Alabama Medicaid DUR Board Meeting Minutes
July 24, 2019

Members Present: Kelli Littlejohn Newman, Rachel Seaman, Bernie Olin, Melinda Rowe, Mary Stallworth, Jessica Jackson, Paula Thompson, Dan McConaghy, Crystal Deas, Kelly Tate, Clinton Martin, Denyse Thornley-Brown

Also Present: Tiffany Minnifield, Lori Thomas, Clemice Hurst, Alex Jenkins, Heather Vega, Julie Jordan

Present via Conference Call: Kristian Testerman, Joshua Lee, Angela Lowe, Tammy Dubuc

Members Absent: Kenny Murray

Call to Order: The DUR meeting was called to order by D. Thornley-Brown at approximately 1:03p.m.

Review and Adoption of Minutes: The minutes of the April 24, 2019 meeting were presented and P. Thompson made a motion to approve the minutes. R. Seaman seconded the motion and the motion was approved unanimously.

Prior Authorization and Overrides Update: L. Thomas began the Prior Authorization and Overrides Update with the Monthly Manual Prior Authorizations and Overrides Report for the month of January 2019. She reported 12,618 total manual requests and 19,396 total electronic requests. From the Prior Authorization and Override Response Time Ratio report for January 2019, L. Thomas reported that approximately 79% of all manual PAs and 73% of all overrides were completed in less than two hours. Ninety-four percent of all manual PAs and 93% of all overrides were completed in less than four hours. Ninety-six percent of all manual PAs and 95% of all overrides were completed in less than eight hours. For the month of February 2019, L. Thomas reported 11,656 manual PA requests and 17,506 electronic PA requests were received. She reported that 76% of all manual PAs and overrides were completed in less than two hours. Ninety-four percent of all manual PAs and 92% of all overrides were completed in less than four hours. Ninety-six percent of all manual PAs and 95% of all overrides were completed in less than eight hours. For the month of March 2019, L. Thomas reported 11,710 manual PA requests and 18,424 electronic PA requests. L. Thomas reported that approximately 72% of all manual PAs and 65% of all overrides were completed in less than two hours. Ninety-two percent of all manual PA requests and 91% of all overrides were completed in less than four hours. Ninety-five percent of all manual PA requests and overrides were completed in less than eight hours.

Program Summary Review: L.Thomas briefly reviewed the Alabama Medicaid Program Summary for the months of October 2018 through March 2019. She reported 3,711,073 total prescriptions, 226,996 average recipients per month using pharmacy benefits, and an average paid per prescription of $113.71.

Cost Management Analysis: L.Thomas reported an average cost per claim of $114.17 for December 2018 and emphasized that the table contained the average cost per claim over the past two years. From the 1st Quarter 2019 Drug Analysis, L.Thomas reported 81% generic utilization, 8% brand single-source, 7% brand multi-source (those requests which required a DAW override), and 4% OTC and "other". From the Top 25 Drugs Based on Number of Claims from 01/01/2019 – 03/31/2019, L.Thomas reported the top five drugs: amoxicillin, cetirizine, oseltamivir phosphate, montelukast sodium, and azithromycin. L. Thomas indicated there has been a significant reduction in hydrocodone-acetaminophen claims and that hydrocodone-acetaminophen is no longer in the top five claims. L. Thomas then reported the top five drugs from the Top 25 Drugs Based on Claims Cost from 01/01/2019 – 03/31/2019: Vyvanse®, Focalin XR®, Invega® Sustenna®, oseltamivir phosphage, and Concerta®. She reminded the Board that Vyvanse® and Focalin XR® were preferred agents during this. From the Top 15 Therapeutic Classes by Total Cost of

Claims for the same time frame, L.Thomas reported the top five classes: Antipsychotic Agents, Respiratory and CNS Stimulants, Amphetamines, Miscellaneous Anticonvulsants, and Insulins.

Opioid Edits: K. Newman reviewed the Short-Acting Opioid Naïve Limit edit that began on November 1, 2018 and also reviewed Phase One of the Morphine Milligram Equivalent (MME) Edit that began May 1, 2019. She also reviewed Phase Two which is set to begin August 1, 2019. K. Newman also gave a brief overview of the Support Act of 2018 and indicated that more information was forthcoming from CMS. She also mentioned that RDUR criteria related to the Support Act was approved during the April 2019 DUR Board Meeting.

RDUR Intervention Report: L. Thomas presented the RDUR Activity Report for April 2019. She reported 532 profiles reviewed and 673 letters sent with 86 responses received as of the date of the report. She reported 50 of 86 physicians indicated that they found the RDUR letters "useful" or "extremely useful". The criteria for the cycle of intervention letters included Overuse Precaution (appropriate use of immediate-release opioids); Drug-Drug Interaction (additive CNS effects – narcotics/opioids and benzodiazepines); and Appropriate Use (concurrent use of buprenorphine and pure opiate agonists).

Proposed Criteria: L.Thomas presented the proposed set of 42 criteria to the Board. T. Minnifield instructed the Board members to mark their ballots. Of the 42 proposed criteria, results from the criteria vote returned 38 approved, 3 approved as amended, and 1 rejected.

Medicaid Update: K. Littlejohn gave the Medicaid update and talked to the group about the ACHN ALERT. T. Minnifield reminded the Board members that all updated Medicaid drug lists and ALERTs were provided to them electronically and are also available online. A vote to elect a new Vice Chair was taken. Results of the vote elected Rachel Seaman as Vice Chair.

P & T Committee Update: C. Hurst began the P & T Update by informing the Board that the last meeting was held on May 8, 2019 and covered the remaining Anti-infective Agents and a review of the Calcitonin Gene-Related Peptide Antagonists. The next P & T Committee meeting will be held on August 7, 2019, and will cover the First Generation Antihistamines; Antidiabetic Agents; Prenatal Vitamins; Agents used to Treat Multiple Sclerosis; and Antigout Agents.

Next Meeting Date: D. Thornley-Brown reminded the Board that the next DUR meeting will be held on October 23, 2019. A motion to adjourn the meeting was made by P. Thompson. B. Olin seconded the motion and the meeting was adjourned at 2:10 p.m.

Respectfully submitted,

Lori Thomas, PharmD

Lori Thomas, PharmD.

ALABAMA MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS

Criteria Recommendations	*Accepted*	*Approved As Amended*	*Rejected*
1. Chronic Opioid Use / Diagnosis of Substance Abuse or Dependence	_____	___V_____	_____

Alert Message: The patient has received more than one prescriptions for controlled substances and/or restricted medications in recent months and has a diagnosis of substance abuse, misuse, or dependence.

Conflict Code: LI - Lock-In Criteria

Drugs/Diseases		
Util A	Util B	Util C **(Include)**
Controlled Substances		Diagnosis of Substance Abuse or Dependence for:
AL Restricted Meds		Opioid
		Sedative, Hypnotic, or Anxiolytic
		Cocaine
		Stimulant
		Hallucinogen
		Alcohol
		Inhalant
		Psychoactive Substances

References:

Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Facts & Comparisons, 2018 Updates, Wolters Kluwer Health.
National Institute of Drug Abuse (NIDA), Misuse of Prescription Drugs. Last Updated January 2018. Available at: https://www.drugabuse.gov/publications/research-reports/misuse-prescription-drugs/how-can-prescription-drug-misuse-be-prevented
Centers for Disease Control and Prevention. 2018 Annual Surveillance Report of Drug-Related Risks and Outcomes - United States. Surveillance Special Report. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. Published August 31, 2018. Available at: https://www.cdc.gov/drugoverdose/pdf/pubs/2018-cdc-drug surveillance-report.pdf

Criteria Recommendations	*Accepted*	*Approved As Amended*	*Rejected*

2. Chronic Opioid Use / Diagnosis of Medication-Related Poisoning _____ ___√_____ _____

Alert Message: The patient has more than one prescription for controlled substances and/or restricted medications in recent months and has a diagnosis of drug-related poisoning.

Conflict Code: LI - Lock-In Criteria

Drugs/Diseases

Util A	Util B	Util C **(Include)**
Controlled Substances		Diagnosis of Poisoning by:
AL Restricted Meds		Opioid
		Sedative, Hypnotic, or Anxiolytic
		Cocaine
		Stimulant
		Hallucinogen
		Alcohol
		Inhalant
		Psychoactive Substance

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Facts & Comparisons, 2018 Updates, Wolters Kluwer Health.
National Institute of Drug Abuse (NIDA), Misuse of Prescription Drugs. Last Updated January 2018. Available at: https://www.drugabuse.gov/publications/research-reports/misuse-prescription-drugs/how-can-prescription-drug-misuse-be-prevented
Centers for Disease Control and Prevention. 2018 Annual Surveillance Report of Drug-Related Risks and Outcomes - United States. Surveillance Special Report. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. Published August 31, 2018. Available at: https://www.cdc.gov/drugoverdose/pdf/pubs/2018-cdc-drug surveillance-report.pdf

3. Doxylamine/Pyridoxine / Overutilization ___√_____ _____ _____

Alert Message: The maximum recommended dose of Bonjesta (doxylamine/pyridoxine extended-release) is two tablets per day: one in the morning and one at bedtime.

Conflict Code: ER - Overutilization

Drugs/Diseases

Util A	Util B	Util C
Doxylamine/Pyridoxine		

Max Dose: 2 tablets/day

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Bonjesta Prescribing Information, June 2018. Duchesnay Inc.

Criteria Recommendations	*Accepted*	*Approved As Amended*	*Rejected*

4. Doxylamine/Pyridoxine / MAO Inhibitors _____ ___√___ _____

Alert Message: The use of Bonjesta (doxylamine/pyridoxine extended-release) is contraindicated in women who are taking monoamine oxidase inhibitors (MAOIs). Concurrent use of MAOIs with doxylamine/pyridoxine can prolong and intensify the adverse central nervous system effects of the doxylamine component of the combination antiemetic.

Conflict Code: DD - Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Doxylamine/Pyridoxine	Isocarboxazid	
	Phenelzine	
	Tranylcypromine	
	Selegiline	
	Linezolid	

References:
Bonjesta Prescribing Information, June 2018. Duchesnay Inc.

5. Doxylamine/Pyridoxine / CNS Depressants ___√_____ _____ _____

Alert Message: Concurrent use of Bonjesta (doxylamine/pyridoxine extended-release) with other CNS depressants, including alcohol, is not recommended. The doxylamine component of the antiemetic may cause somnolence and severe drowsiness. Coadministration with CNS depressants may enhance the sedative effects of doxylamine.

Conflict Code: DD - Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Doxylamine/Pyridoxine	Sedatives	
	Anxiolytics	
	Narcotics	
	Barbiturates	
	Muscle Relaxants	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Bonjesta Prescribing Information, June 2018. Duchesnay Inc.

Criteria Recommendations	*Accepted*	*Approved As Amended*	*Rejected*

6. Doxylamine/Pyridoxine / Certain Disease State ___√___ _____ _____

Alert Message: Bonjesta (doxylamine/pyridoxine extended-release) should be used with caution in patients with asthma, increased intraocular pressure, narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, and urinary bladder-neck obstruction. The anticholinergic effects of the doxylamine component of the antiemetic product may worsen symptoms of these conditions.

Conflict Code: MC - Drug (Actual) Disease Precaution/Warning

Drugs/Diseases

Util A	Util B	Util C
Doxylamine/Pyridoxine	Asthma	
	Increased Intraocular Pressure	
	Narrow Angle Glaucoma	
	Peptic Ulcer	
	Obstruction of Duodenum	
	Bladder-neck Obstruction	

References:

Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Bonjesta Prescribing Information, June 2018. Duchesnay Inc.

7. Tezacaftor/Ivacaftor;Ivacaftor / Overutilization ___√_____ _____ _____

Alert Message: Symdeko (tezacaftor/ivacaftor;ivacaftor) may be over-utilized. The manufacturer's recommended maximum daily dose is one (1) tezacaftor 100 mg/ivacaftor 150 mg fixed-dose combination tablet in the morning and one (1) 150 mg ivacaftor tablet in the evening, given 12 hours apart.

Conflict Code: ER - Overutilization

Drugs/Diseases

Util A	Util B	Util C
Tezacaftor/Ivacaftor;Ivacaftor		

Max Dose: 1 Box/month = 60 tablets/month

References:

Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Symdeko Prescribing Information, Feb. 2018, Vertex Pharmaceuticals Incorporated.

Criteria Recommendations	*Accepted*	*Approved As Amended*	*Rejected*

8. Tezacaftor/Ivacaftor;Ivacaftor / Nonadherence ___√_____ _____ _____

Alert Message: Based on refill history, your patient may be under-utilizing Symdeko (tezacaftor/ivacaftor;ivacaftor). Nonadherence to the prescribed dosing regimen may result in sub-therapeutic effects, which may lead to decreased patient outcomes and additional healthcare costs.

Conflict Code: LR - Nonadherence
Drugs/Diseases

Util A	Util B	Util C
Tezacaftor/Ivacaftor;Ivacaftor		

References:
Symdeko Prescribing Information, Feb. 2018, Vertex Pharmaceuticals Incorporated.
Eakin MN, Bilderback A, Boyle MP, Mogayzel PJ, Riekert KA. Longitudinal Association between Medication Adherence and Lung Health in People with Cystic Fibrosis. Jrnl Cyst Fib. 2011;10(4):258-264.
Bishay LC, Sawicki. Strategies to Optimize Treatment Adherence in Adolescent Patients with Cystic Fibrosis. Adolesc
Health, Med & Ther. 2016 Oct 21;7:117-124.

9. Tezacaftor/Ivacaftor;Ivacaftor / Therapeutic Appropriateness (0-11 yoa) _____ _____ __√___

Alert Message: The safety and efficacy of Symdeko (tezacaftor/ivacaftor;ivacaftor) in patients younger than 12 years of age have not been established.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Tezacaftor/Ivacaftor;Ivacaftor		

Age Range: 0 – 11 yoa

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Symdeko Prescribing Information, Feb. 2018, Vertex Pharmaceuticals Incorporated.

10. Tezacaftor/Ivacaftor;Ivacaftor / Strong CYP3A4 Inducers ___√_____ _____ _____

Alert Message: Concurrent use of Symdeko (tezacaftor/ivacaftor;ivacaftor) with a strong CYP3A4 inducer is not recommended. Both tezacaftor and ivacaftor are CYP3A4 substrates, and concomitant use with strong 3A4 inducers may result in reduced exposure and reduced efficacy.

Conflict Code: DD - Drug/Drug Interaction
Drugs/Diseases

Util A	Util B		Util C
Tezacaftor/Ivacaftor;Ivacaftor	Carbamazepine	Rifampin	
	Phenytoin	Mitotane	
	Phenobarbital	Enzalutamide	
	Primidone		

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Symdeko Prescribing Information, Feb. 2018, Vertex Pharmaceuticals Incorporated.

Criteria Recommendations	*Accepted*	*Approved As Amended*	*Rejected*

11. Tezacaftor/Ivacaftor;Ivacaftor / Strong CYP3A4 Inhibitors __√_____ _____ _____

Alert Message: When Symdeko (tezacaftor/ivacaftor;ivacaftor) is co-administered with a strong CYP3A4 inhibitor, the dosing of tezacaftor/ivacaftor should be adjusted to one (1) tezacaftor 100 mg/ivacaftor 150 mg fixed-dose combination tablet twice a week (taken approximately 3 to 4 days apart). The evening dose of ivacaftor 150 mg should not be taken. Both tezacaftor and ivacaftor are CYP3A4 substrates, and concomitant use with strong CYP3A4 inhibitors may significantly increase substrate exposure and risk of adverse effects.

Conflict Code: DD - Drug/Drug Interaction
Drugs/Diseases

Util A	Util B		Util C
Tezacaftor/Ivacaftor;Ivacaftor	Clarithromycin	Indinavir	
	Nefazodone	Ketoconazole	
	Cobicistat	Itraconazole	
	Saquinavir	Posaconazole	
	Ritonavir	Voriconazole	
	Nelfinavir		

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Symdeko Prescribing Information, Feb. 2018, Vertex Pharmaceuticals Incorporated.

12. Tezacaftor/Ivacaftor;Ivacaftor / Moderate CYP3A4 Inhibitors ___√_____ _____ _____

Alert Message: When Symdeko (tezacaftor/ivacaftor;ivacaftor) is co-administered with a moderate CYP3A4 inhibitor, the dosing of tezacaftor/ivacaftor should be adjusted to one (1) tezacaftor 100 mg/ivacaftor 150 mg fixed-dose combination tablet every other day in the morning, and one (1) ivacaftor 150 mg tablet every other day in the morning on alternate days (i.e., tezacaftor/ivacaftor tablet on Day 1 and ivacaftor tablet on Day 2). The evening dose of ivacaftor should not be taken.

Conflict Code: DD - Drug/Drug Interaction
Drugs/Diseases

Util A	Util B			Util C
Tezacaftor/Ivacaftor;Ivacaftor	Diltiazem	Dronedarone	Crizotinib	
	Verapamil	Cyclosporine	Clotrimazole	
	Fluconazole	Imatinib		
	Erythromycin	Fluvoxamine		
	Aprepitant	Cimetidine		

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Symdeko Prescribing Information, Feb. 2018, Vertex Pharmaceuticals Incorporated.

Criteria Recommendations	*Accepted*	*Approved As Amended*	*Rejected*

13. Tezacaftor/Ivacaftor;Ivacaftor / Moderate to Severe Hepatic Impairment ___√_____ _____ _____

Alert Message: A reduced dose of Symdeko (tezacaftor/ivacaftor;ivacaftor) is recommended in patients with moderate hepatic impairment (Child-Pugh Class B) and severe hepatic impairment (Child-Pugh Class C). Patients with moderate impairment should receive one (1) tezacaftor 100 mg/ivacaftor 150 mg fixed-dose combination tablet once daily and NO ivacaftor 150 mg dose. Patients with severe impairment should receive one (1) tezacaftor 100 mg/ivacaftor 150 mg fixed-dose combination tablet once daily (or less frequently) and NO ivacaftor 150 mg dose.

Conflict Code: MC - Drug (Actual) Disease Precaution
Drugs/Diseases

Util A	Util B	Util C
Tezacaftor/Ivacaftor;Ivacaftor	Cirrhosis	
	Hepatic Failure	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Symdeko Prescribing Information, Feb. 2018, Vertex Pharmaceuticals Incorporated.

14. Tezacaftor/Ivacaftor;Ivacaftor / P-gp Substrates w/ NTI ___√_____ _____ _____

Alert Message: Caution and appropriate monitoring should be used when Symdeko (tezacaftor/ivacaftor;ivacaftor) is co-administered with a P-gp substrate with a narrow therapeutic index. The ivacaftor component of the co-packaged combination product is a P-gp inhibitor, and concurrent use with a P-gp substrate may result in increased substrate exposure.

Conflict Code: DD - Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Tezacaftor/Ivacaftor;Ivacaftor	Digoxin	
	Cyclosporine	
	Everolimus	
	Sirolimus	
	Tacrolimus	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Symdeko Prescribing Information, Feb. 2018, Vertex Pharmaceuticals Incorporated.

Criteria Recommendations	*Accepted*	*Approved As Amended*	*Rejected*

15. Asenapine / Therapeutic Appropriateness ___√_____ _____ _____

Alert Message: The safety and efficacy of Saphris (asenapine) for the treatment of Bipolar I disorder in pediatric patients below 10 years of age have not been established.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Asenapine		Bipolar I Disorder Mania & Mixed Episodes

Age Range: 0 – 9 yoa

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Facts & Comparisons, 2018 Updates, Wolters Kluwer Health.

16. Mepolizumab / Overutilization ____√_____ _____ _____

Alert Message: The manufacturer's recommended dose of Nucala (mepolizumab) for eosinophilic granulomatosis with polyangiitis (EGPA) is 300 mg administered once every 4 weeks by subcutaneous injection.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Mepolizumab		Polyarteritis with lung involvement [Churg-Strauss]

Max Dose: 3 injections/4 weeks

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Facts & Comparisons, 2018 Updates, Wolters Kluwer Health.

17. Mepolizumab / Therapeutic Appropriateness ___√_____ _____ _____

Alert Message: The safety and efficacy of Nucala (mepolizumab) for the treatment of eosinophilic granulomatosis with polyangiitis in pediatric patients have not been established.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Mepolizumab		Polyarteritis with lung involvement [Churg-Strauss]

Age Range: ≤ 18 yoa

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Facts & Comparisons, 2018 Updates, Wolters Kluwer Health.

Criteria Recommendations	*Accepted*	*Approved As Amended*	*Rejected*

18. Midostaurin / Overutilization ___v_____ _____ _____

Alert Message: The manufacturer's recommended dose of Rydapt (midostaurin) for patients with acute myeloid leukemia (AML) is 50 mg twice daily.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Midostaurin		Acute Myeloid Leukemia

Max Dose: 100 mg/day

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Rydapt Prescribing Information, June 2018, Novartis Pharmaceuticals Corp.

19. Midostaurin / Overutilization __v_____ _____ _____

Alert Message: The manufacturer's recommended dose of Rydapt (midostaurin) for patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN) or mast cell leukemia (MCL) is 100 mg twice daily.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Midostaurin		Aggressive Systemic Mastocytosis (ASM) Mast Cell Leukemia

Max Dose: 200 mg/day

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Rydapt Prescribing Information, June 2018, Novartis Pharmaceuticals Corp.

20. Midostaurin / Strong CYP3A4 Inducers ___v_____ _____ _____

Alert Message: Concurrent use of Rydapt (midostaurin), a CYP3A4 substrate, with a strong CYP3A4 inducer should be avoided as concomitant use may result in decreased midostaurin concentrations and reduced efficacy.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B		Util C
Midostaurin	Carbamazepine Phenobarbital Primidone Phenytoin	Rifampin Enzalutamide	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Rydapt Prescribing Information, June 2018, Novartis Pharmaceuticals Corp.

Criteria Recommendations	*Accepted*	*Approved As Amended*	*Rejected*

21. Midostaurin / Strong CYP3A4 Inhibitors ___√_____ _____ _____

Alert Message: Concurrent use of Rydapt (midostaurin), a CYP3A4 substrate, with a strong CYP3A4 inhibitor may increase exposure to midostaurin and its active metabolites, increasing the risk of midostaurin toxicity. Consider alternative therapies that do not strongly inhibit CYP3A4 or monitor for increased risk of midostaurin-related adverse reactions.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B		Util C
Midostaurin	Clarithromycin	Nefazodone	
	Cobicistat	Ketoconazole	
	Conivaptan	Itraconazole	
	Ritonavir	Posaconazole	
	Saquinavir	Voriconazole	
	Indinavir		
	Nelfinavir		

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Rydapt Prescribing Information, June 2018, Novartis Pharmaceuticals Corp.

22. Midostaurin / Pregnancy / Pregnancy Negating ___√_____ _____ _____

Alert Message: Rydapt (midostaurin) may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus.

Conflict Code: MC – Drug (Actual) Disease Precaution
Drugs/Diseases

Util A	Util B	Util C **(Negating)**
Midostaurin	Pregnancy	Miscarriage
		Abortion
		Delivery

Gender: Female
Age Range: 11 – 50 yoa

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Rydapt Prescribing Information, June 2018, Novartis Pharmaceuticals Corp.

Criteria Recommendations	*Accepted*	*Approved As Amended*	*Rejected*

23. Midostaurin / Therapeutic Appropriateness ___√_____ _____ _____

Alert Message: Advise males with female sexual partners of reproductive potential that effective contraception should be used during treatment with Rydapt (midostaurin) and for 4 months after the last dose. Based on its mechanism of action and findings from animal reproduction studies, midostaurin may cause embryo-fetal toxicity.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases
Util A Util B Util C
Midostaurin

Gender: Male

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Rydapt Prescribing Information, June 2018, Novartis Pharmaceuticals Corp.

24. Midostaurin / Therapeutic Appropriateness ___√_____ _____ _____

Alert Message: Based on its mechanism of action and findings from animal reproduction studies, Rydapt (midostaurin) may cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with midostaurin and for at least 4 months after the last dose.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases
Util A Util B Util C
Midostaurin

Gender: Female
Age Range: 11 – 50 yoa

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Rydapt Prescribing Information, June 2018, Novartis Pharmaceuticals Corp.

25. Midostaurin / Therapeutic Appropriateness ___√_____ _____ _____

Alert Message: The safety and effectiveness of Rydapt (midostaurin) have not been established in pediatric patients.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases
Util A Util B Util C
Midostaurin

Age Range: 0-17 yoa

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Rydapt Prescribing Information, June 2018, Novartis Pharmaceuticals Corp.

Criteria Recommendations	*Accepted*	*Approved As Amended*	*Rejected*

26. Midostaurin / Pulmonary Toxicity __√_____ _____ _____

Alert Message: Cases of interstitial lung disease and pneumonitis, some fatal, have occurred in patients treated with Rydapt (midostaurin) as monotherapy or with chemotherapy. Monitor patients for pulmonary symptoms. Discontinue midostaurin in patients who experience signs and symptoms of interstitial lung disease or pneumonitis without an infectious etiology.

Conflict Code: MC – Drug (Actual) Disease Precaution
Drugs/Diseases

Util A	Util B	Util C
Midostaurin	Acute Interstitial Pneumonia	
	Dyspnea	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Rydapt Prescribing Information, June 2018, Novartis Pharmaceuticals Corp.

27. Delafloxacin / Overutilization ___√_____ _____ _____

Alert Message: Baxdela (delafloxacin) may be over-utilized. The recommended maximum dosage of delafloxacin is 450 mg orally every 12 hours for a total duration of 5 to 14 days.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Delafloxacin		

Max Dose: 900 mg/day

References:
Baxdela Prescribing Information, Oct. 2018, Melinta Therapeutics, Inc.

28. Delafloxacin / Therapeutic Appropriateness ___√_____ _____ _____

Alert Message: The use of Baxdela (delafloxacin) in patients with end-stage renal disease (ESRD) is not recommended. There is insufficient information to provide dosing recommendations in this patient population.

Conflict Code: MC – Drug Disease Precaution/Warning
Drugs/Diseases

Util A	Util B	Util C
Delafloxacin	End-Stage Renal Disease	

References:
Baxdela Prescribing Information, Oct. 2018, Melinta Therapeutics, Inc.

Criteria Recommendations	*Accepted*	*Approved As Amended*	*Rejected*

29. Delafloxacin / Therapeutic Appropriateness ___√_____ _____ _____

Alert Message: Fluoroquinolones have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together, including; tendinitis and tendon rupture, peripheral neuropathy, and CNS effects. Discontinue Baxdela (delafloxacin) immediately and avoid the use of fluoroquinolones in patients who experience any of these adverse reactions.

Conflict Code: TA - Therapeutic Appropriateness

Drugs/Diseases

Util A	Util B	Util C
Delafloxacin		

References:

Baxdela Prescribing Information, Oct. 2018, Melinta Therapeutics, Inc.

30. Cannabidiol / Therapeutic Appropriateness ___√_____ _____ _____

Alert Message: Epidiolex (cannabidiol) causes dose-related elevations of liver transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]). Prior to starting treatment with cannabidiol, obtain serum transaminases (ALT and AST) and total bilirubin levels. Serum transaminases and total bilirubin levels should be obtained at 1 month, 3 months, and 6 months after initiation of treatment with cannabidiol, and periodically thereafter or as clinically indicated.

Drugs/Diseases

Util A	Util B	Util C
Cannabidiol		

References:

Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Epidiolex Prescribing Information, June 2018, Greenwich Biosciences.

Criteria Recommendations	*Accepted*	*Approved As Amended*	*Rejected*

31. Cannabidiol / Nonadherence ___V_____ _____ _____

Alert Message: Based on the refill history, your patient may be underutilizing Epidiolex (cannabidiol). Nonadherence to the prescribed dosing regimen may result in sub-therapeutic effects, which may lead to decreased patient outcomes and additional healthcare costs.

Drugs/Diseases

Util A	Util B	Util C
Cannabidiol		

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Epidiolex Prescribing Information, June 2018, Greenwich Biosciences.

32. Cannabidiol / Moderate & Strong CYP3A4 & CYP2C19 Inhibitors ___V_____ _____ _____

Alert Message: Epidiolex (cannabidiol) is metabolized by CYP3A4 and CYP2C19. Therefore, coadministration with a moderate to strong inhibitor of CYP3A4 or CYP2C19 will increase cannabidiol plasma concentrations, which may result in a greater risk of adverse reactions. Consider a reduction in the cannabidiol dosage when coadministered with a moderate to strong inhibitor of CYP3A4 or CYP2C19.

Drugs/Diseases

Util A	Util B			Util C
Cannabidiol	Nefazodone	Diltiazem	Ticlopidine	Fosamprenavir
	Clarithromycin	Verapamil	Cobicistat	
	Ketoconazole	Fluconazole	Fluoxetine	
	Itraconazole	Aprepitant	Atazanavir	
	Posaconazole	Cimetidine	Imatinib	
	Voriconazole	Ciprofloxacin	Indinavir	
	Saquinavir	Crizotinib	Fluvoxamine	
	Ritonavir	Cyclosporine	Erythromycin	
	Nelfinavir	Dronedarone	Delavirdine	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Epidiolex Prescribing Information, June 2018, Greenwich Biosciences.

Criteria Recommendations	*Accepted*	*Approved As Amended*	*Rejected*

33. Cannabidiol / Strong CYP3A4 & CYP2C19 Inducers ___√_____ _____ _____

Alert Message: Epidiolex (cannabidiol) is metabolized by CYP3A4 and CYP2C19. Coadministration with a strong CYP3A4 or CYP2C19 inducer will decrease cannabidiol plasma concentrations, which may lower the efficacy of cannabidiol. Consider an increase in the cannabidiol dosage (based on clinical response and tolerability) when coadministered with a strong CYP3A4 or CYP2C19 inducer.

Drugs/Diseases

Util A	Util B	Util C
Cannabidiol	Carbamazepine	
	Phenytoin	
	Primidone	
	Phenobarbital	
	Rifampin	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Epidiolex Prescribing Information, June 2018, Greenwich Biosciences.

34. Cannabidiol / Clobazam ___√_____ _____ _____

Alert Message: Coadministration of Epidiolex (cannabidiol) with clobazam produces a 3-fold increase in plasma concentrations of N-desmethylclobazam, the active metabolite of clobazam (a substrate of CYP2C19). This may increase the risk of clobazam-related adverse reactions. Consider a reduction in the dosage of clobazam if adverse reactions known to occur with clobazam are experienced when co-administered with cannabidiol.

Drugs/Diseases

Util A	Util B	Util C
Cannabidiol	Clobazam	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Epidiolex Prescribing Information, June 2018, Greenwich Biosciences.

Criteria Recommendations	*Accepted*	*Approved As Amended*	*Rejected*

35. Cannabidiol / Sensitive CYP2C19 Substrates ___√_____ _____ _____

Alert Message: In vivo data show that coadministration of Epidiolex (cannabidiol) with a drug that is a CYP2C19 substrate will result in an increase in the plasma concentrations of the substrate and may increase the risk of substrate-related adverse reactions. Consider a reduction in the dosage of sensitive CYP2C19 substrates, as clinically appropriate, when coadministered with cannabidiol.

Drugs/Diseases

Util A	Util B	Util C
Cannabidiol	Diazepam	
	Omeprazole	
	Lansoprazole	
	Rabeprazole	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Epidiolex Prescribing Information, June 2018, Greenwich Biosciences.
FDA: Drug Development and Drug Interactions: Tables of Substrates, Inhibitors and Inducers. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResourcesDrugInteractionaLabeling/ucm093664.htm

36. Cannabidiol / Valproate ___√_____ _____ _____

Alert Message: Concomitant use of Epidiolex (cannabidiol) and valproate may increase the risk of hepatotoxicity. Discontinuation or reduction of cannabidiol and/or concomitant valproate should be considered if liver enzyme elevations occur.

Drugs/Diseases

Util A	Util B	Util C
Cannabidiol	Valproate	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Epidiolex Prescribing Information, June 2018, Greenwich Biosciences.

37. Cannabidiol / Pregnancy / Pregnancy Negating ___√_____ _____ _____

Alert Message: There are no adequate data on the development risks associated with the use of Epidiolex (cannabidiol) in pregnant women. Administration of cannabidiol to pregnant animals produced evidence of developmental toxicity at maternal plasma exposure similar to (rabbit) or greater than (rat) that in humans at therapeutic doses. Encourage women who are taking cannabidiol to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant.

Drugs/Diseases

Util A	Util B	Util C (Negating)
Cannabidiol	Pregnancy	Miscarriage
		Delivery
		Abortion

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Epidiolex Prescribing Information, June 2018, Greenwich Biosciences.

Criteria Recommendations	*Accepted*	*Approved As Amended*	*Rejected*

38. Cannabidiol / Lactation ___√___ _____ _____

Alert Message: There are no data on the presence of Epidiolex (cannabidiol) or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for cannabidiol and any potential adverse effects on the breastfed infant from cannabidiol or from the underlying maternal condition.

Drugs/Diseases

Util A	Util B	Util C
Cannabidiol	Lactation	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Epidiolex Prescribing Information, June 2018, Greenwich Biosciences.

39. Aspirin/Omeprazole / Overutilization ___√___ _____ _____

Alert Message: Yosprala (aspirin/omeprazole) may be over-utilized. The recommended daily dose of aspirin/omeprazole is one tablet once daily.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Aspirin/Omeprazole		

Max Dose: 1 tablet/day

References:
Clinical Pharmacology, 2018 Updates, Elsevier/Gold Standard.
Facts & Comparisons, 2018 Updates, Wolters Kluwer Health.

40. Ramelteon / Donepezil ___√___ _____ _____

Alert Message: The concurrent use of a donepezil-containing agent with ramelteon may result in increased ramelteon exposure. In a drug interaction study, the AUC0-inf and Cmax of ramelteon increased by approximately 100% and 87%, respectively, upon coadministration of donepezil with ramelteon. Patients should be closely monitored when ramelteon is coadministered with a donepezil-containing agent.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Ramelteon	Donepezil	
	Donepezil/Memantine	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
IBM Micromedex DRUGDEX (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. 2018.

Criteria Recommendations	*Accepted*	*Approved As Amended*	*Rejected*

41. Ramelteon / Doxepin ___V_____ _____ _____

Alert Message: The concurrent use of doxepin with ramelteon may result in increased ramelteon exposure. In a drug interaction study, the AUC0-inf and Cmax of ramelteon increased by approximately 66% and 69%, respectively, upon coadministration of doxepin with ramelteon. Patients should be closely monitored when ramelteon is coadministered with doxepin.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Ramelteon	Doxepin	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
IBM Micromedex DRUGDEX (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. 2018.

42. Pimavanserin / Nonadherence ___V_____ _____ _____

Alert Message: Based on refill history, your patient may be under-utilizing Nuplazid (pimavanserin). Non-adherence to the prescribed dosing regimen may result in sub-therapeutic effects, which may lead to decreased patient outcomes and additional healthcare costs.

Conflict Code: LR - Nonadherence
Drugs/Diseases

Util A	Util B	Util C
Pimavanserin		

References:
Osterberg L, Blaschke T. Adherence to Medication. N Engl J Med 2005;353:487-97.
Stephenson JJ, Tuncelli O, Gu T, et al., Adherence to Oral Second-Generation Antipsychotic Medications in Patients with Schizophrenia and Bipolar Disorder: Physicians' Perceptions of Adherence vs. Pharmacy Claims. Int J Clin Pract, June 2012, 66, 6, 565-573.
Fleisher JE, Stern MB. Medication Non-adherence in Parkinson's Disease. Curr Neurol Neurosci Rep. 2013;13(10):382. doi 10 01007/s11910-013-0382-z

Stephanie McGee Azar, Commissioner — (X) Approve ( ) Deny — 8/23/19 Date

Robert Moon, M.D., Deputy Commissioner and Medical Director — (X) Approve ( ) Deny — 8/22/19 Date

Kathy Hall, Deputy Commissioner — (X) Approve ( ) Deny — 8/22/19 Date