Division of Medicaid

Office of the Governor

State of Mississippi

DUR Board Meeting

August 20, 2009

2:00 p.m.

Woolfolk Building, Room 117

Jackson, MS

Drug Utilization Review Board

Lee Merritt, R.Ph.
Medfusion
2211 5th Street North
Columbus, MS 39705
Term expires: June 30, 2010

Edgar Donahoe, M.D.
Indianola Family Medical Group
122 Baker Street
Indianola, MS 38751
Term expires: June 30, 2010

Mark Reed, M.D.
University of Mississippi Medical Center
2500 North State Street, Trailer 16
Jackson, MS 39216
Term Expires: June 30, 2010

Vickie Veazey, R.Ph.
MS State Hospital at Whitfield
Building #50
Whitfield, MS 39193
Term expires: June 30, 2010

Frank Wade, M.D.
Family Medical Clinic
376A Simpson Highway 149
Magee, MS 39111
Term Expires: June 30, 2011

Alvin Dixon, R.Ph.
182 Cherry Street
Clarksdale, MS 38614
Term expires: June 30, 2011

Jason Strong, Pharm.D.
Canton Discount
726 East Peace Street
Canton, MS 39046
Term Expires: June 30, 2011

William Bastian, M.D.
Bastian Center of Pediatric Endocrinology
1860 Chadwick Drive, Suite 206
Jackson, MS 39204
Term Expires: June 30, 2011

Upcoming Mississippi DUR Board Meeting Dates

November 19, 2009
February 18, 2010
May 20, 2010
August 19, 2010

DIVISION OF MEDICAID
OFFICE OF THE GOVERNOR
DRUG UTILIZATION REVIEW BOARD
AGENDA

August 20, 2009

Welcome

Old Business

- **Approval of Meeting Minutes**
- **Review of 2nd Quarter 2009 Materials**

Cost Management Analysis — **Ashleigh Holeman, Pharm.D.**

Pharmacy Program Update — **Paige Clayton, Pharm.D.**

New Business — **Ashleigh Holeman, Pharm.D.**

- **DUR Overview**
- **Benefit of Prophylactic PPI Use in Asthmatics**
- **Carisoprodol Utilization Update**
- **Dyslipidemia and Metabolic Syndrome Medicaid Prescribing Updates**
- **Other Criteria Recommendations**
- **FDA Updates**

Next Meeting Information

In an effort to save time, please familiarize yourself with the following sets of minutes and criteria as the information included in this section has previously been clinically reviewed with the DUR Board but has yet to be implemented due to the lack of a voting quorum. While these items are important business to the DUR Board, it is believed that the time and efforts of the current Board would be better utilized on new business that has yet to be reviewed.

Accordingly, the Board will entertain a motion to accept all previously reviewed minutes and criteria in one vote rather than reading through all items individually.

Mississippi Division of Medicaid
Drug Utilization Review (DUR) Board
Minutes of the February 19, 2009 Meeting

Members Attending: William Bastian, M.D.; Alvin Dixon, R.Ph.; Edgar Donahoe, M.D.; Laura Gray, M.D.; Lee Merritt, R.Ph.; Mark Reed, M.D.; Jason Strong, Pharm. D.; Vickie Veazey, R.Ph.; Frank Wade, M.D.;
Members Absent: Roy Arnold, R.Ph.; Lee Voulters, M.D.; John Wallace, M.D.

Also Present:
DOM Staff: Judith Clark, R.Ph., DOM Pharmacy Bureau Director; Paige Clayton, Pharm. D., DOM DUR Coordinator, Terri Kirby, R.Ph., Clinical Pharmacist
HID Staff: Ashleigh Holeman, Pharm. D., Project Manager; Leslie Leon, Pharm. D., Clinical Pharmacist; Kathleen Burns, R.N., Call Center Manager

Call to order:
Laura Gray, Chairperson of the Board, called the meeting to order at 2:12 p.m.
Dr. Gray asked for the Board members to introduce themselves as some of the members were new to the Board. Dr. Gray continued by asking for a motion to approve the minutes of the last meeting. Dr. Reed motioned to accept as written; Dr. Donahoe seconded the motion. All voted in favor of the minutes as written.

New Business:
Dr. Clayton introduced a visiting speaker to the Board, Dr. Jennifer Gholson, IQH Chief Medical Officer. Dr. Gholson began her presentation on the potentially inappropriate medications prescribed in the elderly population. She continued stating that the cooperation of the Division of Medicaid will serve as a most valuable asset in this educational effort to enlighten the prescribing Medicaid physicians . In sharing her information, Dr. Gholson alerted the Board that the chief medication prescribed in this manner was Darvocet®, ranking Mississippi second in the nation for inappropriate prescribing habits in the elderly. Dr. Gholson continued with a handout to the Board, indicating that Skeletal Muscle Relaxants were also highly prescribed by Mississippi prescribers with Flexeril® leading this chart. The chart also indicated Antihistamines, Antiemetics and Long Acting Benzodiazepines are prescribed inappropriately in the elderly. After much interest indicated by the Board, Dr. Gholson thanked the Board for their time and consideration in this very important matter. Dr. Holeman then continued with studies that HID had reported in the packet . She pointed out that paid claims analyses showed during a six month period that 4655 prescriptions for 1585 beneficiaries were identified for these potentially inappropriate medications in the MS Medicaid elderly. Dr. Holeman reviewed an additional chart HID had provided on alprazolam and lorazepam. Even though these two medications were not included on the IQH report, Dr. Holeman continued that they were included on the Beer's list (higher doses only). The utilization of these two medications in beneficiaries 65 and older was significantly higher than any of the others provided in the first charts. A total of 14,576 claims for 4,088 beneficiaries were found for these two medications, indicating a considerable risk to the elderly Medicaid population.
Recommendation:
In the effort to reduce or prevent the incidence of adverse events, HID provided two recommendations for the DUR Board to consider:

1. HID recommended the development of a RDUR criterion identifying elderly patients (>65) who are receiving one or more of the potentially inappropriate medications to educate prescribers about the risks associated with their use in this population
2. HID recommended an edit at the point of sale that would require prior authorization for these medications for any beneficiary>65 years of age.

After much open discussion, Dr. Donahoe moved that Darvocet® and its generic products be required to have a prior authorization for all ages as there are other medications that could be used with safer outcomes. Also, he continued that for the other potentially inappropriate medications, educational letters be sent to the prescribing physicians to alert them of these potentially problematic medications in the elderly. Dr. Reed seconded the motion. All voted in favor of the recommendations. Dr. Clayton explained to the Board that the RDUR process

would target any beneficiary over 65 who received over one of these medications and send an educational letter to the prescriber making them aware of the risks associated with use of these medications in the elderly.

Vitamin D Utilization in the Mississippi Medicaid beneficiaries:
Dr. Holeman began her presentation informing the Board that one of the members had asked HID to run reports on the utilization, in the Mississippi Medicaid population, for vitamin D. Since 2006, there has been a 328% increase in the number of beneficiaries receiving vitamin D supplementation through Mississippi Medicaid. The utilization was highest in the ages 50-59, with the next highest being in ages 40-49, followed by pediatric beneficiaries ages 10-19, and then lastly, beneficiaries ages 60-69. In 2008, 78% of Vitamin D utilization was in women and 22% in men. This is indicative of postmenopausal women most likely receiving Vitamin D in conjunction with calcium supplementation for osteoporosis. Of the 226 beneficiaries ≤ 19 years of age, a significant number had an endocrine or metabolic disorder of some type. These diagnoses account for 35% of the total claims for pediatric beneficiaries, followed by 34% diagnosed with obesity. These numbers mirrored those seen in national literature and research trends. Dr. Holeman asked Board member Dr. Bastian, Pediatric Endocrinologist, to elaborate on these findings. Dr. Bastian started by supporting the findings stating that approximately 75 to 80% of the pediatric population he services is noted to have below the normal range of vitamin D in laboratory findings. This, he stated, seems to be independent of seasonal changes, which one would think would significantly affect these lab results. Dr. Bastian stated that the majority of these patients did not have a diagnosis of rickets and did not have low calcium levels reported in testing. He continued that even with aggressive treatments with vitamin D, these patients seem to return to these low levels which he has confirmed by lab tests. Dr. Bastian stated that this is a very serious problem state wide and he is requesting the Board/DOM to develop a plan to identify these patients for early treatment. Dr. Bastian made a motion to recommend that Maternal and Child Health Services for Medicaid be asked to add in their EPSDT screenings a test for vitamin D deficiencies. Dr. Donahoe seconded the motion. All voted in favor of the motion.

Over-the-counter minimally sedating antihistamines in children under age 2:
Dr. Holeman pointed out that there had been several reports from the CDC and FDA related to the risks of serious injury or fatal overdose from the administration of cough and cold products to children less than two years of age. Recently, DOM closed coverage of the OTC cough and cold products to this age group. Due to the pushback from the provider community, DOM chose to leave OTC loratadine and cetirizine open for this age group. HID conducted claim analyses to determine utilization for the OTC second generation antihistamines in the Medicaid population under age 2.From June 2008 through November 2008, there were a total of 3286 claims for 2626 beneficiaries under age two. DOM wanted the DUR Board's counsel regarding whether OTC loratadine and cetirizine should be left open for coverage for beneficiaries under the age of two. Dr. Reed voiced his disapproval of any child under the age of 6 being treated with these medications. He stated only those with an allergy-related diagnosis, not cough, cold or flu, should receive these medications. He continued that viral syndromes would clear up over time without medication intervention, and that there was no evidence that antihistamines provide any symptomatic relief in viral syndromes. Dr. Donahoe interjected that there would be an appropriate time to prescribe these medications, agreeing with Dr. Reed that only with the mentioned indications should DOM approve these medications in this age group. Dr. Gray motioned that DOM require a prior authorization for the OTC minimally sedating antihistamines, with approval only for allergy-related diagnoses, for beneficiaries of ages two and under. Dr. Reed seconded the motion. All voted in favor of the motion.

Other Criteria Recommendations:
Dr. Gray motioned that the Board accept the recommended criteria additions with a group vote. All voted in favor of the motion.

Cost Management Analysis:
Due to the guest speaker, this report was moved to the end of the meeting. Dr. Holeman reviewed briefly the Top 15 therapeutic classes by total cost for the three month span of September 2008 through November 2008. The atypical antipsychotic agents continued to remain the leading therapeutic class, followed by anticonvulsants. Monoclonal antibodies were noted to take the number three place in October and November, as Synagis® began its season in October. The top 25 drugs based on the number of claims for the three month span were led by hydrocodone followed by antibiotics. The top 25 drugs based on total claims costs for September 2008 through November 2008 were led by Singulair® replaced by Synagis® in October and November.

Pharmacy Program Updates:
Dr. Clayton began by noting that Suboxone®/Subutex® Criteria were being developed per the Board's request by DOM and HID and will be sent for further review to the legal department and Executive Director of Medicaid when completed. Dr. Clayton also noted that, due to some HIPPA regulations specific for patients receiving addiction treatment, there has been some delay in this development. DOM and HID want to make sure that these regulations are addressed in the appropriate manner. Ms. Clark reported on the E-prescribing Program which has brought national attention to the Mississippi Medicaid Pharmacy program as being a leader in the futuristic use of this important tool by providers. Ms. Clark also requested comments from the Board on any issues in the providers' practices that might be addressed by DOM. The Board physicians brought to DOM's attention that they continue to have issues with chain pharmacies telling their patients that "Medicaid does not pay for this medication, you will have to pay" when it is an issue of the child needing a prior authorization to receive prescriptions above the 2/5 service limit. They stated that the pharmacists never alert them when there is a problem with the pharmacy claim, therefore leaving their patient without needed medications. Ms. Clark said that she has made several attempts to correct this issue with the chain pharmacies and plans to address this in a more assertive manner. Dr. Clayton then stated that DOM is working with the claims vendor to complete the hydrocodone accumulation edit which should be complete by the end of March. Once this endeavor has been completed, the benzodiazepine and sedative/hypnotic quantity and duplicate therapy edits will be instated.

Dr. Gray reminded the Board of the next meeting on May 21, 2009 and requested a motion for the meeting to be adjourned at 3:20 p.m. Motioned: Dr. Donahoe; Seconded by Dr. Reed.

Respectfully Submitted:
Health Information Designs, Inc.

Mississippi Division of Medicaid
Drug Utilization Review (DUR) Board
Minutes of the May 21, 2009 Meeting

Members Attending: William Bastian, M.D.; Laura Gray, M.D.; Mark Reed, M.D.; Jason Strong, Pharm.D; Vickie Veazey, RPh.
Members Absent: Roy Arnold, RPh.; Alvin Dixon, RPh.; Edgar Donahoe, M.D.; Lee Merritt, RPh.; Lee Volters, M.D.; Frank Wade, M.D.; John Wallace, M.D.

Also Present:
DOM Staff: Judith Clark, RPh.,DOM Pharmacy Bureau Director; Paige Clayton, Pharm.D., DOM DUR Coordinator; Carlis Faler, DOM Director of Program Integrity
HID Staff: Ashleigh Holeman, Pharm.D., Project Manager; Leslie Leon, Pharm.D., Clinical Pharmacist; Kathleen Burns, R.N. Call Center Manager

Ms Clark asked for a delay awaiting the remainder of the Board to arrive in order to have a quorum.

Call To Order:
Dr. Gray, Chairperson of the Board, called the meeting to order at 2:20 p.m. It was acknowledged to all that there was not a quorum to address any of the issues to be voted on at this time.

Cost Management Analysis:
Dr. Holeman reviewed the Top 15 Therapeutic Classes for the months of December 2008 thru February 2009. The top 3 agents remain the same with Antipsychotic agents as number one for the three month studied. The Top 25 drugs based on claims volume for the same three month analysis were then reviewed; ranking number one in MS Medicaid as well as the national top 200, remains Hydrocodone-Acetaminophen. Continuing, Dr. Holeman noted that in the 3 month analysis of the Top 25 Drugs based on cost was led by Synagis®, which is appropriate for the season reviewed.

Pharmacy Program Update:
Dr. Clayton noted the implementation by DOM on May 15, 2009 of new claims edits that were put in place addressing: Anxiolytic Agents, Oxycodone short-acting agents, Oxycodone oral Liquids and Sedative Hypnotics. This was in accordance with the DUR Board's recommendations at an earlier meeting. The Suboxone® update was addressed also by Dr. Clayton to notify the Board that the Legal Division was reviewing the recommendations along with the HIPPA issues associated with treatment for substance abuse. Dr. Gray asked if there was an indication for Pain Management. Dr. Clayton responded that Medicaid paid for opioid dependence only. Ms. Clark continued reminding the Board that a New PDL would be implemented July 1, 2009. Also, the New Children's edits were implemented to facilitate the pharmacists with claims on Children under age 21. The 2 brand or 5 drug limit does not apply to a child under the age of 21 when the medication is deemed medically necessary by the physician. There are overrides in place to allow the child to obtain their medication with a PA.

New Business:

Concurrent Use of ACEI and ARBS

Dr Holeman reviewed briefly the Concurrent use of ACE inhibitors and Angiotensin-Receptor Blockers with the Board. The information presented showed that 4% of all beneficiaries on an ACEI or ARB had received concurrent therapy with the other class as well. A RDUR criterion was created but not voted on due to lack of quorum.

Pharmacological Interventions for Dyslipidemia in Children

Dr. Holeman presented data regarding Mississippi Medicaid pediatric beneficiaries diagnosed with dyslipidemia who have not received pharmacological treatment for the disorder. It was found that during 2008, only 11% of all pediatric beneficiaries ages 8-18 diagnosed with a lipid disorder had received medication. Dr. Bastian interjected several very important thoughts to be revisited with more data for the full Board at the next meeting. Ms. Clark suggested that HID produce a "one-pager" to address issues in Children with Metabolic Syndromes, Obesity and Dyslipidemia. These would be overseen by Dr. Bastian, who graciously agreed to provide his services.

Metoclopramide: New Boxed Warning

The new boxed warning for metoclopramide was the next topic of discussion. The FDA now requires manufacturers of metoclopramide to add a Boxed Warning to their product labeling regarding the risk of tardive dyskinesia with long-term or high-dose use. Several RDUR criteria were created but not voted on due to lack of quorum.

Effects of PPIs on Plavix Efficacy

The use of Plavix® and proton pump inhibitors was the next topic for Dr. Holeman to present. Recent studies have shown that PPIs may decrease the efficacy of Plavix. During the 3-month interval presented to the DUR Board, 14% of beneficiaries who had received Plavix had also received a PPI. Again, a RDUR criterion was created but not voted on due to lack of quorum.

Potential for the Overutilization of Strattera

The final discussion related to the potential for overutilization of Strattera. DOM has learned from other Medicaid agencies that this is an issue in other states, and DOM wants to address the issue before it becomes a problem in Mississippi. From the data presented, it appears that there is potential overutilization already occurring in Mississippi Medicaid. There are beneficiaries who are receiving more than 62 capsules of Strattera per month, taking more than one strength of Strattera, and receiving more than 100mg/day, the maximum recommended daily dose. DOM is considering implementation of cumulative quantity limits of 62 capsules per month for Strattera, with any beneficiary needing more than this limit requiring a Maximum Unit Override.

Dr. Gray reminded the Board of the next meeting date on August 20, 2009. The meeting was adjourned at 3:06 p.m.

Respectfully Submitted:
Health Information Designs, Inc.

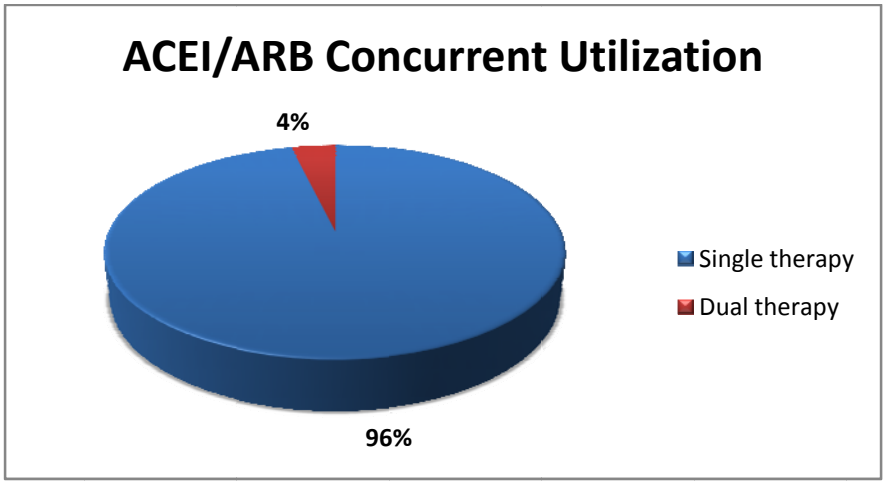
Dual Renin-Angiotensin-Aldosterone System (RAS) Blockade with ACE Inhibitors and Angiotensin Receptor Blockers

The renin-angiotensin-aldosterone system (RAS) plays an important role in the regulation of sodium, potassium and fluid balance, and it appreciably influences vascular tone and sympathetic nervous system activity. All of these factors contribute to blood pressure homeostasis. Angiotensin II, one of the end products of the RAS, can cause hypertension through several different mechanisms, including vasoconstriction, increased sympathetic nervous system activity, and retention of sodium and fluid. A common belief held by many physicians has been that more complete blockade of the RAS would lead to better blood pressure control and potential cardioprotective and nephroprotective effects. However, a recent study published has shown that use of ACE inhibitors and ARBs concurrently was associated with more adverse events and no increased benefits. One analysis of the ONTARGET study showed that ACEI/ARB combination was associated with an increased risk of dialysis, doubling of serum creatinine, and death, compared with using either agent alone. As a result of these findings, a Viewpoint in the Journal of the American College of Cardiology is calling on physicians to avoid using dual RAS blockade with ACE inhibitors and ARBs in clinical practice.

Mississippi Medicaid

Based on the concerns raised by the ONTARGET study, HID conducted claims analyses to determine the extent of ACEI/ARB combination therapy in Mississippi Medicaid beneficiaries. Claims for a 6-month interval from 7/24/08 to 1/23/09 (the most recent date for which claims data was available) were examined. The results are shown below.

Medication	Beneficiary Count
ACEI	15058
ARB	6762
Dual therapy	813



A total of 21,820 Mississippi Medicaid beneficiaries received either an ACEI or ARB during the 6-month period studied. Of these beneficiaries, 813 (4%) received dual therapy with both an ACEI and ARB, putting them at risk for the adverse events detailed in the ONTARGET analysis results.

Recommendation

In an effort to reduce the risk associated with dual RAS blockade, HID recommends the development and implementation of an RDUR criterion to identify those beneficiaries who are receiving concurrent treatment with an ACEI and ARB and educate their providers about the risks associated with ACEI/ARB combination therapy.

MISSISSIPPI MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS

Criteria Recommendations ***Approved Rejected***

1. ACE Inhibitors / ARBs _____ _____

Alert Message: The concurrent use of an ACEI (angiotensin converting enzyme inhibitor) with an ARB (angiotensin II receptor blocker) may result in significant adverse effects (e.g., hyperkalemia, hypotension, and renal impairment) without improving patient outcomes. Consider switching the patient to a safer recommended combination therapy. If an ACEI/ARB combination therapy is unavoidable closely monitor the patient for adverse effects.

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

Util A		Util B		Util C
Enalapril	Lisinopril	Losartan	Eprosartan	
Captopril	Moexipril	Valsartan	Olmesartan	
Benazepril	Perindopril	Irbesartan		
Fosinopril	Quinapril	Candesartan		
Trandolapril	Ramipril	Telmisartan		

References:

Yusuf S, Teo KK, Pogue J, et al for the ONTARGET investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008: 358:1547-1559.
Phillips CO, Kashani A, Ko D, et al. Adverse Effects of Combination Angiotension II Receptor Blockers Plus Angiotension-Converting Enzyme Inhibitors for Left Ventricular Dysfunction. Arch Intern Med. 2007;167(18):1930-1936.
Mann JFE, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both in people at high vascular risk (the ONTARGET study): a multicentre, randomized, double-blind controlled trial. *Lancet* 2008; 372:547-553.
The Seventh Report of the Joint National Committee on Prevention, Detection,\Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. JAMA. 2003;289(19):2560-71.
Jessup M, Abraham WT, Casey DE., et al., Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2009 Mar 26; doi 10.1161/CIRCULATIONAHA.109.192064.

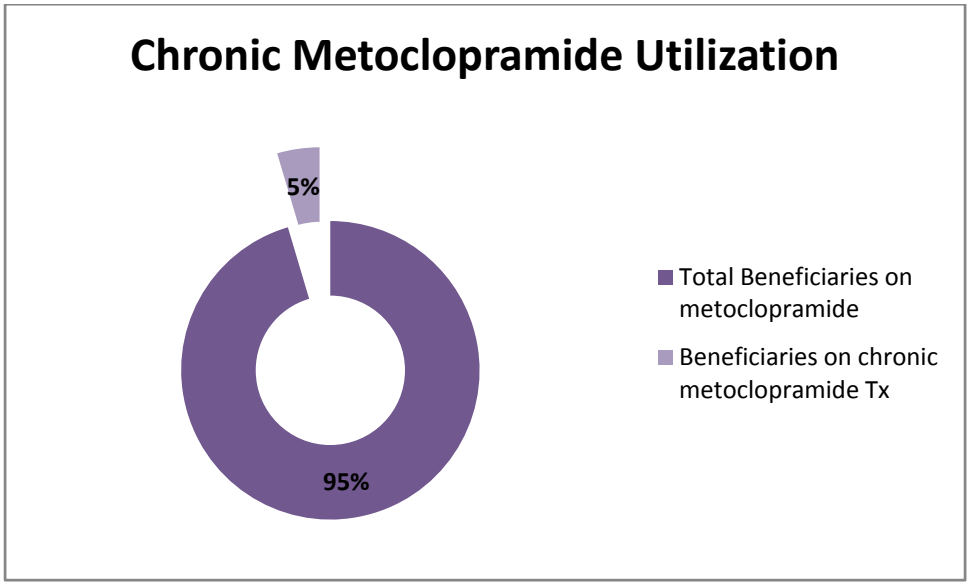
Metoclopramide: New Boxed Warning

Metoclopramide is a prokinetic agent that stimulates motility of the upper gastrointestinal tract and speeds up stomach emptying. It is indicated for the short-term treatment of several disorders, including gastroesophageal reflux disease, diabetic gastroparesis, and nausea. However, it is often used in a variety of other ailments, including hiccups and lactation induction. While the manufacturer does not recommend treatment past 12 weeks, the FDA has become aware of reports of tardive dyskinesia in patients, a majority of whom had taken the medication for longer than the recommended 12 weeks. Tardive dyskinesia is a neurologic syndrome characterized by involuntary, repetitive movements of the body including grimacing, tongue protrusion, lip smacking, and rapid movement of the extremities. Symptoms of tardive dyskinesia are rarely reversible and may remain long after the causative agent has been discontinued. Current product labeling for metoclopramide contains warnings about the risk of tardive dyskinesia with chronic use, and recently published analyses suggest that metoclopramide is the most common cause of drug-induced movement disorders.

With all of this information considered, the FDA will now require manufacturers of metoclopramide to add a Boxed Warning to their product labeling regarding the risk of tardive dyskinesia with long-term or high-dose use. In addition, the FDA will require that manufacturers develop a medication guide to be given to patients informing them of this risk.

Mississippi Medicaid

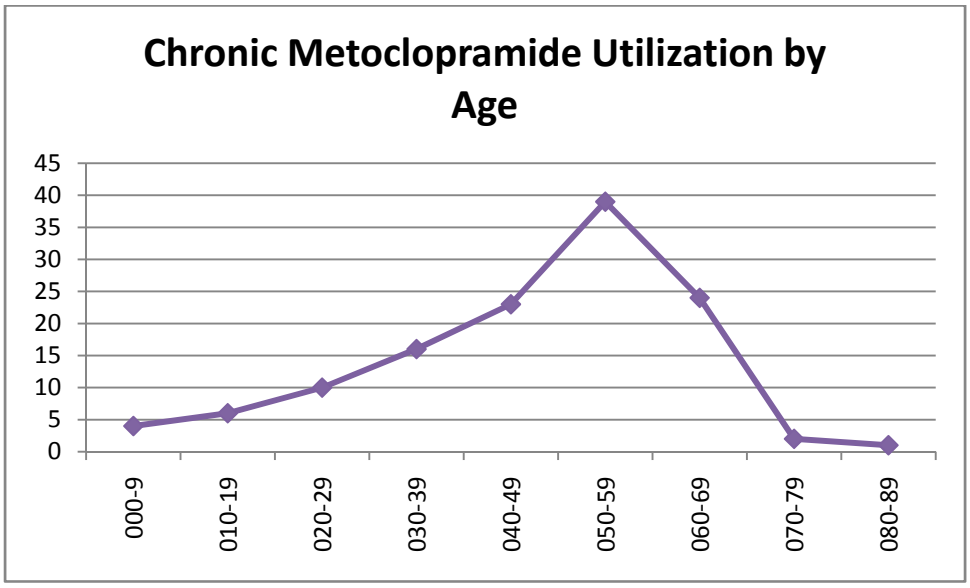
HID conducted claims analyses to determine the extent of chronic use of metoclopramide in the Mississippi Medicaid population. Three searches were conducted over a 6 month time span to identify those beneficiaries who were using metoclopramide continually. The results are included below.



A total of 2,598 beneficiaries received metoclopramide during the six-month time frame studied. Of these beneficiaries, 125, or approximately 5%, received metoclopramide consistently during the entire

six month time period, which is twice the recommended duration of treatment provided by the manufacturer.

The manufacturer also does not recommend use of metoclopramide in children, as they are more likely to experience the extrapyramidal effects from the medication. However, it has been used off-label in children for certain indications, such as GERD. HID looked at the chronic utilizers of metoclopramide and further examined the data by age.



As shown above, the chronic utilization of metoclopramide does not appear to be a significant problem. A total of 10 (8%) beneficiaries under the age of 19 received metoclopramide consistently during the time period analyzed.

Conclusion

Data suggests that metoclopramide is the most common cause of drug-induced tardive dyskinesia, and current product labeling for this medication includes warnings regarding the risk of tardive dyskinesia with chronic use. However, the FDA will now require manufacturers of metoclopramide to add a Boxed Warning to their product labeling regarding the risk of tardive dyskinesia with long-term or high-dose use, due to reports of tardive dyskinesia in patients using metoclopramide, many of whom had taken the drug for more than the recommended 3 months.

Recommendation

HID recommends the development of three RDUR criteria regarding metoclopramide use in Mississippi Medicaid beneficiaries.

1) A RDUR criterion identifying those beneficiaries who have received metoclopramide therapy for more than 12 weeks, the recommendation set forth by the manufacturer, in an effort to educate prescribers of the risks of tardive dyskinesia associated with chronic metoclopramide use.

2) A RDUR criterion identifying pediatric beneficiaries who have received metoclopramide therapy, in an effort to educate prescribers of the risks of tardive dyskinesia associated with metoclopramide use in this population.

3) A RDUR criterion identifying those beneficiaries who have received metoclopramide and any other medication known to cause extrapyramidal symptoms, in an effort to educate prescribers of the increased risk to the beneficiary associated with using these medications concurrently.

MISSISSIPPI MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS

Criteria Recommendations ***Approved Rejected***

1. Metoclopramide / Over-utilization _____ _____

Alert Message: Therapy with metoclopramide should not exceed 12 weeks. This agent is FDA approved for short-term therapy (4 -12 weeks) for adults with symptomatic documented GERD who fail to respond to conventional therapy and for treatment of diabetic gastroparesis (2 - 8 weeks). Chronic use of metoclopramide has been linked to tardive dyskinesia even after the drug is no longer taken. The risk of tardive dyskinesia and other adverse effects of metoclopramide increases with duration of treatment and cumulative dose.

Conflict Code: TA – Therapeutic Appropriateness **(Black Box Warning)**
Drugs/Diseases
Util A Util B Util C
Metoclopramide

Duration: 90 days or greater

References:
MedWatch: FDA Safety Information and Adverse Event Reporting Program, 2009.
Reglan Prescribing Information, Feb. 2004, Schwarz Pharma.
Facts & Comparisons, 2009 Updates.

2. Metoclopramide /Therapeutic Appropriateness _____ _____

Alert Message: The safety and effectiveness of metoclopramide in pediatric patients has not been established. Dystonias and other extrapyramidal reactions associated with metoclopramide are more common in the pediatric population than in adults. Both the risk of developing metoclopramide-induced tardive dyskinesia and the likelihood it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose.
Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases
Util A Util B Util C
Metoclopramide

Age Range: 0 – 17 years of age

References:
Clinical Pharmacology, Gold Standard Media 2009.
Facts & Comparisons, 2009 Updates.
Reglan Prescribing Information, Feb. 2004, Schwarz Pharma.

Criteria Recommendations ***Approved Rejected***

3. Metoclopramide / Meds Causing Extrapyramidal Symptoms _____ _____

Alert Message: Metoclopramide is contraindicated in patients receiving other drugs that are likely to cause extrapyramidal reactions. The concurrent use of these agents may increase the frequency or severity of these reactions.

Conflict Code: DD – Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Metoclopramide	Antidepressants	Phenytoin
	Antipsychotics	Reserpine
	Valproic Acid	Amiodarone
	Promethazine	
	Methylphenidate	
	Amphetamines	
	Methamphetamine	
	Prochlorperazine	

References:
Clinical Pharmacology, Gold Standard Media 2009.
Facts & Comparisons, 2009 Updates.
Reglan Prescribing Information, Feb. 2004, Schwarz Pharma.
Moses S. Drug-Induced Movement Disorders. April 2008. Family Practice Notebook. Available at: http://www.fpnotebook.com/Neuro/Pharm/DrgIndcdMvmntDsrdrs.htm
Factor SA, Leffler JB, Murray CF, Drug-induced Movement Disorders: A Clinical Review CME. Medscape CME. 2009. Available at: http://www.medscape.com/viewprogram/18880_pnt

4. Metoclopramide / Seizure Disorders _____ _____

Alert Message: Metoclopramide is contraindicated in patients with epilepsy since the drug may increase the frequency or severity of seizures.

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

Util A	Util B	Util C
Metoclopramide	Epilepsy ICD-9s	
	Seizure Disorders ICD-9s	

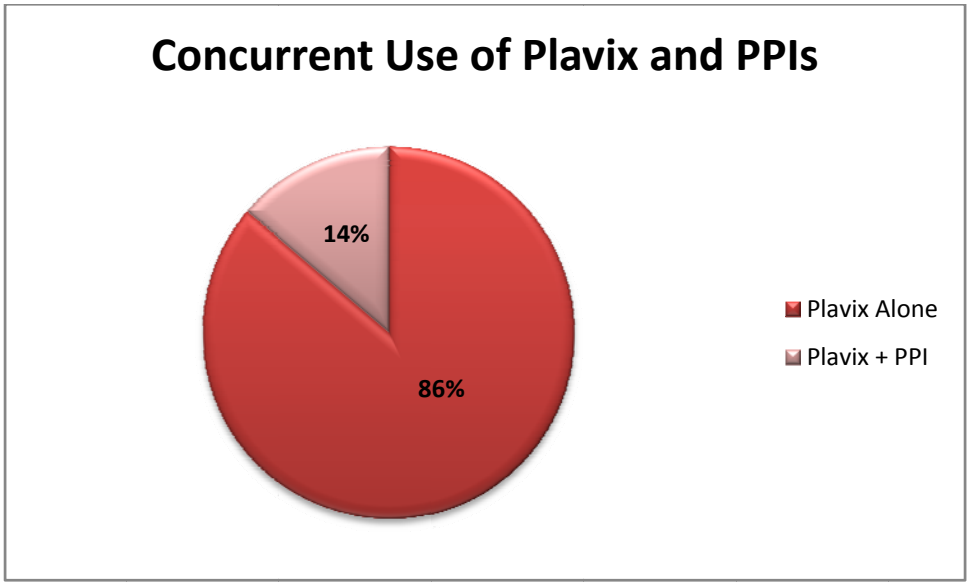
References:
Facts & Comparisons, 2009 Updates.
Reglan Prescribing Information, Feb. 2004, Schwarz Pharma.
Micromedex Healthcare Series, DrugDex Drug Evaluations, 2009.
AHFS Drug Information 2009.

Effect of Proton Pump Inhibitors on Plavix® (Clopidogrel) Efficacy

Plavix® is an oral antiplatelet agent that was approved by the FDA for reduction of atherosclerotic events associated with recent myocardial infarction (MI) or stroke or established peripheral arterial disease (PAD) In November 1997. Since that time it has also gained approval for reduction of atherosclerotic events in patients with acute coronary syndromes. Its overall tolerability appears to be similar to that of aspirin, but gastrointestinal bleeding may occur less often with clopidogrel.

Because of the now universal acceptance of antiplatelet therapy in coronary artery disease, specialists from the American College of Cardiology, the American Heart Association, and the American College of Gastroenterology developed a series of recommendations to minimize the risk of bleeding incidents, specifically GI bleeding, in these patients. One of the components of this consensus statement recommends PPIs as the principal therapy to treat and prevent gastric ulcers and bleeding in patients on antiplatelet therapy such as Plavix®. But, some studies indicate that concurrent use of Plavix® with proton pump inhibitors may decrease the effectiveness of clopidogrel. The most recent study, published in the March 4 issue of the *Journal of the American Medical Association*, showed that patients with acute coronary syndrome discharged on both Plavix® and a PPI had a 25% increased risk of death or rehospitalization for recurrent ACS than those patients treated with Plavix® only. 64% of the patients in this study were on Plavix® and a PPI, most likely explained by the consensus statement aforementioned. The FDA recently issued a notice that it has begun studies in conjunction with the manufacturer of Plavix® to determine, among other things, the effects of other drugs such as PPIs on the effectiveness of clopidogrel.

HID conducted claims analyses to determine the rate of concurrent utilization of Plavix® and PPIs in the Mississippi Medicaid population. The claims search covered October 2008 through December 2008 for all ages. Two searches were conducted: one for Plavix® for the mentioned time period and one for all PPIs for the same time period. These searches were then intersected to determine how many beneficiaries received both medications.



A total of 2,034 beneficiaries received Plavix® during the 3-month interval studied. Of these, 279 (14%) also received a proton pump inhibitor.

Conclusion

Recent data indicates that concurrent use of Plavix® and proton pump inhibitors may decrease the effectiveness of clopidogrel, potentially leading to rehospitalization for cardiac symptoms or even death. Although it appears that only a small percentage of Mississippi Medicaid beneficiaries received both treatment modalities simultaneously, the consequences related to this concurrent use could be hazardous for these beneficiaries. HID recommends a RDUR criterion identifying those beneficiaries who are taking both Plavix® and a PPI in an effort to educate prescribers of the risks associated with their concurrent use.

MISSISSIPPI MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS

Criteria Recommendations	***Approved***	***Rejected***

1. Clopidogrel / Proton Pump Inhibitors _____ _____

Alert Message: Some recent studies suggest a possible interaction if clopidogrel (Plavix) is given concurrently with a proton pump inhibitor (PPI). Coadministration of these agents may cause decreased clopidogrel anti-platelet efficacy which may lead to an increased incidence of adverse cardiovascular events. Monitor these patients closely for loss of clopidogrel efficacy. Current ACC/ACF/AHA guidelines have not changed and a PPI is still recommended for gastroprotection in patients receiving clopidogrel and NSAIDS who are at high risk for GI bleeds.

Conflict Code: DD – Drug/Drug Interaction
Drug/Disease:

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

References:

Aubert RE et al. Proton pump inhibitors effect on clopidogrel effectiveness: the clopidogrel Medco outcomes study (abstract 3998). Circulation. 2008;118:S815.
Dunn SP et al. Baseline proton pump inhibitor use is associated with increased cardiovascular events with and without use of clopidogrel in the CREDO trial (abstract 3999). Circulation. 2008;118:S815.
American Heart Association. American College of Cardiology (ACC)/American College of Gastroenterology (ACG)/American Heart Association (AHA) Joint Committee on Studies Regarding Possible Interaction of Clopidogrel and Proton Pump Inhibitors.
Available at: http://americanheart.mediaroom.com/index.php?s=43&item=611&printable Accessed January 1, 2009.
Do proton pump inhibitors decrease clopidogrel activity? Pharmacist Letter/Prescriber's Letter 2008;24(11):241114.

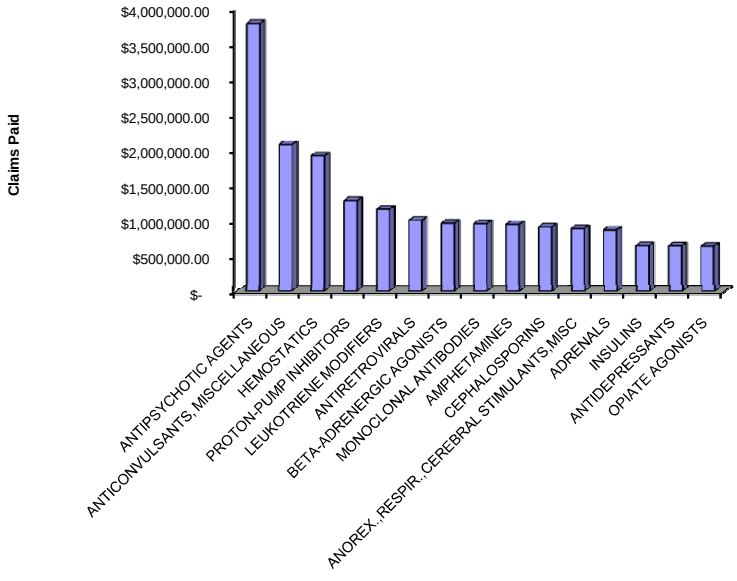
MISSISSIPPI MEDICAID
Cost Management Analysis

TOP 15 THERAPEUTIC CLASSES BY TOTAL COST OF CLAIMS FROM 03/01/09-03/31/09

AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
ANTIPSYCHOTIC AGENTS	12,272	$ 3,784,192.14	$ 308.36	2.58%
ANTICONVULSANTS, MISCELLANEOUS	13,389	$ 2,078,556.34	$ 155.24	2.81%
HEMOSTATICS	55	$ 1,919,989.74	$34,908.90	0.01%
PROTON-PUMP INHIBITORS	8,356	$ 1,286,240.52	$ 153.93	1.76%
LEUKOTRIENE MODIFIERS	10,068	$ 1,163,388.60	$ 115.55	2.12%
ANTIRETROVIRALS	1,274	$ 1,008,511.14	$ 791.61	0.27%
BETA-ADRENERGIC AGONISTS	15,816	$ 968,829.87	$ 61.26	3.32%
MONOCLONAL ANTIBODIES	638	$ 962,551.36	$ 1,508.70	0.13%
AMPHETAMINES	6,217	$ 953,026.49	$ 153.29	1.31%
CEPHALOSPORINS	15,909	$ 916,642.33	$ 57.62	3.34%
ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	6,717	$ 892,171.99	$ 132.82	1.41%
ADRENALS	12,846	$ 872,404.72	$ 67.91	2.70%
INSULINS	4,095	$ 652,906.09	$ 159.44	0.86%
ANTIDEPRESSANTS	15,947	$ 649,206.09	$ 40.71	3.35%
OPIATE AGONISTS	30,752	$ 643,024.65	$ 20.91	6.46%
TOTAL TOP 15	154,351	$ 18,751,642.07	$ 121.49	32.44%

Total Rx Claims	475,861
From 03/01/09-03/31/09	

Top 15 Therapeutic Classes
Based on Total Cost of Claims



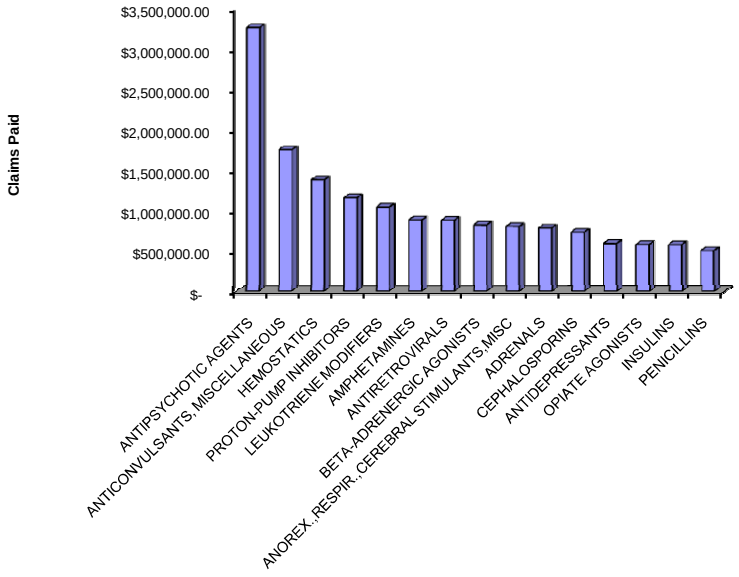
MISSISSIPPI MEDICAID
Cost Management Analysis

TOP 15 THERAPEUTIC CLASSES BY TOTAL COST OF CLAIMS FROM 04/01/09-04/30/09

AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
ANTIPSYCHOTIC AGENTS	11,028	$ 3,262,463.91	$ 295.83	2.68%
ANTICONVULSANTS, MISCELLANEOUS	12,428	$ 1,754,661.48	$ 141.19	3.02%
HEMOSTATICS	60	$ 1,383,668.50	$23,061.14	0.01%
PROTON-PUMP INHIBITORS	7,516	$ 1,162,689.86	$ 154.70	1.82%
LEUKOTRIENE MODIFIERS	9,052	$ 1,045,842.41	$ 115.54	2.20%
AMPHETAMINES	5,947	$ 887,933.07	$ 149.31	1.44%
ANTIRETROVIRALS	1,124	$ 883,674.96	$ 786.19	0.27%
BETA-ADRENERGIC AGONISTS	13,296	$ 825,498.91	$ 62.09	3.23%
ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	6,080	$ 807,523.29	$ 132.82	1.48%
ADRENALS	11,313	$ 787,765.46	$ 69.63	2.75%
CEPHALOSPORINS	12,848	$ 735,010.70	$ 57.21	3.12%
ANTIDEPRESSANTS	14,359	$ 596,166.02	$ 41.52	3.49%
OPIATE AGONISTS	27,935	$ 583,389.30	$ 20.88	6.78%
INSULINS	3,626	$ 581,549.56	$ 160.38	0.88%
PENICILLINS	21,472	$ 508,014.88	$ 23.66	5.21%
TOTAL TOP 15	158,084	$ 15,805,852.31	$ 99.98	38.37%

Total Rx Claims	412,020
From 04/01/09-04/30/09	

Top 15 Therapeutic Classes
Based on Total Cost of Claims



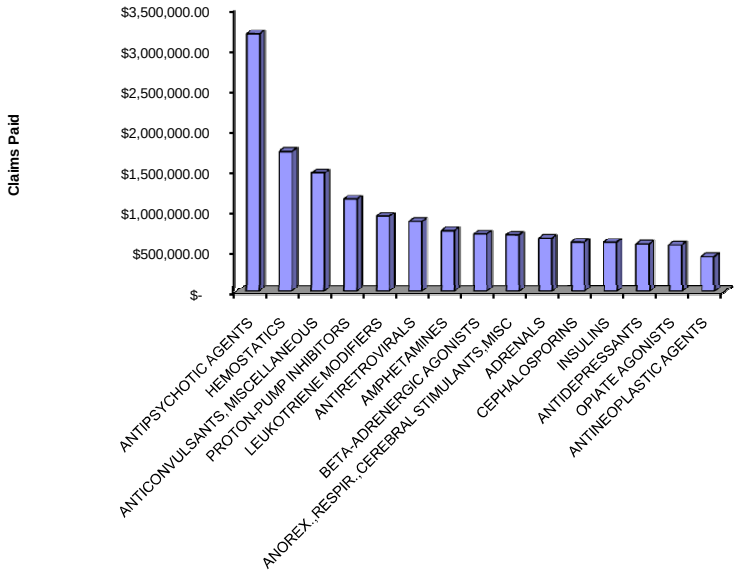
MISSISSIPPI MEDICAID
Cost Management Analysis

TOP 15 THERAPEUTIC CLASSES BY TOTAL COST OF CLAIMS FROM 05/01/09-05/31/09

AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
ANTIPSYCHOTIC AGENTS	10,899	$ 3,184,630.36	$ 292.19	2.90%
HEMOSTATICS	50	$ 1,733,373.08	$34,667.46	0.01%
ANTICONVULSANTS, MISCELLANEOUS	11,085	$ 1,469,025.41	$ 132.52	2.95%
PROTON-PUMP INHIBITORS	7,386	$ 1,146,930.03	$ 155.28	1.97%
LEUKOTRIENE MODIFIERS	8,096	$ 933,908.19	$ 115.35	2.15%
ANTIRETROVIRALS	1,097	$ 870,108.35	$ 793.17	0.29%
AMPHETAMINES	5,196	$ 755,604.04	$ 145.42	1.38%
BETA-ADRENERGIC AGONISTS	11,195	$ 712,941.39	$ 63.68	2.98%
ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	5,215	$ 702,373.86	$ 134.68	1.39%
ADRENALS	9,352	$ 660,858.00	$ 70.66	2.49%
CEPHALOSPORINS	10,820	$ 614,104.25	$ 56.76	2.88%
INSULINS	3,709	$ 612,842.79	$ 165.23	0.99%
ANTIDEPRESSANTS	14,167	$ 591,500.65	$ 41.75	3.77%
OPIATE AGONISTS	26,767	$ 578,490.21	$ 21.61	7.12%
ANTINEOPLASTIC AGENTS	819	$ 434,269.11	$ 530.24	0.22%
TOTAL TOP 15	125,853	$ 15,000,959.72	$ 119.19	33.49%

Total Rx Claims	375,848
From 05/01/09-05/31/09	

Top 15 Therapeutic Classes
Based on Total Cost of Claims



MISSISSIPPI MEDICAID
Cost Management Analysis

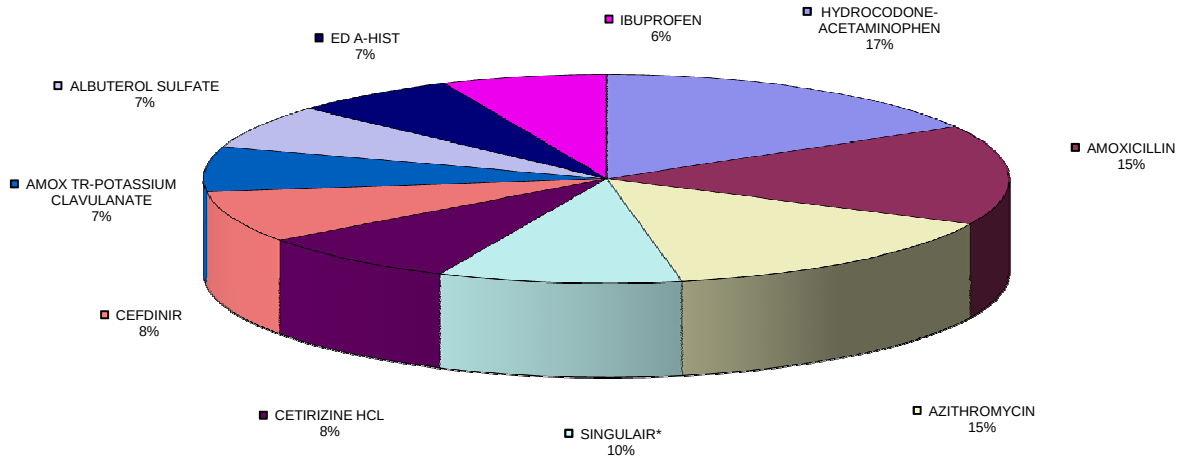
TOP 25 DRUGS BASED ON NUMBER OF CLAIMS FROM 03/01/09-03/31/09

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
HYDROCODONE-ACETAMINOPHEN	OPIATE AGONISTS	17,186	$ 237,944.93	1
AMOXICILLIN	PENICILLINS	15,967	$ 152,272.17	5
AZITHROMYCIN	MACROLIDES	15,320	$ 446,846.33	6
SINGULAIR*	LEUKOTRIENE MODIFIERS	10,055	$ 1,161,336.99	4
CETIRIZINE HCL	SECOND GENERATION ANTIHISTAMINES	8,492	$ 136,168.94	~
CEFDINIR	CEPHALOSPORINS	8,228	$ 615,619.87	68
AMOX TR-POTASSIUM CLAVULANATE	PENICILLINS	7,203	$ 385,079.76	32
ALBUTEROL SULFATE	BETA-ADRENERGIC AGONISTS	7,017	$ 225,970.42	67
ED A-HIST	PROPYLAMINE DERIVATIVES	6,860	$ 62,063.85	~
IBUPROFEN	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS	6,786	$ 54,654.60	18
PREVACID*	PROTON-PUMP INHIBITORS	5,852	$ 991,923.62	7
SULFAMETHOXAZOLE-TRIMETHOPRIM	SULFONAMIDES (SYSTEMIC)	5,487	$ 63,951.90	39
ALPRAZOLAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	5,460	$ 45,290.88	8
CLONAZEPAM	BENZODIAZEPINES (ANTICONVULSANTS)	4,379	$ 33,515.34	24
PROMETHAZINE HCL	PHENOTHIAZINE DERIVATIVES	4,225	$ 47,873.00	59
ACETAMINOPHEN-CODEINE	OPIATE AGONISTS	4,166	$ 34,989.55	43
PROAIR HFA*	BETA-ADRENERGIC AGONISTS	4,160	$ 179,182.90	14
CEPHALEXIN	CEPHALOSPORINS	3,967	$ 61,090.14	22
RISPERIDONE	ANTIPSYCHOTIC AGENTS	3,781	$ 613,937.56	140
TAMIFLU	NEURAMINIDASE INHIBITORS	3,510	$ 287,019.32	80
ADDERALL XR*	AMPHETAMINES	3,470	$ 686,787.58	30
LORAZEPAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	3,222	$ 22,968.36	23
CONCERTA*	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	3,063	$ 443,886.79	34
NYSTATIN	ANTIFUNGALS (SKIN & MUCOUS MEMBRANE)	3,051	$ 38,223.20	142
RANITIDINE HCL	HISTAMINE H2-ANTAGONISTS	3,013	$ 78,764.15	50
TOTAL TOP 25		163,920	$ 7,107,362.15	

Total Rx Claims From 03/01/09-03/31/09	475,861

** Indicates preferred products on Preferred Drug List*

Top 10 Drugs
Based on Number of Claims



MISSISSIPPI MEDICAID
Cost Management Analysis

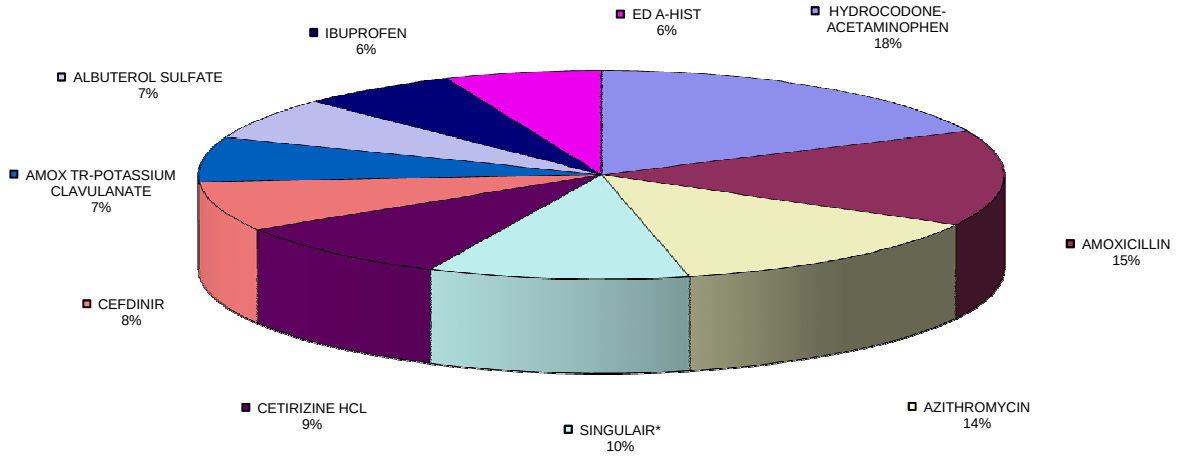
TOP 25 DRUGS BASED ON NUMBER OF CLAIMS FROM 04/01/09-04/30/09

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
HYDROCODONE-ACETAMINOPHEN	OPIATE AGONISTS	15,692	$ 217,338.13	1
AMOXICILLIN	PENICILLINS	12,861	$ 120,305.41	5
AZITHROMYCIN	MACROLIDES	11,709	$ 341,383.65	6
SINGULAIR*	LEUKOTRIENE MODIFIERS	9,042	$ 1,044,281.43	4
CETIRIZINE HCL	SECOND GENERATION ANTIHISTAMINES	8,013	$ 127,520.42	~
CEFDINIR	CEPHALOSPORINS	6,647	$ 489,750.20	68
AMOX TR-POTASSIUM CLAVULANATE	PENICILLINS	6,006	$ 317,754.96	32
ALBUTEROL SULFATE	BETA-ADRENERGIC AGONISTS	5,675	$ 164,495.00	67
IBUPROFEN	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS	5,505	$ 42,713.08	18
ED A-HIST	PROPYLAMINE DERIVATIVES	5,419	$ 46,470.78	~
SULFAMETHOXAZOLE-TRIMETHOPRIM	SULFONAMIDES (SYSTEMIC)	5,353	$ 65,353.12	39
PREVACID*	PROTON-PUMP INHIBITORS	5,248	$ 891,285.98	7
ALPRAZOLAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	5,052	$ 41,911.51	8
CLONAZEPAM	BENZODIAZEPINES (ANTICONVULSANTS)	4,010	$ 30,639.77	24
ACETAMINOPHEN-CODEINE	OPIATE AGONISTS	3,622	$ 29,966.16	43
PROAIR HFA*	BETA-ADRENERGIC AGONISTS	3,577	$ 155,554.65	14
PROMETHAZINE HCL	PHENOTHIAZINE DERIVATIVES	3,393	$ 39,972.41	59
RISPERIDONE	ANTIPSYCHOTIC AGENTS	3,366	$ 344,441.50	140
CEPHALEXIN	CEPHALOSPORINS	3,309	$ 51,190.50	22
CONCERTA*	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	2,752	$ 402,962.13	34
LORAZEPAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	2,740	$ 19,804.11	23
NYSTATIN	ANTIFUNGALS (SKIN & MUCOUS MEMBRANE)	2,724	$ 33,518.95	142
AMLODIPINE BESYLATE	DIHYDROPYRIDINES	2,673	$ 18,534.25	~
RANITIDINE HCL	HISTAMINE H2-ANTAGONISTS	2,641	$ 68,389.82	50
ADDERALL XR*	AMPHETAMINES	2,488	$ 491,796.04	30
TOTAL TOP 25		139,517	$ 5,597,333.96	

Total Rx Claims From 04/01/09-04/30/09	412,020

** Indicates preferred products on Preferred Drug List*

Top 10 Drugs
Based on Number of Claims



MISSISSIPPI MEDICAID
Cost Management Analysis

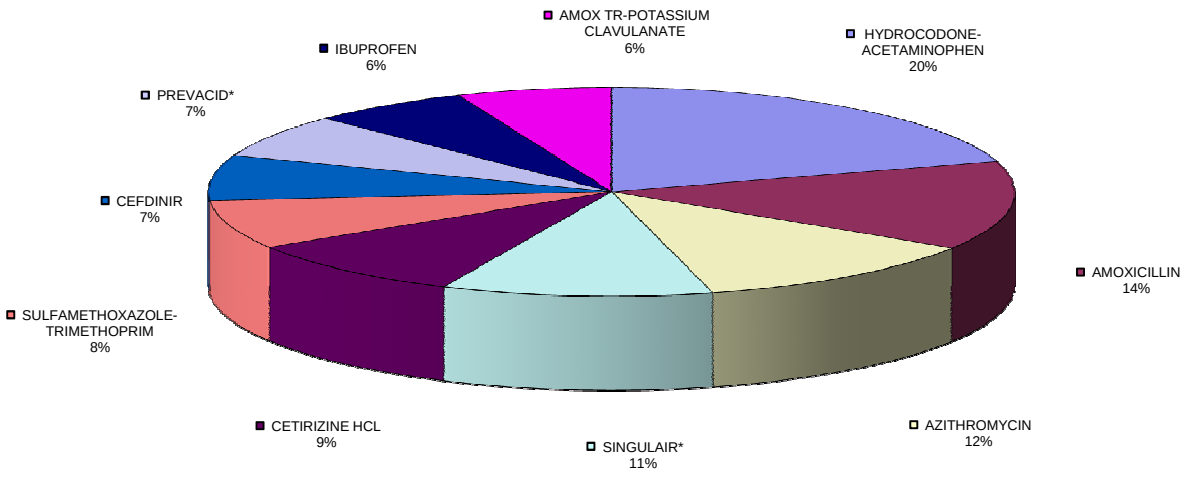
TOP 25 DRUGS BASED ON NUMBER OF CLAIMS FROM 05/01/09-05/31/09

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
HYDROCODONE-ACETAMINOPHEN	OPIATE AGONISTS	15,148	$ 210,726.36	1
AMOXICILLIN	PENICILLINS	10,261	$ 94,444.61	5
AZITHROMYCIN	MACROLIDES	8,875	$ 257,470.35	6
SINGULAIR*	LEUKOTRIENE MODIFIERS	8,080	$ 932,155.98	4
CETIRIZINE HCL	SECOND GENERATION ANTIHISTAMINES	6,912	$ 122,155.45	~
SULFAMETHOXAZOLE-TRIMETHOPRIM	SULFONAMIDES (SYSTEMIC)	5,643	$ 69,517.40	39
CEFDINIR	CEPHALOSPORINS	5,234	$ 387,297.00	68
PREVACID*	PROTON-PUMP INHIBITORS	5,032	$ 867,291.17	7
IBUPROFEN	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS	4,774	$ 37,043.01	18
AMOX TR-POTASSIUM CLAVULANATE	PENICILLINS	4,611	$ 242,864.59	32
ALPRAZOLAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	4,604	$ 36,662.29	8
ALBUTEROL SULFATE	BETA-ADRENERGIC AGONISTS	4,363	$ 110,080.23	67
CLONAZEPAM	BENZODIAZEPINES (ANTICONVULSANTS)	3,921	$ 30,088.36	24
ED A-HIST	PROPYLAMINE DERIVATIVES	3,838	$ 30,903.21	~
RISPERIDONE	ANTIPSYCHOTIC AGENTS	3,309	$ 290,416.52	140
CEPHALEXIN	CEPHALOSPORINS	3,142	$ 48,882.16	22
ACETAMINOPHEN-CODEINE	OPIATE AGONISTS	3,117	$ 26,070.43	43
PROAIR HFA*	BETA-ADRENERGIC AGONISTS	3,102	$ 134,076.91	14
PROMETHAZINE HCL	PHENOTHIAZINE DERIVATIVES	3,098	$ 36,468.71	59
LORAZEPAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	2,708	$ 18,947.84	23
AMLODIPINE BESYLATE	DIHYDROPYRIDINES	2,622	$ 18,138.17	~
NYSTATIN	ANTIFUNGALS (SKIN & MUCOUS MEMBRANE)	2,578	$ 32,592.72	142
LISINOPRIL	ANGIOTENSIN-CONVERTING ENZYME INHIBITORS	2,546	$ 12,287.75	2
RANITIDINE HCL	HISTAMINE H2-ANTAGONISTS	2,465	$ 61,632.28	50
CITALOPRAM HBR	ANTIDEPRESSANTS	2,434	$ 26,911.94	25
TOTAL TOP 25		122,417	$ 4,135,125.44	

Total Rx Claims From 05/01/09-05/31/09	375,848

** Indicates preferred products on Preferred Drug List*

Top 10 Drugs
Based on Number of Claims



MISSISSIPPI MEDICAID
Cost Management Analysis

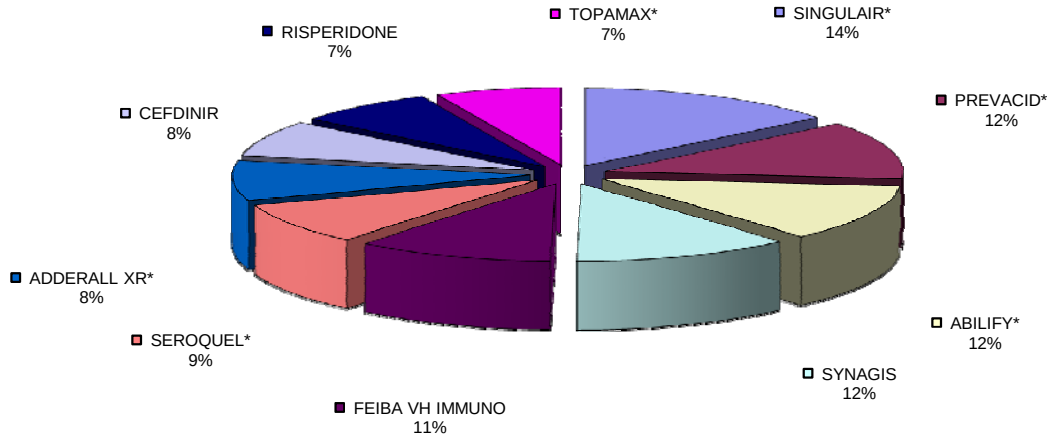
TOP 25 DRUGS BASED ON TOTAL CLAIMS COST FROM 03/01/09-03/31/09

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
SINGULAIR*	LEUKOTRIENE MODIFIERS	10,055	$ 1,161,336.99	7
PREVACID*	PROTON-PUMP INHIBITORS	5,852	$ 991,923.62	5
ABILIFY*	ANTIPSYCHOTIC AGENTS	1,951	$ 972,253.22	12
SYNAGIS	MONOCLONAL ANTIBODIES	638	$ 962,551.36	~
FEIBA VH IMMUNO	HEMOSTATICS	10	$ 874,474.10	~
SEROQUEL*	ANTIPSYCHOTIC AGENTS	1,919	$ 704,879.47	6
ADDERALL XR*	AMPHETAMINES	3,470	$ 686,787.58	23
CEFDINIR	CEPHALOSPORINS	8,228	$ 615,619.87	17
RISPERIDONE	ANTIPSYCHOTIC AGENTS	3,781	$ 613,937.56	24
TOPAMAX*	ANTICONVULSANTS, MISCELLANEOUS	1,529	$ 552,014.08	13
ZYPREXA	ANTIPSYCHOTIC AGENTS	894	$ 536,070.46	15
AZITHROMYCIN	MACROLIDES	15,320	$ 446,846.33	3
CONCERTA*	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	3,063	$ 443,886.79	33
AMOX TR-POTASSIUM CL	PENICILLINS	7,203	$ 385,079.76	10
NOVOSEVEN RT	HEMOSTATICS	9	$ 364,775.67	~
ADVAIR DISKUS*	BETA-ADRENERGIC AGONISTS	1,735	$ 347,761.82	4
PULMICORT*	ADRENALS	1,035	$ 327,659.48	55
GEODON*	ANTIPSYCHOTIC AGENTS	796	$ 313,639.11	45
BUDESONIDE	ADRENALS	1,244	$ 291,676.48	~
TAMIFLU	NEURAMINIDASE INHIBITORS	3,510	$ 287,019.32	122
FOCALIN XR*	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	1,956	$ 269,193.28	113
EXJADE	HEAVY METAL ANTAGONISTS	54	$ 253,114.04	~
NASONEX*	CORTICOSTEROIDS (EENT)	2,602	$ 242,618.28	42
HYDROCODONE-ACETAM	OPIATE AGONISTS	17,186	$ 237,944.93	1
STRATTERA*	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	1,388	$ 235,310.68	78
TOTAL TOP 25		95,428	$ 13,118,374.28	

Total Rx Claims From 03/01/09-03/31/09	475,861

** Indicates preferred products on Preferred Drug List*

Top 10 Drugs
Based on Total Claims Cost



MISSISSIPPI MEDICAID
Cost Management Analysis

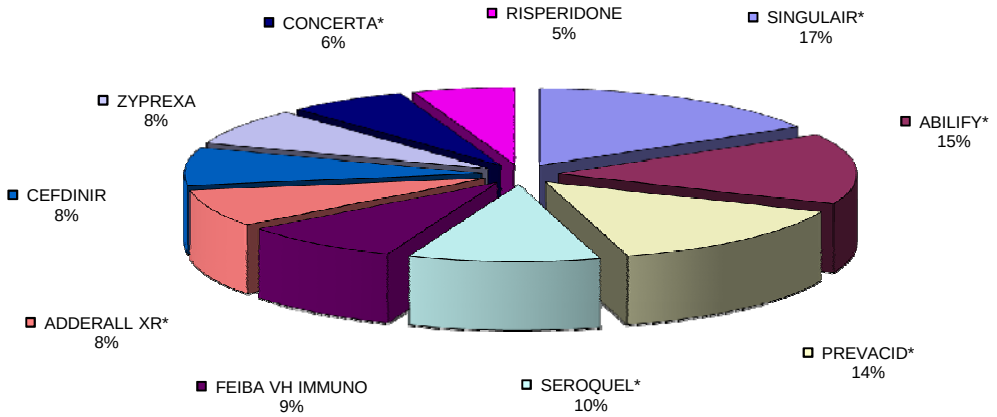
TOP 25 DRUGS BASED ON TOTAL CLAIMS COST FROM 04/01/09-04/30/09

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
SINGULAIR*	LEUKOTRIENE MODIFIERS	9,042	$ 1,044,281.43	7
ABILIFY*	ANTIPSYCHOTIC AGENTS	1,873	$ 922,651.92	12
PREVACID*	PROTON-PUMP INHIBITORS	5,248	$ 891,285.98	5
SEROQUEL*	ANTIPSYCHOTIC AGENTS	1,706	$ 649,776.03	6
FEIBA VH IMMUNO	HEMOSTATICS	8	$ 545,470.43	~
ADDERALL XR*	AMPHETAMINES	2,488	$ 491,796.04	23
CEFDINIR	CEPHALOSPORINS	6,647	$ 489,750.20	17
ZYPREXA	ANTIPSYCHOTIC AGENTS	795	$ 485,388.31	15
CONCERTA*	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	2,752	$ 402,962.13	33
RISPERIDONE	ANTIPSYCHOTIC AGENTS	3,366	$ 344,441.50	24
AZITHROMYCIN	MACROLIDES	11,709	$ 341,383.65	3
PULMICORT*	ADRENALS	1,009	$ 325,659.56	55
ADVAIR DISKUS*	BETA-ADRENERGIC AGONISTS	1,588	$ 322,322.00	4
AMOX TR-POTASSIUM CL	PENICILLINS	6,006	$ 317,754.96	10
GEODON*	ANTIPSYCHOTIC AGENTS	729	$ 292,227.80	45
TOPAMAX*	ANTICONVULSANTS, MISCELLANEOUS	774	$ 289,761.39	13
FOCALIN XR*	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	1,702	$ 236,662.81	113
BUDESONIDE	ADRENALS	966	$ 224,723.05	~
PLAVIX*	PLATELET-AGGREGATION INHIBITORS	1,472	$ 220,486.14	3
HYDROCODONE-ACETAM	OPIATE AGONISTS	15,692	$ 217,338.13	1
VYVANSE*	AMPHETAMINES	1,623	$ 215,169.43	96
NASONEX*	CORTICOSTEROIDS (EENT)	2,308	$ 215,062.84	42
EFFEXOR XR*	ANTIDEPRESSANTS	1,111	$ 208,539.71	8
NOVOSEVEN RT	HEMOSTATICS	6	$ 205,771.86	~
STRATTERA*	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	1,198	$ 203,128.59	78
TOTAL TOP 25		81,818	$ 10,103,795.89	

Total Rx Claims From 04/01/09-04/30/09	412,020

** Indicates preferred products on Preferred Drug List*

Top 10 Drugs
Based on Total Claims Cost



MISSISSIPPI MEDICAID
Cost Management Analysis

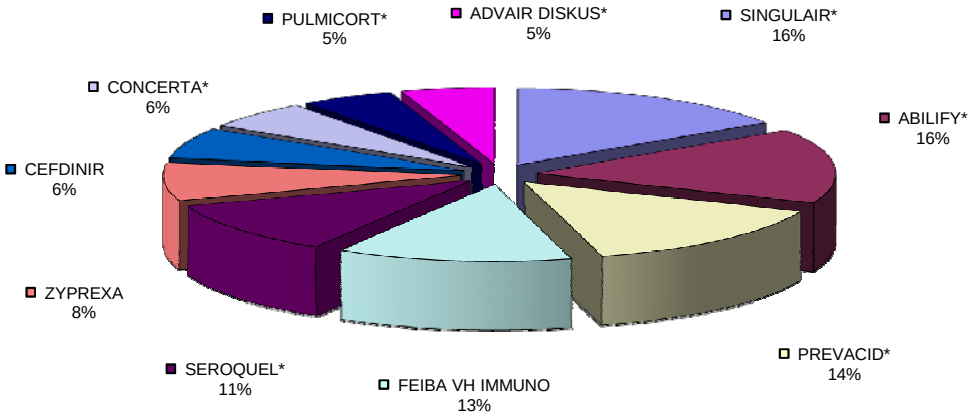
TOP 25 DRUGS BASED ON TOTAL CLAIMS COST FROM 05/01/09-05/31/09

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
SINGULAIR*	LEUKOTRIENE MODIFIERS	8,080	$ 932,155.98	7
ABILIFY*	ANTIPSYCHOTIC AGENTS	1,853	$ 927,397.96	12
PREVACID*	PROTON-PUMP INHIBITORS	5,032	$ 867,291.17	5
FEIBA VH IMMUNO	HEMOSTATICS	8	$ 758,293.21	~
SEROQUEL*	ANTIPSYCHOTIC AGENTS	1,745	$ 658,023.55	6
ZYPREXA	ANTIPSYCHOTIC AGENTS	783	$ 467,283.31	15
CEFDINIR	CEPHALOSPORINS	5,234	$ 387,297.00	17
CONCERTA*	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	2,388	$ 350,856.41	33
PULMICORT*	ADRENALS	948	$ 300,870.03	55
ADVAIR DISKUS*	BETA-ADRENERGIC AGONISTS	1,474	$ 298,869.85	4
GEODON*	ANTIPSYCHOTIC AGENTS	717	$ 293,081.90	45
RISPERIDONE	ANTIPSYCHOTIC AGENTS	3,309	$ 290,416.52	24
ADDERALL XR*	AMPHETAMINES	1,384	$ 277,504.56	23
AZITHROMYCIN	MACROLIDES	8,875	$ 257,470.35	3
AMOX TR-POTASSIUM CL	PENICILLINS	4,611	$ 242,864.59	10
DEXTROAMPHETAMINE-A	AMPHETAMINES	1,254	$ 222,256.47	~
PLAVIX*	PLATELET-AGGREGATION INHIBITORS	1,475	$ 221,274.23	3
HYDROCODONE-ACETAM	OPIATE AGONISTS	15,148	$ 210,726.36	1
EFFEXOR XR*	ANTIDEPRESSANTS	1,111	$ 208,962.85	8
ATRIPLA	ANTIRETROVIRALS	139	$ 204,138.45	39
FOCALIN XR*	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	1,461	$ 203,428.31	113
VYVANSE*	AMPHETAMINES	1,535	$ 203,207.79	96
LIPITOR*	HMG-COA REDUCTASE INHIBITORS	1,702	$ 195,484.75	1
LEVETIRACETAM	ANTICONVULSANTS, MISCELLANEOUS	900	$ 192,875.82	182
RISPERDAL CONSTA	ANTIPSYCHOTIC AGENTS	231	$ 191,475.82	129
TOTAL TOP 25		71,397	$ 9,363,507.24	

Total Rx Claims From 05/01/09-05/31/09	375,848

** Indicates preferred products on Preferred Drug List*

Top 10 Drugs
Based on Total Claims Cost



Drug Utilization Review (DUR): An Overview of OBRA 90

Overview

"The Omnibus Budget Reconciliation Act of 1990 (OBRA 90) is the compromise of federal budget legislation that integrated both House and Senate versions of the federal budget. The objective of section 4401 of OBRA 90 is to save taxpayer money by reducing the cost of drug therapy for Medicaid patients. The legislation's approach to achieving this savings is through reducing the amount that Medicaid pays for pharmaceuticals and increasing pharmacist responsibility for patient outcomes with drug therapy."[1]

OBRA 90 required each state to establish a Drug Utilization Review (DUR) program for outpatient medications within the Medicaid program by January 1, 1993. This program consists of 3 parts:

- Prospective drug review
- Retrospective drug use review
- Educational program

Prospective DUR

OBRA 90 requires that pharmacists perform Point of Sale (POS) review of drug therapy prior to filling or delivering a prescription to a recipient. Prospective DUR is significant because it increases the pharmacist's responsibility for patient outcomes with drug therapy[1]. The review must include screening for the following drug therapy problems:

- Therapeutic duplication
- Drug-disease contraindication
- Drug-drug interaction
- Incorrect drug dosage
- Incorrect drug duration
- Drug-allergy interaction
- Clinical abuse/misuse

If a drug therapy problem is identified the pharmacist must take appropriate action. The pharmacist must also counsel or attempt to counsel Medicaid recipients on new prescriptions. If the recipient or the recipient's caregiver refuses counseling, documentation of this refusal is required.

Retrospective DUR

Retrospective DUR is an educational tool to help physicians and pharmacists:
"…identify and reduce the frequency of patterns of fraud, abuse, gross overuse, or inappropriate or medically unnecessary care, among physicians, pharmacists, and Medicaid recipients, or associated with specific drugs or groups of drugs." [2]

Retrospective DUR include using predetermined standards (clinical criteria) to monitor the following areas:

- Therapeutic appropriateness
- Overutilization and underutilization
- Appropriate use of generic products

- Therapeutic duplication
- Drug-disease contraindication
- Drug-drug interaction
- Incorrect drug dosage
- Incorrect drug duration
- Clinical abuse/misuse

Clinical criteria, used in the DUR program must be developed from:

- Peer reviewed medical literature; and/or
- American Hospital Formulary Service Drug Information; and/or
- United States Pharmacopeia Drug Information; and/or
- American Medical Association Drug Evaluations[4]

The purpose of retrospective DUR is to prevent future drug utilization problems. Therefore, State retrospective DUR programs must introduce educational programs to improve care and preserve Medicaid dollars.

Educational Program

"The state plan must provide for ongoing educational outreach programs that, using DUR Board data on common drug therapy problems, educate practitioners on common drug therapy problems with the aim of improving prescribing and dispensing practices." [2] The educational program must include the following interventions:

- Dissemination of information to physicians and pharmacists in the State concerning the duties and powers of the DUR Board and the basis for the standards used in assessing drug use
- Written, oral, or electronic reminders containing patient specific or drug specific information (or both) and suggested changes in prescribing or dispensing practices
- Face to face discussions, with follow up discussions when necessary, between health care professionals proficient in appropriate drug therapy and selected prescribers and pharmacists who have been targeted for educational intervention on optimal prescribing
- Intensified review or monitoring of selected prescribers or dispensers

DUR Board

State DUR Board Requirement and member qualifications

Each State is required to establish a DUR Board consisting of health care professionals who have recognized knowledge and expertise in at least one of the following areas:

- Clinically appropriate prescribing of covered outpatient drugs
- Clinically appropriate dispensing of outpatient drugs
- Drug use review, evaluation, and intervention
- Medical quality assurance

Board Composition

The Board must consist of at least one-third but not more than 51 percent physicians, and at least one-third of the Board members must be pharmacists. These physicians and pharmacists must be actively practicing and licensed.

Medicaid Agency/DUR Board relationship

It is the responsibility of the Medicaid agency to ensure that the DUR program is operational. The state Medicaid Agency has the authority to accept or reject any recommendation or decision of the DUR Board.

DUR Board Role

- Review and make recommendations on clinical criteria submitted
- Evaluate the use of the clinical criteria
- Identify and develop educational topics if education of practitioners on common drug therapy problems is needed to improve prescribing or dispensing practices
- Make recommendations as to which mix of the interventions would most effectively lead to improvement in the quality of drug therapy
- Periodically re-evaluate and, if necessary, modify the interventions
- Review annual CMS report

Medicaid Agency or Agency's Contractor Role

- Submit clinical criteria to the DUR Board for its review and recommendations prior to applying them to drug claims data
- Once the clinical criteria is approved by the Board apply it to drug claims data in order to generate reports that identify patterns of fraud, abuse, gross overuse, or inappropriate or medically unnecessary care.
- Carry out the educational programs and interventions specified by the Board

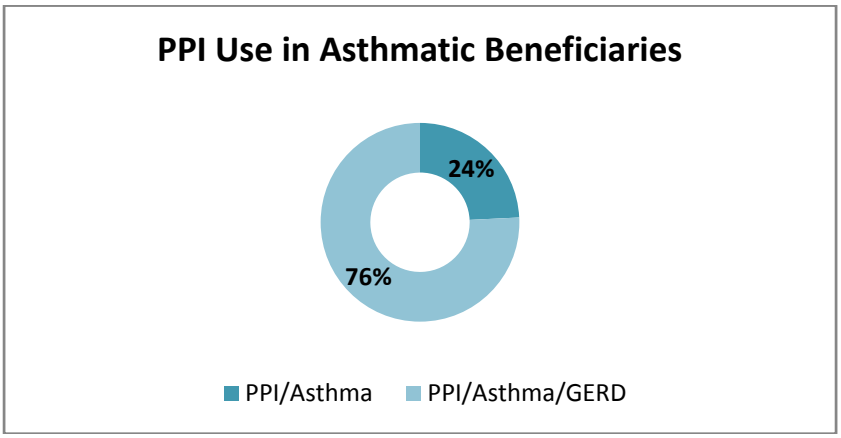
OBRA 90 is significant for pharmacists because it identified pharmaceutical care as a means of achieving Medicaid cost savings and increased the pharmacists' responsibility for patient outcomes with drug therapy[1]. "The goal of the State's DUR program must be to ensure appropriate drug therapy, while permitting sufficient professional prerogatives to allow for individualized drug therapy."

1. Brushwood DB: OBRA 90 and Managed Care Pharmacy. Drug Benefit Trends 7(8): 34-39, 42, 1995. © 1995 SCP Communications, Inc.
2. The Omnibus Budget Reconciliation Act of 1990. 57 FR 49408 (Nov. 2, 1992)
3. The Omnibus Budget Reconciliation Act of 1990. 59 FR 48824 (Sept. 23, 1994)
4. This reference is no longer available; CMS had yet to define a successor at the time of printing.

Benefit of Prophylactic Proton Pump Inhibitor Use in Asthmatics

It is estimated that anywhere from 32% to 84% of patients with asthma also have gastroesophageal reflux disease (GERD), but do not experience the classic symptoms of the disease (commonly referred to as silent GERD). A common belief is that GERD may contribute to asthma symptoms by resultant airway inflammation and obstruction from gastric contents that have aspirated into the lungs. A recent study in *The New England Journal of Medicine* has demonstrated that silent GERD is not a factor in poorly controlled asthma; accordingly, the use of PPIs in asthmatics that had little or no acid reflux symptoms did not improve asthma control. This study included poorly controlled asthmatics with no acid reflux symptoms or minimal symptoms, and they were given either a PPI or placebo. Those subjects that were given a PPI did not show any significant difference in asthma symptoms over the course of the six month study. These findings indicate that many asthma patients with silent GERD may be taking PPIs for no reason.

HID gathered claims data for calendar year 2008 to determine if PPI use in Mississippi Medicaid beneficiaries with an asthma diagnosis could be associated with an appropriate diagnosis or was prophylactic in nature. The chart below illustrates the findings.



Clearly, an overwhelming majority (76%) of Mississippi Medicaid asthmatic beneficiaries that received a PPI in 2008 had a GERD diagnosis. This would indicate that PPI use in the Mississippi Medicaid asthma population is not prophylactic but based on an actual GERD diagnosis, for the most part.

Conclusion

It has become a common practice to prescribe PPIs prophylactically in beneficiaries whose asthma is not well controlled, even if they are not experiencing acid reflux symptoms. A recent government-funded study has indicated that such use does not improve asthma control in these patients. Fortunately, data obtained for this report does not indicate that this is a problem in the Mississippi Medicaid population, with a large percentage of asthmatic beneficiaries receiving a PPI also having a GERD diagnosis. However, HID recommends the development of a RDUR criterion to identify those beneficiaries diagnosed with asthma receiving a PPI without a corresponding diagnosis, such as GERD, for such treatment. This intervention would result in an educational letter to the prescribing physician of the PPI to inform them of recent findings indicating that prophylactic use of PPIs in asthmatics provides no additional benefits but results in higher health care costs.

MISSISSIPPI MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS

Criteria Recommendations ***Approved Rejected***

1. PPIs / Asthma / GERD Negating _____ _____

Alert Message: A recent review of the patient's diagnostic history did not reveal a diagnosis of GERD to support the use of a proton pump inhibitor (PPI). The patient does have asthma and PPIs are commonly used to help manage asthma if the patient has symptomatic GERD. However, studies suggest that patients with poorly controlled asthma who have asymptomatic "silent" GERD do not benefit from treatment with a PPI. Consider reassessing the need for acid suppression therapy in this patient.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C (Negating)
Omeprazole	Asthma	GERD
Esomeprazole		
Lansoprazole		
Dexlansoprazole		
Pantoprazole		
Rabeprazole		

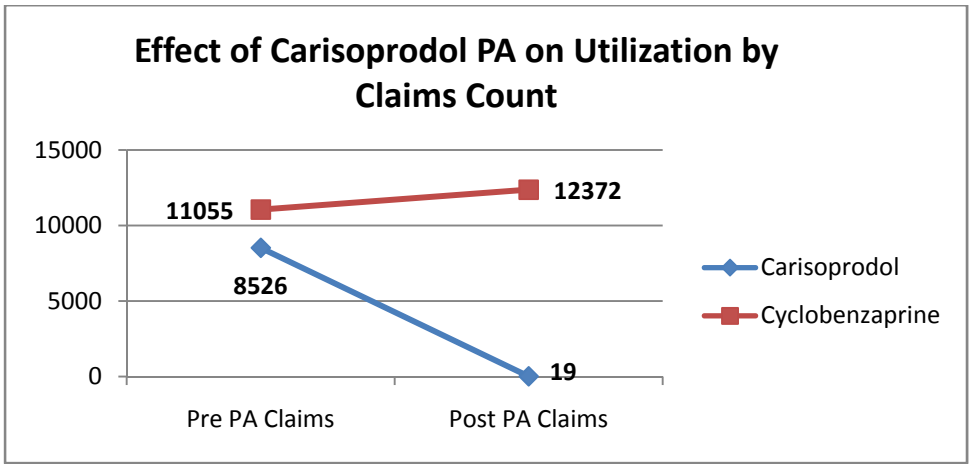
References:

The American Lung Association Asthma Clinical Research Center. Efficacy of Esomeprazole for Treatment of Poorly Controlled Asthma. N Engl J Med 2009;360:1487-99.
Kiljander TO et al. Effects of Esomeprazole 40 mg Twice Daily on Asthma: A Randomized Placebo-Controlled Trial. AM J Respir Crit Care Med. 2006 May 15; 173:1091-1097.
Sopo SM, Radzik D, Calvani M, Does the Treatment with Proton Pump Inhibitors for Gastroesophageal reflux disease (GERD) Improve Asthma Symptoms in Children with Asthma and GERD? J Investig Clin Immunol. 2009;19(1(:1-5.

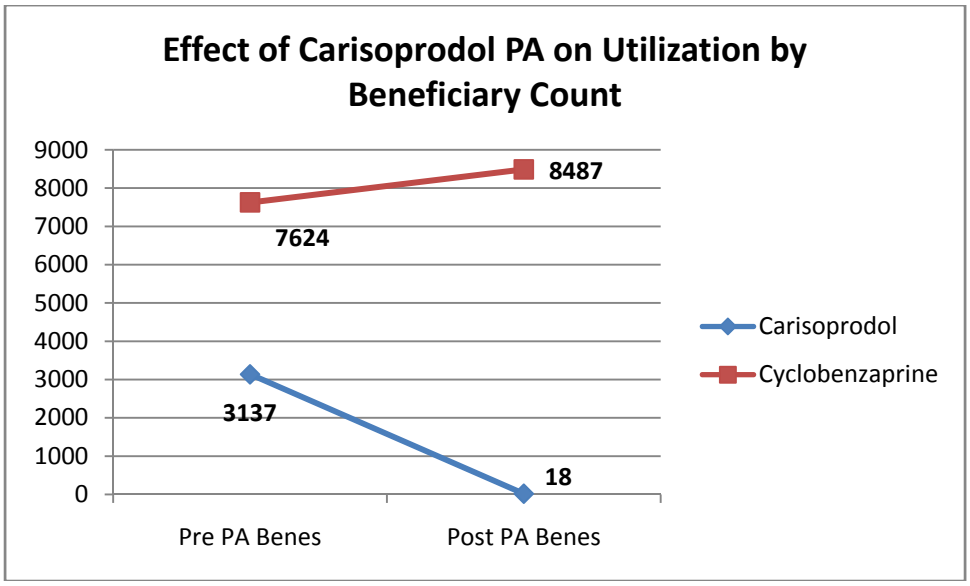
Carisoprodol Utilization Update

Based on directives from the DUR Board and P & T Committee, the Division of Medicaid began requiring prior authorization for carisoprodol-containing products on July 1, 2008. Carisoprodol is a centrally-acting skeletal muscle relaxant that is indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions in adults. It should only be used for short periods (up to 2 or 3 weeks) because adequate evidence of effectiveness for more prolonged use has not been established and because acute, painful musculoskeletal conditions are generally of short duration. Although carisoprodol is not a controlled substance, abuse associated with this drug is well-documented. Carisoprodol is used frequently by poly-drug abusers, especially those dependent on opioids. This troubling trend, coupled with the FDA-approved labeling for these products, generated the need for the prior authorization of these agents. The purpose of this report is to analyze the effectiveness of the prior authorization process concerning carisoprodol products, and to investigate whether the carisoprodol prior authorization led to increased utilization of cyclobenzaprine, another skeletal muscle relaxant. Criteria for approval of carisoprodol-containing products require trial and failure of cyclobenzaprine within the last 21 days. As a result, some increase in cyclobenzaprine utilization is to be expected.

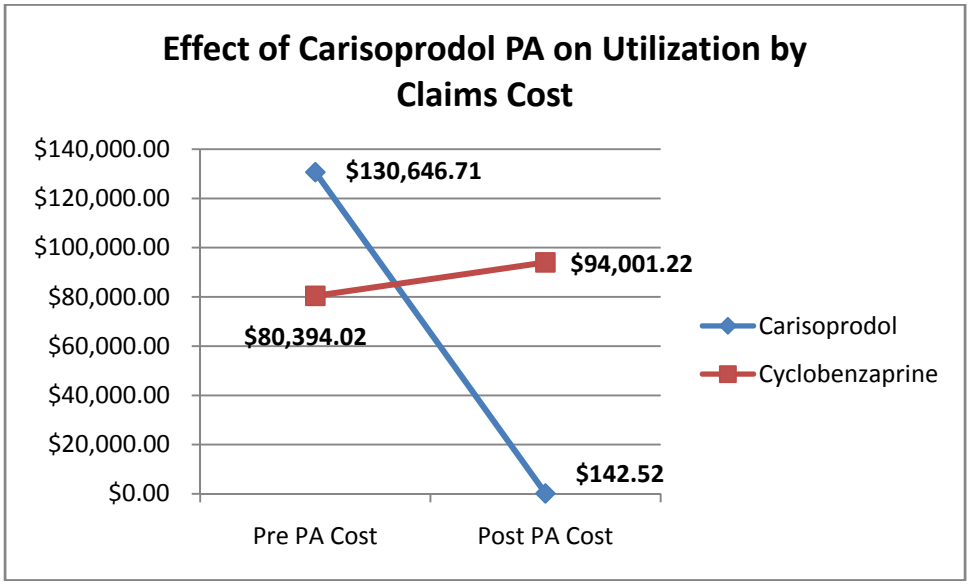
Utilization data was gathered for the 6 month interval prior to (1/1/08 – 6/30/08) and after (7/1/08 – 12/31/08) the implementation of the carisoprodol prior authorization. The charts below illustrate the utilization data from three different perspectives: claims count, beneficiary count, and claims cost.



Claims for carisoprodol decreased dramatically after the implementation of the prior authorization for these products. There were 19 claims for carisoprodol-containing products in the 6 month time period after the prior authorization implementation, which is less than 0.5% of the claim volume prior to the prior authorization for these products. Claims for cyclobenzaprine increased by nearly 12%.



The number of Mississippi Medicaid beneficiaries receiving carisoprodol-containing products also decreased considerably. In the 6 months following the carisoprodol prior authorization, there were 18 beneficiaries who received a prescription for a carisoprodol product, a notable decrease from 3,137 beneficiaries prior to the implementation of the carisoprodol prior authorization. The number of beneficiaries receiving cyclobenzaprine did increase from 7,624 to 8,487, or approximately 11%.



The total cost to DOM for carisoprodol-containing products showed a sharp decline as well. The claims cost for carisoprodol-containing products decreased by more than 99% in the 6 months following the enforcement of the carisoprodol PA, from $130,646.71 to $142.52. The claims cost for cyclobenzaprine increased by nearly 17%, from $80,394.02 to $94,001.22.

From the data presented in this report, it is evident that the creation and enforcement of the carisoprodol prior authorization was a success in discouraging chronic use of a medication that is only indicated for short-term use and is associated with a potential for abuse. It does appear that this prior authorization process has shifted some of the utilization of carisoprodol-containing products to cyclobenzaprine, although this increase does not appear to be troubling. It is evident that the Division of Medicaid took the proper steps in reigning in potential misuse of carisoprodol products at the expense of the State.

Lipid Screening and Cardiovascular Health in Childhood: New AAP Cholesterol Screening and Treatment Recommendations

Due to the growing epidemic of obesity, type 2 diabetes mellitus, hypertension and cardiovascular disease in children, the American Academy of Pediatrics felt an urgent need to address the issue of dyslipidemia in the pediatric population. As a result, the AAP revised their guidelines regarding lipid screening and treatment in children in July 2008. This clinical report replaced the 1998 AAP policy statement on cholesterol in childhood. This statement from the AAP provides guidelines not only for targeted cholesterol screening of children, but also recommendations for lifestyle modifications and pharmacological treatment options.

Based on a directive from DOM and the DUR Board, HID developed the following Medicaid Prescribing Updates to:

1) highlight the updated treatment recommendations found within the new AAP clinical report on lipid screening and treatment in children ≥ 8 years old and
2) provide an overview of metabolic syndrome.

These Medicaid Prescribing Updates will be distributed to prescribers by the HID Academic Detailers; they will also be available, along with others on additional topics, by a link from the Division of Medicaid website.

Prescribing Information Update

Dyslipidemia in Children

Mississippi Division of Medicaid

- *Research has shown that atherosclerosis begins in childhood.*
- *Children with identified risk factors should be targeted for cholesterol screening.*
- *First-line treatment of lipid abnormalities in children should include dietary changes and increased physical activity.*
- *For those children needing pharmacological therapy for dyslipidemia, statins have been proven to be safe and effective with proper monitoring.*

Research has shown that the atherosclerotic process begins in childhood. Therefore, it stands to reason that elevated cholesterol concentrations in childhood and adolescence are associated with an increased risk of atherosclerosis and cardiovascular disease in adulthood for children diagnosed with type 2 diabetes, hypertension, cardiovascular disease and obesity. Due to the growing epidemic of these disease states in children, the American Academy of Pediatrics felt an urgent need to address the issue of dyslipidemia in the pediatric population. As a result, the AAP revised their guidelines regarding lipid screening and treatment in children in July 2008.

Screening

The current recommendations for cholesterol screening in children were taken from the National Cholesterol Education Program (NCEP) and adopted by the AAP. Those children with the following risk factors should be targeted for cholesterol screening:

- Positive family history of dyslipidemia or premature CVD or dyslipidemia
- Obesity
- Hypertension
- Diabetes mellitus
- Cigarette smoking

Treatment

First-line treatment of lipid abnormalities in children should include the a combination of diet and exercise. A diet low in saturated fats with increased fiber intake should be encouraged, and consultation with a dietician will likely be required. For those children ≥ 8 years old who have tried and failed nonpharmacological therapy, or who initially meet the following criteria, pharmacological therapy is recommended.

Risk factors	LDL Level
No other risk factors for CVD	>190mg/dL
Obesity, hypertension, cigarette smoking, or family history of premature CVD	>160mg/dL
Diabetes Mellitus	≥130mg/dL

Mississippi Medicaid Preferred Drug List Status for Statins

Preferred	FDA-approved Age	**Non-preferred**	FDA-approved Age
Lescol, Lescol XL	10	Altoprev	18
Lipitor	10	Crestor	18
Lovastatin	10		
Pravastatin	8		
Simvastatin	10		

The *AAP Clinical Report on Lipid Screening and Cardiovascular Health in Children* can be found at http://aappolicy.aappublications.org/cgi/content/full/pediatrics;122/1/198.

Prescribing Information Update

Metabolic Syndrome

Mississippi Division of Medicaid

- *It is estimated that 50 million Americans currently suffer from the metabolic syndrome.*
- *Metabolic syndrome patients are at increased risk of coronary heart disease, stroke, peripheral vascular disease, and type 2 diabetes.*
- *The safest and most effective way to decrease insulin resistance is weight loss and increased physical activity.*
- *In patients with metabolic syndrome, individual risk factors such as hypertension and dyslipidemia should be treated based on established guidelines.*

Current estimates indicate that approximately 50 million Americans are victims of metabolic syndrome, which is the presence of a group of metabolic risk factors in one person. These risk factors include:

⇒ Abdominal obesity
⇒ Dyslipidemia
⇒ Hypertension
⇒ Insulin resistance or glucose intolerance
⇒ Prothrombotic state
⇒ Proinflammatory state

The primary causes of metabolic syndrome are obesity, physical inactivity, and genetic predisposition. People who suffer from this syndrome are at increased risk of coronary heart disease, stroke, peripheral vascular disease, and type 2 diabetes, among others.

Diagnosis

The most commonly used criteria for diagnosing metabolic syndrome come from the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III). According to these criteria, metabolic syndrome is identified by the presence of three or more of the following conditions.

Diagnostic Criteria for Metabolic Syndrome
Central obesity as measured by waist circumference: Men ≥ 40 inches, Women ≥ 35 inches
Fasting blood triglycerides ≥ 150mg/dL
Blood HDL cholesterol: Men < 40mg/dL, Women < 50mg/dL
Blood pressure ≥ 130/85mmHg
Fasting glucose ≥ 100mg/dL

Treatment

Because the metabolic syndrome is so closely associated with insulin resistance, this must be the target of treatment for metabolic syndrome in order to gain the most benefit of modifying other metabolic risk factors. According to the American Heart Association (AHA), the safest and most effective way to decrease insulin resistance in overweight and obese people is weight loss and increased physical activity. Other AHA recommendations for managing metabolic syndrome include:

⇒ Routinely monitor body weight (especially abdominal obesity), blood glucose, lipoproteins, and blood pressure.
⇒ Treat individual risk factors (hypertension, dyslipidemia, and elevated blood glucose) according to established guidelines.
⇒ Carefully choose antihypertensive medications based on their effects on insulin sensitivity.

MISSISSIPPI MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS
3rd QUARTER 2009

Criteria Recommendations ***Approved Rejected***

1. Iloperidone / High Dose _____ _____

Alert Message: The maximum recommended dose of Fanapt (iloperidone) is 12 mg twice daily (24 mg/day). Doses above 24 mg/day have not been systematically evaluated in clinical trials. Iloperidone must be titrated slowly from a low starting dose (1 mg twice daily) to avoid orthostatic hypotension.

Conflict Code: ER – Over Utilization
Drug/Disease

Util A	Util B	Util C (Negating – Potent 2D6 & 3A4 Inhibitors)			
Iloperidone		Bupropion	Indinavir	Itraconazole	Telithromycin
		Fluoxetine	Nelfinavir	Ketoconazole	Clarithromycin
		Paroxetine	Ritonavir	Nefazodone	
		Quinidine	Saquinavir		

Max Dose: 24 mg/day

References:
Fanapt Prescribing Information, May 2009, Vanda Pharmaceuticals Inc.
Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). http://medicine.iupui.edu/clinpharm/ddis/table.asp. Accessed June 09, 2009.

2. Iloperidone / Nonadherence _____ _____

Alert Message: Nonadherence to the prescribed antipsychotic therapy with Fanapt (iloperidone) may lead to decreased patient outcomes and additional medical cost.

Conflict Code: LR – Nonadherence
Drug/Disease

Util A	Util B	Util C
Iloperidone		

References:
Fanapt Prescribing Information, May 2009, Vanda Pharmaceuticals Inc.

3. Iloperidone / Potent 2D6 and/or 3A4 Inhibitors _____ _____

Alert Message: The dose of Fanapt (iloperidone) should be reduced by one-half when administered concomitantly with a strong CYP2D6 and/or CYP3A4 inhibitor. Iloperidone is metabolized by both CYP2D6 and CYP3A4 enzymes and concurrent therapy with these agents may cause increased iloperidone blood levels leading to adverse effects (e.g., QT prolongation, hypotension and tachycardia). If the inhibitor agent is withdrawn from combination therapy the iloperidone dose should be increased.

Conflict Code: DD – Drug/Drug Interaction
Drug/Disease

Util A	Util B	Util C (Inclusive)			
Iloperidone		Bupropion	Indinavir	Itraconazole	Telithromycin
		Fluoxetine	Nelfinavir	Ketoconazole	
		Paroxetine	Ritonavir	Nefazodone	
		Quinidine	Clarithromycin	Saquinavir	

Max Dose: 12 mg/day
References:
Fanapt Prescribing Information, May 2009, Vanda Pharmaceuticals Inc.
Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). http://medicine.iupui.edu/clinpharm/ddis/table.asp. Accessed June 09, 2009.

Criteria Recommendations ***Approved Rejected***

4. Iloperidone / QT Prolongation Drugs _____ _____

Alert Message: Fanapt (iloperidone) prolongs the QT interval and may be associated with arrhythmias and sudden death. Avoid the use of iloperidone in combination with drugs that are known to prolong the QTc or inhibit iloperidone metabolism.

Conflict Code: DD – Drug/Drug Interaction
Drug/Disease

Util A	Util B				Util C
Iloperidone	Alfuzosin	Doxepin	Paliperidone	Risperidone	
	Amantadine	Fluconazole	Ketoconazole	Salmeterol	
	Amitriptyline	Isradipine	Telithromycin	Tacrolimus	
	Atazanavir	Procainamide	Lapatinib	Terbutaline	
	Azithromycin	Methadone	Levofloxacin	Tizanidine	
	Clomipramine	Tolterodine	Vardenafil	Trimipramine	
	Dolasetron	Erythromycin	Methadone	Chlorpromazine	
	Moxifloxacin	Lithium	Mexiletine	Protriptyline	
	Sotalol	Venlafaxine	Moexipril/HCTZ	Solifenacin	
	Trimethoprim-Sulfa	Felbamate	Thioridazine	Voriconazole	
	Chloral Hydrate	Fluoxetine	Nilotinib	Sertraline	
	Ciprofloxacin	Flecainide	Nortriptyline	Procainamide	
	Citalopram	Foscarnet	Pentamidine	Ranolazine	
	Clozapine	Gemifloxacin	Tamoxifen	Itraconazole	
	Fosphenytoin	Granisetron	Octreotide	Dofetilide	
	Nicardipine	Ziprasidone	Ondansetron	Quinidine	
	Quinidine	Haloperidol	Pimozide	Indapamide	
	Desipramine	Imipramine	Quetiapine	Disopyramide	

References:
Fanapt Prescribing Information, May 2009, Vanda Pharmaceuticals Inc.
ArizonaCERT: Drugs That Prolong the QT Interval and/or Induce Torsades de Pointes
Available at: http://www.azcert.org/consumers/interaction-advisory.cfm

5. Iloperidone / QT Prolongation or Problems Associated w/ Prolongation _____ _____

Alert Message: Fanapt (iloperidone) prolongs the QT interval and may be associated with arrhythmias and sudden death. Avoid the use of iloperidone in patients who have congenital prolongation of the QT interval, a recent acute myocardial infarction, cardiac arrhythmia, hypokalemia and/or uncompensated heart failure.

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

Util A	Util B	Util C
Iloperidone	Prolongation of QT Interval	
	Myocardial Infarction	
	Uncompensated Heart Failure	
	Hypokalemia	
	Arrhythmias	

References:
Fanapt Prescribing Information, May 2009, Vanda Pharmaceuticals Inc.

6. Iloperidone / Hepatic Impairment _____ _____

Alert Message: Fanapt (iloperidone) is not recommended for use in patients with hepatic impairment. No study has been conducted in patients with mild or moderate liver impairment.

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

Util A	Util B	Util C
Iloperidone	Hepatic Impairment	

References:
Fanapt Prescribing Information, May 2009, Vanda Pharmaceuticals Inc.

Criteria Recommendations ***Approved Rejected***

7. Iloperidone / Alpha1-Adrenergic Receptor Blockers _____ _____

Alert Message: Due to its alpha-1 adrenergic receptor antagonist properties, Fanapt (iloperidone) has the potential to enhance the effect of certain antihypertensive agents that have the same mechanism of action and may result in problematic hypotension.

Conflict Code: DD – Drug/Drug Interaction
Drug/Disease

Util A	Util B	Util C
Iloperidone	Silodosin	
	Prazosin	
	Terazosin	
	Doxazosin	
	Tamsulosin	
	Alfuzosin	

References:
Fanapt Prescribing Information, May 2009, Vanda Pharmaceuticals Inc.

8. Leukotriene Modifiers / Neuropsychiatric Events _____ _____

Alert Message: Neuropsychiatric events have been reported in some patients taking leukotriene modifiers (i.e. montelukast, zafirlukast and zileuton). These adverse events include cases of agitation, aggression, anxiousness, dream abnormalities and hallucinations, depression, insomnia, irritability, restlessness, suicidal thinking/behavior, and tremor. Consider discontinuing these medications if patients develop neuropsychiatric events.

Conflict Code: TA – Therapeutic Appropriateness
Drug/Disease

Util A	Util B	Util C
Montelukast		
Zafirlukast		
Zileuton		

References:
FDA Drug Safety and Availability: Postmarket Drug Safety Information for Patients and Providers: Updated Information on Leukotriene Inhibitors: Montelukast (marketed as Singulair), Zafirlukast (marketed as Accolate), and Zileuton (marketed as Zyflo and Zyflo CR). June 12, 2009.

9. Tamoxifen / Mod. to Potent 2D6 Inhibitor Antidepressants _____ _____

Alert Message: The concurrent use of tamoxifen with an antidepressant that is a moderate or potent CYP2D6 inhibitor (e.g., paroxetine, fluoxetine, sertraline and bupropion) should be avoided. Use of tamoxifen with one of these agents may result in a reduced tamoxifen response due to inhibition of the CYP2D6-mediated drug activation. If appropriate for this patient, consider using an alternative antidepressant that has only weak CYP2D6 inhibition (e.g. citalopram, escitalopram, fluvoxamine, venlafaxine or desvenlafaxine).

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

Util A	Util B	Util C (Negating)
Tamoxifen	Fluoxetine	
	Paroxetine	
	Sertraline	
	Bupropion	
	Duloxetine	

References:
Facts & Comparisons, 2009 Updates.
In Brief: Tamoxifen and SSRI Interactions. Medical Letter. Volume 51 (Issue 1314), June 15, 2009.
Clinical Pharmacology, Gold Standard 2009.
Drug Interactions with Tamoxifen: A Guide for Breast Cancer Patients and Physicians. Consortium on Breast Cancer Pharmacogenomics. January 2008.
Available at: http://medicine.iupui.edu/clinpharm/COBRA/TamoxifenGuide.pdf

Criteria Recommendations ***Approved Rejected***

10. Tamoxifen / Moderate to Potent 2D6 Inhibitors _____ _____

Alert Message: The concurrent use of tamoxifen with a moderate or potent CYP2D6 inhibitor (e.g., quinidine, amiodarone, thioridazine and cimetidine) should be avoided. Use of tamoxifen with one of these agents may result in a reduced tamoxifen response due to inhibition of the CYP2D6-mediated drug activation. If appropriate for this patient consider alternate therapy with an agent that does not inhibit the CYP2D6 enzyme.

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

Util A	Util B	Util C
Tamoxifen	Quinidine	
	Amiodarone	
	Diphenhydramine	
	Cimetidine	
	Thioridazine	

References:
Facts & Comparisons, 2009 Updates.
Clinical Pharmacology, Gold Standard 2009.
Drug Interactions with Tamoxifen: A Guide for Breast Cancer Patients and Physicians. Consortium on Brest Cancer Pharmacogenomics. January 2008.
Available at: http://medicine.iupui.edu/clinpharm/COBRA/TamoxifenGuide.pdf

11. Tolvaptan / Potent CYP3A4 Inhibitors _____ _____

Alert Message: The concurrent use of Samsca (tolvaptan) with a potent CYP3A4inhibitor is contraindicated. Tolvaptan is a CYP3A4 substrate and coadministration with inhibitors of this enzyme can lead to marked increases in tolvaptan concentrations. The use of moderate 3A4 inhibitors with tolvaptan should be avoided.

Conflict Code: DD – Drug/Drug Interaction
Drug/Disease

Util A	Util B	Util C
Tolvaptan	Ketoconazole	
	Itraconazole	
	Clarithromycin	
	Telithromycin	
	Ritonavir	
	Indinavir	
	Nelfinavir	
	Saquinavir	
	Nefazodone	

References:
Samsca Prescribing Information, May 2009, Otsuka American Pharmaceutical, Inc.
Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). Available at: http://medicine.iupui.edu/clinpharm/ddis/table.asp. Accessed June 09, 2009.

Criteria Recommendations ***Approved Rejected***

12. Tolvaptan / Moderate CYP3A4 Inhibitors _____ _____

Alert Message: The concurrent use Samsca (tolvaptan) with a moderate 3A4 inhibitor should be avoided. Tolvaptan is a CYP3A4 substrate and coadministration with inhibitors of this enzyme can lead to marked increases in tolvaptan concentrations. The use of tolvaptan with potent CYP3A4 inhibitors is contraindicated.

Conflict Code: DD – Drug/Drug Interaction
Drug/Disease

Util A	Util B	Util C
Tolvaptan	Verapamil	
	Diltiazem	
	Aprepitant	
	Erythromycin	
	Fluconazole	
	Fosamprenavir	

References:
Samsca Prescribing Information, May 2009, Otsuka American Pharmaceutical, Inc.
Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). Available at: http://medicine.iupui.edu/clinpharm/ddis/table.asp. Accessed June 18, 2009.

13. Tolvaptan / CYP3A4 Inducers _____ _____

Alert Message: The concurrent use Samsca (tolvaptan) with a CYP3A4 inducer should be avoided. Tolvaptan is a CYP3A4 substrate and coadministration with an inducer of this enzyme may result in up to an 85% decreases in tolvaptan concentrations. The dose of tolvaptan may have to be increased.

Conflict Code: DD – Drug/Drug Interaction
Drug/Disease

Util A	Util B			Util C
Tolvaptan	Rifampin	Rifabutin	Secobarbital	
	Efavirenz	Nevirapine	Pentobarbital	
	Carbamazepine	Dexamethasone	Primidone	
	Modafinil	Prednisone	Pioglitazone	
	Oxcarbazepine	Phenobarbital	Butabarbital	
	Phenytoin	Mephobarbital		

References:
Samsca Prescribing Information, May 2009, Otsuka American Pharmaceutical, Inc.
Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). Available at: http://medicine.iupui.edu/clinpharm/ddis/table.asp. Accessed June 18, 2009.

14. Tolvaptan / P-glycoprotein Inhibitors _____ _____

Alert Message: The concurrent use Samsca (tolvaptan) with a P-glycoprotein inhibitor should be avoided. Tolvaptan is a P-gp substrate and coadministration with a P-gp inhibitor may result in a marked increase in tolvaptan concentrations. The dose of tolvaptan may need to be reduced.

Conflict Code: DD – Drug/Drug Interaction
Drug/Disease

Util A	Util B				Util C
Tolvaptan	Cyclosporine	Nifedipine	Fluphenazine	Nicardipine	
	Amiodarone	Progesterone	Hydrocortisone	Felodipine	
	Chlorpromazine	Propranolol	Lidocaine	Tamoxifen	
	Diltiazem	Quinidine	Mifepristone	Verapamil	
	Erythromycin	Reserpine	Testosterone		
	Diltiazem	Tacrolimus	Trifluoperazine		

References:
Samsca Prescribing Information, May 2009, Otsuka American Pharmaceutical, Inc.
Hartshorn ED and Tatro DS. Principles of Drug Interactions - Drug Interaction Facts, Facts & Comparisons 4.0, Wolters Kluwer Health, Inc., 2009.

Criteria Recommendations ***Approved Rejected***

15. Ryzolt / High Dose _____ _____

Alert Message: Ryzolt (tramadol extended-release) may be overutilized. The manufacturer's recommended maximum daily dose is 300 mg. Clinical studies of extended-release tramadol products have not demonstrated a clinical benefit at doses exceeding 300 mg per day.

Conflict Code: ER - Overutilization
Drug/Disease:

Util A	Util B	Util C
Ryzolt		

Max Dose: 300mg/day

References:
Ryzolt Prescribing Information, Dec. 2008, Purdue Pharma L.P.
Facts & Comparisons, 2009 Updates.

16. Tramadol / Therapeutic Duplication _____ _____

Alert Message: Therapeutic duplication of tramadol-containing products may be occurring. The concurrent use of different tramadol-containing products is not recommended. Patients may be receiving excessive amounts of tramadol which can lead to serious adverse effects (e.g., respiratory depression, seizures and death).

Conflict Code: TD – Therapeutic Duplication
Drug/Disease:

Util A	Util B	Util C
Tramadol		

References:
Ryzolt Prescribing Information, Dec. 2008, Purdue Pharma L.P.
Facts & Comparisons, 2009 Updates.
Ultracet Prescribing information, April, 2004. Ortho-McNeil Pharmaceuticals, Inc.
Ultram Prescribing Information, Feb. 2007, Ortho-McNeil, Pharmaceuticals, Inc.

17. Tramadol ER / Suicidal and Addiction _____ _____

Alert Message: Extended-release tramadol products (Ultram ER and Ryzolt) should not be prescribed in patients who are suicidal or addiction-prone. Many of the tramadol related deaths have occurred in patients with previous histories of misuse of tranquilizers, alcohol and other CNS-active drugs. If appropriate consideration should be given to the use of non-narcotic analgesics in these patients.

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

Util A	Util B	Util C
Tramadol ER	Attempted Suicide	
	Suicidality	
	Drug Abuse/Dependence	

References:
Ryzolt Prescribing Information, Dec. 2008, Purdue Pharma L.P.
Ultram ER Prescribing information, Dec. 2007. Ortho-McNeil Pharmaceuticals, Inc.

FDA Updates

The following information is provided to the DUR Board to assist in identifying drug products with potential for concern surrounding safety and appropriate utilization. Most of the safety alert information provided is derived from recent FDA safety alerts. While many of the alerts included are not Black Box Warning additions or updates, they are labeling changes or updates with relevance worthy of action by FDA.

Included for reference, the following is the Code of Federal Regulations definition for Black Box Warnings. (Citation: Title 21 CFR 201.57 Section E)

(e) Warnings. Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. A specific warning relating to a use not provided for under the "Indications and Usage: section of labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease of condition, and there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with serious risk or hazard. Special problems, particularly those that may lead to death or serious risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. If a boxed warning is required, its location will be specified by the Food and Drug Administration. The frequency of these adverse reactions and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective used of the drug, shall be expressed as provided under the "Adverse Reactions" section of the labeling.

Licensed botulinum toxin products
FDA notified healthcare professionals that after an ongoing safety review initiated in February 2008, the manufacturers of licensed botulinum toxin products will be required by FDA to strengthen warnings in product labeling and add a boxed warning regarding the risk of adverse events when the effects of the toxin spread beyond the site where it was injected.

FDA will also require that manufacturers develop and implement a Risk Evaluation and Mitigation Strategy [REMS], including a communication plan to provide more information regarding the risk for distant spread of botulinum toxin effects after local injection, as well as information to explain that botulinum toxin products cannot be interchanged. The REMS would also include a Medication Guide that explains the risks to patients, their families, and caregivers. FDA is requiring the manufacturers to submit safety data after multiple administrations of the product in a specified number of children and adults with spasticity to assess the signal of serious risk regarding distant spread of toxin effects.

FDA's evaluation of the data continues to support the recommendations made in the 2008 Early Communication.

Digoxin, USP 0.125 mg, Digoxin, USP 0.25 mg (Caraco brand)
AS Medication Solutions, LLC, a drug repackage company, announced today that all tablets of Caraco brand Digoxin, USP, 0.25 mg, distributed prior to March 31, 2009, which are not expired and are within the expiration date of August, 2011, are being voluntarily recalled to the consumer level. The tablets are being recalled because they may differ in size and therefore could have more or less of the active ingredient, digoxin. Caraco Pharmaceutical Laboratories, Ltd manufactured the recalled tablets. The recalled product is a scored round biconvex white tablet imprinted with "441", with an NDC number of 54569-5758-0 (30-count). Consumers with the product that are within expiration should return these products to their pharmacy or place of purchase.

Simponi (golimumab)
Centocor Ortho Biotech and FDA reminded healthcare professionals of the risk of serious fungal infections associated with TNF-αlpha blockers, including Simponi [golimumab]. FDA has reported that histoplasmosis and other invasive fungal infections are not consistently recognized in patients taking other TNF-αlpha blockers including Cimzia (certolizumab pegol), Enbrel (etanercept), Humira (adalimumab), and Remicade (infliximab). This has resulted in delays in appropriate antifungal treatment, sometimes even resulting in death. It is important that all adverse events potentially associated with Simponi be reported so that the adverse event profile reported in the prescribing information can be updated appropriately as post-approval experience is gathered. Centocor encourages reporting adverse events to Centocor at 1-800-457-6399 or to the FDA MedWatch program at 1-800-332-1088.

Propylthiouracil (PTU)
FDA notified healthcare professionals of the risk of serious liver injury, including liver failure and death, with the use of propylthiouracil (PTU) in adult and pediatric patients. Reports to FDA's Adverse Event Reporting System (AERS) suggest there is an increased risk of hepatotoxicity with PTU when compared to methimazole (MMI). FDA has identified 32 (AERS) cases (22 adult and 10 pediatric) of serious liver injury associated with PTU use. Although both PTU and MMI are indicated for the treatment of hyperthyroidism due to Graves' disease, healthcare professionals should carefully consider which drug to initiate in a patient recently diagnosed with Graves' disease. Physicians should closely monitor patients on PTU therapy for symptoms and signs of liver injury, especially during the first six months after initiation of therapy. PTU should not be used in pediatric patients unless the patient is allergic to or intolerant of MMI, and there are no other treatment options available.

Sirolimus (marketed as Rapamune)
FDA notified healthcare professionals of clinical trial data that suggest increased mortality in stable liver transplant patients after conversion from a calcineurin inhibitor (CNI)-based immunosuppressive regimen to sirolimus (Rapamune). The trial was conducted by sirolimus manufacturer, Wyeth. The Agency will continue to examine the data on mortality and other adverse events in this study, and will make further recommendations, as appropriate. The FDA is determining whether a labeling change for sirolimus is needed. In the interim, physicians should continue to use the drug's professional labeling as a guide to therapy. See the FDA Healthcare Professional Information sheet for current FDA recommendations.

Levemir Insulin (Novo Nordisk)
FDA notified patients and healthcare professionals that some stolen vials of the long-acting insulin Levemir made by Novo Nordisk Inc. are being sold in the U.S. market, may not have been stored and

handled properly, and may be dangerous for patients to use. The agency is advising patients who use Levemir insulin to:

- Check your personal supply of insulin to determine if you have Levemir insulin from one of the following lots: XZF0036, XZF0037, and XZF0038.
- Do not use your Levemir insulin if it is from one of these lots.
- Always visually inspect your insulin before using it. Levemir is a clear and colorless solution.
- Contact the Novo Nordisk Customer Care Center at 1-800-727-6500 for what to do with vials from these lots or if you have any other questions.

Stimulant Medications used in Children with Attention-Deficit/Hyperactivity Disorder

Products involved include: Focalin, Focalin XR (dexmethylphenidate HCl); Dexedrine, Dexedrine Spansules, Dextroamphetamine ER, Dextrostat (dextroamphetamine sulfate); Vyvanse (lisdexamfetamine dimesylate); Desoxyn (methamphetamine); Concerta, Daytrana, Metadate CD, Metadate ER, Methylin, Methylin ER, Ritalin, Ritalin-LA, Ritalin-SR (methylphenidate); Adderall, Adderall XR (mixed salts amphetamine); Cylert (pemoline) and generics.

FDA notified healthcare professionals that it is providing its perspective on study data published in the American Journal of Psychiatry on the potential risks of stimulant medications used to treat Attention-Deficit/Hyperactivity Disorder (ADHD) in children. This study, funded by the FDA and the National Institute of Mental Health (NIMH), compared the use of stimulant medications in 564 healthy children from across the United States who died suddenly to the use of stimulant medications in 564 children who died as passengers in a motor vehicle accident. The study authors concluded that there may be an association between the use of stimulant medications and sudden death in healthy children. Given the limitations of this study's methodology, the FDA is unable to conclude that these data affect the overall risk and benefit profile of stimulant medications used to treat ADHD in children. FDA believes that this study should not serve as a basis for parents to stop a child's stimulant medication. Parents should discuss concerns about the use of these medicines with the prescribing healthcare professional. Any child who develops cardiovascular symptoms (such as chest pain, shortness of breath or fainting) during stimulant medication treatment should immediately be seen by a doctor.

FDA is continuing its review of the strengths and limitations of this and other epidemiological studies that evaluate the risks of stimulant medications used to treat ADHD in children. FDA and the Agency for Healthcare Research and Quality are sponsoring a large epidemiological study that will provide further information about the potential risks associated with stimulant medication use in children. The data collection for this study will be complete later in 2009.

Cefepime (marketed as Maxipime)

FDA notified healthcare professionals that it has finished its analysis of a possible risk of higher death with cefepime, an antibiotic, following publication of a study that suggested a higher rate of death in patients treated with this drug, as compared to patients treated with similar drugs. FDA reviewed this study data and conducted additional analyses based on additional data, including data submitted by Bristol Meyers Squibb. FDA has determined that the data do not indicate a higher rate of death in cefepime-treated patients. Cefepime remains an appropriate therapy for its approved indications. FDA will continue to review the safety of cefepime. As part of this ongoing review, both FDA and Bristol Meyers Squib are conducting separate analyses of death potentially associated with cefepime, using hospital drug use data.

Lantus (insulin glargine)
FDA notified healthcare professionals and patients that it is aware of four recently-published observational studies that looked at the use of Lantus (insulin glargine) and possible risk for cancer in patients with diabetes. Three of the four studies suggest an increased risk for cancer associated with use of Lantus. Based on the currently available data, the FDA recommends that patients should not stop taking their insulin therapy without consulting a physician, since uncontrolled blood sugar levels can have both immediate and long-term serious adverse effects.

FDA is currently reviewing many sources of safety data for Lantus, including these newly published observational studies, data from all completed controlled clinical trials, and information about ongoing controlled clinical trials, to better understand the risk, if any, for cancer associated with use of Lantus. Discussions are also ongoing between FDA and the manufacturer of Lantus as to whether any additional studies evaluating the safety and efficacy of this drug will need to be performed. FDA will communicate the results on its ongoing review to the public, as appropriate, as our review continues.

Varenicline (marketed as Chantix) and Bupropion (marketed as Zyban, Wellbutrin, and generics)
FDA notified healthcare professionals and patients that it has required the manufacturers of the smoking cessation aids varenicline (Chantix) and bupropion (Zyban and generics) to add new Boxed Warnings and develop patient Medication Guides highlighting the risk of serious neuropsychiatric symptoms in patients using these products. These symptoms include changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide. The added warnings are based on the continued review of postmarketing adverse event reports for varenicline and bupropion received by the FDA. These reports included those with a temporal relationship between the use of varenicline or bupropion and suicidal events and the occurrence of suicidal ideation and suicidal behavior in patients with no history of psychiatric disease.

Healthcare professionals should advise patients to stop taking varenicline or bupropion and contact a healthcare provider immediately if they experience agitation, depressed mood, and any changes in behavior that are not typical of nicotine withdrawal, or if they experience suicidal thoughts or behavior.

Propoxyphene-containing Products
FDA notified healthcare professionals that it is taking several actions to reduce the risk of overdose in patients using pain medications that contain propoxyphene because of data linking propoxyphene and fatal overdoses. The agency will require manufacturers of propoxyphene-containing products to strengthen the label, including the boxed warning, emphasizing the potential for overdose when using these products and to provide a medication guide to patients stressing the importance of using the drugs as directed.
FDA is requiring a new safety study assessing unanswered questions about the effects of propoxyphene on the heart at higher than recommended doses. Findings from this study, as well as other data, could lead to additional regulatory action. To further evaluate the safety of propoxyphene, FDA plans to work with several groups including the Centers for Medicare & Medicaid Services and the Veterans Health Administration to study how often the elderly are prescribed propoxyphene instead of other pain relievers and the difference in the safety profiles of propoxyphene compared to other drugs.

Sirolimus (marketed as Rapamune), Cyclosporine (marketed as Sandimmune and generics), Cyclosporine modified (marketed as Neoral and generics), Mycophenolate mofetil (marketed as Cellcept and generics), Mycophenolic acid (marketed as Myfortic)

The FDA is requiring the makers of certain immunosuppressant drugs to update their labeling to reflect that immunosuppressed patients are at increased risk for opportunistic infections, such as activation of latent viral infections, including BK virus-associated nephropathy. These immunosuppressant drugs are used to protect against the rejection of certain organ transplants. The association of BK virus-associated nephropathy has previously been reported for another immunosuppressant drug, tacrolimus (marketed as Prograf). Monitoring for this serious risk and early intervention by the health care provider is critical. Adjustments in immunosuppression therapy should be considered for patients who develop BK virus-associated nephropathy.

Xolair (omalizumab)

FDA is evaluating interim safety findings from an ongoing study of Xolair (omalizumab) titled *Evaluating the Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma* (EXCELS) that suggests a disproportionate increase in ischemic heart disease, arrhythmias, cardiomyopathy and cardiac failure, pulmonary hypertension, cerebrovascular disorders, and embolic, thrombotic and thrombophlebitic events in patients treated with Xolair compared to the control group of patients not given the drug. Xolair is approved for use by adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who test positive for reactivity to a perennial airborne allergen, and whose symptoms are inadequately controlled with inhaled corticosteroids.

FDA is not recommending any changes to the prescribing information for Xolair and is not advising patients to stop taking Xolair at this time. Until the evaluation of the EXCELS study is completed, healthcare providers and patients should be aware of the risks and benefits described in the prescribing information, as well as the new information from the ongoing EXCELS study that may suggest a risk of cardiovascular and cerebrovascular adverse events.