Alabama Medicaid DUR Board Meeting Minutes
July 23, 2014

Members Present: Paula Thompson, Kelli Littlejohn, Denyse Thornley-Brown, Frank Pettyjohn, , Dan McConaghy, Jimmy Jackson, Rhonda Harden, Richard Glaze, Robert Moon, Donald Kern

Also Present: Tiffany Minnifield, Heather Vega, Lori Thomas, Clemice Hurst, Brooke Devore, Erin Grant, Kayla Brackett

Present via Conference Call: Kristian Testerman, Amy Donaldson, Tammy Dubuc

Members Absent: Jared Johnson, Sandra Parker, Bernie Olin

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 April 23, 2014 meeting were presented and reviewed. J. Johnson made a motion to approve the minutes and D. Thornley-Brown seconded the motion. The motion was approved unanimously.

Prior Authorization and Overrides Update: L. Thomas began the Prior Authorization and Overrides Update with the Monthly Manual Prior Authorizations and Overrides Report for the month of January 2014. She pointed out the addition of the maintenance supply override, opt out override, and stable therapy override to the overrides section of the chart. She reported 8,972 total manual requests. She then reported 19,893 electronic requests for the same time frame. From the Prior Authorization and Override Response Time Ratio report for January 2014, L. Thomas reported that approximately 54% of all manual PAs and 50% of all overrides were responded to in less than two hours. Eighty-four percent of all manual PAs and 82% of all overrides were responded to in less than four hours and 92-93% of all manual PAs and overrides were responded to in less than eight hours. For the month of February 2014, L. Thomas reported 8,051 manual PA requests and 17,866 electronic PA requests. She reported that 60% of manual PAs and 58% of overrides were responded to in less than two hours, 88-89% in less than four hours, and 99% in less than eight hours. For the month of March 2014, L. Thomas reported 7,998 manual PA requests and 18,234 electronic PA requests. L. Thomas reported over 61% of requests were reviewed in less than two hours, approximately 90% in less than four hours, and over 99% reviewed in less than eight hours.

Program Summary Review: L. Thomas briefly reviewed the Alabama Medicaid Program Summary. She reported 3,818,186 total prescriptions, 222,827 average recipients per month using pharmacy benefits and an average paid per prescription of $75.90 for the months of October 2013 through March 2014.

Cost Management Analysis: L. Thomas reported an average cost per claim of $84.30 for March 2014. L. Thomas reminded the Board members that the Maintenance Supply was phased in on October 1st and became mandatory on January 1, 2014. This includes 84-, 90-, and 91-day supplies. L. Thomas reported that an average cost per claim for a maintenance supply prescription was approximately $40.00. K. Littlejohn reminded the Board that the costs included are gross prices. L. Thomas also reminded the Board members that Synagis season began October 1st. From the 1st Quarter 2014 Drug Analysis, L. Thomas reported 79.3% generic utilization, 11.8% brand single-source, 5.3% brand multi-source (those requests which required a DAW override), and 3.6% OTC and "other". L. Thomas reminded the Board that OTC coverage was discontinued on October 1, 2013, but that OTC insulin and nutritionals are still covered. From the Top 25 Drugs Based on Number of Claims from 01/01/2014-03/31/2014, L. Thomas reported the top five drugs: hydrocodone-acetaminophen, amoxicillin, ProAir® HFA, montelukast sodium, and omeprazole. She then reported the top five drugs from the Top 25 Drugs Based on Claims Cost from 01/01/2014 – 03/31/2014: Abilify®, Vyvanse® Synagis®, Invega® Sustenna® , and Adderall XR®. K. Littlejohn mentioned the utilization of Sovaldi and pointed out the current spend on this particular medication. She mentioned that this drug is being monitored closely and that PA criteria were drafted specifically for this medication. 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, Corticosteroids (Respiratory Tract), Hemostatics, and Respiratory and CNS Stimulants.

UPDATES

Hydrocodone Utilization: L. Thomas briefly reminded the Board members that in 2012 the Board voted to review hydrocodone utilization data and in early 2013 a special letter was hand-delivered to the top 100 prescribers of hydrocodone. L. Thomas reviewed the number of hydrocodone claims from the past three years. L Thomas revisited the chart comparing the top 100 prescribers of hydrocodone in 2012 and 2013. L. Thomas reported that 20 prescribers who were in the top 100 in 2012 dropped out of the top 100 in 2013. Board members asked if the average quantity dispensed per hydrocodone claim could be added to the chart and if the percent of hydrocodone prescriptions compared to prescriber's total prescriptions could be added. A sample letter was presented to the Board members. Minor changes were made to the letter and it was approved for distribution. This letter will be hand-delivered to the top 100 prescribers of hydrocodone. The letter will inform each physician of their ranking based on the number of hydrocodone prescriptions written.

RDUR Intervention Report: L. Thomas informed the Board members that HID and Alabama Medicaid entered into a new contract which began November 1st. With this new contract, HID will review 2000 profiles per quarter. L. Thomas presented the RDUR Activity Report for January 2014. She reported 704 profiles reviewed and 673 letters sent with 105 responses received as of the date of the report. She reported 47 of 69 physicians indicated that they found the RDUR letters "useful" or "extremely useful". The criteria for the cycle of intervention letters were the duplicate use of SSRIs and the increased risk of suicidality related to antidepressants. L. Thomas then presented the RDUR Activity Report for February 2014. She reported 706 profiles reviewed and 341 letters sent with 99 responses received as of the date of the report. She reported 38 of 61 physicians indicated that they found the RDUR letters "useful" or "extremely useful". The criteria for the cycle of intervention letters were the overutilization of stimulants. The March 2014 Activity Report indicated 663 profiles reviewed and 527 letters sent with 52 responses received as of the date of the report. She reported 30 of 38 physicians indicated that they found the RDUR letters "useful" or "extremely useful". The criteria for the cycle of intervention letters were the clinical appropriateness of multi-class polypsychopharmacy (antipsychotics and antidepressants) and the over-utilization of citalopram.

Proposed Criteria: L. Thomas presented the proposed set of 40 criteria to the Board. T. Minnifield instructed the Board members to mark their ballots. Of the 40 criteria, results from the criteria vote returned 39 approved and 1 approved as amended (#31).

Medicaid Update: T. Minnifield began the Medicaid Update by reminding the Board members that all Medicaid information discussed is available online, as well as any new Medicaid ALERTs. T. Minnifield reminded the Board that the every July the Board would vote on a Vice Chair and asked the members to mark their ballots and pass them to the front.

P & T Committee Update: C. Hurst began the P & T Update by informing the Board that the last meeting was held on May 14, 2014 and covered the Skin and Mucous Membrane Agents, Alzheimer's Agents, Antidepressants, Cerebral Stimulants Used for ADHD, Wakefulness Promoting Agents, Genitourinary Smooth Muscle Relaxants, and Anxiolytics, Sedatives, and Hypnotics. The next P and T meeting is scheduled for August 13, 2014 at 9am and will cover the first half of the Anti-infective agents.

New Business: T. Minnifield notified the Board that the next DUR meeting will be held on October 22, 2014. D. Thornley-Brown made a motion to adjourn the meeting. The motion was seconded by R. Moon. A voice vote to adjourn was unanimous. The meeting was adjourned at 2:40p.m.

Next Meeting Date: The next DUR Board meeting will be held on October 22, 2014.

Respectfully submitted,

Lori Thomas, PharmD

Lori Thomas, PharmD

ALABAMA MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS

Criteria Recommendations	*Accepted*	*Approved As Amended*	*Rejected*
1. Ospemifene / Therapeutic Appropriateness Alert Message: The safety and effectiveness of Osphena (ospemifene) have not been established in pediatric patients. Conflict Code: TA – Therapeutic Appropriateness Drugs/Diseases Util A: Ospemifene Util B: Util C: Age Range: 0 – 18 yoa References: Osphena Prescribing Information, Feb. 2013, Shionogi, Inc. Clinical Pharmacology, 2014 Elsevier/Gold Standard.	___✓___	_____	_____
2. Ospemifene / Pregnancy / Pregnancy Negating Alert Message: Osphena (ospemifene) is FDA pregnancy category X and is contraindicated in women who are or may become pregnant. In nonclinical animal studies, ospemifene was embryo-fetal lethal. If a woman becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus. Conflict Code: MC – Drug/Diagnosis Precaution/Warning/Contraindication Drugs/Diseases Util A: Ospemifene Util B: Pregnancy ICD-9s Util C **(Negating)**: Delivery, Miscarriage, Abortion References: Osphena Prescribing Information, Feb. 2013, Shionogi, Inc. Clinical Pharmacology, 2014 Elsevier/Gold Standard.	___✓___	_____	_____
3. Ospemifene / Overuse Alert Message: Osphena (ospemifene) may be over-utilized. The manufacturer's maximum recommended dose is 60 mg daily. Conflict Code: ER - Overutilization Drugs/Diseases Util A: Ospemifene Util B: Util C: Max Dose: 60 mg/day References: Osphena Prescribing Information, Feb. 2013, Shionogi, Inc. Clinical Pharmacology, 2014 Elsevier/Gold Standard.	___✓___	_____	_____

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

4. Ospemifene / Severe Hepatic Impairment ___√___ _____ _____

Alert Message: The safety and efficacy of Osphena (ospemifene) have not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population.

Conflict Code: MC – Drug/Diagnosis Precaution/Warning/Contraindication
Drugs/Diseases

Util A	Util B	Util C
Ospemifene	Chronic Liver Disease Cirrhosis	

References:
Osphena Prescribing Information, Feb. 2013, Shionogi, Inc.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

5. Ospemifene / Fluconazole ___√___ _____ _____

Alert Message: Osphena (ospemifene) should not be used with fluconazole, a moderate CYP3A4 / strong CYP2C9 / moderate CYP2C19 inhibitor. In clinical trials, fluconazole increased the systemic exposure of ospemifene by 2.7 fold and may increase the risk of ospemifene-related adverse reactions.

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

Util A	Util B	Util C
Ospemifene	Fluconazole	

References:
Osphena Prescribing Information, Feb. 2013, Shionogi, Inc.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

6. Ospemifene / Estrogens &/ Estrogen agonist/antagonist ___√___ _____ _____

Alert Message: Osphena (ospemifene) should not be used concomitantly with estrogens and estrogen agonist/antagonists. The safety and efficacy of ospemifene with these agents has not been studied.

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

Util A	Util B	Util C
Ospemifene	Conjugated Estrogens Esterified Estrogens Estradiol (transdermal) Estradiol Valerate Estrogens (Vaginal) Estrogen/Androgen Combos Raloxifene	Estradiol Estradiol Cypionate Conjugated Estrogens A/B Estropipate Estrogen/Progestin Combos Tamoxifen

References:
Osphena Prescribing Information, Feb. 2013, Shionogi, Inc.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

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

7. Ospemifene / Rifampin ___√___ _____ _____

Alert Message: Osphena (ospemifene) should not be used with rifampin, a strong CYP3A4 / moderate CYP2C9 / moderate CYP2C19 inducer. In clinical trials, rifampin decreased the systemic exposure of ospemifene by 58%, which may decrease the clinical effects.

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

Util A	Util B	Util C
Ospemifene	Rifampin	

References:
Osphena Prescribing Information, Feb. 2013, Shionogi, Inc.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

8. Ospemifene / Ketoconazole ___√___ _____ _____

Alert Message: Osphena (ospemifene) is metabolized by CYP3A4 and CYP2C9. Ketoconazole, a strong CYP3A4 inhibitor, increases the systemic exposure of ospemifene by 1.4 fold. Concurrent, chronic use of these two agents may increase the risk of ospemifene-related adverse reactions.

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

Util A	Util B	Util C
Ospemifene	Ketoconazole	

References:
Osphena Prescribing Information, Feb. 2013, Shionogi, Inc.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

9. Ospemifene / Black Box Warning Endometrial Cancer ___√___ _____ _____

Alert Message: Osphena (ospemifene) has estrogen agonistic effects in the endometrium. There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy reduces the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Negating)**
Ospemifene		Progestins

References:
Osphena Prescribing Information, Feb. 2013, Shionogi, Inc.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

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

10. Ospemifene / DVT / Black Box Warning ___J___ _____ _____

Alert Message: Osphena (ospemifene) is an estrogen agonist/antagonist and has an increased risk of stroke and deep vein thrombosis (DVT). Use of ospemifene is contraindicated in patients that have a history of or active DVT, pulmonary embolism and/or arterial thromboembolic disease.

Conflict Code: MC – Drug/Diagnosis Precaution/Warning/Contraindication
Drugs/Diseases

Util A	Util B	Util C
Ospemifene	DVT	
	Pulmonary Embolism	
	Stroke	
	MI	

References:
Osphena Prescribing Information, Feb. 2013, Shionogi, Inc.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

11. Ospemifene / Genital Bleeding ___J___ _____ _____

Alert Message: Osphena (ospemifene) is contraindicated for use in patients that have undiagnosed abnormal genital bleeding

Conflict Code: MC – Drug/Diagnosis Precaution/Warning/Contraindication
Drugs/Diseases

Util A	Util B	Util C
Ospemifene	Abnormal genital bleeding	

References:
Osphena Prescribing Information, Feb. 2013, Shionogi, Inc.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

12. Ospemifene / Estrogen-dependent Neoplasia ___J___ _____ _____

Alert Message: Osphena (ospemifene) is contraindicated for use in patients that have a known or suspected estrogen-dependent neoplasia.

Conflict Code: MC – Drug/Diagnosis Precaution/Warning/Contraindication
Drugs/Diseases

Util A	Util B	Util C
Ospemifene	Estrogen-dependent Neoplasia (Ovarian, uterine, breast or endometrial Ca)	

References:
Osphena Prescribing Information, Feb. 2013, Shionogi, Inc.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

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

13. Ospemifene / Multiple Enzyme Inhibitors CYP3A4 & CYP2C9 ___√___ _____ _____

Alert Message: Co-administration of Osphena (ospemifene) with a drug known to inhibit CYP3A4 and CYP2C9 isoenzymes may increase the risk of ospemifene-related adverse reactions.

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

Util A	Util B	Util C
Ospemifene	Voriconazole	
	Amiodarone	

References:
Osphena Prescribing Information, Feb. 2013, Shionogi, Inc.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
Cordarone Prescribing Information, Oct. 2011, Pfizer.

14. Dapagliflozin / Overutilization ___√___ _____ _____

Alert Message: The manufacturer's maximum recommended dose of Farxiga (dapagliflozin) is 10 mg once daily.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C **(Negating)**
Dapagliflozin		Renal Impairment

Max Dose: 10mg/day

References:
Farxiga Prescribing Information, Jan. 2014, Bristol-Myers Squibb.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

15. Dapagliflozin / Moderate Renal impairment ___√___ _____ _____

Alert Message: Assessment of renal function is recommended prior to initiation of Farxiga (dapagliflozin) therapy and periodically thereafter. Dapagliflozin should not be initiated in patients with an eGFR less than 60 mL/min/1.73m^2 and should be discontinued when eGFR is persistently less than 60mL/ min/1.73m^2.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Dapagliflozin		CKD Stage 1, 2 & 3

References:
Farxiga Prescribing Information, Jan. 2014, Bristol-Myers Squibb.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

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

16. Dapagliflozin / Severe Renal Impairment, ESRD & Dialysis ___√___ _____ _____

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

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Dapagliflozin		CKD Stage 4, & 5
		End-Stage Renal Disease
		Dialysis

References:
Farxiga Prescribing Information, Jan. 2014, Bristol-Myers Squibb.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

17. Dapagliflozin / Nonadherence ___√___ _____ _____

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

Conflict Code: LR - Nonadherence
Drugs/Diseases

Util A	Util B	Util C
Dapagliflozin		

References:
Farxiga Prescribing Information, Jan. 2014, Bristol-Myers Squibb.
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.

18. Dapagliflozin / Hypotension ___√___ _____ _____

Alert Message: Farxiga (dapagliflozin) causes osmotic diuresis which can lead to volume depletion and hypotension, particularly in patients with impaired renal function, elderly patients, or patients on loop diuretics. Monitor patients for signs and symptoms during therapy. Before initiating dapagliflozin in patients with one or more of these characteristics, volume status should be assessed and corrected.

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

Util A	Util B	Util C
Dapagliflozin	Hypotension	
	Hypovolemia	
	CKD Stage 3	
	Dehydration	

References:
Farxiga Prescribing Information, Jan. 2014, Bristol-Myers Squibb.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

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

19. Dapagliflozin / Loop Diuretics ___√___ _____ _____

Alert Message: Farxiga (dapagliflozin) causes osmotic diuresis which can lead to volume depletion and hypotension, particularly in patients with impaired renal function, elderly patients, or patients on loop diuretics. Monitor patients for signs and symptoms during therapy. Before initiating dapagliflozin in patients with one or more of these characteristics, volume status should be assessed and corrected.

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

Util A	Util B	Util C
Dapagliflozin	Furosemide	
	Torsemide	
	Ethacrynate	
	Bumetanide	

References:
Farxiga Prescribing Information, Jan. 2014, Bristol-Myers Squibb.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

20. Dapagliflozin / Insulin & Insulin Secretagogues ___√___ _____ _____

Alert Message: The concurrent use of Farxiga (dapagliflozin) 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 dapagliflozin.

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

Util A	Util B	Util C
Dapagliflozin	Insulins	
	Sulfonylureas	

References:
Farxiga Prescribing Information, Jan. 2014, Bristol-Myers Squibb.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

21. Dapagliflozin / LDL-C Increases ___√___ _____ _____

Alert Message: The use of Farxiga (dapagliflozin) can cause dose-related increases in LDL-C levels. Patients receiving dapagliflozin 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
Dapagliflozin	Hypercholesterolemia	

References:
Farxiga Prescribing Information, Jan. 2014, Bristol-Myers Squibb.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

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

22. Dapagliflozin / Bladder Cancer ___√___ _____ _____

Alert Message: An imbalance in bladder cancers was observed in Farxiga (dapagliflozin) clinical trials. Dapagliflozin should not be used in patients with active bladder cancer and used with caution in patients with a prior history of bladder cancer.

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

Util A	Util B	Util C
Dapagliflozin		Neoplasm of Bladder
		History of Malignant Neoplasm of Bladder

References:
Farxiga Prescribing Information, Jan. 2014, Bristol-Myers Squibb.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

23. SGLT2 Inhibitors / Therapeutic Duplication ___√___ _____ _____

Alert Message: Therapeutic duplication of sodium-glucose co-transporter 2 (SGLT2) inhibitors may be occurring.

Conflict Code: TD – Therapeutic Duplication
Drugs/Diseases

Util A	Util B	Util C
Dapagliflozin		
Canagliflozin		

References:
Farxiga Prescribing Information, Jan. 2014, Bristol-Myers Squibb.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

24. ASCVD Inferring Drugs / High-Intensity Statin Therapy (Negating) ___√___ _____ _____

Alert Message: The ACC/AHA Blood Cholesterol Guidelines recommend the use of high-intensity statin therapy, which lowers LDL-C at least 50%, to reduce atherosclerotic cardiovascular risk in adults 75 years of age and younger who have clinical ASCVD (e.g., CHD, stroke, and PAD), unless contraindicated. Moderate-intensity statin therapy should be used as a second-line option if high-intensity statin therapy is not tolerated. Refer to the ACC/AHA guidelines for agents and dosage.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Negating if High-Intensity Therapy Present)**
Nitrates		Atorvastatin 40mg & 80 mg
Cilostazol		Rosuvastatin 20 mg, 40 mg & 80 mg
Clopidogrel		
Prasugrel		
Ticagrelor		
Ticlopidine		
Dipyridamole/Aspirin		

Age Range: ≤ 75 yoa

References:
Stone NJ, Robinson J, Lichtenstein AH, et.al., 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, Jrnl Am Coll Cardiol (2013), doi:10.1016/j.jacc.2013.11.002.

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

25. ASCVD Inferring Drugs / Statins (Negating) - No therapy at all (>75 yoa) ___√___ _____ _____

Alert Message: The ACC/AHA Blood Cholesterol Guidelines state that it is reasonable to consider moderate-intensity statin therapy, which lowers LDL-C 30% to 49%, to reduce atherosclerotic cardiovascular risk in patients > 75 years of age with clinical ASCVD (e.g., CHD, stroke, and PAD), unless contraindicated. Refer to the ACC/AHA guidelines for agents and dosage.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Negating)**
Nitrates		Atorvastatin
Cilostazol		Rosuvastatin
Clopidogrel		Lovastatin
Prasugrel		Fluvastatin
Ticagrelor		Pravastatin
Ticlopidine		Simvastatin
Dipyridamole/Aspirin		Pitavastatin

Age Range: >75 yoa

References:
Stone NJ, Robinson J, Lichtenstein AH, et.al., 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, Jrnl Am Coll Cardiol (2013), doi:10.1016/j.jacc.2013.11.002.

26. Antidiabetic Agents / Statins & ASCVD Inferring (Negating) ___√___ _____ _____

Alert Message: The ACC/AHA Blood Cholesterol Guidelines recommend the use moderate-intensity statin therapy as primary prevention to reduce the risk of atherosclerotic cardiovascular disease in diabetic patients 40 to 75 years of age with a LDL-C of 70 - 189 mg/dL, unless contraindicated. If the diabetic patient has an estimated 10-year ASCVD risk of 7.5% or greater, high-intensity statin therapy is recommended. Refer to the ACC/AHA guidelines for agents and dosage.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Negating)**
Insulin		Lovastatin
Sulfonylureas		Fluvastatin
Alpha-Glucosidase Inhibitors		Simvastatin
Amylin Analogs		Pravastatin
Biguanide		Atorvastatin
DPP4 Inhibitors		Rosuvastatin
Glucagon-like Peptide 1 Receptor Agonist		Pitavastatin
Meglitinides		Cilostazol
Sodium-Glucose Co-Transporter 2 Inhibitors		Clopidogrel
Thiazolidinediones		Prasugrel
		Ticagrelor
		Ticlopidine
		Dipyridamole/Aspirin

Age Range: 40 -75 yoa

References:
Stone NJ, Robinson J, Lichtenstein AH, et.al., 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, Jrnl Am Coll Cardiol (2013), doi:10.1016/j.jacc.2013.11.002.

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

27. Antidiabetic Agents / Statins & ASCVD Inferring (Negating) ___√___ _____ _____

Alert Message: The patient may benefit from the addition of a statin to their drug regimen, if no contraindications exist. The ACC/AHA Blood Cholesterol Guidelines state that it is reasonable to initiate, continue, or intensify statin therapy in diabetic patients < 40 years of age if the patient may derive ASCVD risk reduction benefits. Refer to the ACC/AHA guidelines for agents and dosage.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Negating)**
Insulin		Lovastatin
Sulfonylureas		Fluvastatin
Alpha-Glucosidase Inhibitors		Simvastatin
Amylin Analogs		Pravastatin
Biguanide		Atorvastatin
DPP4 Inhibitors		Rosuvastatin
Glucagon-like Peptide 1 Receptor Agonist		Pitavastatin
Meglitinides		Cilostazol
Sodium-Glucose Co-Transporter 2 Inhibitors		Clopidogrel
Thiazolidinediones		Prasugrel
		Ticagrelor
		Ticlopidine
		Dipyridamole/Aspirin

Age Range: 21 -39 yoa

References:
Stone NJ, Robinson J, Lichtenstein AH, et.al., 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, Jrnl Am Coll Cardiol (2013), doi:10.1016/j.jacc.2013.11.002.

28. Antidiabetic Agents / Statins & ASCVD Inferring (Negating) ___√___ _____ _____

Alert Message: The patient may benefit from the addition of a statin to their drug regimen, if no contraindications exist. The ACC/AHA Blood Cholesterol Guidelines state that it is reasonable to initiate, continue, or intensify statin therapy in diabetic patients > 75 years if the patient may derive ASCVD risk reduction benefit. Refer to the ACC/AHA guidelines for agents and dosage.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Negating)**
Insulin		Lovastatin
Sulfonylureas		Fluvastatin
Alpha-Glucosidase Inhibitors		Simvastatin
Amylin Analogs		Pravastatin
Biguanide		Atorvastatin
DPP4 Inhibitors		Rosuvastatin
Glucagon-like Peptide 1 Receptor Agonist		Pitavastatin
Meglitinides		Cilostazol
Sodium-Glucose Co-Transporter 2 Inhibitors		Clopidogrel
Thiazolidinediones		Prasugrel
		Ticagrelor
		Ticlopidine
		Dipyridamole/Aspirin

Age Range: > 75 yoa

References:
Stone NJ, Robinson J, Lichtenstein AH, et.al., 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, Jrnl Am Coll Cardiol (2013), doi:10.1016/j.jacc.2013.11.002.

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

29. Ketoconazole / Disopyramide ___J___ _____ _____

Alert Message: Concurrent use of ketoconazole and disopyramide is contraindicated due to risk of serious cardiovascular adverse events including QT prolongation. Disopyramide is a CYP3A4 substrate and use with the potent CYP3A4 inhibitor ketoconazole may result in elevated disopyramide plasma concentrations and associated toxicity.

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

Util A	Util B	Util C
Ketoconazole	Disopyramide	

References:
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
Nizoral Prescribing Information, Feb. 2014, Janssen Pharmaceuticals, Inc.

30. Ketoconazole / Colchicine ___J___ _____ _____

Alert Message: Concurrent use of ketoconazole and colchicine is contraindicated due to risk of colchicine toxicity. Colchicine is a CYP3A4 substrate and use with the potent CYP3A4 inhibitor ketoconazole may result in elevated colchicine plasma concentrations and associated toxicity.

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

Util A	Util B	Util C
Ketoconazole	Colchicine	

References:
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
Nizoral Prescribing Information, Feb. 2014, Janssen Pharmaceuticals, Inc.

31. Ketoconazole / Felodipine & Nisoldipine _____ ___J___ _____

Alert Message: Concurrent use of ketoconazole with felodipine or nisoldipine is contraindicated due to risk of calcium channel blocker (CCB) negative inotropic effects. Felodipine and nisoldipine are CYP3A4 substrates and use with the potent CYP3A4 inhibitor ketoconazole may result in increased CCB plasma concentrations and risk of edema and congestive heart failure.

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

Util A	Util B	Util C
Ketoconazole	Nisoldipine Felodipine	

References:
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
Nizoral Prescribing Information, Feb. 2014, Janssen Pharmaceuticals, Inc.

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

32. Ketoconazole / Methadone ___√___ _____ _____

Alert Message: Concurrent use of ketoconazole and methadone is contraindicated due to risk of serious cardiovascular adverse events including QT prolongation and respiratory and/or CNS depression. Methadone is a CYP3A4 substrate and use with the potent CYP3A4 inhibitor ketoconazole may result in elevated methadone plasma concentrations.

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

Util A	Util B	Util C
Ketoconazole	Methadone	

References:
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
Nizoral Prescribing Information, Feb. 2014, Janssen Pharmaceuticals, Inc.

33. Afinitor Tabs / Overutilization / Other Drugs/DZ Requiring Dose Adjustment ___√___ _____ _____

Alert Message: The manufacturer's recommended dose of Afinitor (everolimus) is 10 mg once a day with or without food. If everolimus is being used for SEGA (subependymal giant cell astrocytoma) with TSC (tuberous sclerosis complex) the recommended starting dose is 4.5 mg/m^2 once daily, with dosage adjustments to attain trough concentrations of 5-15 ng/mL.

Conflict Code: ER – Overutilization
Drugs/Diseases

Util A	Util B	Util C **(Negating)**		
Everolimus Tabs		Nefazodone	Telithromycin	Lopinavir/Ritonavir
		Ritonavir	Clarithromycin	Fluconazole
		Saquinavir	Ketoconazole	Diltiazem
		Nelfinavir	Itraconazole	Verapamil
		Indinavir	Posaconazole	Hepatic Impairment
		Fosamprenavir	Voriconazole	
		Atazanavir	Erythromycin	
		Telaprevir	Aprepitant	
		Boceprevir	Imatinib	

Max Dose: 10mg/day

References:
Afinitor Prescribing Information, Feb. 2014, Novartis Pharmaceuticals Corporation.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
FDA: Drug Development and Drug Interactions: Tables of Substrates, Inhibitors and Inducers. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionLabeling/ucm093664.htm

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

34. Everolimus / Strong CYP3A4/P-gp Inhibitors ___√___ _____ _____

Alert Message: Concurrent use of everolimus (Afinitor & Afinitor Disperz), a CYP3A4/P-gp substrate, with a strong CYP3A4/P-gp inhibitor should be avoided due to significant increases in everolimus exposure and risk of everolimus-related adverse effects.

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

Util A	Util B	Util C
Everolimus Tabs & Disperz	Nefazodone	Telithromycin
	Ritonavir	Clarithromycin
	Saquinavir	Ketoconazole
	Nelfinavir	Itraconazole
	Indinavir	Posaconazole
	Atazanavir	Voriconazole
	Telaprevir	
	Boceprevir	

References:
Afinitor Prescribing Information, Feb. 2014, Novartis Pharmaceuticals Corporation.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
FDA: Drug Development and Drug Interactions: Tables of Substrates, Inhibitors and Inducers. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionLabeling/ucm093664.htm

35. Everolimus Tabs / Moderate CYP3A/P-gp Inh / Astrocytoma-Negating ___√___ _____ _____

Alert Message: If concurrent use of Afinitor (everolimus), a CYP3A4/P-gp substrate, with moderate CYP3A4/P-gp inhibitors is required, the everolimus dose should be reduced to 2.5 mg once daily, and only if tolerated, increased to a maximum of 5 mg once daily.

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

Util A	Util B		Util C **(Negate)**
Everolimus Tabs 7.5 & 10 mg	Lopinavir/Ritonavir	Imatinib	Astrocytoma
	Erythromycin	Fluconazole	
	Diltiazem	Fosamprenavir	
	Verapamil	Aprepitant	

References:
Afinitor Prescribing Information, Feb. 2014, Novartis Pharmaceuticals Corporation.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
FDA: Drug Development and Drug Interactions: Tables of Substrates, Inhibitors and Inducers. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionLabeling/ucm093664.htm

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

36. Everolimus / Moderate CYP3A/P-gp Inh / Astrocytoma ___√___ _____ _____

Alert Message: If concurrent use of everolimus (Afinitor & Afinitor Disperz), a CYP3A4/P-gp substrate, with moderate CYP3A4/P-gp inhibitors is required in a patient with SEGA (subependymal giant cell astrocytoma) with TSC (tuberous sclerosis complex), the everolimus dose should be reduced by approximately 50%. Administer everolimus every other day if the patient is receiving the lowest dose available. Everolimus trough concentrations should be maintained at 5 to15 ng/mL.

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

Util A	Util B		Util C (Include)
Everolimus Tabs & Disperz	Lopinavir/Ritonavir	Imatinib	Astrocytoma
	Erythromycin	Fluconazole	
	Diltiazem	Fosamprenavir	
	Verapamil	Aprepitant	

References:
Afinitor Prescribing Information, Feb. 2014, Novartis Pharmaceuticals Corporation.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
FDA: Drug Development and Drug Interactions: Tables of Substrates, Inhibitors and Inducers. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionLabeling/ucm093664.htm

37. Everolimus Tabs / Overutilization - Hepatic Impairment ____√____ _____ _____

Alert Message: Hepatic impairment will increase exposure to Afinitor (everolimus) and dose adjustments are recommended. For patients with advanced neuroendocrine tumors of pancreatic origin, advanced renal cell carcinoma, breast cancer or renal angiomyolipoma and severe hepatic impairment, the everolimus dose must not exceed 2.5 mg daily. The recommended dose in moderate hepatic impairment is 5.0 mg daily and 7.5 mg daily in mild impairment. In patients with SEGA (subependymal giant cell astrocytoma) with TSC (tuberous sclerosis complex) the dosage should be reduced and subsequent dosing based on therapeutic drug monitoring to maintain trough concentrations of 5 to15 ng/mL.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C (Include)
Everolimus Tabs		Hepatic Impairment

Max dose: 7.5mg/day

References:
Afinitor Prescribing Information, Feb. 2014, Novartis Pharmaceuticals Corporation.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

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

38. Everolimus Disperz / Overutilization - Hepatic Impairment ___✓___ _____ _____

Alert Message: Hepatic impairment will increase exposure to Afinitor Disperz (everolimus) and dose adjustments are recommended. The starting dose of everolimus should be reduced by approximately 50% in patients who have SEGA (subependymal giant cell astrocytoma) with TSC (tuberous sclerosis complex) and severe hepatic impairment. Adjustment to the starting dose for patients who have mild or moderate hepatic impairment may be needed. Subsequent dosing should be based on therapeutic drug monitoring to maintain trough concentrations of 5 to 15 ng/mL.

Conflict Code: TA - Therapeutic Appropriateness

Drugs/Diseases

Util A	Util B	Util C **(Include)**
Everolimus Disperz		Hepatic Impairment

References:

Afinitor Prescribing Information, Feb. 2014, Novartis Pharmaceuticals Corporation.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

39. Everolimus Tabs / Strong CYP3A/P-gp Inducers / Astrocytoma-Negating ___✓___ _____ _____

Alert Message: The concurrent use of Afinitor (everolimus), a CYP3A4/P-gp substrate, with a strong CYP3A4/P-gp inducer should be avoided if alternative therapy is available. If treatment with a strong CYP3A4/P-gp inducer is required, consider doubling the everolimus dose using increments of 5 mg or less and assessing tolerability.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

Util A	Util B	Util C **(Negate)**
Everolimus Tabs	Carbamazepine	Astrocytoma
	Rifabutin	
	Rifampin	
	Rifapentine	
	Phenytoin	
	Phenobarbital	
	Primidone	

References:

Afinitor Prescribing Information, Feb. 2014, Novartis Pharmaceuticals Corporation.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
FDA: Drug Development and Drug Interactions: Tables of Substrates, Inhibitors and Inducers. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionLabeling/ucm093664.htm

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

40. Everolimus Disperz / Strong CYP3A/P-gp Inducers / Astrocytoma ___/_____ _____ _____

Alert Message: The concurrent use of Afinitor Disperz (everolimus), CYP3A4/P-gp substrate, with a strong CYP3A4/P-gp inducer should be avoided if alternative therapy is available. If treatment with a strong CYP3A4/P-gp inducer is required, the everolimus dose should be doubled and tolerability assessed. Trough concentrations should be assessed after 2 weeks of doubling the dose and monitored thereafter to maintain trough concentrations of 5 to 15 ng/mL.

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

Util A	Util B	Util C **(Include)**
Everolimus Disperz	Carbamazepine	Astrocytoma
	Rifabutin	
	Rifampin	
	Rifapentine	
	Phenytoin	
	Phenobarbital	
	Primidone	

References:

Afinitor Prescribing Information, Feb. 2014, Novartis Pharmaceuticals Corporation.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
FDA: Drug Development and Drug Interactions: Tables of Substrates, Inhibitors and Inducers. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionLabeling/ucm093664.htm

Stephanie McGee Azar, Acting Commissioner — (X) Approve ( ) Deny — 9-25-14 Date

Robert Moon, M.D., Deputy Commissioner and Medical Director — (X) Approve ( ) Deny — 9-23-14 Date

Kathy Hall, Deputy Commissioner — (X) Approve ( ) Deny — Sept 23, 2014 Date