in the ADA 160/80 group, -74.4 and -81.3 in the ADA 80/40 group, and -27.2 and -37.5 in the placebo group. The mean changes in IOIBD score from baseline to week two and week four, respectively, were -1.2 and -1.5 in the ADA 160/80 group, -0.7 and -0.8 in the ADA 80/40 group, and -0.4 and -0.5 in the placebo group. ADA 160/80 or ADA 80/40 significantly improved SF-36 MCS from baseline to week four compared to placebo. (6.2 and 5.5 vs -1.6, respectively; P<0.05 for both). There were no statistically significant differences in SF-36 PCS and IBDQ between patients receiving ADA 160/80 compared to patients receiving placebo. Maintenance Adalimumab therapy was more effective compared to placebo at each of the four-week evaluations throughout the 52-week trial compared to placebo with regard to CR-100 (P≤0.05) and CR-70 (P≤0.01). Adalimumab was more effective compared to placebo with regard to maintaining clinical remission at weeks eight, 36, 36, 40, 48 and 52 (P<0.05). The mean changes in CDAI from baseline of the induction trial to week zero and week 52, respectively, were -147.7 and -83.7 in the adalimumab-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				treated patients and -139.0 and -9.1 in the placebo-treated patients. The mean changes in IOIBD from baseline to week zero and week 52, respectively, were -2.0 and -0.8 in adalimumab-treated patients and -1.2 and -0.2 in placebo-treated patients, respectively. Adalimumab 40 mg was associated with statistically significant improvements in SF-36 MCS and IBDQ compared to placebo at eight weeks (12.0 vs 2.0; P=0.03 and 34.8 vs 8.3; P=0.05, respectively); however, the changes were not significantly different at 52 weeks.
Shao et al.[84] (2009) Certolizumab vs placebo	MA DB, RCTs in patients with moderate to severe CD	N=1,040 (3 trials) 12 to 26 weeks	Primary: Clinical response (a decrease ≥100 points from baseline in CDAI score) and clinical remission (CDAI score ≤150 points) at week four Secondary: Safety	Primary: Certolizumab was associated with an increased rate of induction of clinical response (RR, 1.36; 95% CI, 1.10 to 1.68; P=0.004) and remission (RR, 1.95; 95% CI, 1.41 to 2.70; P<0.0001) compared to placebo. Secondary: Only infection was reported more frequently with certolizumab compared to placebo (60.6 vs 40.7%).
Targan et al.[85] (1997) Infliximab 5 mg/kg vs infliximab 10 mg/kg vs infliximab 20 mg/kg vs	DB, MC, PC, RCT Adult patients with CD for six months with CDAI scores 220 to 400 and previously receiving mesalamine (for ≥8 weeks and a stable dose for four weeks), corticosteroids (maximum of 40 mg/day for ≥8 weeks and a stable	N=108 12 weeks	Primary: Decrease from baseline in CDAI ≥70 points at four weeks without a change in concomitant medications Secondary: Not reported	Primary: At week four, the primary endpoint was reached in 81, 50, 64 and 17% in the 5 mg/kg, 10 mg/kg, 20 mg/kg and placebo groups, respectively. The overall response of the infliximab groups was significantly higher (65%) compared to the placebo group (P<0.001). At week two, 61% of the infliximab treated patients had a response compared to 17% of the placebo treated patients (P<0.001). A greater proportion of patients was in remission (CDAI score <150) in the infliximab group at two weeks (27%) compared to the placebo group (4%; P=0.06). At week four, 33% of the infliximab treated patients were in remission compared to 4% of the placebo treated patients (P<0.005). The response rate remained significantly higher in the infliximab treated patients through the 12 weeks of the study (41%) compared to placebo treated patients (12%; P=0.008); however, the remission rate was not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	dose for two weeks), mercaptopurine or azathioprine (for ≥6 months and stable dose for eight weeks)			significantly different at 12 weeks (24 vs 8%; P=0.31). Secondary: Not reported
Present et al.[86] (1999) Infliximab 5 mg/kg at weeks 0, 2 and 6 vs infliximab 10 mg/kg at weeks 0, 2 and 6 vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age with ≥1 confirmed draining abdominal or perianal fistulas of ≥3 months as a complication of CD	N=94 18 weeks	Primary: Reduction ≥50% from baseline in number of draining fistulas at two or more consecutive study visits Secondary: Proportion of patients with a complete response (absence of any draining fistula at two consecutive visits), length of time to beginning of response, and duration of response	Primary: There were significantly greater response rates in the infliximab 5 (68%) and 10 mg/kg (56%) groups compared to the placebo group (26%; P=0.002 and P=0.02, respectively). The response rates were not significantly different between the two infliximab groups. Secondary: A greater proportion of patients in the infliximab 5 (55%) and 10 mg/kg (38%) groups had complete response compared to the placebo group (13%; P=0.001 and P=0.04, respectively). In the infliximab group, the median time to the onset of response was two weeks compared to six weeks in the placebo group. The duration of response was approximately three months in patients that reached the primary endpoint. The most frequently reported adverse events in the infliximab group were headache, abscess, upper respiratory tract infection and fatigue.
Hyams et al.[87] (2007) REACH Infliximab 5 mg/kg at weeks 0, 2 and 6; those responding to therapy received	OL, MC, RCT Patients 6 to 17 years of age with a PCDAI >30 at baseline and who initiated immunomodulator	N=112 46 weeks	Primary: Clinical response at week 10 (decrease from baseline to week 10 in PCDAI ≥15 points and total PCDAI no more than 30)	Primary: At week 10, 88.4% of patients responded to the induction regimen (95% CI, 82.5 to 58.9). Secondary: At week 10, 58.6% of patients were in clinical remission (95% CI, 49.8 to 68.0). At week 54, 63.4 and 55.8% of patients treated with infliximab every eight weeks achieved clinical response and clinical remission,

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continued therapy every 8 weeks at weeks 14, 22, 30, 38 and 36 or every 12 weeks at weeks 18, 30 and 42 vs infliximab 5 mg/kg at weeks 0, 2 and 6; those responding to therapy received continued therapy every 12 weeks at weeks 18, 30 and 42	therapy (azathioprine, mercaptopurine or MTX) ≥8 weeks before screening and at stable dose for two weeks		Secondary: Maintenance of clinical response and remission (PCDAI ≤10)	respectively, compared to 33.3 and 23.5% of patients treated with infliximab every 12 weeks (P=0.002 and P<0.001, respectively). At week 10, there was a significant decrease in PCDAI score compared to baseline that continued at weeks 30 and 54 (all P<0.001). There was a significant decrease in corticosteroid use at week 10 compared to baseline that continued at weeks 30 to 54 (all P<0.001). Adverse events were similar between the two groups. Infection was the most common adverse event in both treatment groups.
Van Assche et al.[88] (2012) SWITCH Adalimumab 80 mg at week zero and 40 mg every other week Patients not randomized to adalimumab continued prior infliximab at 5 mg/kg at their regularly scheduled interval. Patients with a disease flare were able to intensify	OL, PRO, RCT Patients ≥18 years with luminal CD treated with infliximab maintenance therapy started for ≥6 months with a complete clinical response (PGA assessment of signs and symptoms, but the CDAI at baseline <200) with stable infliximab dosing intervals of ≥6 weeks	N=73 54 weeks	Primary: Proportion of patients in the adalimumab group preferring adalimumab over infliximab and proportion of patients who needed rescue therapy with short courses of steroids or intensified anti-TNF dosing or who had to stop the assigned anti-TNF agent Secondary: Proportion of	Primary: There was a statistically significant increase in the preference of adalimumab over infliximab for patients who changed from infliximab to adalimumab therapy at all evaluation points (P<0.05), except week 56 (P=0.08). Dose intensification or early treatment termination occurred significantly more frequently over 54 weeks in patients switched to adalimumab (47%) compared to those who continued infliximab (16%; P=0.003). Significantly more patients initiating adalimumab therapy discontinued therapy due to loss of response or intolerance compared those who continued infliximab therapy (28 vs 2%; P<0.01). Of note, the patient who discontinued infliximab was successfully treated with adalimumab and eight of the 10 patients who stopped adalimumab treatment returned to infliximab therapy. The reasons for early discontinuation of treatment were loss of tolerance in six of 10 patients on adalimumab and in the one patient receiving infliximab. Four other patients in the adalimumab group stopped for loss of efficacy. Refractory eczema with fatigue or arthralgias (n=2), general

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
treatment as follows: adalimumab 40 mg every week and in the infliximab group, a decrease of the dosing interval with two-week decrements.			patients with an injection- or infusion-related reaction and proportion of patients with an increase in the CDAI of >100 above baseline and IBDQ	malaise and diarrhea following injections (n=2) and fatigue plus inability to comply with injections (n=2) led to adalimumab intolerance and an infusion reaction to infliximab intolerance. Secondary: There was no difference in the change from baseline in CDAI at time of early termination in the adalimumab group (184 vs 78; P=0.10). Dose intensification occurred in 27.7% of patients in the adalimumab group, three of which later stopped adalimumab for loss of response, and in and 13.5% of patients in the infliximab group (P=0.20). The median time to dose intensification was not significantly different between the adalimumab and infliximab treatment arms (24 vs 32 weeks; P=0.64). An increase in CDAI ≥100 points was observed in 18.9% of patients in the infliximab group and in 27.7% of patients in the adalimumab group while on the initially assigned treatment. Median IBDQ values at baseline and at week 56 were comparable in both groups and the medians stayed well in the range compatible with disease remission throughout the trial.
Behm et al.[89] (2008) Adalimumab, certolizumab, or infliximab vs placebo	SR RCTs including patients ≥18 years of age with CD who had a clinical response or clinical remission with a TNF-α blocker, or patients with CD in remission but unable to wean corticosteroids, who were then randomized to maintenance of remission with a TNF-α blocker or	N=3,586 (9 trials) Duration varied	Primary: Clinical remission, clinical response, and steroid-sparing effects Secondary: Not reported	Primary: Adalimumab demonstrated the ability to maintain clinical remission and clinical response (RR, 2.69; 95% CI, 1.88 to 3.86; P<0.00001), while also having a steroid-sparing effect (data specific to clinical remission and steroid-sparing effect not reported). Certolizumab was shown to maintain both clinical remission (RR, 1.68; 95% CI, 1.30 to 2.16; P=0.000072) and clinical response (RR, 1.74; 95% CI, 1.41 to 2.13; P<0.00001) compared to placebo. Infliximab was more effective than placebo at maintaining fistula healing (RR, 1.87; 95% CI, 1.15 to 3.04; P=0.012), clinical remission (RR, 2.50; 95% CI, 1.64 to 3.80; P=0.000019), clinical response (RR, 1.66; 95% CI, 1.00 to 2.76; P=0.0046, and achieved a steroid sparing effect (RR, 3.13; 95% CI, 1.25 to 7.81; P=0.014). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	placebo			
Giant-Cell Arteritis				
Stone et al.[90] (2017) GiACTA Tocilizumab 162 mg SC weekly plus a 26-week prednisone taper vs tocilizumab 162 mg SC every other week plus a 26-week prednisone taper vs placebo plus a 26-week prednisone taper vs placebo plus a 52-week prednisone taper All patients received a prednisone taper	DB, PC, RCT Patients ≥50 years of age who had active giant-cell arteritis within six weeks before baseline and who had a history of an elevated erythrocyte sedimentation rate attributable to giant-cell arteritis	N=251 52 weeks	Primary: Rate of sustained glucocorticoid-free remission at week 52 between each tocilizumab group and the placebo group with the 26-week taper Secondary: Rate of sustained glucocorticoid-free remission at week 52 between each tocilizumab group and the placebo group with the 52-week taper, cumulative prednisone dose, SF-36, safety	Primary: A total of 56% of the patients in the group that received tocilizumab weekly and 53% of those in the group that received tocilizumab every other week had sustained remission at 52 weeks, as compared with 14% of the patients in the placebo group that underwent the 26-week taper (P<0.001 for the comparison of each tocilizumab group with placebo). Secondary: A total of 56% of the patients in the group that received tocilizumab weekly and 53% of those in the group that received tocilizumab every other week had sustained remission at 52 weeks, as compared with 18% of those in the placebo group that underwent the 52-week taper (P<0.001 for the comparison of each tocilizumab group with placebo). The total median cumulative prednisone dose over the 52-week period was 1862 mg (95% CI, 1582 to 1942) in the group that received tocilizumab weekly and 1862 mg (95% CI, 1568 to 2240) in the group that received tocilizumab every other week, as compared with 3296 mg (95% CI, 2730 to 4024) in the placebo group that underwent the 26-week taper and 3818 mg (95% CI, 2818 to 4426) in the placebo group that underwent the 52-week taper (P<0.001 for all comparisons of tocilizumab with placebo). The mean increase (indicating clinical improvement) from baseline to week 52 in the SF-36 physical component summary score was 4.10 in the group that received tocilizumab weekly and 2.76 in the group that received tocilizumab every other week, whereas scores decreased (indicating a worse condition) in the two placebo groups (−0.28 in the placebo group with the 26-week taper and −1.49 in the placebo group with the 52-week taper). The difference between the group that received tocilizumab weekly and the placebo group that underwent the 52-week taper was 5.59 points (99% CI, 0.86 to 10.32; P=0.002). However, the differences between the group that received tocilizumab every other week and each placebo group with respect to the SF-36 physical component summary score did not reach statistical significance.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The percentages of patients with adverse events were similar in all the trial groups, but fewer patients reported serious adverse events in the group that received tocilizumab weekly (15%) or every other week (14%) than in the placebo group that underwent the 26-week taper (22%) or the placebo group that underwent the 52-week taper (25%).
Hidradenitis Suppurativa				
Kimball et al.[91] (2016) PIONEER I and II Adalimumab 40 mg weekly vs placebo	2 DB, MC, PC, RCTs Men and women who had not received previous anti–TNF-α treatment were eligible if they had moderate-to-severe hidradenitis suppurativa (total abscess and inflammatory-nodule count, ≥3) at baseline and an inadequate response to oral antibiotic treatment. In PIONEER I, patients receiving oral antibiotic agents for hidradenitis suppurativa were required to stop treatment for at least 28 days before baseline; in PIONEER II, patients were allowed to continue	N=633 36 weeks	Primary: Proportion of patients with a clinical response at week 12, defined according to the Hidradenitis Suppurativa Clinical Response measure as at least a 50% reduction from baseline in the total abscess and inflammatory-nodule count, with no increase in the abscess or draining-fistula count Secondary: Total abscess and inflammatory-nodule count of 0, 1, or 2; ≥30% reduction and at least a 1-unit reduction from baseline in the pain score; change from baseline in the	Primary: A higher proportion of patients in the adalimumab group than in the placebo group met the primary efficacy end point of a clinical response at week 12 (PIONEER I: 41.8 v. 26.0%, P=0.003; PIONEER II: 58.9 versus 27.6%, P<0.001). Responses to adalimumab were similar regardless of whether baseline antibiotic therapy was continued (in PIONEER II) and regardless of the baseline Hurley stage. Secondary: Adalimumab treatment resulted in greater improvements than placebo in PIONEER II (P=0.01 for total abscess and inflammatory-nodule count of 0, 1, or 2 for patients with Hurley stage II disease at baseline, P<0.001 for 30% reduction from baseline in the score for skin pain, and P<0.001 for mean improvement in the modified Sartorius score) but did not have a significant effect in PIONEER I.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	treatment with antibiotics (tetracycline class) in stable doses.		modified Sartorius score	
Juvenile Idiopathic/Rheumatoid Arthritis				
Ruperto et al.[92] (2008) Abatacept 10 mg/kg every 28 days vs placebo	DB, MC, PC, RCT (OL lead in period) Patients 6 to 17 years of age with JIA with at least 5 active joints and active disease and who had inadequate response to or intolerance to ≥1 DMARD	N=122 (RCT); 190 (OL lead in period) 6 months (4-month OL lead in)	Primary: Time to flare Secondary: Proportion of patients with a disease flare, changes in baseline in each of six core response variables, and assessment of safety and tolerability	Primary: In the placebo group, the median time to flare was six months; however, insufficient events occurred in the abatacept group to assess median time to flare (P=0.0002). Secondary: There was a significantly greater proportion of patients that experienced a flare in the placebo group compared to the abatacept group (53 vs 12%; P=0.0003). The HR for patients in the abatacept group to experience a flare compared to the placebo group was 0.31 (95% CI, 0.16 to 0.59). After six months or at the time of first flare, 82% of the abatacept group and 69% of the placebo group improved by ≥30% as measured by ACR (P=0.1712), 77% of the abatacept group and 52% of the placebo group improved by ≥50% as measured by ACR (P=0.0071), 53% of the abatacept group and 31% of the placebo group improved by ≥70% as measured by ACR and 40% of the abatacept group and 16% of the placebo group improved by ≥90% as measured by ACR. In the abatacept group, 30% had inactive disease compared to 11% in the placebo group (P=0.0195). Adverse events were similar between the groups.
Lovell et al.[93] (2015) Abatacept 10 mg/kg every 28 days	OL (long-term extension of above study) Patients 6 to 17 years of age with JIA with at least five active joints and active disease and who had inadequate	N=153 5 to 7 years	Primary: Safety Secondary: ACR Pedi responses, CHAQ	Primary: The overall incidence rates of adverse events and serious adverse events reported in the cumulative study period, corresponding to a mean ±SD maximum total exposure of 62.1 ± 20.9 months, were 209.11 (95% CI, 179.11 to 242.70) and 5.62 (95% CI, 3.92 to 7.82) events per 100 patient-years of exposure, respectively. Secondary: ACR Pedi 30 responses, Pedi 70 responses, and clinically inactive disease status were maintained throughout the long-term extension phase in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	response to or intolerance to ≥1 DMARD			patients who continued to receive therapy. Improvements in the Child Health Questionnaire physical and psychosocial summary scores were maintained over time.
Lovell et al.[94] (2008) Adalimumab 24 mg/m^2 (maximum of 40 mg) every other week with or without MTX vs placebo Patients were stratified according to MTX use and received OL adalimumab 24 mg/m^2 (maximum of 40 mg) every other week for 16 weeks. The patients with an ACR Pedi 30 response at week 16 were then randomly assigned to receive adalimumab or placebo.	DB, MC, OL, RCT Patients 4 to 17 years of age with active JRA who had previously received treatment with NSAIDs	N=171 48 weeks	Primary: Rate of disease flare in patients not receiving MTX Secondary: ACR Pedi 30, 50, 70, and 90 responses at week 48, and safety	Primary: Among patients not receiving MTX, flares occurred in 43% receiving adalimumab and 71% receiving placebo (P=0.03). In patients receiving MTX, flares occurred in 37 and 65% in the adalimumab and placebo groups, respectively (P=0.02). Secondary: In patients receiving MTX, ACR Pedi 30, 50, 70, and 90 responses were reported in 63 vs 38% (P=0.03), 63 vs 35% (P=0.03), 63 vs 27% (P=0.002) and 42 vs 27% (P=0.17) in the adalimumab and placebo groups, respectively. In patients not receiving MTX therapy, ACR Pedi 30, 50, 70, and 90 responses were reported in 57 vs 32% (P=0.06), 53 vs 32% (P=0.10), 47 vs 29% (P=0.16) and 30 vs 18% (P=0.28) in the adalimumab and placebo groups, respectively. The most frequently noted adverse events were mild to moderate in nature and included infections and injection site reactions. There were seven cases of serious infection reported with adalimumab use.
Lovell et al.[95] (2000) Etanercept 0.4 mg/kg twice weekly	DB, MC, OL, RCT Patients 4 to 17 years of age with active polyarticular	N=69 7 months	Primary: Rate of disease flare Secondary:	Primary: Seventy-four percent (51/69) of patients demonstrated improvement and were included in the DB part of the trial. The rate of disease flare was significantly higher in the placebo group compared to the etanercept group (81 vs 28%; P=0.003).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo All patients received etanercept 0.4 mg/kg twice weekly for up to 3 months in the OL part of the study; the patients whose condition improved were then randomly assigned to either etanercept or placebo. Concurrent analgesics, NSAIDs, or oral corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.	JRA despite treatment with NSAIDs and MTX ≥10 mg/m^2/week		Median time to flare, safety	Secondary: The median time to flare was reported as 116 days in the active treatment arm compared to 28 days with placebo (P<0.001). During the OL segment of the study the adverse events most often reported included injection-site reaction, upper respiratory tract infections, headache, rhinitis and gastrointestinal side effects. There were no differences noted between groups during the latter part of the study.
Lovell et al.[96] (2006) Etanercept 0.4 mg/kg (maximum of 25 mg) twice weekly Intra-articular and soft-tissue injections of corticosteroids were permitted after	Ongoing ES, MC, OL by Lovell et al[22] (updated efficacy and safety results from the study)	N=58 Median of 4 years	Primary: JRA 30% DOI Secondary: JRA 50% DOI, JRA 70% DOI, an articular severity score (0 to 926), assessment of pain (Likert scale, 0 to 10), CRP levels, safety	Primary: Thirty-two patients were available for efficacy analysis after four years with 94% meeting the JRA 30% DOI. Secondary: Approximately 94 and 78% of participants met the JRA 50% DOI and JRA 70% DOI, respectively. At four years, the median CRP level was lowered to 0.1 mg/dL from 3.4 mg/dL at baseline, the median articular severity score was decreased to 18 from 88 at baseline, and the median patient's assessment of pain score was lowered to 0.9 from 3.6 at baseline.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
12 continuous weeks of etanercept. MTX could be added to treatment after one year. Concurrent analgesics, NSAIDs, or oral corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.				Duration of morning stiffness was only assessed through one year and was reported as 5 minutes at month 12 (from 53 minutes at baseline). After four years, there were five reports of serious adverse events and 0.03 serious infections (requiring intravenous antibiotics or hospitalizations)/ patient year.
Horneff et al.[97] (2004) Etanercept 0.4 mg/kg twice weekly Combination treatment with MTX or oral corticosteroids was permitted.	MC, OL Patients 4 to 17 years of age with active idiopathic juvenile arthritis despite treatment with MTX	N=322 Up to 48 months, median of 12 months	Primary: Change in indices of disease activity, 30, 50, and 70% improvement in idiopathic juvenile arthritis Secondary: Safety	Primary: At 12 months, the mean number of tender joints, swollen joints, and joints with limited range of movement were reduced to 1.7 (SD, 3.5), 2.6 (SD, 4.7), and 7.1 (SD, 8.9) from a baseline of 9.1 (SD, 9.5), 8.4 (SD, 9.0), and 11.8 (SD, 11.8), respectively. The duration of morning stiffness was decreased to 7 (SD, 23) minutes from 45 (SD, 65) minutes and CHAQ scores (on a scale of 0=best to 3=worst) were decreased to 0.4 (SD, 0.6) from 1.0 (SD, 0.8). Patient's and PGA scores (on a scale of 0=best to 100=worst) were reduced to 16 (SD, 18) and 20 (SD, 23) from 56 (SD, 27) and 67 (SD, 25), respectively. At last report (30 months) a 30, 50, and 70% improvement was noted in approximately 60, 48, and 28% of patients remaining on etanercept, respectively. Significant improvements in all indices of disease activity were detected at all points of time (months one, three, six, 12, 18, 24, and 30; P<0.0001 with the exception of swollen joint count at 30 months; P<0.0005 and duration of morning stiffness; P<0.001). Secondary: There were 20 reports of infection or infection related events. Discontinuation of treatment was reported in 53 patients, of which 11 cases were secondary to adverse events.
Hissink Muller et	MC, SB, RCT	N=94	Primary:	Primary:

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Study Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td>al.[98]
(2017)
BeSt-for-kids

Etanercept and MTX combination (arm 3)

vs

DMARD-monotherapy (SSZ or MTX) (arm 1)

vs

MTX / prednisolone-bridging (arm 2)</td><td>Patients 2 to 16 years of age diagnosed as DMARD-naive JIA, either rheumatoid factor negative polyarticular, oligoarticular JIA, or juvenile psoriatic arthritis, in need of systemic DMARD therapy according to treating physician</td><td>3 months</td><td>Percentage inactive disease, adjusted ACR Pedi30, 50 and 70 and Juvenile Arthritis Disease Activity Score after six and 12 weeks of treatment

Secondary:
Adverse effects</td><td>
<table>
<tr><th></th><th>Etanercept + MTX</th><th>DMARD monotherapy</th><th>MTX + prednisone</th><th>P-value</th></tr>
<tr><td>Inactive disease 6-weeks (%)</td><td>3</td><td>0</td><td>13</td><td>0.25</td></tr>
<tr><td>Inactive disease 3-months (%)</td><td>17</td><td>25</td><td>9</td><td>Not reported</td></tr>
<tr><td>aACR Pedi 30 6-weeks (%)</td><td>57</td><td>47</td><td>56</td><td>0.68</td></tr>
<tr><td>aACR Pedi 30 3-months (%)</td><td>73</td><td>50</td><td>53</td><td>0.13</td></tr>
<tr><td>aACR Pedi 50 6-weeks (%)</td><td>37</td><td>28</td><td>44</td><td>0.56</td></tr>
<tr><td>aACR Pedi 50 3-months (%)</td><td>53</td><td>31</td><td>38</td><td>0.19</td></tr>
<tr><td>aACR Pedi 70 6-weeks (%)</td><td>20</td><td>9</td><td>25</td><td>0.25</td></tr>
<tr><td>aACR Pedi 70 3-months (%)</td><td>47</td><td>25</td><td>19</td><td>0.04</td></tr>
<tr><td>JADAS 6-weeks (median)</td><td>12.4</td><td>13.9</td><td>9.6</td><td>0.12</td></tr>
<tr><td>JADAS 3-months (median)</td><td>8.2</td><td>9.0</td><td>11.5</td><td>0.25</td></tr>
</table>

Secondary:
Gastrointestinal symptoms were most frequently reported and were observed 7/32 (22%), 14/32 (44%) and 9/30 (28%) in arm 1, 2 and 3, respectively. Second most reported were mild infectious complications (25% in arm 1, 19% in arm 2 and 43% in arm 3) with eight upper respiratory tract infections documented in arm 3.</td></tr>
<tr><td>De Benedetti et al.[99]
(2010)
TENDER (abstract)

Tocilizumab 8 mg/kg every 2 weeks for patients ≥30 kg or 12 mg/kg every 2 weeks for</td><td>PC, RCT

Patients 2 to 17 years of age with active systemic JIA for ≥6 months with an inadequate response to NSAIDs and corticosteroids</td><td>N=112

12 weeks</td><td>Primary:
Proportion of patients with JRA ACR 30 response plus absence of fever at week 12

Secondary:
Not reported</td><td>Primary:
At week 12, significantly greater proportion of patients treated with tocilizumab achieved JRA 30 response plus absence of fever (85%) compared to patients treated with placebo (24%; P<0.0001).

Significantly greater proportion of patients in the tocilizumab group achieved JRA ACR 50, JRA ACR 70, and JRA ACR 90 responses compared to patients in the placebo group (P<0.0001).

Secondary:</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
patients <30 kg vs placebo				Not reported
Brunner et al.[100] (2015) CHERISH Tocilizumab 8 mg/kg every 4 weeks for patients ≥30 kg vs 8 mg/kg every 4 weeks for patients <30 kg vs 10 mg/kg every 4 weeks for patients <30 kg vs placebo	DB, MC, PC, RCT (OL lead in period) Patients 2 to 17 years of age with active polyarticular JIA for ≥6 months who failed MTX	N=188 24 weeks	Primary: Proportion of patients with JIA ACR 30 flare relative to week 16 Secondary: Proportion of patients with JIA ACR 30, ACR 50, and ACR 70 responses	Primary: Tocilizumab treated patients experienced significantly fewer JIA ACR 30 flare at week 40 compared to patients treated with placebo (25.6 vs 48.1%; P<0.0024). Secondary: At week 40, significantly greater proportion of patients in the tocilizumab group achieved JRA ACR 30 (74.4 vs 54.3%; P=0.0084), JRA ACR 50 (73.2 vs 51.9%; P=0.0050), and JRA ACR 70 (64.6 vs 42.0%; P=0.0032) response compared to patients in the placebo group. The degree of improvement was lower for these endpoints in the tocilizumab 8 mg/kg (<30 kg body weight) group compared to the other two tocilizumab groups (10 mg/kg for patients weighing <30 kg and 8 mg/kg for patients weighing ≥30 kg).
Lupus nephritis				
Rovin et al.[101] (2021) AURORA 1 Voclosporin 23.7 mg orally twice daily	DB, MC, PC, RCT Patients with a diagnosis of systemic lupus erythematosus with lupus nephritis	N=357 52 weeks	Primary: Complete renal response at 52 weeks defined as a composite of urine protein creatinine ratio of 0.5 mg/mg	Primary: The primary endpoint of complete renal response at week 52 was achieved in more patients in the voclosporin group than in the placebo group (41% of patients vs 23% of patients; odds ratio 2.65; 95% CI, 1.64 to 4.27; P<0.0001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo All patients received background of mycophenolate mofetil (1 g twice daily) and rapidly tapered low-dose oral steroids	according to the American College of Rheumatology criteria, and a kidney biopsy within two years that showed class III, IV, or V (alone or in combination with class III or IV)		or less, stable renal function (defined as eGFR≥60 mL/min/1.73 m^2 or no confirmed decrease from baseline in eGFR of >20%), no administration of rescue medication, and no more than 10 mg prednisone equivalent per day for 3 or more consecutive days or for 7 or more days during weeks 44 through 52, just before the primary endpoint assessment Secondary: Safety	The most frequent serious adverse event involving infection was pneumonia, occurring in seven (4%) patients in the voclosporin group and in eight (4%) patients in the placebo group. A total of six patients died during the study or study follow-up period (one [<1%] patient in the voclosporin group and five [3%] patients in the placebo group). None of the events leading to death were considered by the investigators to be related to the study treatments.
Psoriasis				
Saurat et al.[102] (2008) CHAMPION Adalimumab 80 mg at week 0, then 40 mg every other week from week 1 through week 15 vs	DB, DD, MC, RCT Patients ≥18 years of age with moderate to severe psoriasis (>10% of BSA and PASI ≥10), plaque psoriasis for >1 year, stable plaque psoriasis for >2 months, that are	N=271 16 weeks	Primary: Proportion of patients achieving PASI 75 at week 16 relative to baseline Secondary: Proportion of patients achieving PASI 50, PASI 90, PASI 100, and	Primary: At 16 weeks, significantly more patients in the adalimumab group (79.6%) achieved PASI 75 compared to the MTX group (35.5%; RD, 43.7%; 95% CI, 30.8 to 56.7; P<0.001) and placebo group (18.9%; RD, 60.5%; 95% CI, 44.5 to 76.6; P<0.001). The difference in treatment groups was seen starting at two weeks for adalimumab vs MTX (P<0.05) and at four weeks for adalimumab vs placebo (P<0.001). Secondary: At week 16, PASI 100 was achieved in significantly more patients in the adalimumab group (16.7%) compared to the MTX group (7.3%; P<0.04) and the placebo group (1.9%; P<0.001).Significantly more patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
MTX 7.5 mg at week 0, then increased to 10 mg weekly at week 2, then increase to 15 mg weekly at week 4; at week 8, patients not achieving PASI 50 had the dose of MTX increased to 15 mg weekly; at week 12, patients not achieving PASI 50 at week 12 and 8 had the dose of MTX increased to 25 mg weekly vs placebo	candidates for systemic therapy of phototherapy, with plaque psoriasis despite treatment with topical agents and treatment naïve to TNF-antagonists and MTX		PGA	achieved PASI 50, PASI 90 and a PGA of clear or minimal in the adalimumab group compared to the MTX and placebo groups (P<0.001 for all). Rates of reported infectious adverse events were not significantly different between the groups (P value not reported). Total adverse events and serious adverse events were similar.
Papp et al.[103] (2017) Adalimumab 0.8 mg/kg or 0.4 mg/kg SC at week 0, then every other week starting at week one vs methotrexate once weekly by mouth (0.1 to 0.4 mg/kg)	DB, MC, RCT Patients 4 to <18 years of age with severe plaque psoriasis who had not responded to topical therapy	N=114 16 weeks	Primary: PASI75 and clear or minimal PGA score Secondary: PASI90, PASI100, change from baseline in children's dermatology life quality index and Pediatric quality of life inventory scores	Primary: At week 16, the proportion of patients who achieved PASI75 was higher in the adalimumab 0.8 mg/kg group (58%) than in the methotrexate group (32%; P=0.027); 44% of patients in the adalimumab 0.4 mg/kg group achieved PASI75. PASI75 response to adalimumab 0.8 mg/kg was rapid; a significant difference compared with methotrexate was reached by week four (P=0.002). The proportion of patients who achieved PGA score of 0 or 1 after 16 weeks was higher in the adalimumab 0.8 mg/kg group (61%) than in the methotrexate group (41%; P=0.083) or in the adalimumab 0.4 mg/kg group (41%); however, the difference between the adalimumab 0.8 mg/kg and methotrexate groups did not reach significance. Secondary: The proportion of patients who achieved PASI90 at week 16 was higher in the adalimumab 0.8 mg/kg group than in the methotrexate group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P=0.466). A higher, but not significant, proportion of patients achieved PASI100 in the adalimumab 0.8 mg/kg group than in the methotrexate group (P=0.056). The mean decrease (improvement) in children's dermatology life quality index score from baseline was numerically, but not significantly, higher in patients in the adalimumab 0.8 mg/kg group than in patients in the methotrexate group (P=0.304). The mean increase (improvement) from baseline in Pediatric quality of life inventory score was higher in patients in the adalimumab 0.8 mg/kg group than in patients in the methotrexate group (P=0.005).
Strober et al.[104] (2017) UNVEIL Apremilast 30 mg twice daily vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with moderate plaque psoriasis (5 to 10% BSA involvement and sPGA score of 2 on a 6-point scale) who were naïve to systemic and biologic therapy	N=221 16 weeks	Primary: Mean percentage change from baseline in PGAxBSA at week 16 Secondary: Quality of life measures	Primary: At week 16, the mean percentage change from baseline in PGAxBSA score was greater with apremilast (-48.1%) vs placebo (-10.2%; P<0.0001). Secondary: Mean percentage change from baseline in PASI score was greater with apremilast (-40.72%) versus placebo (-3.87%; P<0.0001). DLQI scores were improved with apremilast (-4.8) vs placebo (-2.4; P=0.0008). Mean improvements in the Treatment Satisfaction Questionnaire for Medication, version II, were greater with apremilast versus placebo for global satisfaction (63.2 vs 48.7; P<0.0001) and treatment effectiveness (57.3 vs 38.8; P<0.0001). Most adverse events were mild or moderate; most common were diarrhea, headache, nausea, upper respiratory tract infection, decreased appetite, and vomiting.
Gold et al.[105] (2022) ADVANCE Apremilast 30 mg twice daily vs placebo	DB, PC, RCT Adults with mild-to-moderate psoriasis inadequately controlled or intolerant to ≥1 topical psoriasis therapy who were biologic-naive	N=595 16 weeks	Primary: achievement of sPGA score of 0 (clear) or 1 (almost clear) and ≥2-point reduction at week 16 Secondary: Achievement of BSA-75; change from baseline in BSA; change from	Primary: The primary endpoint was met, with achievement of sPGA scores of 0 (clear) or 1 (almost clear) and ≥2-point reduction from baseline with apremilast compared with placebo at week 16 (21.6% vs 4.1%, P<0.0001). Secondary: All secondary endpoints were met with the achievement of BSA-75 (33.0% vs 7.4%), BSA≤ 3% (61.0% vs 22.9%), ≥4-point reduction in Whole Body Itch Numeric Rating Scale (43.2% vs 18.6%), Scalp PGA 0 or 1 and ≥ 2-point reduction (44.0% vs 16.6 %), and changes from baseline in body surface area, Psoriasis Area and Severity Index, and Dermatology Life Quality Index (all P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			baseline in PASI; achievement of BSA ≤ 3% (baseline BSA > 3%); Whole Body Itch Numeric Rating Scale response (≥ 4-point reduction from baseline; baseline score ≥ 4); achievement of Scalp PGA of 0 (clear) or 1 (almost clear) with a 2-point or greater reduction from baseline (baseline ScPGA ≥ 2); and a change from baseline in Dermatology Life Quality Index total score	
Warren et al.[106] (2021) Certolizumab pegol 200 mg every other week vs certolizumab pegol 400 mg every other week	AC, DB, MC, RCT Adult patients (≥18 years of age) with moderate or severe plaque psoriasis for ≥6 months	N=261 144 weeks	Primary: Proportions of patients achieving PASI 75 Secondary: Safety	Primary: PASI 75 response was maintained in patients continuing 200 mg every other week treatment through Weeks 16 to 144 (Week 144: 96.2%). In patients dosed down at Week 48 (double-blinded 400 mg to 200 mg every other week), PASI 75 decreased (Week 48: 98.7%; Week 144: 85.9%). In patients who received placebo through Weeks 16 to 48, PASI 75 response decreased (Week 48: 60.4%), then increased following Week 48 switch to 200 mg every other week (Week 144: 95.1%). 48 and 36 patients initially randomized to 200 and 400 mg every other week, respectively, were Week 16 PASI 75 non-responders and entered the escape arm; at Week 144, 71.8% and 78.2% achieved PASI 75. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs etanercept biweekly vs placebo At Week 16, certolizumab and etanercept-treated PASI 75 responders were re-randomized to certolizumab 200 mg every other week (Q2W), certolizumab 400 mg Q4W, certolizumab 400 mg Q2W or placebo for maintenance treatment; PASI 75 non-responders entered an OL escape CZP 400 mg Q2W arm. Patients entering the OL extension (OLE; Weeks 48 to 144) from blinded treatment received certolizumab 200 mg Q2W				No new safety signals were identified.
Reich et al.[107] (2017) LIBERATE	DB, PC, RCT Biologic-naive patients ≥18 years of	N=250 104 weeks (outcomes	Primary: Achievement of PASI-75 at Week 16 with apremilast	Primary: At week 16, PASI75 was achieved by more patients receiving apremilast (39.8%) versus placebo (11.9%, P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Apremilast 30 mg BID vs etanercept 50 mg weekly vs placebo through Week 16; thereafter, all patients continued on or switched to apremilast through Week 104. This study was not designed for apremilast vs etanercept comparisons.	age with moderate-to-severe plaque psoriasis	assessed through week 52)	vs placebo Secondary: Achievement of PASI-75 at Week 16 with etanercept vs placebo and improvements in other clinical endpoints vs placebo at Week 16	Secondary: At Week 16, PASI75 response was achieved by significantly more patients receiving etanercept (48.2%) versus placebo (11.9%, P<0.0001). Significant improvements were achieved with apremilast (vs placebo) at Week 16 for the following secondary endpoints: sPGA score of 0 (clear) or 1 (almost clear) (P=0.0005), percentage change from baseline in the psoriasis affected BSA (P=0.0002), PASI-50 response (P=0.0008), change from baseline in DLQI total score and Lattice System Physician's Global Assessment score of 0 (clear) or 1 (almost clear) (P=0.0011).
Bagel et al.[108] (2012) Etanercept 50 mg twice- weekly for 12 weeks followed by etanercept 50 mg weekly plus placebo weekly for 12 additional weeks (Group A)	DB, MC, PC, RCT Patients ≥18 years of age with stable moderate-to-severe plaque psoriasis covering ≥10% of BSA for ≥6 months and PASI scores ≥10 and ≥30% of SSA affected, with PSSI scores ≥15	N=124 24 weeks	Primary: Percentage change in PSSI score at week 12 Secondary: Percentage change in the PSSI score at week 24 for Group B patients, the proportion of patients achieving	Primary: At week 12, Group A experienced a significantly greater mean improvement in PSSI score compared to Group B (86.8 vs 20.4%; P<0.001) with significant improvements as early as week four of treatment. Secondary: At week 24, both Group A and Group B experienced improvements in PSSI scores from baseline (90.6 vs 79.1%, respectively; P value not reported). A significantly greater proportion of patients in Group A compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo twice-weekly for 12 weeks followed by etanercept 50 mg twice- weekly for 12 additional weeks (Group B) Patients discontinued the use of background therapies.			PSSI 75 improvement at week 12, patient satisfaction with treatment at week 12, and safety	Group B experienced a PSSI 75 at week 12 (86 vs 11%; P<0.0001). Significantly more etanercept-treated patients were either satisfied or very satisfied at week 12 compared to placebo (P<0.0001). At week 24, after etanercept treatment, Group B patients' satisfaction increased significantly over their first 12 weeks on placebo (P<0.0001). More than two thirds of Group A patients continued to be satisfied or very satisfied at week 24. The rates of adverse events were comparable between groups, both at week 12 (etanercept vs placebo) and week 24 (etanercept 50 mg twice-weekly vs once-weekly). No serious adverse events were reported at week 12; however, by week 24, three patients had reported serious events. The most commonly reported adverse events were upper respiratory tract infection, injection site reactions, headache, sinus congestion, cough, and ear infection.
Paller et al.[109] (2016) Etanercept once weekly at 0.8 mg/kg (maximum 50 mg)	ES, OL Patients 4 to 17 years of age with moderate to severe plaque psoriasis	N=182 5 years	Primary: Incidence of adverse events Secondary: PASI75, PASI90, clear/almost clear on PGA	Primary: The most commonly reported adverse events were upper respiratory tract infection (37.6%), nasopharyngitis (26.0%), and headache (21.5%). Injection-site reactions were reported by 16 (8.8%) patients. Only one serious adverse event (cellulitis) was considered by the investigator to be related to the investigational product. Secondary: The percentages of patients achieving PASI75 and PASI90 responses from baseline in the parent study remained relatively constant at approximately 60 to 70% and 30 to 40%, respectively, at week 96 through week 264. Similarly, the percentage of patients who achieved sPGA status of clear/almost clear (score 0/1) remained relatively constant at approximately 40 to 50% from week 96 through week 264.
Bachelez et al.[110] (2015) Etanercept 50 mg twice weekly vs	DD, MC, NI, PC, RCT Adult patients with chronic stable plaque psoriasis (for ≥12 months) who were candidates for	N=1101 12 weeks	Primary: Proportion of patients at week 12 with at least a 75% reduction in the PASI score from baseline and the proportion of	Primary: A PASI75 response at week 12 was achieved by 130 (39.5%) of 329 patients in the tofacitinib 5 mg group, 210 (63.6%) of 330 in the tofacitinib 10 mg group, 197 (58.8%) of 335 in the etanercept group, and six (5.6%) of 107 in the placebo group. The proportions of PGA responders at week 12 were 155 (47.1%) in the tofacitinib 5 mg group, 225 (68.2%) in the tofacitinib 10 mg group, 222

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tofacitinib 5 mg twice daily vs tofacitinib 10 mg twice daily vs placebo	systemic or phototherapy and had a PASI score of ≥12 and a PGA of moderate or severe, and had failed to respond to, had a contraindication to, or were intolerant to at least one conventional systemic therapy		patients achieving a PGA score of "clear" or "almost clear" Secondary: Proportion of patients with a 50% reduction and 90% reduction in PASI score, reduction in itch severity item score, decrease in DLQI	(66.3%) in the etanercept group, and 16 (15.0%) in the placebo group. For both coprimary endpoints, tofacitinib 10 mg twice daily was non-inferior to etanercept and was superior to placebo, whereas tofacitinib 5 mg twice daily did not meet the non-inferiority criteria versus etanercept but met the superiority criteria versus placebo. Secondary: PASI50 and PASI90 response rates over time, and the corresponding differences between treatment groups, were similar to those based on the PASI75 outcome. Decreased in itch severity score with active treatments were greater than the clinically important difference of 1.64. At week 12, a clinically meaningful improvement in DLQI score (a reduction by five points or more) was achieved by 66.3% of patients in the tofacitinib 10 mg group, 78.2% of patients in the tofacitinib 5 mg group, 74.7% of patients in the etanercept group, and 31.8% of patients in the placebo group, in patients with a baseline score of five or higher (P<0.0001 for each active treatment vs placebo).
Griffiths et al.[111] (2010) Etanercept 50 mg twice weekly vs ustekinumab 45 mg at weeks 0 and 4 vs ustekinumab 90 mg at weeks 0 and 4	MC, PG, RCT Patients ≥18 years of age, with a diagnosis of plaque psoriasis for ≥6 months, were candidates for phototherapy or systemic therapy, had a baseline PASI score ≥12, had a score ≥3 on physician's global assessment, had ≥10% BSA	N=903 12 weeks	Primary: PASI 75 at week 12 Secondary: Physician's global assessment score of 0 or 1, PASI 90, difference between PASI at week 12 and 12 weeks after retreatment	Primary: A greater number of patients achieved PASI 75 in the ustekinumab 45 mg group (67.5%) and ustekinumab 90 mg group (73.8%) than in the etanercept group (56.8%; P=0.01 vs ustekinumab 45 mg; P<0.001 vs ustekinumab 90 mg). Secondary: A larger proportion of ustekinumab patients met criteria for cleared or minimal on a physician's global assessment (score of 0 or 1) compared to etanercept patients (65.1% on ustekinumab 45 mg and 70.6% on ustekinumab 90 mg vs 49.0% on etanercept; P<0.001 for each comparison vs etanercept). PASI 90 was achieved by 36.4% of ustekinumab 45 mg patients, 44.7% of ustekinumab 90 mg patients and 23.1% of etanercept patients (P<0.001, for each comparison vs etanercept).

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Patients without a response to etanercept at week 12, received ustekinumab 90 mg at weeks 16 and 20; patients without a response to ustekinumab at week 12 received one additional study dose at week 16.	involvement, and had inadequate response, intolerance, or contraindication to ≥1 conventional systemic agent (i.e., MTX, cyclosporine, or psoralen plus ultraviolet A) and no previous treatment with etanercept or ustekinumab			Of the patients that crossed over to ustekinumab from etanercept, 48.9% achieved a PASI 75, 23.4% achieved PASI 90, 40.4% achieved cleared or minimal on the physician's global assessment. Of patients that received retreatment with ustekinumab, 84.4% had a physician's global assessment score of 0 to 2. The most commonly occurring adverse event in the etanercept group was injection site erythema (14.7%) and was reported more often than in the two ustekinumab groups combined (0.7%). At least one serious adverse effect was reported in 1.9, 1.2 and 1.2% of patients in the ustekinumab 45 mg, 90 mg and etanercept groups, respectively.
Schmitt et al.[112] (2008) Adalimumab, cyclosporine, efalizumab*, etanercept, or infliximab vs placebo	MA RCTs in patients with moderate to severe psoriasis	16 trials Duration varied	Primary: PASI 75 Secondary: Tolerability	Primary: Compared to placebo a greater proportion of patients receiving adalimumab (RD, 64%; 95% CI, 61 to 68; P<0.00001), cyclosporine (RD, 33%; 95% CI, 13 to 52; P<0.0009), efalizumab (RD, 24%; 95% CI, 19 to 30; P<0.00001), etanercept 50 mg twice weekly (RD, 44%; 95% CI, 40 to 48; P<0.00001) and etanercept 25 mg twice weekly (RD, 30%; 95% CI, 25 to 35; P<0.00001) achieved PASI 75 response. The infliximab group had the greatest response (RD, 77%; 95% CI, 72 to 81; P<0.00001). Secondary: Average monthly rates of serious adverse events were 0.5% with adalimumab, 2.3% with cyclosporine, 1.2% with efalizumab, 0.6% with etanercept 50 mg twice weekly and 1.1% with infliximab. This outcome was not reported in with etanercept 25 mg twice weekly. Withdrawals due to adverse events occurred on average in 0.3% of adalimumab-treated patients, 16.1% of cyclosporine-treated patients, 1.2% of efalizumab-treated patients, 0.5% of patients on the lower dose of etanercept and 0.4% of patients on the higher dose of etanercept and 1.3% of infliximab-treated individuals/month.
Langley et al.[113] (2014) ERASURE and FIXTURE	DB, DD, MC, PC, PG, RCT (FIXTURE also AC)	N=2,044 (ERASURE: 737 FIXTURE:	Primary: Proportion of patients that had a PASI75 and a score	Primary: <u>ERASURE</u> A greater proportion of patients who received secukinumab 300 mg

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ERASURE: secukinumab 300 mg vs secukinumab 150 mg vs placebo FIXTURE: secukinumab 300 mg vs secukinumab 150 mg vs etanercept vs placebo All drugs were dosed once weekly at baseline and at weeks one, two and three, then every four weeks starting	Patients 18 years of age or older with moderate-to-severe plaque psoriasis for at least six months and poorly controlled with topical treatments, phototherapy, systemic therapy or a combination of those therapies, score ≥12 on the PASI scale, 3 or 4 on the modified investigator global assessment, and 10% or more involvement in body surface area	1,306) 52 weeks	of 0 or 1 in the investigator's global assessment at week 12. Secondary: PASI90 at week 12, maintenance of PASI75 and a 0 or 1 response on the investigator's global assessment from week 12 to week 52, and PASI100 at week 12, , improvement in DLQI, improvement in pain/itching/ scaling	(200/245 [81.6%]) and secukinumab 150 mg (174/243 [71.6%]) had a PASI75 response at week 12 compared to placebo (11/246 [4.5%]; P<0.001 for both comparisons). Additionally, a greater proportion of patients who received secukinumab 300 mg (160/245 [65.3%]) and secukinumab 150 mg (125/244 [51.2%]) had a response of 0 or 1 on the modified investigator's global assessment at week 12 compared to placebo (6/246 [2.4%]; P<0.001 for both comparisons). FIXTURE The proportion of patients who had a PASI75 response at week 12 was 77.1% (249/323), 67.0% (219/327), 44.0% (142/323), and 4.9% (16/324) for secukinumab 300 mg, secukinumab 150 mg, etanercept, and placebo respectively. Both secukinumab 300 mg and 150 mg had a statistically significant greater proportion of patient who achieved PASI75 at week 12 compared with etanercept and placebo (P<0.001 for each secukinumab dose when compared to either etanercept or placebo). The proportion of patients who had a 0 or 1 response on the modified investigator's global assessment at week 12 was 62.5% (202/323), 51.1% (167/327), 27.2% (88/323), and 2.8% (9/324) for secukinumab 300 mg, secukinumab 150 mg, etanercept, and placebo respectively. Both secukinumab 300 mg and 150 mg had a statistically significant greater proportion of patient who had a 0 or 1 response on the modified investigator's global assessment at week 12 compared with etanercept and placebo (P<0.001 for each secukinumab dose when compared to either etanercept or placebo). Secondary: ERASURE A greater proportion of patients who received secukinumab 300 mg (145/245 [59.2%]) and secukinumab 150 mg (95/243 [39.1%]) had a PASI90 response at week 12 compared to placebo (3/246 [1.2%]; P<0.001 for both comparisons).

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from week four.				PASI75 was maintained from week 12 to 52 for 80.5% (161/200) and 72.4% (126/174) of patients in the secukinumab 300 mg and 150 mg groups respectively. A 0 or 1 response on the modified investigator's global assessment was maintained from week 12 to 52 for 74.4% (119/160) and 59.2% (74/125) of patients in the secukinumab 300 mg and 150 mg groups respectively. PASI100 at week 12 was reached by 28.6%, 12.8% and 0.8% of patients in the secukinumab 300 mg, secukinumab 150 mg, and placebo groups respectively. There was a statistically significant greater proportion of patients who achieved PASI100 in both the secukinumab groups compared to placebo (P<0.001 for both comparisons). Patients in both secukinumab groups reported significant improvements in DLQI, itching, pain and scaling by week 12 compared to etanercept and placebo groups (P values not reported). <u>FIXTURE</u> A greater proportion of patients who received secukinumab 300 mg (175/323 [54.2%]) and secukinumab 150 mg (137/327 [41.9%]) had a PASI90 response at week 12 compared to placebo (5/324 [1.5%]; P<0.001 for both comparisons). Additionally both secukinumab groups had a significantly higher proportion of patients that achieved PASI90 at week 12 compared with the etanercept group (67/323 [20.7%]; P<0.001 for both comparisons). PASI75 was maintained from week 12 to 52 for 84.3% (210/249), 82.2% (180/219), and 72.5% (103/142) of patients in the secukinumab 300 mg, secukinumab 150 mg, and etanercept groups respectively. When compared to etanercept, both secukinumab 300 mg and secukinumab 150 mg had a statistically significant greater proportion of patients that maintained PASI75 from week 12 to 52 (P<0.001 and P=0.009 for the 300 mg and 150 mg dose respectively). A 0 or 1 response on the modified investigator's global assessment was

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				maintained from week 12 to 52 for 79.7% (161/202), 67.7% (113/167), and 56.8% (50/88) of patients in the secukinumab 300 mg, secukinumab 150 mg, and etanercept groups respectively. When compared to etanercept, both secukinumab 300 mg and secukinumab 150 mg had a statistically significant greater proportion of patients that maintained 0 or 1 response on the modified investigator's global assessment from week 12 to 52 (P<0.001 and P=0.002 for the 300 mg and 150 mg dose respectively). PASI100 at week 12 was reached by 24.1%, 14.4%, 4.3% and 0% of patients in the secukinumab 300 mg, secukinumab 150 mg, etanercept, and placebo groups respectively. There was a statistically significant greater proportion of patients who achieved PASI100 in both the secukinumab groups compared to etanercept (P<0.001 for both comparisons). There was no comparison done with placebo as no patients achieved PASI100 at week 12. Patients in both secukinumab groups reported significant improvements in DLQI, itching, pain and scaling by week 12 compared to placebo groups (P values not reported).
Bodemer et al.[114] (2021) Secukinumab low dose (LD) vs secukinumab high dose (HD) vs etanercept weekly subcutaneous dose of 0.8 mg/kg (up to a maximum of 50	DB, MC, RCT Patients 6 to <18 years of age with severe chronic plaque psoriasis	N=162 52 weeks	Primary: Proportion of patients achieving PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at week 12 Secondary: Proportion of patients achieving PASI 90 at week 12	Primary: The co-primary objectives of the study were met with both secukinumab doses (LD and HD) showing superior efficacy compared to placebo (P<0.0001) with respect to PASI 75 response (80.0%, 77.5% vs. 14.6%) and IGA mod 2011, 0 or 1 response (70%, 60% vs. 4.9%) at Week 12. Secondary: Both secukinumab doses were superior to placebo (P<0.0001) with respect to PASI 90 response at Week 12 (72.5%, 67.5% vs. 2.4%). The efficacy of both doses was sustained to Week 52 with secukinumab achieving higher responses vs. etanercept (PASI 75/90/100: LD, 87.5%/75.0%/40.0% and HD, 87.5%/80.0%/47.5% vs. etanercept, 68.3%/51.2%/22.0% and IGA 0 or 1: LD, 72.5% and HD, 75.0% vs. etanercept, 56.1%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg) vs placebo Patients randomized to secukinumab treatment arms (HD and LD) received a dose based on their weight category: patients weighing ≥50 kg received 150 mg (LD group) or 300 mg (HD group), those weighing 25 to <50 kg received 75 mg (LD group) or 150 mg (HD group), and patients weighing <25 kg received 75 mg for both dose groups				
Bagel et al.[115] (2021) CLARITY Secukinumab 300 mg at baseline; weeks 1, 2, 3 and 4 and then every 4 weeks thereafter until week 48 vs	DB, MC, PG, RCT Adult patients with moderate to severe chronic plaque psoriasis, as defined by PASI ≥ 12, IGA mod 2011 score ≥ 3 and affected body surface area involvement ≥10% with disease inadequately	N=1,102 52 weeks	Primary: Proportion of patients achieving PASI 90 and IGA mod 2011 0 or 1 response (co-primary endpoints) at week 12 Secondary: Achievement of PASI 75, PASI 90,	Primary: Secukinumab 300 mg showed superiority over ustekinumab 45/90 mg in the achievement of PASI 75, PASI 90 and PASI 100, as well as IGA mod 2011 0/1 and IGA mod 0 responses at every time point from week 4 through 52. Secondary: At week 52, a greater proportion of patients receiving secukinumab 300 mg than those receiving ustekinumab 45/90 mg achieved PASI 75 (89.0% vs. 82.1%; OR, 1.74; 95% CI, 1.21 to 2.50; P=0.0013), PASI 90 (73.2% vs. 59.8%; OR, 1.84; 95% CI, 1.41 to 2.41; P<0.0001) and PASI 100 (48.9% vs. 33.5%; OR, 1.92; 95% CI, 1.48 to 2.47; P<0.0001) responses. A greater proportion of patients receiving secukinumab 300 mg than those

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ustekinumab (45 mg for patients weighing ≤ 100 kg or 90 mg for patients weighing >100 kg) at baseline, week 4, and then every 12 weeks thereafter until week 40	controlled by topical treatments, phototherapy and/or previous systemic therapy		PASI 100, IGA mod 2011 0/1, IGA mod 2011 0 and Dermatology Life Quality Index (DLQI) responses of no effect (0/1) through week 52	receiving ustekinumab 45/90 mg also achieved IGA mod 2011 0/1 (76.0% vs. 60.2%; OR, 2.12; 95% CI, 1.61 to 2.79; P<0.0001) and IGA mod 2011 0 (50.3% vs. 33.8%; OR, 2.00; 95% CI, 1.55 to 2.57; P<0.0001) responses.
Psoriatic Arthritis				
Mease et al.[116] (2017) Abatacept 125 mg SC weekly vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of psoriatic arthritis with a minimum of both three swollen and three tender joints, active plaque psoriasis, and inadequate response or intolerance to ≥1 non-biologic DMARD	N=424 24 weeks	Primary: ACR20 at week 24 Secondary: Proportions of patients with an HAQ-DI response (reduction from baseline, ≥0.35), an ACR20 response in the TNFi-naïve and TNFi-exposed subgroups and a radiographic non-progression (change from baseline score, ≤0)	Primary: Abatacept treatment resulted in a significantly higher proportion of patients achieving an ACR20 response at week 24 versus placebo (39.4 vs 22.3%; P<0.001). Secondary: Although abatacept numerically increased HAQ-DI response rates at week 24, this was not statistically significant (31.0 vs 23.7%; P=0.097). The benefits of abatacept were seen in ACR20 responses regardless of TNF inhibitor exposure and in other musculoskeletal manifestations, but significance could not be attributed due to ranking below HAQ-DI response in hierarchical testing.
Genovese et al.[117] (2007) Adalimumab 40 mg every other week vs placebo	DB, MC, RCT Patients with moderately to severely active PsA with an inadequate response to DMARD therapy	N=100 24 weeks	Primary: ACR 20 response at week 12 Secondary: ACR 50 response, ACR 70 response, PsARC scores, assessments of disability, psoriatic	Primary: At week 12, an ACR 20 response was achieved by 39% of adalimumab patients vs 16% of placebo patients (P=0.012). Secondary: ACR 50 and ACR 70 responses were also achieved by significantly more patients on adalimumab (25 and 14%, respectively) compared to patients on placebo at week 12 (2 and 0%, respectively; P=0.001 for ACR 50 and P=0.013 for ACR 70).

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Patients who completed a 12 week blinded phase could elect to receive OL therapy.			lesions, and quality of life	A PsARC response was achieved by 51% of adalimumab patients vs 24% of placebo patients (P=0.007). At week 12, measures of skin lesions (-3.7 units with adalimumab vs -0.3 units with placebo; P≤0.001) and disability were statistically significantly improved with adalimumab. Adalimumab use was associated with significant mean improvements from baseline in components of quality of life assessments such as physical functioning (P=0.027), bodily pain (P=0.007), general health (P=0.017) and mental health (P=0.009). OL adalimumab provided continued improvement for adalimumab patients and initiated rapid improvement for placebo patients, with ACR 20 response rates of 65 and 57%, respectively, observed at week 24. Serious adverse events occurred at a similar frequency during therapy with placebo (4.1%), blinded adalimumab (2.0%), and OL adalimumab (3.1%). Adalimumab use was not associated with serious infections.
Mease et al.[118] (2005) Adalimumab 40 mg every other week vs placebo Stable doses of MTX were allowed and corticosteroid or DMARD rescue therapy was permitted in patients without at least a	DB, MC, PG, RCT Patients ≥18 years of age with moderately to severely active PsA with active psoriatic skin lesions or a documented history of psoriasis and a history of inadequate response to NSAIDs	N=315 24 weeks	Primary: ACR 20 response at 12 weeks, change in mTSS at week 24 Secondary: ACR 20 response at 24 weeks, ACR 50 and ACR 70 response at weeks 12 and 24, measures of joint disease, disability, quality of life, and severity of skin disease in patients	Primary: At week 12, 58% of the adalimumab treated patients achieved an ACR 20 response, compared to 14% of the placebo-treated patients (P<0.001). The mean change in the mTSS of radiographic structural damage was -0.2 in patients receiving adalimumab and 1.0 in those receiving placebo (P<0.001). Secondary: ACR 20 response at 24 weeks was 57% with adalimumab and 15% with placebo (P<0.001). An ACR 50 response was detected in 36% of adalimumab-treated individuals at 12 weeks and 39% of adalimumab-treated individuals at week 24 compared to 4 and 6% of those on placebo, respectively (P<0.001 for both outcomes).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
20% reduction in swollen and tender joints by week 12.			with psoriasis involving at least 3% of BSA	An ACR 70 response was found in 20% in the adalimumab arm and 1% in the placebo arm at 12 weeks and 23 and 1% at 24 weeks (P<0.001). PsARC response was achieved with adalimumab in 62% at 12 weeks and 60% at 24 weeks compared to 26 and 23% on placebo, respectively (P value not reported). Among the 69 adalimumab treated patients evaluated with the PASI, 59% achieved a PASI 75 improvement response at 24 weeks, compared to 1% of placebo-treated patients (P<0.001). Disability and quality of life measures were also significantly improved with adalimumab treatment compared to placebo treatment (P<0.001 for changes in both HAQ-DI and SF-36 PCS scores at weeks 12 and 24). Changes in SF-36 MCS scores were not statistically significant between groups at both week 12 (P=0.708) and week 24 (P=0.288). The rates of overall and serious adverse events were similar among groups.
McInnes et al.[119] (2020) EXCEED Adalimumab 40 mg was administered every 2 weeks from baseline until week 50 vs secukinumab 300 mg was administered at baseline, weeks 1, 2, 3, and 4, and then every 4 weeks until	AC, DB, MC, PG, RCT Patients ≥18 years of age with a diagnosis of psoriatic arthritis, had active plaque psoriasis with at least one plaque of at least 2 cm diameter or nail changes consistent with psoriasis or documented history of plaque psoriasis, were naive to treatment with	N=853 52 weeks	Primary: Proportion of patients achieving ACR20 at week 52 Secondary: PASI 90 response, ACR50 response, mean change from baseline in HAQ-DI score, and resolution of enthesitis (based on Leeds Enthesitis Index [LEI] criteria) at week 52	Primary: The primary endpoint of superiority of secukinumab versus adalimumab for ACR20 response at week 52 was not met. 67% of patients in the secukinumab group has an ACR20 response at week 52 versus 62% in the adalimumab group (OR, 1.30; 95% CI, 0.98 to 1.72; P=0.0719). Secondary: As the superiority of secukinumab versus adalimumab was not established for the primary endpoint, key secondary endpoints in the hierarchy were not formally tested for statistical significance.

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week 48	biologicals, had previously been treated with csDMARDs (including but not limited to methotrexate) with an inadequate response or had stopped treatment due to safety or tolerability problems, and had a previous inadequate response to NSAIDs for at least 4 weeks before randomization			
McInnes et al.[120] (2021) SELECT-PsA 1 Adalimumab (40 mg subcutaneous every other week) vs upadacitinib 15 mg or 30 mg orally once daily vs placebo	AC, DB, MC, RCT Patients ≥18 years of age, had received a diagnosis of psoriatic arthritis, fulfilled the Classification Criteria for Psoriatic Arthritis, and had historical or current plaque psoriasis	N=1,704 24 weeks	Primary: Proportion of patients achieving ACR20 at week 12 with upadacitinib as compared with placebo Secondary: Comparisons of upadacitinib with adalimumab	Primary & Secondary: At week 12, an ACR20 response occurred in 303 patients (70.6%) receiving the 15-mg dose of upadacitinib, in 332 (78.5%) receiving the 30-mg dose of upadacitinib, in 153 (36.2%) receiving placebo, and in 279 (65.0%) receiving adalimumab. The between-group differences were as follows: 15-mg dose of upadacitinib as compared with placebo, 34.5 percentage points (95% CI, 28.2 to 40.7; P<0.001); 30-mg dose of upadacitinib as compared with placebo, 42.3 percentage points (95% CI, 36.3 to 48.3; P<0.001); 15-mg dose of upadacitinib as compared with adalimumab, 5.6 percentage points (95% CI, −0.6 to 11.8; the hierarchical analysis failed at this point, so no P value is given); and 30-mg dose of upadacitinib as compared with adalimumab, 13.5 percentage points (95% CI, 7.5 to 19.4; P<0.001).
Kavanaugh et al.[121] PALACE 1	PC, RCT	N=504	Primary: Proportion of	Primary: At week 16, significantly more patients receiving apremilast 20 mg BID

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(2014) Apremilast 20 mg BID vs apremilast 30 mg BID vs placebo	Patients ≥18 years of age with a diagnosis of psoriatic arthritis with a minimum of both three swollen and three tender joints, despite prior treatment with traditional DMARDs and/or biologic treatment or concurrent treatment with traditional DMARDs	24 weeks	patients achieving ACR20 at week 16 Secondary: Change from baseline to week 16 in HAQ-DI, safety	(31.3%; P=0.0140) and 30 mg BID (39.8%; P=0.0001) achieved an ACR20 response versus placebo (19.4%). Secondary: At week 16, apremilast was associated with significantly greater reductions (improvements) in HAQ-DI compared with placebo. During the 24 weeks, the adverse events occurring in ≥5% of any treatment group included diarrhea, nausea, headache, and upper respiratory tract infection. Discontinuations due to adverse events were comparable across groups (placebo: 4.8%; apremilast 20 mg BID: 6.0%; apremilast 30 mg BID: 7.1%).
Papp et al.[122] (2013) Apremilast 20 mg QD vs apremilast 20 mg BID vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with a six-month history or longer of moderate to severe plaque psoriasis with a PASI score ≥10 and BSA involvement ≥10%	N=260 12 weeks	Primary: PSAI75 Secondary: Change from baseline in PASI, BSA involvement, and PGA, adverse events	Primary: At week 12, a significantly greater proportion of subjects receiving apremilast 20 mg BID achieved PASI75 vs those receiving placebo [21/86 (24.4%) subjects vs. 9/87 (10.3%); P=0.023]. A similar proportion of subjects receiving apremilast 20 mg QD and placebo achieved a PASI75 score at week 12 (10.3% in each group). Secondary: A statistically significantly greater proportion of subjects receiving apremilast 20 mg BID achieved PASI50 vs placebo (P<0.001). Although a greater proportion of subjects receiving apremilast 20 mg BID achieved PASI90 vs placebo, the difference was not statistically significant (P=0.113). A significantly greater mean per cent reduction in PASI score was achieved with apremilast 20 mg QD and 20 mg BID than with placebo [17.4% with placebo; 30.3% with apremilast 20 mg QD (P=0.021); 52.1% with apremilast 20 mg BID (P<0.001)] at week 12. Mean change from baseline in overall static PGA and BSA was only significant in the apremilast 20 mg BID group. The percentage of subjects reporting one or more treatment emergence adverse events was 59.8% with placebo, 67.8% with apremilast 20 mg QD

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and 54.1% with apremilast 20 mg BID.
Schett et al.[123] (2012) Apremilast 20 mg BID vs apremilast 40 mg QD vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with symptomatic PsA for ≥6 months with ≥3 swollen joints and ≥3 tender joints, and to have discontinued treatment with immunosuppressants other than methotrexate for an adequate washout period	N=204 12 weeks	Primary: ACR20 Secondary: Safety	Primary: A significantly greater proportion of patients achieved an ACR20 response at week 12 among the group receiving apremilast 20 mg twice per day (43.5%) and the group receiving apremilast 40 mg once per day (35.8%), when compared with those receiving placebo (11.8%) (P<0.001 and P=0.002, respectively). In patients achieving an ACR20 response, the median time to response was four weeks. Secondary: The percentage of patients affected by ≥1 adverse event was similar across treatment groups. No significant laboratory abnormalities were observed, and no opportunistic infections were reported.
Cutolo et al.[124] (2016) PALACE 2 Apremilast 20 mg BID vs apremilast 30 mg BID vs placebo Patients whose swollen joint count and tender joint count had not	DB, PC, RCT Patients ≥18 years of age with a diagnosis of psoriatic arthritis with a minimum of both three swollen and three tender joints, despite prior treatment with traditional DMARDs and/or biologic treatment or concurrent treatment with traditional DMARDs	N=484 24 weeks	Primary: Proportion of patients achieving ACR20 at week 16 Secondary: Change from baseline to week 16 in HAQ-DI, safety	Primary: ACR20 at Week 16 was achieved by more patients receiving apremilast 20 mg (37.4%; P=0.0002) and 30 mg (32.1%; P=0.0060) versus placebo (18.9%). Secondary: At Week 16, mean change from baseline in HAQ-DI score was greater with apremilast 20 mg (−0.17, P=0.032) and 30 mg (−0.23, P=0.0042) versus placebo (−0.07). Clinically meaningful improvements in signs and symptoms of PsA, physical function, and psoriasis were observed with apremilast through Week 52. The most common adverse events were diarrhea, nausea, headache, and upper respiratory tract infection.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
improved by ≥20% at Week 16 were defined as nonresponders and re-randomized (1:1) to apremilast 20 mg or 30 mg if initially randomized to placebo; if initially randomized to apremilast, treatment continued without a dose change. At Week 24, all patients who were still receiving placebo were re-randomized to apremilast 20 mg or 30 mg.				
Edwards et al.[125] (2016) PALACE 3 Apremilast 20 mg BID vs apremilast 30 mg BID vs placebo Rescue therapy with	DB, PC, RCT Patients ≥18 years of age with a diagnosis of PsA with a minimum of both three swollen and three tender joints, despite prior treatment with traditional DMARDs and/or biologic treatment or concurrent treatment with traditional DMARDs	N=505 52 weeks	Primary: Proportion of patients achieving ACR20 at week 16 Secondary: Change from baseline to week 16 in HAQ-DI, safety	Primary: At week 16, significantly more apremilast 20 mg and 30 mg patients achieved an ACR20 response versus placebo (placebo: 18%; 20 mg: 28%, P=0.0295; 30 mg: 41%, P<0.0001) Secondary: Apremilast 30 mg was associated with a significant improvement in the HAQ-DI score versus placebo at week 16. Mean change from baseline in the HAQ-DI score at week 16 was −0.20 with apremilast 30 mg versus −0.07 with placebo (P=0.0073). Mean change in the HAQ-DI score with apremilast 20 mg (−0.13) did not reach statistical significance versus placebo. At week 52, observed improvements in these measures demonstrated sustained response with continued apremilast treatment. Most adverse events were mild to moderate in severity; the most common were diarrhoea, nausea, headache and upper respiratory tract infection.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
apremilast was designated at week 16 for placebo patients not achieving 20% improvement in swollen and tender joint counts; at week 24, the remaining placebo patients were then randomized to apremilast 20 or 30 mg twice daily				
Kavanaugh et al.[126] (2019) Extension study of PALACE I, II and III Apremilast 20 mg or 30 mg BID	OL, extension study Patients ≥18 years of age with active PsA for ≥ 6 months and three or more swollen joints and three or more tender joints despite prior treatment with DMARDs	N=1,493 5 years	Primary: Rates of patients achieving ACR 20, ACR 50 and ACR 70 responses Secondary: Changes from baseline in swollen joint count and tender joint count, Maastricht Ankylosing Spondylitis Enthesitis Score, proportions of patients achieving a dactylitis count of 0 among those with dactylitis at baseline and change in physical function and skin	Primary: Of patients receiving apremilast 30 mg BID, 55.3% achieved an ACR 20 response at week 52; at week 260, 67.2% of patients who continued apremilast treatment achieved an ACR 20 response. At week 260, 44.4% and 27.4% achieved ACR 50 and ACR 70 responses, respectively. Secondary: Mean swollen joint count and tender joint count improved by 63.3% and 49.8% at week 52, with improvements reaching 82.3% and 72.7%, respectively, with continued treatment at week 260. Among patients with enthesitis or dactylitis at baseline, mean changes in Maastricht Ankylosing Spondylitis Enthesitis Score and dactylitis at week 260 were -2.9 and -2.8, respectively. The proportions of those achieving a Maastricht Ankylosing Spondylitis Enthesitis Score of 0 or a dactylitis count of 0 increased over 52 weeks and were maintained through week 260 with continued apremilast 30 mg treatment. Improvements in physical function were maintained through week 260 in patients who continued receiving apremilast 30 mg BID, including mean change in HAQ-DI and the proportion achieving a minimal clinically important difference of ≥0.35 in the HAQ-DI score.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			involvement	Among patients involving ≥3% of the body surface area at baseline, the proportion of patients achieving PASI-75 response was generally maintained with continued treatment, with 43.6% of patients having a PASI-75 response at week 260.
Nash et al.[127] (2018) Apremilast 30 mg BID vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with a documented diagnosis of active PsA for ≥3 months, met Classification Criteria for Psoriatic Arthritis and have at least three swollen and three tender joints, CRP of ≥0.2 mg/dL and be biological DMARD-naïve	N=219 52 weeks	Primary: ACR 20 response at 16 weeks Secondary: 28-joint DAS, morning stiffness duration and severity and physical function assessments	Primary: The ACR 20 response rate at week 16 was significantly greater in patients receiving apremilast versus placebo (38.2% [42/110] vs 20.2% [22/109]; P=0.004) with response observed at week 2 (16.4% [18/110] vs 6.4% [7/109]); P=0.025). Secondary: At week 16, apremilast-treated patients demonstrated a significant reduction from baseline in 28-joint DAS score versus placebo (P<0.0001). Reductions continued through week 24 (-1.26 vs -0.76; P=0.005). Improvements in morning stiffness duration were observed with apremilast versus placebo at week 16 (P=0.005) and week 24 (median per cent change: -33.3% vs 0.0%; P=0.001). More apremilast-treated patients showed improvement in morning stiffness severity at week 16 (P=0.015) continuing to week 24 (40.0% vs 20.2%; P=0.002). Apremilast-treated patients experienced improvements in physical disability, as assessed by various outcomes for physical function. Clinically meaningful and significant improvements were observed in physical function, as indicated by decreases in HAQ-DI score at week 16 with apremilast versus placebo (-0.21 vs -0.06; P=0.023). Decreases were observed beginning at week 2 (P=0.040). The improvements seen with apremilast continued through week 24, with a mean reduction of -0.27; however, the mean change did not reach statistical significance compared to placebo (-0.27 vs -0.17; P=0.168).
Mease et al.[128] and van der Heijde et al.[129] (2013) RAPID-PsA Certolizumab 400	DB, MC, PC, RCT Patients ≥18 years of age with adult-onset active PsA for ≥6 months despite treatment with ≥1	N=409 24 weeks	Primary: ACR 20 response at week 12, change from baseline in mTSS at week 24 Secondary:	Primary: A greater proportion of patients treated with CZP 200 mg every two weeks (58.0%) and CZP 400 mg every four weeks (51.9%) achieved an ACR 20 response at week 12 compared to placebo (24.3%; P<0.001 for both comparisons). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg at weeks 0, 2, and 4 then 200 mg every 2 weeks (CZP 200 mg) vs certolizumab 400 mg at weeks 0, 2, and 4 then 400 mg every 2 weeks (CZP 400 mg) vs placebo Concurrent MTX (up to 25 mg/week), SSZ (up to 3 g/day), leflunomide (up to 20 mg/day) at stable doses or oral corticosteroids (≤10 mg/day prednisone or equivalent) were allowed.	DMARD		ACR 20 at week 24, HAQ-DI at week 24, PASI 75 (in patients with least 3% body surface area psoriatic skin involvement) at week 24, and change from baseline in mTSS at week 24	A greater proportion of patients treated with CZP 200 mg every two weeks (63.8%) and CZP 400 mg every four weeks (56.3%) achieved an ACR 20 response at week 24 compared to placebo (23.5%; P<0.001 for both comparisons). At week 24, improvements in HAQ-DI scores from baseline were greater in patients treated with CZP compared to placebo (combined CZP groups: -0.50 vs -0.19; P<0.001). In patients with least 3% body surface area psoriatic skin involvement at baseline, a greater proportion of patients treated with CZP 200 mg every two weeks (62.2%) and CZP 400 mg every four weeks (60.5%) achieved PASI 75 at week 24 compared to placebo (15.1%; P<0.001 for both comparisons). Prespecified imputation analysis led to an estimated mean mTSS change from baseline that was not statistically different between CZP and placebo groups (combined CZP groups: 18.3 vs 28.9; P≥0.05). Post hoc analysis using the median mTSS of the entire population to impute missing values in patients with fewer than two analyzable mTSS suggested that patients treated with CZP had reduced radiographic progression compared to placebo patients (combined CZP groups: 0.06 vs 0.28; P=0.007).
Mease et al.[130] (2000) Etanercept 25 mg twice weekly vs placebo	DB, RCT Patients 18 to 70 years of age with active PsA despite NSAID therapy	N=60 12 weeks	Primary: PsARC, PASI 75 at 12 weeks Secondary: ACR 20 response, ACR 50 response, ACR 70 response, PASI 75, and improvement in	Primary: Eighty-seven percent of etanercept treated patients met the PsARC, compared to 23% of placebo-controlled patients (P<0.0001). PASI 75 improvement was detected in 26% of etanercept-treated patients vs none of placebo treated patients (P=0.0154). Secondary: The ACR 20 was achieved by 73% of etanercept-treated patients compared to 13% of placebo-treated patients (P<0.0001), while

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients on stable doses of corticosteroids (equal to ≤10 mg/day of prednisone) or MTX were permitted to continue therapy.			target psoriasis lesions	approximately 48 and 5% achieved an ACR 50 response and 12% and 0% achieved an ACR 70 response, respectively (P=0.0001 for ACR 50; P value not reported for ACR 70). Of the 19 patients in each treatment group who could be assessed for psoriasis, 26% of etanercept-treated patients achieved a 75% improvement in PASI, compared to none of the placebo-treated patients (P=0.0154). Median target lesion improvements were 50 and 0%, for etanercept and placebo, respectively (P=0.0004). There were no significant differences detected in the rate of adverse events between groups.
Mease et al.[131] (2004) Etanercept 25 mg twice weekly vs placebo Patients who completed a 24 week blinded phase could elect to receive OL therapy in a 48 week extension. Patients on stable doses of corticosteroids (equal to ≤10 mg/day of prednisone) or MTX	DB, MC, RCT Patients 18 to 70 years of age with active PsA despite NSAID therapy	N=205 72 weeks	Primary: ACR 20 response Secondary: ACR 50 response, ACR 70 response, change in mTSS, PsARC, PASI 75, SF-36 Health Survey, HAQ, and safety	Primary: At 12 weeks, 59% of etanercept patients met the ACR 20 improvement criteria for joint response, compared to 15% of placebo patients (P<0.0001), and results were sustained at 24 and 48 weeks. Secondary: At 24 weeks, ACR 50 and ACR 70 responses were achieved in approximately 40 and 15% of etanercept patients and 5 and 1% of placebo patients, respectively (P values not reported). The mean annualized rate of change in the mTSS with etanercept was -0.03 unit, compared to 1.00 unit with placebo (P<0.0001). A PsARC response was achieved by 72 and 70% of etanercept patients at weeks 12 and 24, respectively vs 31 and 23% of placebo patients (P values not reported). At 24 weeks, 23% of etanercept patients eligible for psoriasis evaluation achieved at least 75% improvement in the PASI, compared to 3% of placebo patients (P=0.001). SF-36 PCS scores improved more often with etanercept compared to placebo, but SF-36 MCS scores did not differ significantly between groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
were permitted to continue therapy.				HAQ scores at 24 weeks were significantly improved with etanercept (54%) over placebo (6%; P<0.0001). Injection site reactions occurred at a greater rate with etanercept than placebo (36 vs 9%; P<0.001).
Mease et al.[132] (2019) SEAM-PsA Etanercept 50 mg SC once weekly vs methotrexate 20 mg PO once weekly vs etanercept 50 mg SC and methotrexate 20 mg PO once weekly At or after 24 weeks, patients with an inadequate response to treatment received rescue therapy with etanercept plus methotrexate until week 48	DB, MC, RCT Patients ≥18 years of age with active PsA who were naive to treatment with etanercept and other biologic agents, and had no prior use of methotrexate for PsA	N=851 48 weeks	Primary: ACR 20 response at week 24 Secondary Minimal Disease Activity response, ACR 50 and ACR 70 responses at week 24	Primary: The proportion of patients achieving an ACR 20 response at week 24 was significantly greater among those receiving etanercept monotherapy compared with those receiving methotrexate monotherapy (173/284 [60.9%] versus 144/284 [50.7%]; adjusted P=0.029) and significantly greater among those receiving combination therapy compared with those receiving methotrexate monotherapy (184/283 [65.0%] versus 144/284 [50.7%]; adjusted P=0.005). Secondary: The proportion of patients achieving a Minimal Disease Activity response at week 24 was significantly greater among patients receiving etanercept monotherapy compared with those receiving methotrexate monotherapy (102/284 [35.9%] versus 6/2845 [22.9%]; adjusted P=0.005) and significantly greater among those receiving combination therapy compared with those receiving methotrexate monotherapy (101/283 [35.7%] versus 65/284 [22.9%]; adjusted P=0.005). The proportion of patients achieving an ACR 50 response at week 24 was greater for the etanercept monotherapy group compared with the methotrexate monotherapy group (114/257 [44.4%] versus 77/252 [30.6%]; unadjusted P =0.006) and for the combination therapy group compared with the methotrexate monotherapy group (117/256 [45.7%] versus 77/252 [30.6%]; unadjusted P<0.001). The proportion of patients achieving an ACR 70 response at week 24 was greater with etanercept monotherapy compared with methotrexate monotherapy (75/257 [29.2%] versus 35/253 [13.8%]; unadjusted P<0.001) and greater with combination therapy compared with methotrexate monotherapy (71/256 [27.7%] versus 35/253 [13.8%]; unadjusted P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Kavanaugh et al.[133] (2009) GO-REVEAL Golimumab 50 mg SC once every 4 weeks vs golimumab SC 100 mg once every 4 weeks vs placebo Patients who had used or were currently using MTX, an NSAID, an oral corticosteroid, or a systemic or topical psoriasis treatment were enrolled.	MC, PC, RCT Patients ≥18 years of age with a diagnosis of PsA and active PsA despite current or previous DMARD or NSAID therapy and no evidence of active TB and/or no evidence of latent TB on screening	N=405 24 weeks	Primary: ACR 20 response at week 14 Secondary: Not reported	Primary: Golimumab 50 mg with or without MTX compared to placebo with or without MTX, resulted in a significant improvement in signs and symptoms as demonstrated by ACR 20 response at week 14 (51 vs 9%; P<0.001). Similar ACR 20 responses at week 14 were observed in patients with different PsA subtypes. ACR responses observed in the golimumab treated groups were similar in patients receiving and not receiving concomitant MTX. Secondary: Not reported
Husni et al.[134] (2020) GO-VIBRANT Golimumab 2 mg/kg IV infusion at weeks 0, 4, and every 8 weeks thereafter vs	DB, MC, PC, RCT Adult patients with a diagnosis of PsA for ≥6 months who had not been treated previously with biologics	N=480 52 weeks	Primary: ACR 20 response at week 14 Secondary: Change from baseline in HAQ DI score at week 14, the proportion of patients with an	Primary: At week 14, an ACR20 response was achieved by 75.1% of patients in the golimumab group compared with 21.8% of patients in the placebo group (P<0.001). Greater proportions of patients in the golimumab group achieved an ACR20, ACR50, and ACR70 response at weeks 14 and 24 when compared with placebo. Following placebo-crossover to golimumab at week 24, the proportions of ACR responders in the placebo-crossover group approached those in the golimumab group at week 28. ACR response rates were maintained through week 52 in both groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			ACR50 response at week 14, the proportion of patients with a PASI75 response at week 14, and the change from baseline in total PsA-modified SHS at week 24	Secondary: Greater proportions of golimumab-treated patients had an ACR50 response (43.6% vs 6.3%), an ACR70 response (24.5% vs 2.1%), and a PASI75 response (59.2% vs 13.6%) at week 14 (P<0.001 for all). Patients in the golimumab group had greater mean changes at week 14 in HAQ DI score (–0.60 vs –0.12; P<0.001). At week 24, the mean change in total PsA-modified SHS was –0.4 in the golimumab group and 2.0 in the placebo group (P<0.001). Through week 24, 40.6% of patients in the placebo group and 46.3% of patients in the golimumab group had ≥1 adverse event; infections were the most common type.
Antoni et al.[135] (2005) IMPACT 2 Infliximab 5 mg/kg at weeks 0, 2, 6, 14 and 22 vs placebo	DB, MC, PC, PG, RCT Patients ≥18 year of age with active PsA for ≥6 months, inadequate response to current or previous DMARDs or NSAIDs, ≥1 qualifying lesion and negative serum RF	N=200 24 weeks	Primary: ACR 20 response at week 14 Secondary: PsARC, PASI 75, duration of morning stiffness, dactylitis in hands and feet, and presence or absence of enthesopathy in the feet and SF-36	Primary: At week 14, there was significantly more patients in the infliximab group that achieved an ACR 20 response (58%) compared to the placebo group (11%; P<0.001). This difference continued through week 24 (54 vs 16%; P<0.001). Secondary: A significantly greater percentage of patients in the infliximab treated group had improvement in PsARC (77%) compared to the placebo group (27%; P<0.001) at week 14 and continued through week 24 (70 vs 32%; P<0.001). At weeks 14 and 24, fewer patients in the infliximab group had digits with dactylitis (18 and 12%) compared to the placebo group (30 and 34%; P=0.025 and P<0.001, respectively). Fewer patients in the infliximab group had enthesopathy compared to the placebo group at week 14 (22 vs 34%; P=0.016) and week 24 (20 vs 37%; P=0.002). A significantly higher proportion of patients achieved PASI 75 in the infliximab group compared to the placebo group at weeks 14 and 24 (64 vs 2%; P<0.001 and 60 vs 1%; P<0.001, respectively). At week 14, the physical and mental components of the SF-36 were significantly improved in the infliximab group compared to the placebo group (both P<0.001). There was also significant improvement at week 24

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				in the physical and mental components of the SF-36 in the infliximab group compared to the placebo group (P<0.001 and P=0.047, respectively). Adverse events were similar between the groups. There were a higher proportion of patients who discontinued treatment due to adverse events in the infliximab group compared to the placebo group (4 vs 1%). There were a greater number of patients in the infliximab group that had increased ALT compared to the placebo group (1 vs 6%).
Baranauskaite et al.[136] (2012) RESPOND Infliximab 5 mg/kg infusions at weeks 0, 2, 6 and 14 plus MTX 15 mg/week vs MTX 15 mg/week The use of NSAIDs and oral steroids (maximum dose 10 mg/day of prednisone or equivalent) was allowed if the dose was stable within four weeks before screening and kept stable throughout the study.	MC, OL, PC, PRO Patients ≥18 years of age who were treatment naïve and had active psoriasis in combination with peripheral articular disease with ≥1 of the following for three or more months before screening: distal interphalangeal joint involvement; polyarticular arthritis in the absence of rheumatoid nodules; arthritis mutilans; or asymmetric peripheral arthritis	N=115 16 weeks	Primary: Proportion of patients achieving an ACR 20 response at week 16 Secondary: Proportions of patients with ACR 50 and ACR 70 responses, PASI 75 in patients whose baseline PASI was 2.5 or greater, EULAR response, DAS28 scores, number of digits with dactylitis, Maastricht AS enthesitis score, fatigue scores, and duration of morning stiffness and safety	Primary: In the ITT analysis, an ACR 20 response at week 16 was achieved by significantly more patients treated with infliximab plus MTX compared to patients treated with MTX alone (86.3 vs 66.7%; P=0.021). Secondary: The ACR 50 (72.5 vs 39.6%; P=0.0009) and ACR 70 (49.0 vs 18.8%; P=0.0015) response rates at week 16 were also significantly higher in the infliximab plus MTX group at 16 weeks compared to those receiving MTX alone. In patients with a PASI ≥2.5 or at baseline, a PASI 75 response at week 16 occurred in 97.1% of patients receiving infliximab plus MTX compared to 54.3% of patients receiving MTX alone (P<0.0001). By week 16, the mean reduction in PASI score was 93.3% for patients treated with infliximab plus MTX compared to 67.4% of patients treated with MTX alone (P=0.0029). The mean DAS28 at week 16 improved by 56.5% in the infliximab plus MTX patients compared to 29.7% of patients receiving MTX alone (P<0.0001). The EULAR response at week 16 was achieved in 98% of patients receiving infliximab plus MTX compared to 72.9% of those receiving MTX alone (P<0.0001). A median reduction of two digits with dactylitis was observed at week 16

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				in the patients treated with infliximab plus MTX, while no reduction was observed in the MTX monotherapy group (P=0.0006). Patients treated with infliximab plus MTX experienced a median reduction of two sites with enthesitis at week 16 compared to a reduction of one site in the MTX alone group (P=0.082). A significantly greater reduction from baseline in fatigue scores occurred in the infliximab plus MTX group compared to the MTX monotherapy group at week 16 (70.8 vs 44.0%, respectively; P=0.0003). At week 16, the median change in the duration of morning stiffness was -0.92 hour with combination treatment vs -0.50 hour with MTX alone (P=0.0015). The incidence of adverse events was higher in patients receiving infliximab plus MTX compared to MTX alone. Most adverse events were mild or moderate in severity. One adverse event in each group was considered severe: increased transaminases in the infliximab plus MTX group and renal colic in the MTX-alone group. Treatment related adverse events were reported in 45.6% of the infliximab plus MTX group and 24.1% in the MTX alone group. The most frequent treatment-related adverse event involved hepatic enzyme increases.
Mease et al.[137] (2021) FUTURE 5 Secukinumab 300 mg with a loading dose vs secukinumab 150 mg with a loading dose	DB, MC, PC, RCT Patients (≥18 years of age) with active PsA for at least six months	N=996 2 years	Primary: Clinical end points and radiographic damage Secondary: Safety	Primary: Clinical improvements reported at week 16 were sustained through two years in those patients who were originally randomized to secukinumab and continued to receive secukinumab treatment through two years, based on ACR20 and ACR50 response. The van der Heijde-modified total Sharp score (mean change (SD)) was 0.10 (1.74; 300 mg), 0.52 (2.66; 150 mg) and 0.41 (2.20; 150 mg no load) at two years. The proportion of patients with no radiographic progression (change from baseline in van der Heijde-modified total Sharp score ≤0.5) at two years was 89.5% (300 mg), 82.3% (150 mg) and 81.1% (150 mg no load). Secondary: No new safety findings were reported. The most frequently reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs secukinumab 150 mg without a loading dose vs placebo Drug received at baseline; weeks 1, 2, 3 and 4; and every 4 weeks thereafter; Secukinumab could be escalated from 150 mg to 300 mg starting at week 52				adverse events in any secukinumab group were nasopharyngitis and upper respiratory tract infection.
Nguyen et al.[138] (2022) CHOICE Secukinumab 150 mg vs secukinumab 300 mg vs placebo Patients received treatment every 4 weeks to week 16,	DB, MC, RCT Biologic-naïve patients with moderate to severe psoriatic arthritis in the United States	N=258 52 weeks	Primary: ACR20 response at week 16 of secukinumab 300 mg vs placebo Secondary: Evaluation of efficacy of secukinumab 150 mg vs placebo based on the proportion of patients achieving ACR20 at week 16, and to evaluate the efficacy of secukinumab 300 mg and 150 mg vs	Primary: ACR20 response rates at week 16 were higher with secukinumab 300 mg than with placebo (51.5% vs 23.1%; odds ratio, 3.51; 95% CI, 1.65 to 7.45; P=0.001). Secondary: Secukinumab 150 mg led to a numerically higher ACR20 response rate (36.9%) than placebo, although the OR of 1.92 was not statistically significant (95% CI, 0.89 to 4.15; P=0.10). Secukinumab also led to higher ACR50 and ACR70 response rates at week 16 than placebo. ACR50 response rates were higher with significant ORs for secukinumab 300 mg (28.2%; OR, 6.30; 95% CI, 1.81 to 21.88; P=0.004) and secukinumab 150 mg (24.3%; OR, 4.77; 95% CI, 1.36 to 16.77; P=0.02) vs placebo (5.8%). Both secukinumab doses led to higher ACR70 response rates than placebo, although only secukinumab 300 mg resulted in a significant OR (17.5% vs 1.9%; OR, 10.50; 95% CI, 1.36 to 81.30; P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
with a weekly loading phase from baseline to week 4 (treatment period 1). At week 16, patients randomized to SEC 300 mg continued receiving the same dose and patients randomized to placebo began receiving SEC 300 mg Q4W to week 52 (treatment period 2).			placebo based on the proportion of patients achieving ACR50; ACR70	
Mease et al.[139] (2017) Tofacitinib 5 mg orally twice daily vs tofacitinib 10 mg orally twice daily vs adalimumab 40 mg dose administered SC once every two weeks vs placebo with a blinded switch to the 5 mg tofacitinib	AC, DB, RCT Patients ≥18 years of age with active PsA who previously had an inadequate response to conventional synthetic DMARDs Patients were required to receive a stable background dose of a single conventional synthetic DMARD (methotrexate, sulfasalazine, or leflunomide)	N=422 12 months	Primary: ACR20 and HAQ-DI at month three Secondary: ACR50, ACR70, PASI75 at month three	Primary: At three months, the rate of ACR20 response was 50% in the 5 mg tofacitinib group and 61% in the 10 mg tofacitinib group, as compared with 33% in the placebo group (P=0.01 for the comparison of the 5 mg tofacitinib dose with placebo; P<0.001 for the comparison of the 10 mg dose with placebo). The mean change from baseline in the HAQ-DI score was −0.35 in the 5 mg tofacitinib group and −0.40 in the 10 mg tofacitinib group, as compared with −0.18 in the placebo group (P=0.006 for the comparison of the 5 mg dose with placebo; P<0.001 for the comparison of the 10 mg dose with placebo). Adalimumab resulted in an ACR20 response rate of 52% and in a mean change in the HAQ-DI score of −0.38. Secondary: At month three, the rates of ACR50 response were significantly higher in each tofacitinib group (28% in the 5 mg tofacitinib group and 40% in the 10 mg tofacitinib group) than in the placebo group (10%; P<0.001 for both comparisons), as were the rates of ACR70 response (17% in the 5 mg tofacitinib group and 14% in the 10 mg tofacitinib group, vs 5% in the placebo group; P=0.004 for the comparison of the 5 mg dose with placebo; P=0.02 for the comparison of the 10 mg dose with placebo), and improvements were observed across all ACR components. Adalimumab

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dose at three months vs placebo with a blinded switch to the 10 mg tofacitinib dose at three months				resulted in an ACR50 response rate of 33% and an ACR70 response rate of 19%. Sequential hierarchical testing of the key secondary end points at month three showed a significantly higher rate of PASI75 response in each tofacitinib group than in the placebo group (P<0.001 for both comparisons).
Gladman et al.[140] (2017) OPAL Beyond Tofacitinib 5 mg orally twice daily vs tofacitinib 10 mg orally twice daily vs placebo, with a switch to 5 mg of tofacitinib twice daily at three months vs placebo, with a switch to 10 mg of tofacitinib twice	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of psoriatic arthritis at least six months previously, active plaque psoriasis at baseline, and an inadequate response to at least one TNF inhibitor Patients were required to receive a stable background dose of a single conventional synthetic DMARD (methotrexate, sulfasalazine, or leflunomide)	N=395 6 months	Primary: ACR20 and HAQ-DI at month three Secondary: ACR50, ACR70, PASI75 at month three	Primary: At three months, the rates of ACR20 response were 50% with the 5 mg dose of tofacitinib and 47% with the 10 mg dose of tofacitinib, as compared with 24% with placebo (P<0.001 for both comparisons), and the corresponding mean changes in HAQ-DI score from baseline were −0.39 and −0.35, as compared with −0.14 (P<0.001 for both comparisons). Secondary: The 5 mg and 10 mg doses of tofacitinib yielded a higher response rate than placebo at three months with respect to the ACR50 (P=0.003 and P=0.007, respectively), but not the ACR70. The 10 mg dose of tofacitinib, but not the 5 mg dose, showed a higher rate than placebo with respect to PASI75 response at three months (P<0.001).
Mease et al.[141] (2021)	DB, MC, PC, RCT	N=642	Primary: ACR20 response at	Primary: At week 12, significantly more patients achieved an ACR20 response in

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SELECT-PsA 2 Upadacitinib 15 mg once per day vs upadacitinib 30 mg once per day vs placebo switched to either upadacitinib 15 mg or 30 mg once per day at week 24	Patients ≥18 years of age with active PsA, a diagnosis of PsA with symptom onset for ≥6 months, fulfilled the Classification Criteria for Psoriatic Arthritis (CASPAR),16 had historical or current plaque psoriasis, ≥3 swollen joints (of 66) and ≥3 tender joints (of 68) at screening and at baseline, and an inadequate response or intolerance to at least one biologic DMARD	24 weeks	week 12 Secondary: Multiplicity-controlled additional efficacy assessments	the upadacitinib 15 mg and 30 mg arms versus the placebo arm (56.9%, 63.8% and 24.1%, respectively; P<0.001 for both upadacitinib arms vs placebo). Secondary: The 15 mg and 30 mg doses of upadacitinib showed greater improvement versus placebo with respect to all key secondary endpoints. At week 24, minimal disease activity was achieved by more upadacitinib 15 mg-treated (25.1%) and 30 mg-treated patients (28.9%) versus placebo (2.8%; P<0.001 for both comparisons). By week 12 and through week 24, improvement in psoriasis was observed with both upadacitinib doses versus placebo as measured by PASI75/90/100 (at week 16, P<0.001 for PASI75 and nominal P<0.001 for PASI90/100; nominal P<0.001 for all the other time points) and sIGA 0/1 (P<0.001 at week 16; nominal P<0.001 for weeks 12 and 24). The changes from baseline in self-assessment of psoriasis symptoms were greater for both upadacitinib arms versus placebo at weeks 16 (P<0.001) and 24 (nominal P<0.001).
Rheumatoid Arthritis				
Westhovens et al.[142] (2009) Abatacept intravenous ~10 mg/kg on days 1, 15 and 29 then every four weeks plus MTX 15 mg/weekly vs placebo plus MTX 15 mg/weekly	DB, MC, PC, RCT Patients ≥18 years of age with RA for ≤2 years and ≥12 tender and 10 swollen joints, CRP ≥0.45 mg/dL, RF and/or anti-CCP2 seropositivity and radiographic evidence of bone erosion of the hands/wrists/feet; patients were either	N=509 24 months	Primary: Remission rates (DAS28 <2.6) and structural damage at year one (Genant-modified Sharp scoring system maximum score of 290) Secondary: ACR 50 responses, MCR (ACR 70 maintained for >6 consecutive	Primary: A significantly higher proportion of patients in the abatacept group achieved DAS28-defined remission compared to the placebo group after one year of treatment (41.4 vs 23.3%, respectively; P<0.001). The mean change in structural damage at year one, measured using the Genant-modified Sharp scoring system total scores, was significantly lower in patients treated with abatacept compared to patients treated with placebo (0.63 vs 1.06, respectively; P=0.040). Secondary: A higher proportion of patients treated with abatacept achieved an ACR 50 (57.4 vs 42.3%; P<0.001), ACR 70 (42.6 vs 27.3%; P<0.001) and ACR 90 (16.4 vs 6.7%; P=0.001) compared to patients treated with placebo after one year of treatment.

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	MTX-naive or had previous exposure of 10 mg/week or less for three weeks or less, with none administered		months); DAS28 scores, erosion score (maximum possible 145) and joint-space narrowing score (JSN; maximum possible 145), physical function (improvement of >0.3 units from baseline in the; HAQ-DI), SF-36 scores, proportion of patients achieving ACR 70 and ACR 90 responses, and the proportion of patients without radiographic progression and safety	After one year of abatacept therapy, 27.3% of patients achieved an MCR (ACR 70 maintained for more than six consecutive months) compared to 11.9% of patients receiving placebo alone (P<0.001). Following one year of abatacept treatment, disease activity was significantly reduced compared to patients receiving placebo (-3.22 vs -2.49; P<0.001). Patients treated with abatacept achieved significantly greater improvements from baseline in total score and erosion score compared to patients randomized to the placebo group (P=0.040 and P=0.033, respectively). The changes from baseline in JSN scores were similar between the abatacept and placebo groups (P=0.246). The proportion of patients with no radiographic progression in the abatacept group at one year was 61.2% (95% CI, 55.0 to 67.3) compared to the group receiving placebo 52.9% (95% CI, 46.6 to 59.2), with an estimated difference of 8.3% (95% CI, 21.0 to 17.5). A significantly greater proportion of patients in the abatacept group compared to the placebo group experienced a change from baseline in HAQ-DI score ≥0.3 units following one year of therapy (71.9 vs 62.1%; P=0.024). Abatacept treatment was associated with statistically significant improvements in the mental and physical components of the SF-36 questionnaire compared to the placebo group (P<0.05 for both). The most frequently reported adverse events in the abatacept group were nausea, upper respiratory tract infection and headache. Six deaths were reported; two (0.8%) in the abatacept group and four (1.6%) in the placebo Of the two deaths in the abatacept group, one patient had pneumonia and severe gastrointestinal bleeding and the other had an acute myocardial infarction.

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				The most frequent infections in patients treated with abatacept and placebo respectively, were upper respiratory tract infection in 26 (10.2%) and 26 (10.3%) patients, nasopharyngitis in 21 (8.2%) and 26 (10.3%) patients and influenza in 19 (7.4%) and 23 (9.1%) patients. Serious infections occurred in five (2.0%) abatacept-treated patients (pneumonia, gastroenteritis, cellulitis, pseudomonal lung infection and postoperative wound infection, one patient each) and five (2.0%) patients receiving placebo (pneumonia, three patients; gastroenteritis, one patient; and breast cellulitis and staphylococcal infection, both in the same patient). No patients in the abatacept group discontinued due to an infection. In the abatacept treatment group, autoimmune disorders were reported in six patients compared to five patients in the placebo group. Sixteen patients in the abatacept treatment group experienced infusion related reaction compared to five patients receiving placebo.
Genovese et al.[143] (2011) ACQUIRE Abatacept subcutaneous 125 mg days 1 and 8 then weekly (intravenous loading dose of ~10 mg/kg was also administered on day 1) vs abatacept intravenous ~10 mg/kg on days 1, 15 and 29 then every 4 weeks	DB, DD, MC, RCT Patients with RA (defined by ACR 1987 criteria) and functional class I, II and III (defined by ACR 1991 revised criteria) that had an inadequate response to ≥3 months of MTX therapy (≥15 mg/week), with ≥10 swollen joints, ≥12 tender joints and CRP ≥0.8 mg/dL	N=1,457 6 months	Primary: Proportion of patients achieving ACR 20 at six months Secondary: Proportion of patients achieving ACR 50 and ACR 70	Primary: The proportion of patients achieving ACR 20 with abatacept subcutaneous (76.0%; 95% CI, 72.9 to 79.2) and abatacept intravenous (75.8%; 95% CI, 72.6 to 79.0) was not significantly different (estimated between group difference, 0.3%; 95% CI, -4.2 to 4.8). Secondary: The proportion of patients achieving ACR 50 with abatacept subcutaneous and abatacept intravenous (51.5 vs 50.3%) was not significantly different. The proportion of patients achieving ACR 70 with abatacept subcutaneous and abatacept intravenous (26.4 vs 25.1%) was not significantly different. Adverse events were also similar between the groups.

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Genovese et al.[144] (2018) ACQUIRE extension study Abatacept SC 125 mg weekly	OL, extension study All patients who completed the 6-month DB period from ACQUIRE study	N=1,372 5 years (including initial 6 month DB period)	Primary: Safety, tolerability and efficacy at 5 years Secondary: Not reported	Primary; During long term extension five-year period, 97 (7.1%) patients discontinued treatment because of an adverse event. Incidence rate (IR; event/100 patient-years of exposure; based on long term extension data, 95% CI) for adverse events of interest were the following: serious adverse events 7.73 (6.96 to 8.58), infection 38.60 (36.24 to 41.12), serious infection 1.68 (1.35 to 2.07), malignancies 1.09 (0.84 to 1.42), and autoimmune disorders 1.33 (1.05 to 1.69) and were stable over time. Immunogenicity was assessed in 1,365 patients; during the long-term extension period, a total of 316 (23.2%) patients were positive for anti-abatacept antibodies. No association between immunogenicity and either worsening of abatacept safety or loss of efficacy was noted. Efficacy in the long-term extension was consistent with the DB period and was maintained to the end of the study. As-observed ACR 20, 50, and 70 responses at Day 169 were 80.1% (1,087/1,357), 53.2% (724/1,362), and 27.2% (371/13,62), and at Day 1,821 were 84.6% (356/421), 65.5% (277/423), and 44.9% (191/425), respectively. Secondary: Not reported
Keystone et al.[145] (2012) ATTUNE Abatacept 125 mg subcutaneously once weekly	OL Patients ≥18 years of age with active RA previously refractory to either MTX or anti-TNFs who had received ≥4 years of intravenous abatacept in either of two previous RCTs	N=128 12 months	Primary: Safety at three months Secondary: Immunogenicity at three months, and efficacy at 12 months	Primary: Up to month three, adverse events occurred in 39.8% of patients; no individual adverse events were reported in ≥5% of patients. One adverse event (musculoskeletal pain) led to discontinuation. Overall, 75.6% of patients experienced an adverse event during the cumulative period. After month three, 12 further adverse events were reported, of which three led to discontinuation (breast cancer, sarcoidosis and brain neoplasm). No deaths were reported in the study or during follow-up. Infections reported up to month three (more than one patient) included nasopharyngitis (n=4), urinary tract infection (n=3), bronchitis (n=2), gastroenteritis (n=2), sinusitis (n=2) and upper respiratory tract infection (n=2). No serious infections, malignancies or autoimmune events were reported during the first three months. Serious infections,

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				malignancies or autoimmune events occurring after month three were as follows: one serious infection (pneumonia)), two malignancies (breast and uterine cancer) and two autoimmune events occurred (sarcoidosis and erythema nodosum). Secondary: Eight patients were seropositive based on ELISA through month three. Of these eight, six were already positive prior to enrolment. All seropositive patients continued treatment. Adverse events experienced by the seropositive patients were not consistent with immune-mediated toxicities, except for one patient who developed sarcoidosis and discontinued treatment. None of these patients had an abatacept-induced seropositive result based on the ECL assay. At baseline, mean DAS28 and HAQ-DI scores in the overall population were 3.39 and 0.94, respectively. Improvements in disease activity and physical function achieved during intravenous treatment were maintained through month 12 of subcutaneous treatment.
Haraoui et al.[146] (2011) CanACT Adalimumab 40 mg subcutaneously every other week	MC, OL, PRO Patients ≥18 years of age with RA diagnosed according to the 1987 revised ACR criteria with active disease, (≥5 swollen joints (of 66 joints evaluated) and one of the following: positive RF, ≥1 joint erosions present on x-ray, or a HAQ-DI score ≥1 and an unsatisfactory responses or intolerance to prior	N=879 12 weeks	Primary: Mean change in DAS28 Secondary: Proportion of patients achieving clinical remission (DAS28 <2.6) and low-disease activity (DAS28 <3.2) at week 12, proportion achieving EULAR-moderate and good response, ACR 20, ACR 50, and ACR 70)	Primary: Patients treated with adalimumab achieved significantly lower DAS28 scores at week 12 compared to baseline (4.2 vs 6.1; P<0.001). Secondary: Following 12 weeks of treatment with adalimumab, 15.3 and 28.9% of patients achieved clinical remission (DAS28 <2.6) and low-disease activity (DAS28 <3.2), respectively (P values not reported). At week 12, 25.9% of patients treated with adalimumab were considered EULAR responders to treatment. The proportion of patients who experienced an ACR 20, ACR 50 and ACR 70 response at 12 weeks was 58.4, 30.6 and 12.7%, respectively (P values not reported). At week eight, the proportion of patients who experienced an ACR 20, ACR 50 and ACR 70 response was 52.2, 21.7 and 7.2%, respectively (P values not reported).

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	antirheumatic therapies		responses at weeks four, eight, and 12, mean changes in ACR core components [tender joint count, swollen joint count, ESR, physician and patient assessments, and HAQ-DI	At week four, the proportion of patients who experienced an ACR 20, ACR 50 and ACR 70 response, was 37.6, 10.6 and 2.4%, respectively (P values not reported). Patients treated with adalimumab experienced a decrease in the number of tender joints at week 12 compared to baseline (6.8 vs 19.9; P value not reported) and the number of swollen joints was reduced from 13.2 at baseline to 6.4 after 12 weeks (P value not reported). As measured on a VAS, patient's assessment of pain decreased from a 66.2 at baseline to 37.3 following adalimumab therapy. Patients' assessment of disease activity decreased from 65.1 at baseline to 37.4 at follow up. Similarly physician assessment of disease activity decreased from 63.6 at baseline to 29.0 (P values not reported). The mean HAQ-DI score improved by an average of 0.5 units from 1.5 at baseline to 1.0 after 12 weeks of adalimumab treatment. In addition, the ESR decreased from a mean of 30.3 mm/h at baseline to 20.0 mm/h at 12 weeks (P<0.001). Adverse events were reported in 43.4% of patients treated with adalimumab. Most adverse events were mild to moderate in intensity. The most commonly reported adverse events were injection site reactions (9.9%), headache (5.2%), injection site erythema (3.5%), nausea (3%) and rash (2.8%). Of the treatment-emergent adverse events considered by the investigator to be related to study drug, injection site reaction and headache were the most frequently reported (≥5% of patients).
Keystone et al.[147] (2013) Adalimumab 40 mg subcutaneous injection every other week vs	ES, OL Patients ≥18 years of age with RA (defined by ACR 1987 criteria) despite ≥3 months of MTX (12.5 to 25 mg/week), tender	N=202 10 years	Primary: ACR 20, ACR 50, ACR 70, DAS28-CRP <3.2, clinical remission (DAS 28-CRP <2.6 or SDAI ≤3.3), SDAI, HAQ-DI score, and mTSS at 10 years	Primary: At year 10, 64.2, 49.0, and 17.6% of patients achieved ACR 50, ACR 70, and ACR 90 responses, respectively. Mean DAS28-CRP was 2.6, with 74.1% achieving DAS28-CRP <3.2 at year 10. The proportions of patients achieving DAS28-CRP and SDAI clinical remission states were 59.0 and 33.2%, respectively.

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placebo All patients received concurrent MTX therapy.	joint count ≥9 out of 68, swollen joint count ≥6 out of 66, CRP ≥1 mg/L, and positive for RF or at least one bony erosion		Secondary: Not reported	From baseline to year 10, mean HAQ-DI was reduced by 50%, with 42.2% of patients achieving HAQ-DI <0.5 or normal functionality. Mean change from baseline to year 10 in mTSS was 2.8 units (annual progression rate of approximately 0.3 units/year), suggesting minimal radiographic progression over 10 years. Secondary: Not reported
Genovese et al.[148] (2016) RA-BEACON Baricitinib 4 mg PO daily vs baricitinib 2 mg PO daily vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with IR to ≥1 prior TNF blocker, 6/68 tender joints and 6/66 swollen joints, and hsCRP≥3.6 mg/L without prior biologic DMARD use in one month prior to randomization	N= 527 24 weeks	Primary: Proportion of patients achieving ACR20 at week 12 Secondary: Proportion of patients achieving: DAS28-CRP score ≤3.2 and <2.6, SDAI remission ≤3.3, ACR20/50/70 response rate	Primary: At 12 weeks, there was a greater proportion of patients treated with baricitinib achieving ACR20 at 55% for baricitinib 4 mg, 49% for baricitinib 2 mg, and 27% for placebo (P≤0.001 for both baricitinib groups). Secondary: There was a greater proportion of patients in the baricitinib groups who achieved improvement in DAS28-CRP (16% and 11% vs 4%), ACR50 response rate (28% and 20% vs 8%), and ACR70 response rate (11% and 13% vs 2%) at week 12 compared to placebo (P≤0.01).
Dougados et al.[149] (2016) RA-BUILD Baricitinib 4 mg PO daily plus conventional DMARD vs	DB, MC, PC, RCT Patients ≥18 years of age with IR to ≥1 prior conventional DMARD, ≥3 erosions, 6/68 tender joints and 6/66 swollen joints, and hsCRP≥3.6 mg/L without prior	N= 684 24 weeks	Primary: Proportion of patients achieving ACR20 at week 12 Secondary: Proportion of patients achieving: DAS28-CRP score ≤3.2 and <2.6, SDAI remission	Primary: At 12 weeks, there was a greater proportion of patients treated with baricitinib achieving ACR20 at 62% for baricitinib 4 mg, 66% for baricitinib 2 mg, and 40% for placebo (P≤0.001 for both baricitinib groups). Secondary: There was a greater proportion of patients in the baricitinib groups who achieved improvement in DAS28-CRP (26% and 26% vs 9%), SDAI remission (9% and 9% vs 1%), ACR50 response rate (33% and 34% vs 13%), and ACR70 response rate (18% and 18% vs 3%) at week 12

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baricitinib 2 mg PO daily plus conventional DMARD vs placebo plus conventional DMARD	biologic DMARD use		≤3.3, ACR50/70 response rate	compared to placebo (P≤0.001 for both baricitinib groups).
Taylor et al.[150] (2017) RA-BEAM Baricitinib 4 mg PO daily vs adalimumab 40 mg SQ every two weeks vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with IR to MTX, RF and ACPA positive, ≥3 erosions, 6/68 tender joints and 6/66 swollen joints, and hsCRP≥6 mg/L without prior biologic DMARD use	N= 1,307 52 weeks	Primary: Proportion of patients achieving ACR20 at week 12 Secondary: Proportion of patients achieving: DAS28-CRP score ≤3.2 and <2.6, SDAI remission ≤3.3, ACR20/50/70 response rate	Primary: At 12 weeks, there was a greater proportion of patients treated with baricitinib achieving ACR20 compared to placebo at 70% for baricitinib and 40% for placebo (P≤0.001). Secondary: There was a greater proportion of patients in the baricitinib group who achieved improvement in DAS28-CRP (24% vs 4%), SDAI remission (8% vs 2%), ACR50 response rate (45% vs 17%), and ACR70 response rate (19% vs 5%) at week 12 compared to placebo (P≤0.001). There was a greater proportion of patients in the baricitinib group who achieved DAS28-CRP ≤3.2 (44% versus 35%) and ACR50 response rate (45% versus 35%) at week 12 compared to adalimumab (P≤0.01). Additionally, there was a greater proportion of patients treated with baricitinib who achieved SDAI ≤11 (42% versus 35%) and ACR70 response rate (19% versus 13%) at week 12 compared to adalimumab (P≤0.05).
Fleischmann et al.[151] (2017) RA-BEGIN Baricitinib 4 mg PO daily vs	DB, MC, AC, RCT Patients ≥18 years of age with early active RA, RF or ACPA positive, 6/68 tender joints and 6/66 swollen joints, and limited MTX	N=584 52 weeks	Primary: Noninferiority comparison based on proportion of patients achieving ACR20 at week 24 Secondary: Proportion of	Primary: At 24 weeks, there was a greater proportion of patients achieving ACR20 compared to methotrexate at 77% for baricitinib and 62% for methotrexate (P≤0.001 for noninferiority and P≤0.01 for superiority). Secondary: There was a greater proportion of patients in the baricitinib monotherapy and baricitinib with MTX groups who achieved improvement in DAS28-CRP (40% vs 24%), HAQ-DI score (77% vs 66%), SDAI remission (22%

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baricitinib 4 mg PO daily plus MTX vs MTX	treatment up to three weeks		patients achieving: DAS28-CRP score ≤3.2 and <2.6, improvements in HAQ-DI score, SDAI remission ≤3.3, ACR50/70 response rate	vs 10%), ACR50 response rate (60% vs 43%), and ACR70 response rate (42% vs 21%) at week 24 compared to MTX (P≤0.05 for all comparisons). There was a greater proportion of patients in the baricitinib monotherapy and baricitinib with MTX groups who achieved improvement in DAS28-CRP (44% vs 24%), HAQ-DI score (65% vs 43%), SDAI remission (25% vs 13%), ACR50 response rate (57% vs 38%), and ACR70 response rate (42% vs 25%) at week 52 compared to MTX (P≤0.05 for all comparisons).
Keystone et al.[152] (2008) RAPID 1 Certolizumab 400 mg at weeks 0, 2, and 4 then 200 mg every 2 weeks plus MTX (CZP 200 mg) vs certolizumab 400 mg at weeks 0, 2, and 4 then 400 mg every 2 weeks plus MTX (CZP 400 mg) vs placebo plus MTX Patients were randomized 2:2:1. Concurrent analgesics, NSAIDs or COX2 inhibitors, or oral	DB, MC, PG, RCT Patients ≥18 years of age with a diagnosis of RA (defined by ACR 1987 criteria), for ≥6 months and up to 15 years with active disease despite treatment with MTX	N=982 52 weeks	Primary: ACR 20 at 24 weeks, mean change from baseline in mTSS at 52 weeks Secondary: Mean change from baseline in mTSS at 24 weeks, HAQ-DI, ACR 20 at 52 weeks, ACR 50, and ACR 70 at 24 weeks	Primary: A significantly greater number of ACR 20 responders at 24 weeks were found in the CZP 200 mg group (58.8%) and CZP 400 mg group (60.8%) compared to the placebo group (13.6%; P<0.001). There was no significant difference detected between the two CZP regimens. mTSS were significantly lower with CZP 200 mg (0.4 Sharp units) and 400 mg (0.2 Sharp units) vs placebo (2.8 Sharp units; P<0.001). Secondary: Active treatment was associated with reduced mTSS at 24 weeks compared to placebo (0.2 Sharp units for 200 and 400 mg vs 1.3 Sharp units for placebo; P<0.001). The HAQ-DI score at 52 weeks was -0.60 with CZP 200 mg, -0.63 with CZP 400 mg and -0.18 with placebo (P<0.001). ACR 20 response remained significantly higher with CZP 200 mg over 52 weeks (P<0.001 vs placebo). A significantly greater proportion of individuals achieved ACR 50 and ACR 70 with CZP 200 mg (37.1 and 21.4%) and CZP 400 mg (39.9 and 20.6%) compared to placebo (7.6 and 3.0%; P<0.001) at week 24. Infections and infestations occurred in 56.4% of CZP 200 mg patients, 58.4% of CZP 400 mg patients and 56.9% of placebo patients with serious infections occurring in 5.3, 7.3 and 2.2% of CZP 200 mg, 400 mg and placebo patients, respectively. The most frequent adverse events reported included headache, hypertension and back pain.

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corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.				
Smolen et al.[153] (2009) RAPID 2 Certolizumab 400 mg at weeks 0, 2, and 4 then 200 mg every 2 weeks plus MTX (CZP 200 mg) vs certolizumab 400 mg at weeks 0, 2, and 4 then 400 mg every 2 weeks plus MTX (CZP 400 mg) vs placebo plus MTX Patients were randomized 2:2:1. Concurrent analgesics, NSAIDs or COX2 inhibitors, or oral corticosteroids (≤10 mg/day of prednisone or	DB, MC, RCT Patients ≥18 years of age with a diagnosis of RA (defined by ACR 1987 criteria) for ≥6 months and up to 15 years with active disease despite treatment with MTX	N=619 24 weeks	Primary: ACR 20 at 24 weeks Secondary: ACR 50, ACR 70, mTSS, SF-36 Health Survey and individual ACR core set variables, and safety	Primary: ACR 20 was attained by significantly more individuals receiving CZP 200 mg (57.3%) and CZP 400 mg (57.6%) compared to placebo (8.7%; P≤0.001). Secondary: ACR 50 and ACR 70 were achieved in a significantly greater number of patients in the CZP 200 mg group (32.5 and 15.9%, respectively) and CZP 400 mg group (33.1 and 10.6%, respectively) vs placebo (3.1 and 0.8%, respectively; P≤0.01). CZP 200 mg (0.2; 95% CI, -1.0 to 0.6) and CZP 400 mg (-0.4 mg; 95% CI, -0.7 to -0.1) were associated with a significantly lower change in mTSS than placebo (1.2; 95% CI, 0.5 to 2.0; P≤0.01 compared to CZP 200 mg; P≤0.001 compared to CZP 400 mg). Active treatment resulted in greater improvements in SF-36 scores vs placebo (P<0.001) and ACR core components vs placebo (P<0.001). Serious infection was reported in 3.2% of CZP 200 mg patients, 2.4% of CZP 400 mg patients and 0% of placebo patients. Tuberculosis was reported in five patients receiving certolizumab.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
equivalent) were allowed.				
Fleischmann et al.[154] (2009) FAST4WARD Certolizumab 400 mg every 4 weeks vs placebo Concurrent analgesics, NSAIDs, or oral corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.	DB, MC, RCT Patients 18 to 75 years of age with adult onset RA (defined by ACR 1987 criteria) for ≥6 months, with active disease and failed at least one prior DMARD	N=220 24 weeks	Primary: ACR 20 at 24 weeks Secondary: ACR 50, ACR 70, ACR component scores, DAS 28, patient reported outcomes, and safety	Primary: ACR 20 achievement at 24 weeks was significantly higher with certolizumab (45.5%) than placebo (9.3%; P<0.001). Secondary: A significantly greater proportion of ACR 50 and ACR 70 responders were found in the active treatment group vs the placebo group (22.7 vs 3.7%; P<0.001 and 5.5 vs 0%; P≤0.05, respectively). A significant improvement in all ACR components was also detected among patients on certolizumab vs placebo (P≤0.05). A significantly greater change in DAS 28 was also reported with active treatment (-1.5 vs -0.6 for placebo; P<0.001). Patients reported significant improvements in physical function with certolizumab as measured by HAQ-DI (P<0.001), arthritis pain (P≤0.05) and fatigue (P<0.001). Headache, nasopharyngitis, upper respiratory tract infections, diarrhea and sinusitis occurred in at least 5% of certolizumab patients. There were no reports of tuberculosis or opportunistic infections throughout the study.
Weinblatt et al.[155] (2012) REALISTIC Certolizumab 400 mg at weeks 0, 2 and 4, followed by 200 mg every 2 weeks vs placebo	DB, MC, RCT Patients ≥18 years of age with adult onset RA (defined by ACR 1987 criteria) for ≥3 months, with active disease and failed at least one prior DMARD	N=1063 12 weeks	Primary: ACR 20 at 12 weeks Secondary: ACR 50, ACR 70, DAS 28, and ACR component scores	Primary: ACR 20 achievement at 12 weeks was significantly higher with certolizumab (51.1%) than placebo (25.9%; P < 0.001). Secondary: A significantly greater proportion of ACR 50 and ACR 70 responders were found in the active treatment group vs the placebo group (26.6 vs 9.9%; P<0.001 and 13.0 vs 2.8%; P<0.001, respectively). A significant improvement in all ACR components was also detected among patients on certolizumab vs placebo (P≤0.05). At 12 weeks, 81.1% of patients on certolizumab achieved a DAS28 improvement of at least 1.2 vs 56.5% with placebo (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The most common AEs reported were nausea, upper respiratory tract infections, flare of RA and headaches. Injection and infusion-site reactions occurred in 5.8% of certolizumab patients and 1.0% placebo patients.
Emery et al.[156] (2017) C-EARLY Certolizumab pegol 400 mg SC at weeks 0, 2, 4, then 200 mg every 2 weeks + dose-optimized MTX (CZP+MTX) vs placebo + dose-optimized MTX (PBO+MTX)	DB, MC PC, RCT Patients ≥18 years of age with moderate-to-severe, active, progressive RA with poor prognostic who were DMARD-naïve and had ≤1 year of active RA	N=879 52 weeks	Primary: Proportion of patients with sustained remission (DAS28-ESR <2.6 at both weeks 40 and 52) Secondary: Proportion of patients with sustained low disease activity (DAS28-ESR ≤3.2 at both weeks 40 and 52); hierarchical testing procedure were ACR50 response, change from baseline in HAQ-DI and change from baseline in mTSS, all at Week 52	Primary: Sustained remission was achieved by 28.9% CZP+MTX patients versus 15.0% PBO+MTX patients (P<0.001). Secondary: Sustained low disease activity was achieved by 43.8% CZP+MTX patients versus 28.6% in the PBO+MTX group (P<0.001). All secondary endpoints showed statistically significant differences for CZP+MTX versus PBO+MTX at Week 52, respectively: more patients achieved ACR50 response (61.8 vs 52.6%, P=0.023), greater improvements in physical function (change from baseline in HAQ-DI: −1.00 vs −0.82, P<0.001; HAQ-DI normative function: 48.1 vs 35.7%, P=0.002) and significant inhibition of radiographic progression (change from baseline in mTSS: 0.2 vs 1.8, P<0.001).
Tanaka et al.[157] (2012) GO-FORTH Golimumab 50 mg once every four weeks and MTX (Group 3)	DB, MC, PC, RCT Patients 20 to 75 years of age with RA (diagnosed with ACR 1987criteria) with RA for ≥3 months and were receiving 6 to 8	N=269 24 weeks	Primary: Proportion of patients achieving ACR 20 at week 14 Secondary: Proportion of patients achieving an ACR 50 and	Primary: There was a significantly higher proportion of patients achieving an ACR 20 in the golimumab 50 and 100 mg groups compared to the placebo group (74.7 and 72.1 vs 27.3%; P<0.0001). Secondary: Similarly, more patients in the golimumab 50 and 100 mg groups achieved an ACR 50 compared to the placebo group (43.0 and 37.9 vs 9.1%; P≤0.005).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs golimumab 100 mg once every four weeks and MTX (Group 2) vs placebo and MTX (Group 1)	mg/week oral MTX for RA for ≥3 months before study and active RA (≥4/66 swollen joints and ≥4/68 tender joints at screening/ baseline) and ≥2 of the following criteria at screening/ baseline: CRP >1.5 mg/dL, ESR by the Westergren method of >28 mm/hour, morning stiffness lasting ≥30 minute, radiographic evidence of bone erosion, or anti-cyclic citrullinated peptide antibody-positive or rheumatoid factor-positive		ACR 70 response, ACR-N Index of Improvement, DAS28(ESR) response DAS28(ESR) remission (score <2.6), HAQ-DI, and safety	More patients receiving golimumab 50 or 100 mg achieved an ACR 70 compared to patients receiving placebo (22.1 and 13.8 vs 2.3%; P≤0.005). The ACR-N index of improvement was significantly higher in patients receiving golimumab 50 mg (30%) and golimumab 100 mg (25.85%) compared to placebo (20.00; P<0.001 for both). Significantly more patients in the golimumab 50 mg and 100 mg treatment groups achieved DAS28(ESR) scores for response to treatment compared to placebo (79.5 and 85.5 vs 37.6%; P<0.0001). A higher proportion of patients receiving golimumab 50 mg or 100 mg achieved DAS28(ESR) for remission compared to placebo at 14 weeks (31.4 and 18.4 vs 3.4%; P<0.0001). Patients randomized to golimumab 100 mg and 50 mg treatment groups experienced statistically significant improvements in HAQ-DI scores compared to placebo at 14 weeks (0.32 and 0.39 vs 0.07; P<0.0001). By week 16, 72.7, 75.6 and 78.2% of patients receiving placebo, golimumab 100 mg and 50 mg, respectively, had adverse events. Infections were the most common adverse event in the placebo (39.8%), golimumab 100 mg (38.4%) and golimumab 50 mg (33.3%) treatment groups at week 24. Serious adverse events were relatively uncommon through week 16, occurring in one patient (1.1%) in receiving placebo (intervertebral disc protrusion), one patient (1.2%) in the golimumab 100 mg group (ileus) and two patients receiving golimumab 50 mg (2.3%). By week 24, 11 (5.5%) of the 201 patients treated with golimumab 50 mg or 100 mg had discontinued golimumab due to the following adverse events: infection (n=2), skin disorders (n=2), liver function abnormality (n=2), injury (n=2), bone neoplasm (n=1), aortic dissection (n=1), gastrointestinal disorder (n=1) and elevated blood pressure (n=1 in combination with skin disorder).
Emery et al.[158] (2009)	DB, PC, RCT	N=637	Primary: ACR 50 response	Primary: The golimumab monotherapy group was not statistically different from the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Golimumab 100 mg once every 4 weeks and placebo vs golimumab 50 mg once every 4 weeks and MTX vs golimumab 100 mg once every 4 weeks and MTX vs placebo and MTX	MTX naïve patients ≥18 years of age with a diagnosis of active RA for ≥3 months and not previously treated with a TNF-blocker	24 weeks	at week 24 Secondary: ACR 20, 70, 90 responses at week 24	MTX monotherapy group in ACR response (P=0.053). However, post-hoc modified intent-to-treat analysis (excluding three untreated patients) of the ACR 50 response showed statistically significant difference between the two groups (P=0.049). Secondary: The combined golimumab and MTX groups had greater proportion of patients achieve an ACR 20 response at week 24 compared to placebo and MTX groups (P=0.028 for both groups). ACR 70 response was not significant and ACR 90 response was significant for the golimumab 50 mg and MTX groups.
Keystone et al.[159] (2009) GO-FORWARD Golimumab 100 mg once every 4 weeks and placebo vs golimumab 50 mg once every 4 weeks and MTX vs golimumab 100 mg	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of active RA for ≥3 months despite stable dose of ≥15 mg/week of MTX and not previously treated with a TNF-blocker	N=444 24 weeks	Primary: ACR 20 response at week 14, change from baseline in HAQ at week 24 Secondary: ACR 50, 70, 90 responses and ACR-N EULAR response, remission according to DAS 28, and sustained remission (DAS 28 remission at week 14 and maintained through week 24)	Primary: At week 14, an ACR 20 response was achieved by 33.1% of placebo and MTX-treated patients, 44.4% of golimumab 100 mg and placebo-treated patients (P=0.059), 55.1% of golimumab 50 mg and MTX-treated patients (P=0.001), and 56.2% of golimumab 100 mg and MTX-treated patients (P<0.001). At week 24, the median improvements from baseline in the HAQ-DI scores were -0.13 (P=0.240), -0.38 (P=0.001), and -0.50 (P<0.001), respectively. Secondary: ACR 50 and ACR-N response was significant for all the groups except placebo and MTX; ACR 70 was significant for all the groups except the placebo and MTX and golimumab and placebo groups; ACR 90 was not significant for any of the groups. Greater proportion of patients in the golimumab and MTX groups achieved significant EULAR response.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
once every 4 weeks and MTX vs placebo and MTX				At week 24, clinical remission was achieved by 6.0% of placebo and MTX-treated patients, 12.0% (P=0.087) of golimumab 100 mg and placebo-treated patients, 20.2% (P=0.001) of golimumab 50 mg and MTX-treated patients, and 22.5% (P<0.001) of golimumab 100 mg and MTX-treated patients, respectively. Sustained remission was achieved by 0.8%, 6.3% (P=0.018), 10.2% (P=0.001), and 11.9% (P<0.001), respectively.
Keystone et al.[160] (2016) GO-FORWARD Golimumab 100 mg once every four weeks and placebo vs golimumab 50 mg once every four weeks and MTX vs golimumab 100 mg once every four weeks and MTX vs placebo and MTX Patients with inadequate response could enter early escape at Week 16 to a golimumab +	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of active RA for ≥3 months despite stable dose of ≥15 mg/week of MTX and not previously treated with a TNF-blocker	N=444 5 years	Primary: Adverse events Secondary: ACR and DAS28-CRP scores, HAQ-DI	Primary: Among all patients, 29.5% discontinued study agent through Week 252; of these, 14.4% discontinued because of an adverse event, including worsening of RA (n=6, 1.4%), and 25 (5.6%) discontinued because of unsatisfactory therapeutic effect. Among all golimumab-treated patients, the most common types of adverse event were infections/infestations (80.4%), musculoskeletal and connective tissue disorders (48.4%), and gastrointestinal disorders (46.3%) through Week 268. Common adverse events included upper respiratory tract infection (n=143, 32.9%), bronchitis (n=74, 17.1%), nasopharyngitis (n=74, 17.1%), and cough (n=73, 16.8%). Forty golimumab-treated patients (9.2%) reported ≥1 injection site reaction; none were considered to be serious or severe. A total of 172 (39.6%) golimumab-treated patients had ≥1 serious adverse event, with pneumonia and sepsis being among the most common (n=7, 1.6% for both). The incidence of serious infections was 4.01 (95% CI, 3.14 to 5.05). Secondary: Among all patients, 63.1% had an ACR20, 40.8% had an ACR50, and 24.1% had an ACR70 at Week 256, with no appreciable differences among treatment groups. ACR20 and ACR50 rates were maintained over time through Week 256. At Week 256, 78.2% of all patients had a good or moderate DAS28-CRP response. About 36% of patients were in DAS28-CRP remission, while 21% met either the SDAI or CDAI remission criteria. Mean improvements from baseline to Week 256 in HAQ-DI ranged from 0.34 to 0.52, with an overall mean (SD) improvement of 0.44 (0.71). Among all patients, 61.0% had an improvement in HAQ-DI ≥0.25 and 36.3% achieved a normal HAQ-DI score (≤0.5) at Week 256

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
MTX group, and all remaining placebo + MTX patients crossed over to golimumab 50 mg + MTX at Week 24				compared with 12.6% who had a normal HAQ-DI score at baseline.
Smolen et al.[161] (2009) GO-AFTER Golimumab 50 mg once every 4 weeks vs golimumab 100 mg once every 4 weeks vs placebo Patients were allowed to continue stable doses of concomitant HCQ, MTX, or SSZ during the trial.	DB, PC, RCT Patients ≥18 years of age with a diagnosis of active RA for ≥3 months previously treated with ≥1 dose of a TNF-blocker without a serious adverse reaction	N=461 24 weeks	Primary: ACR 20 response at week 14 Secondary: ACR 50 response at week 14, DAS 28 response at week 14, ACR 20 response at week 24, and improvement from baseline in HAQ scores at week 24	Primary: Golimumab 50 and 100 mg were significantly better than placebo in improving signs and symptoms of RA according to ACR 20 (35.3 and 37.9 vs 18.1%, respectively; P<0.001). ACR 20 responders at week 14 among patients who discontinued previous TNF-blocker therapy due to lack of efficacy included 35.7 and 42.7% of patients in the golimumab 50 and 100 mg groups, respectively, compared to 17.7% of patients in the placebo group (P=0.006, golimumab 50 mg vs placebo; P<0.001, golimumab 100 mg vs placebo). Secondary: ACR 50 response at week 14 was significant for the golimumab-treated groups compared to the placebo group. DAS 28 response was significant for golimumab 50 and 100 mg groups compared to placebo (56.2 and 59.5 vs 30.3%, respectively; P<0.001). ACR 20 response at week 24 was significant for the golimumab-treated groups compared to the placebo group. At week 24, golimumab improved physical function and fatigue according to HAQ and FACIT-F scores, respectively.
Smolen et al.[162] 2012 (GO-AFTER Extension) Golimumab 50 mg once every 4 weeks (Group 1)	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of active RA for ≥3 months previously treated with ≥1 dose of a TNF-blocker	N=459 160 weeks	Primary: ACR 20 Secondary: ACR 50/70,DAS 28, SDAI, and HAQ score	Primary: At week 160, 62.7, 66.7 and 56.8% of patients achieved ACR20 response and 59, 65 and 64% had HAQ improvement ≥0.25 unit in Groups 1, 2 and 3, respectively. Secondary: At week 160, 17.3, 14.8 and 23.5% of patients achieved ACR70 response Groups 1, 2 and 3, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs golimumab 50 mg once every 4 weeks. Dose could be increased to 100 mg if <20% improvement in both tender and swollen joint counts at week 16 of the original study occurred. (Group 2) vs golimumab 100 mg once every 4 weeks (Group 3)	without a serious adverse reaction			DAS 28 response for groups 1, 2 and 3, response was 71.8, 83.8 and 71.4%, respectively. Remission as measured by DAS 28 for groups 1, 2 and 3, response was 16.9, 12.5 and 21.5%, respectively. SDAI remission for groups 1, 2 and 3, response was 11.4, 8.8 and 23.1%, respectively. SDAI scores for low disease activity (3.3 to 11) for groups 1, 2 and 3, response was 34.3, 28.8 and 25.6%, respectively. At week 160, 59, 65 and 64% had HAQ improvement ≥0.25 unit in Groups 1, 2 and 3, respectively.
Weinblatt et al.[163] (2013) GO-FURTHER golimumab 2 mg/kg, at weeks 0 and 4 and every 8 weeks plus MTX vs placebo and MTX	DB, MC, PC, RCT Adult patients with RA for ≥3 months and were receiving 15 to 25 mg/week oral MTX for RA for ≥4 weeks before study and active RA (≥6/66 swollen joints and ≥6/68 tender joints at screening/ baseline) and CRP >1.0 mg/dL, anti- cyclic citrullinated peptide antibody-positive	N=592 24 weeks	Primary: Proportion of patients achieving ACR 20 at week 14 Secondary: DAS28 and HAQ-DI week 14, ACR 50 at week 24, and safety	Primary: There was a significantly higher proportion of patients achieving an ACR 20 in the golimumab group compared to the placebo group (58.5 and 24.9%: P<0.001). Secondary: Significantly more patients in the golimumab treatment groups achieved DAS28 scores for moderate-good response to treatment compared to placebo at 14 weeks (81.3 vs 40.1%; P<0.001). Patients randomized to golimumab treatment groups experienced statistically significant improvements in HAQ-DI scores compared to placebo at 14 weeks (0.5 vs 0.19; P<0.001). Significantly higher proportion of patients randomized to golimumab groups achieved an ACR 50 compared to the placebo group (34.9 vs 13.2%; P≤0.001) at 24 weeks.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	and/or rheumatoid factor-positive			Significantly higher proportion of patients randomized to golimumab groups achieved an ACR 50 compared to the placebo group (34.9 vs 13.2%; P≤0.001) at 24 weeks. Adverse events reported at rates ≥1.0% higher in the golimumab group vs placebo were observed for infections and infestations (24.3 vs 20.8%); nervous system disorders (6.8% vs 4.1%); gastrointestinal disorders (6.6 vs 5.6%); skin and subcutaneous tissue disorders (6.6% vs 3.6%); respiratory, thoracic and mediastinal disorders (4.8 vs 2.5%); vascular disorders (3.8 vs 2.5%); and metabolism and nutrition disorders (2.3 vs 0.0%).
Ishaq et al.[164] (2011) Leflunomide 20 mg once a day vs methotrexate 20 once a week	AC, DB, DD, RCT Patients 18 years of age or older with diagnosis of RA according to ACR criteria for at least four months and less than ten years, who had active disease and have not used a DMARD for at least 28 days prior to the study	N=240 1 year	Primary: Tender joint count, swollen joint count, physician and patient global assessment score Secondary: Morning stiffness, pain intensity, Health Assessment Questionnaire	Primary: Changes in mean scores ± one standard deviation in the tender joint count, swollen joint count, physician and patient global assessments after one year were, respectively, -8.0±7.9, -7.0±7.3, -1.0±1.0 and -1.0±1.1 in the leflunomide group and -10.0±7.9 and -9.0±7.3, -1.0±1.0, 1.0±1.0 in the methotrexate group. The difference between the baseline and the end-point measurements in all the efficacy end-points was significantly greater in patients taking methotrexate compared to patients taking leflunomide (P=0.001). Secondary: Changes in the mean scores ± one standard deviation in morning stiffness (minutes), pain intensity (mm) and the Health Assessment Questionnaire after one year were -87.3±104.1, -27.3±26.6 and -0.48±0.50 in the leflunomide group and -91.5±94.4, -35.2±24.2 and -0.54±0.47 in the methotrexate group, respectively. Withdrawal from the study due to adverse events occurred in 19 and 15% of patients in the leflunomide and methotrexate groups, respectively. Withdrawal from the study due to a lack of efficacy occurred in 7 and 3% of patients in each group, respectively.
Osiri et al.[165] (2003)	MA (33 studies) Patients 18 years	N=not reported	Primary: Tender and swollen joint count, pain	Primary: **Comparison** | **Duration (months)** | **Risk Ratio, 95% CI** ACR 20

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Study Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td>Leflunomide 20 to 25 mg/day

vs

other DMARDs

vs

placebo

Only results pertaining to the scope of this review are included.</td><td>and of age older with active RA</td><td>At least 12 weeks</td><td>level, patient's and physician's global assessment, functional ability, acute phase reactants, radiographic change of bone and joint damage, ACR criteria, DAS 28

Secondary:
Health Related Quality of Life Questionnaire, SF-36, reported side effects, withdrawals</td><td>
<table>
<tr><td>vs methotrexate</td><td>3</td><td>0.96 (0.84, 1.10)</td></tr>
<tr><td>vs methotrexate</td><td>6</td><td>0.96 (0.87, 1.06)</td></tr>
<tr><td>vs methotrexate</td><td>12</td><td>1.08 (0.75, 1.55)</td></tr>
<tr><td>vs methotrexate</td><td>24</td><td>1.05 (0.81, 1.37)</td></tr>
<tr><td>vs sulfasalazine</td><td>6</td><td>1.03 (0.83, 1.28)</td></tr>
<tr><td>vs sulfasalazine</td><td>12</td><td>1.03 (0.83, 1.29)</td></tr>
<tr><td>vs sulfasalazine</td><td>24</td><td>0.73 (0.57, 0.93)</td></tr>
<tr><td colspan="3">ACR 50</td></tr>
<tr><td>vs methotrexate</td><td>12</td><td>0.86 (0.52, 1.44)</td></tr>
<tr><td>vs methotrexate</td><td>24</td><td>0.82 (0.60, 1.10)</td></tr>
<tr><td>vs sulfasalazine</td><td>6</td><td>0.92 (0.64, 1.31)</td></tr>
<tr><td>vs sulfasalazine</td><td>12</td><td>0.93 (0.63, 1.36)</td></tr>
<tr><td>vs sulfasalazine</td><td>24</td><td>0.48 (0.28, 0.80)</td></tr>
<tr><td colspan="3">ACR 70</td></tr>
<tr><td>vs methotrexate</td><td>12</td><td>0.44 (0.26, 0.77)</td></tr>
<tr><td>vs methotrexate</td><td>24</td><td>0.72 (0.44, 1.18)</td></tr>
<tr><td>vs sulfasalazine</td><td>6</td><td>0.66 (0.28, 1.55)</td></tr>
<tr><td>vs sulfasalazine</td><td>12</td><td>1.14 (0.57, 2.25)</td></tr>
<tr><td>vs sulfasalazine</td><td>24</td><td>0.70 (0.34, 1.43)</td></tr>
<tr><td colspan="3">DAS 28<3.2</td></tr>
<tr><td>vs methotrexate</td><td>4</td><td>1.24 (0.64, 2.42)</td></tr>
<tr><td colspan="3">DAS 28 remission</td></tr>
<tr><td>vs methotrexate</td><td>6</td><td>1.0 (0.22, 4.56)</td></tr>
<tr><td colspan="3">DAS 28 low disease activity</td></tr>
<tr><td>vs methotrexate</td><td>6</td><td>1.0 (0.28, 3.63)</td></tr>
<tr><td colspan="3">DAS 28 moderate disease activity</td></tr>
<tr><td>vs methotrexate</td><td>6</td><td>1.05 (0.76, 1.44)</td></tr>
<tr><td colspan="3">DAS 28 high disease activity</td></tr>
<tr><td>vs methotrexate</td><td>6</td><td>0.5 (0.05, 5.22)</td></tr>
</table>
</td></tr>
<tr><td>Scott et al.[166] (2001)

Leflunomide 20 mg/day

vs

sulfasalazine 2</td><td>DB, MC, PC, PG, RCT

Patients ≥18 years of age with active RA functional class I, II, or III with tender joint count ≥6, swollen joint</td><td>N=358

Up to 24 months</td><td>Primary:
Tender and swollen joint counts, doctor and patient global assessments, pain intensity assessment, duration of morning stiffness,</td><td>Primary:
In the six month cohorts, both active groups showed significant improvements in change in tender and swollen joint counts, change in patient and doctor global scores, acute phase reactants, RF, duration of morning stiffness, pain intensity, and functional ability compared with placebo and these continued in the 12 and 24 month cohorts.

At 24 months, the ACR20 response rate with leflunomide was significantly greater than with sulfasalazine (82 vs 60%; P<0.01).</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
grams/day vs placebo	count ≥6; doctor and patient global assessment as fair, poor, or very poor; CRP >20 mg/L or ESR >28 mm/1st hour		ESR, CRP, RF, and functional disability Secondary: Safety	Leflunomide showed significant improvement in functional ability (in both mean health assessment questionnaire scores and functional disability index) compared with placebo and sulfasalazine during the six month placebo controlled phase. Secondary: During the first six months, the most frequent drug related adverse effects in the leflunomide group were diarrhea (leflunomide 17%, sulfasalazine 9%), nausea (leflunomide 10%, sulfasalazine 17%), and alopecia (leflunomide 8%, sulfasalazine 5%). No unexpected adverse events or late toxicity were noted during the two year period. Diarrhea, nausea, and alopecia were less frequent with continued treatment.
Strand et al.[167] (1999) Leflunomide 20 mg per day vs methotrexate 7.5 mg per week vs placebo	DB, MC, RCT Patients ≥18 years of age with active RA for ≥6 months	N=482 12 months	Primary: Comparison of leflunomide therapy with placebo Secondary: Comparisons of leflunomide therapy with methotrexate therapy and methotrexate therapy with placebo	Primary: The ACR20 success rate was significantly higher in the leflunomide treatment group compared with the placebo group (41 vs 19%; P<0.001). Mean changes over time in each component of the ACR response index were significantly better in the leflunomide and methotrexate treatment groups than in the placebo group (P≤0.01). Analyses of function/disability and health-related quality of life demonstrated statistically significant improvement in patients treated with leflunomide compared with patients who received placebo. Secondary: The ACR success rates in the leflunomide and methotrexate treatment groups (41 and 35%, respectively) were statistically equivalent. Responses from patients receiving methotrexate treatment were significantly better than those for patients receiving placebo. The ACR20 response rates over time for patients receiving leflunomide and methotrexate therapy were 52 and 46%, respectively. Onset of effect occurred at a mean of 8.6 weeks for patients in the leflunomide treatment group compared with 9.5 weeks for those in the methotrexate treatment group.
Cohen et al.[168] ULTRA (2001) Leflunomide 20 mg per day	DB, MC, RCT Patients 18 to 75 years of age with active RA for ≥6 months	N=235 24 months	Primary: ACR responses, tender and swollen joint counts, VAS, HAQ, SF-36, safety	Primary: At 24 months, leflunomide treatment was associated with higher ACR ≥20% response rates than was MTX treatment (79 vs 67%; P=0.049; 95% CI, 0.1 to 24.4). ACR ≥50% response rates for patients at 24 months were numerically greater following treatment with leflunomide compared with MTX (leflunomide 56 vs MTX 43%; P=0.053). This was also the case for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs methotrexate 7.5 to 20 mg per week vs placebo			Secondary: Not reported	ACR ≥70% response rates (leflunomide 26 vs MTX 20%; P=0.361). Responses were sustained from 12 months to 24 months, reflecting a consistent treatment effect. Maximal improvements evident at 6 months in the HAQ-DI and the physical component score of the SF-36 were sustained over 12 months and 24 months; improvement in the HAQ-DI with leflunomide (−0.60) was superior to that with MTX (−0.37) at 24 months (P=0.005). Over 24 months in the ITT cohort, serious treatment-related adverse events were reported in 1.6% of the leflunomide-treated patients and 3.7% of the MTX-treated patients. Frequently reported adverse events included upper respiratory tract infections, diarrhea, nausea and vomiting, rash, reversible alopecia, and transient liver enzyme elevations. Secondary: Not reported
De Stefano et al.[169] (2010) Leflunomide-anti-TNF-α combination therapy vs MTX-anti-TNFα combination therapy The anti-TNF-alpha drugs used were etanercept, infliximab, or adalimumab	PRO, RCT Patients 18 to 65 years of age with active RA for >1 year and DAS 28 >5.1 despite MTX or leflunomide treatment	N=120 24 weeks	Primary: Discontinuation rate, DAS 28, clinician's global assessment, VAS score, HAQ, ACR, laboratory parameters Secondary: Not reported	Primary: The discontinuation rates did not differ significantly between the two combination therapies (P=0.63). There were no statistically significant differences in DAS28 variations between the two groups or among the six subgroups (P=0.82). The ACR differences between the two groups and six subgroups were no statistically significant at week four (P=0.69), week 12 (P=0.77), and week 24 (P=0.46). There were no statistically significant differences between the two groups and six subgroups in HAQ score. Secondary: Not reported
Genovese et al.[170] (2015) SARIL-RA-MOBILITY	DB, MC, PC, RCT Patients 18 to 75 years of age with	N= 1,197 52 weeks	Primary: ACR20 improvement response at week	Primary: At 24 weeks, patients treated with sarilumab with MTX achieved a greater improvement in the proportion of patients achieving ACR20 at 66% for sarilumab 200 mg, 58% for sarilumab 150 mg and 33% for placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sarilumab 200 mg SQ every two weeks plus MTX vs sarilumab 150 mg SQ every two weeks plus MTX vs placebo plus MTX	active RA for ≥3 months despite MTX treatment for at least 12 weeks		24, change from baseline in HAQ-DI at week 16, change from baseline in SHS score at week 52 Secondary: ACR70 improvement response, DAS28-CRP <2.6 at week 24	(P<0.0001 compared to placebo). At 52 weeks, patients treated with sarilumab with MTX demonstrated significantly less radiographic progression of structural damage as measured by SHS at 0.25 for sarilumab 200 mg, 0.90 for sarilumab 150 mg and 2.78 for placebo (P<0.0001 compared to placebo). At 16 weeks, patients treated with sarilumab with MTX demonstrated greater improvement from baseline in physical function as measured by the HAQ-DI at -0.58 for sarilumab 200 mg, -0.54 for sarilumab 150 mg and -0.30 for placebo (P<0.001 compared to placebo). Secondary: Patients treated with sarilumab with MTX achieved a greater improvement in the proportion of patients achieving ACR70 at 15% for sarilumab 200 mg, 13% for sarilumab 150 mg and 3% for placebo (P<0.0001 compared to placebo). At 24 weeks, patients treated with sarilumab with MTX achieved a greater improvement in the proportion of patients achieving DAS28-CRP <2.6 at 34% for sarilumab 200 mg, 28% for sarilumab 150 mg and 10% for placebo (P<0.0001 compared to placebo).
Genovese et al.[171] (2019) MOBILITY extension study Sarilumab 200 mg (dose reduction to 150 mg permitted) every 2 weeks plus methotrexate	OL, extension study Patients who completed MOBILITY study	N=901 5 years	Primary: Safety Secondary: Efficacy	Primary: The exposure-adjusted incidence rates of adverse events and serious adverse events were 137.7 and 9.1 per 100 patient-years, respectively, for patients receiving either dose of sarilumab. The most common adverse events (with any dose of sarilumab) were injection-site erythema (incidence rate 13.5 per 100 patient-years), neutropenia (12.8 per 100 patient-years) and upper respiratory tract infection (7.6 per 100 patient-years). The most common adverse events of special interest were infections (incidence rate 55.1 per 100 patient-years), injection-site reactions (21.6 per 100 patient-years) and leucopenia (17.7 per 100 patient-years). The incidence rate of adverse events was generally stable over >5 years of treatment and there was no signal for an increased rate over time for any of the adverse events (including serious adverse events and serious infections) when analyzed by 6-month interval.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Elevations of ALT to >3× ULN occurred in 158 patients (14%) receiving either dose of sarilumab and normalized on treatment in 84 (53%) of these patients. Absolute neutrophil count <1,000 cells/mm^3 was observed but not associated with increased infection rate. Absolute neutrophil count <1,000 cells/mm3 occurred in 143 patients (13%) receiving either dose of sarilumab and normalized on treatment in 104 (73%) of these patients. Platelet counts <100×109 cells/L were observed in 33 patients (3%) receiving either dose of sarilumab and normalized on treatment in 20 (61%) of these patients. Serious infections occurred at a rate of 3.9 events per 100 patient-years in patients treated with either dose of sarilumab. Secondary: Initial treatment with sarilumab 200 mg plus methotrexate was associated with reduced radiographic progression over 5 years versus sarilumab 150 mg + methotrexate or placebo + methotrexate (mean±SE change from baseline in van der Heijde-modified Total Sharp Score: 1.46±0.27, 2.35±0.28 and 3.68±0.27, respectively [P<0.001 for each sarilumab dose vs placebo]). Clinical efficacy was sustained through 5 years according to DAS 28 using CRP, CDAI and HAQ-DI. The number of patients achieving CDAI ≤2.8 at 5 years was similar among initial randomization groups (placebo, 76/398 [19%]; sarilumab 150 mg, 68/400 [17%]; sarilumab 200 mg, 84/399 [21%]).
Fleischmann et al.[172] (2017) SARIL-RA-TARGET Sarilumab 200 mg SQ every two weeks plus DMARD vs sarilumab 150 mg SQ every two weeks plus DMARD	DB, MC, PC, RCT Patients 18 to 75 years of age with active RA for ≥6 months and inadequate response or intolerance to ≥1 anti-TNF therapy	N= 546 24 weeks	Primary: ACR20 improvement response at week 24, change from baseline in HAQ-DI at week 12 Secondary: ACR70 improvement response, ACR50 improvement response, DAS28-CRP <2.6 at week	Primary: At 24 weeks, patients treated with sarilumab with DMARD achieved a greater improvement in the proportion of patients achieving ACR20 at 61% for sarilumab 200 mg, 56% for sarilumab 150 mg and 34% for placebo (P<0.0001 compared to placebo). At 16 weeks, patients treated with sarilumab with DMARD demonstrated greater improvement from baseline in physical function as measured by the HAQ-DI at -0.47 for sarilumab 200 mg, -0.46 for sarilumab 150 mg and -0.26 for placebo (P<0.001 compared to placebo). Secondary: Patients treated with sarilumab with MTX achieved a greater improvement in the proportion of patients achieving ACR70 at 16% for sarilumab 200 mg, 20% for sarilumab 150 mg and 7% for placebo (P<0.001 compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo plus DMARD			24	placebo and P<0.01 compared to placebo, respectively). Patients treated with sarilumab with MTX achieved a greater improvement in the proportion of patients achieving ACR50 at 41% for sarilumab 200 mg, 37% for sarilumab 150 mg and 18% for placebo (P<0.0001 compared to placebo). At 24 weeks, patients treated with sarilumab with MTX achieved a greater improvement in the proportion of patients achieving DAS28-CRP <2.6 at 29% for sarilumab 200 mg, 25% for sarilumab 150 mg and 7% for placebo (P<0.0001 compared to placebo).
Burmester et al.[173] (2017) SARIL-RA-MONARCH Sarilumab 200 mg SQ every two weeks plus placebo vs adalimumab 40 mg SQ every two weeks plus placebo	DB, MC, PC, RCT Patients 18 to 75 years of age with active RA for ≥3 months despite MTX treatment for at least 12 weeks	N= 369 24 weeks	Primary: Change from baseline in DAS28-ESR at week 24 Secondary: DAS28-ESR <2.6 at week 24, change from baseline in HAQ-DI at week 12, ACR70 improvement response, ACR50 improvement response, ACR20 improvement response	Primary: At 24 weeks, patients treated with sarilumab achieved a greater improvement from baseline in DAS28-ESR at -3.28 for the sarilumab group and -2.20 for the adalimumab group (P<0.0001). Secondary: At 24 weeks, patients treated with sarilumab achieved a greater improvement in the proportion of patients achieving DAS28-CRP <2.6 at 27% compared to 7% for adalimumab (P<0.0001). At 12 weeks, patients treated with sarilumab demonstrated greater improvement from baseline in physical function as measured by the HAQ-DI at -0.61 for the sarilumab group and -0.43 for the adalimumab group (P=0.0037). Patients treated with sarilumab achieved a greater improvement in the proportion of patients achieving ACR70, ACR50 and ACR20 at 23%, 46% and 72% for the sarilumab group and 12%, 30% and 58% for the adalimumab group, respectively (P=0.0036, P=0.0017 and P=0.0074, respectively).
Jones et al.[174] (2010) AMBITION Tocilizumab 8 mg/kg every 4	DB, DD, PG, RCT Patients ≥18 years of age, with moderate to severe RA for ≥3 months,	N=673 24 weeks	Primary: Proportion of patients achieving ACR 20 response at week 24	Primary: At week 24, 70.6% of tocilizumab patients as compared to 52.1% of MTX patients achieved an ACR 20 response (P<0.001). Compared to the placebo arm, a larger proportion of patients treated with tocilizumab also achieved an ACR 20 response at week eight (55.6 vs 13.1%; 95% CI, 0.34 to 0.52).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks vs MTX 7.5 to 20 mg every week or placebo for 8 weeks followed by tocilizumab 8 mg/kg from week nine on	oral glucocorticoids (up to 10 mg/day of prednisone or equivalent) and NSAIDs were permitted if the dose was stable for ≥6 weeks		Secondary: Proportion of patients with ACR 50/70 responses at week 24 and the time to onset of ACR 20/50/70 responses, changes from baseline at week 24 in 28-joint count DAS 28, the proportion of patients in clinical remission (DAS 28 <2.6), with low disease activity (DAS 28 ≤3.2) and with good/ moderate responses at week 24, improvement in physical function was assessed by change from baseline at week 24 in HAQ-DI, and adverse events	Secondary: The proportion of patients achieving ACR 50 (44.0%) and ACR 70 (28.0%) at week 24 was also statistically significant for tocilizumab as compared to MTX (P<0.001). Improvements in DAS 28 at week 24 were greater in the tocilizumab group than in the MTX group. Additionally, the proportion of patients in remission at week 24 was higher with tocilizumab (P<0.001). By week 24, tocilizumab patients were five times more likely to achieve DAS 28 remission and four times more likely to achieve at least a moderate response (OR vs MTX, 4.24; 95% CI, 2.92 to 6.14). A greater improvement in physical function was seen by a higher mean change in HAQ-DI with tocilizumab when compared to that of MTX. There was no statistically significant difference with regard to the number of adverse events experienced in the tocilizumab group compared to the MTX group (79.9 vs 77.5%; P=0.484). Infection rates/patient year were also found to be similar (1.06 vs 1.09). However, skin and subcutaneous infections were reported more frequently in the tocilizumab group (4.1 vs 1.4%; P value not reported).
Smolen et al.[175] (2008) OPTION Tocilizumab 8 mg/kg every 4 weeks plus MTX (stable, 10 to 25 mg weekly)	DB, PC, PG, RCT Patients ≥18 years of age, with moderate to severe RA >6 months duration, who had an inadequate response to MTX; all other DMARDs	N=622 24 weeks	Primary: ACR 20 response at week 24 Secondary: ACR 50/70, DAS 28, and EULAR responses at week 24, difference in HAQ-DI, SF-36,	Primary: At week 24, significantly greater proportion of patients receiving tocilizumab 4 and 8 mg/kg had an ACR 20 response than patients who received placebo (59 and 48 vs 26%, respectively; P<0.0001 for both). Secondary: Significantly greater proportion of patients in tocilizumab 4 and 8 mg/kg groups achieved ACR 50 (31 and 44 vs 11%, respectively; P<0.0001) and ACR 70 at week 24 (12 and 22 vs 2%, respectively; P<0.0001) compared to patients in the placebo group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs tocilizumab 4 mg/kg every 4 weeks plus MTX (stable, 10 to 25 mg weekly) vs placebo every 4 weeks plus MTX (stable, 10 to 25 mg weekly)	were discontinued before the start of the study, oral glucocorticoids (≤10 mg/day of prednisone or equivalent) and NSAIDs were permitted if doses were stable for six weeks or more		and FACIT-F, scores from baseline, and adverse events	Significantly greater proportion of patients in tocilizumab 4 and 8 mg/kg groups had reduced disease activity as measured by a DAS 28 score <2.6 (13.0 and 27.0 vs 0.8%, respectively; P<0.0002 for 4 mg/kg and P<0.0001 for 8 mg/kg groups) compared to the placebo group. EULAR response was also found to be significantly decreased in both tocilizumab 4 and 8 mg/kg groups (21 and 38 vs 3%, respectively; P<0.0001 for both) compared to the placebo group. Greater improvements in physical function were seen in both tocilizumab 4 and 8 mg/kg groups as assessed by the HAQ-DI score (-0.52 and -0.55 vs -0.34, respectively; P<0.0296 for 4 mg/kg and P<0.0082 for 8 mg/kg). Significant differences were seen with regard to changes in the SF-36 physical score in both tocilizumab 4 and 8 mg/kg groups (9.7 and 9.5 vs 5.0, respectively; P<0.0001 for both) and in the SF-36 mental score (5.7 and 7.3 vs 2.7, respectively; P<0.0394 for 4 mg/kg and P<0.0012 for 8 mg/kg). The mean change in FACIT-F score from baseline showed significant improvements in both tocilizumab 4 and 8 mg/kg groups (7.3 and 8.6 vs 4.0, respectively; P<0.0063 for 4 mg/kg and P<0.0001 for 8 mg/kg). Greater proportions of patients in the tocilizumab 4 and 8 mg/kg groups reported experiencing at least one adverse event compared to the placebo group (71 and 69 vs 63%, respectively). The rate of all infections/100 patient years was 98.7 in the tocilizumab 4 mg/kg group, 101.9 in the 8 mg/kg group, and 96.1 in the placebo group.
Genovese et al.[176] (2008) TOWARD Tocilizumab 8 mg/kg plus DMARD every 4 weeks	DB, MC, PC, RCT Patients ≥18 years of age, with moderate to severe RA, who received stable doses of permitted DMARDs	N=1,220 24 weeks	Primary: ACR 20 responses at week 24 Secondary: ACR 50/70 responses at week 24, number of	Primary: At week 24, the proportion of patients in the tocilizumab group that were ACR 20 responders was significantly higher than in the control group (61 vs 25%; P<0.0001). No obvious differences were seen in ACR 20 response with regard to patients who received two or more DMARDs. Secondary: At week 24, significantly more patients in the tocilizumab group achieved

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo plus DMARD every 4 weeks	(MTX, chloroquine, HCQ, parenteral gold, SSZ, azathioprine, and leflunomide) for ≥8 weeks prior to study entry and oral glucocorticoids (≤10 mg/day of prednisone or equivalent) and NSAIDs or COX2 inhibitors if the doses were stable for ≥6 weeks		swollen and tender joints, DAS 28, EULAR response, HAQ, FACIT-F score, and SF-36, and adverse events	ACR 50 and ACR 70 responses when compared to the placebo group (ACR 50, 30 vs 9%; ACR 70, 21 vs 3%; P<0.0001 for both). Compared to baseline, a significant decrease was seen in the number of swollen and tender joints in patients receiving tocilizumab when compared to the placebo group (swollen joint count, -10.3 vs -4.9; tender joint count, -15.7 vs -8.5; P<0.0001). Mean DAS 28 improved incrementally over time with greater changes in the tocilizumab group seen by week 24 (-3.17 and -1.16, respectively; P<0.0001). Remission rates at week 24 were also higher in the tocilizumab group when compared to the placebo group (30 vs 3%; P<0.0001). By week 24, 80% of patients in the tocilizumab group and 38% of patients in the placebo group achieved a good or moderate EULAR response (P<0.0001). At week 24, 60% of patients in the tocilizumab group had a clinically meaningful improvement in physical function as compared to 34% with placebo (change from baseline in HAQ ≥0.3). Mean changes from baseline were also significantly higher in the tocilizumab group when compared to the placebo group for the disability index of the HAQ (-0.5 vs -0.2; P<0.0001) and FACIT-F scores (8.0 vs 3.6; P<0.0001). Mean improvements from baseline in SF-36 scores were higher for both physical and mental components at week 24 in the tocilizumab group (8.9 vs 4.1 and 5.3 vs 2.3, respectively; P<0.0001 for both). The occurrence of adverse events was found to be higher with tocilizumab (73 vs 61%). The most frequently occurring adverse events in both groups were infections and infestations (37.4 vs 31.6%), gastrointestinal disorders (20.8 vs 14.7%), and musculoskeletal and connective tissue disorders (13.0 vs 17.9%). Infections with a higher incidence in the tocilizumab group were upper respiratory infections (9 vs 7%), other respiratory infections (12 vs 10%), and skin and subcutaneous tissue infections (5 vs 3%).
Kremer et al.[177]	DB, MC, PC, PG,	N=1,196	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2011) LITHE Tocilizumab 8 mg/kg plus MTX (stable, 10 to 25 mg weekly) for four weeks vs tocilizumab 4 mg/kg plus MTX (stable, 10 to 25 mg weekly) for four weeks vs placebo plus MTX (stable, 10 to 25 mg weekly) for four weeks Oral corticosteroids (≤10 mg/day of prednisone or equivalent) and NSAIDs were permitted if the dosages had been stable for ≥6 weeks before study entry.	RCT Patients with RA, as determined by ACR criteria that was moderate to severe and lasted for ≥6 months; inadequate response to MTX therapy, defined as a swollen joint count of ≥6, a tender joint count of ≥8, and either CRP level ≥1 mg/dl or an ESR ≥28 mm/hour; and had ≥1 radiographically confirmed joint erosion despite having received MTX for ≥12 weeks before baseline	12 months	Change from baseline in the total Genant-modified Sharp score and change in HAQ-DI Secondary: Change from baseline in erosion and JSN scores (at week 24 and 52), total Genant-modified Sharp score at week 24, proportions of patients with no progression of total, erosion, or JSN scores, ACR 20, ACR 50, and ACR 70, change in DAS 28, and proportions of patients with low levels of disease activity (DAS28 ≤3.2) and DAS remission (DAS28 <2.6).	The proportion of patients without radiographic progression (change in total Genant-modified Sharp score ≤0 from baseline to week 52) was significantly higher in patients treated with tocilizumab 8 or 4 mg/kg (84 and 81 vs 67%; P<0.0001). The AUC of the change in the HAQ-DI score from baseline to week 52 demonstrated a significantly greater decrease in the 8 and 4 mg/kg tocilizumab groups compared to the placebo group (-144.1 and -128.4 vs -58.1 units; P<0.0001 for both comparisons). Secondary: At week 52, the ACR 20, ACR 50, and ACR 70 response rates were higher in patients treated with tocilizumab compared to placebo; however the difference was only statistically significant for the 8 mg/kg group compared to the placebo group (P<0.0001 for all response rate comparisons). The DAS28 scores were reduced over 52 weeks in all treatment groups, with mean improvements of -3.8, -3.0, and -2.0 in the tocilizumab 8 mg/kg, 4 mg/kg and placebo groups, respectively; however, the difference was only significant with the 8 mg/kg dose compared to placebo (P<0.0001). At 52 weeks, more patients treated with tocilizumab 8 mg/kg achieved remission (47.2 vs 7.9%; P<0.0001) according to the DAS28 score (<2.6) or had low disease activity (DAS28 ≤3.2) compared to placebo (63.6 vs 45.3%; P<0.0001). DAS28 remission rates continued to improve between weeks 24 and 52, with the highest proportion of patients in remission in the tocilizumab 8 mg/kg treatment group. The progression of structural damage from baseline to week 52 was reduced by 74 and 70% with tocilizumab 8 and 4 mg/kg, respectively, compared to patients treated with placebo (P<0.0001). The total Genant-modified Sharp score at week 52 showed a decreased frequency and severity of disease progression with tocilizumab therapy.
Yazici et al.[178]	DB, MC, PC, RCT	N=619	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2012) ROSE Tocilizumab 8 mg/kg plus DMARD every four weeks vs placebo plus DMARD every four weeks Permitted DMARD (at stable doses ≥7 weeks before study) included MTX, chloroquine, hydroxychloroquine, parenteral gold, SSZ, azathioprine, and leflunomide. Doses were required to remain stable throughout the study; however, dose reductions were allowed as clinically warranted for safety reasons.	Patients ≥18 years of age with active RA for ≥6 months and an inadequate clinical response to DMARD in addition to ≥6 swollen joints and ≥6 tender joints at screening and baseline, with either a CRP ≥95.24 nmol/l or an ESR ≥28 mm/h or greater at screening	24 weeks	ACR 50 response at week 24 Secondary: ACR 20, ACR 50, ACR 70, EULAR response, DAS28, clinically meaningful improvement (change from baseline in DAS28 of ≥1.2), patients achieving low disease activity (DAS28 ≤3.2), clinical remission (DAS28 <2.6), ESR and CRP levels, FACIT-F, and RAPID3 scores	A significantly higher proportion of patients randomized to receive tocilizumab achieved an ACR 50 response at week 24 compared to placebo (30.1 vs 11.2%; P<0.0001). Secondary: A higher proportion of patients randomized to receive tocilizumab achieved an ACR 20 response at all time points evaluated compared to placebo (P<0.0001). Similarly, an ACR 50 response was achieved in significantly more patients in the tocilizumab group compared to placebo at all treatment weeks except week 16 (P<0.05 at all time-points). A significantly greater proportion of patients in the tocilizumab group compared to the placebo group achieved an ACR 70 response at all time points from week eight onward (P<0.05 for all time points). A higher proportions of patients achieved a EULAR good response in the tocilizumab group compared to placebo at all time points starting at week four (13.2 vs 2.0%; P<0.0001). The mean DAS28 score decreased from baseline to week 24 in both treatment groups starting at week four; however, the improvement was significantly greater in tocilizumab group compared to placebo (P<0.0001). Significantly more patients achieved a clinically meaningful decrease in DAS28 (≥1.2 points from baseline) in the tocilizumab group compared to the placebo group at all time points from week four onward (87.9 vs 53.4%; P<0.0001). Moreover, a greater proportion of patients randomized to receive tocilizumab achieved a low disease activity (P<0.0001) and clinical remission at week 24 (P<0.0001) compared to those in the placebo group. There were significantly greater improvements from baseline in the RAPID3 scores at 24 weeks in the tocilizumab treatment group compared to placebo (-2.33 vs -1.29; P<0.0001). There was a statistically significant improvement in mean FACIT-F scores over 24 weeks of treatment with tocilizumab compared to placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P<0.05). Patients treated with tocilizumab achieved significantly lower mean CRP levels at all time points evaluated compared to the placebo group (P<0.0001). Similarly, the mean ESR was significantly reduced from baseline to a greater degree with tocilizumab compared to the placebo group at week 24 (-34.72 vs -5.70 mm/h; P<0.0001).
Emery et al.[179] (2008) RADIATE Tocilizumab 8 mg/kg plus MTX (stable, 10 to 25 mg weekly) for 4 weeks vs tocilizumab 4 mg/kg plus MTX (stable, 10 to 25 mg weekly) for 4 weeks vs placebo plus MTX (stable, 10 to 25 mg weekly) for 4 weeks	DB, PC, PG Patients ≥18 years of age with moderate to severe active RA with failure to respond to one or more TNF antagonists within the past year; patients must have discontinued TNF agents (Enbrel®, Humira®, Remicade®) or DMARDs (other than MTX) before enrolling	N=499 24 weeks	Primary: ACR 20 responses Secondary: DAS 28, number of patients requiring rescue therapy, and adverse events	Primary: ACR 20 was achieved at week 24 by 50.0, 30.4 and 10.1% of patients in the 8 mg/kg, 4 mg/kg and control group respectively (P<0.001). At week four, more patients achieved ACR 20 in the 8 mg/kg tocilizumab group than those in the control group (P<0.001). Patients responded, as measured by ACR 20 response, regardless of the most recently failed TNF antagonist or the number of failed treatments. Secondary: DAS 28 remission rates at week 24 were dose related, being achieved in 30.1, 7.6, and 1.6% of 8 mg/kg, 4 mg/kg and control groups (P<0.001 for 8 mg/kg; P=0.053 for 4 mg/kg vs control). Rescue therapy with 8 mg/kg of tocilizumab plus MTX was offered at week 16 in all cases of treatment failure (<20% improvement in both tender and swollen joints). More patients in the control group (41%) and in the 4 mg/kg group (19%) received rescue therapy after week 16 compared to 11% of patients in the 8 mg/kg group. Adverse events noted were mild or moderate with overall incidences of 84.0% in the tocilizumab 8 mg/kg group, 87.1% in the tocilizumab 4 mg/kg group, and 80.6% in the placebo plus MTX group. The most common adverse events were infections, gastrointestinal symptoms, rash and headache. The incidence of serious adverse events was higher in the control group (11.3%) than in the tocilizumab 8 mg/kg (6.3%) and 4 mg/kg (7.4%) groups.
Burmester et al.[180] (2017) FUNCTION	DB, MC, RCT Patients ≥18 years	N=1,162 104 weeks	Primary: DAS28-ESR remission (<2.6),	Primary: DAS28-ESR remission rates were maintained from weeks 52 through 104. More patients achieved DAS28-ESR remission at weeks 24 and 52 with 8

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tocilizumab 8 mg/kg IV every four weeks + MTX vs tocilizumab 4 mg/kg IV every four weeks + MTX vs tocilizumab 8 mg/kg IV every four weeks + placebo (TCZ monotherapy) vs placebo + MTX	of age with moderate to severe active, early (≤2 years) RA who were MTX-naïve		ACR20/50/70 responses, CDAI remission (<2.8) Secondary: Safety	mg/kg TCZ+MTX than with placebo+MTX (45 vs 15% and 49 vs 20%, respectively; P<0.0001). DAS28-ESR remission was achieved by 49.3% of patients in the 8 mg/kg TCZ+MTX group at week 52 and by 47.6% at week 104. Proportions of patients achieving ACR20, ACR50 and ACR70 responses were similar at weeks 52 and 104 in the 8 mg/kg TCZ monotherapy and 8 mg/kg TCZ+MTX groups. After 52 weeks of escape therapy, 30.5% (29/95) and 51.4% (73/142) of patients who originally received 4 mg/kg TCZ+MTX and placebo+MTX, respectively, achieved DAS28-ESR remission. ACR20, ACR50 and ACR70 response rates after 52 weeks of escape therapy were 43.0, 30.3, and 16.2%, respectively, in the placebo+MTX escape group and 29.5, 16.8, and 6.3%, respectively, in the 4 mg/kg TCZ+MTX escape group. Similar proportions of patients in each initial treatment arm achieved remission according to CDAI and ACR/EULAR Boolean and Index criteria at weeks 52 and 104. Secondary: Eighty-three serious adverse events were reported in the 8 mg/kg TCZ+MTX group compared with 67, 58 and 31 for the 8 mg/kg TCZ+placebo, 4 mg/kg TCZ+MTX and placebo+MTX groups, respectively. Rates of serious adverse events per 100 patient-years were 11.6 (95% CI, 9.2 to 14.3), 13.3 (95% CI, 10.3 to 16.9), 14.7 (95% CI, 11.2 to 19.0) and 9.1 (95% CI, 6.2 to 13.0), respectively. Most adverse events were mild or moderate in intensity (96 to 97% across the four treatment groups). Infections were the most frequently reported adverse events/serious adverse events in all treatment arms, with adverse event rates per 100 patient years ranging from 89.4 (95% CI, 82.6 to 96.6) for 8 mg/kg TCZ+MTX to 113.3 (95% CI, 103.0 to 124.3) for 4 mg/kg TCZ+MTX.
Kaneko et al.[181] (2016) SURPRISE Tocilizumab added to methotrexate (add-on) vs	PRO, RCT Patients 20 to 75 years of age with moderate or high RA disease activity despite MTX treatment	N=223 52 weeks	Primary: DAS28 remission rate at week 24 Secondary: SDAI, CDAI remission rates, safety	Primary: DAS28-ESR remission rates were significantly higher in the add-on group than in the switch group at weeks four and 24 (both P<0.05), but they became comparable at week 52. At week 24, the rate of DAS28 remission was 55.0% in the switch group and 69.6% in the add-on group. At week 52, rates were 70.3 and 72.2%, respectively. Secondary: Remission rates according to the SDAI and the CDAI were not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tocilizumab switched from methotrexate (switch)				significantly different between the two groups. The number of patients with at least one adverse event was greater in the add-on group than in the switch group (60.0 vs 45.0%, P=0.02), but the percentage of patients with at least one serious adverse event was comparable in the two treatment groups (13.9 vs 8.1%, P=0.20). Adverse events occurring more in the add-on group than in the switch group were infections, gastrointestinal disorders, and liver dysfunction. Eleven patients (9.6%) in the add-on group and 4 (3.6%) in the switch group were withdrawn from the study because of adverse events (P=0.11). There was one death from interstitial pneumonitis in the add-on group in this 1-year observation period.
Dougados et al.[182] (2013) ACT-RAY Tocilizumab 8 mg/kg plus MTX (stable >15 mg weekly) every 4 weeks vs tocilizumab 8 mg/kg plus placebo every 4 weeks	DB, PC, PG Patients ≥18 years of age with active RA with failure to respond to > 12 weeks of MTX treatment (stable dose >15 mg week for 6 weeks prior to study)	N=556 24 weeks	Primary: DAS 28 remission Secondary: DAS 28 low disease activity, ACR 20, ACR 50, ACR 70, ACR 90, and adverse events	Primary: DAS 28 remission rates at week 24 were 40.4% with the tocilizumab/MTX group vs 34.8% with tocilizumab monotherapy (P=0.19). Secondary: DAS 28 scored for low disease activity was significantly lower with combination therapy (tocilizumab/MTX) at week 24 that with the with tocilizumab monotherapy (61.7 vs 51.4%; P=0.029). ACR 20/50/70/90 was 71.5%/45.5%/24.5%/5.8% with tocilizumab/MTX. ACR 20/50/70/90 was 70.3%/40.2%/25.4%/5.1% with tocilizumab monotherapy. The differences between treatment groups were not considered significant. Adverse events noted were comparable in each treatment group with 6.1% of patients on tocilizumab/MTX reporting a serious adverse event while 5.8% reported a serious adverse event with tocilizumab monotherapy. Discontinuations and dose modifications occurred in 3.6% and 27.4% of tocilizumab/MTX patients and 2.5% and 18.5% of tocilizumab monotherapy patients, respectively. Increases in alanine aminotransferase elevations from normal at baseline to greater than upper limit of normal and to more than three times upper limit of normal at one or more time points during 24 weeks occurred in 48.8% and 7.8% on tocilizumab/MTX and in 27.6% and 1.2% of tocilizumab monotherapy patients, respectively.
Bijlsma et al.[183]	DB, MC, RCT	N=317	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2016) U-Act-Early Tocilizumab plus methotrexate vs tocilizumab plus placebo vs methotrexate plus placebo Tocilizumab was given at 8 mg/kg IV every four weeks with a maximum of 800 mg per dose	Patients who had been diagnosed with rheumatoid arthritis within one year before inclusion, were DMARD-naive, ≥18 years of age, met current RA classification criteria, and had a DAS28 score of ≥2.6	2 years	Proportion of patients achieving sustained remission (defined as DAS28 <2.6 with a swollen joint count ≤4, persisting for at least 24 weeks) Secondary: EULAR and ACR response rates, HAQ scores	Sustained remission on the initial treatment regimen was attained by 86% of patients in the tocilizumab plus methotrexate arm, 84% in the tocilizumab arm, and 44% in the methotrexate arm (RR, 2.00; 95% CI, 1.59 to 2.51 for the tocilizumab plus methotrexate arm vs the methotrexate arm and 1.86; 95% CI, 1.48 to 2.32 for the tocilizumab arm vs the methotrexate arm, both P<0.0001). Sustained remission was not different between the tocilizumab plus methotrexate arm versus the tocilizumab arm (P=0.62). Secondary: Proportions of patients with EULAR good response at week 24 were significantly greater in the tocilizumab plus methotrexate arm versus the methotrexate arm and for the tocilizumab arm versus the methotrexate arm (P<0.0001 for both comparisons). At week 52, the proportion of patients with EULAR good response in the tocilizumab arm was significantly greater than that in the methotrexate arm (P=0.0074); at week 104, there were no significant between-group differences. ACR response rates showed a similar pattern over time. The difference between treatment groups for physical function (HAQ scores) was significant only at week 24 (the tocilizumab plus methotrexate arm versus the methotrexate arm; P=0.0275).
Choy et al.[184] (2018) TOZURA Tocilizumab 162 mg weekly SC Concomitant csDMARDs (AZA, chloroquine, HCQ, LEF, MTX or SSZ) were permitted if patients maintained a stable dose for ⩾4 weeks before baseline.	MC, OL, SA Tocilizumab- naïve patients ≥18 years of age with active RA who had an inadequate response to a csDMARD or an anti-TNF agent or who were MTX naïve	N=1,804 24 weeks	Primary: Total tender joint count, total swollen joint count of 28 joints, PGA, HAQ-DI, DAS28-ESR, ACR response scores, EULAR response criteria, CDAI, Simplified Disease Activity Index and glucocorticoid dose reduction and/or discontinuations	Primary: Of 1,804 patients, 353 (19.6%) received monotherapy and 1451 (80.4%) received combination therapy. The 28-joint DAS-ESR in both groups decreased significantly from baseline to week 24 (mean change: monotherapy, -3.40; combination therapy; -3.46), with no significant difference between groups (P=0.46). The CDAI score decreased comparably from baseline to week 24 in both groups (mean change: monotherapy, 23.54; combination therapy, −23.83; P<0.0001 for both), with no significant difference between groups (P=0.57). EULAR and ACR20/50/70/90 response rates were similar between treatment groups at week 24, with 73.3 and 77.5% of patients achieving a EULAR good response and 57.2 and 57.7% achieving an ACR50 response in the monotherapy and combination therapy groups, respectively. Swollen joint counts and tender joint counts over time were similar between the monotherapy and combination therapy groups. The HAQ-DI score decreased comparably from baseline to week 24 in both groups (mean

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Safety	change: monotherapy, −0.56; combination therapy, −0.57; P<0.0001 for both), with no significant difference between groups (P=0.72). Secondary: Overall, the adverse event rate per 100 patient-years was 622.4, with similar rates between the monotherapy and combination therapy groups (622.1 vs 622.5). The most common adverse events were infections and infestations, occurring in 42.0% of patients (monotherapy 43.1%, combination therapy 41.8%), with nasopharyngitis occurring the most frequently. Overall, 6.2% of patients discontinued the study due to safety reasons (monotherapy 8.8%, combination therapy 5.5%). The most common reasons for withdrawal due to adverse events were skin and subcutaneous disorders in the monotherapy group [5 patients (1.4%)] and laboratory findings [16 patients (1.1%)] in the combination therapy group. There were 29 patients (1.6%) who withdrew due to insufficient therapeutic response, slightly more in the monotherapy than in the combination therapy group.
Van der Heijdge et al.[185] (2019) ORAL Scan Tofacitinib 5 mg BID, vs tofacitinib 10 mg BID vs placebo switched to tofacitinib 5 BID vs	DB, PC, PG, RCT Patients ≥18 years of age with a diagnosis of active RA (≥6 tender or painful joints [68 joint count] and ≥6 swollen joints [66 joint count] and either ESR>28 mm/hour or CRP>7 mg/L) and evidence of ≥3 joint erosions on posteroanterior hand and wrist radiographs or anteroposterior foot radiographs (if radiographic	N=539 24 months	Primary: Efficacy including ACR 20, ACR 50, and ACR 70 responses, mean changes from baseline in the DAS28-ESR, remission and low disease activity Secondary: Safety	Primary: ACR 20, ACR 50, and ACR 70, the proportion of patients in whom remission or low disease activity was achieved according to the DAS28-ESR, CDAI, or SDAI, Boolean remission and HAQ-DI scores were maintained from month 12 to 24 and were similar between tofacitinib dosages. Responses were similar between treatment sequences once all patients were receiving tofacitinib. Patients receiving tofacitinib 10 mg BID had numerically higher responses than those receiving 5 mg BID; however, since the study was not powered for this comparison, no formal statistical comparison between dosages was conducted. Patients receiving tofacitinib 10 mg BID had low disease activity and disease in remission for a modestly higher number of months, with numerically higher proportions of patients experiencing ≥12 months of uninterrupted low disease activity or remission, compared with the other treatment groups. Patients who switched from placebo to tofacitinib 5 mg BID showed a modestly lower total number of months in remission and proportion of patients achieving ≥12 months' uninterrupted low disease activity or remission versus other groups. These trends remained similar when only patients who completed the study were analyzed. Furthermore,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo switched to tofacitinib 10 BID	evidence of joint erosions was unavailable, presence of IgM rheumatoid factor positivity or antibodies to cyclic citrullinated peptide).			no patient in any treatment group had more than one flare after month 6. Secondary: Safety events were similar in type and frequency for both tofacitinib dosages and were consistent with those previously reported. The most common treatment emergent adverse events (affecting ≥5% of patients) for months 0 to 24 by treatment sequence were: nasopharyngitis, upper respiratory tract infection, and headache for patients receiving tofacitinib 5 mg BID; nasopharyngitis, upper respiratory tract infection, urinary tract infection, herpes zoster, and bronchitis for patients receiving tofacitinib 10 mg BID; nasopharyngitis, upper respiratory tract infection, and hypertension for patients receiving placebo and then switching to tofacitinib 5 mg BID; and upper respiratory tract infection, nasopharyngitis, herpes zoster, increased ALT level, increased AST level, stomatitis, and diarrhea for patients receiving placebo and then switching to tofacitinib 10 mg BID.
Wollenhaupt et al.[186] (2019) Tofacitinib 5 mg or 10 mb BID Stable background therapy (including conventional synthetic DMARDs) continued	OL, extension study Patients with RA previously completing a phase 1, 2 or 3 qualifying index study of tofacitinib	N=4,481 Up to 9.5 years	Primary: Long-term safety and tolerability profile (including evaluation of adverse event reports and clinical laboratory data) Secondary: Long-term persistence of efficacy (including ACR 20/50/70 response rates, observed mean and improvement in in HAQ-DI, DAS 28, proportions of patients achieving remission)	Primary: The majority of all-cause adverse events were mild (59%) or moderate (36%) in severity for all tofacitinib; corresponding data for tofacitinib 5 mg BID were 57% and 36%, respectively, and for tofacitinib 10 mg BID were 59% and 36%, respectively. For all tofacitinib, the most common all-cause adverse event by system organ class leading to discontinuation included infections and infestations (9.4% [n=423/4,481]), investigations (4.6% [n=206/4,481]), and benign, malignant, and unspecified neoplasms (3.7% [n=165/4,481]), and by preferred term included pneumonia (1.8% [n=80/4,481]), blood creatinine increased (1.5% [n=69/4,481]), and herpes zoster (0.7% [n=32/4,481]). The IR (95% CI) for all-cause adverse events leading to discontinuation was 6.78 (6.39, 7.20) for all tofacitinib. For all tofacitinib, the most common (≥ 5% in any treatment group) all-cause serious adverse events by system organ class included infections and infestations (9.0% [n=405/4,481]) and musculoskeletal and connective tissue disorders (5.5% [n=246/4,481]), and by preferred term included pneumonia (2.1% [n=96/4,481]), osteoarthritis (1.9% [n=86/4,481]), and RA (0.8% [n=34/4,481]). The IR (95% CI) for serious adverse events was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				9.03 (8.55, 9.53) for all tofacitinib. A total of 88 deaths occurred in the study. Laboratory variables of interest, including total cholesterol and low-density lipoprotein, ALT, AST and serum creatinine remained generally stable over time, with variability attributable to smaller patient numbers at later time points. Secondary: ACR 20, ACR 50 and ACR 70 response rates were maintained over time between months one and 96 and were generally similar with tofacitinib 5 mg BID (months one to 96) and 10 mg BID (months one to 72). Improvements in mean HAQ-DI scores at month one remained stable over time with tofacitinib 5 mg and 10 mg BID, HAQ-DI ≥ 0.22 improvement from baseline was observed in 64.8% (n=103/159) of patients with all tofacitinib at month 96; in 63.6% (n=91/143) of patients with tofacitinib 5 mg BID at month 96; and in 70.3% (n=201/286) of patients with tofacitinib 10 mg BID at month 72. Mean DAS28 decreased at month one and then remained consistent over time with tofacitinib 5 mg and 10 mg BID. DAS28 defined remission was observed in 24.7% (n=39/158) of patients with all tofacitinib at month 96, in 25.4% (n=36/142) of patients with tofacitinib 5 mg BID at month 96, and in 25.0% (n=71/284) of patients with tofacitinib 10 mg BID at month 72.
Emery et al.[187] (2019) ASCERTAIN Sarilumab 150 mg SC every two weeks vs sarilumab 200 mg SC every two weeks vs tocilizumab 4 mg/kg	DB, PG, RCT Patients ≥18 years of age with an RA diagnosis for ≥3 months and continuous treatment with one or a combination of conventional synthetic DMARDs for ≥12 consecutive weeks before screening and were on a stable dose for	N=202 24 weeks	Primary: Incidences of treatment-emergent adverse events, adverse events of special interest, serious adverse events, and potentially clinically significant laboratory abnormalities Secondary:	Primary: The incidence of treatment-emergent adverse events was similar between the sarilumab and tocilizumab groups. A numerically higher incidence of treatment-emergent adverse events leading to treatment discontinuation was observed with sarilumab (150 mg every two weeks, n=6 [12.2%]; 200 mg every two weeks, n=8 [15.7%]) than with tocilizumab (n=4 [3.9%]). The most frequently reported treatment-emergent adverse events were neutropenia, injection-site erythema and nasopharyngitis in the sarilumab groups and accidental overdose, upper respiratory tract infection and nausea in the tocilizumab group. There were two serious infections in the tocilizumab group and one in the sarilumab 200 mg every two weeks group Five patients who received sarilumab discontinued because of laboratory

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(could be increased to 8 mg) IV every four weeks	≥6 weeks		Not reported	abnormalities (neutropenia, leukopenia and increased transaminases); none of these laboratory changes were associated with clinical manifestations. Three of these five patients had resumed their sarilumab SC injections but were discontinued (placebo for tocilizumab). No discontinuations due to laboratory abnormalities were reported in the tocilizumab group. Two patients in each of the sarilumab groups and one patient in the tocilizumab group discontinued because of infections. Two patients who received sarilumab 200 mg every two weeks discontinued because of injection-site reactions and one patient who received sarilumab 200 mg every two weeks discontinued because of an infusion-related reaction while receiving IV placebo. Secondary: Not reported
Maxwell et al.[188] (2009) Abatacept 2 to 10 mg/kg alone or in combination with DMARDs or biologics vs placebo or DMARDs or biologics	SR RCTs of patients ≥16 years of age with RA meeting the ACR 1987 revised criteria	N=2,908 (7 trials) ≥3 months	Primary: ACR 50 response and safety Secondary: ACR 20, ACR 70, components of ACR radiographic progression, DAS, EULAR response criteria, and changes in HAQ and SF-36	Primary: At three months, the ACR 50 response in the abatacept group was not significantly higher than the control group (RR, 2.50; 95% CI, 0.52 to 11.96). At six and 12 months, the ACR 50 response was significantly higher in the abatacept group compared to the control group (RR, 2.47; 95% CI, 2.00 to 3.07 and RR, 2.21; 95% CI, 1.73 to 2.82, respectively). At one year the NNT in order to achieve ACR 50 was 5 (95% CI, 4 to 7). The RR for adverse events with abatacept compared to controls was 1.05 (95% CI, 1.01 to 1.08). There was a greater number of serious adverse infections with abatacept compared to controls (OR, 1.91; 95% CI, 1.07 to 3.42). However, after removing a study in which patients were treated with combination of etanercept and abatacept, the OR decreased to 1.82 (95% CI, 1.00 to 3.32). Abatacept treated patients had increased number of headaches and infusion reactions (RR, 1.45; 95% CI, 1.20 to 1.74 and RR, 1.30; 95% CI, 1.13 to 1.50). Secondary: ACR 20 response was achieved in significantly more patients treated with abatacept compared to controls at six and 12 months (RR, 1.79; 95% CI, 1.59 to 2.02 and RR, 1.79; 95% CI, 1.55 to 2.07, respectively) but not at three months (RR, 1.70; 95% CI, 0.93 to 3.12).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				More patients treated with abatacept achieved an ACR 70 at six and 12 months (RR, 3.53; 95% CI, 2.41 to 5.16 and RR, 4.02; 95% CI, 2.62 to 6.18) but not at three months (RR, 5.00; 95% CI, 0.25 to 100.20). There was a statistically significant reduction in the progression of joint damage at 12 months with abatacept (mean difference, -0.27; 95% CI, -0.42 to -0.12). The abatacept treated patients were significantly more likely to reach low DAS (DAS 28 <3.2) compared to controls at 6 and 12 months (RR, 3.36; 95% CI, 2.28 to 4.96 and RR, 4.33; 95% CI, 2.84 to 6.59), and a NNT of 4 (95% CI, 3 to 5). At 12 months, patients in the abatacept group were significantly more likely to achieve DAS remission (DAS 28 <2.6) with RR of 12.74 (95% CI, 4.76 to 34.15). For clinically meaningful improvement on the HAQ; RR, 1.69 (95% CI, 1.51 to 1.90) in favor of abatacept. There was an absolute difference of 24% (95% CI, 16 to 32) and a NNT to achieve HAQ >0.3 of 5 (95% CI, 4 to 7). Improvement in the physical component of the SF-36 was significantly more likely in the abatacept group (RR, 1.90, 95% CI, 1.52 to 2.39). There was no significant difference between the groups in likelihood of scoring worse. The RR of scoring the same was 0.66 in favor of placebo (95% CI, 0.56 to 0.78). There were significantly fewer patients that scored worse on the mental component of the SF-36 (RR, 0.64; 95% CI, 0.44 to 0.94). Scoring the same was not significantly different between the groups. A score of better was significantly higher in the abatacept group (RR, 1.42; 95% CI, 1.14 to 1.76).
Navarro-Sarabia et al.[189] (2005) Adalimumab 20, 40, 80 mg every week to every other week, alone or in	SR RCTs of patients with confirmed RA (defined by ACR 1987 criteria), who had active disease and who either	N=2,381 (6 trials) 12 to 52 weeks	Primary: ACR, EULAR responses, DAS 28, components of ACR responses, and radiographic data	Primary: Adalimumab 40 mg every other week was associated with a RR of 1.52 to 4.63 to attain an ACR 20 response at 24 weeks with a NNT of 1.9 to 5.4. The RR to achieve an ACR 50 response was 4.63 (95% CI, 3.04 to 7.05) and NNT was 3.0 (95% CI, 2.0 to 6.0). The RR to achieve an ACR 70 response was reported as 5.14 (95% CI,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
combination with DMARDs vs placebo or placebo plus DMARDs	failed MTX or other DMARDs therapy, or DMARD naive		Secondary: Safety	3.14 to 8.41) and a NNT of 7 (95% CI, 5 to 13). At 52 weeks, the RRs were reported for ACR 20, ACR 50 and ACR 70 as 2.46 (95% CI, 1.87 to 3.22), 4.37 (95% CI, 2.77 to 6.91) and 5.15 (95% CI, 2.60 to 10.22) and NNTs were 2.9, 3.1 and 5.3, respectively. A significantly slower rate of radiological progression was detected with either adalimumab 40 mg every other week or 20 mg every week in combination with MTX compared to placebo plus MTX, at 52 weeks. Adalimumab monotherapy (40 mg every other week) was associated with a RR of 1.91 (95% CI, 1.17 to 3.10), 2.84 (95% CI, 1.58 to 5.12) and 7.33 (95% CI, 2.25 to 33.90) to achieve an ACR 20, ACR 50 and ACR 70 response, respectively, with NNTs of 5 (95% CI, 3 to 9), 7 (95% CI, 4 to 20) and 9 (95% CI, 3 to 38), respectively at 24 weeks. Secondary: Only one study demonstrated that adalimumab was associated with a significantly higher risk of developing serious infection (RR, 7.64; 95% CI, 1.02 to 57.18; NNH, 30.2).
Smolen et al.[190] (2016) EXXELERATE Certolizumab pegol (400 mg weeks 0, 2, and 4, then 200 mg once every 2 weeks) plus methotrexate vs adalimumab (40 mg once every two weeks) plus methotrexate	PG, SB, RCT Patients >18 years of age with RA who were DMARD-naive and with active disease despite a minimum 12-week course of methotrexate therapy	N=908 104 weeks	Primary: ACR20 at week 12, low disease activity at week 104 Secondary: Percentage of patients with low disease activity at weeks 6, 12, and 52; change from baseline in HAQ-DI	Primary: The results of the primary analysis showed no significant difference in week 12 ACR20 response (69% and 71%; OR, 0.90; 95% CI, 0.67 to 1.20; P=0.467) or week 104 DAS28-ESR low disease activity (35% and 33%; OR, 1.09; 95% CI, 0.82; 1.45; P=0.532) between certolizumab pegol plus methotrexate and adalimumab plus methotrexate, respectively. At week 12, 65 non-responders to certolizumab pegol were switched to adalimumab and 57 non-responders to adalimumab were switched to certolizumab pegol; 58% of patients switching to certolizumab pegol and 62% of patients switching to adalimumab responded 12 weeks later by achieving low disease activity or a DAS28-ESR reduction 1.2 or greater. Secondary: The secondary efficacy endpoints were similar between certolizumab pegol plus methotrexate and adalimumab plus methotrexate patients. Physical functioning improved for both treatment groups. Change from

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
At week 12, patients were classified as responders (by either achieving low disease activity according to DAS28-ESR ≤3.2 or DAS28-ESR reduction ≥1.2 from baseline) or as non-responders; Non-responders to the first TNF inhibitor to which they were randomized were switched to the other TNF inhibitor with no washout period				baseline in HAQ-DI at week 104 was −0.62 for patients assigned to certolizumab pegol plus methotrexate and −0.72 for patients assigned to adalimumab plus methotrexate, and post-hoc analysis shows that normative physical function (HAQ-DI ≤0.25) was achieved by 20% of patients assigned to certolizumab pegol plus methotrexate and 22% of patients assigned to adalimumab plus methotrexate.
Mertens et al.[191] (2009) Anakinra 50 to 150 mg daily vs placebo	SR RCTs of patients >18 years of age with RA	N=2,876 (5 trials) 24 weeks	Primary: Patients achieving ACR 20 Secondary: Patients achieving ACR 50 and ACR 70, and safety	Primary: ACR 20 achievement was noted in significantly more participants taking anakinra (38%) compared to patients taking placebo (23%; RR, 1.61; 95% CI, 1.32 to 1.98). It was concluded that this 15% difference represented a modest yet clinically meaningful difference. Secondary: Both ACR 50 and ACR 70 were obtained at a significantly greater rate with anakinra as opposed to placebo (18 vs 7%; RR, 2.52; 95% CI, 1.56 to 4.03 and 7 vs 2%; RR, 3.71; 95% CI, 1.44 to 9.57, respectively). Anakinra was also associated with significant improvements in HAQ, visual analog score, Larsen radiographic scores and change in ESR compared to placebo. The number of withdrawals, deaths, adverse events and infections were not significantly different between active treatment and placebo. However, injection site reaction was significantly more prevalent in the anakinra group vs the placebo group (71 vs 28%).
Blumenauer et al.[192]	SR	N=949	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2003) Etanercept 10 mg or 25 mg twice weekly alone or in combination with MTX vs MTX or placebo	RCTs of patients ≥16 years of age meeting the ACR 1987 revised criteria for RA with evidence of active disease as demonstrated by ≥2 of the following: tender joint count, swollen joint count, duration of early morning stiffness >30 minutes, acute phase reactants such as Westergren ESR or CRP	(3 trials) ≥6 months	ACR 20, ACR 50, ACR 70 responses, and erosion scores Secondary: Safety	At six months, 64% of individuals on etanercept 25 mg attained an ACR 20 response vs 15% of patients on control with either MTX alone or placebo (RR, 3.8; 95% CI, 2.5 to 6.0; NNT, 2). ACR 50 was achieved by 39% in the etanercept group compared to 4% in the control group (RR, 8.89; 95% CI, 3.61 to 21.89; NNT, 3). An ACR 70 response was reported in 15 and 1% of etanercept and control patients, respectively (RR, 11.31; 95% CI, 2.19 to 58.30; NNT, 7). Etanercept 10 mg was only associated with significant ACR 20 (51 vs 11% of controls; RR, 4.6; 95% CI, 2.4 to 8.8; NNT, 3) and ACR 50 responses (24 vs 5% of controls; RR, 4.74; 95% CI, 1.68 to 13.36; NNT, 5). Seventy-two percent of patients receiving etanercept had no increase in Sharp erosion score vs 60% of MTX patients. The Sharp erosion scores and JSN were not significantly reduced by either etanercept dose, however etanercept 25 mg was associated with a significantly reduced total Sharp score (WMD, -10.50; 95% CI, -13.33 to -7.67). Secondary: Injection site reactions were reported in 34% of patients on etanercept 10 mg compared to 9% of controls (RR, 3.86; 95% CI, 2.59 to 5.77; NNH, 4) and 41% of patients receiving etanercept 25 mg vs 9% of controls (RR, 4.77; 95% CI, 3.26 to 6.97; NNH, 3.1). The number of withdrawals was reported less frequently in the etanercept 25 mg group (4%) compared to the control group (8%; RR, 0.50; 95% CI, 0.27 to 0.94) and no difference was found between the etanercept 10 mg group and control in the rate of discontinuation.
van Vollenhoven et al.[193] (2012) SWEFOT Infliximab 3 mg/kg at weeks zero, two	MC, OL, PG, RCT Patients ≥18 years of age with RA (ACR) criteria, no previous DMARD treatment, no oral	N=487 24 months	Primary: Proportion of patients achieving a EULAR-define good response (a decrease of DAS28 by ≥1.2 and a	Primary: At month 18, there was no statistically significant difference in the proportion of patients achieving an EULAR-defined good response for patients treated with infliximab compared to conventional therapy (38 vs 29%, respectively; 95% CI, 0.93 to 1.85). Furthermore, there was no statistically significant difference between the treatment groups at 24 months (38 vs 31%, respectively; P=0.204).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
and six then every eight weeks plus MTX 20 mg weekly (Group B) vs MTX 20 mg weekly plus SSZ 1,000 mg twice-daily plus hydroxychloroquine 400 mg daily (Group A)	glucocorticoid treatment or stable glucocorticoid treatment for ≥4 weeks of at most 10 mg daily prednisolone (or equivalent), a DAS28 >3.2		resulting DAS28 ≤3.2 or less Secondary: EULAR and ACR responses at months 18 and 24, radiological outcomes at months 24	Secondary: At 18 months, no statistically significant differences were reported between infliximab and conventional therapy with regard to ACR 20 (45 vs 34%, respectively; 95% CI, 0.99 to 1.82) ACR 70 (17 vs 11%, respectively; 95% CI, 0.86 to 2.98) or EULAR good or moderate response (58 vs 47%, respectively; 95% CI, 0.97 to 1.56). There was, however, a statistically significant difference favoring infliximab with regard to ACR 50 (30 vs 19%, respectively; 95% CI, 1.02 to 2.46). At 24 months there was no statistically significant difference between infliximab and conventional therapy with regard to ACR 20 response (40 vs 33%, respectively; P=0.259), ACR 50 (30 vs 22%; P=0.134), ACR 70 (16 vs 14%; P=0.566) or EULAR good to moderate response (59 vs 50%; P=0.166). Radiological outcomes were not statistically significant between infliximab and conventional therapy at 24 months with regard to total score (P=0.118), erosion score (P=0.0730) or joint-space narrowing score (P=0.054).
Wiens et al.[194] (2009) Infliximab 3 mg/kg at weeks 0, 2 and 6 then every 8 weeks plus MTX vs placebo plus MTX	MA RCTs of adult patients with RA	N=2,129 (7 trials) ≥14 weeks	Primary: ACR 20, ACR 50, and ACR 70 response Secondary: Safety and discontinuation of therapy	Primary: Through 30 weeks, the proportion of patients achieving an ACR 20 was 59% in the infliximab group compared to the control group (RR, 1.87; 95% CI, 1.43 to 2.45). An ACR 50 was achieved in 33% of infliximab treated patients and 12% of controls (RR, 2.68; 95% CI, 1.79 to 3.99). The RR of achieving an ACR 70 was 2.68 (95% CI, 1.78 to 4.03) with 17 and 5% of infliximab and control groups achieving an ACR 70, respectively. After ≥1 year of treatment, 62% of patients in the infliximab group and 26% of controls achieved an ACR 20 (RR, 2.33; 95% CI, 1.90 to 2.87). An ACR 50 was achieved in 43% of the infliximab treated patients and 27% of controls (RR, 1.61; 95% CI, 1.14 to 2.27). The RR for reaching ACR 70 was 1.69 (95% CI, 0.87 to 3.28), and 29% of patients in the infliximab group compared to 17% of patients in the control group achieved an ACR 70. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were no statistically significant differences in serious adverse events. There was a higher number of patients that withdrew due to adverse events in the infliximab group compared to the placebo group (7 vs 3%; RR, 2.05, 95% CI, 1.33 to 3.16); however, fewer patients in the infliximab group withdrew due to lack of efficacy compared to the control group (4 vs 12%; RR, 0.41; 95% CI, 0.18 to 0.95).
Nixon et al.[195] (2007) Adalimumab, anakinra, etanercept, or infliximab with or without MTX vs MTX or placebo	MA RCTs of patients with a clinical diagnosis of RA	N=6,694 (13 trials) ≥6 months	Primary: ACR 20 response and ACR 50 response Secondary: Not reported	Primary: The OR for an ACR 20 response was 3.19 (95% CI, 1.97 to 5.48) with adalimumab, 1.70 (95% CI, 0.90 to 3.29) with anakinra, 3.58 (95% CI, 2.09 to 6.91) with etanercept and 3.47 (95% CI, 1.66 to 7.14) with infliximab, all compared to placebo. The OR to achieve an ACR 50 response with adalimumab was 3.97 (95% CI, 2.73 to 6.07), 2.13 (95% CI, 1.27 to 4.22) with anakinra, 4.21 (95% CI, 2.74 to 7.43) with etanercept and 4.14 (95% CI, 2.42 to 7.46) with infliximab, all compared to placebo. The addition of MTX to any of the agents was found to enhance the efficacy of each treatment. The TNF blockers in combination with MTX were associated with higher ACR 20 and ACR 50 responses than anakinra and MTX (OR, 6.35 vs 3.20 and OR, 8.53 vs 4.56, respectively). Further analysis of each agent against another was performed and no significant difference was determined between individual agents in obtaining an ACR 20 and ACR 50 response (adalimumab vs anakinra; OR, 1.88; 95% CI, 0.83 to 4.49 and OR, 1.84; 95% CI, 0.84 to 3.70; adalimumab vs etanercept; OR, 0.89; 95% CI, 0.42 to 1.79 and OR, 0.94; 95% CI, 0.50 to 1.62; adalimumab vs infliximab; OR, 0.92; 95% CI, 0.39 to 2.37 and OR, 0.96; 95% CI, 0.48 to 1.90; etanercept vs anakinra; OR, 2.11; 95% CI, 0.90 to 5.68 and OR, 1.94; 95% CI, 0.87 to 4.36; infliximab vs anakinra; OR, 2.05; 95% CI, 0.74 to 5.50 and OR, 1.93; 95% CI, 0.79 to 4.29; and infliximab vs etanercept; OR, 0.97; 95% CI, 0.34 to 2.33 and OR, 0.98; 95% CI, 0.45 to 1.93. However, the TNF blockers as a class showed a greater ACR 20 and ACR 50 response compared to anakinra (OR, 1.96; 95% CI, 1.03 to 4.01 and OR, 1.93; 95% CI, 1.05 to 3.50; P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Gabay et al.[196] (2013) ADACTA Tocilizumab 8 mg/kg vs adalimumab 40 mg every 2 weeks	DB, PG, RCT Patients ≥18 years of age with RA > 6 months, intolerant to MTX or were inappropriate for continued MTX treatment	N=326 24 weeks	Primary: DAS 28 improvement Secondary: Percentage of patients with: a remission response (DAS28 <2.6); low disease activity (DAS28 ≤ 3.2); improvements of at least 20%, 50%, or 70% in ACR Score (ACR 20, ACR 50, and ACR 70); and with a EULAR good Response, and a EULAR good or moderate response	Primary: The change from baseline in DAS28 was significantly greater in the tocilizumab group (-3.3) than in the adalimumab group (-1.8) patients (difference -1.5; 95% CI, -1.8 to -1.1; P<0·0001). Secondary: DAS 28 remission rates at week 24 were achieved in 39.9% with tocilizumab and 10.5% in the adalimumab group (difference -1.5, 95% CI, -1.8 to -1.1; P<0·0001). The proportion of patients with low disease activity (DAS 28 ≤3.2) at 24 weeks was 51.5% in tocilizumab group and 19.8% in the adalimumab group (difference -1.5, 95% CI, -1.8 to -1.1; P<0.0001). The proportion of patients on tocilizumab vs adalimumab with improvements of at least 20% in ACR score was 65.0 vs 49.4%, respectively, a 50% improvement was seen in 47.2 vs 27.8% respectively and a 70% improvement was observed in 32.5 vs 17.9%, respectively. The proportion of patients on tocilizumab vs adalimumab with a EULAR good response was 51.5 vs 19.8%, respectively, and percentage with a EULAR good or moderate was response 77.9 vs 54.9%, respectively.
Weinblatt et al.[197] (2013) Abatacept 125 mg subcutaneously once weekly and MTX vs	MC, RCT Patients 18 years of age with a confirmed diagnosis of RA for ≤5 years, inadequate response to MTX, and who had not received previous biologic therapy	N=646 12 months	Primary: Noninferiority, assessed based on ACR20 at one year Secondary: ACR 50, ACR 70, DAS 28, remission response (DAS28 <2.6), low disease activity (DAS28 ≤ 3.2), and HAQ-DI	Primary: The proportions of patients achieving ACR 20 response were comparable between abatacept and adalimumab treatment groups (59.7 and 60.1%, respectively; difference 1.8%; 95% CI, -5.6 to 9.2%). Secondary: The proportions of patients achieving ACR 50 response were comparable between abatacept and adalimumab treatment groups (46.2 and 46%, respectively; 95% CI not reported). The proportions of patients achieving ACR 70 response were comparable between abatacept and adalimumab treatment groups (29.2 and 26%, respectively; 95% CI not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
adalimumab 40 mg subcutaneously every other week and MTX Patients were concomitantly treated with a stable dosage of MTX (15 to 25 mg weekly, or ≥7.5 mg weekly in patients with intolerance to higher doses). Concomitant treatment with SSZ, HCQ, NSAIDs and stable low-dose oral corticosteroids (≤10 mg/day prednisone equivalent) were allowed.				Mean improvements in DAS 28 were comparable between abatacept and adalimumab treatment groups (-2.30 and -2.27, respectively; 95% CI not reported). The proportions of patients achieving remission (DAS28 <2.6) were also comparable between abatacept and adalimumab treatment groups (43.3 and 41.9%, respectively; 95% CI not reported). In addition, the proportions of patients achieving low disease activity (DAS28 ≤3.2) were comparable between abatacept and adalimumab treatment groups (59.3 and 61.4%, respectively; 95% CI not reported). Improvements in the HAQ-DI score were comparable between abatacept and adalimumab treatment groups (60.4 and 57.0%, respectively; difference, 3.4%; 95% CI, -4.5 to 11.3%).
Schiff et al.[198] (2013) AMPLE Abatacept 125 mg subcutaneously once weekly and MTX vs	MC, RCT Patients 18 years of age with a confirmed diagnosis of RA for ≤5 years, inadequate response to MTX, and who had not received previous biologic therapy	N=646 2 years	Primary: ACR20 at two years Secondary: ACR 50, ACR 70, DAS 28, remission response (DAS28 <2.6), low disease activity (DAS28 ≤3.2), HAQ-DI, and mTSS	Primary: The proportions of patients achieving ACR 20 response were comparable between abatacept and adalimumab treatment groups (59.7 and 60.1%, respectively; 95% CI not reported). Secondary: The proportions of patients achieving ACR 50 response were comparable between abatacept and adalimumab treatment groups (44.7 and 46.6%, respectively; 95% CI not reported). The proportions of patients achieving ACR 70 response were comparable between abatacept and adalimumab treatment groups (31.1 and 29.3%, respectively; 95% CI not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
adalimumab 40 mg subcutaneously every other week and MTX Patients were concomitantly treated with a stable dosage of MTX (15 to 25 mg weekly, or ≥7.5 mg weekly in patients with intolerance to higher doses). Concomitant treatment with SSZ, HCQ, NSAIDs and stable low-dose oral corticosteroids (≤10 mg/day prednisone equivalent) were allowed.				Mean improvements in DAS 28 were comparable between abatacept and adalimumab treatment groups (-2.35 and -2.33, respectively; 95% CI not reported). The proportions of patients achieving remission (DAS28 <2.6) were also comparable between abatacept and adalimumab treatment groups (50.6 and 53.3%, respectively; 95% CI not reported). In addition, the proportions of patients achieving low disease activity (DAS28 ≤3.2) were comparable between abatacept and adalimumab treatment groups (65.3 and 68.0%, respectively; 95% CI not reported). Improvements in the HAQ-DI score were comparable between abatacept and adalimumab treatment groups (54.1 and 48.8%, respectively; 95% CI not reported). The non-progression rate (change from baseline mTSS ≤smallest detectable change of 2.2) was 84.8% (95% CI, 80.4 to 89.2) vs 83.8% (95% CI, 79.4 to 88.3) in the abatacept and adalimumab groups, respectively.
Fleischmann et al.[199] (2012) ORAL Solo Tofacitinib 5 mg twice daily vs tofacitinib 10 mg twice daily	DB, PC, PG, RCT Patients ≥18 years of age with a diagnosis of active RA (≥6 tender or painful joints [68 joint count] and ≥6 swollen joints [66 joint count] and either ESR>28 mm/hour or CRP>7	N=611 6 month	Primary: ACR20 response rate at month three, change from baseline in HAQ-DI at month three, and proportion of patients with DAS28-4(ESR) <2.6 at month three Secondary:	Primary: Greater proportions of patients receiving tofacitinib 5 mg and tofacitinib 10 mg twice daily met the criteria for an ACR20 response at month three than those receiving placebo (59.8 and 65.7 vs 26.7%; P<0.001 for both comparisons). Greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 5 and 10 mg twice daily at month three than those receiving placebo (least-squares mean changes from baseline, -0.50 and -0.57 vs -0.19; P<0.001 for both comparisons). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	mg/L), and inadequate response or adverse reaction to at least one DMARD; all DMARDs except stable doses of antimalarial agents had to be discontinued; the use of NSAIDs and glucocorticoids (≤10 mg of a prednisone equivalent daily) was permitted		ACR50, and ACR70 response rates, change from baseline in HAQ-DI score, DAS28-4(ESR) and DAS28-4(CRP), proportion of patients with DAS28-4(ESR) and DAS28-4(CRP) <2.6 and ≤3.2 at all visits up to month six, and FACIT-F scores at month three	daily achieved DAS28-4(ESR) <2.6 at month three than those receiving placebo (5.6 and 8.7 vs 4.4%; P=0.62 and P=0.10, respectively); however, improvement was not statistically significant. Secondary: Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR50 response at month three than those receiving placebo (31.1 and 36.8 vs 12.5%; P<0.001 for both comparisons). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR70 response at month three than those receiving placebo (15.4 and 20.3 vs 5.8%; P=0.003 and P<0.001, respectively). Proportions of patients receiving tofacitinib 5 and 10 mg twice daily who achieved DAS28-4(ESR) <2.6 at month six were 9.8 and 14.2%, respectively. Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) ≤3.2 at month three than those receiving placebo (12.5 and 17.0 vs 5.3%; P=0.02 and P<0.001, respectively). Proportions of patients receiving tofacitinib 5 and 10 mg twice daily who achieved DAS28-4(ESR) ≤3.2 at month six were 22.0% and 28.0%, respectively. Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(CRP) <2.6 at month three than those receiving placebo (18.7 and 24.4 vs 5.0%; P<0.001 for both comparisons). Proportions of patients receiving tofacitinib 5 and 10 mg twice daily who achieved DAS28-4(CRP) <2.6 at month six were 26.6 and 34.3%, respectively). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(CRP) ≤3.2 at month three than those receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				placebo (28.2 and 36.8 vs 6.7%; P<0.001 for both comparisons). Proportions of patients receiving tofacitinib 5 and 10 mg twice daily who achieved DAS28-4(CRP) ≤3.2 at month six were 43.6 and 50.8%, respectively. The least-squares mean changes from baseline at month three in FACIT-F scores were 6.7 points with the tofacitinib 5 mg and 8.0 points with the tofacitinib 10 mg doses, as compared to 2.8 points with placebo (P<0.001).
van Vollenhoven et al.[200] (2012) ORAL Standard Tofacitinib 5 mg twice daily vs tofacitinib 10 mg twice daily vs adalimumab 40 mg once every 2 weeks vs placebo Patients were also receiving MTX 7.5 to 25 mg weekly with an incomplete response.	DB, PG, RCT Patients ≥18 years of age with a diagnosis of active RA (≥6 tender or painful joints [68 joint count] and ≥6 swollen joints [66 joint count] and either ESR>28 mm/hour or CRP>7 mg/L)	N=717 12 month	Primary: ACR20 response rate at month six, change in HAQ-DI at month three, and proportion of patients with DAS28-4(ESR) <2.6 at month six Secondary: ACR20, ACR50, and ACR70 response rates, change from baseline in HAQ-DI, and DAS28-4(ESR) over time	Primary: Greater proportions of patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily and adalimumab met the criteria for an ACR20 response at month six than those receiving placebo (51.5, 52.6, and 47.2 vs 28.3%; P<0.001 for all comparisons). Greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily and adalimumab at month three than those receiving placebo (least-squares mean changes from baseline: -0.55, -0.61 and -0.49 vs -0.24; P≤0.001 for all comparisons). Greater proportions of patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily and adalimumab achieved DAS28-4(ESR) <2.6 at month six than those receiving placebo (6.2, 12.5, and 6.7 vs 1.1%; P≤0.05, P≤0.001, and P≤0.05, respectively). Secondary: Compared to placebo, significantly greater proportions of patient receiving active treatments achieved ACR50 and ACR70 responses and the changes from baseline in DAS28-4(ESR) and HAQ-DI scores over time (P≤0.05 for all comparisons). A significant difference in ACR20 and ACR50 responses with each tofacitinib treatment as compared to placebo was noted after one month (P≤0.001 for all comparisons). Data on comparison between adalimumab and placebo was not reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Burmester et al.[201] (2013) ORAL Step Tofacitinib 5 mg twice daily vs tofacitinib 10 mg twice daily vs placebo for 3 months, followed by tofacitinib 5 mg or 10 mg twice daily Patients were also receiving oral or parenteral MTX continuously for ≥4 months at a stable dose of 7.5 to 25 mg weekly for ≥6 weeks. Stable background doses of antimalarial agents (≥8 weeks) were permitted.	DB, MC, PG, RCT Patients ≥18 years of age with a diagnosis of moderate to severe active RA (≥6 tender or painful joints [68 joint count] and ≥6 swollen joints [66 joint count] and either ESR>28 mm/hour or CRP>7 mg/L) and inadequate response or intolerance to ≥1 TNF-blocking agents	N=399 6 month	Primary: ACR20 response rate at month three, change from baseline in HAQ-DI score at month three, and proportion of patients with DAS28-4(ESR) <2.6 at month three Secondary: ACR20, ACR50, and ACR70 response rates, change from baseline in HAQ-DI score, changes in DAS28-4(ESR) and DAS28-3(CRP), rates of DAS28-4(ESR) and DAS28-3(CRP) <2.6 and ≤3.2, patient's assessment of arthritis pain, and FACIT-F at all visits	Primary: Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR20 response at month three than those receiving placebo (41.7 and 48.1 vs 24.4%; P=0.0024 and P<0.0001, respectively). Greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 5 mg and 10 mg twice daily at month three than those receiving placebo (least-squares mean changes from baseline: -0.43 and -0.46 vs -0.18; P<0.0001 for both comparisons). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) <2.6 at month three than those receiving placebo (6.7 and 8.8 vs 1.7%; P=0.0496 and P=0.0105, respectively). Secondary: Compared to placebo, significantly greater proportions of patients in the tofacitinib 5 mg and 10 mg twice daily met the criteria for an ACR20 response at all visits through month three (P≤0.05 for all visits, except P<0.0001 for 10 mg group vs placebo at month three). Compared to placebo, significantly greater proportion of patients in the tofacitinib 5 mg twice daily group achieved ACR50 at all visits through month three (P≤0.05 at two week and one month visits and P<0.0001 at three month visit). Compared to placebo, significantly greater proportion of patients in the tofacitinib 10 mg twice daily group achieved the ACR50 at three month study visit (P<0.0001); however, responses at two week and at one month visits were not significantly different (P values not reported). Compared to placebo, significantly greater proportions of patients in the tofacitinib 5 mg and 10 mg twice daily groups achieved ACR70 at one month and three months visits (P≤0.05 for all visits, except P<0.001 for 5 mg group vs placebo at month three). The responses between both active treatment groups and placebo at two week visit were not significantly different (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Compared to placebo, significantly greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 10 mg twice daily at all visits through month three (P≤0.05 for all comparisons, except P<0.0001 at month three). Compared to placebo, significantly greater reductions from baseline in the HAQ-DI score were also observed at three month visit in patients receiving tofacitinib 5 mg twice daily (P<0.0001); however, the changes at two week and one month visits were not significantly different (P values not reported). Compared to placebo, changes from baseline in DAS28-4(ESR) were greater in patients receiving tofacitinib 5 and 10 mg twice daily at all visits through month three (P=0.01 for both comparisons; P values not reported for all other visits). Compared to placebo, significantly greater changes from baseline in DAS28-3(CRP) were observed in patients receiving tofacitinib 5 and 10 mg twice daily at all visits through month three (P<0.0001 for all comparisons). Compared to placebo, significantly greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) <2.6 at month three (P=0.0496 and P=0.0105, respectively; P values not reported for all other visits). Compared to placebo, significantly greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-3(CRP) <2.6 at month three (P<0.0001 for both comparisons; P values not reported for all other visits). Compared to placebo, significantly greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) ≤3.2 at month three (P≤0.05 and P<0.0001, respectively; P values not reported for all other visits). Compared to placebo, significantly greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-3(CRP) ≤3.2 at month three (P<0.0001 for both comparisons; P values not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				reported for all other visits). Changes from baseline in patient's assessment of arthritis pain at month three were greater in tofacitinib 5 and 10 mg twice daily treatment groups than in those receiving placebo (−27.2 and −25.0 vs −8.3; P<0.0001 for both comparisons; P values not reported for all other visits). Improvements in FACIT-F at month three were greater in patients receiving tofacitinib 5 and 10 mg twice daily than in those receiving placebo (6.3 and 4.6 vs 1.1; P<0·0001 and P=0.0043, respectively; P values not reported for all other visits).
Van der Heijde et al.[202] (2013) ORAL Scan Tofacitinib 5 mg twice daily vs tofacitinib 10 mg twice daily vs placebo Patients receiving placebo and not achieving ≥20% improvement in swollen and tender joint counts after 3 months were switched to a predetermined dose	DB, MC, PG, RCT Patients ≥18 years of age with a diagnosis of active RA (≥6 tender or painful joints [68 joint count] and ≥6 swollen joints [66 joint count] and either ESR>28 mm/hour or CRP>7 mg/L) and evidence of ≥3 joint erosions on posteroanterior hand and wrist radiographs or anteroposterior foot radiographs (if radiographic evidence of joint erosions was unavailable, presence of IgM rheumatoid factor positivity or	N=797 12 month	Primary: ACR20 response rate at month six, mean change from baseline in mTSS at month six, change from baseline in HAQ-DI score at month three, and proportion of patients with DAS28-4(ESR) <2.6 at month six Secondary: ACR20, ACR50, and ACR70 response rates, DAS28-4(ESR) at all visits, changes from baseline in the ACR code disease activity measures at month six, rates of	Primary: Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR20 response at month six than those receiving placebo (51.5 and 61.8% vs 25.3%; P=0.0001 for both comparisons). The least squares mean changes in mTSS at month six were 0.12 and 0.06 for patients receiving tofacitinib 5 and 10 mg twice daily, respectively, vs 0.47 for placebo (P=0.0792 and P≤0.05, respectively). The least squares mean changes in the HAQ-DI score at month three for tofacitinib at 5 and 10 mg twice daily were -0.40 and -0.54, respectively, vs -0.15 for placebo (P value not reported and P<0.0001, respectively). Proportions of patients achieving DAS28-ESR <2.6 at month six were 7.2% and 16.0% for tofacitinib at 5 and 10 mg twice daily, respectively, vs 1.6% for placebo (P value not reported and P<0.0001, respectively). Secondary: Compared to placebo at month six, significantly greater proportions of patients in the tofacitinib 5 mg and 10 mg twice daily groups achieved ACR50 (32.4 and 43.7 vs 8.4%; P<0.0001 for both comparisons) and ACR70 (14.6 and 22.3 vs 1.3%; P<0.0001 for both comparisons). At month 12, ACR20, ACR50, and ACR70 response rates were 48.5, 32.7, and 18.8%, respectively, for tofacitinib 5 mg and 57.0, 41.1, and 27.5%, respectively, for tofacitinib 10 mg.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
of tofacitinib 5 mg or 10 mg twice daily. All patients continuing to receive placebo were switched in a blinded manner to tofacitinib after 6 months. Patients were also receiving stable doses of MTX (15 to 25 mg weekly or <15 mg if there were safety issues at higher doses) for ≥6 weeks. Stable doses of low-dose corticosteroids (≤10 mg daily prednisone or equivalent) and NSAIDs were permitted. Prior use of biologic or nonbiologic DMARDs was permitted.	antibodies to cyclic citrullinated peptide).		nonprogressors (≤0.5 unit change from baseline in mTSS or erosion score) at months six, 12, and 24, changes from baseline in mTSS (at months 12 and 24), changes from baseline in erosion score and JSN score (at months six, 12, and 24), change from baseline in HAQ-DI score, the FACIT-F, and the patient's assessment of arthritis pain	At month 12, the proportions of patients with DAS28-ESR <2.6 were 10.6 and 15.2% in the groups receiving tofacitinib 5 and 10 mg twice daily, respectively. At month six, the proportions of patients with DAS28-ESR ≤3.2 were 14.3 and 28.4% in the groups receiving tofacitinib 5 and 10 mg twice daily, respectively, compared to 3.1% of patients receiving placebo (P<0.0001 for both comparisons). At month 12, the rates of DAS28-ESR <3.2 for patients receiving tofacitinib at 5 and 10 mg twice daily increased to 23.4 and 30.7%, respectively. At month six, least squares mean changes from baseline in DAS28-ESR were greater for tofacitinib 5 and 10 mg twice daily compared to placebo (-2.1 and -2.5 vs -1.3; P<0.0001 for both comparisons); at month 12, least squares mean changes from baseline in DAS28-ESR were -2.3 and -2.5 for tofacitinib 5 and 10 mg twice daily, respectively. Compared to placebo a month six, statistically significant improvements from baseline were observed in all ACR core components in both tofacitinib 5 and 10 mg twice daily groups, including improvements in tender or painful joint count (P≤0.05 and P<0.01, respectively), swollen joint count (P<0.01 and P<0.0001, respectively), CRP (P<0.0001 for both comparisons), patient's global assessment of disease activity (P<0.0001 for both comparisons), physician's global assessment of disease activity (P<0.0001 for both comparisons), patient's assessment of pain (P<0.01 and P<0.0001, respectively), and HAQ-DI (P<0.0001 for both comparisons). The proportion of patients with no radiographic progression (≤0.5 unit increase from baseline in mTSS) at months six and 12 was similar in both tofacitinib treatment groups and significantly greater than in the placebo treatment group (P≤0.05 for both). At month six, the proportion of patients with no progression in erosion score (≤0.5 unit increase from baseline) was numerically greater, but not statistically significantly different, in the tofacitinib treatment groups compared to the placebo-treated group (P>0.05). The proportion of patients with no progression in erosion score at month 12 was significantly greater in both tofacitinib treatment groups compared to the placebo-treated group (P≤0.05).

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				The plots of changes from baseline in mTSS, JSN score, and erosion score at months six and 12 for both tofacitinib-treated groups were very similar and were different from the plot for the placebo-treated group (P values not reported). Compared to placebo, greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 5 and 10 mg twice daily at all visits (P<0.001 for all comparisons, except P<0.01 for tofacitinib 5 mg vs placebo at one month visit). Improvements in FACIT-F from baseline to month six were greater in patients receiving tofacitinib 5 and 10 mg twice daily than in those receiving placebo (5.6 and 6.9 vs 2.1; P<0.001 and P<0.0001, respectively; P values not reported for all other visits). Changes from baseline in patient's assessment of arthritis pain at month six were greater in 5 and 10 mg twice daily treatment groups than in those receiving placebo (-26.4 and -29.7 vs -15.70; P<0.01 and P<0.0001, respectively; P values not reported for all other visits).
Kremer et al.[203] (2013) ORAL Sync Tofacitinib 5 mg twice daily vs tofacitinib 10 mg twice daily vs placebo Patients receiving placebo and not	DB, MC, PG, RCT Patients ≥18 years of age with a diagnosis of active RA (≥4 tender or painful joints [68 joint count] and ≥4 swollen joints [66 joint count] and either ESR>28 mm/hour or CRP>7 mg/L) and inadequate response to ≥1 stably dosed nonbiologic or biologic DMARDs	N=792 12 month	Primary: ACR20 response rate at month six, change from baseline in HAQ-DI score at month three, and proportion of patients with DAS28-4(ESR) <2.6 at month six Secondary: ACR20, ACR50, and ACR70 response rates, change from baseline in HAQ-	Primary: Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR20 response at month six than those receiving placebo (52.1 and 56.6 vs 30.8%; P<0.001 for both comparisons). Greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 5 and 10 mg twice daily at month three than those receiving placebo (least-squares mean changes from baseline: -0.44 and -0.53 vs -0.16; P<0.001 for both comparisons). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) <2.6 at month six than those receiving placebo (8.5 and 12.5 vs 2.6%; P=0.005 and P<0.001, respectively). Secondary: Over time, statistically significant response rates were observed for ACR20 and ACR50 by week two in both tofacitinib groups compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
achieving ≥20% improvement in swollen and tender joint counts after 3 months were switched to a predetermined dose of tofacitinib 5 or 10 mg twice daily. All patients continuing to receive placebo were switched in a blinded manner to tofacitinib after 6 months. Patients were also receiving ≥1 nonbiologic DMARDs. Patients receiving MTX ≤25 mg weekly required ≥4 months of therapy at a stable dose for ≥6 weeks. Stable doses of low-dose corticosteroids (≤10 mg daily prednisone or equivalent) were permitted.			DI score, changes in DAS28-4(ESR), and FACIT-F score over time	placebo (P≤0.001 for all comparisons) and for ACR70 by week two in the tofacitinib 10 mg group (P≤0.05 at week two and P≤0.001 at all visits thereafter) and one month in the tofacitinib 5 mg group (P≤0.001 for all comparisons). Mean treatment differences in changes from baseline in HAQ-DI, DAS28-4(ESR), and FACIT-F response rates for both tofacitinib groups compared to placebo were statistically significant over time (P≤0.001 for all).
Fleischmann et al.[204] (2017) ORAL Strategy	DB, MC, NI, RCT patients ≥18 years of	N=1,146 1 year	Primary: ACR50 at 6 months	Primary: At six months, ACR50 response was attained in 147 (38%) of 384 patients who received tofacitinib monotherapy, 173 (46%) of 376 patients who

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Tofacitinib 5 mg twice daily by mouth vs tofacitinib 5 mg twice daily by mouth plus methotrexate vs adalimumab 40 mg every other week SC plus methotrexate	age with active RA despite methotrexate therapy		Secondary: ACR 20 and ACR70 at six months, proportion of patients achieving low disease activity	received tofacitinib and methotrexate, and 169 (44%) of 386 patients who received adalimumab and methotrexate. Tofacitinib and methotrexate was deemed non-inferior to adalimumab and methotrexate: the difference in the proportion of patients with an ACR50 response for tofacitinib and methotrexate compared with adalimumab and methotrexate was 2% (98.34%; CI, −6 to 11), with the lower bound of the CI above the prespecified non-inferiority boundary (−13%). Non-inferiority of the ACR50 response at six months was not shown for tofacitinib monotherapy versus tofacitinib and methotrexate (difference, −8%; 98.34% CI, −16 to 1) or versus adalimumab and methotrexate (−6%; 98.34% CI, −14 to 3); superiority was not shown for any comparison between the treatment groups. Secondary: ACR20 and ACR70 response rates in each treatment arm showed similar trends to those noted for ACR50, and were maintained over 12 months. In general, secondary efficacy endpoint responses were similar between combination arms, which were higher than in the tofacitinib monotherapy group. The proportions of patients who had low disease activity at six months, as indicated by SDAI (≤11), were similar between combination therapy groups (50% in the tofacitinib and methotrexate group and 47% in the adalimumab and methotrexate group), which were higher than in the tofacitinib monotherapy group (43%); these were maintained at 12 months in each treatment group. The proportions of patients who had low disease activity at six months and at 12 months in all treatment groups, as indicated by CDAI, DAS28-4(ESR), and DAS28-4(CRP), were consistent with those reported when assessing low disease activity as indicated by SDAI.
He et al.[205] (2013) Tofacitinib 1, 3, 5, 10, or 15 mg twice daily vs	MA, SR RCTs including patients ≥18 years of age with a diagnosis of RA	N=3,791 (8 trials) 12 to 24 weeks	Primary: ACR20 and ACR50 response rate at month three and six Secondary: Incidence of infections,	Primary: At month three, the differences in ACR20 response rates between tofacitinib 1 mg twice daily and placebo groups did not reach statistical significance (RR, 1.83; 95% CI, 1.00 to 3.32). Greater proportions of patients receiving tofacitinib 3 mg twice daily met the criteria for an ACR20 response at month three than those receiving placebo (RR, 2.20; 95% CI, 1.20 to 4.04).

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adalimumab 40 mg once every 2 weeks vs placebo			immunological or hematological adverse events, incidence of withdrawal from the trials, changes in neutrophil count, hemoglobin and serum creatinine levels, incidence of ALT and AST more than one times upper limit of the normal range, and mean percentage changes of LDL and HDL	Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR20 response at month three than those receiving placebo (RR, 2.20; 95% CI, 1.58 to 3.07) and (RR, 2.38; 95% CI, 1.81 to 3.14), respectively. The effect was maintained at month six for both 5 mg twice daily (RR, 1.94; 95% CI, 1.55 to 2.44) and 10 mg twice daily (RR, 2.20; 95% CI, 1.76 to 2.75) treatment groups. Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR50 response at month three than those receiving placebo (RR, 2.91; 95% CI, 2.03 to 4.16) and (RR, 3.32; 95% CI, 2.33 to 4.72), respectively. Greater proportions of patients receiving tofacitinib 15 mg twice daily met the criteria for an ACR20 response at month three than those receiving placebo (RR, 2.29; 95% CI, 1.19 to 4.41). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR20 response at month three than those receiving adalimumab (RR, 1.65; 95% CI, 1.08 to 2.53) and (RR, 1.97; 95% CI, 1.32 to 2.92), respectively. At month six, there were no significant differences in ACR20 response rates in patients receiving tofacitinib vs adalimumab (P values not reported). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR50 response at month three than those receiving adalimumab (RR, 1.95; 95% CI, 1.00 to 3.80) and (RR, 2.35; 95% CI, 1.26 to 4.38), respectively. Secondary: Compared to placebo, there were no statistically significant differences in the incidences of infections, neutropenia and withdrawal due to adverse events in patients receiving tofacitinib (P values not reported). However, significantly fewer patients withdrew from tofacitinib than placebo (RR, 0.60; 95% CI, 0.45 to 0.78). The withdrawal rate due to lack of efficacy was significantly lower in the patients receiving tofacitinib than placebo (RR, 0.18; 95% CI, 0.09 to 0.35).

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				Compared to placebo, the mean neutrophil count significantly declined in patients receiving tofacitinib (P value not reported). The mean hemoglobin level was not significantly different in tofacitinib group compared to placebo group (P value not reported). Compared to placebo, the mean serum creatinine was found to be significantly higher for tofacitinib 10 mg twice daily (P value not reported). The risk ratios of the mean changes of ALT or AST exceeding one times upper limit of the normal range were statistically significant (P values not reported). Compared to placebo, the mean percentage change of HDL and LDL was significant higher in patients receiving tofacitinib (P values not reported).
Berhan et al.[206] (2013) Tofacitinib 3, 5, 10, or 15 mg twice daily (with or without MTX) vs placebo	MA DB, RCT including patients with a diagnosis of active RA for ≥6 months who were on at least one of nonbiologic or biologic DMARD	N=3,260 (8 trials) 12 to 24 weeks	Primary: ACR20 response rate, change from baseline in HAQ-DI score Secondary: Safety	Primary: Compared to placebo, tofacitinib treated patients had higher odds of meeting the criteria for an ACR20 response (OR, 4.15; 95% CI, 3.23 to 5.32). With the exception of one study, ACR20 response rates for patients receiving tofacitinib dosages ≥3 mg twice daily was significantly greater than those who received placebo (P value not reported). The subgroup odds ratios in the subgroups of tofacitinib 10 mg twice daily (OR, 4.3; 95% CI, 3.023 to 6.376) and 15 mg twice daily (OR, 6.06; 95% CI, 2.383 to 15.428) was higher than 3 mg twice daily (OR, 4.06; 95% CI, 1.340 to 12.305) and 5 mg twice daily (OR, 3.55; 95% CI, 2.435 to 5.169) treated groups. A statistically significant improvement in HAQ-DI scores were seen in patients receiving tofacitinib than placebo treated patients (SMD, −0.62; 95% CI, -0.735 to -0.506). Patients treated with tofacitinib dosages ≥5 mg twice daily have shown a statistically significant reduction in HAQ-DI scores (P value not reported). Secondary: The proportion of infections was higher in the tofacitinib treated groups than in the placebo groups (SMD, 1.96, 95% CI, 1.428 to 2.676). In contrast to the subgroups of tofacitinib 10 mg (SMD, 3.08; 95% CI, 1.694 to 5.570) and 15 mg (SMD, 1.97; 95% CI, 1.088 to 3.558), the proportion of infections in the subgroups of tofacitinib 3 mg (SMD, 1.64; 95% CI,

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				0.858 to 3.142) and 5 mg (SMD, 1.52; 95% CI, 0.644 to 3.594) were not significantly different from placebo. There were significant increases from baseline in tofacitinib treated groups in the mean hemoglobin level (SMD, 0.11; 95% CI, 0.130 to 0.210), mean serum creatinine (SMD, 0.24; 95% CI, 0.112 to 0.372), HDL (SMD, 1.01; 95% CI, 0.332 to 1.682), and LDL (SMD, 0.95; 95% CI, 0.337 to 1.555). A significant number of patients with ALT (OR, 1.7; 95% CI, 1.29 to 2.46) and AST (OR, 2.19; 95% CI, 1.50 to 3.19) exceeding one times upper limit of the normal range were reported among tofacitinib treated groups. The rate of tofacitinib discontinuation due to adverse events was not significantly different from placebo (SMD, 1.27; 95% CI, 0.949 to 1.700).
Burmester et al.[207] (2018) SELECT-NEXT Upadacitinib 15 mg or 30 mg PO once daily vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with moderate-to-severe active RA and had an inadequate response to at least one csDMARD (methotrexate, sulfasalazine, or leflunomide)	N=661 12 weeks	Primary: Proportion of patients achieving ACR20 at week 12 and proportion of patients who achieved DAS28-CRP of ≤3.2 at week 12 Secondary: Proportion of patients achieving ACR50 at week 12, proportion of patients achieving DAS28-CRP <2.6 at week 12, proportion of patients with CDAI ≤10 and	Primary: At week 12, an ACR20 response was achieved by 64% of patients receiving upadacitinib 15 mg and 66% of patients receiving upadacitinib 30 mg, compared with 36% of patients receiving placebo (P<0·0001 for both doses). At week 12, DAS28-CRP ≤3.2 was met by 48% of patients receiving upadacitinib 15 mg and 48% of patients receiving upadacitinib 30 mg, compared with 17% receiving placebo (P<0·0001 for both doses). Secondary: At week 12, the proportion of patients who achieved ACR50 was 31% for patients receiving upadacitinib 15 mg, 43% for upadacitinib 30 mg, and 15% for placebo (P≤0.0001). At week 12, the proportion of patients who achieved DAS28-CRP <2.6 was 31% for patients receiving upadacitinib 15 mg, 28% for upadacitinib 30 mg and 10% for placebo (P≤0.0001). The proportion of patients who achieved CDAI ≤10 was 40% for patients receiving upadacitinib 15 mg, 42% for upadacitinib 30 mg and 9% for placebo (P≤0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			mean changes from baseline in DAS28-CRP	The mean change from baseline in DAS28-CRP was -2.125 for patients receiving upadacitinib 15 mg, -2.38 for upadacitinib 30 mg and -1.02 for placebo (P≤0.0001).
Genovese MC et al.[208] (2018) SELECT-BEYOND Upadacitinib 15 mg or upadacitinib 30 mg PO once daily vs placebo	DB, MC, PG, PC RCT Patients ≥18 years of age, with moderate-to-severe active RA and previous inadequate response or intolerance to biologic DMARDs, receiving concomitant background csDMARDs	N=499 24 weeks	Primary: Proportions of patients achieving ACR20 at week 12 and proportion of patients achieving DAS28-CRP of ≤3.2 at week 12 Secondary: Proportion of patients achieving ACR50 at week 12, mean change from baseline in the DAS28-CRP at week 12 and mean change in HAQ-DI score at week 12	Primary: At week 12, ACR20 was achieved by 65% of patients receiving upadacitinib 15 mg and 56% of patients receiving upadacitinib 30 mg compared to 28% of patients receiving placebo (P<0.0001 for both doses). At week 12, DAS28-CRP ≤3.2 was achieved by 43% of patients receiving upadacitinib 15 mg and 42% of patients receiving upadacitinib 30 mg compared to 14% of patients receiving placebo (P<0.0001 for both doses). Secondary: The proportion of patients who achieved ACR50 was 38% for upadacitinib 15 mg, 43% for upadacitinib 30 mg, and 15% for placebo (P<0·001 for both doses). Both doses of upadacitinib had significantly greater DAS28-CRP change than placebo (P<0.0001). Mean change in the HAQ-DI score was -0.41 for upadacitinib 15 mg and -0.44 for upadacitinib 30 mg compared to -0.16 for placebo (P<0·0001).
Rubbert-Roth et al.[209] (2020) SELECT-CHOICE Upadacitinib 15 mg by mouth once daily vs Abatacept IV (at day 1 and weeks 2, 4, 8, 12, 16, and 20 [500	DB, MC, RCT Patients ≥18 years of age, with moderate-to-severe active RA and previous inadequate response or intolerance to biologic DMARDs, receiving concomitant background	N=612 24 weeks	Primary: Change in baseline in DAS28-CRP at week 12 (assessed for NI) Secondary: DAS28-CRP superiority and percentage of patients having clinical remission according to a	Primary: From baseline DAS28-CRP values of 5.70 in the upadacitinib group and 5.88 in the abatacept group, the mean change at week 12 was -2.52 and -2.00, respectively (difference, -0.52 points; 95% CI, -0.69 to -0.35; P<0.001 for noninferiority; P<0.001 for superiority). Secondary: The percentage of patients having remission according to a DAS28-CRP of less than 2.6 was 30.0% with upadacitinib and 13.3% with abatacept (difference, 16.8 percentage points; 95% CI, 10.4 to 23.2; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg in patients with a body weight of <60 kg, 750 mg in those with a weight of 60 to 100 kg, and 1000 mg in those with a weight of >100 kg]) each in combination with stable synthetic DMARDs	csDMARDs		DAS28-CRP of less than 2.6	
Van Vollenhoven R et al.[210] (2020) SELECT-EARLY Upadacitinib PO 15 mg or 30 mg once daily vs methotrexate PO once weekly	AC, DB, MC, PG, RCT Patients ≥18 years of age with moderate-to-severe active RA who were methotrexate-naïve	N=945 24 weeks	Primary: Proportion of patients achieving ACR50 at week 12 and proportion of patients achieving DAS28-CRP <2.6 at week 24 Secondary: Mean changes from baseline in mTSS and proportion of patients with no radiographic progression at week 24	Primary: At week 12, a significantly higher proportion of patients receiving upadacitinib 15 and 30 mg compared to methotrexate achieved ACR50 responses at 52.1% and 56.4% compared to 28.3% (P<0.001). At week 24, a significantly higher proportion of patients receiving upadacitinib 15 and 30 mg compared to methotrexate achieved DAS28-CRP<2.6 at 48.3% and 50.0% compared to 18.5% (P<0.001). Secondary: At week 24, mean changes from baseline in mTSS were significantly lower with upadacitinib 15 and 30 mg compared to methotrexate at 0.14, 0.07 compared to 0.67 (P<0.001). At week 24, a significantly higher proportion of patients upadacitinib 15 and 30 mg compared to methotrexate had no radiographic progression (P<0.001).
Smolen JS et al.[211] (2019) SELECT-MONOTHERAPY Upadacitinib PO 15 mg or 30 mg once daily	AC, DB, MC, PG, RCT Patients ≥18 years of age with moderate-to-severe active RA and an inadequate response to	N= 598 14 weeks	Primary: Proportion of patients achieving ACR20 at week 14 and proportion of patients achieving DAS28-CRP ≤3.2 at week 14	Primary: At week 14, an ACR20 response was achieved by 41% in the continued methotrexate group compared to 68% of patients receiving upadacitinib 15 mg and 71% of patients receiving upadacitinib 30 mg (P<0·0001 for both doses). At week 14, 19% in the continued methotrexate group, 45% receiving upadacitinib 15 mg, and 53%receiving upadacitinib 30 mg had achieved DAS28-CRP ≤3.2 (P<0·0001 for

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vs methotrexate PO once weekly	methotrexate		Secondary: Mean changes from baseline in DAS28-CRP at week 14, mean changes from baseline in HAQ-DI at week 14, proportion of patients achieving ACR50 and proportion of patients achieving DAS28-CRP <2.6	both doses). Secondary: At week 14, the mean change from baseline in DAS28-CRP was -2.7 for patients receiving upadacitinib 15 mg, -2.7 for upadacitinib 30 mg and -1.2 for methotrexate (P≤0.0001). At week 14, the mean change from baseline in HAQ-DI was -0.65 for patients receiving upadacitinib 15 mg, -0.73 for upadacitinib 30mg and -0.32 for methotrexate (P≤0.001). At week 14, the proportion of patients who achieved ACR50 was 68% for patients receiving upadacitinib 15 mg, 71% for upadacitinib 30 mg and 41% for methotrexate (P≤0.0001). At week 14, the proportion of patients who achieved DAS28-CRP <2.6 was 28% for patients receiving upadacitinib 15 mg, 41% for upadacitinib 30 mg and 8% for methotrexate (P≤0.0001).
Fleischmann R et al.[212] (2019) SELECT-COMPARE Methotrexate weekly plus upadacitinib 15 mg PO once daily vs methotrexate weekly plus adalimumab SQ 40 mg every other week vs	DB, MC, PG, PC RCT Patients ≥18 years of age with moderate-to-severe active RA, hsCRP≥5 and evidence of erosive disease and/or seropositivity receiving stable methotrexate background therapy	N=1,629 48 weeks	Primary: Proportion of patients achieving ACR20 at week 12 and proportion of patients who DAS28-CRP <2.6 at week 12 Secondary: Mean change from baseline in the DAS28-CRP, proportion of patients achieving a DAS28-CRP of ≤3.2 and mean change in HAQ-DI score at week 12	Primary: At week 12, an ACR20 response was achieved by 71% of patients receiving upadacitinib compared to 36% receiving placebo (P≤0.001) and compared to 63% receiving adalimumab (P≤0.05). At week 12, a DAS28-CRP <2.6 was achieved by 29% of patients receiving upadacitinib compared to 6% receiving placebo (P≤0.001) and compared to 18% receiving adalimumab (P≤0.001). Secondary: Significantly greater improvements from baseline in the DAS28-CRP were observed in patients receiving upadacitinib compared to those receiving either placebo or adalimumab at -2.48 in the upadacitinib group versus -1.14 in the placebo and adalimumab groups (P≤0.001). Significantly higher proportions of patients receiving upadacitinib compared to placebo achieved a DAS28-CRP≤3.2 (P≤0.001). Upadacitinib met the noninferiority comparison to adalimumab for achievement of a DAS28-CRP ≤3.2 at 45% versus 29% (P≤0.001).

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methotrexate PO weekly plus placebo				At week 12, the mean change in HAQ-DI score was -0.60 in the upadacitinib group versus -0.49 in the adalimumab group (P≤0.01).
Hetland et al.[213] (2020) Active conventional treatment (either prednisolone tapered to 5 mg/day, or sulfasalazine combined with hydroxychloroquine and intra-articular corticosteroids) vs certolizumab pegol vs abatacept vs tocilizumab All patients started methotrexate	Blinded assessor, MC, OL, RCT Patients ≥18 years of age with treatment naive rheumatoid arthritis, symptom duration less than 24 months, moderate to severe disease activity, and rheumatoid factor or anti-citrullinated protein antibody positivity, or increased C reactive protein	N=812 24 weeks	Primary: Adjusted clinical disease activity index remission (CDAI≤2.8) at 24 weeks with active conventional treatment as the reference Secondary: CDAI remission at 12 weeks and over time, other remission criteria, non-inferiority analysis, and adverse events	Primary: Baseline disease activity score of 28 joints was 5.0 (standard deviation 1.1). Adjusted 24 week CDAI remission rates were 42.7% (95% CI, 36.1% to 49.3%) for active conventional treatment, 46.5% (95% CI, 39.9% to 53.1%) for certolizumab pegol, 52.0% (95% CI, 45.5% to 58.6%) for abatacept, and 42.1% (95% CI, 35.3% to 48.8%) for tocilizumab. Corresponding absolute differences were 3.9% (95% CI, −5.5% to 13.2%) for certolizumab pegol, 9.4% (95% CI, 0.1% to 18.7%) for abatacept, and −0.6% (95% CI, −10.1% to 8.9%) for tocilizumab. Secondary: Key secondary outcomes showed no major differences among the four treatments. Differences in CDAI remission rates for active conventional treatment versus certolizumab pegol and tocilizumab, but not abatacept, remained within the prespecified non-inferiority margin of 15% (per protocol population). The total number of serious adverse events was 13 (percentage of patients who experienced at least one event 5.6%) for active conventional treatment, 20 (8.4%) for certolizumab pegol, 10 (4.9%) for abatacept, and 10 (4.9%) for tocilizumab. Eleven patients treated with abatacept stopped treatment early compared with 20, 23, and 22 patients in the active conventional treatment, certolizumab pegol, and tocilizumab arms, respectively.
Systemic Sclerosis-Associated Interstitial Lung Disease				
Khanna et al.[214] (2020) focuSSced Tocilizumab 162 mg weekly	DB, MC, PC, RCT Adults with diffuse cutaneous systemic sclerosis for 60 months or less and a	N=210 48 weeks	Primary: Difference in change from baseline to week 48 in mRSS	Primary: In the intention-to-treat population, least squares mean change from baseline to week 48 in mRSS was -6.14 for tocilizumab and -4.41 for placebo (adjusted difference, -1.73; 95% CI, -3.78 to 0.32; P=0.10). Secondary:

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vs placebo	modified Rodnan skin score (mRSS) of 10 to 35 at screening		Secondary: Percentage of predicted forced vital capacity (FVC% predicted) at week 48, time to treatment failure, and patient-reported and physician-reported outcomes	The shift in distribution of change from baseline in FVC% predicted at week 48 favored tocilizumab (van Elteren nominal P=0.002 vs placebo), with a difference in LSM of 4.2 (95% CI, 2.0 to 6.4; nominal P=0.0002), as did time to treatment failure (hazard ratio, 0.63; 95% CI, 0.37 to 1.06; nominal P=0.08). Change in LSM from baseline to week 48 in Health Assessment Questionnaire-Disability Index and in patient-global and physician-global visual analogue scale assessments did not differ between tocilizumab and placebo. In the safety set, infections were the most common adverse events (54 [52%] of 104 participants in the tocilizumab group, 53 [50%] of 106 in the placebo group). Serious adverse events were reported in 13 participants treated with tocilizumab and 18 with placebo, primarily infections (three events, eight events) and cardiac events (two events, seven events).
Ulcerative Colitis				
Rutgeerts et al.[215] (2005) ACT 1 and ACT 2 Infliximab 5 to 10 mg/kg at weeks 0, 2, 6 and then every 8 weeks vs placebo	DB, MC, PC, RCT Adult patients with endoscopy confirmed active ulcerative colitis (Mayo score 6 to 12) and moderate to severe active disease on sigmoidoscopy despite concurrent treatment with corticosteroids alone or in combination with azathioprine or mercaptopurine (ACT 1) or despite concurrent treatment with corticosteroids alone or mercaptopurine and medications containing 5-	N=364 (ACT 1) N=364 (ACT 2) 30 weeks (ACT 2) 54 weeks (ACT1)	Primary: Clinical response at week eight Secondary: Clinical response or clinical remission with discontinuation of corticosteroids at week 30 (ACT 1 and ACT 2) and week 54 (ACT 1), clinical remission and mucosal healing at weeks eight and 30 (ACT 1 and ACT 2) and week 54 (ACT 1), and clinical response at week eight in patients with a history of	Primary: At week eight in ACT 1, the proportion of patients with clinical response was significantly higher in the infliximab 5 and 10 mg/kg groups (69.4 and 61.5%) compared to the placebo group (37.2%; P<0.001 for both). In ACT 2 at week eight, the proportion of patients with clinical response was significantly higher in the infliximab 5 and 10 mg/kg groups (64.5 and 69.2%) compared to the placebo group (29.3%; P<0.001 for both). Secondary: In ACT 1, the proportion of patients with clinical response at week 30 was significantly higher in the infliximab 5 and 10 mg/kg groups (52.1 and 50.8%) compared to the placebo group (29.8%; P<0.001 and P=0.002, respectively). In ACT 2 at week 30, the proportion of patients with clinical response was significantly higher in the infliximab 5 and 10 mg/kg groups (47.1 and 60.0%) compared to the placebo group (26.0%; P<0.001 for both). In ACT 1 at week 54, the clinical response rate was significantly higher in the infliximab 5 and 10 mg/kg groups compared to the placebo group (45.5 and 44.3 vs 19.8%; P<0.001 for both). In ACT 1, the proportion of patients with clinical remission at week eight was significantly higher in the infliximab 5 and 10 mg/kg groups (38.8 and 32.0%) compared to the placebo group (14.9%; P<0.001 and P=0.002, respectively). In ACT 2 at week eight, the proportion of patients with

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	aminosalicylates (ACT 2)		corticosteroid refractory disease	clinical remission was significantly higher in the infliximab 5 and 10 mg/kg groups (33.9 and 27.5%) compared to the placebo group (5.7%; P<0.001 for both). In ACT 1, the proportion of patients with clinical remission at week 30 was significantly higher in the infliximab 5 and 10 mg/kg groups (33.9 and 36.9%) compared to the placebo group (15.7%; P=0.001 and P<0.001, respectively). In ACT 2 at week 30, the proportion of patients with clinical remission was significantly higher in the infliximab 5 and 10 mg/kg groups (25.6 and 35.8%) compared to the placebo group (10.6%; P=0.003 and P<0.001, respectively). In ACT 1 at week 54, the clinical remission rate was significantly higher in the infliximab 5 and 10 mg/kg groups compared to the placebo group (34.7 and 34.4 vs 16.5%; P=0.001 for both). In ACT 1 at week eight, the proportion of patients refractory to corticosteroids that had a clinical response was significantly higher in the infliximab 5 and 10 mg/kg groups compared to the placebo group (77.4 and 67.7 vs 35.3%; P<0.001 and P=0.010, respectively). In ACT 2 at week eight when compared to the placebo group (37.5%), the proportion of patients refractory to corticosteroids that had a clinical response was significantly higher in the infliximab 10 mg/kg (65.5%; P=0.011), but not 5 mg/kg group (63.3%; P=0.053). In ACT 1, the proportion of patients with mucosal healing at week eight was significantly higher in the infliximab 5 and 10 mg/kg groups (62.0 and 59.0%) compared to the placebo group (33.9%; P<0.001 for both). In ACT 2 at week eight, the proportion of patients with mucosal healing was significantly higher in the infliximab 5 and 10 mg/kg groups (60.3 and 61.7%) compared to the placebo group (30.9%; P<0.001 for both). In ACT 1, the proportion of patients with mucosal healing at week 30 was significantly higher in the infliximab 5 and 10 mg/kg groups (50.4 and 49.2%) compared to the placebo group (24.8; P<0.001 for both). In ACT 2 at week 30, the proportion of patients with mucosal healing was significantly higher in the infliximab 5 and 10 mg/kg groups (46.3 and 56.7%) compared to the placebo group (30.1%; P=0.009 and P<0.001, respectively). In ACT 1 at week 54, the mucosal healing rate was significantly higher in the infliximab 5 and 10 mg/kg groups compared to the placebo group (45.5 and 46.7 vs 18.2%; P=0.001 for both).

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Hyams et al.[216] (2011) (abstract) Infliximab 5 mg/kg at weeks 0, 2 and 6 then 5 mg/kg every 8 weeks through week 46 vs infliximab 5 mg/kg at weeks 0, 2 and 6 then 5 mg/kg every 12 weeks through week 42	MC, OL, R Patients 6 to 17 years of age with active ulcerative colitis (Mayo score 6 to 12, including endoscopic subscore ≥2) who failed to respond to or tolerate treatment with mercaptopurine, azathioprine, corticosteroids, and/or 5-aminosalicylates	N=60 54 weeks	Primary: Clinical response at week eight (decrease from baseline in Mayo score ≥30% and ≥3 points, with a decrease in rectal bleeding subscore of 0/1) compared to baseline Secondary: Not reported	Primary: At week eight, 73.3% of patients had a clinical response with infliximab (95% CI, 62.1 to 84.5). Clinical remission by Mayo score was achieved in 33.3% of patients. At week 54, there was a greater proportion of patients achieving clinical remission with infliximab 5 mg/kg every eight weeks compared to infliximab 5 mg/kg every 12 weeks; though, this difference was not significant (P=0.146). Secondary: Not reported
Reinisch et al.[217] (2011) Adalimumab 160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6 (ADA 160/80 group) vs Adalimumab 80 mg at week 0, 40 mg at weeks 2, 4 and 6 (ADA 80/40 group) vs placebo	DB, MC, PC, RCT Adult patients with moderate to severe active ulcerative colitis, (Mayo score of 6 to 12 with an endoscopy subscore of 2–3) who failed concurrent and stable treatment with oral corticosteroids and/or immunomodulators	N=390 8 weeks	Primary: Proportion of patients in remission (Mayo score ≤2 and no subscore >1) compared to baseline Secondary: Proportion of patients with a clinical response (decrease in Mayo Score ≥3 points and ≥30% from baseline plus decrease in rectal bleeding subscore ≥1 or an absolute	Primary: At week eight, 18.5% of patients in the ADA 160/80 group (P=0.031 vs placebo) and 10.0% in the ADA 80/40 group (P=0.833 vs placebo) were in remission compared to placebo (9.2%). Secondary: At week eight, 54.6% of patients in the ADA 160/80 group (P vs placebo not reported), 51.5% in the ADA 80/40 group (P vs placebo not reported) and 44.6% in the placebo group had a clinical response. At week eight, 46.9% of patients in the ADA 160/80 group (P vs placebo not reported), 37.7% in the ADA 80/40 group (P vs placebo not reported) and 41.5% in the placebo group had mucosal healing. At week eight, 77.7% of patients in the ADA 160/80 group (P=0.038 vs placebo), 70.0% in the ADA 80/40 group (P vs placebo not reported) and 66.2% in the placebo group had a rectal bleeding subscore of ≤ 1. At week eight, 60.0% of patients in the ADA 160/80 group (P=0.035 vs placebo), 53.8% in the ADA 80/40 group (P vs placebo not reported) and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			rectal bleeding subscore of 0 or 1); proportion of patients with mucosal healing (endoscopy subscore of 0 or 1); proportion of patients with rectal bleeding subscore ≤1, PGA subscore ≤1, or stool frequency subscore ≤1	46.9% in the placebo group had a PGA subscore of ≤ 1 At week eight, 48.5% of patients in the ADA 160/80 group (P vs placebo not reported), 36.2% in the ADA 80/40 group (P vs placebo not reported) and 37.7% in the placebo group had a stool frequency subscore of ≤ 1
Sandborn et al.[218] (2012) Adalimumab 160 mg at week 0, 80 mg at week 2, then 40 mg every other week vs placebo	DB, MC, PC, RCT Adult patients with moderate to severe active ulcerative colitis >3 months, (Mayo score of 6 to 12 with an endoscopy subscore >2) despite concurrent treatment with oral corticosteroids and/or azathioprine or 6-mercaptopurine.	N=494 52 weeks	Primary: Proportion of patients in remission (Mayo score ≤2 and no subscore >1) at week 8 and 52 Secondary: Proportion of patients in remission at week 8 and 52; proportion of patients with a clinical response (decrease in Mayo Score ≥3 points and ≥30% from baseline plus decrease in rectal bleeding subscore ≥1 or an absolute	Primary: At week 8, 16.5% of patients in the adalimumab group were in remission compared to placebo (9.3%; P=0.019; 95% CI, 1.2 to 12.9). At week 52, 17.3% of patients in the adalimumab group were in remission compared to placebo (8.5%; P=0.004; 95% CI, 2.8 to 14.5). Secondary: At week 8 and 52, 8.5% of patients in the adalimumab group (P=0.47 vs placebo) and 4.1% in the placebo group were in sustained remission. At week 8, 50.4% of patients in the adalimumab group (P<0.001 vs placebo) and 34.6% in the placebo group had a clinical response. At week 52, 30.2% of patients in the adalimumab group and 18.3% in the placebo group had a clinical response. (P=0.002). At week 8 and 52, 23.8% of patients in the adalimumab group (P<0.001 vs placebo) and 12.2% in the placebo group were in sustained remission. Mucosal healing was achieved at week 8 in 41.1% of patients in the adalimumab group and 31.7% of patients receiving placebo (P=0.032). At week 52, 25% of patients in the adalimumab group and 15.4% of patients receiving placebo (P=0.009) had mucosal healing. Mucosal healing at week 8 and 52, 18.5% of patients in the adalimumab group (P<0.013 vs

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			rectal bleeding subscore of 0 or 1); proportion of patients with mucosal healing (endoscopy subscore of 0 or 1); proportion of patients who discontinued corticosteroid; proportion of patients with rectal bleeding subscore ≤1, PGA subscore ≤1, or stool frequency subscore ≤1	placebo) and 10.6% in the placebo group. At week 8, 46.0% of patients in the adalimumab group (P=0.028 vs placebo) and 37.4% in the placebo group had a PGA subscore of ≤ 1. At week 8, 37.9% of patients in the adalimumab group (P=0.058 vs placebo) and 28.5% in the placebo group had a stool frequency subscore of ≤ 1. At week 8, 70.2% of patients in the adalimumab group (P=0.006 vs placebo) and 58.1% in the placebo group had a rectal bleeding subscore of ≤ 1. Proportion of patients that discontinued corticosteroid use before week 52 and achieved remission at week 52 was13.3% of patients in the adalimumab group (P=0.35 vs placebo) and 5.7% in the placebo group. Proportion of patients that for ≥90 days before week 52 and achieved remission at week 52 was 13.3% of patients in the adalimumab group (P=0.35 vs placebo) and 5.7% in the placebo group.
Croft et al.[219] (2021) ENVISION I High-dose induction adalimumab (2.4 mg/kg [maximum 160 mg] at weeks 0 and 1) vs standard-dose induction adalimumab (2.4 mg/kg at week 0 and placebo at week 1);	DB, MC, RCT Children (4 to 17 years of age) with moderate-to-severe ulcerative colitis despite stable doses of concurrent treatment with oral corticosteroids or immunosuppressants Patients with partial Mayo score (PMS) response at week 8 (defined as a decrease of two or	N=93 (77 were randomly assigned [double-blind] to receive high-dose or standard-dose induction adalimumab; 16 received open-label high-dose induction adalimumab	Primary: Proportion of patients with partial Mayo (PMS) score remission at week 8 (intent-to-treat [ITT]-E population, not including those patients who were not randomized in the induction phase) and full Mayo score (FMS) remission at week 52 in week 8 PMS responders (mITT-E population)	Primary: In patients in the ITT-E population who were randomly assigned to receive high-dose induction adalimumab, a higher proportion of patients were in PMS remission at week eight (28 [60%] of 47) compared with external placebo (19.8%; P=0.0001). Thirteen (43%) of 30 patients in the standard-dose induction adalimumab group were in PMS remission at week eight versus an external placebo rate of 19.8%, but this difference was not significant (P=0.38). FMS remission at week 52 in children who were week eight PMS responders was reported in a higher proportion of patients in mITT-E population who received high-dose maintenance adalimumab (14 [45%] of 31 patients) versus external placebo at week 52 (18.4%; P=0.0001). Nine (29%) of 31 patients in the standard-dose maintenance adalimumab group were in FMS remission at week 52 versus an external placebo rate of 18.4%, but this difference was not significant (P=0.38). Remission rates in the pooled adalimumab groups were significantly better compared with external placebo (PMS remission at week eight: 41 [53%] of 77 patients; P<0.0001; FMS remission at week

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
both groups received 1.2 mg/kg (maximum 80 mg) at week 2 and 0.6 mg/kg (maximum 40 mg) at weeks 4 and 6	more points and a decrease of ≥30% from baseline in PMS) were randomly assigned (2:2:1) to receive either high-dose maintenance adalimumab (0.6 mg/kg weekly), standard-dose maintenance adalimumab (0.6 mg/kg every other week), or placebo up to week 52 (random assignment to the placebo group was ceased mid-trial, as was randomization in the induction phase with all subsequent patients receiving open-label high-dose induction adalimumab)	after study design change. At week 8, 74 children who were PMS responders continued to the maintenance period)	Secondary: Safety	52: 23 [37%] of 62 patients; P=0.0001). Secondary: Twenty-one (23%) of 93 patients in the main study had one or more treatment-emergent serious adverse events during any adalimumab exposure. The most common adverse events were headache, anaemia, and ulcerative colitis flare during the induction period and ulcerative colitis flare, headache, and nasopharyngitis during the maintenance period.
Sandborn et al.[220] (2013) PURSUIT-SC Phase 2 (dose-finding): Golimumab 400 mg subcutaneously at week 0 and 200 mg subcutaneously at week 2 (400 mg/200	2 DB, MC, PC, RCT Patients ≥18 years of age with moderate to severe active ulcerative colitis (Mayo score of 6 to 12 with an endoscopy subscore ≥2) despite treatment with ≥1	Phase 2 N=169 Phase 3 N=774 6 weeks	Primary: Phase 2: Change in Mayo score from baseline to week six Phase 3: Clinical response at week six defined as a decrease from baseline in	Primary: In phase 2, median changes from baseline in the Mayo score were -3.0, -2.0, and -3.0 in the 100 mg/50 mg, 200 mg/100 mg, and 400 mg/200 mg golimumab treatment groups, respectively, compared to -0.1 in the placebo group (P=0.038, P=0.332 and P=0.038, respectively). In phase 3, the proportion of patients with clinical response at week six was greater for patients treated with golimumab 200 mg/100 mg and 400 mg/200 mg compared to placebo (51.0 and 54.9 vs 30.3%; P≤0.0001 for both comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg) vs golimumab 200 mg subcutaneously at week 0 and 100 mg subcutaneously at week 2 (200 mg/100 mg) vs golimumab 100 mg subcutaneously at week 0 and 50 mg subcutaneously at week 2 (100 mg/50 mg) vs placebo Phase 3 (dose-confirming): Golimumab 400 mg subcutaneously at week 0 and 200 mg subcutaneously at week 2 (400 mg/200 mg) vs golimumab 200 mg	conventional therapy (oral mesalamine, oral corticosteroids, azathioprine or 6-mercaptopurine) or corticosteroid dependent		the Mayo score ≥30% and ≥3 points with either a rectal bleeding subscore of 0 to 1 or a decrease from baseline in the rectal bleeding subscore ≥1 Secondary: Phase 2: Not reported Phase 3: Clinical remission defined as Mayo score ≤2 points, with no individual subscore >1, mucosal healing defined as a Mayo endoscopy subscore of 0 or 1, and IBDQ change from baseline, all at week 6	Secondary: In phase 3, the proportion of patients in clinical remission at week six was greater for patients treated with golimumab 200 mg/100 mg and 400 mg/200 mg compared to placebo (17.8 and 17.9 vs 6.4%; P≤0.0001 for both comparisons). In phase 3, the proportion of patients achieving mucosal healing at week six was greater for patients treated with golimumab 200 mg/100 mg and 400 mg/200 mg compared to placebo (42.3 and 45.1 vs 28.7%; P=0.0014 and P≤0.0001, respectively). In phase 3, the improvements from baseline in IBDQ score at week six were greater in patients treated with golimumab 200 mg/100 mg and 400 mg/200 mg compared to placebo (mean 27.0±33.72 and 26.9±34.28 vs 14.8±31.25%; P<0.0001 for both comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
subcutaneously at week 0 and 100 mg subcutaneously at week 2 (200 mg/100 mg) vs placebo Patients were required to maintain stable doses of concurrent oral aminosalicylates, oral corticosteroids (<40 mg/day), azathioprine, 6-mercaptopurine, and/or MTX.				
Sandborn et al.[221] (2013) PURSUIT-M Golimumab 50 mg SC every four weeks vs golimumab 100 mg SC every four weeks vs placebo Patients were	DB, MC, PC, RCT Patients ≥18 years of age with moderate to severe active ulcerative colitis (Mayo score of 6 to 12 with an endoscopy subscore ≥2) despite treatment with ≥1 conventional therapy (oral mesalamine, oral corticosteroids, azathioprine or 6-mercaptopurine) or	N=464 54 weeks	Primary: Clinical response through week 54 among golimumab-induction responders Secondary: Clinical remission at weeks 30 and 54, mucosal healing at weeks 30 and 54, clinical remission at both weeks 30 and 54 among patients who had	Primary: The proportion of patients who maintained a clinical response through week 54 was greater for patients treated with golimumab 100 mg and 50 mg compared to placebo (49.7 and 47.0 vs 31.2%; P<0.001 and P=0.010, respectively). Secondary: The proportion of patients in clinical remission at both weeks 30 and 54 was greater for patients treated with golimumab 100 mg and 50 mg compared to placebo (27.8 and 23.2 vs 15.6%; P=0.004 and P=0.091, respectively); however, the difference was only statistically significant for golimumab 100 mg treatment group. The proportion of patients with mucosal healing at both weeks 30 and 54 was significantly greater for patients receiving golimumab 100 mg compared to placebo (42.4 vs 26.6%; P=0.002). The mucosal healing rate for patients receiving golimumab 50 mg was 41.7% (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
required to maintain stable doses of concurrent oral aminosalicylates, oral corticosteroids (<40 mg/day), azathioprine, 6-mercaptopurine, and/or MTX. After induction, patients in clinical response and receiving concomitant corticosteroids at baseline were required to taper corticosteroids (for dose of >20 mg/day prednisone or equivalent: taper daily dose by 5 mg/week; for dose of ≤20 mg/day prednisone or equivalent: taper daily dose by 2.5 mg/week) beginning at baseline.	corticosteroid dependent who completed PURSUIT-IV or PURSUIT-SC studies		clinical remission at baseline, and corticosteroid-free clinical remission at week 54 among patients receiving concomitant corticosteroids at baseline	Greater proportions of patients who received golimumab 100 mg or 50 mg maintained clinical remission compared to placebo (40.4 and 36.5 vs 24.1%; P=0.073 and P=0.365, respectively); however, the differences were not statistically significant. Greater proportions of patients who received golimumab 100 mg or 50 mg were in corticosteroid-free clinical remission at week 54 compared to placebo (22.9 and 27.8 vs 18.4%; P=0.464 and P=0.299, respectively) ; however, the differences were not statistically significant.
Danese et al.[222] (2022) Two replicate induction studies (U-ACHIEVE induction [UC1] and U-ACCOMPLISH	DB, MC, PC, RCT Patients 16 to 75 years of age with moderately to severely active ulcerative colitis for	N=474 (UC1) N=522 (UC2) N=451 (UC3; clinical responders	Primary: Clinical remission per Adapted Mayo score at week 8 (induction) and week 52 (maintenance)	Primary: More patients achieved clinical remission with upadacitinib 45 mg (83 [26%] of 319 patients in UC1 and 114 [34%] of 341 patients in UC2) than in the placebo group (seven [5%] of 154 patients in UC1 and seven [4%] of 174 patients; P<0.0001; adjusted treatment difference, 21.6%; 95% CI, 15.8 to 27.4 for UC1 and 29.0%; 95% CI, 23.2 to 34.7 for UC2). In the maintenance study, clinical remission was achieved by more patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
[UC2]) and a single maintenance study (U-ACHIEVE maintenance [UC3]) Upadacitinib 45 mg orally once daily vs placebo for 8 weeks (induction studies) Patients who achieved clinical response following 8-week upadacitinib induction were re-randomly assigned (1:1:1) to upadacitinib 15 mg, upadacitinib 30 mg, or placebo for 52 weeks (maintenance study)	at least 90 days	after 8 weeks induction)	Secondary: Additional clinical outcomes	receiving upadacitinib (15 mg 63 [42%] of 148; 30 mg 80 [52%] of 154) than those receiving placebo (18 [12%] of 149; P<0.0001; adjusted treatment difference, 30.7%; 95% CI, 21.7 to 39.8 for upadacitinib 15 mg vs placebo and 39.0%; 95% CI, 29.7 to 48.2 for upadacitinib 30 mg vs placebo). Secondary: All secondary endpoints in both induction studies were achieved in the upadacitinib 45 mg once daily group compared with the placebo group. At week eight, disease activity and symptoms were statistically significantly improved as shown by achievement of clinical response, no abdominal pain, and no bowel urgency. Endoscopic, histological, and QOL (IBDQ and FACIT-F) improvements were also achieved. The proportion of patients achieving clinical response at week two with upadacitinib was statistically significantly greater than with placebo in both UC1 and UC2 (192 [60%] of 319 vs 42 [27%] of 154 and 216 [63%] of 341 vs 45 [26%] of 174, respectively; both P<0.0001). All secondary endpoints in the maintenance study were achieved in the upadacitinib 15 mg once daily and 30 mg once daily groups compared with the placebo group. A sustained treatment effect was demonstrated in both upadacitinib 15 mg and 30 mg once daily groups versus placebo, with more patients achieving the endpoints of maintenance of clinical remission, clinical response, and endoscopic improvement. Corticosteroid-free clinical remission was achieved by 27 (57%) of 47 patients in the upadacitinib 15 mg group and 39 (68%) of 58 patients in the upadacitinib 30 mg group versus 12 (22%) of 54 patients receiving placebo (all P<0.0001). Statistically significantly more patients achieved histological-endoscopic mucosal improvement, and improvement in symptoms (no abdominal pain or no bowel urgency) and QOL (IBDQ and FACIT-F) with upadacitinib 15 mg or 30 mg versus placebo (all p<0·0001).
Uveitis				
Jaffe et al.[223] (2016) VISUAL I Adalimumab 80 mg	MC, RCT Patients ≥18 years of age and had a diagnosis of active	N=217 80 weeks	Primary: Time to treatment failure at or after week six (treatment failure was a	Primary: The median time to treatment failure was 24 weeks in the adalimumab group and 13 weeks in the placebo group. Patients who received adalimumab were significantly less likely than those who received placebo to have treatment failure (HR, 0.50; 95% CI, 0.36 to 0.70; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SC loading dose followed by 40 mg every two weeks vs placebo All patients received a standardized, 60-mg-per-day prednisone burst at trial entry (week 0), after which a mandatory tapering schedule was followed	noninfectious intermediate uveitis, posterior uveitis, or panuveitis		multicomponent outcome that was based on assessment of new inflammatory lesions, best corrected visual acuity, anterior chamber cell grade, and vitreous haze grade) Secondary: Nine ranked secondary efficacy end points related to disease state were tested for significance	Secondary: Hierarchical testing of the ranked secondary outcomes showed that worsening of anterior chamber cell grade, worsening of vitreous haze grade, and worsening of best corrected visual acuity were significantly less common among patients who received adalimumab than among those who received placebo (P≤0.01 for all three end points). The difference between the groups in the time to optical coherence tomographic evidence of macular edema was not significant; therefore, no further confirmatory statistical testing of secondary end points was performed.
Nguyen et al.[224] (2016) VISUAL II Adalimumab 80 mg SC loading dose followed by 40 mg every 2 weeks vs placebo All patients received a standardized, 60-mg-per-day prednisone burst at trial entry (week 0),	Double-masked, MC, RCT Patients ≥18 years of age with inactive, non-infectious intermediate, posterior, or panuveitic uveitis controlled by 10 to 35 mg/day of prednisone	N=229 80 weeks	Primary: Time to treatment failure, a multicomponent endpoint encompassing new active inflammatory chorioretinal or inflammatory retinal vascular lesions, anterior chamber cell grade, vitreous haze grade, and visual acuity Secondary:	Primary: Treatment failure occurred in 61 (55%) of 111 patients in the placebo group compared with 45 (39%) of 115 patients in the adalimumab group. Time to treatment failure was improved in the adalimumab group compared with the placebo group (43% risk reduction; median not estimated [>18 months; more than half the adalimumab-treated patients did not have treatment failure] vs 8.3 months; HR, 0.57; 95% CI 0.39 to 0.84; P=0.004). Secondary: Hierarchical testing of the nine ranked secondary variables was stopped after the first ranked endpoint because no statistically significant difference was shown between groups. The most common adverse events were arthralgia (11% patients in the placebo group and 23% patients in the adalimumab group), nasopharyngitis (17% and 16% patients, respectively), and headache (15% patients in each group).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
after which a mandatory tapering schedule was followed			Nine ranked secondary efficacy end points related to disease state were tested for significance	
Suhler et al.[225] (2018) VISUAL III Adalimumab 40 mg every other week	MC, OL, ongoing ES Patients ≥18 years of age, diagnosed with noninfectious intermediate, posterior, or panuveitis and had either discontinued from VISUAL I or VISUAL II trials for having met predefined treatment failure criteria or successfully completed the parent study without treatment failure	N=371 78 weeks	Primary: Disease quiescence, steroid-free quiescence, active inflammatory chorioretinal/retinal vascular lesions, anterior chamber cell grade, vitreous haze grade, best-corrected visual acuity and corticosteroid dose Secondary: Safety	Primary: At study entry, 242/371 (65%) patients had active uveitis; 60% (145/242, nonresponder imputation) achieved quiescence at week 78, and 66% (95/143, as-observed) of those were corticosteroid free. At study entry, 129/371 (35%) patients had inactive uveitis; 74% (96/129, nonresponder imputation) achieved quiescence at week 78, and 93% (89/96, as-observed) of those were corticosteroid free. Inflammatory lesions, anterior chamber grade, and vitreous haze grade showed initial improvement followed by decline in patients with active uveitis and remained stable in patients with inactive uveitis. Best-corrected visual acuity improved in patients with active uveitis from weeks 0 to 78 and remained stable in patients with inactive uveitis. Mean corticosteroid dose decreased from 13.6 mg/day (week 0) to 2.6 mg/day (week 78) in patients with active uveitis and remained stable in those with inactive uveitis (1.5 to 1.2 mg/day). Secondary: The overall exposure-adjusted rate of any adverse event was 424 events/100 patient years. There were 82 adverse events leading to study discontinuation (8.6 events/100 patient years) and 157 serious adverse events (16.5 events/100 patient years).
Ramanan et al.[226] (2019) Adalimumab (20 mg/0.8 mL for patients weighing < 30 kg or 40 mg/0.8 ml for patients weighing ≥ 30 kg) SC every	DB, MC, PC, PG RCT Patients 2 to 18 years of age with persistently active JIA-associated uveitis despite optimized MTX treatment for at least	N=90 18 months	Primary: Number of patients failing treatment Secondary: Safety and tolerability	Primary: There were 14 (23%) treatment failures in the adalimumab group and 17 (57%) in the placebo group. The HR of treatment failure was significantly reduced, by 75%, for participants in the adalimumab group (HR, 0.25; 95% CI, 0.12 to 0.51; P<0.0001). Secondary: Adalimumab-treated patients had a much higher incidence of adverse events and serious adverse events. However, this difference was not deemed to be clinically significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
two weeks vs placebo Both given in combination with a stable dose of MTX	12 weeks			
Neonatal-Onset Multisystem Inflammatory Disease				
Sibley et al.[227] (2012) Anakinra 1 to 5 mg/kg/day	OL Patients with NOMID with at least 2 of the following clinical manifestations: urticaria-like rash, CNS involvement (papilledema, cerebrospinal fluid CSF pleocytosis, or sensorineural hearing loss), or epiphyseal and/or patellar overgrowth on radiographs	N=43 60 months	Primary: Sustained improvements in diary scores, parent's/patient's and physician's global scores of disease activity, CHAQ scores, parent's/patient's pain scores, and inflammatory markers (CRP level, ESR, and SAA) Secondary: Reduction or elimination CNS organ inflammation and damage and the absence of leptomeningeal enhancement on MRI, and in the eyes as the absence of eye	Primary: Scores for daily diaries, parent's and physician's global assessment of disease activity, parent's assessment of pain, and C-HAQ decreased significantly from baseline to 36 months (P=0.0016 for C-HAQ and P<0.001 for all other assessments). These parameters did not show significant change from month 36 to month 60. Significant decreases in inflammatory markers (CRP level, ESR, and SAA) were observed from baseline to 12 months and from baseline to 36 months (all P<0.001). These parameters did not show significant change from month 36 to month 60. Secondary: CNS inflammation, including CSF leukocyte count and elevated opening pressure, decreased significantly at the study end points 36 and 60 months compared to baseline (P=0.0026 and P=0.0076, respectively, for CSF WBC count and P=0.0012 and P<0.001, respectively, for opening pressure). These parameters did not show significant change from month 36 to month 60. The number of patients with leptomeningeal enhancement decreased to three of 26 patients at 36 months (P=0.039) and one of 20 patients at 60 months (P=0.016). Improvement in hearing occurred in 30% of ears, and progression of hearing loss was halted in the majority of the patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			inflammation on examination. Other endpoints include improvements in hearing, vision, bone lesions and growth, and safety.	Visual acuity and peripheral vision improved or stabilized in most patients over five years. One patient had worsening of visual acuity, and two other patients had worsening of peripheral vision in the absence of clinically detectable intraocular inflammation. (Note-All three of these patients had severely atrophic nerves at baseline). Bony overgrowth was present in 10 of 26 patients, and during the study period the volume of the bony lesions increased significantly; however, no new bone lesions developed in patients while they were receiving anakinra therapy. No dose-limiting toxicity was observed during the study. Upper respiratory infections (58 to 62%), rash (27 to 32%), malaise (17 to 19%) gastroenteritis (11 to 12%), and urinary tract infections (4 to 12%), nausea/vomiting (10 to 11%) injection site reactions (1 to 10%) were frequently observed.
Oral Ulcers Associated with Behcet's Disease				
Hatemi et al.[228] (2019) RELIEF Apremilast 30 mg BID vs placebo	DB, MC, PC, RCT Patients ≥18 years of age, had received a diagnosis of Behçet's syndrome and had active oral ulcers that had occurred at least three times in the previous 12-month period despite the previous use of at least one nonbiologic medication	N=207 12 weeks	Primary: AUC for the total number of oral ulcers during 12 weeks Secondary: Complete response of oral ulcers, change from baseline in pain associated with oral ulcers and change from baseline in the Behçet's Disease Quality of Life score	Primary: The AUC for the number of oral ulcers was 129.5 for apremilast, as compared with 222.1 for placebo (least-squares mean difference, -92.6; 95% CI, -130.6 to -54.6; P<0.001). Secondary: The percentage of patients who were free from oral ulcers by week 6 and who remained ulcer-free at each visit for at least 6 more weeks was 30% in the apremilast group (31/104 patients) and 5% in the placebo group (5/103 patients) (difference, 25 percentage points; 95% CI, 16 to 35). The median time to oral ulcer resolution was 2.1 weeks in the apremilast group and 8.1 weeks in the placebo group (HR for complete resolution of oral ulcers, 2.4; 95% CI, 1.7 to 3.4). The percentage of patients who were free from oral ulcers at week 12 was 53% in the apremilast group (55 patients) and 22% in the placebo group (23 patients) (adjusted difference, 31 percentage points; 95% CI, 18 to 43). At week 12, the mean reduction from baseline in the pain associated with oral ulcers as assessed on a 100-mm VAS was -42.7 in the apremilast group, as compared with -18.7 in the placebo group (least-squares mean

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				difference, -24.1; 95% CI, -32.4 to -15.7). The change from baseline in the Behçet's Disease Quality of Life score was -4.3 points in the apremilast group, as compared with -1.2 points in the placebo group (least-squares mean difference, -3.1 points; 95% CI, -4.9 to -1.3).

*Not currently available in the United States.
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double dummy, ES=extension study, HR=hazard ratio, IR=incidence rate, MA=meta-analysis, MC=multicenter, NNH=number needed to harm, NNT=number needed to treat, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel group, PRO=prospective, R=randomized, RCT=randomized controlled trial, RD=risk difference, RR=relative risk, SD=standard deviation, SR=systematic review, WMD=weighted mean difference
Miscellaneous abbreviations: ACR=American College of Rheumatology, ACR-N=numeric index of the ACR response, ACR pedi 30=American College of Rheumatology pediatric 30% improvement criteria, ALT=alanine transaminase, AS=ankylosing spondylitis, ASDAS=ankylosing spondylitis disease activity score, ASAS=Assessment of Spondyloarthritis International Society criteria, AST=aspartate aminotransferase, AUC=area under the curve, BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, BASFI=Bath Ankylosing Spondylitis Functional Index, BASMI=Bath Ankylosing Spondylitis Metrology Index, BSA=body surface area, CCP=cyclic citrullinated protein CD=Crohn's disease, CDAI=Crohn's disease activity index, CDAI-100=Crohn's disease activity index decrease of ≥100 points from baseline, CHAQ=Childhood Health Assessment Questionnaire, CNS=central nervous system, COX=cyclooxygenase, CR-70=clinical remission, CR-100=clinical remission 100, CRP=C-reactive protein, CSF=cerebrospinal fluid, CT=computed tomography, DAS 28=Disease Activity Score in 28 joints, DLQI=Dermatology Life Quality Index, DMARD=disease-modifying antirheumatic drug, DOI=definition of improvement, ECL=electrogenerated chemiluminescence, EIM=extra-intestinal manifestations, ELISA=enzyme-linked immunosorbent assay, ESR=erythrocyte sedimentation rate, EULAR=European League Against Rheumatism Response criteria, FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue, HAQ=health assessment questionnaire, HAQ-DI=health assessment questionnaire–disability index, HBI=Harvey-Bradshaw index, HCQ=hydroxychloroquine, HDL=high density lipoprotein, IBDQ=inflammatory bowel disease questionnaire, IOIBD=international organization for the study of inflammatory bowel disease, ITT=intent to treat, JIA=juvenile idiopathic arthritis, JRA=juvenile rheumatoid arthritis, JSN=joint space narrowing, LDL=low density lipoprotein, MCR=major clinical response, MRE=magnetic resonance enterography, MRI=magnetic resonance imaging, mTSS=modified Total Sharp Scores, MTX=methotrexate, NOMID=neonatal-onset multisystem inflammatory disease, nr-axSpA= non-radiographic-axial spondyloarthritis, NSAIDs=nonsteroidal anti-inflammatory drugs, PASI=psoriasis area and severity index, PCDAI=pediatric Crohn's disease activity index, PGA=physician global assessment, PsA=psoriatic arthritis, PsARC=psoriatic arthritis response criteria, PSSI=psoriasis scalp severity index, SIAQ=Self-Injection Assessment Questionnaire, RA=rheumatic arthritis, RF=rheumatoid factor, SF-36=short form-36, SF-36 MCS=short form-36-mental component, SF-36 PCS=short form-36-physical component, SAA=serum amyloid A, SHS=Sharp van der Heijde Score, SMD=standardized mean differences, SSZ=sulfasalazine, TB=tuberculosis, TNF=tumor necrosis factor, VAS=visual analog scale

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 18. Relative Cost of the Disease-Modifying Antirheumatic Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Abatacept	injection	Orencia®	$$$$$	N/A
Abrocitinib	tablet	Cibinqo®	$$$$$	N/A
Adalimumab	injection	Humira®	$$$$$	N/A
Anakinra	injection	Kineret®	$$$$$	N/A
Apremilast	tablet	Otezla®	$$$$$	N/A
Baricitinib	tablet	Olumiant®	$$$$$	N/A
Certolizumab pegol	injection	Cimzia®	$$$$$	N/A
Etanercept	injection	Enbrel®	$$$$$	N/A
Golimumab	injection	Simponi®, Simponi Aria®	$$$$$	N/A
Infliximab	injection	Avsola®^, Inflectra®^, Remicade®*, Renflexis®^	$$$$$	N/A
Leflunomide	tablet	Arava®*	$$$$$	$$
Sarilumab	injection	Kevzara®	$$$$$	N/A
Secukinumab	injection	Cosentyx®	$$$$$	N/A
Sulfasalazine	delayed-release tablet, tablet	Azulfidine®*	$$$$$	$$
Tocilizumab	injection	Actemra®	$$$$$	N/A
Tofacitinib	extended-release tablet, tablet, oral solution	Xeljanz®, Xeljanz XR®	$$$$$	N/A
Upadacitinib	extended-release	Rinvoq®	$$$$$	N/A

	tablet			
Voclosporin	capsule	Lupkynis®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available
^Biosimilar product.

X. Conclusions

The disease-modifying antirheumatic drugs (DMARDs) are used for a variety of inflammatory and immunologic conditions.[1-24] Leflunomide is the only product available in a generic formulation. Adalimumab, etanercept, and infliximab are available in biosimilar formulations. Remicade® is also available as an unbranded product.

Current clinical guidelines support the use of the DMARDs with respect to their FDA-approved indications, particularly in conditions where patients were unresponsive or refractory to traditional treatments, which usually include nonsteroidal anti-inflammatory drugs (NSAIDs) and/or methotrexate depending on the disease state.[27-52] As more recent guidelines are published, the recommendations for use tumor necrosis factor (TNF)-α inhibitors earlier in therapy is becoming a more common occurance.[38] The adverse event profiles are similar across the TNF-α inhibitors; however, routes of administration and dosing frequency may vary. In general, no one TNF-α inhibitor is preferred over another.[27-52] Leflunomide is FDA-approved for use in rheumatoid arthritis. Guidelines for rheumatoid arthritis, psoriatic arthritis, and juvenile idiopathic arthritis recommend leflunomide as an alternative treatment to methotrexate.[14,35-37,44] Clinical trials directly comparing methotrexate and leflunomide have shown mixed results.[164,166,168,169]

Abrocitinib (Cibinqo®), secukinumab (Cosentyx®), sulfasalazine (Azulfidine®), and voclosporin (Lupkynis®) have been added since the last review. Abrocitinib is a Janus kinase inhibitor indicated for the treatment of adults with refractory, moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable.[2] Abrocitinib 200 mg daily may have beneficial effects compared to dupilumab for improvement from baseline itch response at two weeks.[54,58] (Secukinumab is an interleukin-17A blocker and it is indicated for the treatment of moderate to severe plaque psoriasis in patients six years and older who are candidates for systemic therapy or phototherapy, active psoriatic arthritis in patients two years of age and older, adult patients with active ankylosing spondylitis, adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation, and active enthesitis-related arthritis in patients four years of age and older.[16] Sulfasalazine is a conventional synthetic DMARD approved for the treatment of juvenile arthritis, rheumatoid arthritis, and ulcerative colitis.[17,25] Voclosporin is a calcineurin-inhibitor immunosuppressant indicated in combination with a background immunosuppressive therapy regimen for the treatment of adult patients with active lupus nephritis.[21] Additionally, many agents have received approval for new indications since the last review, including abatacept for prophylaxis of acute graft versus host disease, anakinra for deficiency of interleukin-1 receptor antagonist, baricitinib for alopecia areata and COVID-19, tofacitinib for systemic sclerosis-associated interstitial lung disease, and upadacitinib for ankylosing spondylitis, atopic dermatitis, non-radiographic axial spondyloarthritis, psoriatic arthritis, and ulcerative colitis.[1-24]

Most research with these agents is for rheumatoid arthritis. In these trials, the DMARD was compared directly to placebo or methotrexate, either as monotherapy or in combination with methotrexate. Consistently, DMARDs have shown greater improvement in symptoms over the comparator.[142-206] To date, the majority of trials conducted have been placebo-controlled, with few trials directly comparing two DMARDs head-to-head for any of the FDA-approved indications.[53-228] In those that have been conducted, most have shown comparable results.[196-198] In one trial in rheumatoid arthritis patients who were either intolerant or were not candidates for methotrexate treatment, significantly greater improvements were observed in patients treated with tocilizumab compared to adalimumab.[196] In another trial in rheumatoid arthritis patients with inadequate response to methotrexate, similar responses were observed in patients treated with abatacept and adalimumab.[202,203] The inclusion of adalimumab arm in one phase 3 trial of tofacitinib allowed establishing relative safety and efficacy of tofacitinib; however, formal noninferiority comparison was not performed.[199] The MONARCH trial compared sarilumab and adalimumab in patients with active rheumatoid arthritis. At 24 weeks, patients treated with sarilumab achieved a greater improvement from baseline in DAS28-ESR at -3.28 for the sarilumab group and -2.20 for the adalimumab group (P<0.0001).[173] The EXXELERATE trial compared certolizumab and adalimumab in patients with active rheumatoid arthritis. The results of the primary analysis showed no significant difference in week 12 ACR20 response (69 and 71%; P=0.467) or week 104 DAS28-ESR low disease activity (35 and 33%; P=0.532) between

certolizumab pegol plus methotrexate and adalimumab plus methotrexate, respectively.[190] The SELECT-CHOICE trial compared oral upadacitinib to intravenous abatacept in adults with moderate-to-severe active rheumatoid arthritis. From baseline DAS28-CRP values of 5.70 in the upadacitinib group and 5.88 in the abatacept group, the mean change at week 12 was -2.52 and -2.00, respectively (difference, -0.52 points; 95% CI, -0.69 to -0.35; P<0.001 for noninferiority; P<0.001 for superiority).[209] The few direct head-to-head trials available prevent clearly determining superiority of one agent over another. In the EXCEED trial, the primary endpoint of superiority of secukinumab versus adalimumab for ACR20 response in patients with psoriatic arthritis at week 52 was not met.[119]

There is insufficient evidence to support that one brand disease-modifying antirheumatic agent is safer or more efficacious than another within its FDA-approved indication(s). The drugs in this AHFS class are used in a specific patient population. Because these agents have narrow indications with limited usage and serious adverse events, these agents should be managed through the medical justification portion of the prior authorization process.

Therefore, all disease-modifying antirheumatic agents within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand disease-modifying antirheumatic agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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