Alabama Medicaid DUR Board Meeting Minutes
January 23, 2019

Members Present: Kelli Littlejohn Newman, Rachel Seaman, Bernie Olin, Denyse Thornley-Brown, Robert Moon, Mary Stallworth, Jessica Jackson, Dan McConaghy, Chris Phung

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

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

Members Absent: Paula Thompson, Kenny Murray

Call to Order: The DUR meeting was called to order by D. Thornley-Brown at approximately 1:05p.m.

Review and Adoption of Minutes: The minutes of the October 24, 2018 meeting were presented and R. Seaman made a motion to approve the minutes. C. Phung 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 July 2018. She reported 11,693 total manual requests and 22,938 total electronic requests. From the Prior Authorization and Override Response Time Ratio report for July 2018, L. Thomas reported that approximately 63% of all manual PAs and 60% of all overrides were completed in less than two hours. Eighty-seven percent of all manual PAs and 85% of 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 August 2018, L. Thomas reported 12,608 manual PA requests and 24,189 electronic PA requests were received. She reported that 62% of all manual PAs and 61% 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 September 2018, L. Thomas reported 10,858 manual PA requests and 19,629 electronic PA requests. L. Thomas reported that approximately 54% of all manual PAs and 47% of all overrides were completed in less than two hours. Eighty-one percent of all manual PA requests and 79% of all overrides were completed in less than four hours. Ninety-one percent of all manual PA requests and 89% 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 April 2018 through September 2018. She reported 3,505,541 total prescriptions, 210,098 average recipients per month using pharmacy benefits, and an average paid per prescription of $111.87.

Cost Management Analysis: L.Thomas reported an average cost per claim of $115.22 for June 2018 and emphasized that the table contained the average cost per claim over the past two years. From the 3rd Quarter 2018 Drug Analysis, L.Thomas reported 79% generic utilization, 9% brand single-source, 8% 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 07/01/2018 – 09/30/2018, L.Thomas reported the top five drugs: amoxicillin, cetirizine, ProAir® HFA, hydrocodone-acetaminophen, and montelukast sodium. L. Thomas then reported the top five drugs from the Top 25 Drugs Based on Claims Cost from 07/01/2018 – 09/30/2018: Vyvanse®, Focalin XR®, Invega® Sustenna®, Concerta®, and ProAir® HFA. She reminded the Board that Vyvanse® and Focalin XR® are preferred agents and that this list was very similar to the top 5 last quarter. 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.

Opioid Prescribing/Pharmacy Trends: K. Newman began the presentation with a brief overview of prescription opioid use in the State of Alabama and among Alabama Medicaid recipients. She discussed the average days' supply of opioid claims broken out by age group for Alabama Medicaid members in 2016: children (0-12years), teenagers (13-18 years), and adults (19-64 years). She also presented a comparison of opioid pharmacy claims for November and December 2017 with November and December 2018. K. Newman also reviewed the Short-Acting Opioid Naïve Limit edit that began on November 1, 2018. She presented a comparison of opioid pharmacy claims with a days' supply of one to seven days for November and December 2017 with November and December 2018. She then compared opioid pharmacy claims with a days' supply of eight to 34 days for November and December 2017 with November and December 2018. Short-Acting Opioid Naïve Overrides for the months of November 2018 and December 2018 were also reviewed. In closing, K. Newman briefly described upcoming Morphine Milligram Equivalent (MME) Edits that AL Medicaid will be phasing in.

RDUR Intervention Report: L. Thomas presented the RDUR Activity Report for October 2018. She reported 545 profiles reviewed and 463 letters sent with 20 responses received as of the date of the report. She reported 13 of 21 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); Appropriate Use (risk versus benefits of opioids versus non-opioid analgesics); Appropriate Use (concurrent use of buprenorphine and pure opiate agonists).

Proposed Criteria: L.Thomas presented the proposed set of 35 criteria to the Board. T. Minnifield instructed the Board members to mark their ballots. Of the 35 proposed criteria, results from the criteria vote returned 35 approved.

Medicaid Update: T. Minnifield reminded the Board members that all updated Medicaid drug lists and the Short-Acting Opioid Naïve Limit ALERT were provided to them electronically and is also available online. T. Minnifield also reminded the Board members that the next DUR Meeting would be April 23, 2019.

P & T Committee Update: C. Hurst began the P & T Update by informing the Board that the last meeting was held on November 7, 2018 and covered the Skin and Mucous Membrane Agents. C. Hurst also informed the Board that the P & T Committee voted for Xofluza to become preferred prior to January 1, 2019, and Eucrisa became preferred with clinical criteria effective January 1, 2019. The next P & T Committee meeting will be held on February 6, 2019 and will cover the Anti-infective agents and a review of the Growth Hormone Agents.

Next Meeting Date: D. Thornley-Brown reminded the Board that the next DUR meeting will be held on April 23, 2019. A motion to adjourn the meeting was made by R. Seaman. B. Olin seconded the motion and the meeting was adjourned at 2:27 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. Biktarvy / Overutilization	___√____	_____	_____

Alert Message: The manufacturer's recommended dose of Biktarvy (bictegravir/ emtricitabine/tenofovir alafenamide) is one tablet once daily.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Bictegravir/Emtricitabine/Tenofovir alafenamide		

Max Dose: 1 tablet/day

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Biktarvy Prescribing Information, Feb. 2018, Gilead Sciences, Inc.

2. Biktarvy / All Other Antiretrovirals	___√____	_____	_____

Alert Message: The patient appears to be receiving other antiretroviral therapy in addition to Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide). Biktarvy is a complete regimen for the treatment of HIV-1 infections and should not be administered with other antiretroviral medications.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Bictegravir/Emtricitabine/Tenofovir alafenamide	Cellular Chemokine Receptor (CCR5) Antagonist	
	Fusion Inhibitors	
	Integrase Inhibitors	
	NNRTIs	
	NRTIs	
	Nucleotide Analog Reverse Transcriptase Inhibitors	
	Protease Inhibitors	
	Antiretroviral Combos	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Biktarvy Prescribing Information, Feb. 2018, Gilead Sciences, Inc.

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

3. Biktarvy / Severe Renal Impairment _____ ___V____ _____

Alert Message: Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) use is not recommended in patients with estimated creatinine clearance below 30 mL per minute, (estimated by Cockcroft-Gault (C-G)). No dosage adjustment of bictegravir/emtricitabine/tenofovir alafenamide is recommended in patients with CrCl greater than or equal to 30 mL per minute.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Bictegravir/Emtricitabine/Tenofovir alafenamide		CKD 4 CKD 5 ESRD

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Biktarvy Prescribing Information, Feb. 2018, Gilead Sciences, Inc.

4. Biktarvy / Hepatic Impairment ___V____ _____ _____

Alert Message: Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and therefore, it is not recommended for use in this patient population. No dosage adjustment of bictegravir/emtricitabine/tenofovir alafenamide is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Bictegravir/Emtricitabine/Tenofovir alafenamide		Cirrhosis Hepatic Fibrosis

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Biktarvy Prescribing Information, Feb. 2018, Gilead Sciences, Inc.

5. Biktarvy / Dofetilide ___V____ _____ _____

Alert Message: The concurrent use of Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) with dofetilide is contraindicated due to the risk of dofetilide-related serious and/or life-threatening events. The bictegravir component of the antiretroviral is an inhibitor of renal organic cation transporter (OCT2) and multidrug and toxin extrusion transporter (MATE1) which are responsible for dofetilide elimination and co-administration of these agents may result in increased dofetilide plasma concentrations.

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

Util A	Util B	Util C
Bictegravir/Emtricitabine/Tenofovir alafenamide	Dofetilide	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.

Biktarvy Prescribing Information, Feb. 2018, Gilead Sciences, Inc.

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

6. Biktarvy / Rifampin ___√____ _____ _____

Alert Message: The concurrent use of Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) with rifampin is contraindicated due to the risk for the loss of therapeutic efficacy and development of resistance to bictegravir/emtricitabine/tenofovir alafenamide. The bictegravir component of the antiretroviral is a CYP3A4 substrate and UGT1A1 substrate and rifampin is a strong inducer of both CYP3A4 and UGT1A1. Co-administration of these agents may lead to substantially decreased bictegravir plasma concentrations.

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

Util A	Util B	Util C
Bictegravir/Emtricitabine/Tenofovir alafenamide	Rifampin	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Biktarvy Prescribing Information, Feb. 2018, Gilead Sciences, Inc.

7. Biktarvy / P-gp & BCRP Inhibitors ___√____ _____ _____

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

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

Util A	Util B	Util C
Bictegravir/Emtricitabine/Tenofovir alafenamide	Amiodarone Cobicistat Cyclosporine Glecaprevir/Pibrentasvir Ledipasvir/Sofosbuvir Osimertinib Regorafenib Rolapitant Simeprevir Tedizolid Velpatasvir Vemurafenib	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Biktarvy Prescribing Information, Feb. 2018, Gilead Sciences, Inc.

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

8. Biktarvy / Anticonvulsants CYP3A4 Inducers ___√___ _____ _____

Alert Message: Concurrent use of Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) with anticonvulsants that induce CYP3A4 may cause a decrease in the plasma concentrations of the bictegravir and tenofovir alafenamide components (both CYP3A4 substrates) of the antiretroviral. Decreased plasma concentrations of the antiretrovirals may lead to loss of antiretroviral therapeutic effect and development of resistance. Alternative anticonvulsants should be considered.

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

Util A	Util B	Util C
Bictegravir/Emtricitabine/Tenofovir alafenamide	Carbamazepine Oxcarbazepine Phenobarbital Primidone Phenytoin	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Biktarvy Prescribing Information, Feb. 2018, Gilead Sciences, Inc.

9. Biktarvy / Rifabutin & Rifapentine ___√___ _____ _____

Alert Message: Concurrent use of Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) with rifabutin or rifapentine is not recommended. The bictegravir component of the combination antiretroviral is a CYP3A4 substrate and induction of its CYP3A4 metabolism by rifabutin or rifapentine may result in decreased plasma concentrations of the antiretroviral and may lead to loss of antiretroviral therapeutic effect and development of resistance.

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

Util A	Util B	Util C
Bictegravir/Emtricitabine/Tenofovir alafenamide	Rifabutin Rifapentine	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Biktarvy Prescribing Information, Feb. 2018, Gilead Sciences, Inc.

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

10. Biktarvy / Al & Mg & Ca Antacids ___V_____ _____ _____

Alert Message: Caution should be exercised when Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) is prescribed concomitantly with antacids containing the polyvalent cations aluminum, magnesium, or calcium as the bioavailability of the bictegravir component of the antiretroviral may be decreased. Bictegravir/emtricitabine/tenofovir alafenamide) can be taken under fasting conditions 2 hours before these antacids. Routine administration of bictegravir/emtricitabine/tenofovir alafenamide with, or 2 hours after, these antacids are not recommended.

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

Util A	Util B	Util C
Bictegravir/Emtricitabine/Tenofovir alafenamide	Aluminum Hydroxide	
	Magnesium Hydroxide	
	Calcium Carbonate Antacid	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Biktarvy Prescribing Information, Feb. 2018, Gilead Sciences, Inc.

11. Biktarvy / Calcium & Iron Supplements ___V_____ _____ _____

Alert Message: Caution should be exercised when Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) is prescribed concomitantly with supplements containing polyvalent calcium (Ca) or iron (Fe) as the bioavailability of the bictegravir component of the antiretroviral may be decreased. Bictegravir/emtricitabine/tenofovir alafenamide and Ca or Fe supplements can be taken together with food. Routine administration of bictegravir/emtricitabine/tenofovir alafenamide under fasting conditions simultaneously with, or 2 hours after, these supplements are not recommended.

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

Util A	Util B	Util C
Bictegravir/Emtricitabine/Tenofovir alafenamide	Calcium Carbonate Supplements	
	Calcium Citrate	
	Calcium Gluconate	
	Calcium Lactate	
	Iron Supplements	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Biktarvy Prescribing Information, Feb. 2018, Gilead Sciences, Inc.

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

12. Biktarvy / Metformin ___V___ _____ _____

Alert Message: Concurrent use of Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) with metformin may result in reduced metformin clearance and increased risk of metformin-related adverse effects (i.e., hypoglycemia and lactic acidosis). Metformin undergoes renal elimination via organic cation transporter 2 (OCT2) and multidrug and toxin extrusion (MATE1) transport and the bictegravir component of the antiretroviral is an OCT2 and MATE1 inhibitor. Consider the benefits and risks of concomitant use.

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

Util A	Util B	Util C
Bictegravir/Emtricitabine/Tenofovir alafenamide	Metformin	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Biktarvy Prescribing Information, Feb. 2018, Gilead Sciences, Inc.

13. Biktarvy / Nonadherence ___V___ _____ _____

Alert Message: Nonadherence to antiretroviral therapy may result in insufficient plasma levels and partial suppression of viral load leading to the development of Resistance, HIV progression, and increased mortality.

Conflict Code: LR - Nonadherence
Drugs/Diseases

Util A	Util B	Util C
Bictegravir/Emtricitabine/Tenofovir alafenamide		

References:
Osterberg L, Blaschke T. Adherence to Medication. N Engl J Med 2005; 353:487- 497.
Beer L, Heffelfinger J, Frazier E, et al. Use of and Adherence to Antiretroviral Therapy in a Large U.S. Sample of HIV-Infected Adults in Care, 2007-2008. Open AIDS J.2012;6:213-223.
Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents. Department of Health and Human Services. October 17, 2017. Available at: http://www.aidsinfo.nih.gov/contentfiles/adultandadolescentgl.pdf.
Panel on Antiretroviral Therapy and Medical Management of HIV-Infected\Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. April 27, 2017. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf

14. Biktarvy / Therapeutic Appropriateness ___V___ _____ _____

Alert Message: Safety and effectiveness of Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) in pediatric patients less than 18 years of age have not been established.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Bictegravir/Emtricitabine/Tenofovir alafenamide		

Age Range 0 -17 yoa

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.

Biktarvy Prescribing Information, Feb. 2018, Gilead Sciences, Inc.

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

15. Pregabalin / Therapeutic Appropriateness ____V____ _____ _____

Alert Message: Pregabalin may have the potential for misuse and abuse. Patients should be evaluated carefully for a history of drug abuse and observed closely for signs of misuse or abuse of pregabalin (e.g., development of tolerance, self-dose escalation, and drug-seeking behavior).

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Pregabalin	History of Substance Abuse	
	Opioids	
	Sedative Hypnotics	
	Anxiolytics	
	Skeletal Muscle Relaxants	
	Stimulants	

References:

Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Facts & Comparisons, 2018 Updates, Wolters Kluwer Health.
Lyrica Prescribing Information, December 2016, Pfizer, Inc.
Lyrica CR Prescribing Information, October 2017, Pfizer, Inc.
Schifano F. Misuse and Abuse of Pregabalin and Gabapentin: Cause for Concern? CNS Drugs (2014) 28:490-496.
Filipetto FA, Zipp, CP, Coren JS. Potential for Pregabalin Abuse or Diversion after Past Drug-Seeking Behavior. J Am Osteopath Assoc. 2010; 110(10);605-607.

16. Gabapentin / Therapeutic Appropriateness ___V____ _____ _____

Alert Message: Gabapentin may have the potential for misuse and abuse. Patients should be evaluated carefully for a history of drug abuse and observed closely for signs of misuse or abuse of gabapentin (e.g., development of tolerance, self-dose escalation, and drug-seeking behavior).

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Gabapentin	History of Substance Abuse	
	Opioids	
	Sedative Hypnotics	
	Anxiolytics	
	Skeletal Muscle Relaxants	
	Stimulants	

References:

Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Neurontin Prescribing Information, October 2017, Pfizer, Inc.
Schifano F. Misuse and Abuse of Pregabalin and Gabapentin: Cause for Concern? CNS Drugs (2014) 28:490-496.
Smith RV, Havens JR, Walsh SL. Gabapentin Misuse, Abuse, and Diversion: A Systemic Review. Addiction. 2016 Jul; 111(7):1160-1174.
Quintero, GC. Review of Gabapentin Misuse, Interaction, Contraindications and Side Effects. J Exp Pharmcol. 2017 9; 9 13-21

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

17. Opiates / Skeletal Muscle Relaxants / Sedatives ___V___ _____ _____

Alert Message: The triple drug combination involving an opioid agonist, a skeletal muscle relaxant (particularly carisoprodol), and a benzodiazepine can cause a heroin-like euphoria as well as lethal CNS depression. This poly drug combo is often sought for illicit use and diversion. Use extreme caution when prescribing this drug combination especially in patients with a history of drug abuse/dependence.

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

Util A	Util B	Util C
Morphine	Baclofen	Alprazolam
Meperidine	Carisoprodol	Chlordiazepoxide
Methadone	Chlorzoxazone	Clobazam
Codeine	Cyclobenzaprine	Clonazepam
Fentanyl	Metaxalone	Clorazepate
Hydrocodone	Methocarbamol	Diazepam
Hydromorphone	Orphenadrine	Estazolam
Levorphanol	Tizanidine	Flurazepam
Oxycodone	Dantrolene	Lorazepam
Oxymorphone		Oxazepam
Tapentadol		Quazepam
Tramadol		Temazepam
		Triazolam

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Horsfa, JT, Sprague JE. The Pharmacology and Toxicology of the "Holy Trinity". Basic Clin Pharmacol Toxicol. 2017 Feb;120(2):1415-119.
Fudin J, The Perfect Storm: Opioid Risks and "The Holy Trinity". Pharmacy Times. Published Online Sept. 24, 2014. Available at: http://www.pharmacytimes.com/contributor/jeffery-fudin/2014/09/the-perfect-storm-opioid-opioid-risks-and-the-holy-trinity
Drugs of Abuse a DEA Resource Guide. 2017 Edition. U.S. Department of Justice Drug Enforcement Administration. Available at:https://www.dea.gov/pr/multimedia-library/publications/drug_of_abuse.pdf

18. Arnuity Ellipta / Overutilization (5-11 yoa) ___V___ _____ _____

Alert Message: Arnuity Ellipta (fluticasone furoate inhalation) may be over-utilized. The manufacturer's recommended maximum dose in patients 5 to 11 years of age is 50 mcg once daily.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Fluticasone Furoate		

Age Range 5 – 11 yoa

References:
Arnuity Ellipta Prescribing Information, May 2018, GlaxoSmithKline.

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

19. Ertugliflozin-Metformin / Overutilization ___V___ _____ _____

Alert Message: The manufacturer's recommended dose of Segluromet (ertugliflozin/metformin) is 7.5 mg ertugliflozin/1000 mg metformin twice daily.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Ertugliflozin/Metformin		

Max Dose: 15/2000mg per day

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Segluromet Prescribing Information, Dec. 2017, Merck Sharp & Dohme Corp.

20. Ertugliflozin-Metformin / Severe Renal Impairment, ESRD & Dialysis ___V____ _____ _____

Alert Message: Segluromet (ertugliflozin/metformin) is contraindicated in patients with severe renal impairment, end-stage renal disease, or patients on dialysis. Based on the mechanism of action of the ertugliflozin component (inhibition of SGLT2 in the proximal renal tubules), ertugliflozin is not expected to be effective in these patients.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Ertugliflozin/Metformin		CKD Stage 4 & 5 ESRD Dialysis

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Segluromet Prescribing Information, Dec. 2017, Merck Sharp & Dohme Corp.

21. Ertugliflozin-Metformin / Mild to Moderate Renal impairment ___V____ _____ _____

Alert Message: Assessment of renal function is recommended prior to initiation of Segluromet (ertugliflozin/metformin) therapy and periodically thereafter. Initiation of ertugliflozin/metformin is not recommended in patients with an eGFR of 30 to less than 60 mL/min/1.73m^2. Continued use is not recommended when eGFR is persistently between 30 and less than 60 mL/min/1.73m^2.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Ertugliflozin/Metformin		CKD Stage 1, 2, & 3

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Segluromet Prescribing Information, Dec. 2017, Merck Sharp & Dohme Corp.

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

22. Ertugliflozin-Metformin / Hypotension ___V____ _____ _____

Alert Message: The ertugliflozin component of Segluromet (ertugliflozin/metformin) can cause intravascular volume contraction. Therefore, symptomatic hypotension may occur after initiating ertugliflozin/metformin particularly in patients with impaired renal function, elderly patients, or patients on diuretics. Before initiating ertugliflozin/metformin, volume status should be assessed and corrected if indicated. Monitor for signs and symptoms of hypotension after initiating therapy.

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

Util A	Util B	Util C
Ertugliflozin/Metformin	Hypotension	
	Hypovolemia	
	CKD Stage 3	
	Dehydration	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Segluromet Prescribing Information, Dec. 2017, Merck Sharp & Dohme Corp.

23. Ertugliflozin-Metformin / Diuretics ___V____ _____ _____

Alert Message: The ertugliflozin component of Segluromet (ertugliflozin/metformin) can cause intravascular volume contraction. Therefore, symptomatic hypotension may occur after initiating ertugliflozin/metformin particularly in patients with impaired renal function, elderly patients, or patients on diuretics. Monitor patients for signs and symptoms during therapy. Before initiating ertugliflozin/metformin in patients with one or more of these characteristics, volume status should be assessed and corrected if indicated.

Conflict Code:
Drugs/Diseases

Util A	Util B			Util C
Ertugliflozin/Metformin	Furosemide	Chlorthalidone	Triamterene	
	Torsemide	Indapamide	Eplerenone	
	Ethacrynate	Methyclothiazide		
	Bumetanide	Metolazone		
	HCTZ	Amiloride		
	Chlorothiazide	Spironolactone		

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Segluromet Prescribing Information, Dec. 2017, Merck Sharp & Dohme Corp.

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

24. Ertugliflozin-Metformin / Insulin & Insulin Secretagogues ___√___ _____ _____

Alert Message: The concurrent use of Segluromet (ertugliflozin/metformin) with insulin and insulin secretagogues can increase the risk of hypoglycemia. A lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with ertugliflozin/metformin.

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

Util A	Util B	Util C
Ertugliflozin/Metformin	Insulins	
	Sulfonylureas	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Segluromet Prescribing Information, Dec. 2017, Merck Sharp & Dohme Corp.

25. Ertugliflozin-Metformin / LDL-C Increases ___√___ _____ _____

Alert Message: Dose-related increases in LDL-C levels can occur with the use of ertugliflozin, a component of Segluromet (ertugliflozin/metformin). Patients receiving ertugliflozin/metformin should have their LDL-C levels monitored and treated per standard of care.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Ertugliflozin/Metformin		Hypercholesterolemia

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Segluromet Prescribing Information, Dec. 2017, Merck Sharp & Dohme Corp.

26. Ertugliflozin-Metformin / Pregnancy ___√___ _____ _____

Alert Message: Based on animal data showing adverse renal effects, Segluromet (ertugliflozin/metformin) use is not recommended during the second and third trimesters of pregnancy. In animal studies, adverse renal changes were observed in rats when ertugliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy.

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

Util A	Util B	Util C **(Negating)**
Ertugliflozin/Metformin	Pregnancy	Delivery
		Abortion
		Miscarriage

Age Range: 11 - 50 yoa
Gender: Female

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Segluromet Prescribing Information, Dec. 2017, Merck Sharp & Dohme Corp.
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.

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

27. Ertugliflozin-Metformin / Nonadherence ___V___ _____ _____

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

Conflict Code: LR - Nonadherence
Drugs/Diseases

Util A	Util B	Util C
Ertugliflozin/Metformin		

References:
Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005; 353:487-97.
Ho PM, Rumsfeld JS, Masoudi FA, et al., Effect of Medication Nonadherence in Diabetes Mellitus. Cardiology Review, April 2007.
Currie CJ, Peyrot M, Morgan CL, et al. The Impact of Treatment Noncompliance on Mortality in People With Type 2 Diabetes. Diabetes Care 35:1279-1284, June 2012.
Segluromet Prescribing Information, Dec. 2017, Merck Sharp & Dohme Corp.

28. Ertugliflozin-Metformin / Therapeutic Appropriateness ___V___ _____ _____

Alert Message: Safety and effectiveness of Segluromet (ertugliflozin/metformin) in pediatric patients under 18 years of age have not been established.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Ertugliflozin/Metformin		

Age Range 0 -17 yoa

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Segluromet Prescribing Information, Dec. 2017, Merck Sharp & Dohme Corp.

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

29. Nuedexta / Pseudobulbar Affect (Negating) ___V___ _____ _____

Alert Message: A recent review of the patient's medical profile does not reveal a supporting diagnosis for the use of Nuedexta (dextromethorphan/quinidine). Dextromethorphan/quinidine is only approved for the treatment of pseudobulbar affect (PBA). Clinical research on the safety and efficacy of dextromethorphan/quinidine for other indications has not been conducted. This agent has serious adverse effects as well as significant drug interactions and should only be used for the FDA approved indication.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Negating)**
Dextromethorphan/quinidine		Pseudobulbar Affect

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Facts & Comparisons, 2018 Updates, Wolters Kluwer Health.
Nuedexta Prescribing Information, Jan. 2015, Avanir Pharmaceuticals, Inc.

30. Neratinib / Overutilization ___V___ _____ _____

Alert Message: The manufacturer's recommended dose of Nerlynx (neratinib) is 240 mg (6 tablets) orally once daily.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Neratinib		

Max Dose: 240 mg/day

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Nerlynx Prescribing Information, July 2017, Puma Biotechnology, Inc.

31. Neratinib / Diarrhea ____V___ _____ _____

Alert Message: Nerlynx (neratinib) can cause severe diarrhea. Aggressively manage diarrhea occurring despite recommended prophylaxis with additional antidiarrheals, fluids, and electrolytes as clinically indicated. Withhold neratinib in patients who experience severe and/or persistent diarrhea. Permanently discontinue neratinib in patients experiencing Grade 4 diarrhea or Grade >/= 2 diarrhea that occurs after maximal dose reduction.

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

Util A	Util B	Util C
Neratinib	Diarrhea	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Nerlynx Prescribing Information, July 2017, Puma Biotechnology, Inc.

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

32. Neratinib / Therapeutic Appropriateness-Hepatotoxicity ___V___ _____ _____

Alert Message: Nerlynx (neratinib) has been associated with hepatotoxicity characterized by increased liver enzymes. Monitor liver function tests monthly for the first 3 months of treatment, then every 3 months while on treatment and as clinically indicated. Withhold neratinib in patients experiencing Grade 3 liver abnormalities and permanently discontinue neratinib in patients experiencing Grade 4 liver abnormalities.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Neratinib		

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Nerlynx Prescribing Information, July 2017, Puma Biotechnology, Inc.

33. Neratinib / Pregnancy ___V___ _____ _____

Alert Message: Based on findings from animal studies and its mechanism of action, Nerlynx (neratinib) can cause fetal harm when administered to a pregnant woman. In animal reproductive studies, administration of neratinib to pregnant rabbits during organogenesis caused abortions, embryo-fetal death and fetal abnormalities.

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

Util A	Util B	Util C
Neratinib	Pregnancy	Miscarriage
		Abortion
		Delivery

Gender: Female
Age Range: 11 – 50 yoa

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Nerlynx Prescribing Information, July 2017, Puma Biotechnology, Inc.

34. Neratinib / Therapeutic Appropriateness ____V____ _____ _____

Alert Message: Nerlynx (neratinib) may cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with neratinib and for 1 month after the last dose. Females of reproductive potential should have a pregnancy test prior to starting treatment with neratinib.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Neratinib		

Gender: Female
Age Range: 11 – 50 yoa

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Nerlynx Prescribing Information, July 2017, Puma Biotechnology, Inc.

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

35. Neratinib / Therapeutic Appropriateness ___√___ _____ _____

Alert Message: Based on findings in animal reproductive studies, advise males with female partners of reproductive potential to use effective contraception during treatment with Nerlynx (neratinib) and for 3 months after the last dose of neratinib.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Neratinib		

Gender: Male

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Nerlynx Prescribing Information, July 2017, Puma Biotechnology, Inc.

36. Neratinib / Proton Pump Inhibitors ___√___ _____ _____

Alert Message: Concurrent use of Nerlynx (neratinib) with a proton pump inhibitor should be avoided as concomitant use of these agents may result in decreased neratinib exposure and efficacy. Drug interaction studies with neratinib and lansoprazole resulted in a decrease in neratinib Cmax and AUC of 71% and 65%, respectively.

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

Util A	Util B	Util C
Neratinib	Omeprazole	
	Esomeprazole	
	Lansoprazole	
	Rabeprazole	
	Dexlansoprazole	
	Pantoprazole	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Nerlynx Prescribing Information, July 2017, Puma Biotechnology, Inc.

37. Neratinib / H2-Receptor Antagonists ___√___ _____ _____

Alert Message: Concurrent use of Nerlynx (neratinib) with an H-2-receptor blocker should be avoided as concomitant use of these agents may result in decreased neratinib exposure and efficacy. The solubility of neratinib is pH dependent and its solubility decreases as gastric pH increases.

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

Util A	Util B	Util C
Neratinib	Cimetidine	
	Famotidine	
	Nizatidine	
	Ranitidine	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Nerlynx Prescribing Information, July 2017, Puma Biotechnology, Inc.

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

38. Neratinib / Antacids ___√___ _____ _____

Alert Message: Concurrent use of Nerlynx (neratinib) with an antacid may result in decreased neratinib exposure and efficacy. The solubility of neratinib is pH dependent and its solubility decreases as gastric pH increases. If concomitant use is warranted separate the dosing of neratinib and antacids by 3 hours.

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

Util A	Util B	Util C
Neratinib	Magnesium Hydroxide	
	Aluminum Hydroxide	
	Calcium Carbonate	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Nerlynx Prescribing Information, July 2017, Puma Biotechnology, Inc.

39. Neratinib / Moderate & Strong CYP3A4 Inhibitors ___√___ _____ _____

Alert Message: Concurrent use of Nerlynx (neratinib), a CYP substrate, with a moderate or strong CYP3A4 inhibitor should be avoided as concomitant use may result in increased neratinib plasma concentrations and neratinib toxicity.

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

Util A	Util B			Util C
Neratinib	Clarithromycin	Nefazodone	Erythromycin	Cimetidine
	Cobicistat	Ketoconazole	Ciprofloxacin	
	Conivaptan	Itraconazole	Crizotinib	
	Ritonavir	Posaconazole	Cyclosporine	
	Saquinavir	Voriconazole	Dronedarone	
	Indinavir	Diltiazem	Fluvoxamine	
	Nelfinavir	Verapamil	Imatinib	
	Atazanavir	Aprepitant	Clotrimazole	
	Tipranavir	Fluconazole	Idelalisib	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Nerlynx Prescribing Information, July 2017, Puma Biotechnology, Inc.

40. Neratinib / Moderate & Strong CYP3A4 Inducers ___√___ _____ _____

Alert Message: Concurrent use of Nerlynx (neratinib), a CYP3A4 substrate, with a moderate or strong CYP3A4 inducer should be avoided as concomitant use may result in decreased neratinib plasma concentrations and loss of neratinib efficacy.

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

Util A	Util B		Util C
Neratinib	Carbamazepine	Rifampin	Bosentan
	Phenobarbital	Rifabutin	Efavirenz
	Primidone	Rifapentine	Etravirine
	Phenytoin	Mitotane	Modafinil
	Enzalutamide	Nevirapine	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Nerlynx Prescribing Information, July 2017, Puma Biotechnology, Inc.

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

41. Neratinib / Digoxin ____√____ _____ _____

Alert Message: Concurrent use of Nerlynx (neratinib) with digoxin may result in increased digoxin concentrations and risk of digoxin toxicity due to neratinib inhibition of digoxin P-gp-mediated transport. In drug studies, concomitant use of digoxin with multiple oral doses of neratinib in healthy subjects increased the mean digoxin Cmax by 54% and the AUC by 32%. Dosage adjustment of digoxin may be required.

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

Util A	Util B	Util C
Neratinib	Digoxin	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Nerlynx Prescribing Information, July 2017, Puma Biotechnology, Inc.

42. Neratinib / P-gp Substrates ____√____ _____ _____

Alert Message: Concurrent use of Nerlynx (neratinib), a P-gp inhibitor, with a P-gp substrate may result in increased concentrations of the substrate. Monitor patient for P-gp substrate-related adverse reactions.

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

Util A	Util B	Util C
Neratinib	Dabigatran	
	Fexofenadine	
	Quinidine	
	Loperamide	
	Afatinib	
	Colchicine	
	Dapagliflozin	
	Edoxaban	
	Empagliflozin	
	Everolimus	
	Maraviroc	
	Methotrexate	
	Morphine	
	Paliperidone	
	Pazopanib	
	Ranolazine	
	Rivaroxaban	
	Saxagliptin	
	Sirolimus	
	Sitagliptin	
	Tacrolimus	
	Tolvaptan	
	Venetoclax	

References:
Clinical Pharmacology, 2018 Elsevier/Gold Standard.
Nerlynx Prescribing Information, July 2017, Puma Biotechnology, Inc.

Stephanie McGee Azar, Commissioner — (X) Approve ( ) Deny — 3-14-19 Date

Robert Moon, M.D., Deputy Commissioner and Medical Director — (X) Approve ( ) Deny — 3-12-19 Date

Kathy Hall, Deputy Commissioner — (X) Approve ( ) Deny — 3/11/19 Date