



Division of Medicaid  
Office of the Governor  
State of Mississippi  
**DUR Board Meeting**

May 15, 2008  
2:00 p.m.  
Woolfolk Building, Room 117  
Jackson, MS

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

**May 15, 2008**

<b>Welcome</b>	<b>Frank Marascalco, RPh</b>
<b>Approval of Meeting Minutes</b>	<b>Frank Marascalco, RPh</b>
<b>Cost Management Analysis</b>	<b>Dennis Smith, RPh</b>
<b>Pharmacy Program Update</b>	<b>Paige Clayton, Pharm.D.</b>
<b>New Business</b>	<b>Dennis Smith, RPh Ashleigh Holeman, Pharm.D.</b>

**FDA Updates**

**Review of 1<sup>st</sup> Quarter Meeting Materials**

**Carisoprodol Prior Authorization Update**

**Off-label Use of Atypical Antipsychotics for Children with ADHD/ODD**

**Synagis Trending Report**

**Generalized Anxiety Disorder**

**Risperdal Consta**

**Criteria Recommendations**

<b>Next Meeting Information</b>	<b>Frank Marascalco, RPh</b>
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## **Drug Utilization Review Board**

Roy L. Arnold, Jr., R.Ph.  
Clayton Drug Store  
216 Main Street  
Collins, MS 39428-0787  
Term Expires: June 30, 2009

Frank Marascalco, R.Ph  
Sav-Mor Drugs  
1967 Commerce Street  
Grenada, MS 38901  
Term Expires: June 30, 2008

Harold B. Blakely, R.Ph.  
Delta Area Hospice Care  
5357 Cliff Gookin Boulevard  
Tupelo, MS 38801  
Term Expires: June 30, 2008

Wallace Strickland  
Rush Foundation Hospital  
8219 Sycamore Creek Drive  
Meridian, MS 39305  
Term Expires: June 30, 2008

Laura Gray, M.D.  
905 Garfield Street  
Tupelo, MS 38801  
Term Expires: June 30, 2008

Lee Voulters, M.D.  
1340 Broad Ave Suite 440  
Gulfport, MS 39501  
Term Expires: June 30, 2009

John M. Wallace, M.D.  
Jefferson Medical Clinic  
1203 Jefferson Street  
Laurel, MS 39440  
Term Expires: June 30, 2009

Randy Calvert, R.Ph.  
Brent's Drugs  
655 Duling Avenue  
Jackson, MS 39216  
Term Expires: June 30, 2007

Billy R. Brown, Pharm.D.  
Sonny Montgomery Veteran's Hospital  
2825 Glenn Derry Street  
Jackson, MS 39212  
Term Expires: June 30, 2007

Andrea Phillips, M.D.  
Phillips Medical Services  
P.O. Box 21214  
Jackson, MS 39289-1214  
Term Expires: June 30, 2007

## **Upcoming Mississippi DUR Board Meeting Dates**

August 21, 2008  
November 20, 2008

February 19, 2009  
May 21, 2009

**Mississippi Division of Medicaid  
Drug Utilization Review (DUR) Board  
Minutes of the November 15, 2007 Meeting**

**Members Attending:** Billy Brown, PharmD.; Randy Calvert, R.Ph., Laura Gray, M.D.; Frank Marascalco, R.Ph., Chair; Andrea Phillips, M.D.; Lee Voulters, M.D.; Wallace Strickland

**Members Absent:** Roy Arnold, R.Ph.; Harold Blakely, R.Ph.; John Wallace, M.D.

**Also Present:**

**DOM Staff:** Judith Clark, R.Ph., DOM Pharmacy Bureau Director; Paige Clayton, PharmD, DOM DUR Coordinator; Carlis Faler, DOM Program Integrity Director

**HID Staff:** Dennis Smith, R.Ph., Project Manager; Ashleigh Holeman, PharmD; Kathleen Burns, R.N.

**Call to Order:**

Frank Marascalco, Chairman of the Board, called the meeting to order at 2:10 p.m.

Dr. Clayton asked that the Board proceed with business not requiring a vote while awaiting arrival of enough members to constitute a quorum.

**Updates:**

**Cost Management Analysis**

Mr. Smith began by presenting reports reflecting several months of data. Antipsychotic agents continued to lead the top 15 therapeutic classes by total cost of claims throughout the five month period reported. The top drugs based on number of claims were led by hydrocodone-acetaminophen and followed by Zyrtec. Dr. Holeman added that the top 200 national ranking for each drug has been added to the report for reference. This report also designates by an asterisk those products classified as preferred on the preferred drug list. These additions were made to facilitate the understanding of the number of claims for these top medications. The top drugs based on total claims cost were led by Singulair<sup>®</sup> in April 2007. At this time, Mr. Smith and Dr. Holeman reviewed the findings of the analysis of Singulair<sup>®</sup> utilization that was presented during the previous DUR Board meeting. Of 4,500 patients not having a diagnosis of either asthma or allergic rhinitis, the majority were found to have had a non-specific upper respiratory diagnosis. The report further found that from May 2006 to May 2007, approximately 62 percent of patients receiving Singulair<sup>®</sup> had an asthma diagnosis, while approximately 65 percent of patients who received Singulair<sup>®</sup> had an allergic rhinitis diagnosis. According to this information, there did not appear to be gross over utilization of Singulair<sup>®</sup>. The Board agreed with these findings. Dr. Holeman continued with the top 25 drugs based on total claims cost by pointing out the remaining four months was led by Risperdal<sup>®</sup>.

**Old Business:**

Due to the lack of a quorum at the September 20, 2007 meeting, Mr. Smith briefly summarized several reports that were presented during the meeting.

### **Potential Misuse of ADHD Agents**

The first of these reports was a review of the utilization of stimulants indicated for the treatment of ADHD. Although the study findings did not indicate extensive over-prescription of these agents among adults, a retrospective DUR criterion was recommended to identify adult patients who may be using these medications inappropriately. After discussion, Mr. Strickland made a motion to approve the criterion and Dr. Phillips offered a second. The motion was unanimously approved.

### **Inappropriate Use of Antibiotics**

Mr. Smith next introduced the report which focused on the possible negative impact of the over-prescription of antibiotics to very young children. He reiterated that the Board had reached a consensus during the September meeting to not address this issue from a retrospective DUR perspective at this time.

### **HIV Criteria Report**

Dr. Holeman presented a synopsis of the retrospective DUR activity that has resulted from the DUR Board's approval in May of a large group of criteria focusing on the encouragement of appropriate antiretroviral therapy. A focused inquiry into the severity of the exceptions generated in May and June revealed that there is not a significant drug therapy problem in HIV patients enrolled in Mississippi Medicaid. Dr. Holeman continued that since the appropriate use of HIV medications is imperative for each patient, retrospective DUR criteria will continue to be used to assist physicians in providing effective treatment for their HIV patients.

### **New Business:**

#### **Alprazolam and Lorazepam Utilization**

Due to a high number of claims for alprazolam and lorazepam and at the request of the board during the September meeting, Mr. Smith presented a review of the utilization of these agents. Due to their anxiolytic effects, these medications tend to have a very high abuse potential. The results of this review were somewhat surprising in that the highest utilization occurred among beneficiaries in the 30 to 59 age range. Utilization was also determined in the long-term care population and found that there were a relatively small number of claims in this group. It was noted that while Medicare Part D provides the majority of drug coverage for dually-eligible patients, coverage of generic benzodiazepines such as alprazolam and lorazepam falls through to Medicaid. The board members recommended further study of this utilization by HID with the removal of the one time fills for all groups. Dr. Voulters also requested that HID review chronic users such as those with two or more refills. Dr. Gray suggested that HID identify patients on concurrent SSRI therapy. Mr. Strickland pointed out that, with the new wavier program allowing patients to receive long term care at home from a relative, this data might be skewed. It was suggested that HID include plan number and category of eligibility when the reports are re-run. Dr Voulters also requested that HID look at the long-acting benzodiazepines focusing on the LTC and elderly groups. Dr. Phillips continued with a

request to add diazepam to the review as she is seeing it used more frequently in her practice with patients requesting refills from other physicians. Carlis Faler, Program Integrity Director, added that it may be helpful for these reports to also reflect gender.

### **Hydrocodone Utilization**

Hydrocodone remains consistently one of the top five drugs based on the number of claims. This has generated a concern with the DUR Board as to how Medicaid can address this over-utilization with its beneficiaries. While high rates of hydrocodone use are cause for concern both at the state and national level, it is difficult to identify the complexity of the problem as Medicaid has set a monthly dispensing limit of 62, or two doses per day per running 31 days. It was noted that in some cases, beneficiaries are paying cash for the remainder of the prescription. Medicaid is working with the State Pharmacy Board to gain access to available data on cash purchases by Medicaid beneficiaries. This is expected to add valuable input into the possible abuse of these products and other medications of interest. Dr. Voulters requested an age analysis be generated as was done on the benzodiazepines. In addition, he further requested that other medications with abuse potential have the same detailed reports run. Dr. Gray requested that HID continue to review carisoprodol and run a comparison on all three of these medications with their age, diagnosis and long term utilization. She also suggested that HID report on the effectiveness of the carisoprodol Medicaid Prescribing Update, or “one-pager” that was previously approved by the DUR Board.

### **Impact of Quinine Removal on Utilization of Gabapentin and Lyrica®**

Dr. Holeman presented a review of the impact of FDA action in removing quinine products from the market. On December 11, 2006, the FDA ordered all manufacturers to stop marketing unapproved products containing quinine. Currently, Quaalun® is the only FDA approved product that contains quinine. Quinine is approved for the treatment of malaria but is often used off-label for leg cramps. Because of the drug’s risks, FDA believes that it should not be used to prevent and treat leg cramps. At the request of the DUR Board, utilization data was gathered by HID on the continued use of quinine after the FDA mandate. The searches performed by HID were for utilization of quinine, gabapentin and Lyrica® and attempted to identify trends based on the date that firms had to cease marketing quinine, February 13, 2007. While some increase was noted in utilization of gabapentin and Lyrica®, it was not as large as expected. HID generated a second chart reflecting the use of Requip® and Mirapex® which are indicated for restless leg syndrome and concluded that physicians are possibly utilizing these medications in place of quinine products. The data presented was interpreted to indicate that appropriate therapy has generally been implemented by treating physicians in the wake of the change in the marketplace.

### **Duplicate Utilization of Risperdal Consta® and Oral Atypical Antipsychotic Agents**

Mr. Smith next presented a review of the utilization of Risperdal Consta®, a long-acting atypical antipsychotic injection approved for the treatment of schizophrenia. This agent is well-suited for patients for whom medication compliance is a challenge. According to the FDA-approved prescribing information, tolerability to oral Risperdal® should be established prior to initiating therapy with Risperdal Consta®. The labeling also stated

that oral risperidone or another antipsychotic medication should be given with the first injection of Risperdal Consta<sup>®</sup>, continued for three weeks, then discontinued to ensure that effective therapeutic plasma concentrations are reached and maintained prior to the main release phase of risperidone from the injection site. Mr. Smith continued by presenting findings of searches made by HID of the utilization from 1/1/2007 through 09/21/2007. The beneficiaries identified in these searches were intersected to determine those with utilization of Risperdal Consta<sup>®</sup> and one or more oral atypical antipsychotic agents. Beneficiaries with claims totaling less than 32 days of treatment with an oral agent were excluded from the study. The search resulted in 191 beneficiaries who received long-acting injectable risperidone and oral atypical antipsychotic therapy during the time period searched. According to this analysis, over 50 percent of the beneficiaries on Risperdal Consta<sup>®</sup> received greater than 31 days of treatment with an oral atypical antipsychotic during the reviewed time. These findings indicate that many beneficiaries are receiving duplicate atypical antipsychotic treatment in addition to Risperdal Consta<sup>®</sup>. As a result, a retrospective DUR criterion was recommended to alert prescribers to the appropriate prescribing guidelines for this product. HID will bring such a criteria before the DUR Board at the next meeting for review and approval.

### **Approval of Minutes**

Dr. Phillips voiced the need to be excused and requested that voting on appropriate matters take place due to the fact that when she left there would no longer be a quorum. The minutes of the previous two DUR board meetings on May 19, 2007 and September 20, 2007 were approved with a motion by Mr. Strickland and a second from Dr. Phillips. All members voted in favor of the motion.

### **Fourth Quarter Criteria Recommendations**

In order to allow for voting on retrospective criteria recommendations, Mr. Smith presented the following criteria to the Board for approval.

- Elidel or Protopic/ Therapeutic Appropriateness - The topical calcineurin inhibitor, Elidel (pimecrolimus) or Protopic (tacrolimus), is indicated as second-line therapy for the short-term, non-continuous chronic treatment of mild to moderate atopic dermatitis in patients who are unresponsive or intolerant to other agents. Rare cases of malignancy (i.e., skin cancer and lymphoma) have been reported in patients treated with topical pimecrolimus. Application should be limited to the areas affected with atopic dermatitis.
- Protopic or Elidel / Age Appropriateness - The topical calcineurin inhibitors, Protopic (tacrolimus) and Elidel (pimecrolimus), are not recommended for use in children less than 2 years of age. The long-term safety and effects of these agents on the developing immune system are unknown.
- Protopic 0.1% / Age Appropriateness - The use of Protopic 0.1% ointment (topical tacrolimus) is not recommended in children less than 15 years of age. The 0.03% tacrolimus ointment is approved for use in children ages 2 to 15. Application should be limited to areas affected with atopic dermatitis. If signs and symptoms have not resolved within 6 weeks patient should be re-examined to confirm diagnosis.

- Elidel or Protopic/ Immunocompromised Patients - Elidel (topical pimecrolimus) or Protopic (topical tacrolimus) should not be used in immunocompromised adults and children. These patients are at risk for increased systemic exposure and adverse effects of pimecrolimus or tacrolimus.
- Topical Immunomodulators / Therapeutic Duplication - Therapeutic duplication of topical immunomodulator agents may be occurring.
- Tizanidine / Ciprofloxacin - Concurrent use of tizanidine and ciprofloxacin, a potent CYP 1A2 inhibitor, is contraindicated. Co-administration of these agents has been shown to cause significant increases in the AUC and Cmax of tizanidine resulting in hypotension, excessive sedation, and psychomotor impairment.
- Tizanidine / Fluvoxamine - Concurrent use of tizanidine and fluvoxamine, a potent CYP 1A2 inhibitor, is contraindicated. Significant alterations of pharmacokinetic parameters of tizanidine, including AUC, t1/2, Cmax, increased oral bioavailability and decreased plasma clearance, have been observed with concomitant fluvoxamine administration. Coadministration of these agents has resulted in profound hypotension, bradycardia and excessive drowsiness.
- Pioglitazone / Therapeutic Appropriateness - Pioglitazone-containing products (Actos/ActoPlusMet/Duetact) may increase the risk of fractures in female patients. Analysis of clinical trial data revealed an increased incidence of fractures in female patients taking long-term pioglitazone therapy as compared to females taking a comparator (placebo or active). Consider the risk of fractures when initiating or treating female, type 2 diabetic patients with pioglitazone.
- Rosiglitazone or pioglitazone/ Congestive Heart Failure & Fluid Retention – Rosiglitazone or pioglitazone-containing products may cause or exacerbate congestive heart failure. Their use is contraindicated in patients with NYHA class 3 or 4 heart failure and not recommended in patients with symptomatic heart failure. Patients should be observed for signs and symptoms of heart failure (rapid weight gain, dyspnea, and /or edema). If heart failure develops initiate appropriate therapy and consider alternative antidiabetic therapy.
- Codeine / Pregnancy - Nursing infants may be at an increased risk of morphine overdose if their mothers are taking codeine-containing products and are ultra-rapid metabolizers of codeine. If codeine use is necessary in the nursing mothers prescribe the lowest effective dose for the shortest amount of time. Inform mothers receiving codeine of the potential risks and signs of morphine overdose in themselves and their infants.
- Stimulants / Therapeutic Duplication - Therapeutic duplication of stimulants may be occurring (methylphenidate, dexamethylphenidate, amphetamine mixtures, methamphetamine, dextroamphetamine, lisdexamfetamine).
- Immediate Release Stimulants / Drug Abuse / Negating Agents - The patient has a diagnosis of substance use disorder (SUD) and is receiving immediate-release stimulant medication. Treatment recommendations for patients with the dual diagnosis of ADHD and SUD suggest that ADHD be treated with non-stimulant agents, extended-release stimulants or transdermal stimulant formulations to reduce the potential for misuse, abuse and/or diversion.



- Amphetamines / History of Drug Abuse - Amphetamines are contraindicated in patients with a history of drug abuse. Chronic, abusive use can lead to tolerance, extreme psychological dependence, and severe social disability.
- Stimulants / Arrhythmias & Cardiac Conditions - Stimulant products generally should not be used in children or adolescents with known structural cardiac abnormalities, cardiomyopathy, serious rhythm abnormalities or other serious cardiac problems. Sudden death has been reported in association with CNS stimulant treatment at usual doses in this population. All patients treated with stimulant medications should have a careful history (including family history of sudden death or ventricular arrhythmia) and physical exam to assess presence of cardiac disease.
- Stimulants /Bipolar Disorder - Particular care should be taken when using stimulants to treat ADHD patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder, and such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression.
- Selzentry / Nonadherence - A review of the patient's prescription refill history suggests that the patient may not be taking the drug in the manner it was prescribed. Non-adherence to antiretroviral therapy may result in insufficient drug plasma levels and partial suppression of viral load leading to the development of resistance, HIV progression, and increased mortality.
- Selzentry /Therapeutic Appropriateness - Selzentry (maraviroc) is FDA approved to be used in combination with other antiretroviral agents to treat adult patients infected with only CCR5-tropic HIV-1 detectable virus, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. There is insufficient data to recommend monotherapy with this agent.
- Selzentry /Cardiovascular Events - Selzentry (maraviroc) should be used with caution in patients at increased risk for cardiovascular events. In clinical studies, more cardiovascular events, including myocardial ischemia and/or infarction, were observed in patients who received maraviroc as compared to placebo (1.3% vs. 0%).
- Selzentry /Liver Impairment - Selzentry (maraviroc) has been linked to hepatotoxicity that may be preceded by a systemic allergic reaction (e.g., pruritic rash, eosinophilia, or elevated IgE). Discontinuation of maraviroc should be considered in any patient with signs and symptoms of hepatitis, or with increased liver transaminases combined with rash or other systemic symptoms. Caution is advised if maraviroc is used in patients with pre-existing liver dysfunction or who are co-infected with hepatitis B or C.
- Selzentry / High Dose - The recommended dose of Selzentry (maraviroc) for patients receiving concomitant therapy with NRTIs, tipranavir/ritonavir, nevirapine, and other drugs that are not strong CYP3A inhibitors or CYP3A inducers is 300 mg twice daily.
- Selzentry / High Dose - Selzentry (maraviroc) is metabolized by the CYP3A isoenzyme and patients receiving concomitant therapy with protease inhibitors

- (except tipranavir/ritonavir), delavirdine, ketoconazole, itraconazole, clarithromycin, or other strong CYP3A inhibitors (e.g., nefazodone and telithromycin) should receive a reduced dose of 150 mg of maraviroc twice daily.
- Selzentry / Low Dose - Selzentry (maraviroc) is metabolized by the CYP3A isoenzyme and patients receiving concomitant treatment with CYP3A inducers (e.g., efavirenz, rifampin, carbamazepine, phenobarbital, and phenytoin), without a strong inhibitor, should receive a dose of 600 mg of maraviroc twice daily.
  - Selzentry / Renal Impairment - Selzentry (maraviroc) should be used with caution in patients with renal impairment, particularly in those with concurrent use of a CYP3A inhibitor and a CrCl < 50 mg/mL. Approximately 25% of maraviroc is renally eliminated and impairment may lead to increased drug concentrations and risk of dose-related adverse effects (e.g., dizziness and postural hypotension). Patients should be monitored for adverse effects.
  - Selzentry / Hypotension - Selzentry (maraviroc) should be used with caution in patients with a history of postural hypotension or who are on concomitant medication known to lower blood pressure. The frequency of postural hypotension is increased at higher than recommended doses of maraviroc.
  - Selzentry / Therapeutic Appropriateness - Selzentry (maraviroc) should only be used in combination with other antiretroviral agents in adult treatment-experienced patients infected with CCR5-tropic HIV-1 detectable virus, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. The agent is not active against CXCR4-tropic and dual-tropic viruses. Tropism testing and treatment history should guide use of maraviroc.
  - Viracept / Therapeutic Appropriateness - Viracept (nelfinavir) has been found to contain the process-related impurity ethyl methanesulfonate (EMS), a potential human carcinogen. The FDA states that pediatric patients stable on nelfinavir therapy may continue therapy due to a favorable benefit-risk ratio. Pediatric patients who need to begin HIV treatment should not start on a regimen containing nelfinavir until further notice.
  - Viracept / Therapeutic Appropriateness - Viracept (nelfinavir) has been found to contain the process-related impurity ethyl methanesulfonate (EMS), a potential human carcinogen. The FDA has recommended that pregnant patients currently receiving nelfinavir be switched to an alternative agent if possible and that those needing to begin HIV treatment not be offered nelfinavir until further notice. Pregnant women with no alternative treatment options may continue to receive nelfinavir because the benefit-risk ratio remains favorable.
  - Haloperidol / Therapeutic Appropriateness - Higher doses and intravenous administration of haloperidol appear to be associated with an increased risk of QT prolongation, torsades de pointes and even sudden death. Particular caution is advised when prescribing haloperidol to patients with predisposing factors (e.g., cardiac abnormalities, hypothyroidism and electrolyte imbalance) that could cause an even greater risk of these serious adverse effects.
  - Haloperidol / Over utilization - Haloperidol may be over-utilized. The recommended maximum dose is 100 mg per day. Exceeding this dose may enhance the risk of adverse effects (e.g., QT prolongation, torsades de pointes, extrapyramidal symptoms, seizures, and hypertension).

- Fentora / Therapeutic Appropriateness - Fentora (buccal fentanyl) is only approved for the treatment of breakthrough pain in patients with cancer who are already receiving and are tolerant to opioid therapy. Buccal fentanyl must not be used in opioid non-tolerant patients. The improper selection of patients, incorrect dosing and improper product substitution may result in a fatal overdose with this agent.
- Quetiapine / Substance Abuse - Seroquel (quetiapine) should be prescribed with caution to patients with a history of substance abuse. The agent has sedative and anxiolytic properties and may be misused by some patients. Closely observe patients for signs of misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior). Inappropriate use of quetiapine may put patients at risk for arrhythmias, hypotension, weight gain, and diabetes.

Mr. Marascalco continued with a vote on the criteria presented by HID. Dr. Phillips made a motion to approve the criteria presented with the exceptions of the pioglitazone/therapeutic appropriateness criteria and the pioglitazone/congestive heart failure and fluid retention criteria. Dr. Gray seconded the motion and all voted in favor.

### **Appropriate Antibiotic Use**

Dr. Holeman presented a review of the appropriate utilization of antibiotics by Medicaid prescribers. Antimicrobial resistance among pathogens has become a common clinical problem and the association of resistance with the use of antimicrobial drugs has been documented in both inpatient and outpatient settings. This seems to have been given credence by the spread of organisms, such as MRSA, all essentially untreatable with routinely available antibiotics. Dr. Holeman continued by stating that decreasing the inappropriate use of antimicrobials has been listed as a primary solution to address the threat that antimicrobial resistance poses. To help combat the risk, HID presented and recommended the use of a Medicaid Prescribing Information Update, or “one-pager”, which outlines the importance of appropriate treatment of upper respiratory tract infections and of prudent prescribing of antibiotics. HID recommends distribution of this document to prescribers by the Academic Detailing Staff and availability from the Division of Medicaid’s website. After discussion of this approach, the Board’s consensus was to support the distribution of this information as recommended.

Dr. Holeman then addressed the use of Zyvox<sup>®</sup>. At present, this antibiotic is non-preferred and subject to manual prior authorization review. Several recent studies have shown that outpatient use of Zyvox<sup>®</sup> may lower costs and prevent or shorten hospitalizations. Dr. Brown asked about the turn-around time of the prior authorization process. Mr. Smith answered that DOM requires that requests be processed within 24 hours, although most are responded to in less time. After discussion, the clear consensus of the DUR Board was to recommend no change to the present status of this product, continuing to require prior authorization approval, while encouraging appropriate use of this product.

### **Other**

Dr. Gray suggested that HID analyze the utilization trends of Provigil® for the next Board meeting.

### **Boxed Warnings Update**

Mr. Smith presented black box warnings, other warnings, and labeling changes issued by the FDA concerning the following:

#### **Avandia (rosiglitazone)**

FDA informed healthcare professionals of a potential safety issue related to Avandia (rosiglitazone). An on-going analysis of safety data for the treatment of type 2 diabetes mellitus using Avandia showed differing rates of ischemic cardiovascular events including heart attack or heart-related adverse events, some fatal, relative to other drugs used to treat diabetes mellitus. The clinical studies reviewed to date vary with respect to their populations, treatment regimens, and length of follow-up. Based on these data, the risk of ischemic cardiovascular events due to Avandia remain unclear. Prescribers should continue to carefully make individualized treatment decisions for patients with diabetes mellitus.

#### **Exjade (deferasirox) Tablets For Oral Suspension**

Novartis and FDA notified healthcare professionals of changes to the WARNINGS and ADVERSE REACTIONS sections of the product labeling for Exjade, a drug used to treat chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older. Cases of acute renal failure, some with a fatal outcome, have been reported following the post marketing use of Exjade. Most of the fatalities occurred in patients with multiple co-morbidities and who were in advanced stages of their hematological disorders. Additionally, there were post marketing reports of cytopenias, including agranulocytosis, neutropenia and thrombocytopenia in patients treated with Exjade where some of the patients died. The relationship of these episodes to treatment with Exjade is uncertain. Most of these patients had preexisting hematologic disorders that are frequently associated with bone marrow failure. Further, cases of leukocytoclastic vasculitis, urticaria, and hypersensitivity reactions (including anaphylaxis and angioedema) were reported. Healthcare professionals should monitor serum creatinine in patients who are at increased risk of complications, having preexisting renal conditions, are elderly, have co-morbid conditions, or are receiving medicinal products that depress renal function. Blood counts should also be monitored regularly and treatment should be interrupted in patients who develop unexplained cytopenia.

#### **Propofol (marketed as Diprivan and generic products)**

FDA informed healthcare professionals about several clusters of patients who experienced chills, fever, and body aches shortly after receiving propofol for sedation or general anesthesia. Multiple vials and several lots of propofol used in patients who experienced these symptoms were tested and there was no evidence that the propofol vials or prefilled syringes used were contaminated with bacteria or endotoxins. Propofol is an intravenous sedative-hypnotic agent for use in the induction and maintenance of anesthesia or sedation. To minimize the potential for bacterial contamination, propofol

vials and prefilled syringes should be used within six hours of opening and one vial should be used for one patient only. Patients who develop fever, chills, body aches or other symptoms of acute febrile reactions shortly after receiving propofol should be evaluated for bacterial sepsis. Healthcare professionals who administer propofol for sedation or general anesthesia should carefully follow the recommendations for handling and use in the product's full prescribing information.

#### **Rocephin (ceftriaxone sodium) for Injection**

Roche and FDA informed healthcare professionals of revisions to the CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections of the prescribing information for Rocephin for Injection. The revisions are based on new information that describes the potential risk associated with concomitant use of Rocephin with calcium or calcium containing solutions or products. Cases of fatal reactions with calcium-ceftriaxone precipitates in the lungs and kidneys in both term and premature neonates were reported. Hyperbilirubinemic neonates, especially prematures, should not be treated with Rocephin. The drug must not be mixed or administered simultaneously with calcium-containing solutions or products, even via different infusion lines. Additionally, calcium-containing solutions or products must not be administered within 48-hours of the last administration of ceftriaxone.

#### **Use of CellCept (mycophenolate mofetil) associated with increased pregnancy loss and congenital malformations**

Roche and FDA notified healthcare providers that use of CellCept (mycophenolate mofetil) is associated with increased risk of first trimester pregnancy loss and increased risk of congenital malformations, especially external ear and facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney.

Based on postmarketing data from the United States National Transplantation Pregnancy Registry and additional postmarketing data collected in women exposed to systemic mycophenolate mofetil during pregnancy, the pregnancy category for CellCept has been changed from Category C (risk of fetal harm cannot be ruled out) to Category D (positive evidence of fetal risk). Labeling changes include the following sections: BOXED WARNING, WARNINGS/Pregnancy and Pregnancy Exposure Prevention, PRECAUTIONS/Information for Patients, and ADVERSE REACTIONS/Postmarketing Experience.

Within one week of beginning CellCept therapy, women of childbearing potential should have a negative serum or urine pregnancy test. In addition, women of childbearing potential (including pubertal girls and peri-menopausal woman) taking CellCept must receive contraceptive counseling and use effective contraception. Healthcare professionals and patients should be aware that CellCept reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness. See the Dear Healthcare Professional Letter for additional recommendations for women of childbearing potential.

**Provigil (modafinil) Tablets- WARNINGS Added To Prescribing Information Regarding Serious Rash And Hypersensitivity Reactions, And Psychiatric Symptoms**

FDA and Cephalon notified healthcare professionals of Warnings added to prescribing information for Provigil (modafinil). Provigil is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder. The revised prescribing information updates safety information to include warnings regarding serious rash, including Stevens-Johnson Syndrome (SJS) and hypersensitivity reactions, and psychiatric symptoms. Rare cases of serious or life-threatening rash, including Toxic Epidermal Necrolysis, and Drug Rash with Eosinophilia and Systemic Symptoms have been reported in adults and children in worldwide postmarketing experience. Angioedema and multi-organ hypersensitivity reactions have also been reported in postmarketing experience.

Physicians should instruct their patients to immediately discontinue the use of Provigil and contact them if a rash or other hypersensitivity reaction occurs. Healthcare professionals and consumers should also be aware that Provigil is not approved for use in pediatric patients for any indication. In addition, psychiatric adverse experiences (including anxiety, mania, hallucinations, and suicidal ideation) have been reported in patients treated with Provigil. Caution should be exercised when Provigil is given to patients with a history of psychosis, depression, or mania.

Additional labeling revisions were made to the CLINICAL PHARMACOLOGY, PRECAUTIONS, and PATIENT PACKAGE INSERT sections.

**Byetta (exenatide) and postmarketing reports of acute pancreatitis**

FDA has reviewed 30 postmarketing reports of acute pancreatitis in patients taking Byetta (exenatide), a drug used to treat adults with type 2 diabetes. An association between Byetta and acute pancreatitis is suspected in some of these cases. Amylin Pharmaceuticals, Inc. has agreed to include information about acute pancreatitis in the PRECAUTIONS section of the product label.

Healthcare professionals should be alert to the signs and symptoms of acute pancreatitis and instruct patients taking Byetta to seek prompt medical care if they experience unexplained, persistent, severe abdominal pain which may or may not be accompanied by vomiting. If pancreatitis is suspected, Byetta should be discontinued. If pancreatitis is confirmed, Byetta should not be restarted unless an alternative etiology is identified.

**Early Communication Issued Regarding Atrial Fibrillation With Oral And Intravenous Bisphosphonates**

FDA issued an early communication about the ongoing review of new safety data regarding the association of atrial fibrillation with the use of bisphosphonates. Bisphosphonates are a class of drugs used primarily to increase bone mass and reduce the risk for fracture in patients with osteoporosis, slow bone turnover in patients with Paget's

disease of the bone, treat bone metastases, and lower elevated levels of blood calcium in patients with cancer.

FDA reviewed spontaneous postmarketing reports of atrial fibrillation reported in association with oral and intravenous bisphosphonates and did not identify a population of bisphosphonate users at increased risk of atrial fibrillation. In addition, as part of the data review for the recent approval of once-yearly Reclast for the treatment of postmenopausal osteoporosis, FDA evaluated the possible association between atrial fibrillation and the use of Reclast. Most cases of atrial fibrillation occurred more than a month after drug infusion. Also, in a subset of patients monitored by electrocardiogram up to the 11th day following infusion, there was no significant difference in the prevalence of atrial fibrillation between patients who received Reclast and patients who received placebo.

Upon initial review, it is unclear how these data on serious atrial fibrillation should be interpreted. Therefore, FDA does not believe that healthcare providers or patients should change either their prescribing practices or their use of bisphosphonates at this time.

#### **Haloperidol Marketed As Haldol, Haldol Decanoate, And Haldol Lactate Get New Warnings And Revised Prescription Information**

Johnson and Johnson and FDA informed healthcare professionals that the WARNINGS section of the prescribing information for haloperidol has been revised to include a new Cardiovascular subsection regarding cases of sudden death, QT prolongation and Torsades de Pointes (TdP) in patients treated with haloperidol, especially when given intravenously, or at doses higher than recommended. Although injectable haloperidol is only approved by the FDA for intramuscular injection, there is considerable evidence that the intravenous administration of haloperidol is a relatively common off-label clinical practice.

There are at least 28 case reports of QT prolongation and TdP, some with fatal outcome in the context of off-label intravenous haloperidol.

Healthcare professionals should consider this new risk information when making individual treatment decisions for their patients.

#### **Fentora (fentanyl buccal tablet) and the occurrence of serious adverse events, including deaths as a result of improper patient selection, improper dosing, and/or improper product substitution**

Cephalon issued two Dear Healthcare Professional Letters to inform prescribers and other healthcare providers of important safety information regarding Fentora. Fentora is indicated only for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Serious adverse events, including deaths, have occurred in patients treated with Fentora. These deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients), improper dosing, and/or improper product substitution. The healthcare professional letters provide key points regarding appropriate patient selection

and proper dosing and administration of Fentora to reduce the risk of respiratory depression.

**Next Meeting Information:**

Mr. Marascalco reminded the Board of the next meeting scheduled for February 21, 2008.

Mr. Marascalco called for a motion of adjournment at 4:10 p.m. Mr. Strickland made the motion, which was seconded by Dr. Gray. All voted in favor of the motion to adjourn.

Respectfully Submitted:  
Health Information Designs



**Mississippi Division of Medicaid  
Drug Utilization Review (DUR) Board  
Minutes of the February 21, 2008 Meeting**

**Members Attending:** Billy Brown, Pharm.D; Randy Calvert, R.Ph.; Laura Gray, M.D.; Frank Marascalco, R.Ph; Lee Montgomery, M.D.;

**Members Absent:** Roy Arnold, R.Ph; Harold Blakely, R.Ph; Wallace Strickland; 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; Carlis Faler, DOM Program Integrity Director; Terri Kirby, R.Ph., Ella Holmes, Andrea McNeal,

**HID Staff:** Dennis Smith, R.Ph, Project Manager; Ashleigh Holeman, Pharm.D; Kathleen Burns, R.N.

**Call to Order:**

Frank Marascalco, Chairman of the Board, called the meeting to order at 2:10 p.m.

Dr. Clayton asked that the Board proceed with business acknowledging that the Board would not have a quorum to vote on the issues presented today

**Updates:**

**Cost Management Analysis:**

Mr. Smith presented an overview of the reports to the Board reflecting several months of data. He continued noting that the same agents continue to top the 15 therapeutic classes by total cost of claims throughout the reports. Dr. Brown noted that the antibiotics continue to remain as one of the top agents and the Board still questions if this reflects an over utilization of antibiotics for unnecessary indications. Ms. Clark interjected the thoughts that HID might run reports on beneficiaries from birth to the age of 12 to determine misuse. She continued to recommend that the months of October plus a forward 6 month study could be done on individuals receiving more than one antibiotic with multiple prescribers. Dr. Montgomery questioned that the possibility of removing cold/cough preparations might have driven this over-use of antibiotics. He recommended that HID look at the previous year during the same timeframe and compare it with this year's data. Ms. Clark suggested that DOM might consider using HID's Newsletter for the educational purpose of informing the prescribers of this important antibiotic overuse. Dr. Brown suggested that DOM might utilize the different Regional Offices and Rural Health Clinics to post information for the parents to read.

**Pharmacy Program Update:**

Ms. Clark informed the Board that the Tamper-Proof prescription requirements go into effect April 1<sup>st</sup>, 2008. DOM will communicate with providers prior to this implementation date by faxes and other appropriate notices. The March 1<sup>st</sup> Bulletin will also have articles to address this April 1<sup>st</sup> deadline for Tamper-Proof prescription pads.

Dr. Clayton introduced at this time the pharmacy intern working with DOM, Eric Cornell. Eric was asked to present information regarding the abuse of promethazine with codeine syrup in MS. He informed the Board that this “street abuse” possibly started 10 years ago in Houston, Texas under many street names. The idea is to take 1 ounce of promethazine with codeine, mix it with Sprite and a piece of candy, turning it purple. He noted that 1 ounce is the entire daily dose allowance of codeine for an adult, which results in a person receiving 60mg of codeine in one drink. The DEA informed Eric that it is a growing concern in Jackson and they have noted an increase since September 2006. DOM elected to remove promethazine with codeine syrup from their approved OTC list as of November 1, 2007, without knowing about this method of abuse. When the OTC list for Medicaid patients was outsourced, this removal was recommended at that time from the respective vendor for other reasons. Mr. Smith continued by presenting an updated February 2008 report from the CDC on the prevalence of RSV in Mississippi. This graphic report indicated that Mississippi-specific occurrence was decreasing starting in January 2008. The Synagis® Season for MS Medicaid patients will end March 31<sup>st</sup>, 2008.

#### **New Business:**

##### **Overview of rDur Process:**

This was tabled per recommendation of Dr. Clayton until the next meeting of the Board

##### **Utilization of Benzodiazepines, Carisoprodol, Hydrocodone, Ambien®, and Provigil®:**

Dr. Holeman presented a lengthy requested study on these potential drugs of abuse. These medications have continued to concern the Board with the overuse and their continuation to remain on the Top 25 drug reports for the number of reported claims. Dr. Montgomery questioned how Medicare Part D entered into the number of reported claims. Dr. Holeman answered that Medicaid is the primary payer for the benzodiazepines for this group as Medicare Part D does not cover these medications. She continued that Medicare does cover hydrocodone, however, on the dual eligibles. In regard to the Ambien® overuse, Dr. Montgomery suggested informing the physician responsible, possibly with an education letter. This might alter the physician’s prescribing habits on Ambien®. Dr. Brown suggested that HID look at these reports and see if there might be a pattern of the same physician prescribing all three of these medications per patient. Dr. Gray commented that the Board might recommend even further decreasing the limits on these medications for the Medicaid beneficiaries. However, Mr. Marascalco stated that in the pharmacy business, the beneficiary would just pay cash for the extra medication that Medicaid limited. He stated that it should start with the physician writing this excessive amount. HID will continue to monitor these medications and the physicians prescribing them.

##### **Labeling Update for Desmopressin Acetate Nasal Spray**

Dr. Holeman continued reporting on labeling updates on Desmopressin Acetate Nasal Spray. Based on gathered information, there was not extensive utilization for the nasal spray in children ages 5 to 15 in the Medicaid population. It was also noted that of those children receiving the nasal spray, a very small number received long-term treatment.

Retrospective DUR criteria are recommended to identify these patients receiving this medication in violation of the recent position of the FDA.

### **Pharmacy Coverage of Tobacco Cessation Products**

The next topic covered by Dr. Holeman was the recent addition of Chantix® to the Tobacco Cessation products covered by MS Medicaid. Based on HID's reportings, the additional coverage of this medication has shown utilization of approximately 5 times that of the nicotine-replacement products also on the list. Approximately 15% of the beneficiaries have received a second prescription of either agent to continue their efforts to stop smoking. This indicates that MS Medicaid has made a positive step in the right direction to potentially lower health-care costs in the future by providing another option to support those beneficiaries who are making the effort to stop smoking.

### **New Criteria:**

Mr. Smith reviewed these new recommendations with the Board but due to a lack of a quorum there was no voting.

### **Boxed Warning Updates**

Mr. Smith presented black box warnings, other warnings, and labeling changes issued by the FDA concerning the following:

#### ***Ortho Evra Contraceptive Transdermal Patch***

1/19/2008: FDA modified the prescribing information for the Ortho Evra Contraceptive Transdermal (Skin) Patch to include the results of a new epidemiology study that found that users of the birth control patch were at higher risk of developing serious blood clots, also known as venous thromboembolism (VTE), than women using birth control pills. VTE can lead to pulmonary embolism. The label changes are based on a study conducted by the Boston Collaborative Drug Surveillance Program on behalf of Johnson and Johnson. The patch was studied in women aged 15-44. These findings support an earlier study that also said women in this group were at higher risk for VTE.

FDA believes that Ortho Evra is a safe and effective method of contraception when used according to the labeling, which recommends that women with concerns or risk factors for serious blood clots talk with their health care provider about using Ortho Evra versus other contraceptive options.

#### ***Cough and Cold Medications in Children Less Than Two Years of Age***

1/17/2008: FDA informed consumers and healthcare professionals that the Agency has completed its review of information regarding the safety of over-the-counter (OTC) cough and cold medicines in children under 2 years of age and recommends that these drugs not be used to treat children in this age group because serious and potentially life-threatening side effects can occur. FDA's recommendation is based on both the review of the information the Agency received about serious side effects in children in the referenced age group and the discussion and recommendations made at the October 18 - 19, 2007, public advisory committee meeting at which this issue was discussed. FDA has not completed its review of information about the safety of OTC cough and cold

medicines in children 2 through 11 years of age. See the FDA Public Health Advisory for Agency recommendations regarding this issue.

***Edetate Disodium (marketed as Endrate and generic products)***

1/16/2008: FDA notified healthcare professionals and patients about important safety information concerning Edetate Disodium. There have been cases where children and adults have died when they were mistakenly given Edetate Disodium instead of Edetate Calcium Disodium (Calcium Disodium Versenate) or when Edetate Disodium was used for "chelation therapies" and other uses that are not approved by the FDA. Edetate Disodium was approved as an emergency treatment for certain patients with hypercalcemia (very high levels of calcium in the blood) or certain patients with heart rhythm problems as a result of very high amounts of digitalis in the blood. Edetate Calcium Disodium was approved to reduce dangerously high blood lead levels (severe lead poisoning).

The two drugs have very similar names and are commonly referred to only as EDTA. As a result, the two products are easily mistaken for each other when prescribing, dispensing, and administering them. Edetate Disodium and Edetate Calcium Disodium works by binding with heavy metals or minerals in the body allowing them to be passed out of the body through the urine. Read the FDA Public Health Advisory for recommended and important safety considerations for healthcare professionals until the FDA's ongoing evaluation of the risks and benefits of Edetate Disodium is complete.

***Compounded Menopause Hormone Therapy Drugs***

1/10/2008: FDA informed healthcare professionals and patients that the Agency sent letters warning seven pharmacy operations that the claims they make about the safety and effectiveness of their so-called "bio-identical hormone replacement therapy," or "BHRT" products are unsupported by medical evidence, and are considered false and misleading by the agency. The pharmacy operations improperly claim that their drugs, which contain hormones such as estrogen, progesterone, and estriol (which is not a component of an FDA-approved drug and has not been proven safe and effective for any use) are superior to FDA-approved menopausal hormone therapy drugs and prevent or treat serious diseases, including Alzheimer's disease, stroke, and various forms of cancer. FDA is concerned that the claims for safety, effectiveness, and superiority that these pharmacy operations are making mislead patients, as well as doctors and other healthcare professionals. Compounded drugs are not reviewed by the FDA for safety and effectiveness.

Patients who use compounded hormone therapy drugs should discuss menopausal hormone therapy options with their healthcare provider to determine if compounded drugs are the best option for their specific medical needs.

***Bisphosphonates (marketed as Actonel, Actonel+Ca, Aredia, Boniva, Didronel, Fosamax, Fosamax+D, Reclast, Skelid, and Zometa)***

1/07/2008: FDA informed healthcare professionals and patients of the possibility of severe and sometimes incapacitating bone, joint, and/or muscle (musculoskeletal) pain in

patients taking bisphosphonates. Although severe musculoskeletal pain is included in the prescribing information for all bisphosphonates, the association between bisphosphonates and severe musculoskeletal pain may be overlooked by healthcare professionals, delaying diagnosis, prolonging pain and/or impairment, and necessitating the use of analgesics. The severe musculoskeletal pain may occur within days, months, or years after starting a bisphosphonates. Some patients have reported complete relief of symptoms after discontinuing the bisphosphonate, whereas others have reported slow or incomplete resolution. The risk factors for and incidence of severe musculoskeletal pain associated with bisphosphonates are unknown.

***Fentanyl Transdermal System (marketed as Duragesic and generics)***

12/21/2007: FDA issued an update that highlights important information on appropriate prescribing, dose selection, and the safe use of the fentanyl transdermal system (patch). FDA previously issued a Public Health Advisory and Information for Healthcare Professionals in July 2005 regarding the appropriate and safe use of the transdermal system. However, the Agency continues to receive reports of death and life-threatening adverse events related to fentanyl overdose that have occurred when the fentanyl patch was used to treat pain in opioid-naïve patients and when opioid-tolerant patients have applied more patches than prescribed, changed the patch too frequently, and exposed the patch to a heat source. The fentanyl patch is only indicated for use in patients with persistent, moderate to severe chronic pain who have been taking a regular, daily, around-the-clock narcotic pain medicine for longer than a week and are considered to be opioid-tolerant.

Patients must avoid exposing the patch to excessive heat as this promotes the release of fentanyl from the patch and increases the absorption of fentanyl through the skin which can result in fatal overdose. Directions for prescribing and using the fentanyl patch must be followed exactly to prevent death or other serious side effects from fentanyl overdose.

***Carbamazepine (marketed as Carbatrol, Equetro, Tegretol and generics)***

12/12/2007: FDA informed healthcare professionals that dangerous or even fatal skin reactions (Stevens Johnson syndrome and toxic epidermal necrolysis), that can be caused by carbamazepine therapy, are significantly more common in patients with a particular human leukocyte antigen (HLA) allele, HLA-B\*1502. This allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians. Patients with ancestry from areas in which HLA-B\*1502 is present should be screened for the HLA-B\*1502 allele before starting treatment with carbamazepine. If these individuals test positive, carbamazepine should not be started unless the expected benefit clearly outweighs the increased risk of serious skin reactions. Patients who have been taking carbamazepine for more than a few months without developing skin reactions are at low risk of these events ever developing from carbamazepine. This is true for patients of any ethnicity or genotype, including patients positive for HLA-B\*1502.

***Desmopressin Acetate (marketed as DDAVP Nasal Spray, DDAVP Rhinal Tube, DDAVP, DDVP, Minirin, and Stimate Nasal Spray)***

12/04/2007: FDA notified healthcare professionals and patients of the Agency's request that manufacturers update the prescribing information for desmopressin to include important new safety information about severe hyponatremia and seizures. Certain patients, including children treated with the intranasal formulation of the drug for primary nocturnal enuresis (PNE), are at risk for developing severe hyponatremia that can result in seizures and death. As such, desmopressin intranasal formulations are no longer indicated for the treatment of primary nocturnal enuresis and should not be used in hyponatremic patients or patients with a history of hyponatremia. PNE treatment with desmopressin tablets should be interrupted during acute illnesses that may lead to fluid and/or electrolyte imbalance. All desmopressin formulations should be used cautiously in patients at risk for water intoxication with hyponatremia.

***Chantix (Varenicline)***

11/20/2007: FDA informed healthcare professionals of reports of suicidal thoughts and aggressive and erratic behavior in patient who have taken Chantix, a smoking cessation product. There are also reports of patients experiencing drowsiness that affected their ability to drive or operate machinery. FDA is currently reviewing these cases, along with other recent reports. A preliminary assessment reveals that many of the cases reflect new-onset of depressed mood, suicidal ideation, and changes in emotion and behavior within days to weeks of initiating Chantix treatment. The role of Chantix in these cases is not clear because smoking cessation, with or without treatment, is associated with nicotine withdrawal symptoms and has also been associated with the exacerbation of underlying psychiatric illness. However, not all patients described in the cases had preexisting psychiatric illness and not all had discontinued smoking.

Healthcare professionals should monitor patients taking Chantix for behavior and mood changes. Patients taking this product should report behavior or mood changes to their doctor and use caution when driving or operating machinery until they know how quitting smoking with Chantix may affect them.

***Erythropoiesis Stimulating Agents: Aranesp (darbepoetin alfa), Epogen (epoetin alfa), and Procrit (epoetin alfa)***

Updated 1/03/2008: FDA informed healthcare professionals of findings from two additional clinical studies, Preoperative Epirubicin Paclitaxel Aranesp Study (PREPARE), and the National Cancer Institute Gynecologic Oncology Group (COG-19), showing an increase in mortality and shorter time to tumor progression in patients with cancer receiving an Erythropoiesis-Stimulating Agent (ESA). Both the PREPARE study in breast cancer and the COG-19 study in cervical cancer showed higher rates of death and or tumor progression in patients who received an ESA compared to patients who did not receive an ESA. FDA strongly recommends that healthcare professionals discuss the risks of ESA-associated tumor progression and shortened survival in patients with cancer before starting or continuing ESA therapy.

Posted 11/08/2007: FDA notified healthcare professionals of revised boxed warnings and other safety-related product labeling changes for erythropoiesis-stimulating agents (ESAs), which treat certain types of anemia. These new statements address the risks that

the drugs Aranesp, Epogen, and Procrit pose to patients with cancer and patients with chronic kidney failure. For patients with cancer, the new boxed warnings emphasize that ESAs caused tumor growth and shortened survival in patients with advanced breast, head and neck, lymphoid and non-small cell lung cancer when they received a dose that attempted to achieve a hemoglobin level of 12 grams per deciliter (g/dL) or greater. For patients with chronic kidney failure, the new boxed warning states that ESAs should be used to maintain a hemoglobin level between 10 g/dL to 12 g/dL. Maintaining higher hemoglobin levels in patients with chronic kidney failure increases the risk of death and other serious conditions. The new labeling provides specific instructions for dosage adjustments and hemoglobin monitoring for chronic kidney failure patients who do not respond to ESA treatment with an adequate increase in their hemoglobin levels. Additionally, the new boxed warnings clarify that ESAs should only be used in patients with cancer when treating anemia specifically caused by chemotherapy and not for other causes of anemia. Further, it states that ESAs should be discontinued once the patient's chemotherapy course has been completed.

***CellCept (mycophenolate mofetil)***

Updated 11/27/2007: Prescribing information for Mycophenolic Acid (marketed as Myfortic Delayed Released Tablets) revised to include information that use of drug during pregnancy is associated with increased risks of pregnancy loss and congenital malformations. See the MedWatch alert for Myfortic (mycophenolic acid).

[Posted 10/29/2007] Roche and FDA notified healthcare providers that use of CellCept (mycophenolate mofetil) is associated with increased risk of first trimester pregnancy loss and increased risk of congenital malformations, especially external ear and facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney. Based on postmarketing data from the United States National Transplantation Pregnancy Registry and additional postmarketing data collected in women exposed to systemic mycophenolate mofetil during pregnancy, the pregnancy category for CellCept has been changed from Category C (risk of fetal harm cannot be ruled out) to Category D (positive evidence of fetal risk). Labeling changes include the following sections: BOXED WARNING, WARNINGS/Pregnancy and Pregnancy Exposure Prevention, PRECAUTIONS/Information for Patients, and ADVERSE REACTIONS/Postmarketing Experience.

Within one week of beginning CellCept therapy, women of childbearing potential should have a negative serum or urine pregnancy test. In addition, women of childbearing potential (including pubertal girls and peri-menopausal woman) taking CellCept must receive contraceptive counseling and use effective contraception. Healthcare professionals and patients should be aware that CellCept reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness. See the Dear Healthcare Professional Letter for additional recommendations for women of childbearing potential.

***Provigil (modafinil) Tablets***

10/24/2007: FDA and Cephalon notified healthcare professionals of updates to the WARNINGS section of the prescribing information for Provigil (modafinil). Provigil is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder. The revised labeling updates safety information to include warnings regarding serious rash, including Stevens-Johnson Syndrome (SJS) and hypersensitivity reactions, and psychiatric symptoms. Rare cases of serious or life-threatening rash, including Toxic Epidermal Necrolysis, and Drug Rash with Eosinophilia and Systemic Symptoms have been reported in adults and children in worldwide postmarketing experience. Angioedema and multi-organ hypersensitivity reactions have also been reported in postmarketing experience.

Physicians should instruct their patients to immediately discontinue the use of Provigil and contact them if a rash or other hypersensitivity reaction occurs. Healthcare professionals and consumers should also be aware that Provigil is not approved for use in pediatric patients for any indication. In addition, psychiatric adverse experiences (including anxiety, mania, hallucinations, and suicidal ideation) have been reported in patients treated with Provigil. Caution should be exercised when Provigil is given to patients with a history of psychosis, depression, or mania.

Additional labeling revisions were made to the CLINICAL PHARMACOLOGY, PRECAUTIONS, and PATIENT PACKAGE INSERT sections. See revised labeling below.

***Viagra (sildenafil), Cialis (tadalafil), Levitra (vardenafil), Revatio (sildenafil)***

10/18/2007: FDA informed healthcare professionals of reports of sudden decreases or loss of hearing following the use of PDE5 inhibitors Viagra, Levitra, Cialis for the treatment of erectile dysfunction, and Revatio for the treatment of pulmonary arterial hypertension. In some cases, the sudden hearing loss was accompanied by tinnitus and dizziness. Medical follow-up on these reports was often limited which makes it difficult to determine if the loss of hearing was related to the use of one of the drugs, an underlying medical condition or other risk factors for hearing loss, a combination of these factors or other factors. The PRECAUTIONS and ADVERSE REACTIONS sections of the approved product labeling for Viagra, Levitra, and Cialis were revised. FDA is working with the manufacturer to revise the labeling for Revatio.

***Byetta (exenatide)***

10/16/2007: FDA has reviewed 30 postmarketing reports of acute pancreatitis in patients taking Byetta (exenatide), a drug used to treat adults with type 2 diabetes. An association between Byetta and acute pancreatitis is suspected in some of these cases. Amylin Pharmaceuticals, Inc. has agreed to include information about acute pancreatitis in the PRECAUTIONS section of the product label.

Healthcare professionals should be alert to the signs and symptoms of acute pancreatitis and instruct patients taking Byetta to seek prompt medical care if they experience unexplained, persistent, severe abdominal pain which may or may not be accompanied by



vomiting. If pancreatitis is suspected, Byetta should be discontinued. If pancreatitis is confirmed, Byetta should not be restarted unless an alternative etiology is identified.

**Next Meeting Information:**

Mr. Marascalco reminded the Board of the next meeting scheduled for May 15<sup>th</sup>, 2008.

Mr. Marascalco called for adjournment at 3:45p.m.

Respectfully Submitted:  
Health Information Designs

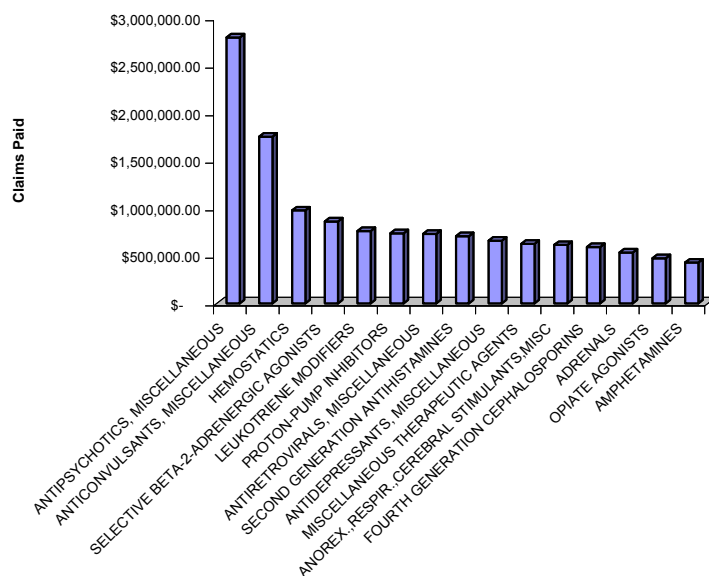
**MISSISSIPPI MEDICAID  
Cost Management Analysis**

**TOP 15 THERAPEUTIC CLASSES BY TOTAL COST OF CLAIMS FROM 09/01/07-09/30/07**

<b>AHFS Therapeutic Class</b>	<b>Rx</b>	<b>Paid</b>	<b>Paid/Rx</b>	<b>% Total Claims</b>
ANTIPSYCHOTICS, MISCELLANEOUS	9,421	\$ 2,798,383.43	\$ 297.04	2.60%
ANTICONVULSANTS, MISCELLANEOUS	10,134	\$ 1,754,013.03	\$ 173.08	2.80%
HEMOSTATICS	39	\$ 977,416.86	\$25,061.97	0.01%
SELECTIVE BETA-2-ADRENERGIC AGONISTS	11,794	\$ 861,753.68	\$ 73.07	3.26%
LEUKOTRIENE MODIFIERS	7,409	\$ 760,079.46	\$ 102.59	2.05%
PROTON-PUMP INHIBITORS	5,076	\$ 737,680.31	\$ 145.33	1.40%
ANTIRETROVIRALS, MISCELLANEOUS	1,084	\$ 730,533.42	\$ 673.92	0.30%
SECOND GENERATION ANTIHISTAMINES	13,204	\$ 707,499.46	\$ 53.58	3.65%
ANTIDEPRESSANTS, MISCELLANEOUS	12,983	\$ 659,200.97	\$ 50.77	3.59%
MISCELLANEOUS THERAPEUTIC AGENTS	2,193	\$ 626,026.43	\$ 285.47	0.61%
ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	5,374	\$ 614,157.89	\$ 114.28	1.48%
FOURTH GENERATION CEPHALOSPORINS	11,436	\$ 591,644.15	\$ 51.74	3.16%
ADRENALS	8,794	\$ 534,466.57	\$ 60.78	2.43%
OPIATE AGONISTS	24,669	\$ 474,692.47	\$ 19.24	6.81%
AMPHETAMINES	3,850	\$ 428,848.18	\$ 111.39	1.06%
<b>TOTAL TOP 15</b>	<b>127,460</b>	<b>\$ 13,256,396.31</b>	<b>\$ 104.00</b>	<b>35.21%</b>

Total Rx Claims	361,985
From 09/01/07-09/30/07	

**Top 15 Therapeutic Classes  
Based on Total Cost of Claims**



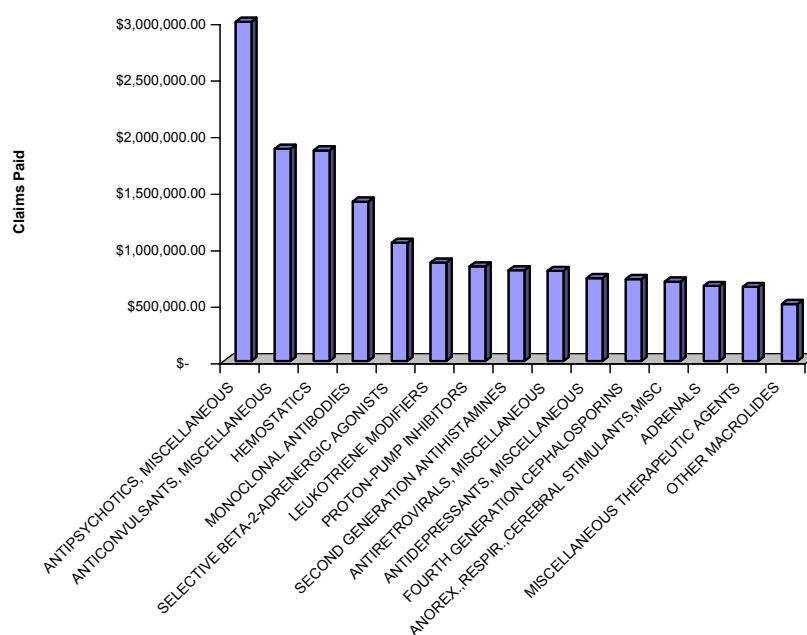
**MISSISSIPPI MEDICAID  
Cost Management Analysis**

**TOP 15 THERAPEUTIC CLASSES BY TOTAL COST OF CLAIMS FROM 10/01/07-10/31/07**

<b>AHFS Therapeutic Class</b>	<b>Rx</b>	<b>Paid</b>	<b>Paid/Rx</b>	<b>% Total Claims</b>
ANTIPSYCHOTICS, MISCELLANEOUS	10,227	\$ 2,997,412.94	\$ 293.09	2.52%
ANTICONVULSANTS, MISCELLANEOUS	10,802	\$ 1,874,275.26	\$ 173.51	2.66%
HEMOSTATICS	56	\$ 1,859,967.02	\$33,213.70	0.01%
MONOCLONAL ANTIBODIES	976	\$ 1,408,180.53	\$ 1,442.81	0.24%
SELECTIVE BETA-2-ADRENERGIC AGONISTS	14,259	\$ 1,044,246.78	\$ 73.23	3.51%
LEUKOTRIENE MODIFIERS	8,483	\$ 869,034.79	\$ 102.44	2.09%
PROTON-PUMP INHIBITORS	5,659	\$ 835,389.86	\$ 147.62	1.39%
SECOND GENERATION ANTIHISTAMINES	15,036	\$ 801,292.29	\$ 53.29	3.70%
ANTIRETROVIRALS, MISCELLANEOUS	1,163	\$ 795,344.68	\$ 683.87	0.29%
ANTIDEPRESSANTS, MISCELLANEOUS	14,289	\$ 732,675.33	\$ 51.28	3.52%
FOURTH GENERATION CEPHALOSPORINS	13,385	\$ 722,820.03	\$ 54.00	3.29%
ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	6,162	\$ 701,126.60	\$ 113.78	1.52%
ADRENALS	10,609	\$ 662,664.76	\$ 62.46	2.61%
MISCELLANEOUS THERAPEUTIC AGENTS	2,382	\$ 654,404.28	\$ 274.73	0.59%
OTHER MACROLIDES	13,676	\$ 503,132.37	\$ 36.79	3.37%
<b>TOTAL TOP 15</b>	<b>127,164</b>	<b>\$ 16,461,967.52</b>	<b>\$ 129.45</b>	<b>31.30%</b>

Total Rx Claims	406,295
From 10/01/07-10/31/07	

**Top 15 Therapeutic Classes  
Based on Total Cost of Claims**



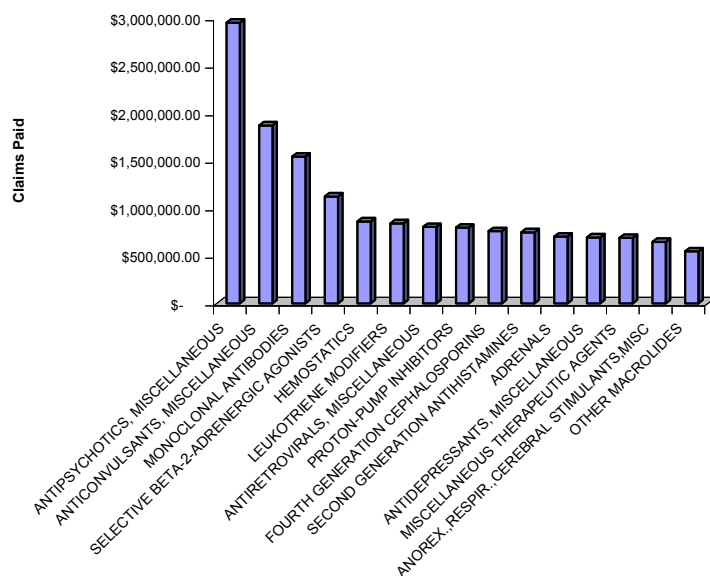
**MISSISSIPPI MEDICAID  
Cost Management Analysis**

**TOP 15 THERAPEUTIC CLASSES BY TOTAL COST OF CLAIMS FROM 11/01/07-11/30/07**

<b>AHFS Therapeutic Class</b>	<b>Rx</b>	<b>Paid</b>	<b>Paid/Rx</b>	<b>% Total Claims</b>
ANTIPSYCHOTICS, MISCELLANEOUS	10,068	\$ 2,953,154.87	\$ 293.32	2.53%
ANTICONVULSANTS, MISCELLANEOUS	10,762	\$ 1,873,159.99	\$ 174.05	2.71%
MONOCLONAL ANTIBODIES	1,088	\$ 1,544,256.21	\$ 1,419.35	0.27%
SELECTIVE BETA-2-ADRENERGIC AGONISTS	15,107	\$ 1,124,919.40	\$ 74.46	3.80%
HEMOSTATICS	34	\$ 862,135.58	\$25,356.93	0.01%
LEUKOTRIENE MODIFIERS	8,203	\$ 841,572.34	\$ 102.59	2.06%
ANTIRETROVIRALS, MISCELLANEOUS	1,150	\$ 802,548.33	\$ 697.87	0.29%
PROTON-PUMP INHIBITORS	5,415	\$ 795,846.96	\$ 146.97	1.36%
FOURTH GENERATION CEPHALOSPORINS	13,703	\$ 758,982.73	\$ 55.39	3.44%
SECOND GENERATION ANTIHISTAMINES	14,073	\$ 746,554.22	\$ 53.05	3.54%
ADRENALS	11,347	\$ 702,177.88	\$ 61.88	2.85%
ANTIDEPRESSANTS, MISCELLANEOUS	13,621	\$ 693,912.97	\$ 50.94	3.42%
MISCELLANEOUS THERAPEUTIC AGENTS	2,246	\$ 688,545.25	\$ 306.57	0.56%
ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	5,614	\$ 646,790.69	\$ 115.21	1.41%
OTHER MACROLIDES	14,967	\$ 546,698.25	\$ 36.53	3.76%
<b>TOTAL TOP 15</b>	<b>127,398</b>	<b>\$ 15,581,255.67</b>	<b>\$ 122.30</b>	<b>32.02%</b>

Total Rx Claims	397,855
From 11/01/07-11/30/07	

**Top 15 Therapeutic Classes  
Based on Total Cost of Claims**



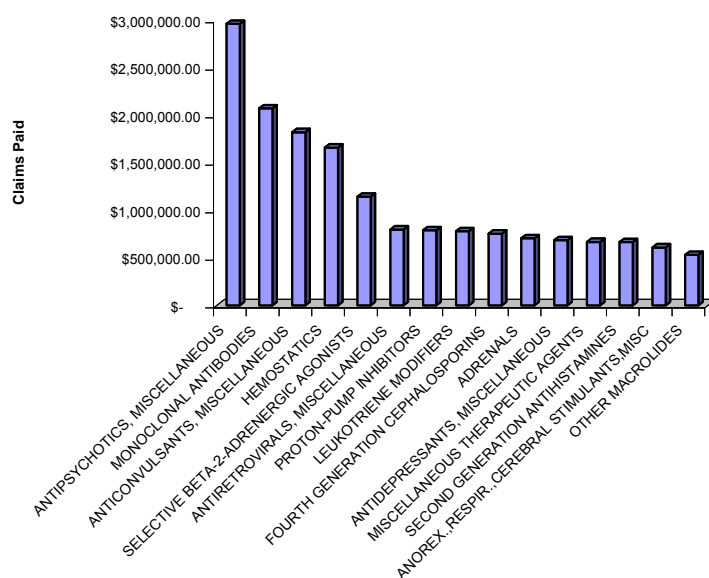
**MISSISSIPPI MEDICAID  
Cost Management Analysis**

**TOP 15 THERAPEUTIC CLASSES BY TOTAL COST OF CLAIMS FROM 12/01/07-12/31/07**

<b>AHFS Therapeutic Class</b>	<b>Rx</b>	<b>Paid</b>	<b>Paid/Rx</b>	<b>% Total Claims</b>
ANTIPSYCHOTICS, MISCELLANEOUS	9,892	\$ 2,962,706.50	\$ 299.51	2.60%
MONOCLONAL ANTIBODIES	1,455	\$ 2,072,144.41	\$ 1,424.15	0.38%
ANTICONVULSANTS, MISCELLANEOUS	10,580	\$ 1,822,733.29	\$ 172.28	2.78%
HEMOSTATICS	53	\$ 1,659,330.52	\$31,308.12	0.01%
SELECTIVE BETA-2-ADRENERGIC AGONISTS	15,105	\$ 1,143,321.22	\$ 75.69	3.97%
ANTIRETROVIRALS, MISCELLANEOUS	1,146	\$ 798,581.17	\$ 696.84	0.30%
PROTON-PUMP INHIBITORS	5,334	\$ 788,462.95	\$ 147.82	1.40%
LEUKOTRIENE MODIFIERS	7,618	\$ 779,297.71	\$ 102.30	2.00%
FOURTH GENERATION CEPHALOSPORINS	13,427	\$ 753,319.99	\$ 56.10	3.53%
ADRENALS	11,034	\$ 705,145.89	\$ 63.91	2.90%
ANTIDEPRESSANTS, MISCELLANEOUS	13,105	\$ 684,653.24	\$ 52.24	3.44%
MISCELLANEOUS THERAPEUTIC AGENTS	2,168	\$ 666,530.99	\$ 307.44	0.57%
SECOND GENERATION ANTIHISTAMINES	12,620	\$ 665,135.26	\$ 52.70	3.31%
ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	5,253	\$ 609,207.65	\$ 115.97	1.38%
OTHER MACROLIDES	14,579	\$ 529,961.49	\$ 36.35	3.83%
<b>TOTAL TOP 15</b>	<b>123,369</b>	<b>\$ 16,640,532.28</b>	<b>\$ 134.88</b>	<b>32.39%</b>

Total Rx Claims	380,900
From 12/01/07-12/31/07	

**Top 15 Therapeutic Classes  
Based on Total Cost of Claims**



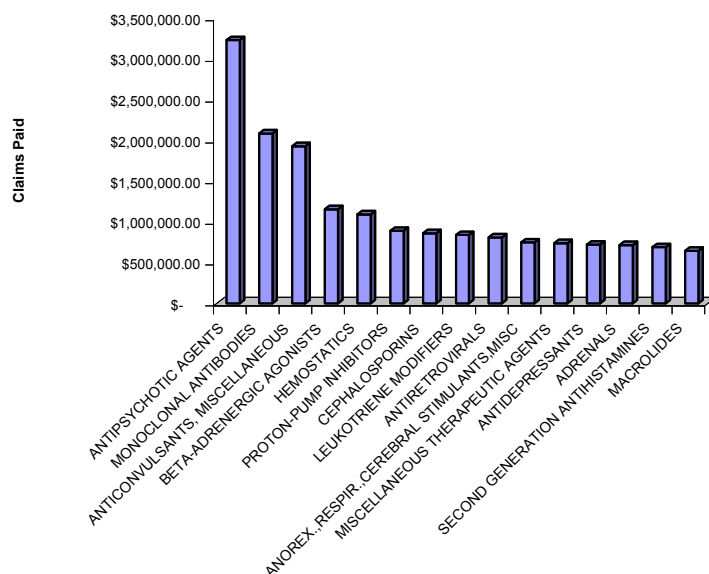
**MISSISSIPPI MEDICAID  
Cost Management Analysis**

**TOP 15 THERAPEUTIC CLASSES BY TOTAL COST OF CLAIMS FROM 01/01/08-01/31/08**

AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
ANTIPSYCHOTIC AGENTS	10,281	\$ 3,232,357.48	\$ 314.40	2.41%
MONOCLONAL ANTIBODIES	1,472	\$ 2,087,036.04	\$ 1,417.82	0.35%
ANTICONVULSANTS, MISCELLANEOUS	10,972	\$ 1,928,948.22	\$ 175.81	2.58%
BETA-ADRENERGIC AGONISTS	15,192	\$ 1,155,198.46	\$ 76.04	3.57%
HEMOSTATICS	46	\$ 1,091,533.93	\$23,729.00	0.01%
PROTON-PUMP INHIBITORS	5,810	\$ 889,648.08	\$ 153.12	1.36%
CEPHALOSPORINS	15,202	\$ 860,717.60	\$ 56.62	3.57%
LEUKOTRIENE MODIFIERS	8,178	\$ 838,312.96	\$ 102.51	1.92%
ANTIRETROVIRALS	1,126	\$ 807,749.16	\$ 717.36	0.26%
ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	6,170	\$ 748,426.19	\$ 121.30	1.45%
MISCELLANEOUS THERAPEUTIC AGENTS	2,318	\$ 738,880.27	\$ 318.76	0.54%
ANTIDEPRESSANTS	13,899	\$ 719,844.60	\$ 51.79	3.26%
ADRENALS	10,884	\$ 713,381.29	\$ 65.54	2.56%
SECOND GENERATION ANTIHISTAMINES	13,142	\$ 688,122.78	\$ 52.36	3.09%
MACROLIDES	17,404	\$ 642,685.79	\$ 36.93	4.09%
TOTAL TOP 15	132,096	\$ 17,142,842.85	\$ 129.78	31.01%

Total Rx Claims	425,968
From 01/01/08-01/31/08	

**Top 15 Therapeutic Classes  
Based on Total Cost of Claims**



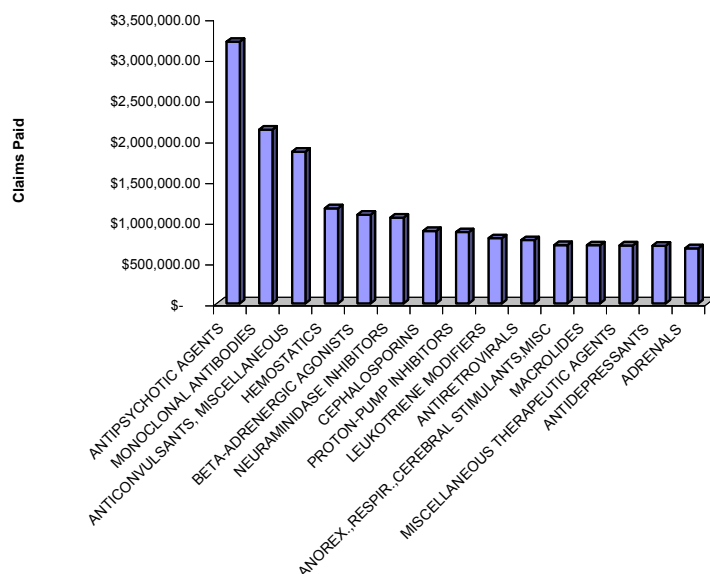
**MISSISSIPPI MEDICAID  
Cost Management Analysis**

**TOP 15 THERAPEUTIC CLASSES BY TOTAL COST OF CLAIMS FROM 02/01/08-02/29/08**

AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
ANTIPSYCHOTIC AGENTS	9,967	\$ 3,211,817.88	\$ 322.25	2.35%
MONOCLONAL ANTIBODIES	1,483	\$ 2,132,377.55	\$ 1,437.88	0.35%
ANTICONVULSANTS, MISCELLANEOUS	10,587	\$ 1,862,673.84	\$ 175.94	2.49%
HEMOSTATICS	42	\$ 1,165,991.22	\$27,761.70	0.01%
BETA-ADRENERGIC AGONISTS	13,819	\$ 1,086,994.13	\$ 78.66	3.25%
NEURAMINIDASE INHIBITORS	14,155	\$ 1,051,456.22	\$ 74.28	3.33%
CEPHALOSPORINS	15,853	\$ 888,303.83	\$ 56.03	3.73%
PROTON-PUMP INHIBITORS	5,656	\$ 873,073.97	\$ 154.36	1.33%
LEUKOTRIENE MODIFIERS	7,415	\$ 798,603.02	\$ 107.70	1.75%
ANTIRETROVIRALS	1,072	\$ 775,635.48	\$ 723.54	0.25%
ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	5,895	\$ 715,191.61	\$ 121.32	1.39%
MACROLIDES	19,269	\$ 712,410.95	\$ 36.97	4.54%
MISCELLANEOUS THERAPEUTIC AGENTS	2,257	\$ 711,380.50	\$ 315.19	0.53%
ANTIDEPRESSANTS	13,425	\$ 706,768.73	\$ 52.65	3.16%
ADRENALS	10,302	\$ 674,526.29	\$ 65.48	2.43%
TOTAL TOP 15	131,197	\$ 17,367,205.22	\$ 132.38	30.90%

Total Rx Claims	424,560
From 02/01/08-02/29/08	

**Top 15 Therapeutic Classes  
Based on Total Cost of Claims**



MISSISSIPPI MEDICAID  
Cost Management Analysis

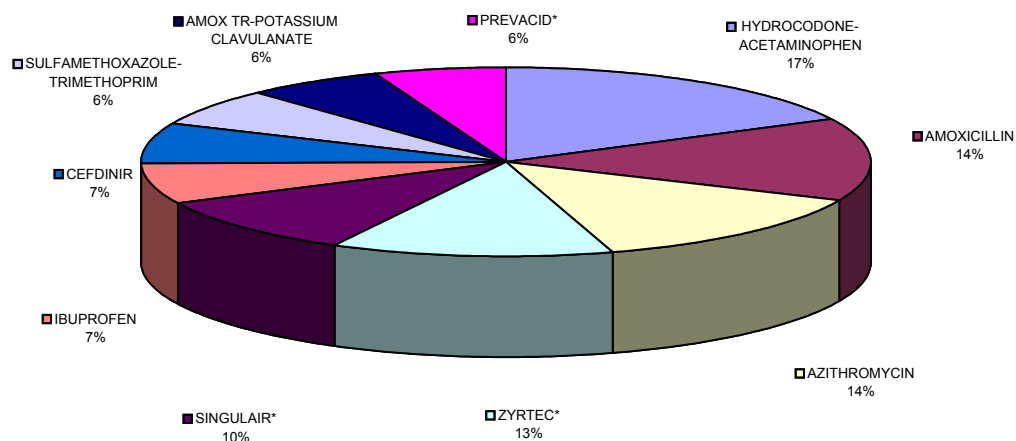
TOP 25 DRUGS BASED ON NUMBER OF CLAIMS FROM 09/01/07-09/30/07

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
HYDROCODONE-ACETAMINOPHEN	OPIATE AGONISTS	13,227	\$ 136,480.99	1
AMOXICILLIN	EXTENDED-SPECTRUM PENICILLINS	10,476	\$ 98,818.64	3
AZITHROMYCIN	OTHER MACROLIDES	10,292	\$ 360,736.51	9
ZYRTEC*	SECOND GENERATION ANTIHISTAMINES	9,443	\$ 546,484.65	12
SINGULAIR*	LEUKOTRIENE MODIFIERS	7,403	\$ 759,192.84	7
IBUPROFEN	OTHER NONSTEROIDAL ANTI-INFLAM. AGENTS	5,291	\$ 42,571.16	13
CEFDINIR	FOURTH GENERATION CEPHALOSPORINS	5,187	\$ 379,890.76	-----
SULFAMETHOXAZOLE-TRIMETHOPRIM	SULFONAMIDES (SYSTEMIC)	4,740	\$ 55,837.42	40
AMOX TR-POTASSIUM CLAVULANATE	EXTENDED-SPECTRUM PENICILLINS	4,539	\$ 242,633.97	22
PREVACID*	PROTON-PUMP INHIBITORS	4,450	\$ 653,860.38	8
ALPRAZOLAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	4,271	\$ 35,506.19	7
ED A-HIST	PROPYLAMINE DERIVATIVES	3,924	\$ 34,828.85	-----
CEPHALEXIN	FOURTH GENERATION CEPHALOSPORINS	3,592	\$ 58,775.42	14
ALBUTEROL SULFATE	SELECTIVE BETA-2-ADRENERGIC AGONISTS	3,454	\$ 87,420.53	61
ACETAMINOPHEN-CODEINE	OPIATE AGONISTS	3,222	\$ 25,751.36	31
CLONAZEPAM	BENZODIAZEPINES (ANTICONVULSANTS)	3,140	\$ 60,365.94	23
ADDERALL XR*	AMPHETAMINES	3,028	\$ 381,824.90	42
RISPERDAL*	ANTIPSYCHOTICS, MISCELLANEOUS	3,015	\$ 821,285.60	48
PROMETHAZINE HCL	PHENOTHIAZINE DERIVATIVES	2,984	\$ 35,793.18	53
ALBUTEROL	SELECTIVE BETA-2-ADRENERGIC AGONISTS	2,764	\$ 69,007.59	106
LORAZEPAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	2,707	\$ 71,546.49	19
FERROUS SULFATE	IRON PREPARATIONS	2,641	\$ 9,588.52	106
MUPIROCIN	ANTIBACTERIALS (SKIN & MUCOUS MEMBRANE)	2,575	\$ 97,658.87	119
RANITIDINE HCL	HISTAMINE H2-ANTAGONISTS	2,545	\$ 81,308.15	42
CONCERTA*	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	2,433	\$ 306,342.00	46
TOTAL TOP 25		121,343	\$ 5,453,510.91	

Total Rx Claims	361,985
From 09/01/07-09/30/07	

\* Indicates preferred products on the Preferred Drug List

Top 10 Drugs  
Based on Number of Claims





MISSISSIPPI MEDICAID  
Cost Management Analysis

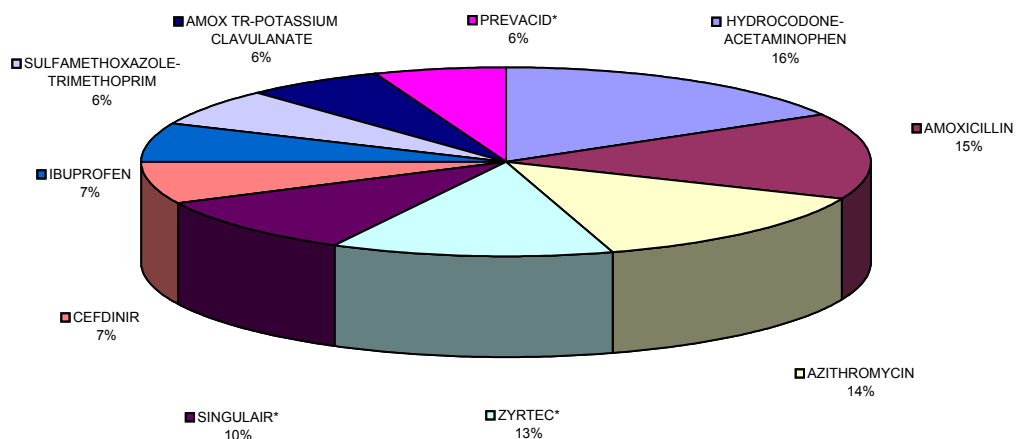
TOP 25 DRUGS BASED ON NUMBER OF CLAIMS FROM 10/01/07-10/31/07

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
HYDROCODONE-ACETAMINOPHEN	OPIATE AGONISTS	14,284	\$ 147,045.21	1
AMOXICILLIN	EXTENDED-SPECTRUM PENICILLINS	12,669	\$ 121,547.43	3
AZITHROMYCIN	OTHER MACROLIDES	11,877	\$ 422,158.04	9
ZYRTEC*	SECOND GENERATION ANTIHISTAMINES	10,782	\$ 618,060.63	12
SINGULAIR*	LEUKOTRIENE MODIFIERS	8,478	\$ 868,235.64	7
CEFDINIR	FOURTH GENERATION CEPHALOSPORINS	6,247	\$ 462,207.41	-----
IBUPROFEN	OTHER NONSTEROIDAL ANTI-INFLAM. AGENTS	5,674	\$ 46,262.10	13
SULFAMETHOXAZOLE-TRIMETHOPRIM	SULFONAMIDES (SYSTEMIC)	5,452	\$ 64,749.34	40
AMOX TR-POTASSIUM CLAVULANATE	EXTENDED-SPECTRUM PENICILLINS	5,340	\$ 285,759.79	22
PREVACID*	PROTON-PUMP INHIBITORS	4,961	\$ 738,948.81	8
ED A-HIST	PROPYLAMINE DERIVATIVES	4,960	\$ 43,626.14	-----
ALPRAZOLAM	BENZODIAZEPINES (ANXIOLYTIC, SEDATIV/HYP)	4,750	\$ 39,862.97	7
ALBUTEROL SULFATE	SELECTIVE BETA-2-ADRENERGIC AGONISTS	4,429	\$ 109,319.98	61
CEPHALEXIN	FOURTH GENERATION CEPHALOSPORINS	3,924	\$ 63,689.45	14
PROMETHAZINE HCL	PHENOTHIAZINE DERIVATIVES	3,750	\$ 44,011.70	53
ACETAMINOPHEN-CODEINE	OPIATE AGONISTS	3,615	\$ 28,744.34	31
CLONAZEPAM	BENZODIAZEPINES (ANTICONVULSANTS)	3,411	\$ 65,252.44	23
ADDERALL XR*	AMPHETAMINES	3,296	\$ 437,284.52	42
RISPERDAL*	ANTIPSYCHOTICS, MISCELLANEOUS	3,249	\$ 873,716.84	48
ALBUTEROL	SELECTIVE BETA-2-ADRENERGIC AGONISTS	3,068	\$ 78,135.04	11
LORAZEPAM	BENZODIAZEPINES (ANXIOLYTIC, SEDATIV/HYP)	2,929	\$ 78,886.61	19
RANITIDINE HCL	HISTAMINE H2-ANTAGONISTS	2,878	\$ 93,044.48	42
MUPIROCIN	ANTIBACTERIALS (SKIN & MUCOUS MEMBRANE)	2,866	\$ 108,149.10	119
FERROUS SULFATE	IRON PREPARATIONS	2,862	\$ 10,258.40	106
CONCERTA*	ANOREX., RESPIR., CEREBRAL STIMULANTS, MISC	2,778	\$ 349,624.20	46
TOTAL TOP 25		138,529	\$ 6,198,580.61	

Total Rx Claims	406,295
From 10/01/07-10/31/07	

\* Indicates preferred products on the Preferred Drug List

Top 10 Drugs  
Based on Number of Claims



MISSISSIPPI MEDICAID  
Cost Management Analysis

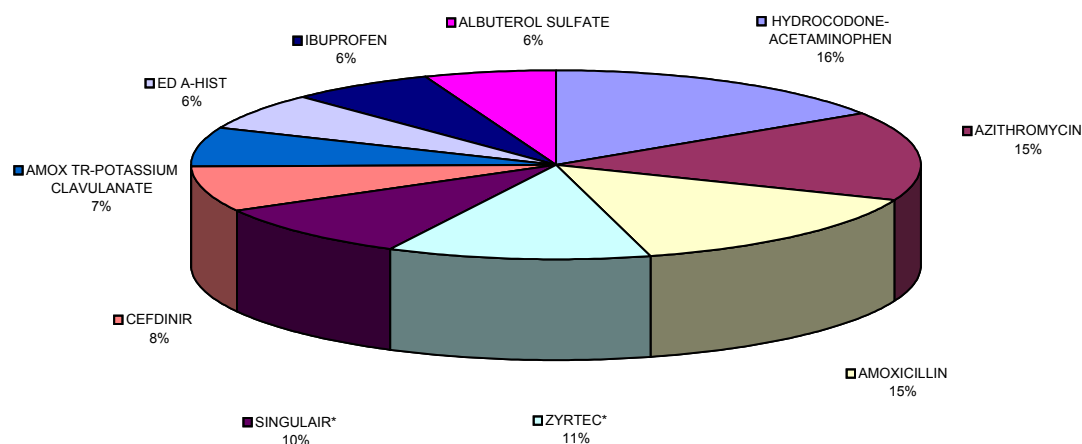
TOP 25 DRUGS BASED ON NUMBER OF CLAIMS FROM 11/01/07-11/30/07

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
HYDROCODONE-ACETAMINOPHEN	OPIATE AGONISTS	13,724	\$ 144,879.62	1
AZITHROMYCIN	OTHER MACROLIDES	12,995	\$ 460,730.87	9
AMOXICILLIN	EXTENDED-SPECTRUM PENICILLINS	12,739	\$ 122,540.42	3
ZYRTEC*	SECOND GENERATION ANTIHISTAMINES	9,881	\$ 569,052.93	12
SINGULAIR*	LEUKOTRIENE MODIFIERS	8,198	\$ 840,955.59	7
CEFDINIR	FOURTH GENERATION CEPHALOSPORINS	6,680	\$ 491,715.59	-----
AMOX TR-POTASSIUM CLAVULANATE	EXTENDED-SPECTRUM PENICILLINS	5,744	\$ 304,998.58	22
ED A-HIST	PROPYLAMINE DERIVATIVES	5,539	\$ 48,368.38	-----
IBUPROFEN	OTHER NONSTEROIDAL ANTI-INFLAM. AGENTS	5,430	\$ 44,435.12	13
ALBUTEROL SULFATE	SELECTIVE BETA-2-ADRENERGIC AGONISTS	5,071	\$ 122,399.93	61
SULFAMETHOXAZOLE-TRIMETHOPRIM	SULFONAMIDES (SYSTEMIC)	4,895	\$ 57,621.86	40
PREVACID*	PROTON-PUMP INHIBITORS	4,807	\$ 714,568.76	8
ALPRAZOLAM	BENZODIAZEPINES (ANXIOLYTIC, SEDATIV/HYP)	4,724	\$ 39,889.68	7
CEPHALEXIN	FOURTH GENERATION CEPHALOSPORINS	3,579	\$ 57,051.19	14
CLONAZEPAM	BENZODIAZEPINES (ANTICONVULSANTS)	3,397	\$ 64,874.11	23
ACETAMINOPHEN-CODEINE	OPIATE AGONISTS	3,375	\$ 26,883.22	31
PROMETHAZINE HCL	PHENOTHIAZINE DERIVATIVES	3,322	\$ 40,367.02	53
RISPERDAL*	ANTIPSYCHOTICS, MISCELLANEOUS	3,273	\$ 878,614.69	48
ADDERALL XR*	AMPHETAMINES	3,041	\$ 412,454.67	42
ALBUTEROL	SELECTIVE BETA-2-ADRENERGIC AGONISTS	2,862	\$ 73,400.56	11
PREDNISOLONE	ADRENALS	2,812	\$ 35,152.20	132
LORAZEPAM	BENZODIAZEPINES (ANXIOLYTIC, SEDATIV/HYP)	2,773	\$ 77,432.98	19
RANITIDINE HCL	HISTAMINE H2-ANTAGONISTS	2,707	\$ 85,518.57	42
FERROUS SULFATE	IRON PREPARATIONS	2,707	\$ 9,603.42	106
XOPENEX*	SELECTIVE BETA-2-ADRENERGIC AGONISTS	2,689	\$ 461,766.23	131
TOTAL TOP 25		136,964	\$ 6,185,276.19	

Total Rx Claims	397,855
From 11/01/07-11/30/07	

\* Indicates preferred products on the Preferred Drug List

Top 10 Drugs  
Based on Number of Claims



MISSISSIPPI MEDICAID  
Cost Management Analysis

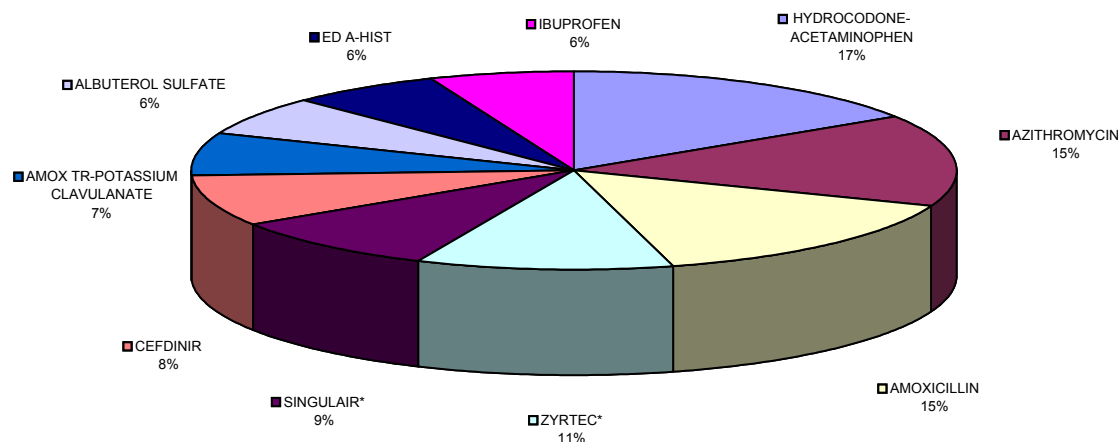
TOP 25 DRUGS BASED ON NUMBER OF CLAIMS FROM 12/01/07-12/31/07

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
HYDROCODONE-ACETAMINOPHEN	OPIATE AGONISTS	13,140	\$ 138,700.02	1
AZITHROMYCIN	OTHER MACROLIDES	12,558	\$ 446,305.37	9
AMOXICILLIN	EXTENDED-SPECTRUM PENICILLINS	12,325	\$ 117,750.09	3
ZYRTEC*	SECOND GENERATION ANTIHISTAMINES	8,934	\$ 508,751.49	12
SINGULAIR*	LEUKOTRIENE MODIFIERS	7,611	\$ 778,144.22	7
CEFDINIR	FOURTH GENERATION CEPHALOSPORINS	6,971	\$ 506,659.42	-----
AMOX TR-POTASSIUM CLAVULANATE	EXTENDED-SPECTRUM PENICILLINS	5,707	\$ 299,791.78	22
ALBUTEROL SULFATE	SELECTIVE BETA-2-ADRENERGIC AGONISTS	5,391	\$ 128,770.47	61
ED A-HIST	PROPYLAMINE DERIVATIVES	5,302	\$ 45,967.27	-----
IBUPROFEN	OTHER NONSTEROIDAL ANTI-INFLAM. AGENTS	5,074	\$ 41,911.12	13
PREVACID*	PROTON-PUMP INHIBITORS	4,705	\$ 707,230.39	8
ALPRAZOLAM	BENZODIAZEPINES (ANXIOLYTIC, SEDATIV/HYP)	4,494	\$ 38,287.26	7
SULFAMETHOXAZOLE-TRIMETHOPRIM	SULFONAMIDES (SYSTEMIC)	4,258	\$ 49,403.91	40
CLONAZEPAM	BENZODIAZEPINES (ANTICONSULSANTS)	3,337	\$ 63,856.87	23
RISPERDAL*	ANTIPSYCHOTICS, MISCELLANEOUS	3,210	\$ 872,325.85	48
CEPHALEXIN	FOURTH GENERATION CEPHALOSPORINS	3,202	\$ 51,588.99	14
PROMETHAZINE HCL	PHENOTHIAZINE DERIVATIVES	3,135	\$ 38,070.03	53
ACETAMINOPHEN-CODEINE	OPIATE AGONISTS	3,084	\$ 24,694.53	31
XOPENEX*	SELECTIVE BETA-2-ADRENERGIC AGONISTS	2,941	\$ 504,120.25	131
PREDNISOLONE	ADRENALS	2,813	\$ 34,080.75	-----
ADDERALL XR*	AMPHETAMINES	2,808	\$ 382,096.22	42
PREDNISOLONE SODIUM PHOSPHATE	ADRENALS	2,650	\$ 49,010.37	132
LORAZEPAM	BENZODIAZEPINES (ANXIOLYTIC, SEDATIV/HYP)	2,635	\$ 72,813.94	19
ALBUTEROL	SELECTIVE BETA-2-ADRENERGIC AGONISTS	2,634	\$ 68,442.25	11
RANITIDINE HCL	HISTAMINE H2-ANTAGONISTS	2,587	\$ 79,754.62	42
TOTAL TOP 25		131,506	\$ 6,048,527.48	

Total Rx Claims	380,900
From 12/01/07-12/31/07	

\* Indicates preferred products on the Preferred Drug List

Top 10 Drugs  
Based on Number of Claims



MISSISSIPPI MEDICAID  
Cost Management Analysis

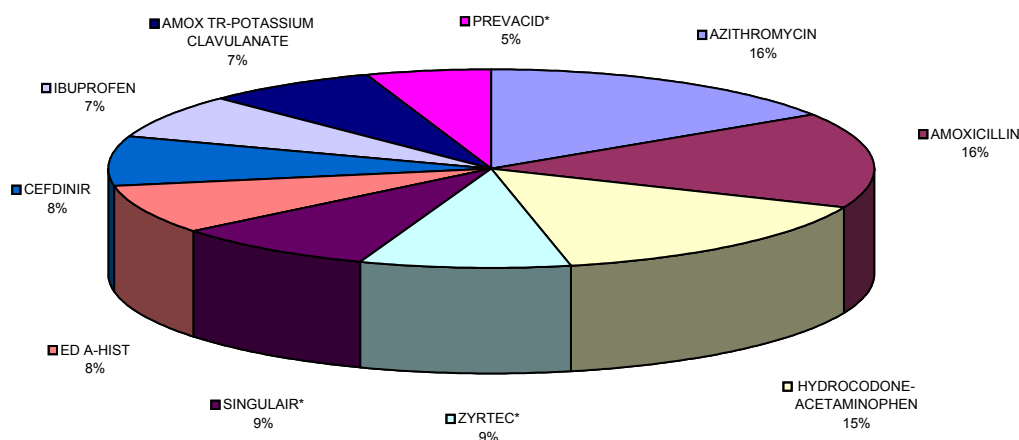
TOP 25 DRUGS BASED ON NUMBER OF CLAIMS FROM 01/01/08-01/31/08

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
AZITHROMYCIN	MACROLIDES	15,041	\$ 540,038.84	9
AMOXICILLIN	PENICILLINS	14,845	\$ 141,718.45	3
HYDROCODONE-ACETAMINOPHEN	OPIATE AGONISTS	14,409	\$ 151,363.10	1
ZYRTEC*	SECOND GENERATION ANTIHISTAMINES	8,618	\$ 491,978.68	12
SINGULAIR*	LEUKOTRIENE MODIFIERS	8,174	\$ 837,780.22	7
ED A-HIST	PROPYLAMINE DERIVATIVES	7,647	\$ 68,093.80	-----
CEFDINIR	CEPHALOSPORINS	7,473	\$ 554,185.63	-----
IBUPROFEN	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS	7,048	\$ 60,464.03	13
AMOX TR-POTASSIUM CLAVULANATE	PENICILLINS	6,650	\$ 360,581.07	22
PREVACID*	PROTON-PUMP INHIBITORS	5,135	\$ 795,947.05	8
ALBUTEROL SULFATE	BETA-ADRENERGIC AGONISTS	4,949	\$ 124,404.12	61
SULFAMETHOXAZOLE-TRIMETHOPRIM	SULFONAMIDES (SYSTEMIC)	4,830	\$ 56,813.20	40
TAMIFLU	NEURAMINIDASE INHIBITORS	4,826	\$ 362,890.00	153
ALPRAZOLAM	BENZODIAZEPINES (ANXIOLYTIC, SEDATIV/HYP)	4,629	\$ 39,347.96	7
CEPHALEXIN	CEPHALOSPORINS	4,065	\$ 66,472.50	14
PROMETHAZINE HCL	PHENOTHIAZINE DERIVATIVES	3,826	\$ 44,764.72	53
ACETAMINOPHEN-CODEINE	OPIATE AGONISTS	3,589	\$ 28,472.98	31
CLONAZEPAM	BENZODIAZEPINES (ANTICONVULSANTS)	3,450	\$ 65,601.33	23
ADDERALL XR*	AMPHETAMINES	3,307	\$ 449,814.57	42
RISPERDAL*	ANTIPSYCHOTIC AGENTS	3,300	\$ 933,741.84	48
ALBUTEROL	BETA-ADRENERGIC AGONISTS	2,910	\$ 75,088.18	11
RANITIDINE HCL	HISTAMINE H2-ANTAGONISTS	2,889	\$ 94,800.54	42
CONCERTA*	ANOREX., RESPIR., CEREBRAL STIMULANTS, MISC	2,791	\$ 367,382.74	46
LORAZEPAM	BENZODIAZEPINES (ANXIOLYTIC, SEDATIV/HYP)	2,788	\$ 76,524.83	19
XOPENEX*	BETA-ADRENERGIC AGONISTS	2,782	\$ 482,187.41	131
TOTAL TOP 25		149,971	\$ 7,270,457.79	

Total Rx Claims	425,968
From 01/01/08-01/31/08	

\* Indicates preferred products on the Preferred Drug List

Top 10 Drugs  
Based on Number of Claims



MISSISSIPPI MEDICAID  
Cost Management Analysis

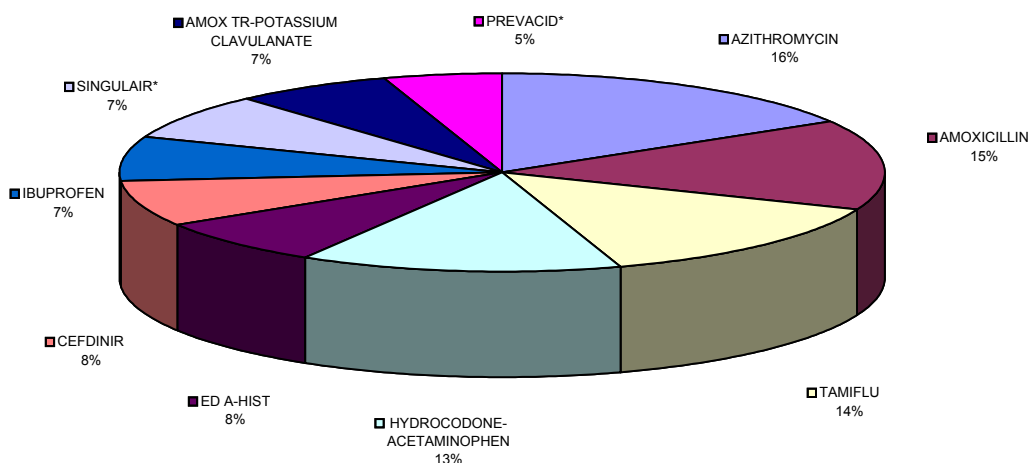
TOP 25 DRUGS BASED ON NUMBER OF CLAIMS FROM 02/01/08-02/29/08

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
AZITHROMYCIN	MACROLIDES	16,695	\$ 600,974.35	9
AMOXICILLIN	PENICILLINS	15,205	\$ 145,735.98	3
TAMIFLU	NEURAMINIDASE INHIBITORS	14,155	\$ 1,051,456.22	153
HYDROCODONE-ACETAMINOPHEN	OPIATE AGONISTS	13,742	\$ 147,023.26	1
ED A-HIST	PROPYLAMINE DERIVATIVES	7,871	\$ 69,676.42	-----
CEFDINIR	CEPHALOSPORINS	7,683	\$ 569,676.50	-----
IBUPROFEN	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS	7,411	\$ 65,072.75	13
SINGULAIR*	LEUKOTRIENE MODIFIERS	7,409	\$ 797,503.46	7
AMOX TR-POTASSIUM CLAVULANATE	PENICILLINS	7,037	\$ 384,786.83	22
PREVACID*	PROTON-PUMP INHIBITORS	5,015	\$ 782,241.74	8
PROMETHAZINE HCL	PHENOTHIAZINE DERIVATIVES	4,548	\$ 50,893.66	53
ALPRAZOLAM	BENZODIAZEPINES (ANXIOLYTIC, SEDATIV/HYP)	4,452	\$ 37,482.86	7
SULFAMETHOXAZOLE-TRIMETHOPRIM	SULFONAMIDES (SYSTEMIC)	4,417	\$ 51,447.70	40
ZYRTEC*	SECOND GENERATION ANTIHISTAMINES	4,301	\$ 244,083.98	12
ALBUTEROL SULFATE	BETA-ADRENERGIC AGONISTS	4,231	\$ 109,794.43	61
CEPHALEXIN	CEPHALOSPORINS	4,169	\$ 67,064.48	14
ACETAMINOPHEN-CODEINE	OPIATE AGONISTS	3,544	\$ 28,414.92	31
CLONAZEPAM	BENZODIAZEPINES (ANTICONVULSANTS)	3,302	\$ 62,746.40	23
RISPERDAL*	ANTIPSYCHOTIC AGENTS	3,175	\$ 920,281.78	48
ADDERALL XR*	AMPHETAMINES	3,136	\$ 423,885.67	42
ALBUTEROL	BETA-ADRENERGIC AGONISTS	2,693	\$ 69,252.02	11
CONCERTA*	ANOREX., RESPIR., CEREBRAL STIMULANTS, MISC	2,669	\$ 351,120.33	46
RANITIDINE HCL	HISTAMINE H2-ANTAGONISTS	2,646	\$ 84,779.38	42
FERROUS SULFATE	IRON PREPARATIONS	2,561	\$ 8,940.80	106
LORAZEPAM	BENZODIAZEPINES (ANXIOLYTIC, SEDATIV/HYP)	2,551	\$ 70,353.18	19
TOTAL TOP 25		154,618	\$ 7,194,689.10	

Total Rx Claims	424,560
From 02/01/08-02/29/08	

\* Indicates preferred products on the Preferred Drug List

Top 10 Drugs  
Based on Number of Claims



MISSISSIPPI MEDICAID  
Cost Management Analysis

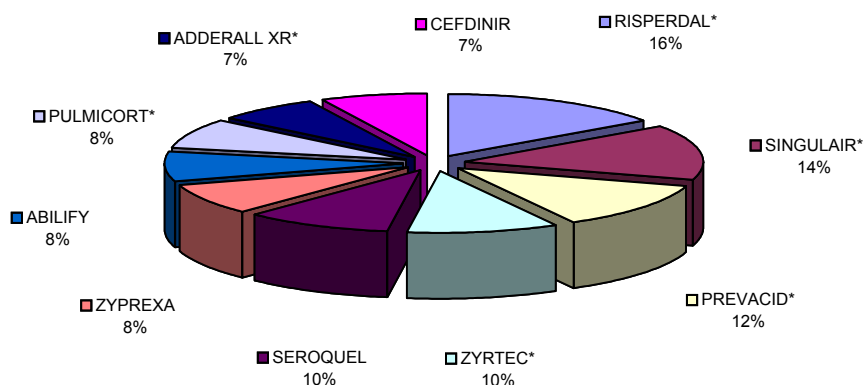
TOP 25 DRUGS BASED ON TOTAL CLAIMS COST FROM 09/01/07-09/30/07

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
RISPERDAL*	ANTIPSYCHOTICS, MISCELLANEOUS	3,015	\$ 821,285.60	18
SINGULAIR*	LEUKOTRIENE MODIFIERS	7,403	\$ 759,192.84	5
PREVACID*	PROTON-PUMP INHIBITORS	4,450	\$ 653,860.38	3
ZYRTEC*	SECOND GENERATION ANTIHISTAMINES	9,443	\$ 546,484.65	29
SEROQUEL	ANTIPSYCHOTICS, MISCELLANEOUS	1,681	\$ 531,816.56	11
ZYPREXA	ANTIPSYCHOTICS, MISCELLANEOUS	896	\$ 436,186.74	19
ABILIFY	ANTIPSYCHOTICS, MISCELLANEOUS	950	\$ 417,321.93	24
PULMICORT*	ADRENALS	1,721	\$ 405,830.67	73
ADDERALL XR*	AMPHETAMINES	3,028	\$ 381,824.90	33
CEFDINIR	FOURTH GENERATION CEPHALOSPORINS	5,187	\$ 379,890.76	-----
AZITHROMYCIN	OTHER MACROLIDES	10,292	\$ 360,736.51	3
TOPAMAX*	ANTICONVULSANTS, MISCELLANEOUS	1,159	\$ 347,967.03	20
CONCERTA*	ANOREX., RESPIR., CEREBRAL STIMULANTS, MISC	2,433	\$ 306,342.00	41
XOPENEX*	SELECTIVE BETA-2-ADRENERGIC AGONISTS	1,713	\$ 287,344.02	107
ADVAIR DISKUS*	SELECTIVE BETA-2-ADRENERGIC AGONISTS	1,553	\$ 275,687.27	4
GEODON*	ANTIPSYCHOTICS, MISCELLANEOUS	795	\$ 256,840.97	72
ADVATE	HEMOSTATICS	7	\$ 242,639.22	-----
AMOX TR-POTASSIUM CL	EXTENDED-SPECTRUM PENICILLINS	4,539	\$ 242,633.97	6
LAMICTAL*	ANTICONVULSANTS, MISCELLANEOUS	744	\$ 237,079.75	26
EXJADE	HEAVY METAL ANTAGONISTS	53	\$ 222,907.58	-----
TRILEPTAL*	ANTICONVULSANTS, MISCELLANEOUS	1,119	\$ 214,636.64	74
FEIBA VH IMMUNO	HEMOSTATICS	4	\$ 213,379.99	-----
GABAPENTIN	ANTICONVULSANTS, MISCELLANEOUS	1,787	\$ 201,860.49	5
STRATTERA*	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	1,298	\$ 195,455.43	63
KEPPRA*	ANTICONVULSANTS, MISCELLANEOUS	782	\$ 186,233.51	81
TOTAL TOP 25		66,052	\$ 9,125,439.41	

Total Rx Claims	361,985
From 09/01/07-09/30/07	

\* Indicates preferred products on the Preferred Drug List

Top 10 Drugs  
Based on Total Claims Cost



MISSISSIPPI MEDICAID  
Cost Management Analysis

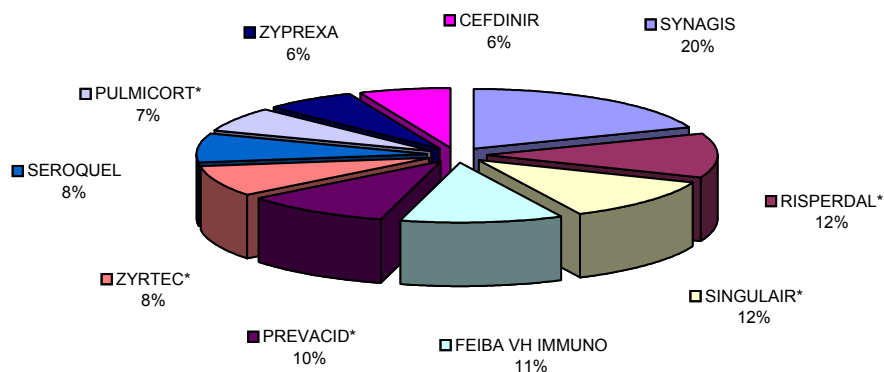
TOP 25 DRUGS BASED ON TOTAL CLAIMS COST FROM 10/01/07-10/31/07

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
SYNAGIS	MONOCLONAL ANTIBODIES	976	\$ 1,408,180.53	-----
RISPERDAL*	ANTIPSYCHOTICS, MISCELLANEOUS	3,249	\$ 873,716.84	18
SINGULAIR*	LEUKOTRIENE MODIFIERS	8,478	\$ 868,235.64	5
FEIBA VH IMMUNO	HEMOSTATICS	11	\$ 844,940.59	-----
PREVACID*	PROTON-PUMP INHIBITORS	4,961	\$ 738,948.81	3
ZYRTEC*	SECOND GENERATION ANTIHISTAMINES	10,782	\$ 618,060.63	29
SEROQUEL	ANTIPSYCHOTICS, MISCELLANEOUS	1,795	\$ 565,031.46	11
PULMICORT*	ADRENALS	2,150	\$ 509,538.82	73
ZYPREXA	ANTIPSYCHOTICS, MISCELLANEOUS	949	\$ 468,062.10	19
CEFDINIR	FOURTH GENERATION CEPHALOSPORINS	6,247	\$ 462,207.41	-----
ADDERALL XR*	AMPHETAMINES	3,296	\$ 437,284.52	33
ABILIFY	ANTIPSYCHOTICS, MISCELLANEOUS	976	\$ 431,763.94	24
AZITHROMYCIN	OTHER MACROLIDES	11,877	\$ 422,158.04	3
TOPAMAX*	ANTICONVULSANTS, MISCELLANEOUS	1,248	\$ 370,907.64	20
XOPENEX*	SELECTIVE BETA-2-ADRENERGIC AGONISTS	2,214	\$ 370,247.42	107
CONCERTA*	ANOREX., RESPIR., CEREBRAL STIMULANTS, MISC	2,778	\$ 349,624.20	41
ADVAIR DISKUS*	SELECTIVE BETA-2-ADRENERGIC AGONISTS	1,673	\$ 309,935.06	4
AMOX TR-POTASSIUM CL	EXTENDED-SPECTRUM PENICILLINS	5,340	\$ 285,759.79	6
GEODON*	ANTIPSYCHOTICS, MISCELLANEOUS	845	\$ 270,997.26	72
ADVATE	HEMOSTATICS	11	\$ 266,051.62	-----
LAMICTAL*	ANTICONVULSANTS, MISCELLANEOUS	808	\$ 246,760.09	26
GABAPENTIN	ANTICONVULSANTS, MISCELLANEOUS	1,851	\$ 214,201.70	5
KEPPRA*	ANTICONVULSANTS, MISCELLANEOUS	843	\$ 207,534.79	81
STRATTERA*	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	1,396	\$ 207,347.52	63
EFFEXOR XR*	ANTIDEPRESSANTS, MISCELLANEOUS	1,304	\$ 198,001.45	6
TOTAL TOP 25		76,058	\$ 11,945,497.87	

Total Rx Claims	406,295
From 10/01/07-10/31/07	

\* Indicates preferred products on the Preferred Drug List

Top 10 Drugs  
Based on Total Claims Cost



MISSISSIPPI MEDICAID  
Cost Management Analysis

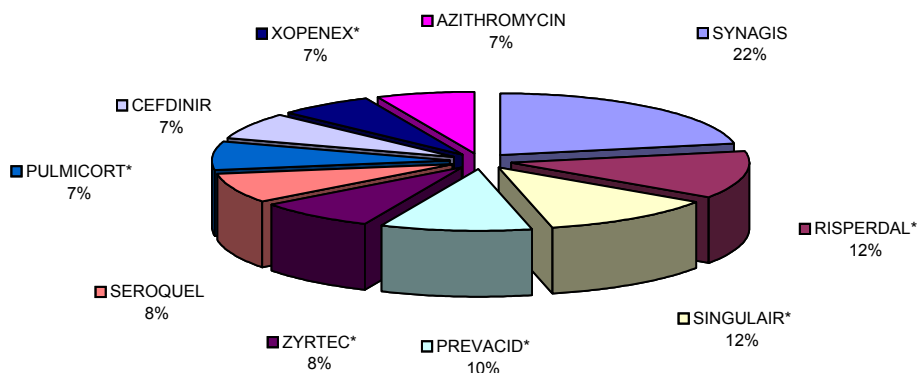
TOP 25 DRUGS BASED ON TOTAL CLAIMS COST FROM 11/01/07-11/30/07

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
SYNAGIS	MONOCLONAL ANTIBODIES	1,088	\$ 1,544,256.21	-----
RISPERDAL*	ANTIPSYCHOTICS, MISCELLANEOUS	3,273	\$ 878,614.69	18
SINGULAIR*	LEUKOTRIENE MODIFIERS	8,198	\$ 840,955.59	5
PREVACID*	PROTON-PUMP INHIBITORS	4,807	\$ 714,568.76	3
ZYRTEC*	SECOND GENERATION ANTIHISTAMINES	9,881	\$ 569,052.93	29
SEROQUEL	ANTIPSYCHOTICS, MISCELLANEOUS	1,742	\$ 552,658.56	11
PULMICORT*	ADRENALS	2,167	\$ 523,188.82	73
CEFDINIR	FOURTH GENERATION CEPHALOSPORINS	6,680	\$ 491,715.59	-----
XOPENEX*	SELECTIVE BETA-2-ADRENERGIC AGONISTS	2,689	\$ 461,766.23	107
AZITHROMYCIN	OTHER MACROLIDES	12,995	\$ 460,730.87	3
ZYPREXA	ANTIPSYCHOTICS, MISCELLANEOUS	901	\$ 438,708.09	19
ABILIFY	ANTIPSYCHOTICS, MISCELLANEOUS	964	\$ 420,059.62	24
ADDERALL XR*	AMPHETAMINES	3,041	\$ 412,454.67	33
TOPAMAX*	ANTICONVULSANTS, MISCELLANEOUS	1,288	\$ 374,237.82	20
CONCERTA*	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	2,469	\$ 314,450.80	41
AMOX TR-POTASSIUM CL	EXTENDED-SPECTRUM PENICILLINS	5,744	\$ 304,998.58	6
ADVAIR DISKUS*	SELECTIVE BETA-2-ADRENERGIC AGONISTS	1,621	\$ 299,759.06	4
GEODON*	ANTIPSYCHOTICS, MISCELLANEOUS	850	\$ 272,324.49	72
LAMICTAL*	ANTICONVULSANTS, MISCELLANEOUS	818	\$ 253,091.41	26
FEIBA VH IMMUNO	HEMOSTATICS	2	\$ 225,894.46	-----
KEPPRA*	ANTICONVULSANTS, MISCELLANEOUS	832	\$ 214,892.55	81
GABAPENTIN	ANTICONVULSANTS, MISCELLANEOUS	1,841	\$ 208,763.61	5
STRATTERA*	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	1,312	\$ 197,089.21	63
EFFEXOR XR*	ANTIDEPRESSANTS, MISCELLANEOUS	1,221	\$ 190,280.79	6
DEPAKOTE*	ANTICONVULSANTS, MISCELLANEOUS	974	\$ 186,729.70	69
TOTAL TOP 25		77,398	\$ 11,351,243.11	

Total Rx Claims	397,855
From 11/01/07-11/30/07	

\* Indicates preferred products on the Preferred Drug List

Top 10 Drugs  
Based on Total Claims Cost





MISSISSIPPI MEDICAID  
Cost Management Analysis

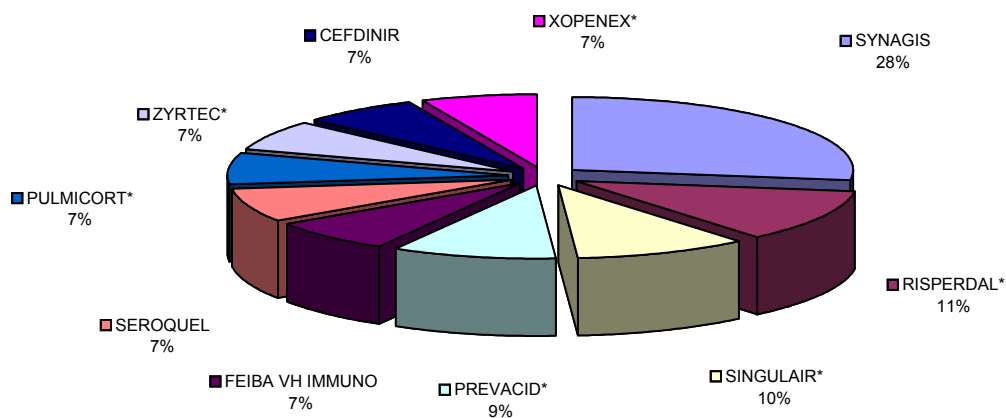
TOP 25 DRUGS BASED ON TOTAL CLAIMS COST FROM 12/01/07-12/31/07

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
SYNAGIS	MONOCLONAL ANTIBODIES	1,455	\$ 2,072,144.41	-----
RISPERDAL*	ANTIPSYCHOTICS, MISCELLANEOUS	3,210	\$ 872,325.85	18
SINGULAIR*	LEUKOTRIENE MODIFIERS	7,611	\$ 778,144.22	5
PREVACID*	PROTON-PUMP INHIBITORS	4,705	\$ 707,230.39	3
FEIBA VH IMMUNO	HEMOSTATICS	6	\$ 560,514.12	-----
SEROQUEL	ANTIPSYCHOTICS, MISCELLANEOUS	1,741	\$ 552,093.35	11
PULMICORT*	ADRENALS	2,194	\$ 536,049.61	73
ZYRTEC*	SECOND GENERATION ANTIHISTAMINES	8,934	\$ 508,751.49	29
CEFDINIR	FOURTH GENERATION CEPHALOSPORINS	6,971	\$ 506,659.42	-----
XOPENEX*	SELECTIVE BETA-2-ADRENERGIC AGONISTS	2,941	\$ 504,120.25	107
ZYPREXA	ANTIPSYCHOTICS, MISCELLANEOUS	912	\$ 452,209.48	19
AZITHROMYCIN	OTHER MACROLIDES	12,558	\$ 446,305.37	3
ABILIFY	ANTIPSYCHOTICS, MISCELLANEOUS	922	\$ 423,050.46	24
ADDERALL XR*	AMPHETAMINES	2,808	\$ 382,096.22	33
TOPAMAX*	ANTICONVULSANTS, MISCELLANEOUS	1,195	\$ 352,138.61	20
ADVATE	HEMOSTATICS	6	\$ 308,824.49	-----
AMOX TR-POTASSIUM CL	EXTENDED-SPECTRUM PENICILLINS	5,707	\$ 299,791.78	6
CONCERTA*	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	2,304	\$ 292,044.03	41
ADVAIR DISKUS*	SELECTIVE BETA-2-ADRENERGIC AGONISTS	1,513	\$ 283,058.01	4
GEODON*	ANTIPSYCHOTICS, MISCELLANEOUS	852	\$ 270,739.07	72
LAMICTAL*	ANTICONVULSANTS, MISCELLANEOUS	807	\$ 242,792.77	26
HELIXATE FS	HEMOSTATICS	11	\$ 222,001.01	-----
GABAPENTIN	ANTICONVULSANTS, MISCELLANEOUS	1,836	\$ 210,845.56	5
KEPPRA*	ANTICONVULSANTS, MISCELLANEOUS	827	\$ 205,693.36	81
EFFEXOR XR*	ANTIDEPRESSANTS, MISCELLANEOUS	1,204	\$ 189,248.40	6
TOTAL TOP 25		73,230	\$ 12,178,871.73	

Total Rx Claims	380,900
From 12/01/07-12/31/07	

\* Indicates preferred products on the Preferred Drug List

Top 10 Drugs  
Based on Total Claims Cost



MISSISSIPPI MEDICAID  
Cost Management Analysis

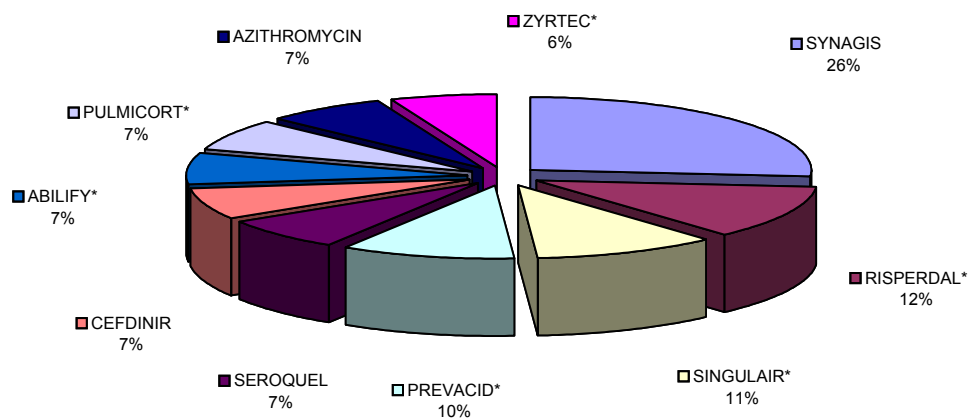
TOP 25 DRUGS BASED ON TOTAL CLAIMS COST FROM 01/01/08-01/31/08

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
SYNAGIS	MONOCLONAL ANTIBODIES	1,472	\$ 2,087,036.04	-----
RISPERDAL*	ANTIPSYCHOTIC AGENTS	3,300	\$ 933,741.84	18
SINGULAIR*	LEUKOTRIENE MODIFIERS	8,174	\$ 837,780.22	5
PREVACID*	PROTON-PUMP INHIBITORS	5,135	\$ 795,947.05	3
SEROQUEL	ANTIPSYCHOTIC AGENTS	1,673	\$ 575,261.49	11
CEFdinIR	CEPHALOSPORINS	7,473	\$ 554,185.63	-----
ABILIFY*	ANTIPSYCHOTIC AGENTS	1,185	\$ 548,834.84	24
PULMICORT*	ADRENALS	2,083	\$ 540,665.38	73
AZITHROMYCIN	MACROLIDES	15,041	\$ 540,038.84	3
ZYRTEC*	SECOND GENERATION ANTIHISTAMINES	8,618	\$ 491,978.68	29
XOPENEX*	BETA-ADRENERGIC AGONISTS	2,782	\$ 482,187.41	107
ZYPREXA	ANTIPSYCHOTIC AGENTS	892	\$ 469,491.17	19
ADDERALL XR*	AMPHETAMINES	3,307	\$ 449,814.57	33
FEIBA VH IMMUNO	HEMOSTATICS	7	\$ 386,057.29	-----
CONCERTA*	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	2,791	\$ 367,382.74	41
TAMIFLU	NEURAMINIDASE INHIBITORS	4,826	\$ 362,890.00	-----
TOPAMAX*	ANTICONVULSANTS, MISCELLANEOUS	1,240	\$ 362,318.80	20
AMOX TR-POTASSIUM CL	PENICILLINS	6,650	\$ 360,581.07	6
ADVAIR DISKUS*	BETA-ADRENERGIC AGONISTS	1,606	\$ 298,574.86	4
GEODON*	ANTIPSYCHOTIC AGENTS	830	\$ 279,372.65	72
LAMICTAL*	ANTICONVULSANTS, MISCELLANEOUS	855	\$ 261,275.72	26
ADVATE	HEMOSTATICS	8	\$ 240,127.93	-----
KEPPRA*	ANTICONVULSANTS, MISCELLANEOUS	864	\$ 219,813.28	81
GABAPENTIN	ANTICONVULSANTS, MISCELLANEOUS	1,901	\$ 214,547.09	5
STRATTERA*	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	1,384	\$ 208,115.08	63
TOTAL TOP 25		84,097	\$ 12,868,019.67	

Total Rx Claims	425,968
From 01/01/08-01/31/08	

\* Indicates preferred products on the Preferred Drug List

Top 10 Drugs  
Based on Total Claims Cost



MISSISSIPPI MEDICAID  
Cost Management Analysis

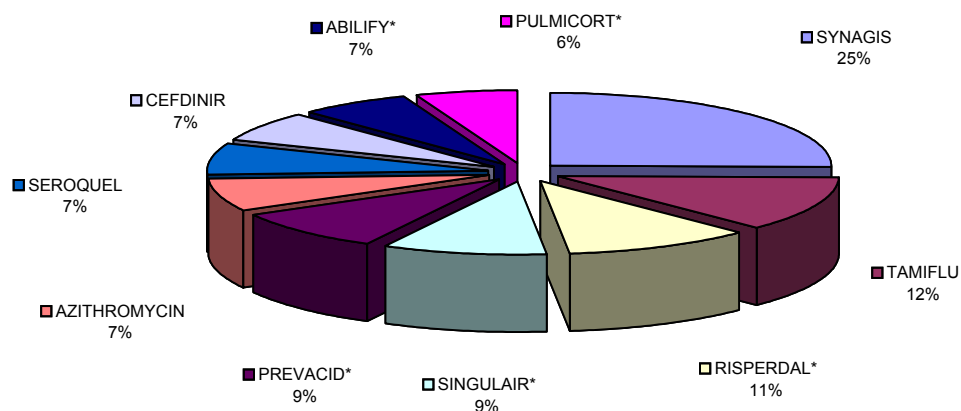
TOP 25 DRUGS BASED ON TOTAL CLAIMS COST FROM 02/01/08-02/29/08

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
SYNAGIS	MONOCLONAL ANTIBODIES	1,483	\$ 2,132,377.55	-----
TAMIFLU	NEURAMINIDASE INHIBITORS	14,155	\$ 1,051,456.22	-----
RISPERDAL*	ANTIPSYCHOTIC AGENTS	3,175	\$ 920,281.78	18
SINGULAIR*	LEUKOTRIENE MODIFIERS	7,409	\$ 797,503.46	5
PREVACID*	PROTON-PUMP INHIBITORS	5,015	\$ 782,241.74	3
AZITHROMYCIN	MACROLIDES	16,695	\$ 600,974.35	3
SEROQUEL	ANTIPSYCHOTIC AGENTS	1,632	\$ 580,388.63	11
CEFDINIR	CEPHALOSPORINS	7,683	\$ 569,676.50	-----
ABILIFY*	ANTIPSYCHOTIC AGENTS	1,173	\$ 552,485.33	24
PULMICORT*	ADRENALS	1,890	\$ 490,013.59	73
ZYPREXA	ANTIPSYCHOTIC AGENTS	861	\$ 456,428.19	19
XOPENEX*	BETA-ADRENERGIC AGONISTS	2,538	\$ 441,442.51	107
ADDERALL XR*	AMPHETAMINES	3,136	\$ 423,885.67	33
AMOX TR-POTASSIUM CL	PENICILLINS	7,037	\$ 384,786.83	6
TOPAMAX*	ANTICONVULSANTS, MISCELLANEOUS	1,221	\$ 353,020.76	20
CONCERTA*	ANOREX., RESPIR., CEREBRAL STIMULANTS, MISC	2,669	\$ 351,120.33	41
GEODON*	ANTIPSYCHOTIC AGENTS	826	\$ 286,419.51	72
FEIBA VH IMMUNO	HEMOSTATICS	3	\$ 285,130.89	-----
ADVAIR DISKUS*	BETA-ADRENERGIC AGONISTS	1,508	\$ 281,963.38	4
LAMICTAL*	ANTICONVULSANTS, MISCELLANEOUS	808	\$ 250,975.75	26
ZYRTEC*	SECOND GENERATION ANTIHISTAMINES	4,301	\$ 244,083.98	29
NOVOSEVEN	HEMOSTATICS	3	\$ 243,712.29	-----
KEPPRA*	ANTICONVULSANTS, MISCELLANEOUS	843	\$ 211,167.69	81
GABAPENTIN	ANTICONVULSANTS, MISCELLANEOUS	1,852	\$ 209,391.21	5
ADVATE	HEMOSTATICS	6	\$ 194,641.45	-----
TOTAL TOP 25		87,922	\$ 13,095,569.59	

Total Rx Claims	424,560
From 02/01/08-02/29/08	

\* Indicates preferred products on the Preferred Drug List

Top 10 Drugs  
Based on Total Claims Cost



## 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 or 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 use of the drug, shall be expressed as provided under the "Adverse Reactions" section of the labeling.

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### **CellCept (mycophenolate mofetil)**

### **Myfortic (mycophenolate acid)**

4/10/2008: FDA informed healthcare professionals that the Agency is investigating a potential association between the use of CellCept and Myfortic, medicines used to prevent organ rejection, and the development of progressive multifocal leukoencephalopathy (PML), a life-threatening disease. PML is a rare disorder that affects the central nervous system usually occurring in patients with immune systems suppressed by disease or medicines. FDA is reviewing data submitted by Roche, including postmarketing reports it has received of PML in patients who took CellCept or Myfortic, and the proposed revisions to the CellCept prescribing information. FDA has asked Novartis, the maker of Myfortic, for data on PML cases and to revise the Myfortic prescribing information to include the same information about PML included in the CellCept prescribing information. FDA anticipates it may take about 2 months to complete its review of the postmarketing reports and the proposed revisions to the

prescribing information. As soon as the review is completed, FDA will communicate the conclusions and recommendations to the public.

Until further information is available, patients and healthcare professionals should be aware of the possibility of PML, such as localized neurologic signs and symptoms in the setting of a suppressed immune system, including during therapy with CellCept and Myfortic.

**Neupro (rotigotine transdermal system)**

4/09/2008: Schwarz Pharma informed healthcare professionals and patients of the recall of Neupro, a transdermal delivery system worn on the skin and used to treat early stage Parkinson's disease, at the end of April 2008, because of the formation of rotigotine crystals in the patches. When the drug crystallizes, less drug is available to be absorbed through the skin and the efficacy of the product may vary. Healthcare professionals should not initiate any new patients on Neupro and should begin to down-titrate all patients currently using the product per the guidelines in the product labeling. Patients should NOT abruptly discontinue therapy. Abrupt withdrawal of dopamine agonists has been associated with a syndrome resembling neuroleptic malignant syndrome or akinetic crises.

**Exubera (insulin human rDNA origin) Inhalation Powder**

4/09/2008: Pfizer informed healthcare professionals and patients of updated safety information in the WARNINGS section of prescribing information for Exubera, a short-acting insulin you breathe in through your mouth using the Exubera inhaler that helps to control high blood sugar in adults with diabetes. There have been 6 newly diagnosed cases of primary lung malignancies in clinical trials among Exubera-treated patients, and 1 newly diagnosed case among comparator treated patients. There has also been 1 post-marketing report of a primary lung malignancy in an Exubera-treated patient. There were too few cases to determine whether the emergence of these events is related to Exubera. All patients who were diagnosed with lung cancer had a prior history of cigarette smoking. Because of limited availability of Exubera, healthcare professionals should seek alternative treatment options to maintain patients' glycemic control.

**Relenza (zanamivir)**

4/01/2008: GlaxoSmithKline informed healthcare professionals of changes to the WARNINGS AND PRECAUTIONS sections of prescribing information for Relenza regarding information from postmarketing reports (mostly from Japan) of delirium and abnormal behavior leading to injury in patients with influenza who are receiving neuraminidase inhibitors, including Relenza. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution. The contribution of Relenza to these events has not been established. Influenza can be associated with a variety of neurologic and behavioral symptoms which can include seizures, hallucinations, delirium, and abnormal behavior, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease.

Patients with influenza should be closely monitored for signs of abnormal behavior. If

neuropsychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient.

**Ziagen (abacavir)**

**Videx (didanosine)**

3/27/2008: The FDA issued an Early Communication about recent findings of The Data Collection on Adverse Events of Anti-HIV Drugs Study. Data analyses from this study indicate a higher risk of heart attack in patients infected with HIV-1 who were taking Ziagen (abacavir) or Videx (didanosine) as part of their drug therapy. The study is a large observational study of 33,347 HIV-1 infected patients living in North America, Europe and Australia. Patients in this study are being followed to evaluate the short and long term adverse effects of treatment with anti-HIV drugs. FDA continues to evaluate the overall risks and benefits of abacavir and didanosine. This evaluation may result in the need to revise labeling for the products. Until the FDA's review is complete, health care professionals should evaluate the potential risks and benefits of each HIV-1 antiretroviral drug their patients are taking.

**Regranex (becaplermin) Gel**

3/27/2008: The FDA is conducting a safety review based on study data suggesting there may be an increased risk of death from cancer in diabetic patients using Regranex (becaplermin) Gel, a skin product used to heal leg and foot ulcers. While the review is ongoing, the FDA recommends health care professionals discuss the potential risks and benefits of using Regranex with their patients.

**Singulair (montelukast)**

3/27/2008: FDA informed healthcare professionals and patients of the Agency's investigation of the possible association between the use of Singulair and behavior/mood changes, suicidality (suicidal thinking and behavior) and suicide. Singulair is a leukotriene receptor antagonist used to treat asthma and the symptoms of allergic rhinitis, and to prevent exercise-induced asthma. Patients should not stop taking Singulair before talking to their doctor if they have questions about the new information. Healthcare professionals and caregivers should monitor patients taking Singulair for suicidality (suicidal thinking and behavior) and changes in behavior and mood.

**Tiotropium (marketed as Spiriva HandiHaler)**

3/18/2008: Boehringer Ingelheim and FDA notified healthcare professionals that ongoing safety monitoring has identified a possible increased risk of stroke in patients who take Spiriva. This product contains tiotropium bromide and is used to treat bronchospasm associated with chronic obstructive pulmonary disease. Boehringer Ingelheim reported to the FDA that it has conducted an analysis of the safety data from 29 placebo controlled clinical studies ("pooled analysis"). Based on data from these studies, the preliminary estimates of the risk of stroke are 8 patients per 1000 patients treated for one year with Spiriva, and 6 patients per 1000 patients treated for one year with placebo. This means that the estimated excess risk of any type of stroke due to Spiriva is 2 patients for each 1000 patients using Spiriva over a one year period.

It is important to interpret these preliminary results with caution. FDA is working with Boehringer Ingelheim to further evaluate the potential association between Spiriva and stroke. FDA has not confirmed these analyses and while pooled analyses can provide early information about potential safety issues, these analyses have inherent limitations and uncertainty that require further investigation using other data sources. Patients should not stop taking Spiriva HandiHaler before talking to their doctor, if they have questions about this new information. This early communication is in keeping with FDA's commitment to inform the public about its ongoing safety reviews of drugs.

**Erythropoiesis Stimulating Agents: Aranesp (darbepoetin alfa), Epogen (epoetin alfa), and Procrit (epoetin alfa)**

3/12/2008: Amgen and FDA notified healthcare professionals of changes to the Boxed Warnings/WARNINGS: Increased Mortality and/or Tumor Progression section of the Aranesp and EPOGEN/PROCRT labeling to update information describing the results of two additional studies showing increased mortality and more rapid tumor progression in patients with cancer receiving ESAs. Based on the results of these studies, the prescribing information has been revised as follows: ESAs shortened overall survival and/or time to tumor progression in clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers when dosed to target a hemoglobin of  $\geq 12$  g/dL.

**Prezista (darunavir)**

3/21/2008: FDA issued a new "Information for Healthcare Professionals" sheet highlighting the addition of hepatotoxicity information to the WARNINGS section of prescribing information for Prezista.

3/12/2008: FDA and Tibotec Therapeutics notified healthcare professionals of changes to the WARNINGS section of the prescribing information for Prezista (darunavir) tablets regarding the risk of hepatotoxicity. In clinical trials and postmarketing experience, drug induced hepatitis has been reported in patients receiving combination therapy with Prezista/ritonavir. Appropriate laboratory testing should be conducted prior to initiating therapy with Prezista/ritonavir and patients should be monitored during treatment. Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pretreatment elevations of transaminases, especially during the first several months of Prezista/ritonavir treatment.

**Long-Acting Hydrocodone-Containing Cough Product (marketed as Tussionex Pennkinetic Extended-Release Suspension)**

3/11/2008: FDA informed healthcare professionals of life-threatening adverse events and death in patients, including children, who have received Tussionex Pennkinetic Extended-Release Suspension (Tussionex). The reports indicate that healthcare professionals have prescribed Tussionex for patients younger than the approved age group of 6 years old and older, and more frequently than the labeled dosing interval of every 12 hours. Tussionex is contraindicated for use in patients less than 6 years of age because of their susceptibility to life-threatening and fatal respiratory depression.

Patients have administered the incorrect dose due to misinterpretation of the dosing directions, and have used inappropriate devices to measure the suspension. Overdose of Tussionex in older children, adolescents, and adults has also been associated with life-threatening and fatal respiratory depression. Prescribers should be familiar with the dosing recommendations of Tussionex before prescribing. In addition, patients and caregivers should use a properly marked measuring device to measure Tussionex to prevent overdose.

**Tamiflu (oseltamivir phosphate)**

3/04/2008, updated 3/04/2008: Roche and FDA informed healthcare professionals of neuropsychiatric events associated with the use of Tamiflu, in patients with influenza. The label has been revised as follows: Influenza can be associated with a variety of neurologic and behavioral symptoms which can include events such as hallucinations, delirium, and abnormal behavior, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease. There have been postmarketing reports (mostly from Japan) of delirium and abnormal behavior leading to injury, and in some cases resulting in fatal outcomes, in patients with influenza who were receiving Tamiflu. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made but they appear to be uncommon based on Tamiflu usage data. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution. The contribution of Tamiflu to these events has not been established. Patients with influenza should be closely monitored for signs of abnormal behavior. If neuropsychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient.

**Spiriva (tiotropium bromide inhalation powder) Capsules**

**Foradil (formoterol fumarate inhalation powder) Capsules**

2/29/2008: FDA informed healthcare professionals and consumers of the correct way to use Spiriva and Foradil inhalation powder capsules. FDA and the American Association of Poison Control Center's (AAPCC) National Poison Data System have received many reports of patients swallowing Spiriva and Foradil capsules rather than placing the capsules in the inhalation devices. Both products are to be used in the HandiHaler (Spiriva) and Aerolizer (Foradil) devices to deliver the medicine to the lungs to improve breathing in patients with asthma, and in individuals affected by chronic obstructive lung disease and bronchitis. Both products will not treat a patient's breathing condition if the contents of a capsule are swallowed rather than inhaled. Healthcare professionals should discuss with patients how to correctly use the Spiriva HandiHaler or Foradil Aerolizer. See the Public Health Advisory for important information on the correct use of both products.

**Tysabri (natalizumab)**

2/27/2008: Biogen Idec, Elan and FDA notified healthcare professionals of reports of clinically significant liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, occurred as early as six days after the first dose of Tysabri. The combination of transaminase elevations and elevated bilirubin without evidence of



obstruction is recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients. Tysabri should be discontinued in patients with jaundice or other evidence of significant liver injury. Physicians should inform patients that Tysabri may cause liver injury.

**Avandia (rosiglitazone maleate)**

2/26/2008: FDA and GlaxoSmithKline notified pharmacists and physicians of a new Medication Guide for Avandia (rosiglitazone maleate). The FDA regulation 21CFR 208 requires a Medication Guide to be provided with each prescription that is dispensed for products that FDA determines pose a serious and significant public health concern. A list of currently approved Medication Guides are available at [http://www.fda.gov/cder/Offices/ODS/medication\\_guides.htm](http://www.fda.gov/cder/Offices/ODS/medication_guides.htm). The Medication Guide and current Prescribing Information for Avandia are provided below.

**Fentanyl transdermal system CII Patches**

3/03/2008: Actavis Inc. has voluntarily recalled of all lots of Fentanyl Transdermal System CII patches sold in the United States.

2/19/2008: Actavis Inc. announced a nationwide recall of certain lots of Fentanyl transdermal system CII Patches sold in the United States and labelled with an Abrika or Actavis label. The product may have a fold-over defect which can cause the patch to leak and expose patients or caregivers directly to the fentanyl gel. Exposure to fentanyl gel may lead to serious adverse events, including respiratory depression and possible overdose, which may be fatal. The lots covered by this recall include doses of 25, 50, 75, and 100 mcg/hr and are listed in the firm's press release.

**Duragesic 25 mcg/hr (fentanyl transdermal system) CII Pain Patches**

2/15/2008: PriCara and Sandoz Inc. announced a nationwide recall of all lots of 25 mcg/hr Duragesic Patches sold in the United States. The product is being recalled because the patches may have a cut along one side of the drug reservoir within the patch which may result in the possible release of fentanyl gel that may expose patients or caregivers directly to fentanyl gel on the skin. Fentanyl is a potent Schedule II opioid medication and exposure to the gel may lead to serious adverse events, including respiratory depression and possible overdose, that may be fatal. Patches with a cut edge should not be used. These recalled patches have expiration dates on or before December 2009 and are all manufactured by ALZA Corporation.

**Heparin Sodium Injection (Baxter)**

2/28/2008: Baxter Healthcare Corporation has voluntarily recalled all of their multi-dose and single-use vials of heparin sodium for injection, and their heparin lock flush solutions.

2/11/2008: FDA informed healthcare professionals of important warnings and instructions for Heparin Sodium Injection use. There have been reports of serious adverse events including allergic or hypersensitivity-type reactions, with symptoms of oral swelling, nausea, vomiting, sweating, shortness of breath, and cases of severe hypotension. Most events developed within minutes of heparin initiation although the

possibility for a delayed response has not been excluded. The reports have largely involved use of multiple-dose vials. However, there have been several cases in which product from multiple, single-dose vials have been combined to administer a bolus dose. Heparin sodium is an anticoagulant (blood thinner) that is used in patients undergoing kidney dialysis, certain types of cardiac surgery, and treatment or prevention of other serious medical conditions, including deep venous thrombosis and pulmonary emboli. Heparin treatment is initiated using high doses (5000-50,000 units) given directly into the blood stream (intravenously) as a bolus. Serious adverse events have recently been reported in patients who received these higher bolus doses.

The manufacture of multiple-dose vials of heparin sodium has been suspended pending the completion of an extensive ongoing investigation to determine the root cause of the problem. Because heparin sodium is a medically necessary product and serious public health consequences would result if there were a sudden shortage of the drug, the multiple-dose vials of heparin sodium manufactured by Baxter that are currently in distribution will not be recalled. See the FDA Public Health Advisory for Agency recommendations to healthcare professionals on the use of heparin sodium for injection.

**Botox, Botox Cosmetic (Botulinum toxin Type A), Myobloc (Botulinum toxin Type B)**

2/07/2008: FDA issued an early communication about an ongoing safety review regarding Botox and Botox Cosmetic. FDA has received reports of systemic adverse reactions including respiratory compromise and death following the use of botulinum toxins types A and B for both FDA-approved and unapproved uses. The reactions reported are suggestive of botulism, which occurs when botulinum toxin spreads in the body beyond the site where it was injected. The most serious cases had outcomes that included hospitalization and death, and occurred mostly in children treated for cerebral palsy-associated limb spasticity. Use of botulinum toxins for treatment of limb spasticity (severe arm and leg muscle spasms) in children or adults is not an approved use in the U.S. See the FDA's "Early Communication about an Ongoing Safety Review" for Agency recommendations and additional information for healthcare professionals.

**Injectable Colchicine (including drugs containing colchicine)**

2/06/2008: FDA announced its intention to take enforcement action against companies marketing unapproved, injectable colchicine, a drug used to treat gout. Colchicine is a highly toxic drug that can easily be administered in excessive doses, especially when given intravenously. There is a narrow margin between an effective dose of the drug and a toxic dose that can result in serious health risks, including death. The FDA is aware of 50 reports of adverse events associated with the use of intravenous colchicine, including 23 deaths. Potentially fatal effects include low blood cell counts, cardiac events, and organ failure. This action does not affect colchicine products that are dispensed in tablet form.

Individuals and companies must stop making these products within 30 days and stop shipping the product within 180 days or face regulatory action. After these dates, all injectable colchicine drug products must have FDA approval to be manufactured or

shipped interstate.

**Varenicline (marketed as Chantix)**

2/01/2008: FDA informed healthcare professionals and consumers of important revisions to the WARNINGS and PRECAUTIONS sections of the prescribing information for Chantix regarding serious neuropsychiatric symptoms experienced in patients taking Chantix. These symptoms include changes in behavior, agitation, depressed mood, suicidal ideation, and attempted and completed suicide. While some patients may have experienced these types of symptoms and events as a result of nicotine withdrawal, some patients taking Chantix who experienced serious neuropsychiatric symptoms and events had not yet discontinued smoking. In most cases, neuropsychiatric symptoms developed during Chantix treatment, but in others, symptoms developed following withdrawal of Chantix therapy. See the FDA Information for Healthcare Professionals Sheet for recommendations and considerations for healthcare professionals on using Chantix therapy for patients.

**Antiepileptic Drugs**

1/31/2008: FDA informed healthcare professionals that the Agency has analyzed reports of suicidality (suicidal behavior or ideation) from placebo-controlled clinical studies of eleven drugs used to treat epilepsy as well as psychiatric disorders, and other conditions. In the FDA's analysis, patients receiving antiepileptic drugs had approximately twice the risk of suicidal behavior or ideation (0.43%) compared to patients receiving placebo (0.22%). The increased risk of suicidal behavior and suicidal ideation was observed as early as one week after starting the antiepileptic drug and continued through 24 weeks. The results were generally consistent among the eleven drugs. The relative risk for suicidality was higher in patients with epilepsy compared to patients who were given one of the drugs in the class for psychiatric or other conditions.

Healthcare professionals should closely monitor all patients currently taking or starting any antiepileptic drug for notable changes in behavior that could indicate the emergence or worsening of suicidal thoughts or behavior or depression.

The drugs included in the analyses include (some of these drugs are also available in generic form):

Carbamazepine (marketed as Carbatrol, Equetro, Tegretol, Tegretol XR)  
Felbamate (marketed as Felbatol)  
Gabapentin (marketed as Neurontin)  
Lamotrigine (marketed as Lamictal)  
Levetiracetam (marketed as Keppra)  
Oxcarbazepine (marketed as Trileptal)  
Pregabalin (marketed as Lyrica)  
Tiagabine (marketed as Gabitril)  
Topiramate (marketed as Topamax)  
Valproate (marketed as Depakote, Depakote ER, Depakene, Depacon)  
Zonisamide (marketed as Zonegran)

Although the 11 drugs listed above were the ones included in the analysis, FDA expects that the increased risk of suicidality is shared by all antiepileptic drugs and anticipates that the class labeling changes will be applied broadly.

#### **NuCel Labs Eye Drops and Eye/Ear Wash Products**

1/31/2008: NuCel Labs and FDA informed consumers and healthcare professionals of a voluntary nationwide recall of all Eye Drops and Eye/Ear Wash Products. The products were recalled after testing indicated the presence of bacteria and particulate matter, deeming these products non-sterile. Non-sterile eye drops pose an unacceptable risk of causing eye infections, which in rare cases could lead to blindness. No illnesses or injuries have been reported to date. There are no lot numbers or expiration dates on the products. Consumers who have the product should discontinue use of the product and return it to NuCel Labs. See the manufacturer's press release for return shipping information.

#### **Ezetimibe/Simvastatin (marketed as Vytorin), Ezetimibe (marketed as Zetia), and Simvastatin (marketed as Zocor): Early Communication about an Ongoing Data Review**

1/25/2008: FDA provided healthcare professionals with an early communication about an ongoing data review for Ezetimibe/Simvastatin (marketed as Vytorin), Ezetimibe (marketed as Zetia), and Simvastatin (marketed as Zocor). This early communication is in keeping with FDA's commitment to inform the public about ongoing postmarketing drug issues.

Merck/Schering Plough Pharmaceuticals reported preliminary results from the Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia (ENHANCE) trial. This trial was designed to evaluate the amount of atherosclerotic plaque in blood vessels located in the neck based on images obtained through ultrasound in patients treated with Vytorin (ezetimibe plus simvastatin) or simvastatin alone. Merck/Schering Plough stated that there was no significant difference between Vytorin and simvastatin in the amount of atherosclerotic plaque in the inner walls of the carotid (neck) arteries despite greater lowering of LDL-cholesterol (bad cholesterol) with Vytorin compared to simvastatin. Once Merck/Schering Plough completes the analysis of the unblinded data from ENHANCE, it will submit a final study report to FDA. Once FDA receives the final study report, FDA estimates it will take approximately 6 months to fully evaluate the data. After reviewing the data from the ENHANCE study, and considering all other available information about the link between LDL lowering and reduction of cardiovascular events, FDA will determine whether any further regulatory action is warranted with regard to Zetia and Vytorin and also whether any changes to FDA's current approach to drugs that lower LDL cholesterol are warranted.

Patients should talk to their doctors if they have any questions about the information from the ENHANCE trial.

#### **Leukine (sargramostim)**

1/24/2008 Bayer and FDA informed healthcare professionals of the market withdrawal of the current liquid formulation of Leukine, a growth factor that helps fight infection and disease in appropriate patients by enhancing immune cell function. The product was withdrawn because of an upward trend in spontaneous reports of adverse reactions, including syncope (fainting), which are temporally correlated with a change in the formulation of liquid Leukine to include edetate disodium (EDTA). The upward trend in adverse reaction reporting rates has not been observed with the use of lyophilized Leukine. Healthcare professionals should immediately stop using liquid Leukine and return unused vials to the manufacturer.

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### **Ortho Evra Contraceptive Transdermal Patch**

1/19/2008: FDA modified the prescribing information for the Ortho Evra Contraceptive Transdermal (Skin) Patch to include the results of a new epidemiology study that found that users of the birth control patch were at higher risk of developing serious blood clots, also known as venous thromboembolism (VTE), than women using birth control pills. VTE can lead to pulmonary embolism. The label changes are based on a study conducted by the Boston Collaborative Drug Surveillance Program on behalf of Johnson and Johnson. The patch was studied in women aged 15-44. These findings support an earlier study that also said women in this group were at higher risk for VTE.

FDA believes that Ortho Evra is a safe and effective method of contraception when used according to the labeling, which recommends that women with concerns or risk factors for serious blood clots talk with their health care provider about using Ortho Evra versus other contraceptive options.

### **Cough and Cold Medications in Children Less Than Two Years of Age**

1/17/2008: FDA informed consumers and healthcare professionals that the Agency has completed its review of information regarding the safety of over-the-counter (OTC) cough and cold medicines in children under 2 years of age and recommends that these drugs not be used to treat children in this age group because serious and potentially life-threatening side effects can occur. FDA's recommendation is based on both the review of the information the Agency received about serious side effects in children in the referenced age group and the discussion and recommendations made at the October 18 - 19, 2007, public advisory committee meeting at which this issue was discussed. FDA has not completed its review of information about the safety of OTC cough and cold medicines in children 2 through 11 years of age. See the FDA Public Health Advisory for Agency recommendations regarding this issue.

### **Edetate Disodium (marketed as Endrate and generic products)**

1/16/2008: FDA notified healthcare professionals and patients about important safety information concerning Edetate Disodium. There have been cases where children and adults have died when they were mistakenly given Edetate Disodium instead of Edetate Calcium Disodium (Calcium Disodium Versenate) or when Edetate Disodium was used for "chelation therapies" and other uses that are not approved by the FDA. Edetate Disodium was approved as an emergency treatment for certain patients with

hypercalcemia (very high levels of calcium in the blood) or certain patients with heart rhythm problems as a result of very high amounts of digitalis in the blood. Edetate Calcium Disodium was approved to reduce dangerously high blood lead levels (severe lead poisoning).

The two drugs have very similar names and are commonly referred to only as EDTA. As a result, the two products are easily mistaken for each other when prescribing, dispensing, and administering them. Edetate Disodium and Edetate Calcium Disodium works by binding with heavy metals or minerals in the body allowing them to be passed out of the body through the urine. Read the FDA Public Health Advisory for recommended and important safety considerations for healthcare professionals until the FDA's ongoing evaluation of the risks and benefits of Edetate Disodium is complete.

### **Compounded Menopause Hormone Therapy Drugs**

1/10/2008: FDA informed healthcare professionals and patients that the Agency sent letters warning seven pharmacy operations that the claims they make about the safety and effectiveness of their so-called "bio-identical hormone replacement therapy," or "BHRT" products are unsupported by medical evidence, and are considered false and misleading by the agency. The pharmacy operations improperly claim that their drugs, which contain hormones such as estrogen, progesterone, and estriol (which is not a component of an FDA-approved drug and has not been proven safe and effective for any use) are superior to FDA-approved menopausal hormone therapy drugs and prevent or treat serious diseases, including Alzheimer's disease, stroke, and various forms of cancer. FDA is concerned that the claims for safety, effectiveness, and superiority that these pharmacy operations are making mislead patients, as well as doctors and other healthcare professionals. Compounded drugs are not reviewed by the FDA for safety and effectiveness.

Patients who use compounded hormone therapy drugs should discuss menopausal hormone therapy options with their healthcare provider to determine if compounded drugs are the best option for their specific medical needs.

### **Bisphosphonates (marketed as Actonel, Actonel+Ca, Aredia, Boniva, Didronel, Fosamax, Fosamax+D, Reclast, Skelid, and Zometa)**

1/07/2008: FDA informed healthcare professionals and patients of the possibility of severe and sometimes incapacitating bone, joint, and/or muscle (musculoskeletal) pain in patients taking bisphosphonates. Although severe musculoskeletal pain is included in the prescribing information for all bisphosphonates, the association between bisphosphonates and severe musculoskeletal pain may be overlooked by healthcare professionals, delaying diagnosis, prolonging pain and/or impairment, and necessitating the use of analgesics. The severe musculoskeletal pain may occur within days, months, or years after starting a bisphosphonates. Some patients have reported complete relief of symptoms after discontinuing the bisphosphonate, whereas others have reported slow or incomplete resolution. The risk factors for and incidence of severe musculoskeletal pain associated with bisphosphonates are unknown.

**Fentanyl Transdermal System (marketed as Duragesic and generics)**

12/21/2007: FDA issued an update that highlights important information on appropriate prescribing, dose selection, and the safe use of the fentanyl transdermal system (patch). FDA previously issued a Public Health Advisory and Information for Healthcare Professionals in July 2005 regarding the appropriate and safe use of the transdermal system. However, the Agency continues to receive reports of death and life-threatening adverse events related to fentanyl overdose that have occurred when the fentanyl patch was used to treat pain in opioid-naïve patients and when opioid-tolerant patients have applied more patches than prescribed, changed the patch too frequently, and exposed the patch to a heat source. The fentanyl patch is only indicated for use in patients with persistent, moderate to severe chronic pain who have been taking a regular, daily, around-the-clock narcotic pain medicine for longer than a week and are considered to be opioid-tolerant.

Patients must avoid exposing the patch to excessive heat as this promotes the release of fentanyl from the patch and increases the absorption of fentanyl through the skin which can result in fatal overdose. Directions for prescribing and using the fentanyl patch must be followed exactly to prevent death or other serious side effects from fentanyl overdose.

**Carbamazepine (marketed as Carbatrol, Equetro, Tegretol and generics)**

12/12/2007: FDA informed healthcare professionals that dangerous or even fatal skin reactions (Stevens Johnson syndrome and toxic epidermal necrolysis), that can be caused by carbamazepine therapy, are significantly more common in patients with a particular human leukocyte antigen (HLA) allele, HLA-B\*1502. This allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians. Patients with ancestry from areas in which HLA-B\*1502 is present should be screened for the HLA-B\*1502 allele before starting treatment with carbamazepine. If these individuals test positive, carbamazepine should not be started unless the expected benefit clearly outweighs the increased risk of serious skin reactions. Patients who have been taking carbamazepine for more than a few months without developing skin reactions are at low risk of these events ever developing from carbamazepine. This is true for patients of any ethnicity or genotype, including patients positive for HLA-B\*1502.

**Desmopressin Acetate (marketed as DDAVP Nasal Spray, DDAVP Rhinal Tube, DDAVP, DDVP, Minirin, and Stimat Nasal Spray)**

12/04/2007: FDA notified healthcare professionals and patients of the Agency's request that manufacturers update the prescribing information for desmopressin to include important new safety information about severe hyponatremia and seizures. Certain patients, including children treated with the intranasal formulation of the drug for primary nocturnal enuresis (PNE), are at risk for developing severe hyponatremia that can result in seizures and death. As such, desmopressin intranasal formulations are no longer indicated for the treatment of primary nocturnal enuresis and should not be used in hyponatremic patients or patients with a history of hyponatremia. PNE treatment with desmopressin tablets should be interrupted during acute illnesses that may lead to fluid and/or electrolyte imbalance. All desmopressin formulations should be used cautiously in patients at risk for water intoxication with hyponatremia.

**Chantix (Varenicline)**

11/20/2007: FDA informed healthcare professionals of reports of suicidal thoughts and aggressive and erratic behavior in patient who have taken Chantix, a smoking cessation product. There are also reports of patients experiencing drowsiness that affected their ability to drive or operate machinery. FDA is currently reviewing these cases, along with other recent reports. A preliminary assessment reveals that many of the cases reflect new-onset of depressed mood, suicidal ideation, and changes in emotion and behavior within days to weeks of initiating Chantix treatment. The role of Chantix in these cases is not clear because smoking cessation, with or without treatment, is associated with nicotine withdrawal symptoms and has also been associated with the exacerbation of underlying psychiatric illness. However, not all patients described in the cases had preexisting psychiatric illness and not all had discontinued smoking.

Healthcare professionals should monitor patients taking Chantix for behavior and mood changes. Patients taking this product should report behavior or mood changes to their doctor and use caution when driving or operating machinery until they know how quitting smoking with Chantix may affect them.

**Erythropoiesis Stimulating Agents: Aranesp (darbepoetin alfa), Epogen (epoetin alfa), and Procrit (epoetin alfa)**

Updated 1/03/2008: FDA informed healthcare professionals of findings from two additional clinical studies, Preoperative Epirubicin Paclitaxel Aranesp Study (PREPARE), and the National Cancer Institute Gynecologic Oncology Group (COG-19), showing an increase in mortality and shorter time to tumor progression in patients with cancer receiving an Erythropoiesis-Stimulating Agent (ESA). Both the PREPARE study in breast cancer and the COG-19 study in cervical cancer showed higher rates of death and or tumor progression in patients who received an ESA compared to patients who did not receive an ESA. FDA strongly recommends that healthcare professionals discuss the risks of ESA-associated tumor progression and shortened survival in patients with cancer before starting or continuing ESA therapy.

Posted 11/08/2007: FDA notified healthcare professionals of revised boxed warnings and other safety-related product labeling changes for erythropoiesis-stimulating agents (ESAs), which treat certain types of anemia. These new statements address the risks that the drugs Aranesp, Epogen, and Procrit pose to patients with cancer and patients with chronic kidney failure. For patients with cancer, the new boxed warnings emphasize that ESAs caused tumor growth and shortened survival in patients with advanced breast, head and neck, lymphoid and non-small cell lung cancer when they received a dose that attempted to achieve a hemoglobin level of 12 grams per deciliter (g/dL) or greater. For patients with chronic kidney failure, the new boxed warning states that ESAs should be used to maintain a hemoglobin level between 10 g/dL to 12 g/dL. Maintaining higher hemoglobin levels in patients with chronic kidney failure increases the risk of death and other serious conditions. The new labeling provides specific instructions for dosage adjustments and hemoglobin monitoring for chronic kidney failure patients who do not respond to ESA treatment with an adequate increase in their hemoglobin levels.



Additionally, the new boxed warnings clarify that ESAs should only be used in patients with cancer when treating anemia specifically caused by chemotherapy and not for other causes of anemia. Further, it states that ESAs should be discontinued once the patient's chemotherapy course has been completed.

**CellCept (mycophenolate mofetil)**

Updated 11/27/2007: Prescribing information for Mycophenolic Acid (marketed as Myfortic Delayed Released Tablets) revised to include information that use of drug during pregnancy is associated with increased risks of pregnancy loss and congenital malformations. See the MedWatch alert for Myfortic (mycophenolic acid).

[Posted 10/29/2007] Roche and FDA notified healthcare providers that use of CellCept (mycophenolate mofetil) is associated with increased risk of first trimester pregnancy loss and increased risk of congenital malformations, especially external ear and facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney. Based on postmarketing data from the United States National Transplantation Pregnancy Registry and additional postmarketing data collected in women exposed to systemic mycophenolate mofetil during pregnancy, the pregnancy category for CellCept has been changed from Category C (risk of fetal harm cannot be ruled out) to Category D (positive evidence of fetal risk). Labeling changes include the following sections: BOXED WARNING, WARNINGS/Pregnancy and Pregnancy Exposure Prevention, PRECAUTIONS/Information for Patients, and ADVERSE REACTIONS/Postmarketing Experience.

Within one week of beginning CellCept therapy, women of childbearing potential should have a negative serum or urine pregnancy test. In addition, women of childbearing potential (including pubertal girls and peri-menopausal woman) taking CellCept must receive contraceptive counseling and use effective contraception. Healthcare professionals and patients should be aware that CellCept reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness. See the Dear Healthcare Professional Letter for additional recommendations for women of childbearing potential.

**Provigil (modafinil) Tablets**

10/24/2007: FDA and Cephalon notified healthcare professionals of updates to the WARNINGS section of the prescribing information for Provigil (modafinil). Provigil is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder. The revised labeling updates safety information to include warnings regarding serious rash, including Stevens-Johnson Syndrome (SJS) and hypersensitivity reactions, and psychiatric symptoms. Rare cases of serious or life-threatening rash, including Toxic Epidermal Necrolysis, and Drug Rash with Eosinophilia and Systemic Symptoms have been reported in adults and children in worldwide postmarketing experience. Angioedema and multi-organ hypersensitivity reactions have also been reported in postmarketing experience.

Physicians should instruct their patients to immediately discontinue the use of Provigil and contact them if a rash or other hypersensitivity reaction occurs. Healthcare professionals and consumers should also be aware that Provigil is not approved for use in pediatric patients for any indication. In addition, psychiatric adverse experiences (including anxiety, mania, hallucinations, and suicidal ideation) have been reported in patients treated with Provigil. Caution should be exercised when Provigil is given to patients with a history of psychosis, depression, or mania.

Additional labeling revisions were made to the CLINICAL PHARMACOLOGY, PRECAUTIONS, and PATIENT PACKAGE INSERT sections. See revised labeling below.

**Viagra (sildenafil), Cialis (tadalafil), Levitra (vardenafil), Revatio (sildenafil)**

10/18/2007: FDA informed healthcare professionals of reports of sudden decreases or loss of hearing following the use of PDE5 inhibitors Viagra, Levitra, Cialis for the treatment of erectile dysfunction, and Revatio for the treatment of pulmonary arterial hypertension. In some cases, the sudden hearing loss was accompanied by tinnitus and dizziness. Medical follow-up on these reports was often limited which makes it difficult to determine if the loss of hearing was related to the use of one of the drugs, an underlying medical condition or other risk factors for hearing loss, a combination of these factors or other factors. The PRECAUTIONS and ADVERSE REACTIONS sections of the approved product labeling for Viagra, Levitra, and Cialis were revised. FDA is working with the manufacturer to revise the labeling for Revatio.

**Byetta (exenatide)**

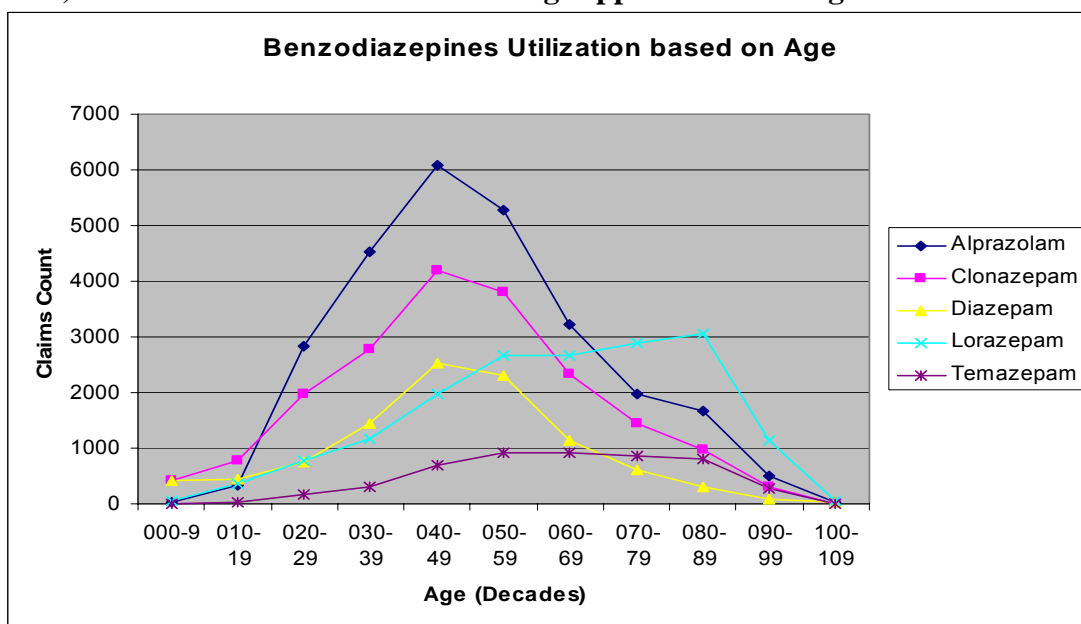
10/16/2007: FDA has reviewed 30 postmarketing reports of acute pancreatitis in patients taking Byetta (exenatide), a drug used to treat adults with type 2 diabetes. An association between Byetta and acute pancreatitis is suspected in some of these cases. Amylin Pharmaceuticals, Inc. has agreed to include information about acute pancreatitis in the PRECAUTIONS section of the product label.

Healthcare professionals should be alert to the signs and symptoms of acute pancreatitis and instruct patients taking Byetta to seek prompt medical care if they experience unexplained, persistent, severe abdominal pain which may or may not be accompanied by vomiting. If pancreatitis is suspected, Byetta should be discontinued. If pancreatitis is confirmed, Byetta should not be restarted unless an alternative etiology is identified.

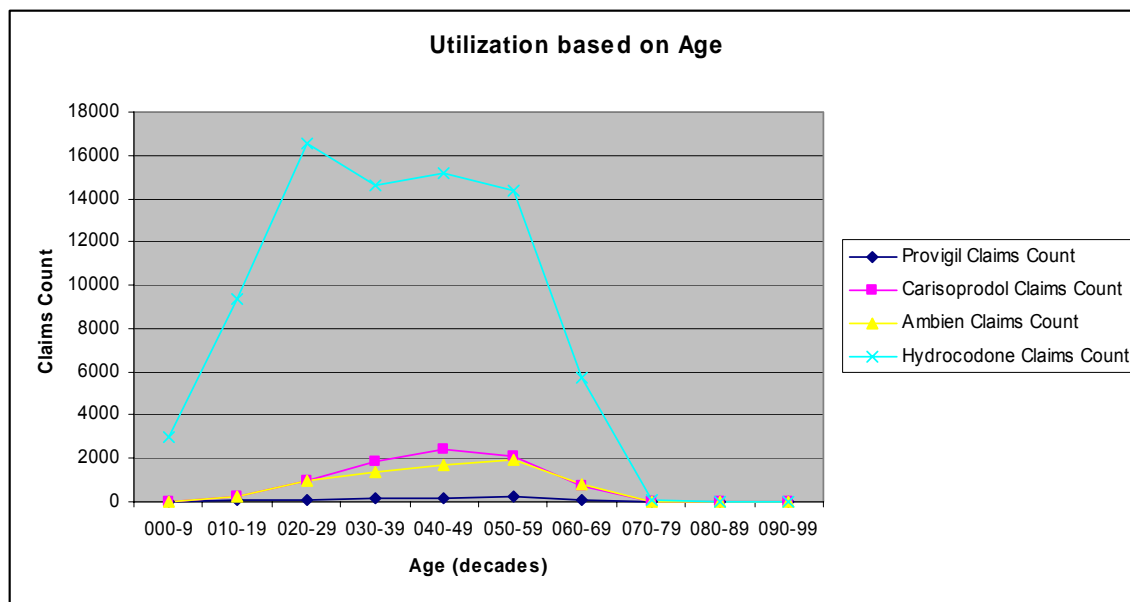
## Common Drugs of Abuse and Their Utilization within the MS Medicaid Population

At the November DUR Board Meeting, HID presented some data regarding hydrocodone, alprazolam, and lorazepam utilization in response to specific requests from the Pharmacy Bureau of MS Medicaid. This presentation of data sparked some very interesting conversations, thoughts, and questions during the meeting. It also left the Board with many questions in regards to the utilization of not only these medications, but others that are commonly abused. As a result, HID has conducted a more thorough and in-depth analysis of this data to provide insight on what the current trends are regarding these medications and to help answer those questions raised at the last DUR Board Meeting.

### 1) How does utilization of these drugs appear based on age?



As the graph above shows, the largest age group that uses the benzodiazepines is the 40-49 age group, with the exception of lorazepam and temazepam. Lorazepam use is strongest among the 80-89 age group, which is not surprising due to its extensive use in the elderly population. Temazepam's utilization peaks with the 50-59 age group and remains at that same level through the 80-89 age group. Once again, this is not surprising due to the higher incidence of insomnia in the elderly population.



### Hydrocodone

According to the chart above, hydrocodone utilization is greatest among the 20-29 year olds, but there is considerable use in the 30-59 age category as well, with use falling sharply after the 50-59 age group.

### Provigil®

Utilization of Provigil® is highest among the 50-59 age category, reflecting the increased incidence of obstructive sleep apnea in individuals over the age of 40. There is also considerable use in the 30-39 age group, which may reflect both narcolepsy and obstructive sleep apnea diagnoses, the FDA-approved indications for Provigil®.

### Carisoprodol

Carisoprodol utilization peaks among the 40-49 year olds.

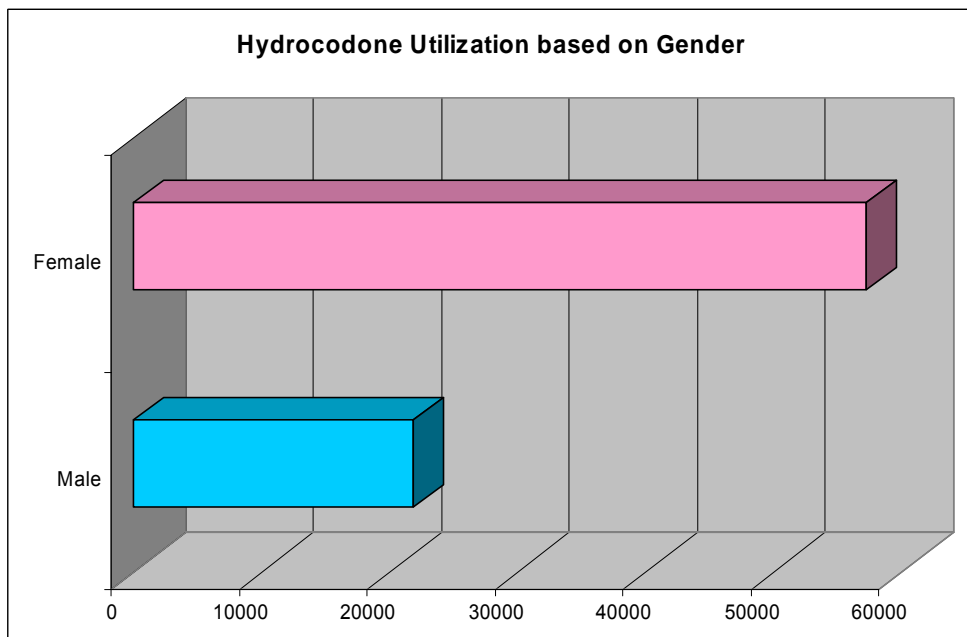
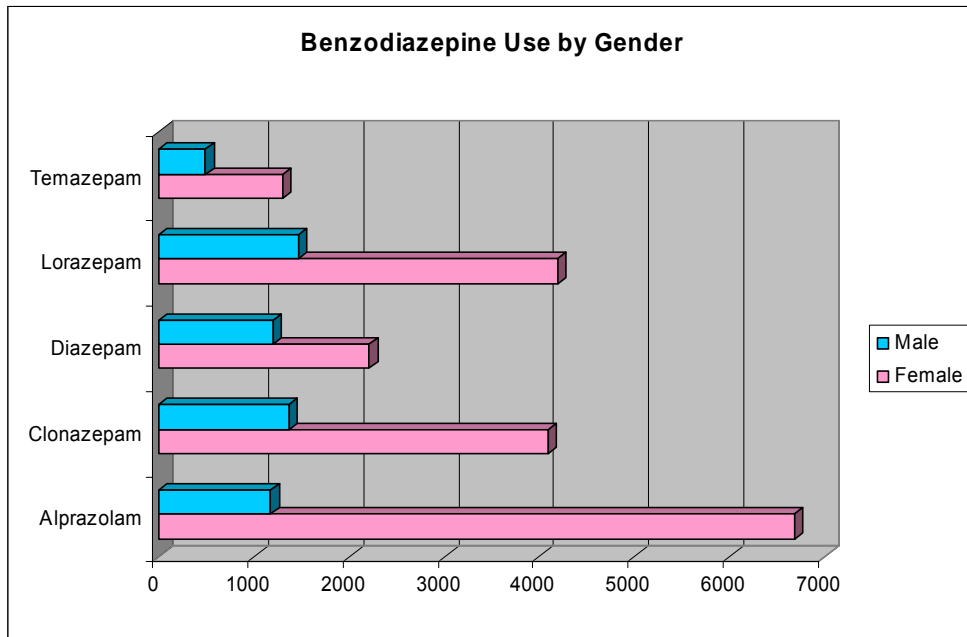
### Zolpidem

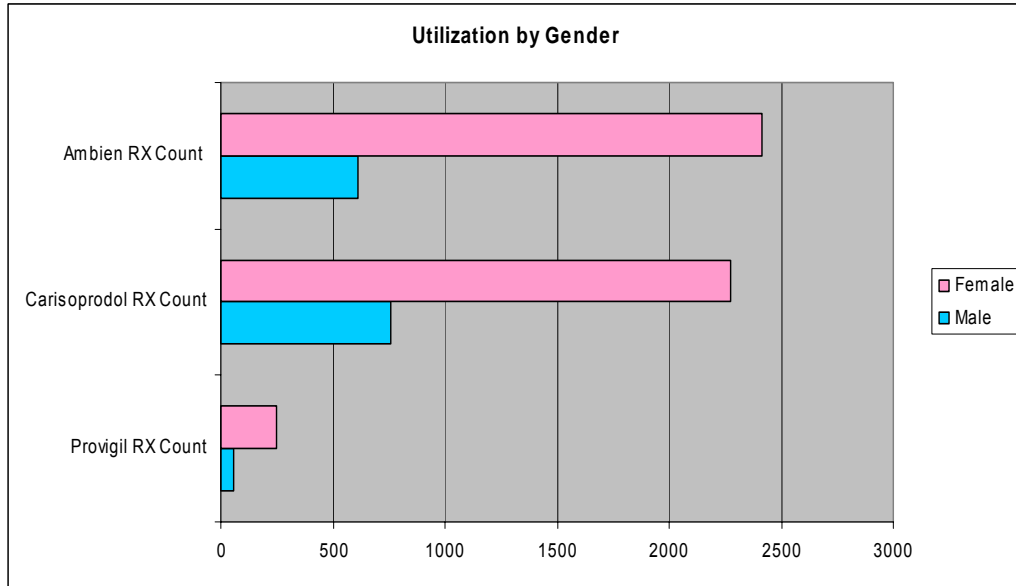
Utilization of zolpidem (Ambien®) climbs steadily until it peaks with the most use in the 50-59 age group. This is consistent with the higher incidence of insomnia that is seen as age increases.

### Summary

With the exception of hydrocodone and lorazepam, the highest utilization of these medications occurs among the 40-59 age group.

**2) How does utilization of these drugs appear based on gender?**

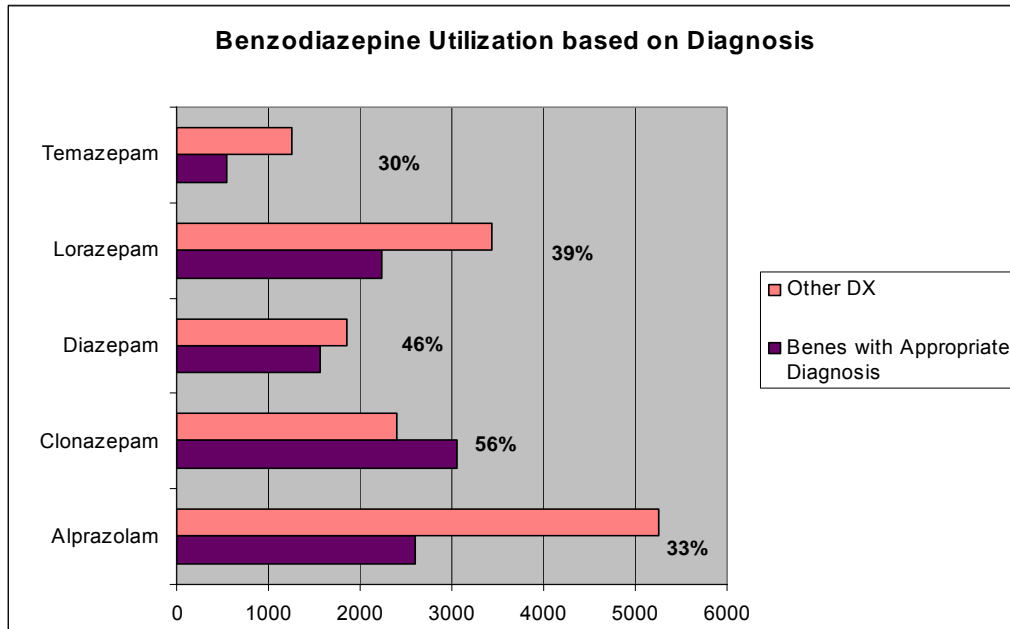




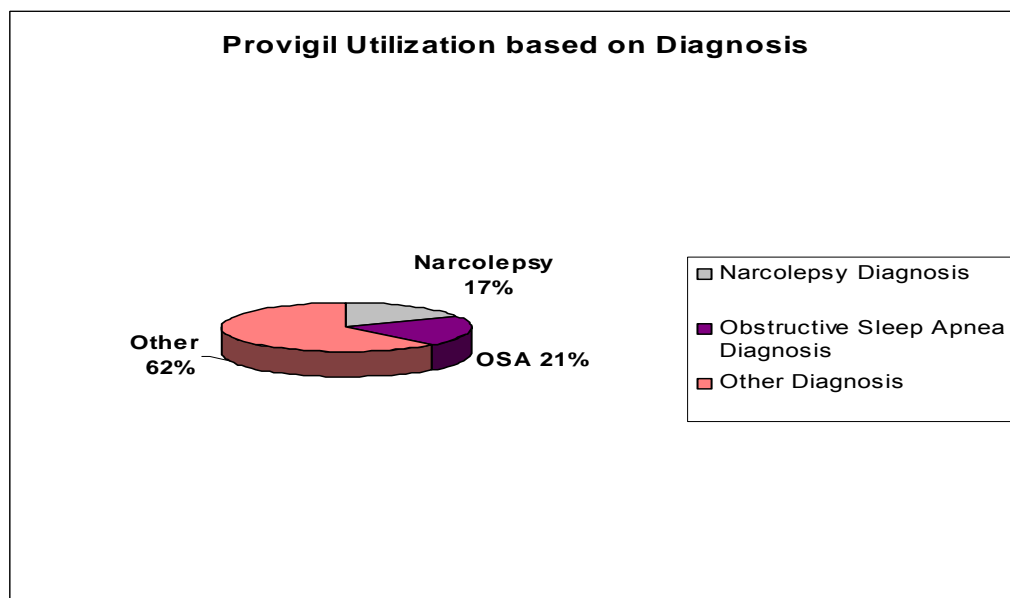
### Summary

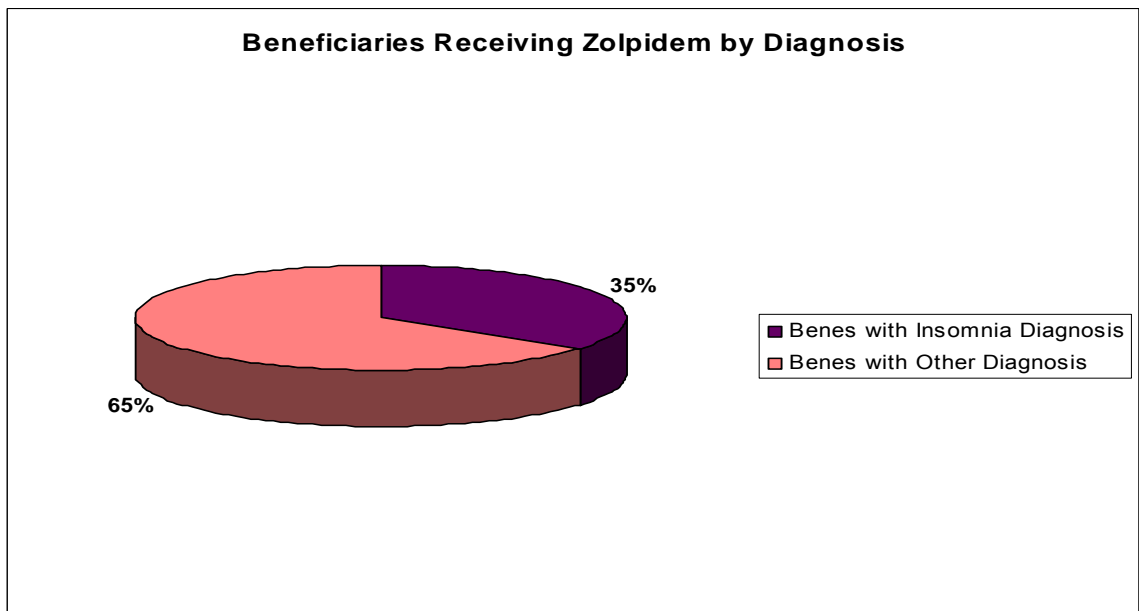
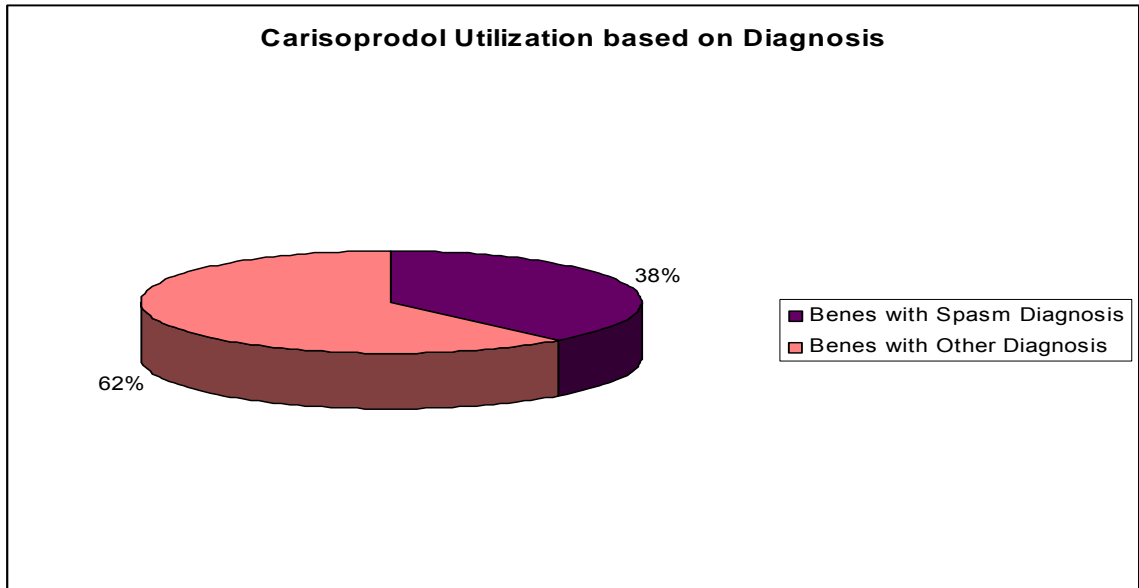
Based on the illustrations below, in all cases, females are clearly the most common recipients of these medications.

**3) Do the beneficiaries that receive these drugs have the appropriate diagnosis that corresponds with the indications for that medication?**



At least one-third of all MS Medicaid beneficiaries who receive a benzodiazepine have a diagnosis that is in line with the approved indications for that drug. For clonazepam and diazepam the percentage is even greater, with 56% and 46% of beneficiaries, respectively, having an appropriate diagnosis that warrants use of these medications.





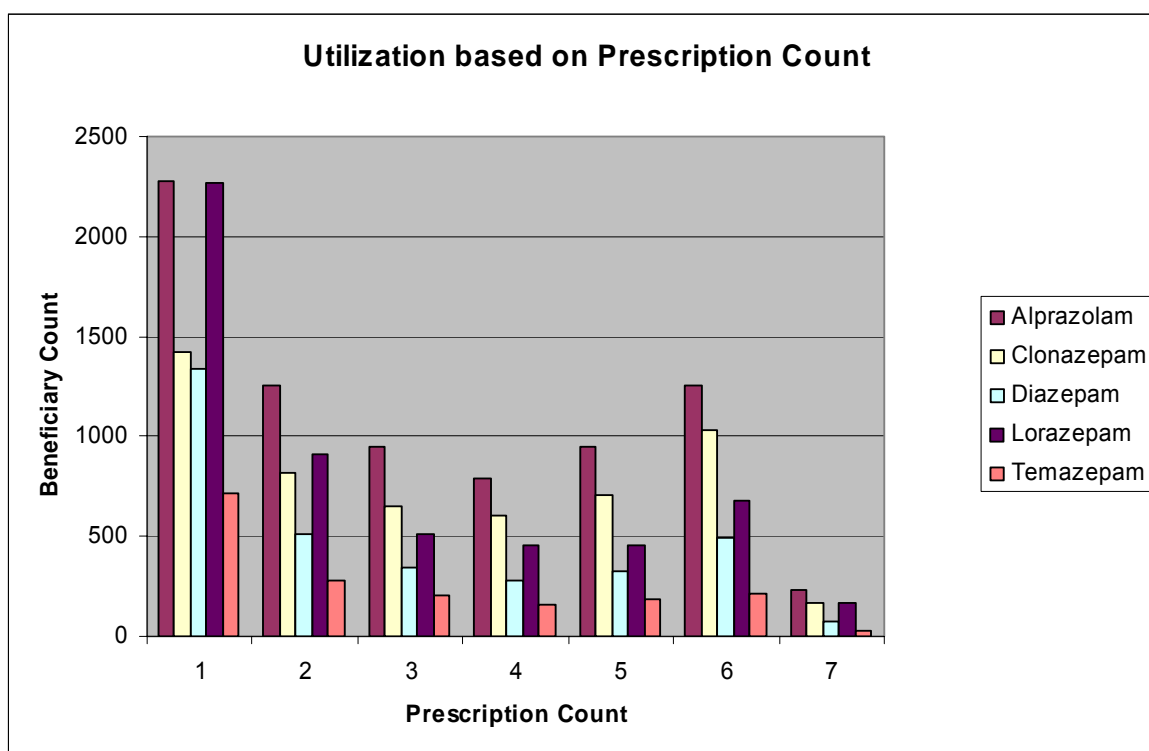
**Provigil®, Carisoprodol and Zolpidem**

For all 3 of these medications, approximately one-third of MS Medicaid beneficiaries who receiving them had a diagnosis that correlated with their respective FDA-approved indications.

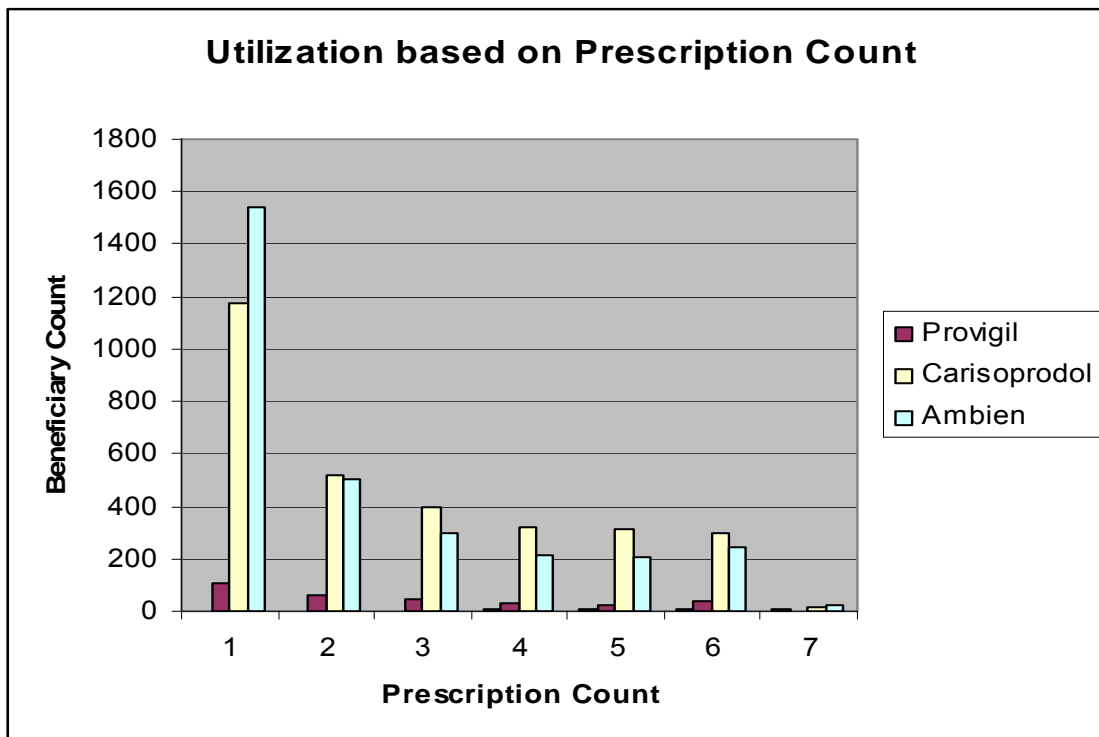


4) What is the prescription count per beneficiary related to these drugs?

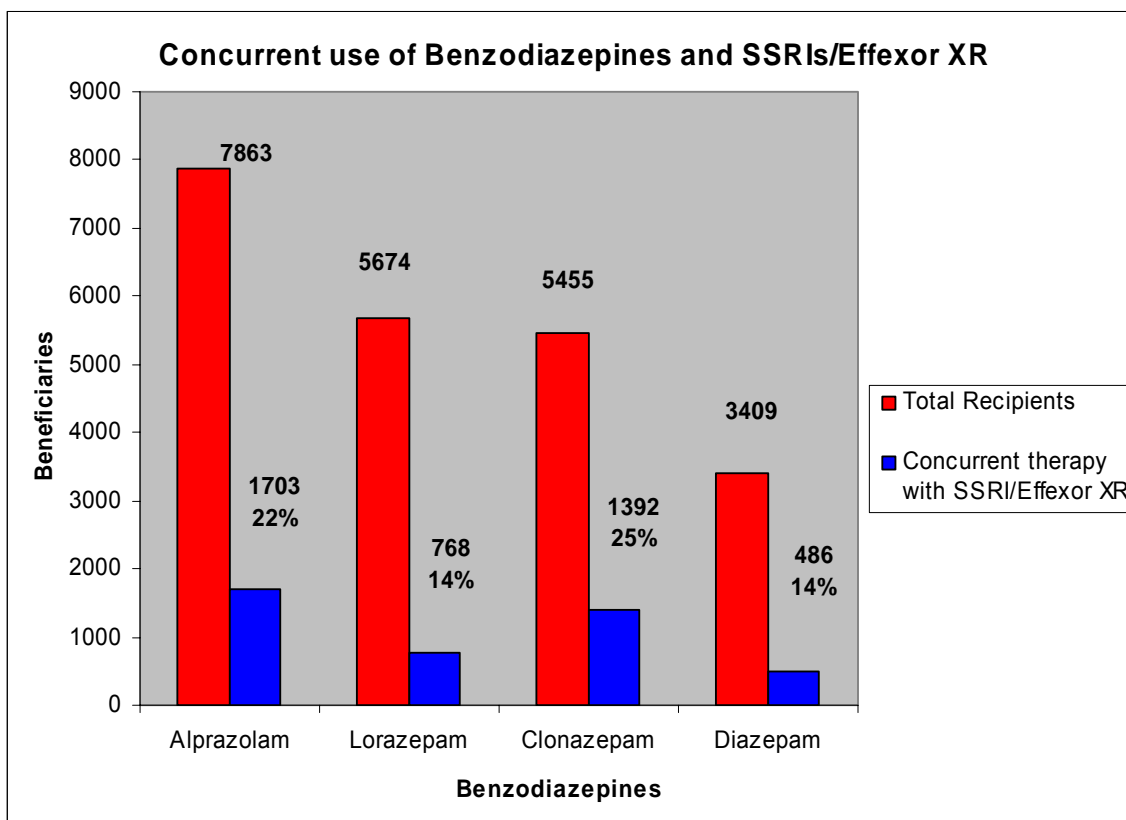
Prescription Count	Alprazolam	Clonazepam	Diazepam	Lorazepam	Temazepam
1	2280	1418	1342	2270	720
2	1258	818	513	908	278
3	944	655	342	511	205
4	786	600	282	454	155
5	944	709	323	454	189
6	1258	1036	494	681	214
7	236	164	71	170	24
8	31	27	14	40	6
9	23	11	15	28	1
≥10	30	45	13	79	2



Prescription Count	Provigil	Carisoprodol	Ambien
1	106	1175	1537
2	63	520	501
3	49	393	298
4	28	320	217
5	25	310	209
6	35	295	245
7	1	19	22
8	1	2	3
9	1	3	1
≥10	0	3	2

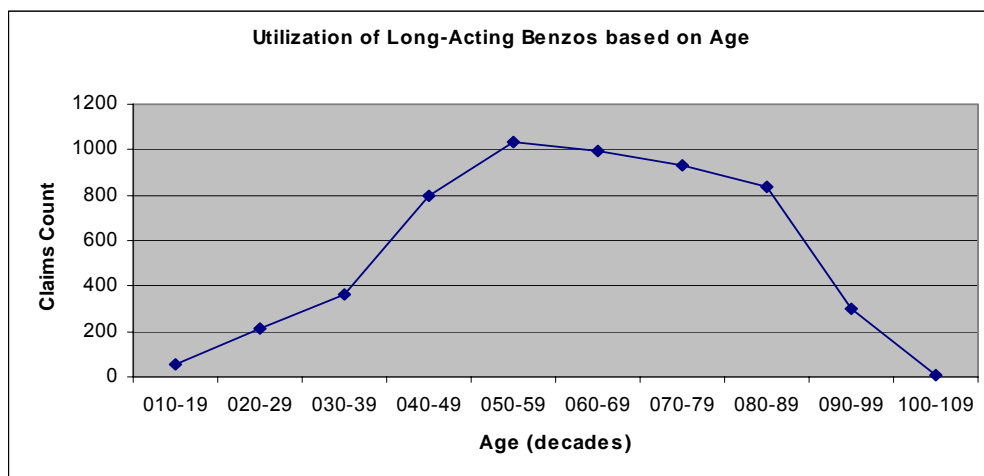


- 5) For beneficiaries who are receiving benzodiazepines, how many are also taking a maintenance medication for anxiety-related disorders in conjunction with the benzodiazepine?

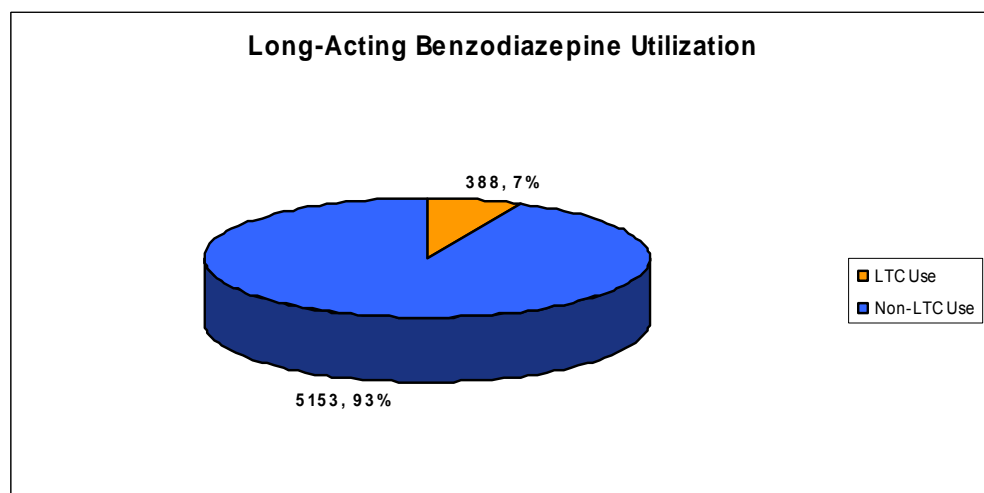


Of the benzodiazepines researched in this analysis, clonazepam had the largest percentage of users who were also taking an SSRI or Effexor XR® at 25%, followed closely by alprazolam. Lorazepam and diazepam had the lowest number of patients concurrently receiving maintenance therapy with an SSRI or Effexor XR®, at 14%.

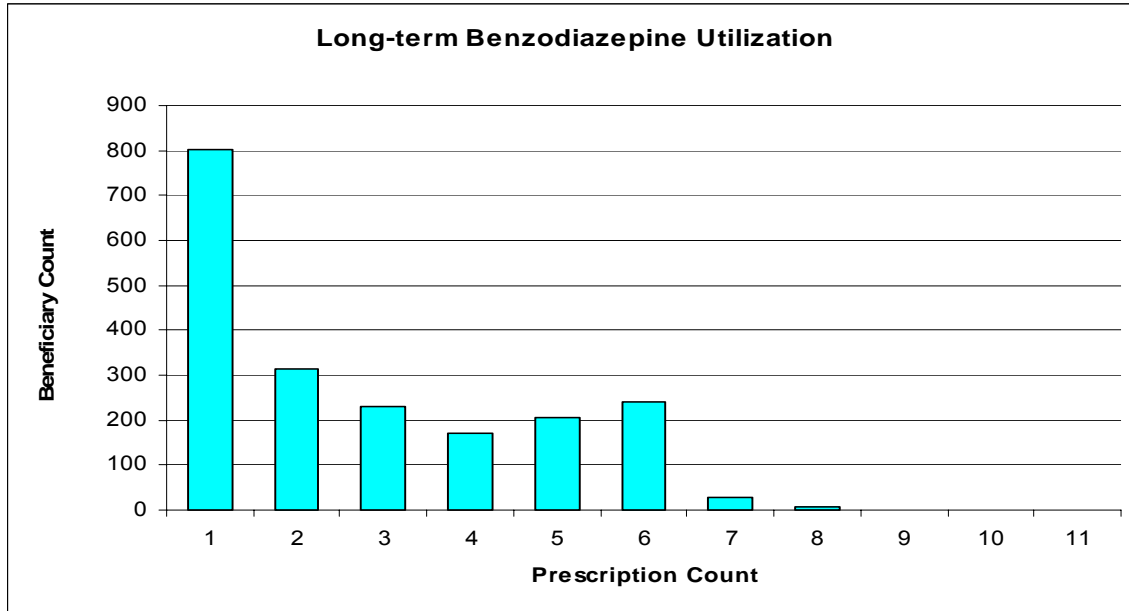
**6) What are the utilization trends for the long-acting benzodiazepines (flurazepam, triazolam, estazolam, and temazepam)?**



Use of the long-acting benzodiazepines peaks in the 50-59 age group, and slowly declines throughout the 60-89 age range, falling off sharply after this point. As mentioned before, the incidence of insomnia increases with age, so this is not a startling discovery.

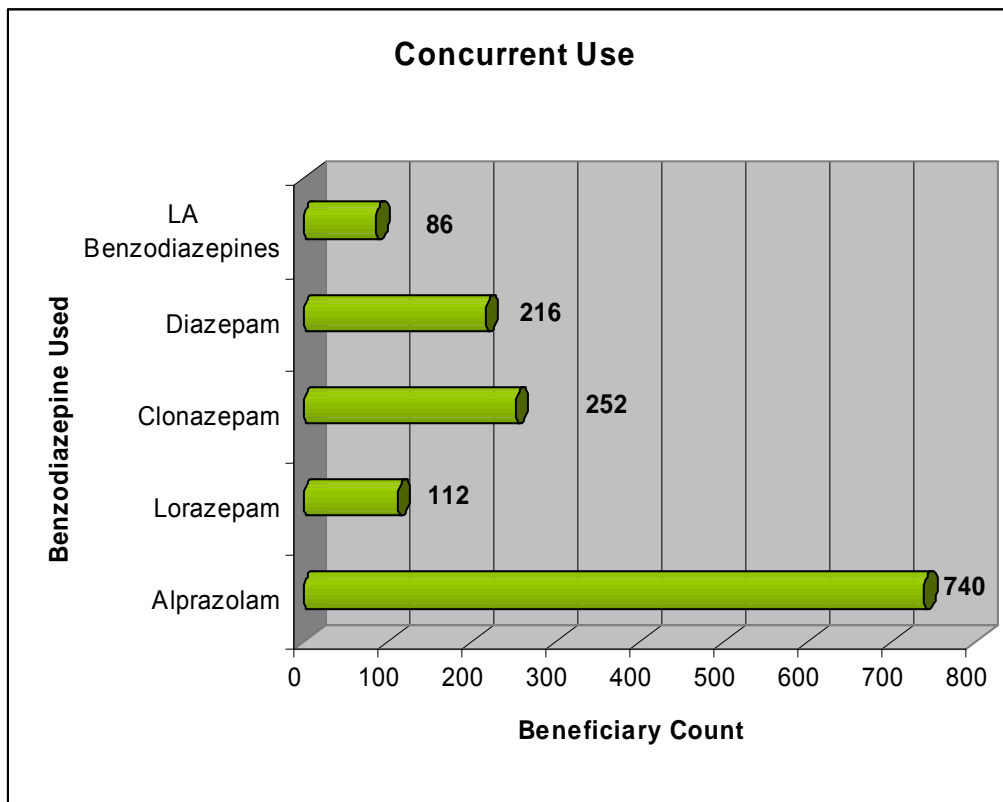


Of the utilization of long-acting benzodiazepines, only 7% of the use of these medications occurs in the traditional long-term care population. This is an encouraging finding, considering that these particular benzodiazepines are considered to be more dangerous for the LTC population with the long-half lives and increased sedation associated with them. These properties can increase the risk of falls and other incidents in an already frail population.



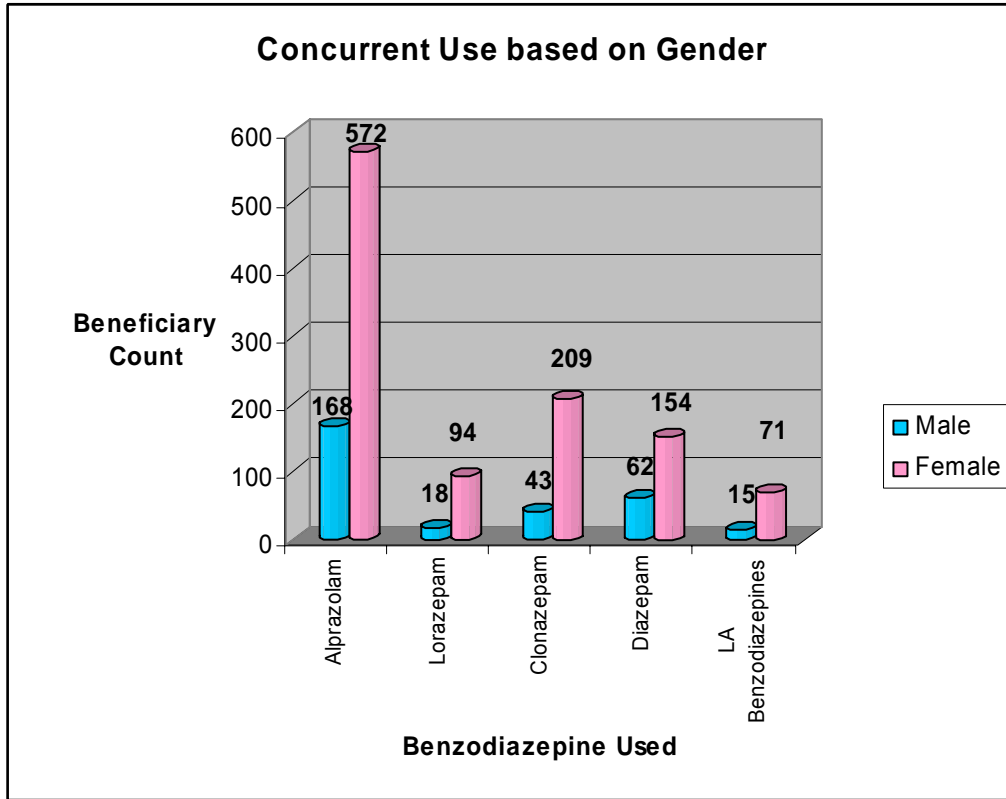
The majority of beneficiaries who received a prescription for a long-acting benzodiazepine did so only once, which represented approximately 800 beneficiaries. A much smaller number received between 2 and 6 prescriptions, with almost none receiving more than 6 prescriptions for a long-acting benzodiazepine.

**7) What is the incidence of beneficiaries receiving a combination of a benzodiazepine, hydrocodone, and carisoprodol?**



The prevalence of concurrent use of these medications varies greatly with the benzodiazepine used. For those beneficiaries taking alprazolam, a much larger number of these patients also received hydrocodone and carisoprodol during the same time frame. However, for those patients taking lorazepam or the long-acting benzodiazepines, the concurrent use with hydrocodone and carisoprodol during the same time period was much less.

As the chart below shows, the females by far are the most common users of all 3 medications concomitantly. For diazepam, the use with hydrocodone and carisoprodol in females is at least double that of males. In the case of alprazolam, females outnumber males 3 to 1 when looking at the use of all 3 medications concurrently. For clonazepam, lorazepam, and long-acting benzodiazepines, female use of hydrocodone and carisoprodol along with the respective benzodiazepine is almost 5 times that of males.



## Labeling Update for Desmopressin Acetate Nasal Spray

### Introduction

Primary nocturnal enuresis (PNE) is a disorder characterized as 1 to 2 bed-wetting incidents a week over a 3 month period in children over the age of 5, and is most commonly seen in boys. There are several causes of PNE, including delayed growth, a small bladder, too little antidiuretic hormone, deep sleeping, or emotional/social factors such as stress. By the age of 15, most children who experience this problem have learned bladder control and no longer experience bed-wetting episodes. Treatment of this syndrome can include alarm devices, behavior therapy, and pharmacological treatment options.

### Problem

On December 4, 2007, the FDA required manufacturers of desmopressin to update prescribing information for their products to include important new safety information about severe hyponatremia and seizures. Certain patients, including children treated with the intranasal formulation of desmopressin for PNE, are at risk for developing severe hyponatremia that can result in seizures and death. As such, desmopressin intranasal formulations are no longer indicated for the treatment of primary nocturnal enuresis and should not be used in hyponatremic patients or patients with a history of hyponatremia. The following chart lists the medications affected by this change.

Drug Name
Desmopressin Acetate Nasal Spray Pump
DDAVP® Nasal Spray Pump and Rhinal Tube Deliver System
Stimate® Nasal Spray
Minirin® Nasal Spray

### Method

Utilization data was gathered through RxExplorer®, which searches through paid claims data submitted to HID by the fiscal agent. A search was conducted covering the period from 1/1/2007 through 11/23/2007, which was the most recent date for which data was available.

The search parameters were desmopressin nasal spray utilization for children ages 5 to 15. The search was then analyzed to determine the current utilization of this medication and delivery system in this population.

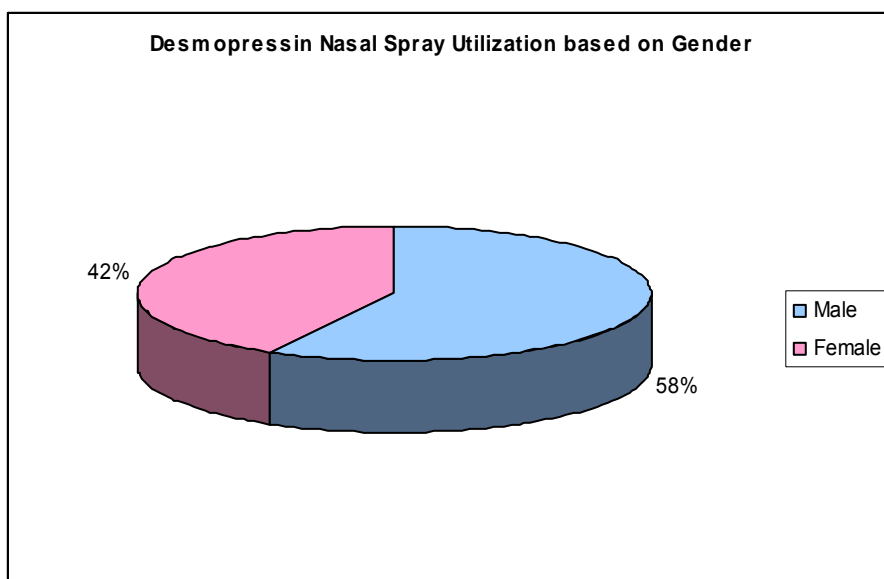


## Results

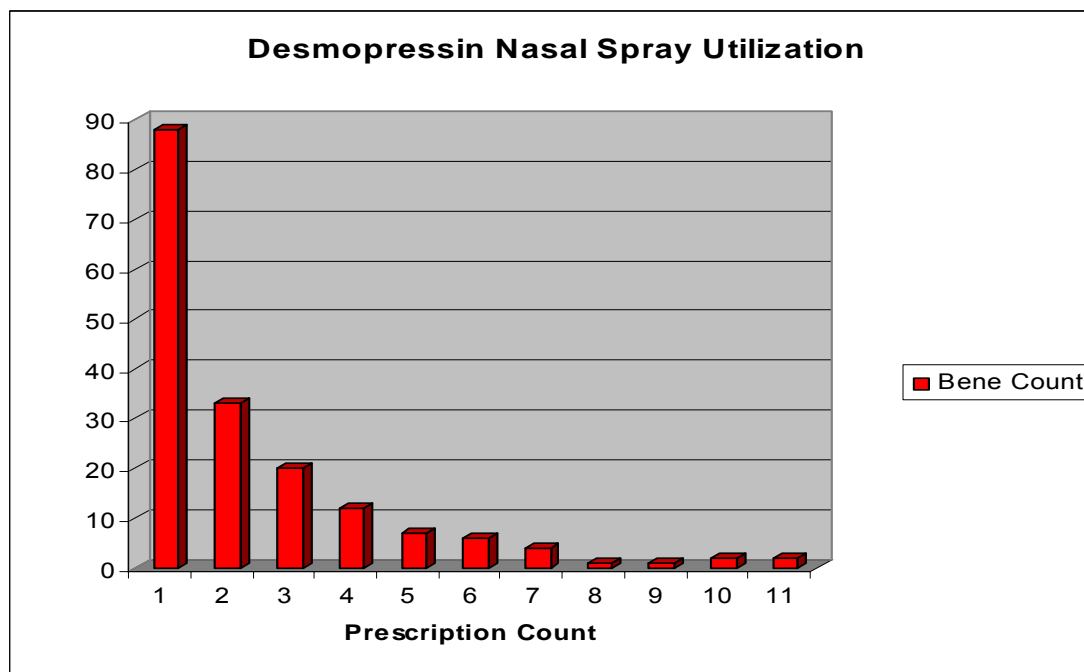
During the time period from January 1, 2007 to November 23, 2007, there were a total of 420 claims for desmopressin acetate nasal spray in children ages 5 to 15, representing a total of 176 beneficiaries. Of these 176 children, 89 (51%) had a diagnosis of either enuresis or nocturnal enuresis.

Drug Name	Rx Count
Desmopressin 0.1mg/mL Spray	417
Stimate® 1.5mg/mL Nasal Spray	3
<b>Total</b>	<b>420</b>

74 females and 102 males received desmopressin nasal spray during this time frame, which is consistent with the normal gender trend for PNE.



Of those beneficiaries who received desmopressin nasal spray, the largest percentage of them received between 1 and 3 prescriptions, with very few receiving long-term treatment with this medication.



## Summary

Based on the information gathered in this data search, there is not extensive utilization of desmopressin nasal spray in children ages 5 to 15 in the Mississippi Medicaid population. Of those beneficiaries receiving this medication, a very small number receive long-term treatment with desmopressin nasal spray.

## Recommendations

While the overall percentage of beneficiaries receiving desmopressin nasal spray is not great, the serious nature of the problems experienced with this medication warrant prudent use of desmopressin nasal spray. Retrospective DUR criteria are recommended to identify those patients who may be receiving this medication in violation of the recent position of the FDA.

**MISSISSIPPI MEDICAID  
RETROSPECTIVE DRUG UTILIZATION REVIEW  
CRITERIA RECOMMENDATIONS  
Desmopressin-related Criteria  
February 2008**

***Criteria Recommendations***

***Accepted      Rejected***

**1. Desmopressin / Therapeutic Appropriateness**

Alert Message: Desmopressin may cause severe hyponatremia which may put patients at risk for seizures and death. Intranasal desmopressin is no longer indicated for the treatment of primary nocturnal enuresis (PNE). The agent should not be used in patients with hyponatremia or a history of hyponatremia. Desmopressin tablets are still indicated for the treatment of PNE but therapy should be interrupted during acute illness that may lead to fluid or electrolyte imbalance.

Conflict Code: TA - Therapeutic Appropriateness

Drugs/Diseases

Util A

Util B

Util C

Desmopressin

**References:**

MedWatch - The FDA Safety Information and Adverse Event Reporting Program, 2007.

DDAVP Prescribing Information, October 2007, Sanofi-Aventis.

**2. Desmopressin / Pressor Agents**

Alert Message: The concomitant administration of drugs that may increase the risk of water intoxication with hyponatremia (e.g., tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine, opiate analgesics, NSAIDS, lamotrigine, and carbamazepine) should be performed with caution.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Diseases

Util A

Util B

Util C

Desmopressin

Tricyclic Antidepressants  
Selective Serotonin Re-uptake Inhibitors  
Chlorpromazine  
Opiate Analgesics  
NSAIDS  
Lamotrigine  
Carbamazepine

**References:**

DDAVP Prescribing Information, October 2007, Sanofi-Aventis.

Facts & Comparisons, 2007 Updates.

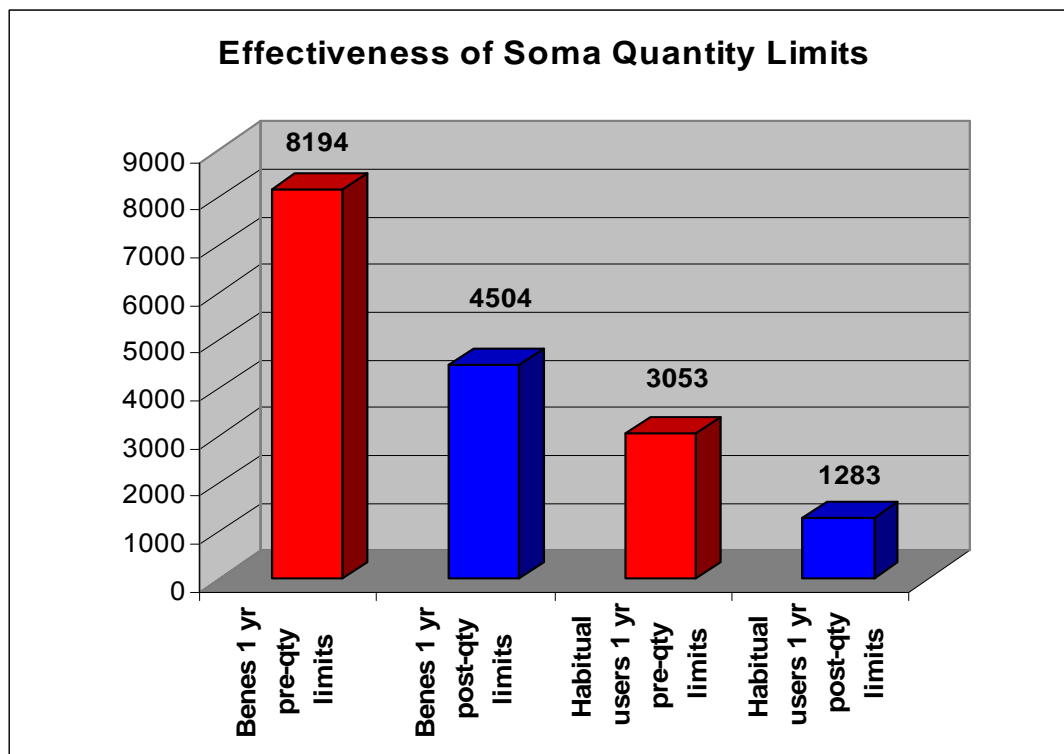
## **Utilization Trends of Carisoprodol**

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 of time, up to two to three weeks, because efficacy in more prolonged cases has not been established. Also, in general, acute musculoskeletal injuries are of short duration.

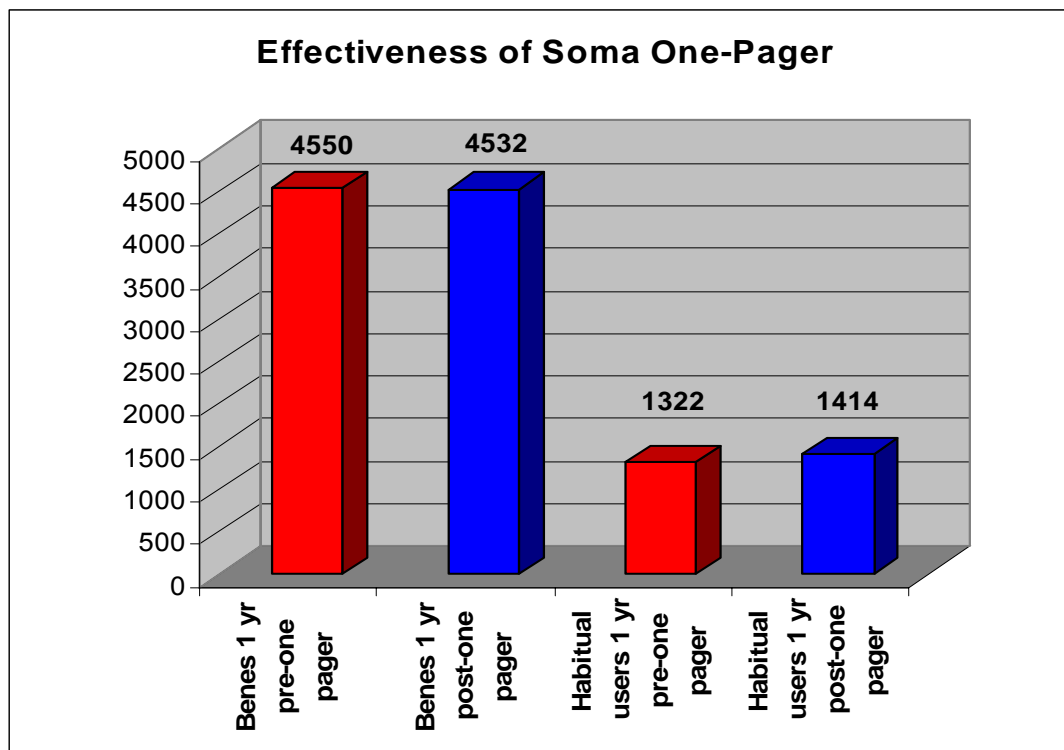
Although carisoprodol is not a controlled substance, abuse associated with this drug is well-documented. It is metabolized to meprobamate, an anxiolytic and schedule IV controlled substance. Carisoprodol is used frequently by poly-drug abusers, especially those dependent on opioids. In the last two DUR board meetings, the utilization of carisoprodol has been discussed in great detail. This subject continues to be of notable concern for the DUR Board and DOM.

Although quantity limits were enacted in 2006, and distribution of a carisoprodol prescribing information update (one-pager) and tapering schedule began in 2007, carisoprodol utilization continues to be high. On February 21, 2008 the DUR Board recommended that the P&T Committee consider making carisoprodol subject to the prior authorization process. With several other generic skeletal muscle relaxants available that do not possess the abuse potential associated with carisoprodol, the DUR Board feels that there is a limited place for carisoprodol therapy in musculoskeletal conditions. In addition, many other states have subjected carisoprodol to the prior authorization process due to the overuse and abuse potential associated with this drug. For example, in Montana, for new carisoprodol prescriptions patients must have tried and failed two other centrally-acting skeletal muscle relaxants before obtaining approval for carisoprodol. Once approval is given, the patient is only allowed 84 tablets within a six-month period (14 tablets per month). For refill prescriptions, a 30-day authorization is granted for patients currently taking carisoprodol to allow for a tapering schedule. These stringent prior authorization criteria allow for carisoprodol use within the FDA-approved indications for this medication and discourage the overuse that leads to potential addiction.

Based on this suggestion, HID looked at the utilization of carisoprodol one year prior to and one year following the implementation of the quantity limits and the carisoprodol one-pager. The graphs below illustrate the findings of these inquiries.



The number of beneficiaries receiving carisoprodol dropped nearly 50% after the implementation of the quantity limits in May 2006, compared to the same time period one year prior. For those beneficiaries considered habitual users of carisoprodol (>90 days supply of carisoprodol within the one year time period examined), the utilization dropped nearly 60% compared to the same time period one year prior. Based on these findings, the implementation of the quantity limits had a significant impact on utilization of carisoprodol within the Mississippi Medicaid population.



After the use of the carisoprodol one-pager and tapering schedule began in March 2007, very little change in the number of beneficiaries using carisoprodol occurred. There was a decrease of 18 beneficiaries using carisoprodol after the distribution of the one-pager began, compared to the same time period one year before the one-pager was developed. In the case of habitual users of carisoprodol, there was actually an increase in the number of beneficiaries receiving >90 days supply of carisoprodol as compared to the year before, from 1322 to 1414 beneficiaries. This information may indicate that the carisoprodol one-pager was not effective at further educating prescribers about the proper prescribing of and potential abuse associated with carisoprodol. However, if carisoprodol is made available only by prior authorization and is limited to a set quantity, the carisoprodol one-pager and tapering schedule will be very useful tools for prescribers in transitioning their patients to more appropriate therapy.

### **Recommendations**

The DUR Board recommends that the P & T Committee make carisoprodol available by prior authorization only.

### **Status**

On April 8, 2008, the P & T Committee voted to move all carisoprodol products to availability by prior authorization only. New prescriptions will be approved for acute musculoskeletal conditions only. Approved requests will be given a one-time prescription for a maximum of 84 tablets to reflect the current dosing recommended in the prescribing information for carisoprodol, and beneficiaries will be limited to one prescription every 6 months. For chronic users, a one-time approval will be given for 18 tablets to allow for tapering these patients off of carisoprodol.

**Carisoprodol**  
**Prior Authorization Criteria**

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.

**Approval criteria**

- ✓ Prior authorization will only be granted for the treatment of *acute* musculoskeletal conditions;
- ✓ Beneficiaries must have tried and failed in the past 21 days or have documented intolerance to cyclobenzaprine

**Denial criteria**

- ✗ Concurrent meprobamate therapy or history of meprobamate use within the past 90 days

**New prescriptions**

- Approval will be limited to a 21-day supply for a maximum of 84 tablets, in accordance with the FDA-approved labeling of carisoprodol
- Patients will only be allowed **one** 84-tablet prescription every six months, for a total of two prescriptions per year

**Chronic carisoprodol users**

- Approval will be limited to one 18-tablet supply to allow for the 9 day tapering schedule. The tapering schedule can be found at [http://www.medicaid.state.ms.us/Pharmacy\\_Services/Carisoprodol\\_Tapering.pdf](http://www.medicaid.state.ms.us/Pharmacy_Services/Carisoprodol_Tapering.pdf)
- Patients will only be allowed **one** 18-tablet prescription to allow for the tapering schedule

**FAX TO: 1-800-459-2135**

HEALTH INFORMATION DESIGNS, INC.  
P.O. BOX 320506  
Flowood, MS 39232  
Phone: (800) 355-0486

**CARISOPRODOL**  
(Includes combination formulations)  
PRIOR AUTHORIZATION REQUEST FORM

**BENEFICIARY INFORMATION**

Beneficiary's Name: \_\_\_\_\_ Beneficiary's Medicaid #: \_\_\_\_\_

DOB: \_\_\_\_\_ City: \_\_\_\_\_  
Month Day 4 Digit Year

**PRESCRIBER INFORMATION**

Prescribing Physician: \_\_\_\_\_

City: \_\_\_\_\_ State: \_\_\_\_\_

NPI #: \_\_\_\_\_

Medicaid ID #: \_\_\_\_\_

Phone #: \_\_\_\_\_

Fax #: \_\_\_\_\_

*I hereby certify that I am the ordering physician/nurse practitioner/physician assistant identified in this form and I deem the prescribed medication to be necessary for the patient listed. I understand that any falsification, omission or concealment of material fact may subject me to civil penalties, fines or criminal prosecution.*

\_\_\_\_\_  
Physician's Signature and date

**PHARMACY INFORMATION**

Dispensing Pharmacy: \_\_\_\_\_

City: \_\_\_\_\_ State: \_\_\_\_\_

Provider ID# \_\_\_\_\_

Phone #: \_\_\_\_\_

Fax #: \_\_\_\_\_

**DRUG/CLINICAL INFORMATION**

Is patient being treated for an **ACUTE** musculoskeletal condition? \_\_\_Yes \_\_\_No (If no, see Chronic Use section below)

Has therapy with a preferred skeletal muscle relaxant (cyclobenzaprine) been attempted? \_\_\_Yes \_\_\_No

Has the beneficiary experienced intolerable side effects on the preferred product(s)? \_\_\_Yes\*\*\* \_\_\_No

If yes, list the side effects: \_\_\_\_\_  
\_\_\_\_\_

Prior authorization approval will be limited to a quantity of 84, reflecting the maximum recommended use of 1 tablet TID and HS for 21 days. Approval will also be limited to 1 prescription every 6 months.

**Chronic Use**

Carisoprodol is labeled for acute use of up to 2 to 3 weeks. Due to potential dependence, upon discontinuation of high doses of carisoprodol, patients may suffer withdrawal symptoms. As a result, the following taper schedule is suggested to assist prescribers in managing the discontinuation of carisoprodol over 9 days (the full tapering schedule can be found at [http://www.medicaid.state.ms.us/Pharmacy\\_Services/Carisoprodol\\_Tapering.pdf](http://www.medicaid.state.ms.us/Pharmacy_Services/Carisoprodol_Tapering.pdf)):

350 mg TID for 3 days,  
then 350 mg BID for 3 days,  
then 350 mg QD for 3 days

For patients who have been taking carisoprodol on a chronic basis, a one-time quantity of 18 will be allowed for tapering.

Do you wish to request authorization of a quantity of 18 tablets for tapering this beneficiary? \_\_\_Yes \_\_\_No

\*\*\*Supporting documentation must be available in the patient record.

FOR HID USE ONLY

Eligibility Verified by \_\_\_\_\_  
Approved \_\_\_\_\_ Denied/Code: \_\_\_\_\_  
From Date \_\_\_\_\_ Thru Date \_\_\_\_\_  
Reviewed by \_\_\_\_\_  
HID# \_\_\_\_\_ PA# \_\_\_\_\_

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## **Off-label Use of Atypical Antipsychotics in Children for ADHD and ODD**

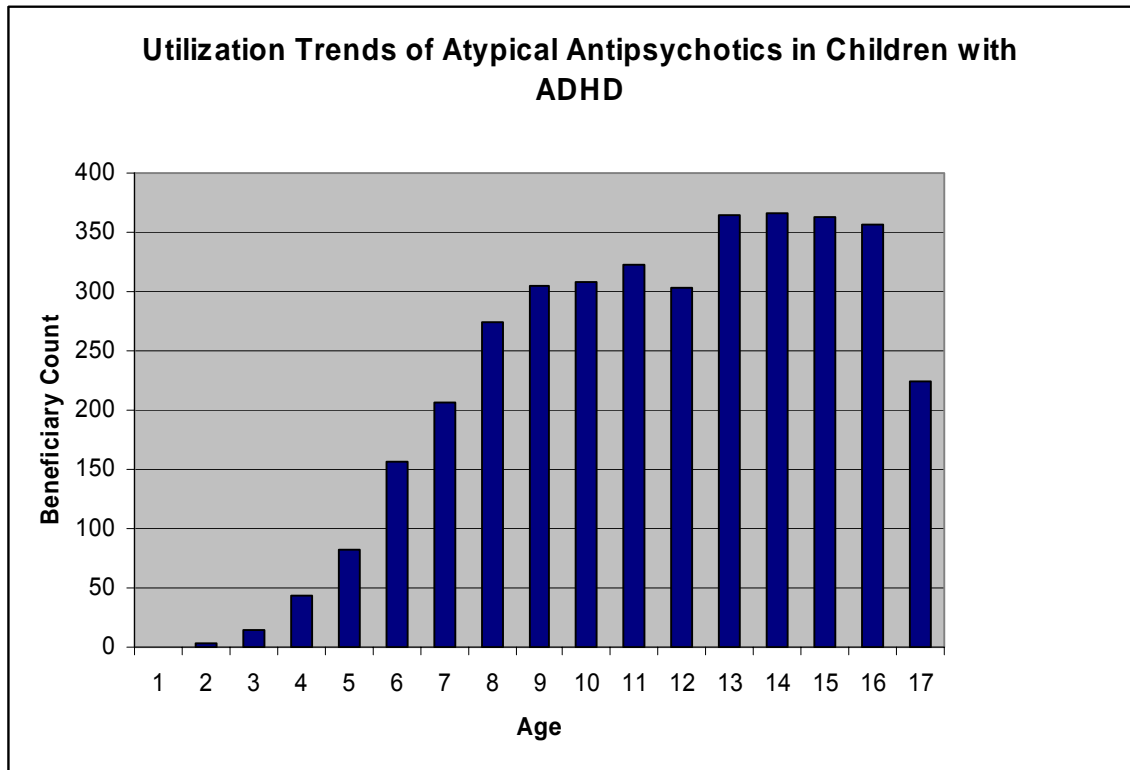
HID receives prior authorization requests every day for atypical antipsychotics for pediatric patients with the only diagnoses provided being ADHD (attention deficit hyperactivity disorder) or ODD (oppositional defiant disorder), neither of which are FDA-approved indications for medications in this class. The youngest age that any of the atypical antipsychotics is approved for is 5 years old, which is Risperdal® for use in children with irritability associated with autistic disorder. Abilify® is approved for adolescents from 13 years of age for schizophrenia. All of the other atypical antipsychotics (Geodon®, Invega®, Zyprexa®, and Seroquel®) are not approved for use in children or adolescents under the age of 18. This information, coupled with the large number of prior authorization requests seen for these medications in the pediatric population, raised concerns about the off-label use of atypical antipsychotics in children with ADHD and/or ODD.

In addition, utilization of atypical antipsychotics in the Mississippi Medicaid population continues to be one of the largest sources of drug expenditures for the program. For the month of February, five of the six atypical antipsychotics were in the Top 25 Drugs Based on Total Claims Cost report included in this packet, representing roughly \$2.8 million in drug expenditures for the month.

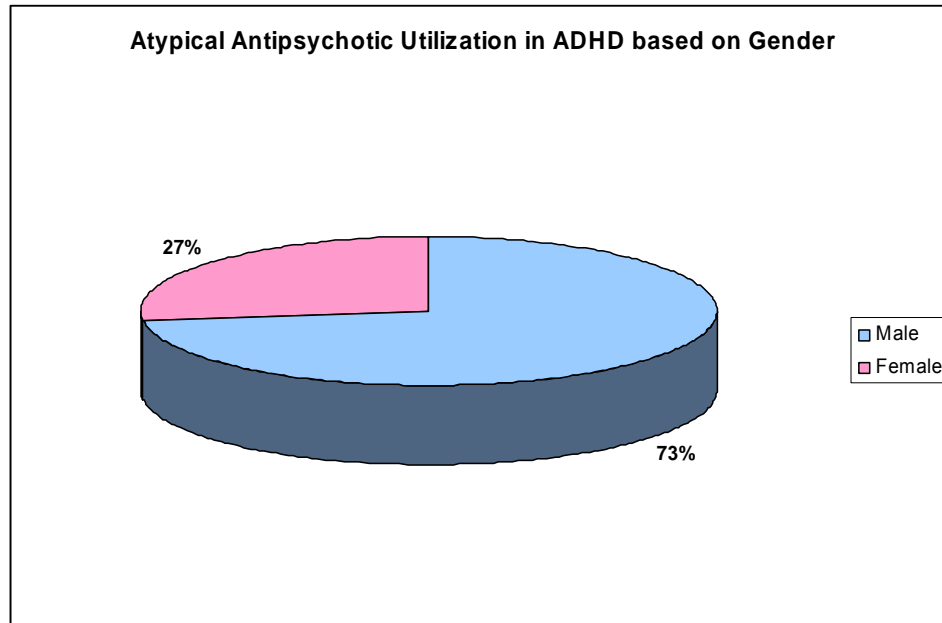
### **Method**

Considering the high costs and potential off-label use of these products, HID conducted an analysis of claims for the entire therapeutic class in children under the age of 18 from 2/23/07 to 2/22/08. In order to be included in the analysis, the beneficiary must have had a diagnosis of ADHD and/or ODD. In addition, those patients with a diagnosis of schizophrenia, bipolar disorder or autism were excluded. Therefore, the data collected represents those patients under the age of 18 with one or more claims for an atypical antipsychotic, presumably for the treatment of ADHD or ODD.

## Results



As the age increases, the number of pediatric beneficiaries receiving atypical antipsychotics for ADHD and/or ODD increases, with the largest number of beneficiaries being between 13 and 16 years old. However, there is substantial use of atypical antipsychotics in children as young as six with ADHD and/or ODD.



The majority of beneficiaries found in this analysis were male, approximately 73%. This is not startling, bearing in mind that ADHD and ODD are more common in male children and adolescents.

### **Summary**

As seen above, it appears that atypical antipsychotics are possibly being used off-label for children with ADHD and/or ODD, with the largest group being male adolescents ages 13 to 16.

### **Recommendation**

In an effort to discourage the off-label use of these powerful medications in a young population, a retrospective DUR criterion is recommended to identify those pediatric patients with ADHD and/or ODD who have received one or more atypical antipsychotics and do not have an FDA-approved diagnosis for these medications.

**MISSISSIPPI MEDICAID**  
**RETROSPECTIVE DRUG UTILIZATION REVIEW**  
**CRITERIA RECOMMENDATIONS**  
**MAY 2008**

***Criteria Recommendations***

***Accepted      Rejected***

**1. Atypical Antipsychotics / Therapeutic Appropriateness**

Alert Message: The patient is under the age of 18 with a diagnosis of ADHD and/or ODD and is receiving an atypical antipsychotic with no evidence, in their diagnostic history, of a FDA approved indication for use. Atypicals antipsychotics have not been shown to be safe and effective for the treatment of ADHD or ODD. These agents have significant adverse effects which can be more prevalent and severe in pediatric patients.

Conflict Code: TA - Therapeutic Appropriateness

Drugs/Diseases:

<u>Util A</u>	<u>Util B</u>	<u>Util C(Negating)</u>
Clozapine	ADHD	Schizophrenia
Risperidone	ODD	Autism
Quetiapine		Bipolar
Olanzapine		Major Depressive Disorder
Ziprasidone		
Aripiprazole		
Paliperidone		

Age Range: < 18 years of age

References:

Facts & Comparisons, 2008 Updates.

Olfson M, Blanco C, Liu L, Moreno C, Laje G: National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. Arch Gen Psychiatry 2006; 63:679-685.

Patel NC, Crismon ML, Hoagwood K, Johnsrud MT, Rascati KL, Wilson JP, Jensen PS: Trends in the use of typical and atypical antipsychotics in children and adolescents. J Am Acad Child Adolesc Psychiatry 2005; 44:548-556.

Correll CU, Carlson HE, Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents, J Am Acad Child Adolesc Psychiatry (2006)45:771-791.

**Due to unavailability of claims data for the full month of March, the Synagis<sup>®</sup> report to be included in this section was not complete at the time of printing. This document will be provided at the DUR meeting.**

## **Generalized Anxiety Disorder (GAD)**

### **Introduction**

Generalized anxiety disorder (GAD) is an anxiety disorder that is characterized by excessive, uncontrollable and often irrational worry about everyday events or issues that is disproportionate to the actual source of worry. These patients continually anticipate disaster and are overly concerned about health issues, money, family problems, or work difficulties. Patients with GAD cannot seem to get rid of their concerns, even though they usually realize that their anxiety is more intense than the situation warrants. They may also have trouble falling asleep or staying asleep. Physical symptoms that often accompany the anxiety include fatigue, headaches, muscle tension, muscle aches, difficulty swallowing, trembling, twitching, irritability, sweating, nausea, lightheadedness, having to go to the bathroom frequently, feeling out of breath, and hot flashes.

GAD affects about 6.8 million adult Americans and about twice as many women as men. This disorder comes on gradually and can begin across the life cycle, though the risk is highest between childhood and middle age. It is diagnosed when someone spends at least 6 months worrying excessively about a number of everyday problems.

### **Pharmacologic Management of GAD**

Antidepressants are the preferred class for the treatment of GAD, with the selective serotonin reuptake inhibitors (SSRIs) being the first-line agents. Lexapro® and paroxetine immediate-release are the only SSRIs with specific indications for generalized anxiety disorder, although most treatment guidelines recommend treatment with any of the SSRIs. Once treatment at optimal dosing with one or more SSRIs has been tried and failed, second-line treatment should be considered with Effexor XR or Cymbalta, both of which are serotonin and norepinephrine reuptake inhibitors (SNRIs). Benzodiazepines do have a place in the treatment of GAD. However, treatment guidelines recommend that their use be short-term, not to exceed 2-4 weeks.

### **Recommendations**

In recent DUR Board meetings, there has been extensive discussion about the improper use of benzodiazepines. In the February meeting, data was presented that showed only 14-25% of patients with an anxiety-related diagnosis who received one or more prescriptions for a benzodiazepine also received one or more prescriptions for maintenance therapy for anxiety, such as an SSRI or Effexor XR. As a result, a Medicaid Prescribing Update, or “one-pager”, has been created for GAD that provides a description of this disorder, and, more importantly, proper treatment recommendations for GAD based on treatment guidelines. HID recommends distribution of this document to prescribers by the Academic Detailing Staff, as well as availability by a link from the Division of Medicaid website.



# Prescribing Information Update

## Generalized Anxiety Disorder (GAD)

### Mississippi Division of Medicaid

- *GAD is characterized by excessive anxiety or worry that has persisted for at least 6 months.*
- *GAD is a chronic illness that often requires prolonged treatment.*
- *The first-line pharmacological treatment option for GAD is a selective serotonin reuptake inhibitor (SSRI).*
- *Benzodiazepine therapy has a small role in the treatment of GAD and should not persist beyond 2-4 weeks.*

Generalized anxiety disorder (GAD) is one of several anxiety disorders classified by the DSM-IV. The characteristic feature associated with GAD is unrealistic or excessive anxiety and worry about a number of events or activities that has persisted for at least 6 months. Other diagnostic criteria include:

- Worry that is difficult to control
- Restlessness
- Easily fatigued
- Difficulty concentrating
- Irritability
- Muscle tension
- Sleep disturbances

Onset of GAD is usually in the early 20s, but it may be precipitated in later life by stressful life events. This illness is chronic in nature with multiple spontaneous exacerbations and remissions.

#### Pharmacologic Management of GAD

Antidepressants are the preferred class for the treatment of GAD, with the selective serotonin reuptake inhibitors (SSRIs) being the first-line agents. Lexapro® and paroxetine immediate-release are the only SSRIs with specific indications for generalized anxiety disorder, although most treatment guidelines recommend treatment with any of the SSRIs. Once treatment at optimal dosing with one or more SSRIs has been tried and failed, second-line treatment should be considered with Effexor XR or Cymbalta, both of which are serotonin and norepinephrine reuptake inhibitors (SNRIs). Benzodiazepines do have a place in the treatment of GAD. However, treatment guidelines recommend that their use be short-term, not to exceed 2-4 weeks.

#### Preferred Drug List Status for GAD Medications

Preferred	Non-preferred
Paroxetine	Lexapro®
Citalopram	Cymbalta®
Sertraline	
Fluoxetine	
Effexor XR®	

#### References:

- Drug Facts and Comparisons 4.0. Copyright 2008 Wolters Kluwer Health, Inc.
- Management of Anxiety (Panic Disorder, with or without Agoraphobia, and Generalized Anxiety Disorder) in Adults in Primary, Secondary, and Community Care. NICE Clinical Guideline 22 (amended). UK, April 2007.
- Clinical Practice Guidelines: Management of Generalized Anxiety Disorder. Canadian Journal of Psychiatry, Vol 51, Suppl 2, July 2006.

## **Impact of Subjecting Risperdal Consta<sup>®</sup> to the Prior Authorization Process**

Risperdal Consta<sup>®</sup> is a long-acting atypical antipsychotic injection approved for the treatment of schizophrenia. This agent is well-suited for patients for whom medication compliance is a challenge. Risperdal Consta<sup>®</sup> is administered as an intramuscular injection every two weeks.

According to the FDA-approved prescribing information, tolerability to oral Risperdal<sup>®</sup> should be established prior to initiating therapy with Risperdal Consta<sup>®</sup>. The labeling also states that oral risperidone or another antipsychotic medication should be given with the first injection of Risperdal Consta<sup>®</sup>, continued for three weeks, then discontinued to ensure that effective therapeutic plasma concentrations are reached and maintained prior to the main release phase of risperidone from the injection site.

In October 2007, HID was given the responsibility for supervising the prior authorization of Risperdal Consta<sup>®</sup>. Based on the prescribing information provided by the drug manufacturer, the prior authorization criteria require that if a patient is currently on oral antipsychotic medication, the prescriber must provide a plan for weaning the patient off the oral medication in order to continue with the Risperdal Consta<sup>®</sup>. The purpose of this report is to determine if the prior authorization process has made an impact the concurrent use of Risperdal Consta<sup>®</sup> and oral antipsychotics.

### **Method**

Utilization data was gathered through RxExplorer<sup>®</sup>, which searches through paid claims data submitted to HID by the fiscal agent. Four unique searches were conducted covering the periods from 4/15/07 through 10/14/07, the 6-month period prior to HID beginning the supervision of prior authorization of Risperdal Consta<sup>®</sup>, and 10/15/07 to 3/21/08, the nearly 6-month period after HID began the supervision of the prior authorization process for Risperdal Consta<sup>®</sup>.

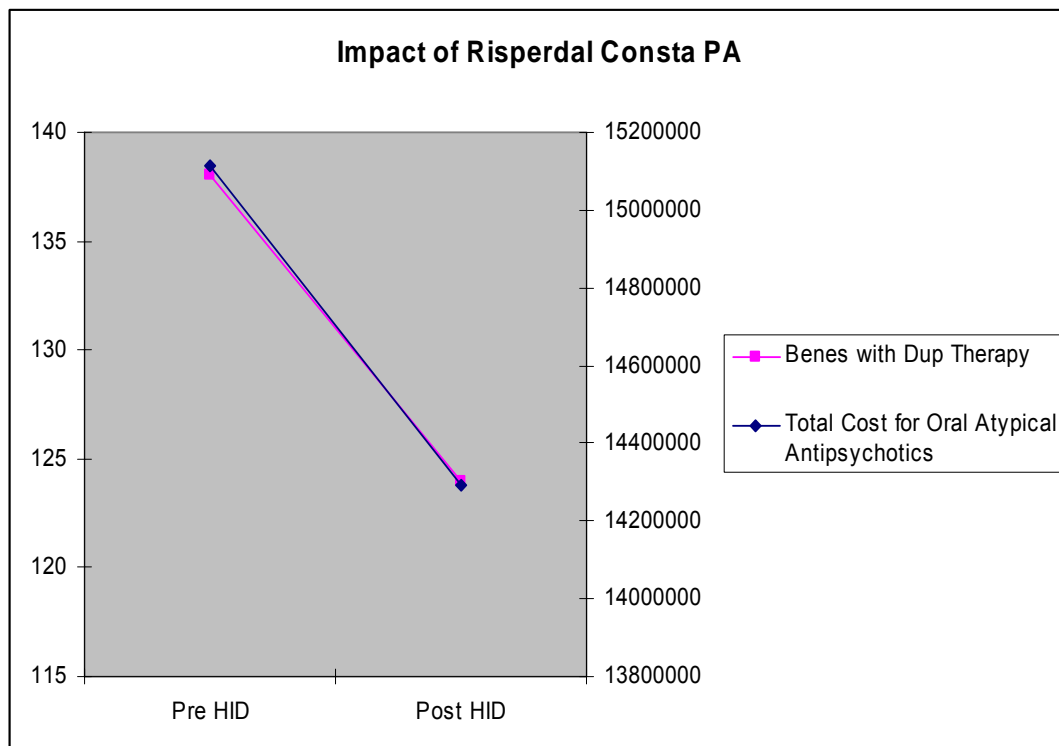
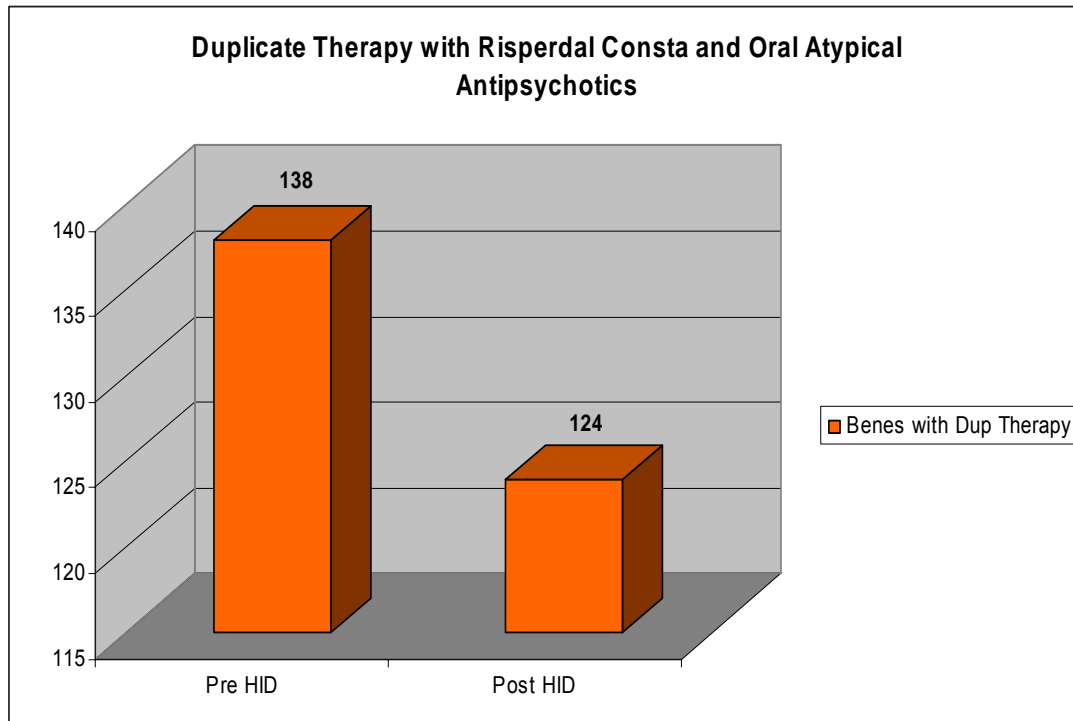
The search parameters were:

1. Utilization of Risperdal Consta, pre- and post-prior authorization of Risperdal Consta<sup>®</sup>
2. Utilization of Oral Atypical Antipsychotics, pre- and post-prior authorization of Risperdal Consta<sup>®</sup>

These searches were then intersected to determine the number of patients in each time period that were receiving both Risperdal Consta and an oral antipsychotic.



## Results



The analysis resulted in 138 beneficiaries receiving Risperdal Consta and an oral antipsychotic prior to the PA process began at HID, and 124 beneficiaries receiving both dosage forms after the PA process began at HID. This was a decrease of 14 beneficiaries, or approximately 10%. From another standpoint, oral atypical antipsychotic cost to DOM decreased by nearly \$900,000 after HID started supervising the prior authorization of Risperdal Consta<sup>®</sup>. More than likely, this decrease is the result of the efforts put forth by HID to closely monitor those patients receiving Risperdal Consta<sup>®</sup>.

### **Conclusion**

HID has made a concentrated effort to ensure that Risperdal Consta is utilized by the patients it was intended for, being those patients who have a history of non-compliance with oral medications. This includes educating prescribers about the prescribing information provided from the manufacturer, monitoring claims data when prior authorization requests are made, and following up with those patients whom the prescriber claimed to be weaning off oral medication. Based on the information obtained in this analysis, this effort has been successful in the beginning stages. HID will continue to monitor the progress of this effort and expects to find continued cost savings as the program continues forward.

**MISSISSIPPI MEDICAID**  
**RETROSPECTIVE DRUG UTILIZATION REVIEW**  
**CRITERIA RECOMMENDATIONS**  
**MAY 2008**

***Criteria Recommendations***

***Accepted      Rejected***

**1. Nebivolol / High Dose**

Alert Message: Bystolic (nebivolol) may be over-utilized. The recommended maximum dose is 40 mg per day.

Conflict Code: HD – High Dose

Drugs/Disease

Util A

Util B

Util C

Nebivolol

Max Dose: 40 mg/day

References:

Bystolic Prescribing Information, December 2007, Forest Pharmaceuticals, Inc.

**2. Nebivolol / Contraindications**

Alert Message: Bystolic (nebivolol) is contraindicated in patients with severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (no permanent pacemaker in place), hypersensitivity to the product, or severe hepatic impairment (Child-Pugh >B).

Conflict Code: MC – Drug Actual Disease Problem

Drugs/Disease

Util A

Util B

Util C

Nebivolol

Bradycardia

Heart Block

Cardiogenic Shock

Cardiac failure

Sick Sinus Syndrome

References:

Bystolic Prescribing Information, December 2007, Forest Pharmaceuticals, Inc.

**3. Nebivolol / Hepatic Impairment**

Alert Message: Bystolic (nebivolol) is contraindicated in patients with severe hepatic impairment and should be used with caution in patients with moderate impairment.

Studies have shown patients with moderate hepatic impairment have an 86% decrease in nebivolol clearance. The recommended initial dose of nebivolol in patients with moderate impairment is 2.5 mg once daily with upward titration performed cautiously if needed.

Conflict Code: DB – Drug/Drug or Drug Disease Precaution

Drugs/Disease

Util A

Util B

Util C

Nebivolol

Hepatic Impairment

References:

Bystolic Prescribing Information, December 2007, Forest Pharmaceuticals, Inc.

**Criteria Recommendations**

**Accepted      Rejected**

**4. Nebivolol / Renal Impairment**

Alert Message: Bystolic (nebivolol) should be used with caution in patient with severe renal impairment. Studies have shown a 53% decrease in the renal clearance of nebivolol in patients with a CrCl < 30 mL/min. The recommended initial dose of nebivolol in this population is 2.5 mg once daily with upward titration performed cautiously if needed.

Conflict Code: DB – Drug/Drug or Drug Disease Precaution

Drugs/Disease

Util A

Nebivolol

Util B

Severe Renal Impairment

Util C

Lanthanum

Sevelamer

Doxercalciferol

Paricalcitol

Calcitriol

References:

Bystolic Prescribing Information, December 2007, Forest Pharmaceuticals, Inc.

**5. Nebivolol / CYP2D6 Inhibitors**

Alert Message: The concurrent administration of Bystolic (nebivolol) and a CYP2D6 inhibitor (e.g., paroxetine, fluoxetine, quinidine, and bupropion) is expected to result in elevated nebivolol plasma concentrations. Patients receiving concurrent therapy with these agents should be monitored closely and the nebivolol dose adjusted according to blood pressure response.

Conflict Code: DD – Drug/Drug Interactions

Drugs/Disease

Util A

Nebivolol

Util B

Paroxetine

Fluoxetine

Quinidine

Bupropion

Duloxetine

Amiodarone

Cimetidine

Propafenone

References:

Bystolic Prescribing Information, December 2007, Forest Pharmaceuticals, Inc.

**6. Nebivolol / CYP2D6 Inducers**

Alert Message: The concurrent administration of Bystolic (nebivolol) and a CYP2D6 inducer (e.g., rifampin and dexamethasone) is expected to result in decreased nebivolol plasma concentrations. Patients receiving concurrent therapy with these agents should be monitored closely and the nebivolol dose adjusted according to blood pressure response.

Conflict Code: DD – Drug/Drug Interactions

Drugs/Disease

Util A

Nebivolol

Util B

Dexamethasone

Rifampin

References:

Bystolic Prescribing Information, December 2007, Forest Pharmaceuticals, Inc.

**Criteria Recommendations**

**Accepted      Rejected**

**7. Atypical Antipsychotics / Therapeutic Duplication**

Alert Message: Therapeutic duplication of atypical antipsychotic agents may be occurring.

Conflict Code: TD – Therapeutic Duplication

Drugs/Disease

Util A                      Util B                      Util C

Clozapine

Risperidone

Olanzapine

Quetiapine

Ziprasidone

Aripiprazole

Paliperidone

References:

Facts & Comparisons, 2007 Updates.

Clinical Pharmacology, Gold Standard, 2007.

Micromedex Healthcare Series, DrugDex Drug Evaluations, 2007.

**8. Risperdal Consta / Oral Atypical Antipsychotics**

Alert Message: Patients prescribed Risperdal Consta (risperidone injection) should receive oral antipsychotic supplementation until risperidone has achieved steady-state plasma concentrations, typically after 4 injections. The use of oral antipsychotics with risperidone injection beyond the recommended transition time period may represent an unnecessary and costly duplication of therapy.

Conflict Code: TD – Therapeutic Duplication (DD-100P)

Drugs/Disease

Util A                      Util B                      Util C

Risperdal Consta

Clozapine

Risperidone (except Consta)

Olanzapine

Quetiapine

Ziprasidone

Aripiprazole

Paliperidone

References:

Risperdal Consta Prescribing Information, Sept 2007, Janssen Pharmaceuticals, Ltd.

Facts & Comparisons, 2007 Updates.

Clinical Pharmacology, Gold Standard, 2007.

Micromedex Healthcare Series, DrugDex Drug Evaluations, 2007.

**9. Clopidogrel / Non-adherence**

Alert Message: Non-adherence to clopidogrel therapy may result in a sub-therapeutic effect increasing mortality, morbidity and healthcare cost.

Conflict Code: LR - Non-Adherence

Drug/Diseases:

Util A                      Util B                      Util C

Clopidogrel

References:

Osterberg L, Blaschke T. Adherence to Medication. N Engl J Med. Aug. 2005;353(5):487-497.

Munger MA, Van Tassel BW, La Fleur J. Medication nonadherence: an unrecognized cardiovascular risk factor.

MedGenMed. Sep. 2007;19;9(3): 58.

**Criteria Recommendations**

**Accepted      Rejected**

**10. Clopidogrel / Over-utilization**

Alert Message: The recommended daily dose of clopidogrel is 75 mg. Exceeding the recommended dose may put the patient at increased risk of bleeding and other adverse effects.

Conflict Code: HD – High Dose

Drug/Diseases:

Util A

Util B

Util C

Clopidogrel

Maximum Dose: 75 mg/day

References:

Facts & Comparisons, 2008 Updates.

Plavix Prescribing Information, Oct. 2007, Bristol-Myers Squibb Company.

**11. Tussionex / Warning**

Alert Message: The FDA has received reports of death and life-threatening side effects in patients who have received Tussionex (hydrocodone/chlorpheniramine). The reports indicate that healthcare professionals have prescribed Tussionex for patients younger than the approved aged group of 6 years old and older, more frequently than the labeled dosing interval of every 12 hours, and that patients have administered the incorrect dose due to misinterpretation of the dosing directions and use of inappropriate devices to measure the suspension. Carefully counsel patients concerning the use of this medication.

Conflict Code: TA – Therapeutic Appropriateness (Public Health Advisory)

Drug/Diseases:

Util A

Util B

Util C

Tussionex

References:

MedWatch - The FDA Safety Information and Adverse Event Reporting Program, 2008.

Tussionex Prescribing Information, Jan. 2008, UCB, Inc.

FDA Public Health Advisory: Important Information for the Safe Use of Tussionex Pennkinetic Extended-Release Suspension. March 2008.

**Recommendations**

**Approved      Rejected**

**12. Tussionex / Contraindication**

Alert Message: The use of Tussionex suspension (hydrocodone/chlorpheniramine) is contraindicated in children less than 6 years of age due to the risk of fatal respiratory depression.

Conflict Code: TA – Therapeutic Appropriateness

Drug/Diseases:

Util A

Util B

Util C

Tussionex

Age Range: 0 – 5 years of age

References:

MedWatch - The FDA Safety Information and Adverse Event Reporting Program, 2008.

Tussionex Prescribing Information, Jan. 2008, UCB, Inc.

**13. Erythropoiesis Stimulating Agents / Black Box Warning**

Alert Message: In clinical trials erythropoiesis stimulating agents (ESAs) have been shown to shorten the overall survival and/or time to tumor progression in patients with breast cancer, non-small cell lung, head and neck, lymphoid and cervical cancers when dosed to target a hemoglobin of  $\geq 12\text{g/dL}$ . To minimize this risk, use the lowest dose needed to avoid red blood cell transfusions.

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

Drug/Diseases:

Util A

Util B

Util C

Aranesp

Breast Cancer

Epogen/Procrit

Non-small Cell Lung Cancer

Head and Neck Cancer

Lymphoid Cancers

Cervical Cancer

References:

MedWatch - The FDA Safety Information and Adverse Event Reporting Program, 2008.

Procrit Prescribing Information, March 2008. Ortho Biotech Products, L.P.

Epogen Prescribing Information, March 2008, Amgen.

Aranesp Prescribing Information, March 2008, Amgen.

**Criteria Recommendations**

**Accepted      Rejected**

**14. Atypical Antipsychotics / Metabolic Syndrome**

Alert Message: The use of second-generation antipsychotics (SGAs) has been associated with the development of serious health risks (e.g., cardiovascular disease, diabetes, dramatic weight gain, and atherogenic lipid profiles). All patients should receive baseline screenings for risk factors associated with metabolic syndrome before receiving a SGA and regular monitoring of metabolic parameters throughout therapy. If metabolic risk factors cannot be controlled consider switching, if clinically possible, to a SGA with a more favorable metabolic risk profile.

Conflict Code: MC – Drug (Actual) Disease Precaution

Drugs/Disease

Util A

Util B

Util C (Negating)

Clozapine

Olanzapine

Risperidone

Quetiapine

Age Range: > 18 years of age

References:

Lieberman JA, Stroup S., McEvoy JP, et al, Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia (CATIE Trial). N Engl J Med 2005;353(12):1209-1223.

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Executive Summary. National Institutes of Health. NIH Publications No. 02-5215, Sept. 2002.

Nasrallah HA, The Roles of Efficacy, Safety and Tolerability in Antipsychotic Effectiveness: Practical Implications of the CATIE Schizophrenia Trial. J Clin Psychiatry 2007;68[suppl 1]:5-11.

Weiden PJ, Preskorn SH, Fahnestock PA, et al. Translating the Psychopharmacology of Antipsychotics to Individualized Treatment for Severe Mental Illness: A Roadmap, J Clin Psychiatry 2007;68[Suppl 7]:3-48.

**15. Atypical Antipsychotics / Pediatric Patients**

Alert Message: The effects of prolonged use of atypical antipsychotics in pediatric patients are unknown. Preliminary evidence suggests that pediatric patients experience more prevalent and severe adverse effects than those reported in adults (e.g., weight gain, extrapyramidal side effects, and insulin resistance). If therapy with these agents is clinically necessary use the lowest effective dose and observe patients closely for adverse events. If adverse effects cannot be controlled consider switching, if clinically possible, to a SGA with a more favorable adverse effect profile.

Conflict Code: TA – Therapeutic Appropriateness

Drugs/Diseases:

Util A

Util B

Util C

Clozapine

Risperidone

Olanzapine

Quetiapine

Ziprasidone

Aripiprazole

Paliperidone

Age Range: < 19 years of age

References:

Kumra S, Oberstar JV, Sikich L et al., Efficacy and Tolerability of Second Generation Antipsychotics in Children and Adolescents with Schizophrenia. Schizophrenia Bulletin. 2008;34(1):61-70.

Cook S, Weitzman M, Auinger P, et al. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988-1994. Arch Pediatr Adolesc Med 2003, 157:821-827.

Correll CU, Carlson HE, Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents, J Am Acad Child Adolesc Psychiatry (2006)45:771-791.

Nasrallah HA, The Roles of Efficacy, Safety and Tolerability in Antipsychotic Effectiveness: Practical Implications of the CATIE Schizophrenia Trial. J Clin Psychiatry 2007;68[suppl 1]:5-11.

Weiden PJ, Preskorn SH, Fahnestock PA, et al. Translating the Psychopharmacology of Antipsychotics to Individualized Treatment for Severe Mental Illness: A Roadmap, J Clin Psychiatry 2007;68[Suppl 7]:3-48.

Cada DJ, Baker DE, Levien T, Formulary Drug Reviews: Paliperidone, Hospital Pharmacy, 2007;42(7):637-647.



[TODAY]

[adrs1]  
[adrs2]  
[adrs3]  
[adrs4]

DEAR [tadrs1]:

In compliance with the OBRA '90 federal legislation, state Medicaid agencies are mandated to institute Retrospective Drug Utilization Review Programs (RDUR). The program's goal is to ensure that Medicaid patients receive optimal drug therapy at the lowest reasonable cost. One way to achieve this goal is to identify potential drug therapy problems that may place patients at risk, particularly if multiple providers are identified. This RDUR program is informational in nature and allows you to incorporate the information provided into your continuing assessment of the patient's drug therapy requirements.

During a recent review of the enclosed drug history profile, it was noted that your patient, **[t1d0-recipe-fst-nm] [t1d0-recipe-lst-nm]**, is receiving **[drug\_a\_name]**. *The use of second-generation antipsychotics (SGAs) has been associated with the development of serious health risks (e.g., cardiovascular disease, diabetes, dramatic weight gain, and atherogenic lipid profiles). All patients should receive baseline screenings for risk factors associated with metabolic syndrome before receiving a SGA and regular monitoring of metabolic parameters throughout therapy. If metabolic risk factors cannot be controlled consider switching, if clinically possible, to a SGA with a more favorable metabolic risk profile.* In presenting this information to you, we recognize that the management of each patient's drug therapy depends upon an assessment of the patient's entire clinical situation about which we are not fully aware.

The success of the DUR program is enhanced by effective two-way exchange of information. Therefore, at your convenience, we would appreciate learning of your assessment of this information and of any action taken in response to this notice. Although your participation in this program is voluntary, we find your feedback helpful in adjusting our program to address clinically important problems. Please use the enclosed response to note your comments and return it in the enclosed envelope or fax it to the number below.

**At the bottom of this letter are the specific prescriptions attributed to you by the dispensing pharmacy. In addition, if multiple prescribers are involved in the therapy identified above, each will receive this information.** Thank you for your professional consideration.

RX #(s): [rx\_no\_a]

Sincerely,



W. Murray Yarbrough, M.D.  
Medical Director

Case#: [case\_no]  
Enclosures

## PRESCRIBER RESPONSE

**All information used to generate the enclosed letter, including Prescriber identification, was obtained from Pharmacy Claims Data. If there appears to be an error in the information provided, please note the discrepancy. Thank you for your cooperation.**

1. This patient is under my care:

\_\_\_\_\_ I have reviewed the information and will continue without change.  
\_\_\_\_\_ however, I did not prescribe the following medication(s)\_\_\_\_\_.  
\_\_\_\_\_ and has an appointment to discuss drug therapy.  
\_\_\_\_\_ however, has not seen me recently.  
\_\_\_\_\_ however, I was not aware of other prescribers.  
\_\_\_\_\_ I have reviewed the information and modified drug therapy.  
\_\_\_\_\_ I have not modified drug therapy because benefits outweigh the risks.  
\_\_\_\_\_ I have tried to modify therapy, however the patient refuses to change.  
\_\_\_\_\_ I have tried to modify therapy, however symptoms reoccurred.

2. This patient is not under my care:

\_\_\_\_\_ however, I did prescribe medication while covering for other MD or in the ER.  
\_\_\_\_\_ but has previously been a patient of mine.  
\_\_\_\_\_ because the patient recently expired.  
\_\_\_\_\_ and has never been under my care.

3. I have reviewed the enclosed information and found it:

\_\_\_\_\_ very useful \_\_\_\_\_ useful \_\_\_\_\_ neutral \_\_\_\_\_ somewhat useful \_\_\_\_\_ not useful.

4. Please check here if you wish to receive reference information on the identified problem\_\_\_\_\_.(Please provide a fax number if available \_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_.)

Comments: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

[adrs1] Case# [case\_no]

Letter Type [letter\_type]

[alert\_msg]

[criteria]

## **METABOLIC SYNDROME AND SECOND GENERATION ANTIPSYCHOTICS**

Metabolic syndrome is the simultaneous occurrence of at least three of five clinical and laboratory risk factors: central obesity (defined by waist circumference), hypertension, hyperglycemia, hypertriglyceridemia, and reduced levels of high-density lipoprotein cholesterol.<sup>1</sup>

<b>Risk Factors for Metabolic Syndrome<sup>1</sup></b>	<b>Clinical Identification<sup>1</sup></b>
Abdominal Obesity	Waist circumference: Males > 40 in Females > 35 in
Atherogenic Dyslipidemia	Low HDL-C Males <40 mg /dL Females < 50 mg/ dL
Hypertriglyceridemia	≥ 150 mg/dL
Hypertension	Blood Pressure (BP) ≥ 130 /80 mmHg
Impaired Glucose Tolerance/Type II Diabetes/ Insulin Resistance/Hyperinsulinemia	Fasting Glucose (FBD) ≥ 110 mg/dL

## **MANAGEMENT OF PATIENTS WITH METABOLIC SYNDROME ON SGA THERAPY<sup>2</sup>**

1. Prescreen all patients for presence of risk factors for metabolic syndrome
2. Select SGA based on risks vs. benefits
3. Monitor patients throughout therapy for adverse effects of SGA therapy
4. Educate and monitor for healthy lifestyle (e.g., diet and exercise)
5. Treat underlying metabolic disorder(s) with lifestyle changes and medication if necessary
6. If adverse effects or metabolic disorders worsen consider switching, if clinically possible, to an alternative SGA with a lower risk profile

## **EFFECTS OF SGAs ON METABOLIC PARAMETERS<sup>2, 3, 4, 5</sup>**

<b>Second Generation Antipsychotics</b>	<b>Weight Gain</b>	<b>Dyslipidemia</b>	<b>Insulin resistance / Glucose Abnormalities</b>	<b>Hypertension</b>
Clozapine	+++	+++	+++	+++
Olanzapine	+++	+++	+++	+
Quetiapine	++	+	+	-
Risperidone	++	+	+	++
Ziprasidone	+	-/+	-/+	++
Aripiprazole	+	-/+	-/+	+
Paliperidone	+	-	-	-

+++ = Highest incidence, ++ = Moderate incidence, + = Low incidence, - = No incidence

1. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Executive Summary. National Institutes of Health. NIH Publications No. 02-5215, Sept. 2002.

2. Nasrallah HA, The Roles of Efficacy, Safety and Tolerability in Antipsychotic Effectiveness: Practical Implications of the CATIE Schizophrenia Trial. J Clin Psychiatry 2007;68[suppl 1]:5-11.

3. Lieberman JA, Stroup S., McEvoy JP, et al, Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia (CATIR Trial). N Engl J Med 2005;353(12):1209-1223.

4. Newcomer JW, Metabolic Considerations in the use of Antipsychotic Medications: A Review of Recent Evidence, J Clin Psychiatry 2007;68[Suppl 1]:20-27.
5. Casey DE, Dyslipidemia and Atypical Antipsychotic Drugs, J Clin Psychiatry;65[Suppl 18]:27-35.

[TODAY]

[adrs1]  
[adrs2]  
[adrs3]  
[adrs4]

DEAR [tadr1]:

In compliance with the OBRA '90 federal legislation, state Medicaid agencies are mandated to institute Retrospective Drug Utilization Review Programs (RDUR). The program's goal is to ensure that Medicaid patients receive optimal drug therapy at the lowest reasonable cost. One way to achieve this goal is to identify potential drug therapy problems that may place patients at risk, particularly if multiple providers are identified. This RDUR program is informational in nature and allows you to incorporate the information provided into your continuing assessment of the patient's drug therapy requirements.

During a recent review of the enclosed drug history profile, it was noted that your patient, **[t1d0-recip-fst-nm] [t1d0-recip-lst-nm]**, is receiving **[drug\_a\_name]**. *The effects of prolonged use of atypical antipsychotics in pediatric and adolescent patients are unknown. Preliminary evidence suggests that these patients experience more prevalent and severe adverse effects than those reported in adults (e.g., weight gain, extrapyramidal side effects, and insulin resistance). If therapy with these agents is clinically necessary use the lowest effective dose and observe patients closely for adverse events. If adverse effects cannot be controlled consider switching, if clinically possible, to a SGA with a more favorable adverse effect profile.* In presenting this information to you, we recognize that the management of each patient's drug therapy depends upon an assessment of the patient's entire clinical situation about which we are not fully aware.

The success of the DUR program is enhanced by effective two-way exchange of information. Therefore, at your convenience, we would appreciate learning of your assessment of this information and of any action taken in response to this notice. Although your participation in this program is voluntary, we find your feedback helpful in adjusting our program to address clinically important problems. Please use the enclosed response to note your comments and return it in the enclosed envelope or fax it to the number below.

**At the bottom of this letter are the specific prescriptions attributed to you by the dispensing pharmacy. In addition, if multiple prescribers are involved in the therapy identified above, each will receive this information.** Thank you for your professional consideration.

RX #(s): [rx\_no\_a]

Sincerely,



W. Murray Yarbrough, M.D.  
Medical Director

Case#: [case\_no]  
Enclosures

## PRESCRIBER RESPONSE

**All information used to generate the enclosed letter, including Prescriber identification, was obtained from Pharmacy Claims Data. If there appears to be an error in the information provided, please note the discrepancy. Thank you for your cooperation.**

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3. I have reviewed the enclosed information and found it:

\_\_\_\_\_ very useful \_\_\_\_\_ useful \_\_\_\_\_ neutral \_\_\_\_\_ somewhat useful \_\_\_\_\_ not useful.

4. Please check here if you wish to receive reference information on the identified problem\_\_\_\_\_.(Please provide a fax number if available \_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_.)

Comments: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

[adrs1] Case# [case\_no]

Letter Type [letter\_type]

[alert\_msg]

[criteria]

## **SECOND GENERATION ANTIPSYCHOTIC (SGA) USE IN PEDIATRIC AND ADOLESCENT PATIENTS**

### **MANAGEMENT OF PEDIATRIC AND ADOLESCENT PATIENTS ON SGA THERAPY<sup>2,3</sup>**

1. Prescreen all patients for presence of risk factors for metabolic syndrome
2. Select SGA based on risks vs. benefits
3. Educate and monitor for healthy lifestyle (e.g., diet and exercise)
4. Monitor patients throughout therapy for adverse effects of SGA therapy
5. Treat underlying metabolic disorder(s) with lifestyle changes and medication if necessary
6. If adverse effects or metabolic disorders worsen consider switching, if clinically possible, to an alternative SGA with a lower risk profile

<b>Risk Factors for Metabolic Syndrome<sup>1</sup></b>	<b>Clinical Identification<sup>1</sup></b>
Abdominal Obesity	Waist circumference: ≥ 90 <sup>th</sup> percentile or BMI 95 <sup>th</sup> percentile (i.e. overweight)
Atherogenic Dyslipidemia	Low HDL-C <40 mg /dL in males and females
Hypertriglyceridemia	≥ 110 mg/dL
Hypertension	Blood Pressure ≥ 90 <sup>th</sup> Percentile for sex and age
Impaired Glucose Tolerance/Type II Diabetes/ Insulin Resistance/Hyperinsulinemia	Fasting glucose (FBG) ≥ 110 mg/dL

**Metabolic syndrome** is the simultaneous occurrence of at least three of five clinical and laboratory risk factors: central obesity (defined by waist circumference), hypertension, hyperglycemia, hypertriglyceridemia, and reduced levels of high-density lipoprotein cholesterol.<sup>6</sup>

### **EFFECTS OF SGAs OF METABOLIC PARAMETERS<sup>4,5</sup>**

<b>Second Generation Antipsychotics</b>	<b>Weight Gain</b>	<b>Dyslipidemia</b>	<b>Insulin resistance / Glucose Abnormalities</b>	<b>Hyperprolactinemia</b>	<b>EPS</b>
Clozapine	+++	+++	+++	+	-
Olanzapine	+++	+++	+++	++	+
Quetiapine	++	++	++	+	-
Risperidone	++	++	+	+++	++
Ziprasidone	+	+	+	++	++
Aripiprazole	+	+	+	-	+
Paliperidone	+	-	-	+++	+

+++ = High Incidence, ++ = Moderate incidence, + = Low incidence, - = No effect

1. Cook S, Weitzman M, Auinger P, et al. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988-1994. Arch Pediatr Adolesc Med 2003, 157:821-827.

2 Correll CU, Carlson HE, Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents, J Am Acad Child Adolesc Psychiatry (2006)45:771-791.

3. Nasrallah HA, The Roles of Efficacy, Safety and Tolerability in Antipsychotic Effectiveness: Practical Implications of the CATIE Schizophrenia Trial. J Clin Psychiatry 2007;68[suppl 1]:5-11.

4. Rosack J, Better Monitoring Urged for Youth Taking Newer Antipsychotics, Psychiatr News Aug 4, 2006, Vo. 41, No. 15, 1.

5. Weiden PJ, Preskorn SH, Fahnestock PA, et al. Translating the Psychopharmacology of Antipsychotics to Individualized Treatment for Severe Mental Illness: A Roadmap, J Clin Psychiatry 2007;68[Suppl 7]:3-48.

6. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Executive Summary. National Institutes of Health. NIH Publications No. 02-5215, Sept. 2002.