

**Alabama Medicaid DUR Board Meeting Minutes**  
**April 27, 2016**

**Members Present:** : Kelli Littlejohn Newman, Melinda Rowe, Paula Thompson, Bernie Olin, Chris Phung, Marilyn Bulloch, Dan McConaghy, Donald Kern, Christopher Randolph

**Also Present:** Tiffany Minnifield, Heather Vega, Lori Thomas, Clemice Hurst, Kristin Marvin

**Present via Conference Call:** Kristian Testerman, Lauren Ward, Samir Hadid, Amy Donaldson, Michelle Stiles, Tammy Dubac

**Members Absent:** Sandra Parker, Richard Glaze, P.J. Hughes, Frank Pettyjohn, Robert Moon

**Call to Order:** The DUR meeting was called to order by P. Thompson at approximately 1:02p.m.

**Review and Adoption of Minutes:** The minutes of the January 27, 2016 meeting were presented and P. Thompson made a motion to update the 3<sup>rd</sup> Quarter Drug Analysis under the Cost Management Analysis section. D. Thornley-Brown 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 2015. She reported 10,138 total manual requests and 25,881 total electronic requests. From the Prior Authorization and Override Response Time Ratio report for October 2015, L. Thomas reported that approximately 44% of all manual PAs and 39% of all overrides were completed in less than two hours. Approximately 77-78% percent of all manual PAs and overrides were completed in less than four hours. Ninety-one percent of all manual PAs and overrides were completed in less than eight hours. For the month of November 2015, L. Thomas reported 8,853 manual PA requests and 22,711 electronic PA requests. She reported that 61% of all manual PAs and 55% of all overrides were completed in less than two hours. Eighty-six percent of all manual PAs and all overrides were completed in less than four hours. Ninety-three percent of all manual PAs and all overrides were completed in less than eight hours. For the month of December 2015, L. Thomas reported 9,792 manual PA requests and 22,102 electronic PA requests. L. Thomas reported that approximately 61% of all manual PAs and 55% of all overrides were completed in less than two hours. Eighty-three percent of all manual PA requests and all overrides were completed in less than four hours. Ninety-two percent of all manual PA requests and all overrides were completed in less than eight hours.

**Program Summary Review:** L.Thomas briefly reviewed the Alabama Medicaid Program Summary. She reported 3,933,131 total prescriptions, 219,103 average recipients per month using pharmacy benefits, and an average paid per prescription of \$95.34 for the months of July 2015 through December 2015.

**Cost Management Analysis:** L.Thomas reported an average cost per claim of \$99.06 for December 2015. From the 4<sup>th</sup> Quarter 2015 Drug Analysis, L.Thomas reported 79.1% generic utilization, 9.7% brand single-source, 7.45% brand multi-source (those requests which required a DAW override) and 3.71% OTC and "other". From the Top 25 Drugs Based on Number of Claims from 10/01/2015-12/31/2015, L.Thomas reported the top five drugs: amoxicillin, hydrocodone-acetaminophen, ProAir<sup>®</sup> HFA, cetirizine, and azithromycin. L. Thomas then reported the top five drugs from the Top 25 Drugs Based on Claims Cost from 10/01/2015-12/31/2015: Vyvanse<sup>®</sup>, Harvoni<sup>®</sup>, Focalin XR<sup>®</sup>, aripiprazole, and Invega<sup>®</sup> Sustenna<sup>®</sup>. 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, Miscellaneous Anticonvulsants, Respiratory and CNS Stimulants, and Respiratory Tract Corticosteroids.

**Hepatitis C Medication Management:** L. Thomas interviewed the top three dispensing pharmacies of Hepatitis C antiviral medications and presented an overview of the medication management programs of each pharmacy. K. Newman reminded the Board that the Health Homes were following up with the patients in their regions to obtain the sustained virologic response (SVR) rates.

**RDUR Intervention Report:** L. Thomas presented the RDUR Activity Report for October 2015. She reported 586 profiles reviewed and 1376 letters sent with 215 responses received as of the date of the report. She reported 110 of 167 physicians indicated that they found the RDUR letters “useful” or “extremely useful”. The criteria for the cycle of intervention letters included Drug-Disease Precaution (adverse fetal effects – valproic acid and divalproex sodium); Drug-Drug Interaction (duplicate antipsychotic therapy – Risperdal Consta and oral antipsychotics; paliperidone injection and oral antipsychotics); Drug-Drug Interaction (additive sedation – antidepressants and sedatives); Appropriate Use (concurrent use of buprenorphine and pure opiate agonists). L. Thomas then presented the RDUR Activity Report for November 2015. She reported 711 profiles reviewed and 711 letters sent with 117 responses received as of the date of the report. She reported 57 of 93 physicians indicated that they found the RDUR letters “useful” or “extremely useful”. The criteria for the cycle of intervention letters included Underuse Precaution (nonadherence to anticonvulsant therapy – carbamazepine, lamotrigine, lacosamide, levetiracetam, oxcarbazepine); Appropriate Use (concurrent use of buprenorphine and pure opiate agonists). The December 2015 Activity Report indicated 618 profiles reviewed and 606 letters sent with 71 responses received as of the date of the report. L. Thomas reported 35 of 56 physicians indicated that they found the RDUR letters “useful” or “extremely useful”. The criteria for the cycle of intervention letters were Drug-Drug Interactions (serotonin reuptake inhibitors and tricyclic antidepressants); Inferred Drug Disease Precaution (quinolone interaction – quinolones may cause CNS stimulation and worsen seizure disorder); 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 criteria, results from the criteria vote returned 38 approved, 2 approved as amended, and 2 rejected.

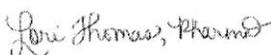
**Medicaid Update:** T. Minnifield reminded the Board members that all Medicaid information discussed is available online.

**P & T Committee Update:** C. Hurst began the P & T Update by informing the Board that the last meeting was held on February 10, 2016 and covered the skeletal muscle relaxants, opiate agonists, selective serotonin agonists, antiemetics, and proton-pump inhibitors. The next P & T meeting is scheduled for May 11, 2016 at 9a.m. and will cover the Alzheimer’s Agents; Antidepressants; Cerebral Stimulants for ADHD; Wakefulness Promoting Agents; Anxiolytics, Sedatives, and Hypnotics; Genitourinary Smooth Muscle Relaxants; and Disease-Modifying Antirheumatic Agents. C. Hurst also discussed the PDL changes that were effective April 1, 2016. C. Hurst mentioned that Nexium® and Relpax® would now be preferred.

**New Business:** K. Newman briefly reviewed the budget shortfall and the potential impact to Alabama Medicaid. P. Thompson notified the Board that the next DUR meeting will be held on July 27, 2016. The meeting was adjourned at 2:28 p.m.

**Next Meeting Date:** The next DUR Board meeting will be held on July 27, 2016.

Respectfully submitted,



Lori Thomas, Pharm

# ALABAMA MEDICAID RETROSPECTIVE DRUG UTILIZATION REVIEW CRITERIA RECOMMENDATIONS

**Criteria Recommendations**

*Accepted Approved Rejected  
As  
Amended*

**1. Sacubitril/Valsartan / Overutilization**

Alert Message: Entresto (sacubitril/valsartan) may be over-utilized. The manufacturer's recommended target maintenance dose of sacubitril/valsartan is 97/103 mg twice daily (total 194/206 mg daily).

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Conflict Code: ER - Overutilization

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
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Sacubitril/Valsartan

Max Dose: 194/206 mg per day

References:

Entresto Prescribing Information, July 2015, Novartis Pharmaceuticals Corporation.  
Clinical Pharmacology 2015 Elsevier/Gold Standard.

**2. Sacubitril/Valsartan / Severe Hepatic Impairment**

Alert Message: Entresto (sacubitril/valsartan) use is not recommended in patients with severe hepatic impairment (Child-Pugh Class C), as the product has not been studied in this patient population. A reduced starting dose of 24/26 mg twice daily is recommended in patients with moderate hepatic disease (Child-Pugh Class B); no dose adjustment is required in patients with mild hepatic impairment (Child-Pugh Class A).

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

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
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Sacubitril/Valsartan	Hepatic Impairment	
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References:

Entresto Prescribing Information, July 2015, Novartis Pharmaceuticals Corporation.  
Clinical Pharmacology 2015 Elsevier/Gold Standard.

**3. Sacubitril/Valsartan / ACE Inhibitors**

Alert Message: The concurrent use of Entresto (sacubitril/valsartan) with an ACE inhibitor is contraindicated due to the increased risk of angioedema. If switching from an ACE inhibitor to sacubitril/valsartan, or vice versa, allow a washout period of 36 hours between administration of the two drugs.

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Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
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Sacubitril/Valsartan	Captopril	Quinapril
	Enalapril	Perindopril
	Lisinopril	Trandolapril
	Ramipril	Moexipril
	Fosinopril	Benazepril

References:

Entresto Prescribing Information, July 2015, Novartis Pharmaceuticals Corporation.  
Clinical Pharmacology 2015 Elsevier/Gold Standard.

**Criteria Recommendations**

**Accepted Approved Rejected  
As  
Amended**

**4. Ledipasvir + Sofosbuvir / Overutilization**

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Alert Message: The recommended dose of Harvoni (ledipasvir/sofosbuvir) is one 90mg/400mg tablet taken once daily with or without food.

Conflict Code: ER - Overutilization  
Drugs/Diseases

Util A                      Util B                      Util C  
Ledipasvir/Sofosbuvir

Max Dose: 90mg/400mg per day

References:  
Harvoni Prescribing Information, March 2015, Gilead Science, Inc.  
Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**5. Ledipasvir + Sofosbuvir /Sofosbuvir**

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Alert Message: The concurrent use of Harvoni (ledipasvir/sofosbuvir) with other products containing sofosbuvir is not recommended.

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

Util A                      Util B                      Util C  
Ledipasvir/Sofosbuvir      Sofosbuvir

References:  
Harvoni Prescribing Information, March 2015, Gilead Science, Inc.  
Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**6. Ledipasvir + Sofosbuvir / Therapeutic Appropriateness < 18 yoa**

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Alert Message: Safety and effectiveness of Harvoni (ledipasvir/sofosbuvir) have not been established in pediatric patients.

Conflict Code: TA – Therapeutic Appropriateness  
Drugs/Diseases

Util A                      Util B                      Util C  
Ledipasvir/Sofosbuvir

Age Range: 0-17 yoa

References:  
Harvoni Prescribing Information, March 2015, Gilead Science, Inc.  
Clinical Pharmacology, 2015 Elsevier/Gold Standard.

## Criteria Recommendations

Accepted Approved Rejected  
As  
Amended

### 7. Ledipasvir + Sofosbuvir / P-gp Inducers

Alert Message: The concurrent use of Harvoni (ledipasvir/sofosbuvir) with a P-gp inducer is not recommended. Both ledipasvir and sofosbuvir are P-gp substrates and co-administration with a P-gp inducer may decrease ledipasvir and sofosbuvir plasma concentrations leading to reduced antiviral efficacy.

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Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

Util A

Ledipasvir/Sofosbuvir

Util B

Rifampin

Carbamazepine

Oxcarbazepine

Phenytoin

Phenobarbital

Primidone

Rifabutin

Rifapentine

Util C

References:

Harvoni Prescribing Information, March 2015, Gilead Science, Inc.

Clinical Pharmacology, 2015 Elsevier/Gold Standard.

### 8. Ledipasvir + Sofosbuvir / Tipranavir / Ritonavir

Alert Message: The concurrent use of Harvoni (ledipasvir/sofosbuvir) with ritonavir-boosted tipranavir is not recommended. Tipranavir is a P-gp inducer and co-administration with the P-gp substrates ledipasvir and sofosbuvir may result in decreased ledipasvir and sofosbuvir plasma concentrations leading to reduced antiviral efficacy.

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Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

Util A

Ledipasvir/Sofosbuvir

Util B

Tipranavir

Util C (Include)

Ritonavir

References:

Harvoni Prescribing Information, March 2015, Gilead Science, Inc.

Clinical Pharmacology, 2015 Elsevier/Gold Standard.

### 9. Ledipasvir + Sofosbuvir / Antacids

Alert Message: It is recommended to separate the administration of an antacid and Harvoni (ledipasvir/sofosbuvir) by 4 hours. The ledipasvir component of the combo product is pH dependent and drugs that increase gastric pH are expected to decrease ledipasvir solubility and therefore its bioavailability.

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Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

Util A

Ledipasvir/Sofosbuvir

Util B

Aluminum hydroxide

Magnesium hydroxide

Calcium carbonate

Sodium bicarbonate

Util C

References:

Harvoni Prescribing Information, March 2015, Gilead Science, Inc.

Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**Criteria Recommendations**

**Accepted Approved Rejected  
As  
Amended**

**10. Ledipasvir + Sofosbuvir / H2 Blockers**

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Alert Message: Caution should be exercised when using Harvoni (ledipasvir/sofosbuvir) with an H-2 receptor antagonist. These agents may be administered simultaneously or separated by 12 hours. The H-2 antagonist dose should not exceed a dose that is comparable to famotidine 40 mg twice daily. The ledipasvir component of the combo product is pH dependent and drugs that increase gastric pH are expected to decrease ledipasvir solubility and therefore its bioavailability.

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

<u>Util A</u>	<u>Util B</u>	<u>Util C (Include)</u>
Cimetidine > 1600mg/day		Ledipasvir/Sofosbuvir
Famotidine > 80mg/day		
Ranitidine > 600mg/day		
Nizatidine > 600mg/day		

References:

Harvoni Prescribing Information, March 2015, Gilead Science, Inc.  
Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**11. Ledipasvir + Sofosbuvir / Proton Pump Inhibitors**

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Alert Message: Caution should be exercised when using Harvoni (ledipasvir/sofosbuvir) with a proton pump inhibitor (PPI). A PPI may be administered simultaneously with ledipasvir/sofosbuvir under fasted conditions if the dose of the PPI does not exceed doses comparable to omeprazole 20 mg daily. The ledipasvir component of the combo product is pH dependent and drugs that increase gastric pH are expected to decrease ledipasvir solubility and therefore its bioavailability.

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

<u>Util A</u>	<u>Util B</u>	<u>Util C (Include)</u>
Omeprazole > 20mg/day		Ledipasvir/Sofosbuvir
Esomeprazole > 20mg/day		
Lansoprazole > 30mg/day		
Dexlansoprazole > 60mg/day		
Rabeprazole > 20mg/day		
Pantoprazole > 40mg/day		

References:

Harvoni Prescribing Information, March 2015, Gilead Science, Inc.  
Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**12. Ledipasvir + Sofosbuvir / Digoxin**

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Alert Message: The concurrent use of Harvoni (ledipasvir/sofosbuvir) with digoxin, a P-gp substrate, may result in an increase in the concentration of digoxin due to inhibition, by the ledipasvir component, of the P-gp efflux transporter system. Digoxin therapeutic concentration monitoring is recommended if the drugs are co-administered.

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

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Ledipasvir/Sofosbuvir	Digoxin	

References:

Harvoni Prescribing Information, March 2015, Gilead Science, Inc.  
Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**Criteria Recommendations**

**Accepted Approved Rejected  
As  
Amended**

**13. Ledipasvir + Sofosbuvir / Efavirenz/Emtricitabine/Tenofovir**

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Alert Message: The concurrent use of Harvoni (ledipasvir/sofosbuvir) with the fixed dose combination product Atripla (efavirenz/emtricitabine/tenofovir) may result in elevated tenofovir plasma concentrations due to the inhibition, by ledipasvir, of P-gp and BCRP transport of tenofovir. Patients should be monitored for tenofovir adverse effects.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

Util A

Ledipasvir/Sofosbuvir

Util B

Efavirenz/Emtricitabine/Tenofovir

Util C

References:

Harvoni Prescribing Information, March 2015, Gilead Science, Inc.

Clinical Pharmacology, 2015 Elsevier/Gold Standard

**14. Ledipasvir + Sofosbuvir / Elvitegravir/Cobicistat/Emtricitabine/Tenofovir**

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Alert Message: The concurrent use of Harvoni (ledipasvir/sofosbuvir) with the fixed dose combination product Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir) is not recommended. Coadministration of these agents may result in elevated tenofovir concentrations and tenofovir-associated adverse reactions due to the inhibition, by ledipasvir, of P-gp and BCRP transport of tenofovir.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

Util A

Ledipasvir/Sofosbuvir

Util B

Elvitegravir/Cobicistat/Emtricitabine/Tenofovir

Util C

References:

Harvoni Prescribing Information, March 2015, Gilead Science, Inc.

Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**15. Ledipasvir + Sofosbuvir / Simeprevir**

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Alert Message: The concurrent use of Harvoni (ledipasvir/sofosbuvir) with Olysio (simeprevir) is not recommended. Concentrations of ledipasvir and simeprevir are increased when simeprevir is co-administered with ledipasvir.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

Util A

Ledipasvir/Sofosbuvir

Util B

Simeprevir

Util C

References:

Harvoni Prescribing Information, March 2015, Gilead Science, Inc.

Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**Criteria Recommendations**

**Accepted Approved Rejected  
As  
Amended**

**16. Ledipasvir + Sofosbuvir / Rosuvastatin**

Alert Message: The concurrent use of Harvoni (ledipasvir/sofosbuvir) with Crestor (rosuvastatin) is not recommended. Coadministration of these agents may result in a significant increase in the concentration of rosuvastatin which is associated with increased risk of myopathy including rhabdomyolysis.

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

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Ledipasvir/Sofosbuvir	Rosuvastatin	

References:

Harvoni Prescribing Information, March 2015, Gilead Science, Inc.  
Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**17. Etravirine / Pitavastatin**

Alert Message: The concurrent use of Intelence (etravirine) and Livalo (pitavastatin) may result in increased plasma concentrations of pitavastatin due to inhibition, by etravirine, of pitavastatin CYP2C9-mediated metabolism. Dosage adjustment of pitavastatin may be necessary if coadministered with etravirine. No interaction is expected between etravirine and pravastatin or rosuvastatin.

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

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Etravirine	Pitavastatin	

References:

Intelence Prescribing Information, August 2014, Janssen Products, LP.

**18. Etravirine / Fosamprenavir / Ritonavir**

Alert Message: Intelence (etravirine) should not be co-administered with fosamprenavir (with or without ritonavir) because the combination may result in a significant increase in the plasma concentrations of fosamprenavir's active metabolite, amprenavir.

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

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Etravirine	Fosamprenavir	

References:

Intelence Prescribing Information, August 2014, Janssen Products, LP.

**19. NSAIDS / Cardiovascular Disease (Negating)**

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Alert Message: NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease. The risk can occur as early as the first weeks of using an NSAID. The risk may increase with longer use and with higher doses. Patients with higher risk at baseline have greater risk. Health care professionals and patients should remain alert for heart-related side effects the entire time NSAIDs are being taken.

Conflict Code: TA – Therapeutic Appropriateness

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C (Negating)</u>
NSAIDS		Stroke Myocardial Infarction Heart Failure Hypertension Conduction Disorders Edema

References:

Non-aspirin Nonsteroidal Antiinflammatory Drugs (NSAIDs): Drug Safety Communication – FDA Strengthens Warning of Increased Chance of Heart Attack or Stroke [07/09/2015]. Available at: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm454141.htm>  
Facts & Comparisons, 2015 Updates, Wolters Kluwer Health.  
Clinical Pharmacology, 2015 Elsevier/Gold Standard.

*\*Criteria already exists for warning with NSAIDS and patients with risk factors*

**20. ACE Inhibitors / MTOR Inhibitors**

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Alert Message: Concurrent use of an ACE Inhibitor and a MTOR (mammalian target of rapamycin) inhibitor may increase the risk of angioedema. Both ACEIs and MTOR inhibitors can cause angioedema and concomitant use may have a synergistic effect.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
ACE Inhibitors	Everolimus Temsirolimus Sirolimus	

References:

Facts & Comparisons, 2015 Updates, Wolters Kluwer Health.  
Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**Criteria Recommendations**

**Accepted Approved Rejected  
As  
Amended**

**21. Avanafil / Overuse**

Alert Message: Stendra (avanafil) may be over-utilized. The manufacturer’s maximum recommended dose is 200 mg daily.

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Conflict Code: ER - Overutilization

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C (Negating)</u>				
Avanafil		Ketoconazole	Itraconazole	Atazanavir	Fosamprenavir	Fluconazole
		Voriconazole	Posaconazole	Cobicistat	Imatinib	Aprepitant
		Nefazodone	Ritonavir	Clarithromycin	Diltiazem	Delavirdine
		Nelfinavir	Indinavir	Boceprevir	Verapamil	Phenobarbital
		Telithromycin	Saquinavir	Erythromycin	Ciprofloxacin	Primidone
		Phenytoin	Carbamazepine	Rifampin	Rifabutin	Rifapentine
		Efavirenz	Nevirapine	Etravirine	Bosentan	

Max Dose: 200 mg/day

References:

Stendra Prescribing Information, Jan. 2015, Vivus, Inc.  
Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**22. Avanafil / Strong CYP3A4 Inhibitors**

Alert Message: Concomitant use of Stendra (avanafil) with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, nefazodone) is not recommended. Coadministration of avanafil with ketoconazole has been shown to increase the avanafil AUC and Cmax by 13-fold and 3-fold, respectively, and prolong its half-life to 9 hours. Other potent CYP3A4 inhibitors would be expected to have similar effects.

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Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>		
Avanafil	Ketoconazole	Itraconazole	Atazanavir	
	Voriconazole	Posaconazole	Cobicistat	
	Nefazodone	Ritonavir	Clarithromycin	
	Nelfinavir	Indinavir	Boceprevir	
	Telithromycin	Saquinavir		

References:

Stendra Prescribing Information, Jan. 2015, Vivus, Inc.  
Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**23. Avanafil 100 & 200 mg / Moderate CYP3A4 Inhibitors**

Alert Message: For patients taking concomitant moderate CYP3A4 inhibitors, the maximum recommended dose of Stendra (avanafil) is 50 mg, not to exceed once every 24 hours. Avanafil is a CYP3A4 substrate and concurrent use with a moderate 3A4 inhibitor would be expected to increase avanafil Cmax, AUC, and half-life.

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Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>		
Avanafil 100 mg	Erythromycin	Fosamprenavir	Delavirdine	
Avanafil 200 mg	Diltiazem	Fluconazole		
	Verapamil	Aprepitant		
	Ciprofloxacin	Imatinib		

References:

Stendra Prescribing Information, Jan. 2015, Vivus, Inc.  
Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**Criteria Recommendations**

**Accepted Approved Rejected  
As  
Amended**

**24. Avanafil / CYP3A4 Inducers**

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Alert Message: The concurrent use of Stendra (avanafil) and CYP inducers has not been studied and is not recommended. Avanafil is primarily metabolized by CYP3A4 and use with a CYP3A4 inducer can be expected to decrease avanafil plasma levels.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Avanafil	Phenobarbital	Primidone
	Phenytoin	Efavirenz
	Carbamazepine	Nevirapine
	Rifampin	Etravirine
	Rifabutin	Bosentan
	Rifapentine	

References:

Stendra Prescribing Information, Jan. 2015, Vivus, Inc.  
Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**25. Avanafil / Cardiovascular Risk**

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Alert Message: Patients with pre-existing cardiovascular disease should be carefully evaluated before starting therapy with Stendra (avanafil). The use of avanafil is not recommended in the following groups: patients who have suffered a myocardial infarction, stroke, life-threatening arrhythmia, or coronary revascularization within the last 6 months; those with resting hypotension or hypertension; and patients with unstable angina, angina with sexual intercourse, or NYHA Class 2 or greater congestive heart failure.

Conflict Code: MC – Drug/Disease Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C (Include)</u>
Avanafil		Myocardial Infarction
		Arrhythmia
		Angina
		Stroke
		Heart Failure

References:

Stendra Prescribing Information, Jan. 2015, Vivus, Inc.  
Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**26. Avanafil / Alpha-1 Adrenergic Blockers**

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Alert Message: Caution should be exercised when Stendra (avanafil) is coadministered with an alpha-1 adrenergic blocker because symptomatic hypotension may occur due to additive vasodilation. When concomitant use is necessary, initiate avanafil at a dose of 50 mg, and initiate it only in patients stable on alpha blocker therapy. When initiating alpha blocker therapy in patients receiving avanafil, start the alpha blocker at the lowest dose.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Avanafil	Alfuzosin	Silodosin
	Doxazosin	Tamsulosin
	Prazosin	Terazosin

References:

Stendra Prescribing Information, Jan. 2015, Vivus, Inc.  
Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**Criteria Recommendations**

**Accepted Approved Rejected  
As  
Amended**

**27. Brexpiprazole / Overutilization- MDD**

\_\_\_\_\_  \_\_\_\_\_ \_\_\_\_\_

Alert Message: Rexulti (brexpiprazole) may be over-utilized. The manufacturer's recommended maximum daily dose of brexpiprazole for patients with major depressive disorder (MDD) is 3 mg once daily.

Conflict Code: ER - Overutilization

Drugs/Diseases

Util A

Util B

Util C (Include)

Brexpiprazole

Major Depressive Disorder

Max Dose: 3 mg/day

References:

Rexulti Prescribing Information, July 2015, Otsuka American Pharmaceutical, Inc.  
Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**28. Brexpiprazole / Overutilization - Schizophrenia**

\_\_\_\_\_  \_\_\_\_\_ \_\_\_\_\_

Alert Message: Rexulti (brexpiprazole) may be over-utilized. The manufacturer's recommended maximum daily dose of brexpiprazole for patients with schizophrenia is 4 mg once daily.

Conflict Code: ER - Overutilization

Drugs/Diseases

Util A

Util B

Util C (Include)

Brexpiprazole

Schizophrenia

Max Dose: 4 mg/day

References:

Rexulti Prescribing Information, July 2015, Otsuka American Pharmaceutical, Inc.  
Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**29. Brexpiprazole 3 mg & 4 mg / Overutilization – MDD Hepatic Imp.**

\_\_\_\_\_  \_\_\_\_\_ \_\_\_\_\_

Alert Message: Rexulti (brexpiprazole) may be over-utilized. The manufacturer's recommended maximum daily dose of brexpiprazole for patients with major depressive disorder (MDD) with moderate to severe hepatic impairment is 2 mg once daily.

Conflict Code: ER - Overutilization

Drugs/Diseases

Util A

Util B

Util C (Include)

Brexpiprazole 3 mg & 4 mg Hepatic Impairment

Major Depressive Disorder

Max Dose: 2 mg/day

References:

Rexulti Prescribing Information, July 2015, Otsuka American Pharmaceutical, Inc.  
Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**Criteria Recommendations**

**Accepted Approved Rejected**  
**As**  
**Amended**

**30. Brexpiprazole 4 mg / Overutilization – Schizophrenia Hepatic Imp.**

\_\_\_√\_\_\_ \_\_\_ \_\_\_

Alert Message: Rexulti (brexpiprazole) may be over-utilized. The manufacturer’s recommended maximum daily dose of brexpiprazole for patients with schizophrenia with moderate to severe hepatic impairment is 3 mg once daily.

Conflict Code: ER - Overutilization

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C (Include)</u>
Brexpiprazole 4mg	Hepatic Impairment	Schizophrenia

Max Dose: 3 mg/day

References:

Rexulti Prescribing Information, July 2015, Otsuka American Pharmaceutical, Inc. Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**31. Brexpiprazole 3 mg & 4 mg / Overutilization – MDD Renal Imp. & ESRD**

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Alert Message: Rexulti (brexpiprazole) may be over-utilized. The manufacturer’s recommended maximum daily dose of brexpiprazole for patients with major depressive disorder with moderate, severe, or end-stage renal impairment is 2 mg once daily.

Conflict Code: ER - Overutilization

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C (Include)</u>
Brexpiprazole 3 mg & 4 mg	CKD Stage 3, 4 & 5 ESRD	Major Depressive Disorder

Max Dose: 2 mg/day

References:

Rexulti Prescribing Information, July 2015, Otsuka American Pharmaceutical, Inc. Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**32. Brexpiprazole 4 mg / Overutilization – Schizophrenia Renal Imp & ESRD**

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Alert Message: Rexulti (brexpiprazole) may be over-utilized. The manufacturer’s recommended maximum daily dose of brexpiprazole for patients with schizophrenia with moderate, severe, or end-stage renal impairment is 3 mg once daily.

Conflict Code: ER - Overutilization

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C (Include)</u>
Brexpiprazole 4 mg	CKD Stage 3, 4 & 5 ESRD	Schizophrenia

Max Dose: 3 mg/day

References:

Rexulti Prescribing Information, July 2015, Otsuka American Pharmaceutical, Inc. Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**Criteria Recommendations**

**Accepted Approved Rejected  
As  
Amended**

**33. Brexpiprazole / Therapeutic Appropriateness**

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

Conflict Code: TA – Therapeutic Appropriateness

Drugs/Diseases

Util A

Util B

Util C

Brexpiprazole

Age Range: 0-18 yoa

References:

Rexulti Prescribing Information, July 2015, Otsuka American Pharmaceutical, Inc. Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**34. Brexpiprazole / Cardio & Cerebrovascular Disease**

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Alert Message: Rexulti (brexpiprazole) should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions which would predispose patients to hypotension (e.g., dehydration, hypovolemia, treatment with antihypertensives). Brexpiprazole has been shown to cause orthostatic hypotension and these patients may be at increased risk.

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

Drugs/Diseases

Util A

Util B

Util C

Brexpiprazole

Heart Failure

Myocardial Infarction

Coronary Artery Disease

Ischemia

Conduction Abnormalities

Dehydration

Hypovolemia

References:

Rexulti Prescribing Information, July 2015, Otsuka American Pharmaceutical, Inc. Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**35. Brexpiprazole / Seizures**

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Alert Message: Rexulti (brexpiprazole) should be used with caution in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Conflict Code: TA - Therapeutic Appropriateness

Drugs/Diseases

Util A

Util B

Util C (Include)

Brexpiprazole

Seizures

References:

Rexulti Prescribing Information, July 2015, Otsuka American Pharmaceutical, Inc. Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**Criteria Recommendations**

**Accepted Approved Rejected  
As  
Amended**

**36. Brexpiprazole / Antihypertensive Medications**

Alert Message: Rexulti (brexpiprazole) should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions which would predispose patients to hypotension (e.g., dehydration, hypovolemia, treatment with antihypertensives). Brexpiprazole has been shown to cause orthostatic hypotension and these patients may be at increased risk.

\_\_\_\_√\_\_\_\_

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Brexpiprazole	Antihypertensives ACEIs ARBs CCBs B-Blockers α-Blockers Direct Renin Inhibitors Selective Aldosterone Antagonist Diuretics Centrally-Acting Adrenergics Peripherally-Acting Adrenergics	

References:

Rexulti Prescribing Information, July 2015, Otsuka American Pharmaceutical, Inc.  
Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**37. Brexpiprazole / Strong CYP3A4 Inhibitors**

Alert Message: Concurrent use of Rexulti (brexpiprazole) with a strong CYP3A4 inhibitor may result in increased brexpiprazole exposure due to inhibition of brexpiprazole CYP3A4-mediated metabolism. Dosage reduction to half the usual brexpiprazole dose is recommended. If the strong CYP3A4 inhibitor is discontinued, adjust brexpiprazole dosage to its original level.

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Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C</u>
Brexpiprazole	Nefazodone Clarithromycin Telithromycin Saquinavir Ritonavir Indinavir Nelfinavir	Cobicistat Boceprevir Ketoconazole Itraconazole Posaconazole Voriconazole

References:

Rexulti Prescribing Information, July 2015, Otsuka American Pharmaceutical, Inc.  
Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**Criteria Recommendations**

**Accepted Approved Rejected  
As  
Amended**

**38. Brexpiprazole / Strong CYP2D6 Inhibitors**

Alert Message: Concurrent use of Rexulti (brexpiprazole) with a strong CYP2D6 inhibitor may result in increased brexpiprazole exposure due to inhibition of brexpiprazole CYP2D6-mediated metabolism. Dosage reduction to half the usual brexpiprazole dose is recommended. If the strong CYP3A4 inhibitor is discontinued, adjust brexpiprazole dosage to its original level. Dosage adjustment is not required if brexpiprazole is used as adjunctive treatment of MDD with the strong 2D6 inhibitors, paroxetine or fluoxetine.

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Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C (Negate)</u>
Brexpiprazole	Paroxetine Fluoxetine Quinidine Bupropion	Major Depressive Disorder

References:

Rexulti Prescribing Information, July 2015, Otsuka American Pharmaceutical, Inc.  
Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**39. Brexpiprazole / Strong or Mod 3A4 Inh / Strong or Mod 2D6 Inh**

Alert Message: Concurrent use of Rexulti (brexpiprazole) with a strong or moderate CYP3A4 inhibitor plus a strong or moderate CYP2D6 inhibitor may result in increased brexpiprazole exposure due to inhibition of brexpiprazole CYP3A4- and CYP2D6-mediated metabolism. Dosage reduction to a quarter of the usual brexpiprazole dose is recommended. If the coadministered inhibitors are discontinued, adjust the brexpiprazole dosage to its original level.

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Conflict Code: TA – Therapeutic Appropriateness

Drugs/Diseases

<u>Util A</u>	<u>Util B</u>	<u>Util C (Include)</u>
Brexpiprazole	Nefazodone Clarithromycin Telithromycin Saquinavir Ritonavir Indinavir Nelfinavir Cobicistat Boceprevir Ketoconazole Itraconazole Posaconazole Voriconazole Fluconazole Aprepitant Atazanavir Fosamprenavir Ciprofloxacin Diltiazem Verapamil Erythromycin Imatinib	Bupropion Fluoxetine Paroxetine Quinidine Cinacalcet Terbinafine

References:

Rexulti Prescribing Information, July 2015, Otsuka American Pharmaceutical, Inc.  
Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**Criteria Recommendations**

**Accepted Approved Rejected  
As  
Amended**

**40. Brexpiprazole / Strong CYP3A4 Inducers**

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Alert Message: Concurrent use of Rexulti (brexpiprazole) with a strong CYP3A4 inducer may result in decreased brexpiprazole exposure due to induction of brexpiprazole CYP3A4-mediated metabolism. Dosage adjustment is recommended to double the usual brexpiprazole dose over 1 to 2 weeks. If the inducer is discontinued, reduce the brexpiprazole dose to the original level over 1 to 2 weeks.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

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

References:

Rexulti Prescribing Information, July 2015, Otsuka American Pharmaceutical, Inc. Clinical Pharmacology, 2015 Elsevier/Gold Standard.

**41. Brexpiprazole / Non-Adherence**

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Alert Message: Based on refill history, your patient may be under-utilizing Rexulti (brexpiprazole). 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 – Non-adherence

Drugs/Diseases

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

References:

Rexulti Prescribing Information, July 2015, Otsuka American Pharmaceutical, Inc.

Theida P, et.al., An Economic Review of Compliance with Medication Therapy in the Treatment of Schizophrenia, Psychiatric Services, 2003;54:508-516.

Acsher-Svanum H, Zhu B, Faries DE, et al., The Cost of Relapse and the Predictors of Relapse in the Treatment of Schizophrenia. BMC Psychiatry 2010, 10:2.

Berger A, Edelsbery J, Sanders KN, et al., Medication Adherence and Utilization in Patients with Schizophrenia or Bipolar Disorder Receiving Aripiprazole, Quetiapine, or Ziprasidone at Hospital Discharge: A Retrospective Cohort Study. BMC Psychiatry 2012,12:99.

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.

Morken G, Widen JH, Grawe RW. Non-adherence to Antipsychotic Medication, Relapse and Rehospitalisation in Recent-Onset Schizophrenia. BMC Psychiatry. 2008, 8:32.

**Criteria Recommendations**

**Accepted Approved Rejected  
As  
Amended**

**42. Naloxegol / Therapeutic Appropriateness**

Alert Message: The review did not reveal current use of opioid medication.  
Movantik (naloxegol) is approved for the treatment of opioid-induced constipation.  
Naloxegol should be discontinued if treatment with the opioid pain medication is discontinued.

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Conflict Code: TA – Therapeutic Appropriateness  
Drugs/Diseases

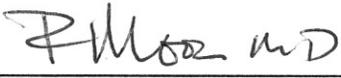
<u>Util A</u>	<u>Util B</u>	<u>Util C (Negating)</u>
Naloxegol		Opioids

References:  
Movantik Prescribing Information, Sept. 2014, AstraZeneca.  
Clinical Pharmacology, 2016, Elsevier/Gold Standard.  
Facts& Comparisons, 2016 Updates, Wolters Kluwer Health.

  
Stephanie McGee Azar, Commissioner

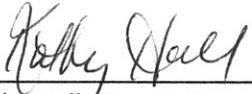
Approve ( ) Deny

6-15-16  
Date

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

Approve ( ) Deny

6-14-16  
Date

  
Kathy Hall, Deputy Commissioner

Approve ( ) Deny

6/10/16  
Date