

Alabama Medicaid DUR Board Meeting Minutes
April 25, 2018

Members Present: Robert Moon, Rachel Seaman, Bernie Olin, Kelli Littlejohn Newman, Marilyn Bulloch, Denyse Thornley-Brown, Dan McConaghy, Chris Phung

Also Present: Tiffany Minnifield, Lori Thomas, Clemice Hurst, Whitney Hughley

Present via Conference Call: Kristian Testerman, Lauren Ward, Allana Alexander, Samir Hadid, Lydia Rather, Joshua Lee

Members Absent: Donald Kern, P.J. Hughes

Call to Order: The DUR meeting was called to order by M. Bulloch at approximately 1:04p.m.

Review and Adoption of Minutes: The minutes of the October 25, 2017 meeting were presented and R. Seaman made a motion to approve the minutes. B. Olin 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 October 2017. She reported 11,428 total manual requests and 19,009 total electronic requests. From the Prior Authorization and Override Response Time Ratio report for October 2017, L. Thomas reported that approximately 62% of all manual PAs and 60% of all overrides were completed in less than two hours. Eighty-three percent of all manual PAs and all overrides were completed in less than four hours. Eighty-three percent of all manual PAs and all overrides were completed in less than eight hours. For the month of November 2017, L. Thomas reported 10,356 manual PA requests and 17,951 electronic PA requests were received. She reported that 75% of all manual PAs and 76% of all overrides were completed in less than two hours. Eighty-seven percent of all manual PAs and overrides were completed in less than four hours. Ninety-one percent of all manual PAs and all overrides were completed in less than eight hours. For the month of December 2017, L. Thomas reported 9,219 manual PA requests and 16,558 electronic PA requests. L. Thomas reported that approximately 86% of all manual PAs and 87% of all overrides were completed in less than two hours. Ninety-three percent of all manual PA requests and all overrides were completed in less than four hours. Ninety-four percent of all manual PA requests and 95% of all overrides were completed in less than eight hours.

Program Summary Review: L. Thomas briefly reviewed the Alabama Medicaid Program Summary for the months of July 2017 through December 2017. She reported 3,605,286 total prescriptions, 218,277 average recipients per month using pharmacy benefits, and an average paid per prescription of \$105.08.

Cost Management Analysis: L. Thomas reported an average cost per claim of \$104.23 for December 2017 and emphasized that the table contained the average cost per claim over the past two years. From the 4th Quarter 2017 Drug Analysis, L. Thomas reported 79.3% generic utilization, 8.9% brand single-source, 8% brand multi-source (those requests which required a DAW override), and 3.8% OTC and "other". From the Top 25 Drugs Based on Number of Claims from 10/01/2017 – 12/31/2017, L. Thomas reported the top five drugs: amoxicillin, cetirizine, ProAir[®] HFA, hydrocodone-acetaminophen, and azithromycin. L. Thomas then reported the top five drugs from the Top 25 Drugs Based on Claims Cost from 10/01/2017 – 12/31/2017: Vyvanse[®], Focalin XR[®], Invega[®] Sustenna[®], Concerta[®], and ProAir[®] HFA. She reminded the Board that Vyvanse[®] and Focalin XR[®] are preferred agents. 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, Amphetamines, Respiratory and CNS Stimulants, Miscellaneous Anticonvulsants, and Insulins.

Proposed Opioid Edits: Dr. Moon began the discussion of opioid utilization by discussing opioid prescribing trends within the state of Alabama. K. Newman introduced the proposed short-acting opiate limits for treatment naïve patients. The Agency proposed an implementation date of July 1st. D. Thornley-Brown made a motion to approve the edit. K. Murray seconded the motion and the motion was approved unanimously. Next, K. Newman introduced the morphine milligram equivalent (MME) cumulative edit. She explained that this would be phased in as an informational edit beginning Fall 2018 and would become a hard edit beginning early 2019. The Board made a motion for the Agency to continue to work on the MME edit and provide more information at future DUR meetings. K. Murray made a motion to approve the edit and B. Olin seconded the motion. The motion was approved unanimously.

RDUR Intervention Report: L. Thomas presented the RDUR Activity Report for October 2017. She reported 545 profiles reviewed and 535 letters sent with 57 responses received as of the date of the report. She reported 44 of 65 physicians indicated that they found the RDUR letters “useful” or “extremely useful”. The criteria for the cycle of intervention letters included Drug-Disease Precaution (stimulant use in patients with hypertension); Drug-Drug Precaution/Drug-Disease Precaution (contraindication of stimulants in patients with anxiety or agitated states); Appropriate Use (appropriate use of immediate-release opioids); Appropriate Use (concurrent use of buprenorphine and pure opiate agonists).

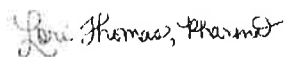
Proposed Criteria: L. Thomas presented the proposed set of 47 criteria to the Board. T. Minnifield instructed the Board members to mark their ballots. Of the 47 proposed criteria, results from the criteria vote returned 47 approved.

Medicaid Update: T. Minnifield reminded the Board members that all updated Medicaid drug lists provided are also available online and that the next DUR Meeting would be July 25th.

P & T Committee Update: C. Hurst began the P & T Update by informing the Board that the last meeting was held on February 21, 2018, and covered the Respiratory Agents. The next P & T meeting is scheduled for May 9, 2018, at 9 a.m. and will cover the Skeletal Muscle Relaxants, Opiate Agonists, Opiate Partial Agonists, Antiemetics, Proton Pump Inhibitors, and EENT agents.

Next Meeting Date: M. Bulloch notified the Board that the next DUR meeting will be held on July 25, 2018. A motion to adjourn the meeting was made by D. Thornley-Brown. R. Seaman seconded the motion and the meeting was adjourned at 3:00 p.m.

Respectfully submitted,



Lori Thomas, PharmD.

**ALABAMA MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS**

Criteria Recommendations

**Accepted Approved Rejected
As
Amended**

1. Tenofovir Alafenamide / Overutilization

_____v_____

Alert Message: Vemlidy (tenofovir alafenamide) maybe over-utilized. The manufacturer's recommended maximum dose is 25 mg once daily.

Conflict Code: ER - Overutilization

Drugs/Diseases

Util A

Util B

Util C (Negating)

Tenofovir ala.

CKD Stage 5

Max Dose: 25 mg/day

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.

Vemlidy Prescribing Information, Nov. 2016, Gilead Sciences, Inc.

2. Tenofovir Alafenamide / Chronic Kidney Disease Stage 5

_____v_____

Alert Message: Vemlidy (tenofovir alafenamide) use is not recommended in patients with end-stage renal disease (estimated creatinine clearance below 15 mL/minute). No dosage adjustment of tenofovir alafenamide is required in patients with mild, moderate, or severe renal impairment.

Conflict Code: TA – Therapeutic Appropriateness

Drugs/Diseases

Util A

Util B

Util C (Include)

Tenofovir ala.

CKD Stage 5

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.

Vemlidy Prescribing Information, Nov. 2016, Gilead Sciences, Inc.

3. Tenofovir Alafenamide / Hepatic Impairment

_____v_____

Alert Message: Vemlidy (tenofovir alafenamide) use is not recommended in patients with decompensated hepatic impairment (Child-Pugh B or C). Tenofovir alafenamide use has been associated with lactic acidosis and severe hepatomegaly with steatosis, including fatal cases. No dosage adjustment of tenofovir alafenamide is required in patients with mild hepatic impairment (Child-Pugh A).

Conflict Code: TA – Therapeutic Appropriateness

Drugs/Diseases

Util A

Util B

Util C (Include)

Tenofovir ala.

Fibrosis and Cirrhosis of the Liver
Chronic Hepatic Failure
Hepatic Failure, Unspecified
Toxic Liver Disease
Alcoholic Liver Disease

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.

Vemlidy Prescribing Information, Nov 2016, Gilead Sciences, Inc.

4. Tenofovir Alafenamide / Carbamazepine _____^v_____

Alert Message: Concurrent use of Vemlidy (tenofovir alafenamide), a P-gp substrate, with carbamazepine may result in decreased tenofovir alafenamide absorption, which may lead to the loss of tenofovir alafenamide's therapeutic effect due to induction by carbamazepine of tenofovir alafenamide P-gp mediated transport. When these agents are co-administered, the dose of tenofovir alafenamide should be increased to two tablets once daily.

Conflict Code: LR – Inappropriate Dosing.

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C (Include)</u>
Tenofovir ala.		Carbamazepine

Minimum Dose: 50 mg/day

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vemlidy Prescribing Information, Nov. 2016, Gilead Sciences, Inc.

5. Tenofovir / Other P-gp Inducers _____^v_____

Alert Message: Concurrent use of Vemlidy (tenofovir alafenamide) with P-gp inducers (e.g., phenytoin, oxcarbazepine, rifampin, and phenobarbital) is not recommended. Tenofovir alafenamide is a P-gp substrate and use with a P-gp inducer may result in decreased tenofovir alafenamide absorption which may lead to loss of therapeutic effect.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Tenofovir ala.	Phenytoin	
	Oxcarbazepine	
	Phenobarbital	
	Rifampin	
	Rifabutin	
	Rifapentine	

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vemlidy Prescribing Information, Dec. 2016, Gilead Sciences, Inc.

6. Tenofovir / P-GP & BCRP Inhibitors

_____ **v** _____

Alert Message: Vemlidy (tenofovir alafenamide) is a substrate of both P-gp and BCRP transport. Concurrent use of tenofovir alafenamide with a P-gp and/or BCRP transport inhibitor may result in increased tenofovir alafenamide absorption and plasma concentrations and risk of tenofovir alafenamide-related adverse effects.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Tenofovir ala.	Alectinib	Rolapitant
	Cobicistat	Tedizolid
	Daclatasvir	Vemurafenib
	Olaparib	Cyclosporine
	Osimertinib	Sorafenib
	Regorafenib	

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vemlidy Prescribing Information, Dec. 2016, Gilead Sciences, Inc.

7. Tenofovir / Drugs Effecting Renal Function

_____ **v** _____

Alert Message: Vemlidy (tenofovir alafenamide) is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, therefore co-administration of tenofovir alafenamide with drugs that reduce renal function or compete for active tubular secretion may increase tenofovir alafenamide concentrations and increase the risk of tenofovir-related adverse reactions.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Tenofovir ala.	Salicylates	Bacitracin
	Acyclovir	Metformin
	Cidofovir	Dofetilide
	Ganciclovir	Cyclosporine
	Valacyclovir	Pamidronate
	Valganciclovir	Probenecid
	NSAIDS	Tacrolimus
	Adefovir	Tobramycin
	Zoledronic Acid	

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vemlidy Prescribing Information, Dec. 2016, Gilead Sciences, Inc.

8. Tenofovir / HIV

_____v_____

Alert Message: The safety and efficacy of Vemlidy (tenofovir alafenamide) have not been established in patients co-infected with hepatitis B (HBV) and HIV-1. HIV-1 antibody testing should be offered to all HBV-infected patients before initiating therapy with tenofovir alafenamide, and, if positive, an appropriate antiretroviral combination regimen that is recommended for patients coinfecting with HIV-1 should be used.

Conflict Code: TA – Therapeutic Appropriateness

Drugs/Diseases

Util A Util B Util C (Include)
Tenofovir ala. HIV-1

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vemlidy Prescribing Information, Dec. 2016, Gilead Sciences, Inc.

9. Tenofovir / Nonadherence

_____v_____

Alert Message: Based on refill history, your patient may be under-utilizing Vemlidy (tenofovir alafenamide). Non-adherence to the prescribed dosing regimen may result in sub-therapeutic effects, which may lead to decreased outcomes and additional healthcare costs. Discontinuation of anti-hepatitis B therapy, including tenofovir alafenamide, may result in severe acute exacerbation of hepatitis B. Advise patients to not discontinue tenofovir alafenamide without first informing their healthcare provider.

Conflict Code: LR - Nonadherence

Drugs/Diseases

Util A Util B Util C
Tenofovir ala.

References:

Osterberg L, Blaschke T. Adherence to Medication. N Engl J Med 2005;353:487-97.
Lieveld FI, van Vlerken LG, Siersema PD, van Erpecum KJ. Patient Adherence to Antiviral Treatment for Chronic Hepatitis B and C: A Systemic Review, Ann Hepatol. 2013 May-Jun;12(3):380-391.
Vemlidy Prescribing Information, Dec. 2016, Gilead Sciences, Inc.

10. Lumacaftor/ivacaftor / Overutilization (≥ 12 yoa)

___v___

Alert Message: The recommended daily dose of Orkambi (lumacaftor/ivacaftor) for patients age 12 years and older is two lumacaftor 200mg/ivacaftor 125 mg tablets every 12 hours with fat-containing food (total daily dose lumacaftor 800 mg/ivacaftor 500 mg).

Conflict Code: ER - Overutilization

Drugs/Diseases

Util A

Util B

Util C (Negating)

Lumacaftor/ivacaftor

Hepatic Impairment

Max Dose: 800mg/500mg (4 tabs)

Age Range: ≥ 12 yoa

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.

Orkambi Prescribing Information, Sept. 2016, Vertex Pharmaceuticals Inc.

11. Lumacaftor/ivacaftor / Overutilization (6 – 11 yoa)

___v___

Alert Message: The recommended daily dose of Orkambi (lumacaftor/ivacaftor) for patients age 6 to 11 years of age is two lumacaftor 100 mg/ivacaftor 125 mg tablets every 12 hours with fat-containing food (total daily dose lumacaftor 400 mg/ivacaftor 500 mg).

Conflict Code: ER - Overutilization

Drugs/Diseases

Util A

Util B

Util C (Negating)

Lumacaftor/ivacaftor

Hepatic Impairment

Max Dose: 400mg/500mg (4 tabs)

Age Range: 6 – 11 yoa

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.

Orkambi Prescribing Information, Sept. 2016, Vertex Pharmaceuticals Inc.

Criteria Recommendations

**Accepted Approved Rejected
As
Amended**

12. Lumacaftor/ivacaftor / Overutilization – Hepatic Imp. (≥ 12 yoa) v _____ _____

Alert Message: The recommended daily dose of Orkambi (lumacaftor/ivacaftor) for patients 12 years of age and older with moderate hepatic impairment, is two lumacaftor 200 mg/ivacaftor 125 mg tablets in the morning and one 200 mg/125 mg tablet in the evening (total of 3 tablets per day). Patients 12 years and older with severe hepatic impairment should receive one 200 mg/125 mg tablet in the morning and one 200 mg/ 125 mg tablet in the evening.

Conflict Code: ER - Overutilization
Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C (Include)</u>
Lumacaftor/ivacaftor		Hepatic Impairment

Max Dose: 600mg/375mg (3 tabs)
Age Range: ≥ 12 yoa

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Orkambi Prescribing Information, Sept. 2016, Vertex Pharmaceuticals Inc.

13. Lumacaftor/ivacaftor / Overutilization – Hepatic Imp. (6 – 11 yoa) v _____ _____

Alert Message: The recommended daily dose of Orkambi (lumacaftor/ivacaftor) for patients age 6 to 11 years of age with moderate hepatic impairment, is two lumacaftor 100 mg/ivacaftor 125 mg tablets in the morning and one 100 mg/125 mg tablet in the evening (total of 3 tablets per day). Patients 6 to 11 years of age with severe hepatic impairment should receive one 100 mg/125 mg tablet in the morning and one 100 mg/125 mg tablet in the evening.

Conflict Code: ER - Overutilization
Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C (Include)</u>
Lumacaftor/ivacaftor		Hepatic Impairment

Max Dose: 300mg/375mg (3 tabs)
Age Range: 6 – 11 yoa

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Orkambi Prescribing Information, Sept. 2016, Vertex Pharmaceuticals Inc.

14. Lumacaftor/ivacaftor / Strong CYP3A4 Inducers

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Alert Message: Concurrent use of Orkambi (lumacaftor/ivacaftor) with strong CYP3A4 inducers is not recommended. The ivacaftor component of the combination agent is a sensitive CYP3A4 substrate and concomitant administration with a strong CYP3A4 inducer may substantially decrease exposure of ivacaftor reducing the therapeutic effectiveness of ivacaftor.

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

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Lumacaftor/ivacaftor	Phenytoin	Rifampin
	Phenobarbital	Rifabutin
	Primidone	Rifapentine
	Carbamazepine	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Orkambi Prescribing Information, Sept. 2016, Vertex Pharmaceuticals Inc.

15. Lumacaftor/ivacaftor / Hormonal Contraceptives

___v___

Alert Message: Orkambi (lumacaftor/ivacaftor) may substantially decrease hormonal contraceptive exposure, reducing their effectiveness and increasing the incidence of menstruation-associated adverse reactions (e.g., amenorrhea, dysmenorrhea, and menorrhagia). Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with lumacaftor/ivacaftor.

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

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Lumacaftor/ivacaftor	Oral Contraceptives	
	Injectable Contraceptives	
	Transdermal Contraceptives	
	Implantable Contraceptives	

Age Range: 11 – 55 yoa
Gender: Female

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Orkambi Prescribing Information, Sept. 2016, Vertex Pharmaceuticals Inc.

16. Lumacaftor/ivacaftor / Sensitive 3A4 Substrates & 3A4 Substrates w/ NTI v _____

Alert Message: Co-administration of Orkambi (lumacaftor/ivacaftor) is not recommend with sensitive CYP3A4 substrates or CYP3A4 substrates with a narrow therapeutic index (NTI). Lumacaftor is a strong CYP3A4 inducer and co-administration with a CYP3A4 substrate with these substrates may decrease systemic exposure of the CYP3A4 substrate and decrease the therapeutic effect.

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

<u>Util A</u>	<u>Util B</u>		<u>Util C</u>
Lumacaftor/ivacaftor	Tacrolimus	Ibrutinib	Dronedarone
	Sirolimus	Lomitapide	Eletriptan
	Everolimus	Lovastatin	Eplerenone
	Cyclosporine	Naloxegol	Felodipine
	Midazolam	Nisoldipine	Indinavir
	Triazolam	Saquinavir	Lurasidone
	Avanafil	Simvastatin	Maraviroc
	Buspirone	Tipranavir	Quetiapine
	Conivaptan	Vardenafil	Sildenafil
	Darifenacin	Budesonide	Ticagrelor
	Darunavir	Dasatinib	Tolvaptan

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Orkambi Prescribing Information, Sept. 2016, Vertex Pharmaceuticals Inc.
FDA: Drug Development and Drug Interactions: Tables of Substrates, Inhibitors\and Inducers. Available at:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionLabeling/ucm093664.htm>

17. Lumacaftor/ivacaftor / Certain Antifungals v _____

Alert Message: Concurrent use of Orkambi (lumacaftor/ivacaftor) with the antifungal agent ketoconazole, itraconazole, voriconazole, or posaconazole may result in decreased antifungal exposure and therefore co-administration is not recommended. The antifungal agents are CYP3A4 substrates and the lumacaftor component of the combination product is a strong CYP3A4 inducer. If concomitant use is necessary, monitor for antifungal efficacy and adjust dose according to official manufacturer labeling. Consider an alternative antifungal such as fluconazole.

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

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Lumacaftor/ivacaftor	Ketoconazole	
	Itraconazole	
	Voriconazole	
	Posaconazole	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Orkambi Prescribing Information, Sept. 2016, Vertex Pharmaceuticals Inc.

18. Lumacaftor/ivacaftor / Digoxin

_____v_____

Alert Message: The concurrent use of Orkambi (lumacaftor/ivacaftor) with digoxin, a P-gp substrate, may result in altered digoxin exposure. Lumacaftor is both an inhibitor and inducer of P-gp efflux pumps and ivacaftor is a weak P-gp inhibitor. Monitor the serum concentration of digoxin and titrate the digoxin dose to obtain the desired clinical effect.

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

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Lumacaftor/ivacaftor	Digoxin	

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Orkambi Prescribing Information, Sept. 2016, Vertex Pharmaceuticals Inc.

19. Lumacaftor/ivacaftor / Sulfonylureas CYP2C9 Substrates

_____v_____

Alert Message: The concurrent use of Orkambi (lumacaftor/ivacaftor) with a sulfonylurea that is a CYP2C9 substrate may alter the substrate exposure. In vitro data suggest that the lumacaftor component of the combo agent may induce and/or inhibit CYP2C9-mediated metabolism. Dose adjustment of the sulfonylurea may be required to obtain the desired clinical effect.

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

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Lumacaftor/ivacaftor	Chlorpropamide Glimepiride Glipizide Glyburide Tolbutamide	

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Orkambi Prescribing Information, Sept. 2016, Vertex Pharmaceuticals Inc.

20. Lumacaftor/ivacaftor / Repaglinide

_____v_____

Alert Message: The concurrent use of Orkambi (lumacaftor/ivacaftor) with the CYP3A4 substrate repaglinide may result in reduced repaglinide exposure and effectiveness. The lumacaftor component of the combo product is a strong CYP3A4 inducer. Dose adjustment of repaglinide may be required to obtain the desired clinical effect.

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

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Lumacaftor/ivacaftor	Repaglinide	

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Orkambi Prescribing Information, Sept. 2016, Vertex Pharmaceuticals Inc.

21. Lumacaftor/ivacaftor / Warfarin

_____v_____

Alert Message: The concurrent use of Orkambi (lumacaftor/ivacaftor) with warfarin, a CYP2C9 substrate, may result in altered warfarin exposure. In vitro data suggest that lumacaftor/ivacaftor can induce and/or inhibit CYP2C9. Monitor the international normalized ratio (INR) when warfarin is co-administered with lumacaftor/ivacaftor.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Lumacaftor/ivacaftor	Warfarin	

References:

Clinical Pharmacology, 2016 Elsevier/Gold Standard.
Orkambi Prescribing Information, Sept. 2016, Vertex Pharmaceuticals Inc.

22. Lumacaftor/ivacaftor / CYP3A4 Substrate Steroids

_____v_____

Alert Message: The concurrent use of Orkambi (lumacaftor/ivacaftor) with a systemic corticosteroid that is a CYP3A4 substrate (e.g., prednisone, methylprednisolone, and dexamethasone) may result in reduced corticosteroid exposure and effectiveness. The lumacaftor component of the combo product is a strong CYP3A4 inducer. A higher dose of the systemic corticosteroid may be required to obtain the desired clinical effects.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Lumacaftor/ivacaftor	Prednisone Dexamethasone Methylprednisolone	

References:

Clinical Pharmacology, 2016 Elsevier/Gold Standard.
Orkambi Prescribing Information, Sept. 2016, Vertex Pharmaceuticals Inc.

23. Lumacaftor/ivacaftor / CYP3A4 Substrate Antibiotics

_____v_____

Alert Message: The concurrent use of Orkambi (lumacaftor/ivacaftor) with a macrolide that is a CYP3A4 substrate (e.g., clarithromycin, erythromycin, and telithromycin) may result in reduced antibiotic exposure and effectiveness. The lumacaftor component of the combo product is a strong CYP3A4 inducer. Consider an alternative to these antibiotics, such as ciprofloxacin or azithromycin.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Lumacaftor/ivacaftor	Clarithromycin Erythromycin Telithromycin	

References:

Clinical Pharmacology, 2016 Elsevier/Gold Standard.
Orkambi Prescribing Information, Sept. 2016, Vertex Pharmaceuticals Inc.

24. Lumacaftor/ivacaftor / Montelukast

___v___

Alert Message: The concurrent use of Orkambi (lumacaftor/ivacaftor) with montelukast may result in decreased montelukast exposure and efficacy. Montelukast is a substrate of CYP3A4, CYP2C8, and CYP2C9. The lumacaftor component of the combo product is a strong CYP3A4 inducer as well as an inducer of CYP2C8 and CYP2C9. Increased monitoring is recommended if these agents are administered concurrently.

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

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Lumacaftor/ivacaftor	Montelukast	

References:

Clinical Pharmacology, 2016 Elsevier/Gold Standard.
Orkambi Prescribing Information, Sept. 2016, Vertex Pharmaceuticals Inc.

25. Lumacaftor/ivacaftor / Nonadherence

___v___

Alert Message: Based on refill history, your patient may be under-utilizing Orkambi (lumacaftor/ivacaftor). 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

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Lumacaftor/ivacaftor		

References:

Orkambi Prescribing Information, Sept. 2016, Vertex Pharmaceuticals Inc.
Osterberg L, Blaschke T. Adherence to Medication. N Engl J Med 2005; 353:487- 497.
Eakin MN, Bilderback A, Boyle MP, Mogayzel PJ, Riekert KA. Longitudinal Association Between Medication Adherence and Lung Health in People with Cystic Fibrosis. J 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.

Criteria Recommendations

**Accepted Approved Rejected
As
Amended**

26. AirDuo Respiclick / Nonadherence

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Alert Message: Non-adherence with prescribed asthma therapy may significantly increase the risk of asthma exacerbations, emergency room visits, hospitalization, and asthma-related deaths. Always verify at each office visit that the patient understands their condition, the treatment plan, and the importance of adherence.

Conflict Code: LR - Nonadherence

Drugs/Diseases

Util A

Util B

Util C

Fluticasone/Salmeterol Inhalation Powder

References:

Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487-97.
Williams LK, Pladevall M, Xi Hy, et al., Relationship between Adherence to Inhaled Corticosteroids and Poor Outcomes Among Adults with Asthma. J Allerg Clin Immunol. December 2004;114(6):1288-1293.
Tan H, Sarawate C, Singer J et al., Impact of Asthma Controller Medications on Clinical, Economic, and Patient-Reported Outcomes. Mayo Clinic Proc. August 2009;84(8):675-684.

27. Calcifediol ER / Overutilization

 v

Alert Message: Rayaldee (calcifediol extended-release) may be over-utilized. The manufacturer's recommended maximum daily dose is 60 mcg once daily.

Conflict Code: ER - Overutilization

Drugs/Diseases

Util A

Util B

Util C

Calcifediol ER

Max Dose: 60 mcg/day

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Rayaldee Prescribing Information, March 2016, OPKO Pharmaceuticals, LLC.

28. Calcifediol ER / Strong CYP3A Inhibitors

___v___

Alert Message: The concurrent use of Rayaldee (calcifediol extended-release) with a CYP3A4 inhibitor may inhibit enzymes involved in vitamin D metabolism (CYP24A1 and CYP27B1) and may alter serum levels of calcifediol. Dose adjustment of calcifediol may be required, and serum 25-hydroxyvitamin D, intact PTH and calcium concentrations should be closely monitored if a patient initiates or discontinues therapy with a strong CYP3A4 inhibitor.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Calcifediol ER	Nefazodone	Saquinavir
	Ketoconazole	Ritonavir
	Itraconazole	Indinavir
	Voriconazole	Nelfinavir
	Posaconazole	Atazanavir
	Clarithromycin	Conivaptan
	Telithromycin	Idelalisib

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
 Rayaldee Prescribing Information, March 2016, OPKO Pharmaceuticals, LLC.
 Wang Z, Schuetz EG, Xu Y, Thummel KE. Interplay between Vitamin D and the Drug Metabolizing Enzyme CYP3A4. The Journal of Steroid Biochemistry and Molecular Biology. 2013;136;54-58. doi:10.1016/j.jsbmb.2012.09.012.

29. Calcifediol ER / Cholestyramine

___v___

Alert Message: The concurrent use of Rayaldee (calcifediol extended-release) with cholestyramine may result in reduced intestinal absorption of calcifediol. Dose adjustment of calcifediol may be required, and serum total 25-hydroxyvitamin D, intact PTH and serum calcium concentrations should be closely monitored if a patient initiates or discontinues therapy with cholestyramine.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Calcifediol ER	Cholestyramine	

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
 Rayaldee Prescribing Information, March 2016, OPKO Pharmaceuticals, LLC.

Criteria Recommendations

**Accepted Approved Rejected
As
Amended**

30. Calcifediol ER / Thiazide or Thiazide-like Diuretics

 v

Alert Message: The concurrent use of Rayaldee (calcifediol extended-release) with a thiazide or thiazide-like diuretic may cause hypercalcemia. These diuretics are known to induce hypercalcemia by reducing excretion of calcium in the urine. Patients may require more frequent serum calcium monitoring in this setting.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Calcifediol ER	Hydrochlorothiazide Chlorthalidone Chlorothiazide Methyclothiazide Bendroflumethiazide Indapamide Metolazone	

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.

Rayaldee Prescribing Information, March 2016, OPKO Pharmaceuticals, LLC.

31. Calcifediol ER / Agents that Stimulate Hydroxylation of Vitamin D

 v

Alert Message: The concurrent use of Rayaldee (calcifediol extended-release) with agents that stimulate microsomal hydroxylation may reduce the half-life of calcifediol. Dose adjustment of calcifediol may be required, and serum 25-hydroxyvitamin D, intact PTH and serum calcium concentrations should be closely monitored if a patient initiates or discontinues therapy with the stimulating agent.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Calcifediol ER	Barbiturates Anticonvulsants Rifampin	

References:

Micromedex 2.0 (Electronic version) Truven Health Analytics.

Rayaldee Prescribing Information, March 2016, OPKO Pharmaceuticals, LLC.

Gupta RP, Hollis BW, Patel SB, Patrick KS, Bell NH. CYP3A4 is a Human Microsomal Vitamin D 25-Hydroxylase. J Bone Miner. Rees 2004;19:680-688.

Wang Z, Schuetz EG, Xu Y, Thummel KE. Interplay between Vitamin D and the Drug Metabolizing Enzyme CYP3A4. The Journal Steroid Biochemistry and Molecular biology. 2013;136:54-58. doi:10.1016/j.jsbmb.2012.09.012.

32. Brodalumab / Therapeutic Appropriateness

 v _____ _____

Alert Message: Suicidal ideation and behavior, including 4 completed suicides, occurred in subjects treated with Siliq (brodalumab) in the psoriasis clinical trials. Advise patients and caregivers to seek medical attention for manifestations of suicidal ideation and behavior, new onset or worsening depression, anxiety, or other mood changes. Reevaluate the risks and benefits of continuing treatment with brodalumab if such events occur.

Conflict Code: TA - Therapeutic Appropriateness (Black Box Warning)

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C (Include)</u>
Brodalumab		Suicidal Ideation Depression Anxiety

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Siliq Prescribing Information, Feb. 2017, Valeant Pharmaceuticals North America, LLC.

33. Brodalumab / Crohn’s Disease

 v _____ _____

Alert Message: Siliq (brodalumab) is contraindicated in patients with Crohn's disease because brodalumab may cause worsening of the disease state. In clinical trials, which excluded subjects with active Crohn's disease, Crohn's occurred in one subject during treatment and lead to discontinuation of therapy. In other trials, exacerbation of Crohn's disease was observed with brodalumab use.

Conflict Code: TA - Therapeutic Appropriateness

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C (Include)</u>
Brodalumab		Crohn’s Disease

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Siliq Prescribing Information, Feb. 2017, Valeant Pharmaceuticals North America, LLC.

34. Brodalumab / Therapeutic Appropriateness (Pediatric)

 v _____ _____

Alert Message: The safety and effectiveness of Siliq (brodalumab) have not been evaluated in pediatric patients.

Conflict Code: TA - Therapeutic Appropriateness

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Brodalumab		

Age Range: 0 – 17 yoa

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Siliq Prescribing Information, Feb. 2017, Valeant Pharmaceuticals North America, LLC.

35. Brodalumab / Pregnancy / Pregnancy Negating

___v___

Alert Message: There is no human data on Siliq (brodalumab) use in pregnant women to inform a drug associated risk. Human IgG antibodies are known to cross the placental barrier; therefore, brodalumab may be transmitted from the mother to the developing fetus. Advise pregnant females of that the drug may cross placental barrier.

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

<u>Util A</u>	<u>Util B</u>	<u>Util C (Negating)</u>
Brodalumab	Pregnancy	Delivery Miscarriage Delivery

Gender: Female
Age Range: 11 – 55 yoa

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Siliq Prescribing Information, Feb. 2017, Valeant Pharmaceuticals North America, LLC.

36. Brodalumab / Lactation & Disorders of Lactation

___v___

Alert Message: There are no data on the presence of Siliq (brodalumab) in human milk, the effects on the breastfed infant, or the effects on milk production. Brodalumab was detected in the milk of lactating cynomolgus monkeys. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for brodalumab and any potential adverse effects on the breastfed infant from brodalumab or from the underlying maternal condition.

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

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Brodalumab	Lactation Disorder of Lactation	

Gender: Female
Age Range: 11 – 55 yoa

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Siliq Prescribing Information, Feb. 2017, Valeant Pharmaceuticals North America, LLC.

37. Telotristat / Overutilization

 v

Alert Message: Xermelo (telotristat ethyl) may be over-utilized. The manufacturer's recommended maximum daily dose of telotristat ethyl is 250 mg three times daily (total 750 mg per day). Exceeding the recommended daily dose may increase the incidence of adverse reactions without increasing benefit, and is not recommended.

Conflict Code: ER - Overutilization

Drugs/Diseases

Util A Util B Util C
Telotristat

Max Dose: 750 mg/day

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Xermelo Prescribing Information, Feb. 2017, Lexicon Pharmaceuticals, Inc.

38. Telotristat / Constipation

 v

Alert Message: Xermelo (telotristat ethyl) reduces bowel movement frequency. Patients receiving telotristat ethyl should be monitored for the development of constipation and/or severe, persistent, or worsening abdominal pain. Discontinue telotristat ethyl if severe constipation or severe persistent or worsening abdominal pain develops.

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

Drugs/Diseases

Util A Util B Util C
Telotristat Constipation

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Xermelo Prescribing Information, Feb. 2017, Lexicon Pharmaceuticals, Inc.

39. Telotristat / CYP3A4 Substrates

_____v_____

Alert Message: Concurrent use of Xermelo (telotristat) with a CYP3A4 substrate may result in decreased substrate systemic exposure and reduced efficacy. Monitor patient for suboptimal efficacy and consider dosage adjustment for the CYP3A4 substrate.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>		<u>Util C</u>
Telotristat	Midazolam	Hydrocodone	Amitriptyline
	Triazolam	Methadone	Trimipramine
	Alprazolam	Oxycodone	Dexamethasone
	Diazepam	Tramadol	Aprepitant
	Ketoconazole	Saquinavir	Alfuzosin
	Itraconazole	Ritonavir	Ondansetron
	Posaconazole	Indinavir	Cariprazine
	Voriconazole	Nelfinavir	Brexiprazole
	Fluconazole	Quetiapine	Pimavanserin
	Nefazodone	Bupirone	Darifenacin
	Aripiprazole	Lurasidone	Darunavir
	Trazodone	Haloperidol	Everolimus
	Pimozide	Vilazodone	Naloxegol
	Clarithromycin	Ticagrelor	Maraviroc
	Erythromycin	Rivaroxaban	Eletriptan
	Telithromycin	Fentanyl	Amiodarone
	Quinidine	Imatinib	
	Cyclosporine	Salmeterol	
	Tacrolimus	Carbamazepine	
	Sirolimus	Sildenafil	
	Amlodipine	Tadalafil	
	Diltiazem	Avanafil	
	Felodipine	Vardenafil	
	Nifedipine	Zolpidem	
	Nisoldipine	Atorvastatin	
	Verapamil	Cerivastatin	
	Propranolol	Lovastatin	
	Aliskiren	Simvastatin	
	Eplerenone	Estradiol	

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.

Xermelo Prescribing Information, Feb. 2017, Lexicon Pharmaceuticals, Inc.

FDA: Drug Development and Drug Interactions: Tables of Substrates, Inhibitors and Inducers. Available at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionLabeling/ucm093664.htm>

40. Codeine / CYP2D6 Inhibitors

___v___

Alert Message: Concurrent use of a codeine-containing agent with a CYP2D6 inhibitor may result in a decrease in the effects of codeine. Codeine must be bioactivated via CYP2D6 to morphine to exert an analgesic effect. Consider the use of an alternative analgesic for patients requiring therapy with an agent that is a CYP2D6 inhibitor.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Codeine	Fluoxetine Paroxetine Bupropion	Propafenone Quinidine Terbinafine

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Facts & Comparisons, 2017 Wolters Kluwer Health.

41. Bupropion / Digoxin

___v___

Alert Message: Concurrent use of bupropion with digoxin may result in decreased digoxin plasma levels. Patients treated concomitantly with bupropion and digoxin should have digoxin levels monitored during concurrent therapy. While the mechanism of interaction is not fully understood the induction, by bupropion, of digoxin OATPAC1-mediated transport in the kidney may play a role.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Bupropion	Digoxin	

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Facts & Comparisons, 2017 Wolters Kluwer Health.
He J, Yu Y, Prasad B, et al. Mechanism of Unusual, But Clinically Significant, Digoxin-Bupropion Drug Interaction. Biopharm Drug Dispos. 2014 Jul;35(5):253-63. doi:10.1002/bdd.1890. Epub 2014 Mar3.
Kirby BJ, Collier AC, Kharasch ER, et al. Complex Drug Interactions of the HIV Protease Inhibitors 3: Effect of Simultaneous or Staggered Dosing of Digoxin and Ritonavir, Nelfinavir, Rifampin, or Bupropion. Drug, Metab Dispos. 2012; Vol. 40:610-616. doi: 10.1224/dmd.111042705. Epub 2011 Dec. 21.

42. Dapagliflozin / Pregnancy / Pregnancy Negating

___v___

Alert Message: There are no adequate and well-controlled studies of Farxiga (dapagliflozin) in pregnant women. Based on results or reproductive and developmental toxicity studies in animals, dapagliflozin may affect renal development and maturation. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters.

Conflict Code: MC – Drug (Actual) Disease Precaution

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C (Negating)</u>
Dapagliflozin	Pregnancy	Delivery Abortion Miscarriage

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
 Blumer I, Hadar E, Hadden DR, et al. Diabetes and Pregnancy: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2013;98(11):4227-4249.
 American Diabetes Association (ADA). 13. Management of Diabetes in Pregnancy. In Standards of Medical Care in Diabetes - 2017. Diabetes Care. 2017c;40(Suppl. 1):S114-S119.

43. Dapagliflozin-Metformin ER / Pregnancy / Pregnancy Negating

___v___

Alert Message: There are no adequate and well-controlled studies of Xigduo XR (dapagliflozin/metformin extended-release) in pregnant women. Based on results of reproductive and developmental toxicity studies in animals, dapagliflozin may affect renal development and maturation. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters.

Conflict Code: MC – Drug (Actual) Disease Precaution

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C (Negating)</u>
Dapagliflozin/Metformin	Pregnancy	Delivery Abortion Miscarriage

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
 Blumer I, Hadar E, Hadden DR, et al. Diabetes and Pregnancy: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2013;98(11):4227-4249.
 American Diabetes Association (ADA). 13. Management of Diabetes in Pregnancy. In Standards of Medical Care in Diabetes - 2017. Diabetes Care. 2017c;40(Suppl. 1):S114-S119.

45. Empagliflozin / Pregnancy / Pregnancy Negating

___v___

Alert Message: Based on animal data showing adverse renal effects, Jardiance (empagliflozin) is not recommended during the second and third trimesters of pregnancy. Limited data available with empagliflozin in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters.

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

<u>Util A</u>	<u>Util B</u>	<u>Util C (Negating)</u>
Empagliflozin	Pregnancy	Delivery Abortion Miscarriage

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
 Blumer I, Hadar E, Hadden DR, et al. Diabetes and Pregnancy: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2013;98(11):4227-4249.
 American Diabetes Association (ADA). 13. Management of Diabetes in Pregnancy. In Standards of Medical Care in Diabetes - 2017. Diabetes Care. 2017c;40(Suppl. 1):S114-S119.

46. Empagliflozin-Metformin / Pregnancy / Pregnancy Negating

___v___

Alert Message: Based on animal data showing adverse renal effects, Synjardy (empagliflozin/metformin) is not recommended during the second and third trimesters of pregnancy. Limited available data with empagliflozin/metformin in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters.

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

<u>Util A</u>	<u>Util B</u>	<u>Util C (Negating)</u>
Empagliflozin/Metformin	Pregnancy	Delivery Abortion Miscarriage

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
 Blumer I, Hadar E, Hadden DR, et al. Diabetes and Pregnancy: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2013;98(11):4227-4249.
 American Diabetes Association (ADA). 13. Management of Diabetes in Pregnancy. In Standards of Medical Care in Diabetes - 2017. Diabetes Care. 2017c;40(Suppl. 1):S114-S119.

47. Empagliflozin-Metformin XR / Pregnancy / Pregnancy Negating

 v _____ _____

Alert Message: Based on animal data showing adverse renal effects, Synjardy XR (empagliflozin/metformin extended-release) is not recommended during the second and third trimesters of pregnancy. Limited available data with empagliflozin/metformin XR in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimester.

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

<u>Util A</u>	<u>Util B</u>	<u>Util C (Negating)</u>
Empagliflozin/Metformin XR	Pregnancy	Delivery Abortion Miscarriage

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
 Blumer I, Hadar E, Hadden DR, et al. Diabetes and Pregnancy: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2013;98(11):4227-4249.
 American Diabetes Association (ADA). 13. Management of Diabetes in Pregnancy. In Standards of Medical Care in Diabetes - 2017. Diabetes Care. 2017c;40(Suppl. 1):S114-S119.



Stephanie McGee Azar, Commissioner

Approve Deny

7-16-18
Date



Robert Moon, M.D., Deputy Commissioner
and Medical Director

Approve Deny

7-16-18
Date



Kathy Hall, Deputy Commissioner

Approve Deny

7/5/18
Date