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

August 24, 2006

Welcome — **Randy Calvert, RPh**

Old Business

- **Approval of Meeting Minutes**
- **CNS Update** — **Frankie Rutledge**
- **Updates** — **Dennis Smith, RPh**
  - **Cost Management Analysis**
  - **DUR Activity Report**

Election of Officers — **Randy Calvert, RPh**

Pharmacy Program Update — **Judith Clark, RPh**

New Business — **Dennis Smith, RPh**

- **Restasis – Concurrent Use with Anticholinergic Agents**
- **Triptans – Concurrent Use with SSRIs and SNRIs**
- **Exubera – Inhaled Insulin**
- **Other Criteria Recommendations**
- **Modafinil – New Information**
- **Hospitalizations among Children – Trends**
- **Boxed Warning Update**

Next Meeting Information — **Randy Calvert, RPh**

Minutes of the May 18, 2006
Drug Utilization Review (DUR) Board Meeting

Members Attending: John Mitchell, M.D., Chair; Billy Brown, PharmD; Frank Marascalco, RPh; Lee Montgomery, M.D.; Rudy Runnels, M.D.; Andrea Phillips, M.D.; Wallace Strickland.

Members Absent: Montez Carter, RPh; Troy Griffin; Harold Blakely, RPh; Randy Calvert, RPh.

Also Present: DOM Staff: Judith Clark, RPh; Terri Kirby, RPh; Susan Brown, RPh.
HID Staff: Dennis Smith, RPh; Sam Warman, RPh; Kathleen Burns, R.N.; Gina Pardue, R.N.

Dr. John Mitchell called the meeting to order at 2:00 p.m.

Approval of the minutes for the November 17, 2005 and February 23, 2006 meetings:
Dr. Rudy Runnels made a motion to accept the minutes for both meetings as submitted. Mr. Frank Marascalco seconded the motion. All voted in favor of approval.

CNS Update:
Due to the absence of Ms. Frankie Rutledge, the CNS update was tabled.

HID Updates:

Cost Management Analysis:
Mr. Dennis Smith presented a brief cost management analysis report for the months of February 2006 and March 2006, detailing the top 25 drugs based on number of claims and total cost of claims. During February 2006, Amoxicillin was the top drug with 9,553 claims, followed by Hydrocodone w/Acetaminophen (8,401) and Zyrtec (8,301). The top drug for cost in February 2006 was Synagis with 1,297 claims totaling $1,612,217, with an average $1,243 per claim. The drug with the highest cost per claim was Feiba HV Immuno ($43,109). For March 2006, Zyrtec was the top drug based on number of claims with 9,797, followed by Hydrocodone w/Acetaminophen (8,886) and Amoxicillin (8,117). The top drug for cost in March 2006 was again Synagis with 1,156 claims totaling $1,443,029, with an average of $1,248 per claim. Three hemostatic drugs had the highest cost per claim in March 2006: Feiba HV Immuno ($41,417), Advate ($31,756), and Recombinate ($28,134).

DUR Activity Report:
Mr. Smith reported on the RDUR activities for the periods of October-December 2005, November 2005-January 2006, and April 2006-present. The data from the first two periods are currently being tabulated with a report to be available at the next DUR Board meeting. For the current activity, Pediatric Use of Potent Topical Corticosteroids, Mr. Smith reported there were 159 unduplicated cases in April 2006, based on claims data. Dr. Mitchell suggested that educational materials be distributed to providers regarding the use of these potent and super potent drugs. Mr. Smith stated that the HID Academic Detailers would be

provided information to present to the physicians. Dr. Lee Montgomery suggested that the number of refills versus a one time fill would be useful information to obtain. Dr. Mitchell suggested that the total number of claims for this classification be provided with a breakdown in percentages of the potent and super potent agents. The Board recommended that HID continue to monitor and report findings at subsequent board meetings.

New Business:

Statins and Diabetes:
Mr. Smith reported that a few years ago, the DUR Board approved criteria and an intervention to encourage appropriate use of statins in patients with diabetes and hypercholesterolemia. The goals of this criterion were to reduce hospitalizations with subsequent improvement in the quality of life and reduced work days. This review assessed the same set of parameters based on data from 2005. Overall the number of beneficiaries with both diagnoses and on statin therapy increased 46% since the implementation of this intervention in 2003. Additionally, the number of hospitalizations per patient decreased from 0.68 in 2002 to 0.40 in 2005.

Recommendations:
Continue to monitor results.

Opioid Utilization – Impact of Hurricane Katrina:
Mr. Smith reported on the Opioid Utilization Review comparing patterns of narcotic medication three months before and three months after Hurricane Katrina, specifically comparing utilization rates from 6/1/05-8/29/05 to those from 8/30/05-11/30/05. Included were the number of prescriptions and the quantity dispensed by generic name, as well as a comparison of county utilization. Based on the data examined for this analysis, there were no significant changes in prescribing or dispensing trends between the three month periods prior to and following the disaster. Ms. Judith Clark reported that this study was driven by requests from the Center for Medicaid and Medicare Services (CMS) and the Office of the Inspector General (OIG). A full report will be forwarded to these federal agencies by DOM.

Recommendation:
No further activity recommended at this time.

Second Quarter Criteria Recommendations:
Mr. Smith presented the following retrospective DUR criteria recommendations:

- Stimulants and Sedatives/Therapeutic Appropriateness – Sleep disturbances are common in patients with ADHD. Stimulant therapy may exacerbate or directly cause sleep disturbances. If the disturbances persist during stimulant therapy, adjusting the dosing schedule of the stimulant may reduce/alleviate the need for the sedative. The last daily dose may be given earlier in the day, or a trial of low-dose stimulant in the evening may be useful.
- Ranolazine/High Dose – Ranexa (ranolazine) may be over-utilized. The maximum recommended daily dosage is 2000 mg (1000 mg b.i.d.). Ranolazine has been shown

to prolong the QTc interval in a dose-related manner. Baseline and follow-up ECGs should be obtained to evaluate the effects on QT interval.

- Ranolazine & QT Prolongation/Drug-Drug Marker and/or Diagnosis - Ranexa may have an additive effect on the QT interval and is contraindicated in patients with known QT prolongation, known history of ventricular tachycardia, and in patients receiving drugs that prolong the QTc interval (e.g. Class Ia and III antiarrhythmics and antipsychotics).
- Ranolazine & Hepatic Impairment/Drug Disease Precaution – Ranexa is contraindicated in patients with mild, moderate or severe liver disease, since it is extensively metabolized by the liver as well as intestine. Hepatic dysfunction may increase the QTc-prolonging effect approximately 3-fold.
- Ranolazine & Potent CYP3A4/Drug-Drug Interaction – Ranexa is contraindicated in patients taking potent or moderately potent CYP3A4 inhibitors, such as diltiazem, azole antifungals, verapamil, macrolides, and protease inhibitors. Ranexa is primarily metabolized by the CYP3A4 pathway and inhibition will increase plasma levels and QTc prolongation.
- Ranolazine & Amlodipine, Beta Blockers, & Nitrates/Therapeutic Appropriateness – Ranexa should only be used in combination with amlodipine, beta blockers or nitrates
- Ranolazine & Digoxin/Drug-Drug Interaction - Concomitant use of Ranexa and digoxin, a P-glycoprotein (P-gp) substrate, may result in a 1.5-fold increase in the digoxin plasma concentrations. Ranexa is a P-gp inhibitor and the concurrent use of these agents may result in the increased absorption and decreased elimination of digoxin. Dose reduction of digoxin may be necessary.
- Ranolazine & Renal Impairment/Drug-Disease Precaution – The use of Ranexa should be avoided in patients with severe renal impairment. In clinical trials, subjects with severe renal impairment receiving Ranexa 500 mg b.i.d., the mean diastolic blood pressure was increased approximately 10 to 15 mmHG. Patients receiving Ranexa therapy need regular blood pressure monitoring.
- Ranolazine & P-gp Inhibitors/Drug-Drug Interaction – Concomitant use of Ranexa and P-glycoprotein (P-gp) inhibitors may result in elevated ranolazine plasma concentrations. Inhibition of the efflux pump may result in increased absorption of ranolazine.
- Ranolazine & CYP2D6 Substrates/Drug-Drug Interaction – Concomitant use of Ranexa, a CYP2D6 inhibitor, with a CYP2D6 substrate such as tricyclic antidepressants, may result in increased plasma concentration of the CTP2D6 substrate. Dose reduction of the substrate may be necessary
- Ranolazine & Simvastatin/Drug-Drug Interaction – Concomitant use of Ranexa and Zocor (simvastatin) may result in a 2-fold increase in plasma concentrations of simvastatin and its active metabolite. Dose reduction of simvastatin may be necessary.

Dr. Runnels made a motion to accept these criteria recommendations. The motion was seconded by Dr. Montgomery. All voted in favor of the motion.

Boxed Warning Update:
Mr. Smith presented black box warnings issued by the FDA concerning the following:

- **Promethazine HCL (Phenergan)**
  Audience: Pediatricians, emergency service professionals, and patients
  [Posted 4/25/06] FDA notified healthcare professionals and patients that cases of breathing problems, some causing death, have been reported to the FDA when the drug was used in children less than two years old. Parents and caregivers should also be careful and get a doctor's advice about giving promethazine HCL in any form to children age two and older. The labeling on all products, brand name and generic, has been changed to reflect these strengthened warnings.

- **Tequin (gatifloxacin)**
  Audience: Healthcare professionals and patients
  [Posted 2/16/2006] BMS notified FDA and healthcare professionals about proposed changes to the prescribing information for Tequin, including an update of the existing WARNING of hypoglycemia and hyperglycemia, and a CONTRADICTION for use in diabetic patients. The changes also include information identifying other risk factors for developing low blood sugar or high blood sugar, including advanced age, renal insufficiency, and concomitant glucose-altering medications while taking Tequin.
  NOTE: This drug has become unavailable since the printing of the information, making this labeling change unnecessary.

- **Tracleer (bosentan)**
  Audience: Cardiopulmonary healthcare professionals
  [Posted 3/2/2006] Actelion and FDA notified healthcare professionals of changes to the prescribing information based on cases of hepatotoxity reported. The notification underscored the need to continue monthly liver function monitoring for the duration of Tracleer treatment and the need to adhere to the recommended dosage adjustment and monitoring guidelines described in the product labeling

Pharmacy Program Update:
Ms. Clark presented information regarding the number of claims submitted and paid in April 2006 (approx. 350,000) compared to December 2005 (approx. 800,000) due in part to Medicare Part D. A review of claims reveal a 59% generic utilization compared to 40% a year ago. The average cost per prescription is $131 for brands, $24 for generic, and $30 for DAW1. Ms. Clark distributed an updated Preferred Drug List (PDL) which will be effective July 1, 2006. A copy of the PDL will be available on the DOM website. Generic drugs are not listed on the abbreviated list, but most are preferred and do not require prior authorization.

Next Meeting Information:
Ms. Clark stated that the next DUR Board meeting is scheduled for August 24, 2006

As there was no further business or discussions, Dr. Mitchell adjourned the meeting at 3:30 p.m.

Respectfully submitted:
Health Information Designs, Inc.

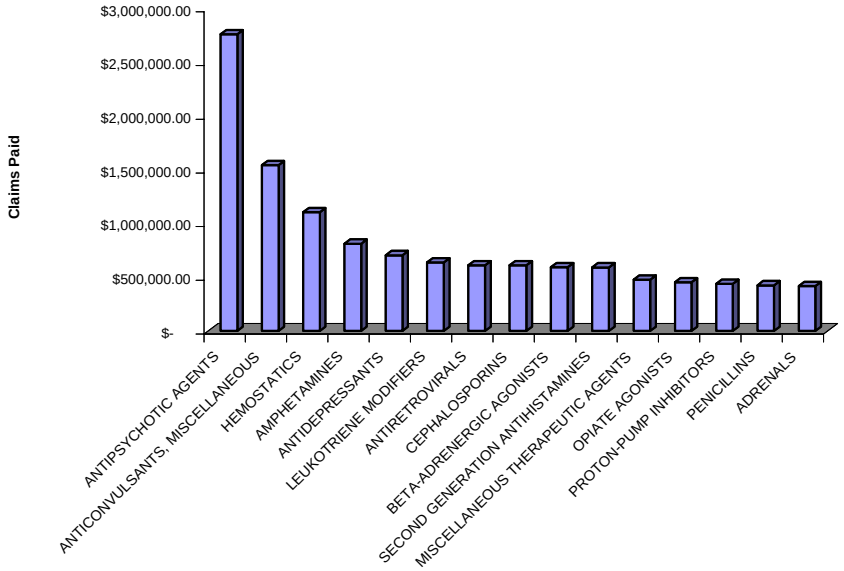
MISSISSIPPI MEDICAID
Cost Management Analysis

TOP 15 THERAPEUTIC CLASSES BY TOTAL COST OF CLAIMS FROM 05/01/06-05/31/06

AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
ANTIPSYCHOTIC AGENTS	10,183	$ 2,762,876.10	$ 271.32	2.89%
ANTICONVULSANTS, MISCELLANEOUS	9,987	$ 1,543,145.51	$ 154.52	2.83%
HEMOSTATICS	42	$ 1,105,372.13	$26,318.38	0.01%
AMPHETAMINES	7,886	$ 811,789.23	$ 102.94	2.24%
ANTIDEPRESSANTS	13,200	$ 703,908.22	$ 53.33	3.74%
LEUKOTRIENE MODIFIERS	6,578	$ 636,802.10	$ 96.81	1.87%
ANTIRETROVIRALS	1,035	$ 610,903.79	$ 590.25	0.29%
CEPHALOSPORINS	11,272	$ 610,377.80	$ 54.15	3.20%
BETA-ADRENERGIC AGONISTS	10,824	$ 591,950.84	$ 54.69	3.07%
SECOND GENERATION ANTIHISTAMINES	12,441	$ 591,369.91	$ 47.53	3.53%
MISCELLANEOUS THERAPEUTIC AGENTS	2,071	$ 475,360.21	$ 229.53	0.59%
OPIATE AGONISTS	23,844	$ 452,574.30	$ 18.98	6.76%
PROTON-PUMP INHIBITORS	3,171	$ 436,897.47	$ 137.78	0.90%
PENICILLINS	17,380	$ 424,249.51	$ 24.41	4.93%
ADRENALS	7,513	$ 416,551.49	$ 55.44	2.13%
TOTAL TOP 15	137,427	$ 12,174,128.61	$ 88.59	38.97%

Total Rx Claims	352,691
From 05/01/06-05/31/06	

Top 15 Therapeutic Classes
Based on Total Cost of Claims



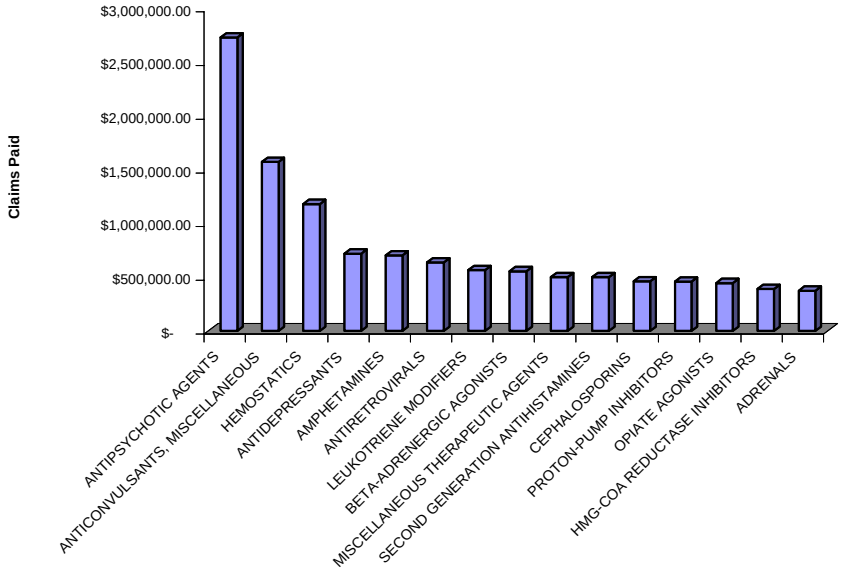
MISSISSIPPI MEDICAID
Cost Management Analysis

TOP 15 THERAPEUTIC CLASSES BY TOTAL COST OF CLAIMS FROM 06/01/06-06/30/06

AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
ANTIPSYCHOTIC AGENTS	10,079	$ 2,732,759.06	$ 271.13	3.10%
ANTICONVULSANTS, MISCELLANEOUS	10,065	$ 1,572,853.88	$ 156.27	3.09%
HEMOSTATICS	48	$ 1,181,167.91	$24,607.66	0.01%
ANTIDEPRESSANTS	13,367	$ 719,471.50	$ 53.82	4.10%
AMPHETAMINES	6,592	$ 702,183.61	$ 106.52	2.02%
ANTIRETROVIRALS	1,080	$ 637,625.49	$ 590.39	0.33%
LEUKOTRIENE MODIFIERS	5,845	$ 565,850.76	$ 96.81	1.79%
BETA-ADRENERGIC AGONISTS	9,468	$ 554,986.99	$ 58.62	2.91%
MISCELLANEOUS THERAPEUTIC AGENTS	2,065	$ 500,769.60	$ 242.50	0.63%
SECOND GENERATION ANTIHISTAMINES	10,353	$ 500,534.05	$ 48.35	3.18%
CEPHALOSPORINS	9,095	$ 461,676.91	$ 50.76	2.79%
PROTON-PUMP INHIBITORS	3,335	$ 457,973.35	$ 137.32	1.02%
OPIATE AGONISTS	23,062	$ 444,486.53	$ 19.27	7.08%
HMG-COA REDUCTASE INHIBITORS	4,171	$ 390,523.39	$ 93.63	1.28%
ADRENALS	6,047	$ 373,014.58	$ 61.69	1.86%
TOTAL TOP 15	114,672	$ 11,795,877.61	$ 102.87	35.21%

Total Rx Claims	325,636
From 06/01/06-06/30/06	

Top 15 Therapeutic Classes
Based on Total Cost of Claims



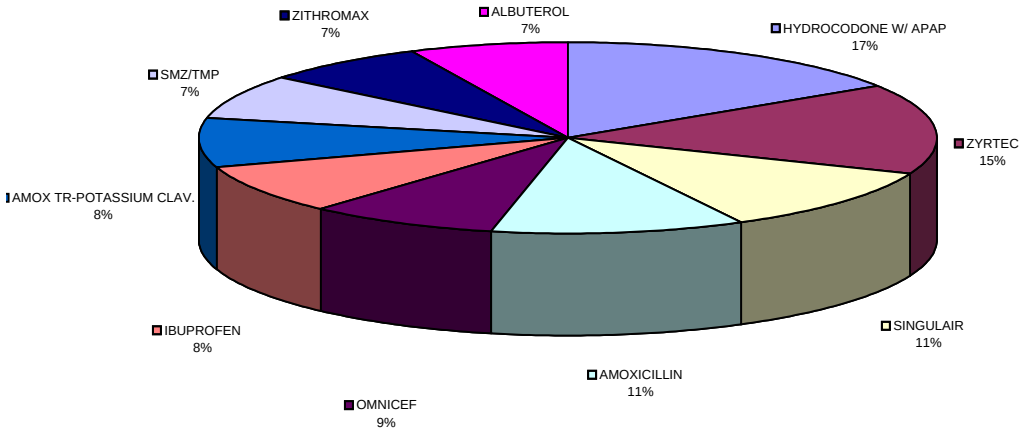
MISSISSIPPI MEDICAID
Cost Management Analysis

TOP 25 DRUGS BASED ON NUMBER OF CLAIMS FROM 05/01/06-05/31/06

Drug	AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
HYDROCODONE W/ APAP	OPIATE AGONISTS	9,237	$ 87,507.66	$ 9.47	2.62%
ZYRTEC	SECOND GENERATION ANTIHISTAMINES	8,853	$ 458,759.05	$ 51.82	2.51%
SINGULAIR	LEUKOTRIENE MODIFIERS	6,565	$ 635,811.75	$ 96.85	1.86%
AMOXICILLIN	PENICILLINS	6,365	$ 54,619.21	$ 8.58	1.80%
OMNICEF	CEPHALOSPORINS	4,949	$ 421,377.09	$ 85.14	1.40%
IBUPROFEN	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS	4,850	$ 40,085.80	$ 8.27	1.38%
AMOX TR-POTASSIUM CLAV.	PENICILLINS	4,843	$ 263,055.65	$ 54.32	1.37%
SMZ/TMP	SULFONAMIDES (SYSTEMIC)	4,337	$ 46,335.25	$ 10.68	1.23%
ZITHROMAX	MACROLIDES	4,137	$ 172,814.24	$ 41.77	1.17%
ALBUTEROL	BETA-ADRENERGIC AGONISTS	4,067	$ 49,819.73	$ 12.25	1.15%
ALPRAZOLAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	4,065	$ 33,271.34	$ 8.18	1.15%
CEPHALEXIN	CEPHALOSPORINS	4,004	$ 65,253.23	$ 16.30	1.14%
ALBUTEROL SULFATE	BETA-ADRENERGIC AGONISTS	3,641	$ 93,274.56	$ 25.62	1.03%
ACETAMINOPHEN W/CODEINE	OPIATE AGONISTS	3,416	$ 29,110.31	$ 8.52	0.97%
PROMETHAZINE HCL	PHENOTHIAZINE DERIVATIVES	3,164	$ 39,720.45	$ 12.55	0.90%
AMOXICILLIN TRIHYDRATE	PENICILLINS	3,150	$ 42,128.49	$ 13.37	0.89%
AZITHROMYCIN	MACROLIDES	3,055	$ 119,339.96	$ 39.06	0.87%
CLONAZEPAM	BENZODIAZEPINES (ANTICONVULSANTS)	2,987	$ 56,951.22	$ 19.07	0.85%
PREVACID	PROTON-PUMP INHIBITORS	2,819	$ 388,333.00	$ 137.76	0.80%
LORAZEPAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	2,699	$ 73,246.29	$ 27.14	0.77%
RISPERDAL	ANTIPSYCHOTIC AGENTS	2,648	$ 693,106.29	$ 261.75	0.75%
ADDERALL XR	AMPHETAMINES	2,642	$ 313,621.06	$ 118.71	0.75%
FERROUS SULFATE	IRON PREPARATIONS	2,566	$ 9,752.51	$ 3.80	0.73%
CONCERTA	AMPHETAMINES	2,540	$ 276,125.57	$ 108.71	0.72%
SEROQUEL	ANTIPSYCHOTIC AGENTS	2,370	$ 650,726.10	$ 274.57	0.67%
TOTAL TOP 25		103,969	$ 5,114,145.81	$ 49.19	29.48%

Total Rx Claims From 05/01/06-05/31/06	352,691

Top 10 Drugs
Based on Number of Claims



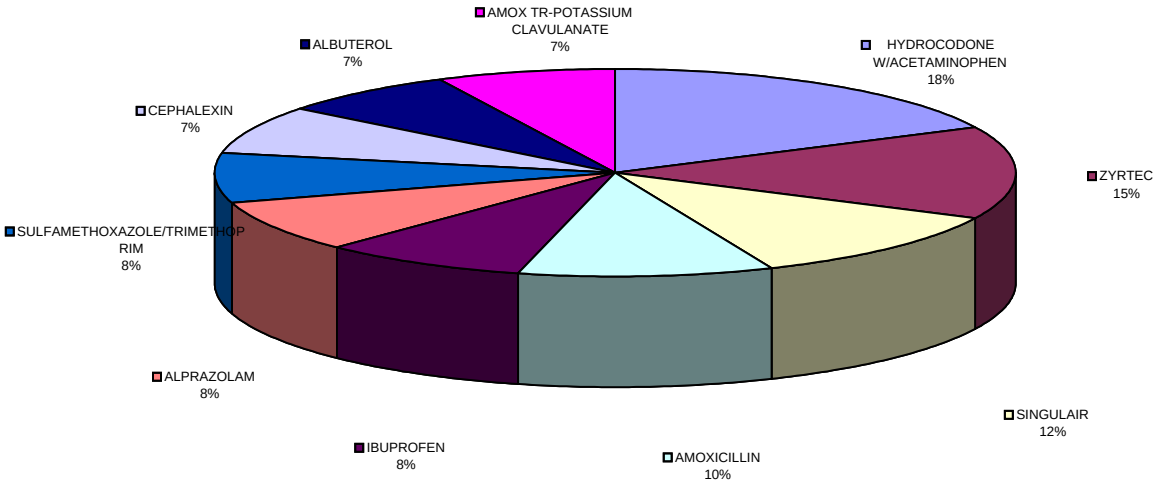
MISSISSIPPI MEDICAID
Cost Management Analysis

TOP 25 DRUGS BASED ON NUMBER OF CLAIMS FROM 06/01/06-06/30/06

Drug	AHFS Therapeutic Class	Rx	Paid	Paid/Rx
HYDROCODONE W/ACETAMINOPHEN	OPIATE AGONISTS	8,907	$ 86,503.04	$ 9.71
ZYRTEC	SECOND GENERATION ANTIHISTAMINES	7,318	$ 383,232.13	$ 52.37
SINGULAIR	LEUKOTRIENE MODIFIERS	5,835	$ 564,959.56	$ 96.82
AMOXICILLIN	PENICILLINS	5,158	$ 43,438.19	$ 8.42
IBUPROFEN	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS	4,132	$ 34,069.73	$ 8.25
ALPRAZOLAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	4,054	$ 33,236.35	$ 8.20
SULFAMETHOXAZOLE/TRIMETHOPRIM	SULFONAMIDES (SYSTEMIC)	4,021	$ 43,586.47	$ 10.84
CEPHALEXIN	CEPHALOSPORINS	3,692	$ 59,719.79	$ 16.18
ALBUTEROL	BETA-ADRENERGIC AGONISTS	3,678	$ 44,883.76	$ 12.20
AMOX TR-POTASSIUM CLAVULANATE	PENICILLINS	3,669	$ 200,344.56	$ 54.60
OMNICEF	CEPHALOSPORINS	3,663	$ 307,318.43	$ 83.90
ACETAMINOPHEN W/CODEINE	OPIATE AGONISTS	3,349	$ 28,708.79	$ 8.57
CLONAZEPAM	BENZODIAZEPINES (ANTICONVULSANTS)	3,032	$ 57,656.46	$ 19.02
PREVACID	PROTON-PUMP INHIBITORS	2,988	$ 413,038.90	$ 138.23
ZITHROMAX	MACROLIDES	2,946	$ 121,596.52	$ 41.28
ALBUTEROL SULFATE	BETA-ADRENERGIC AGONISTS	2,821	$ 75,975.80	$ 26.93
PROMETHAZINE HCL	PHENOTHIAZINE DERIVATIVES	2,686	$ 34,081.62	$ 12.69
LORAZEPAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	2,635	$ 70,607.51	$ 26.80
FERROUS SULFATE	IRON PREPARATIONS	2,628	$ 10,170.39	$ 3.87
RISPERDAL	ANTIPSYCHOTIC AGENTS	2,517	$ 652,032.38	$ 259.05
MUPIROCIN	ANTIBACTERIALS (SKIN & MUCOUS MEMBRANE)	2,429	$ 91,333.81	$ 37.60
SEROQUEL	ANTIPSYCHOTIC AGENTS	2,414	$ 670,309.50	$ 277.68
AMOXICILLIN TRIHYDRATE	PENICILLINS	2,374	$ 32,261.84	$ 13.59
FUROSEMIDE	LOOP DIURETICS	2,304	$ 12,859.92	$ 5.58
AZITHROMYCIN	MACROLIDES	2,291	$ 91,174.44	$ 39.80
TOTAL TOP 25		91,541	$ 4,163,099.89	$ 45.48

Total Rx Claims From 06/01/06-06/30/06	325,636

Top 10 Drugs
Based on Number of Claims



Retrospective Drug Utilization Review
Activities Update

October-December 2005

#541- Diabetes/Proteinuria/Negating ACEI & ARB

- 314 educational intervention letters sent from October-December 2005.
- 40 cases of new ACE inhibitor or ARB therapy post intervention.
- 179 beneficiaries not tracked fully due to zero claims. This may have been due to eligibility issues such as Medicare Part D.
- 266 no responses to intervention letter; 48 responses (15.3% response rate).
- Case Evaluation responses as to the usefulness of this intervention indicate that 24 prescribers found this intervention "useful" or "very useful"; 4 "neutral"; and 8 "somewhat useful" or "not useful".

Recommendation

If those beneficiaries who appear to have switched to Medicare Part D are excluded, this intervention had a nearly 30% positive effect (314 unique beneficiaries – 179 Medicare Part D patients =135 remaining, with 40 of these showing recommended therapy changes). HID recommends that this intervention be conducted for an additional 90 days to more accurately analyze the effects of this criterion post Medicare Part D implementation.

#1536- Diabetes/Hypertension/Cardiovascular Drugs (Negating)

- 56 education intervention letters sent from October-December 2005.
- 9 cases of new antihypertensive therapy post intervention.
- 10 beneficiaries not tracked after December 2005 due to zero claims. This may have been due to eligibility issues such as Medicare Part D.
- 48 no responses to intervention letter; 8 responses for a 14.3% response rate.
- Case Evaluation responses as to the usefulness of this intervention indicate that 2 prescribers found this intervention "useful" while 1 prescriber found it "somewhat useful".

Recommendation

This criterion typically appeared on profiles with criterion 541. In all cases, this alert was attached to the same letter sent for that criterion due to the similarity in alerts. This may account for the low response rate. This is a useful criterion that alerts the prescriber that the beneficiary has a diagnosis of diabetes and hypertension and the benefits of treating the hypertension per the JNC-7 guidelines. When attached with criterion 541 (diabetics normaltensive or with hypertension), there is a reinforcement in the message to treat with ACE inhibitors or ARBs to prevent or impede the progression of renal disease and treat hypertension. HID recommends the continued use of this criterion.

#1607-Certain Antihypertensive Agents/Post MI/Beta-blockers, ACEI and Aldosterone Antagonists

- 30 educational intervention letters sent from October-December 2005.
- 5 cases of ACE inhibitor, beta-blocker, or aldosterone antagonist therapy post intervention.
- 24 beneficiaries identified during this intervention appeared to have switched to Medicare Part D due to zero claims after December 2005. However, there were 4 instances where these beneficiaries identified in October showed a change in therapy prior to the switch.
- 24 no responses to this intervention; 6 responses (20% response rate).

- Case Evaluation responses received indicated that two prescribers found this intervention "useful" or "very useful" while two prescribers found this intervention "not useful".

Recommendation

This intervention appeared to have involved many beneficiaries that are now participating in Medicare Part D. This results in the low exception numbers to this criterion. Considering the importance of the JNC-7 guidelines, HID recommends that this criterion remain available for future interventions at the Board's discretion.

#1608-Certain Antihypertensive Agents/Stroke/Thiazide diuretics & ACEI

- 7 educational intervention letters sent October-December 2005.
- There were no cases of therapy change in those beneficiaries identified by this intervention.
- 4 of the identified beneficiaries appeared to have switched to Medicare Part D.
- 5 no responses to this intervention; 2 responses were received for a 28.6% response rate.
- Case Evaluation responses received indicated that 2 prescribers found this intervention "useful".

Recommendation

This intervention appeared to have involved many beneficiaries that are now participating in Medicare Part D. This results in the low exception numbers to this criterion. Considering the importance of the JNC-7 guidelines, HID recommends that this criterion remain available for future interventions at the Board's discretion.

#1609-Certain Antihypertensive Agents/Chronic Kidney Disease/ACEI & ARB

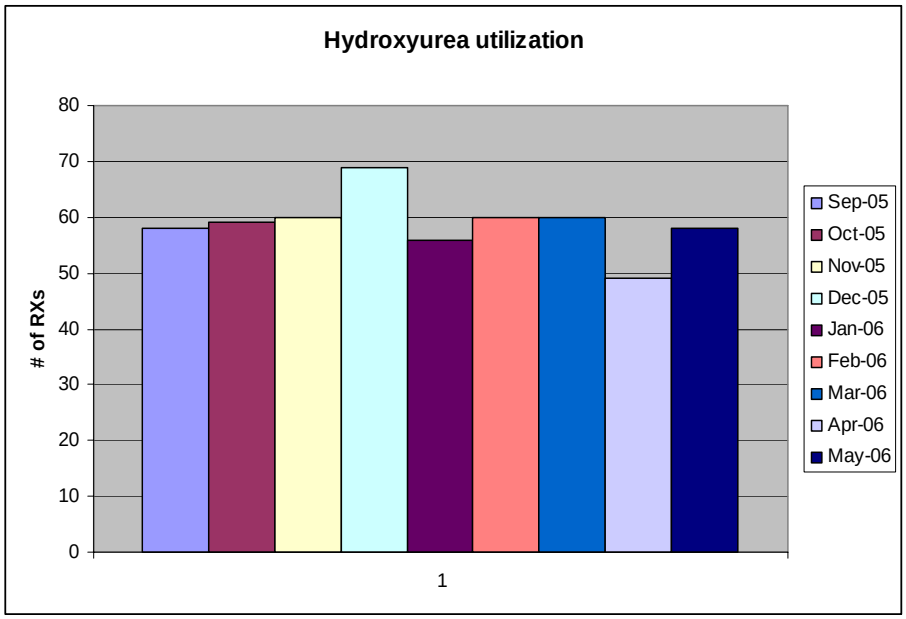
- 142 educational intervention letters sent October-December 2005.
- 8 cases of ACE inhibitor or ARB therapy initiated post intervention.
- 108 beneficiaries identified during the intervention period appeared to have switched to Medicare Part D due to zero claims after December 2005.
- 119 no responses to this intervention; 23 responses received for a 16.2% response rate.
- Case Evaluation responses received indicated that 6 prescribers found this intervention "useful"; 3 "neutral"; 2 "somewhat useful"; and 3 "not useful".

Recommendation
Considering the prevalence of kidney disease in Mississippi, this criterion is valuable in therapy education, as well as therapy assessment. Five of the 23 responses received indicated that the prescriber will discuss drug therapy with their patients and/or reassess and modify drug therapy. Conversely, 13 responses indicated that the problem was insignificant and warranted no change in drug therapy at this time. With increasing rates of obesity and diabetes in this population, chronic kidney disease will likely increase in prevalence. HID recommends this criterion remain available for future interventions.

November 2005-January 2006

#2150-Narcotic (opioids)/Sickle cell anemia/absence of hydroxyurea use

- 176 educational intervention letters sent from November 2005 through January 2006.
- 39 cases of new hydroxyurea use in unique beneficiaries in which letters were sent.
- 67 beneficiaries not tracked after December 2005 due to zero claims. This may have been due to eligibility issues such as Medicare Part D.
- 148 no responses to intervention letters; 28 responses for a 15.9% response rate.
- Narcotic prescribing in those prescribers receiving intervention letters shows a dramatic decrease however it is unable to determine the impact of Medicare Part D among the prescribers receiving intervention letters.
- Hydroxyurea utilization prior to and after interventions is depicted below:



Recommendation
HID recommends continuation of this intervention to determine effects on hydroxyurea and narcotic utilization post Medicare Part D implementation in order to more accurately report utilization trends.

Concurrent Use of Restasis® with Anticholinergic Medications

Introduction

Restasis® (cyclosporine ophthalmic emulsion) is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca (dryness of the cornea and conjunctiva).

When administered systemically, cyclosporine is an immunosuppressive agent. In patients whose tear production is suppressed, cyclosporine emulsion is thought to act as a partial immunomodulator. The exact mechanism of action is not known.

Problem

Many commonly-prescribed medications have varying levels of anticholinergic activity, resulting in such side effects as dry mouth, blurred vision, constipation and urinary retention. These agents can also cause a decrease in tear production with resulting dryness of the eyes.

In some cases, a patient may be treated with Restasis® for eye dryness that is secondary to these anticholinergic agents. A list of common anticholinergic medications is included below.

Commonly-prescribed Anticholinergic Medications			
Generic Name	**Common Trade Name**	**Generic Name**	**Common Trade Name**
amitriptyline	Elavil	tripelennamine	various
chlordiazepoxide/amitriptyline	Limbitrol	dexchlorpheniramine	various
perphenazine/amitriptyline	Etrafon	methcarbamol	Robaxin
dicyclomine	Bentyl	carisoprodol	Soma
hyoscyamine	Levsinex	chlorzoxazone	Parafon
propantheline	Pro-Banthine	metaxalone	Skelaxin
belladonna alkaloids	Donnatal	cyclobenzaprine	Flexeril
clidinium/chlordiazepoxide	Librax	dantrolene	Dantrium
doxepin	Sinequan	orphenadrine	Norflex
chlorpheniramine	Clor-Trimeton	benztropine	Cogentin
hydroxyzine	Vistaril, Atarax	biperiden	Akineton
cyproheptadine	Periactin	procyclidine	Kemadrin
promethazine	Phenergan	trihexyphenidyl	Artane

Method

Utilization data was gathered through RxExplorer®, which searches through paid claims data submitted to HID by the fiscal agent. Two unique searches were conducted covering the period from 1/1/06 through 6/23/06.

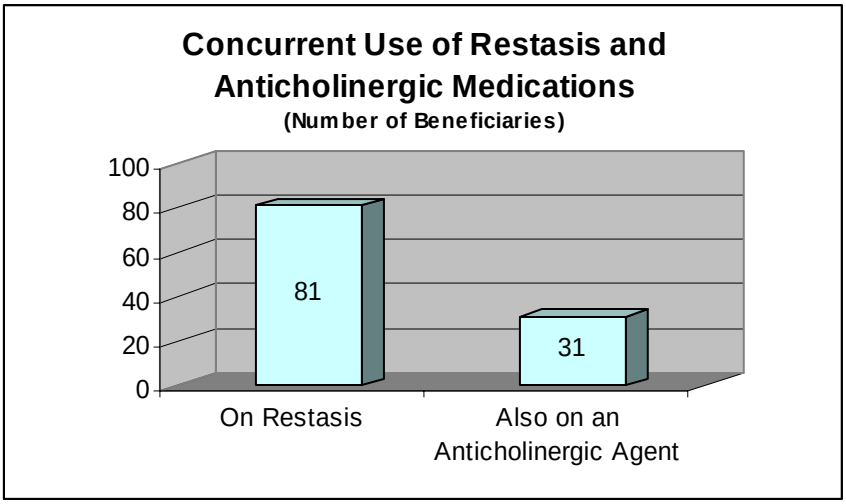
The search parameters were:

1. Restasis® utilization
2. Utilization of any of the anticholinergics medications listed above.

These searches were then intersected to show any beneficiaries who were found in both searches.

Results

During the time period of January 1, 2006 to June 23, 2006, there were 145 Restasis® claims for 81 unique beneficiaries. Of these beneficiaries, 31 also had at least one prescription claim for an anticholinergic medication.



Summary

As the information above reveals, approximately 40 percent of beneficiaries who were treated with Restasis® also received medications that may contribute to dryness of the eyes.

Recommendation

Based on these findings, a retrospective DUR criterion is recommended to identify patients who may benefit from a change in therapy that may allow for discontinuation of Restasis®.

MISSISSIPPI MEDICAID
RETROSPECTIVE DRUG UTILIZATION
REVIEW CRITERIA
AUGUST 2006

Criteria Recommendation	*Approved*	*Rejected*

1. Restasis / Anticholinergic Agents _____ _____

Alert Message: Anticholinergic agents may cause or worsen dry eye. A patient receiving an anticholinergic drug concurrently with Restasis (ophthalmic cyclosporine) may not experience the optimal therapeutic effect of the ophthalmic cyclosporine.
Conflict Code: DD – Drug/Drug Interaction
Drugs/Disease:

Util A	Util B	Util C
Restasis	Amitriptyline	Chlorzoxazone
	Dicyclomine	Metaxalone
	Hyoscyamine	Cyclobenzaprine
	Propantheline	Trihexyphenidyl
	Belladonna Alkaloids	Dantrolene
	Carisoprodol	Clidinium/Chlordiazepoxide
	Doxepin	Orphenadrine
	Chlorpheniramine	Benztropine
	Hydroxyzine	Biperiden
	Cyproheptadine	Procyclidine
	Promethazine	
	Tripelennamine	
	Dexchlorpheniramine	
	Methocarbamol	

References:
Restasis Prescribing Information, February 2004, Allergan Inc.
Dry Eyes: Causes – Mayo Clinic.com, Mayo Clinic Staff, and June 14, 2006.
http://mayoclinic.com/health/dry-eyes/DS00463/DSEDTUIN=3
Facts & Comparisons, 2006 Updates.

Concurrent Use of Triptans with SSRI or SNRI Antidepressants

Introduction

Serotonin 5-HT1 receptor agonists, commonly referred to as triptans, are a very effective tool in the treatment of migraine. The SSRI (selective serotonin reuptake inhibitor) and SNRI (selective serotonin/norepinephrine reuptake inhibitor) antidepressants are very important agents in the treatment of depression and other mood disorders, as well as other emerging indications. The following chart lists the members of these classes.

Generic Name	Trade Name
Triptans	
Almotriptan	Axert®
Eletriptan	Relpax®
Frovatriptan	Frova®
Naratriptan	Amerge®
Rizatriptan	Maxalt®
Sumatriptan	Imitrex®
Zolmitriptan	Zomig®
SNRIs	
Venlafaxine	Effexor®
Duloxetine	Cymbalta®
SSRIs	
Citalopram	Celexa®
Fluoxetine	Prozac®
Paroxetine	Paxil®, Paxil CR®
Fluvoxamine	Luvox®
Escitalopram	Lexapro®
Sertraline	Zoloft®

Problem

Although these agents are generally well-tolerated and safe, recent data has come to light concerning the use of these agents concurrently with certain antidepressants. A portion of the FDA Medical Product Safety Alert is included below:

> July 19, 2006 – FDA notified healthcare professionals and consumers of new safety information regarding taking medications used to treat migraine headaches (triptans) together with certain types of antidepressant and mood disorder medications (selective serotonin reuptake inhibitors (SSRIs) and selective serotonin/norepinephrine reuptake inhibitors (SNRIs). A life-threatening condition called serotonin syndrome may occur when triptans are used together with an SSRI or SNRI.
>
> Serotonin syndrome occurs when the body has too much of a chemical found in the nervous system (serotonin). Each of the above medications (triptans, SSRIs, and SNRIs), cause an increase in serotonin levels. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overactive reflexes, nausea, vomiting, and diarrhea.
>
> Healthcare professionals prescribing a triptan, SSRI or SNRI should keep in mind that triptans are often used intermittently and either the triptan, SSRI or SNRI may be prescribed by a different physician; weigh the potential risk of serotonin syndrome with the expected benefit of using the above combination; discuss the possibility of serotonin syndrome with patients if a triptan and an SSRI or

SNRI will be used together; and follow patients closely during treatment if a triptan and an SSRI or SNRI are used together.

Patients taking a triptan along with an SSRI or SNRI should talk to their doctor before stopping their medication and should immediately seek medical attention if they experience any of the above symptoms.

The FDA requested that all manufacturers of triptans, SSRIs and SNRIs update their prescribing information to warn of the possibility of serotonin syndrome when these medications are taken together.

In light of this safety alert from FDA, it may be prudent to monitor for concurrent use of these agents. It may be of particular importance to identify beneficiaries who are receiving the medications from different prescribers.

Method

Utilization data was gathered through RxExplorer®, which searches through paid claims data submitted to HID by the fiscal agent. Two unique searches were conducted covering the period from 1/1/06 through 6/23/06.

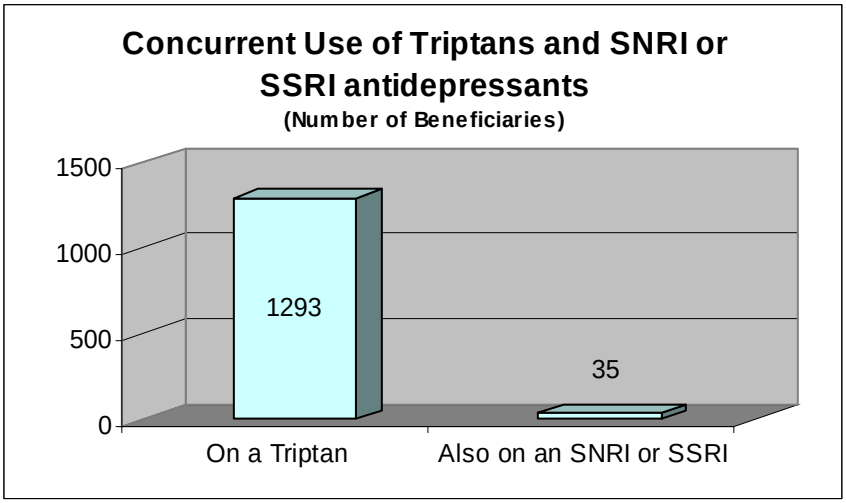
The search parameters were:

1. Utilization of triptans
2. Utilization of SNRI or SSRI antidepressants

These searches were then intersected to show any beneficiaries who were found in both searches.

Results

During the time period of January 1, 2006 to June 23, 2006, there were 1,293 unique beneficiaries with one or more claims for a triptan. Of these beneficiaries, 35 beneficiaries also had at least one prescription claim for an SNRI or SSRI antidepressant.



Summary

As the information above reveals, approximately three percent of patients who were treated with a triptan also received one or more prescriptions for an SNRI or SSRI during the report period.

Recommendation

Based on these findings, a retrospective DUR criterion is recommended to identify patients who may be at risk for serotonin syndrome due to the concurrent use of members of these drug classes.

MISSISSIPPI MEDICAID
RETROSPECTIVE DRUG UTILIZATION
REVIEW CRITERIA
AUGUST 2006

Criteria Recommendation	*Approved*	*Rejected*

1. Triptans / SSRIs & SNRIs _____ _____

Alert Message: Coadministration of triptans and SSRIs or SNRIs should be done with caution. Concomitant use may increase the risk of serotonin syndrome. Prescribers are advised to weigh the potential risk of serotonin syndrome with the expected benefit of using the drugs in combination.

Conflict Code: DD – Drug/Drug Interaction

Drugs/Disease:

Util A	Util B	Util C
Naratriptan	Fluvoxamine	
Almotriptan	Fluoxetine	
Frovatriptan	Sertraline	
Sumatriptan	Paroxetine	
Zolmitriptan	Venlafaxine	
Rizatriptan	Duloxetine	
Eletriptan	Escitalopram	
	Citalopram	

References:

MedWatch – The Safety Information and Adverse Event Reporting Program, 2006.

Exubera® (insulin human [rDNA origin]) Inhalation Powder)

Introduction

Exubera®, the first inhaled insulin delivery system will be introduced in September of this year. This product will be indicated for the control of hyperglycemia in adults with Types I or II diabetes mellitus. In patients with Type 1 diabetes, Exubera® should be used in a treatment regimen that includes long-acting insulin. In patients with Type 2 diabetes, it can be used as monotherapy or in combination with oral agents or longer-acting formulations.

Pharmacodynamically, this product has an onset of action similar to rapid-acting insulin analogs and duration of action similar to subcutaneous regular insulin. The insulin powder is supplied in 1 mg and 3 mg blisters to be administered in a custom inhaler device.

Concerns

Contraindications
Inhaled insulin is not recommended for all patients with diabetes. In particular, Exubera® is not recommended for patients with lung disease, such as asthma and COPD. Also, this product is contraindicated in patients who smoke or have quit smoking within six months prior to starting therapy.

Monitoring
In clinical trials, treatment with Exubera® was associated with small, non-progressive mean declines in pulmonary function relative to comparator treatments. Because of the effect on pulmonary function, all patients should have pulmonary function tests (e.g., spirometry) assessed prior to initiating therapy, after 6 months of therapy, and annually thereafter, even in the absence of pulmonary symptoms.

Waste
The administration of inhaled medications has generally been challenging for many patients. Studies on the use of inhalation devices used in the treatment of asthma and COPD have shown that as many as 38 percent of patients make critical errors during self-administration of these devises. These challenges, combined with the need for individualization and customization of dosing with insulin, create concerns about the potential for waste with Exubera®. As the section on dosing and administration below details, dosing will require combination of the 1 mg and 3 mg blisters. This process may be cumbersome and could result in waste of inappropriately-used blisters.

Pediatric Use
This insulin formulation is approved for use in adults and is not labeled for use in children under the age of 18.

Dosing and Administration

Initial dose

Inhaled insulin doses should be administered no more than ten minutes prior to each meal. The initial dosage should be individualized, and recommended initial pre-meal doses are based on clinical trials in which patients were requested to eat three meals per day. Initial pre-meal doses may be calculated using the following formula:

[Body weight (kg) × 0.05 mg/kg = pre-meal dose (mg)] rounded down to the nearest whole milligram number (e.g., 3.7 mg rounded down to 3 mg).

Approximate guidelines for initial, pre-meal inhaled insulin doses (based on patient body weight) are indicated in the following table:

Approximate Guidelines for Initial, Pre-meal Insulin Inhalation Dose				
Weight(kg)	Weight(lb)	Initial dose per meal	Number of 1 mg blisters/ dose	Number of 3 mg blisters/ dose
30 to 39.9	66 to 87	1 mg	1	—
40 to 59.9	88 to 132	2 mg	2	—
60 to 79.9	133 to 176	3 mg	—	1
80 to 99.9	177 to 220	4 mg	1	1
100 to 119.9	220 to 264	5 mg	2	1
120 to 139.9	265 to 308	6 mg	—	2

As with all insulin products, additional factors such as patient's current glycemic control, previous response to insulin, duration of diabetes, and dietary and exercise habits should be taken into consideration when determining the inhaled insulin starting dose.

Insulin equivalent doses

One 1 mg blister of inhaled insulin is approximately equivalent to 3 IU of subcutaneously injected regular human insulin. One 3 mg blister of inhaled insulin is approximately equivalent to 8 IU of subcutaneously injected regular human insulin. The following table provides the approximate IU dose of regular subcutaneous human insulin for inhaled insulin doses from 1 to 6 mg.

Approximate Equivalent IU Dose of Regular Human Subcutaneous Insulin for Inhaled Insulin Doses			
Dose (mg)	Approximate Regular Insulin SC Dose in IU	Number of 1 mg inhaled insulin blisters per dose	Number of 3 mg inhaled insulin blisters per dose
2	6	2	—
3	8	—	1
4	11	1	1
5	14	2	1
6	16	—	2

Patients should combine 1 and 3 mg blisters so that the least number of blisters per dose are taken. For example, a 4 mg dose should be administered as one 1 mg blister and one

3 mg blister. Consecutive inhalation of three 1 mg unit dose blisters results in significantly greater insulin exposure than inhalation of one 3 mg unit dose blister. Therefore, three 1 mg doses should not be substituted for one 3 mg dose. When a patient is stabilized on a dosing regimen that includes 3 mg blisters, and the 3 mg blisters become temporarily unavailable, the patient can temporarily substitute two 1 mg blisters for one 3 mg blister. Blood glucose should be monitored closely.

Dose adjustments
After initiating inhaled insulin therapy, as with other glucose-lowering agents, dose adjustment may be required based on the patient's need as determined by blood glucose concentrations, meal size and nutrient composition, time of day and recent or anticipated exercise. Each patient should be titrated to their optimal dosage based on blood glucose monitoring results. Close monitoring of blood glucose concentrations and dose adjustment may be required on an individual basis. As with injected insulin, the onset and duration of action of inhaled insulin may vary in different individuals or at different times in the same individual.

Other considerations

Inhaled insulin may be used during simultaneous respiratory illness such as bronchitis, upper respiratory tract infection, or rhinitis. Inhaled medicinal products such as bronchodilators should be administered prior to administration of inhaled insulin.

Summary

While the development of inhaled insulin is an exciting step in the evolution of diabetes therapy, its release to the market may be tempered by concerns around appropriate use. As Exubera® becomes available in the coming weeks, it is important for the Division of Medicaid to play a role in supporting the use of this product only in beneficiaries for whom it is appropriate.

Recommendation

In addition to being subject to prior authorization, retrospective DUR criteria are recommended to support the use of Exubera® within the parameters of its approved labeling.

MISSISSIPPI MEDICAID
RETROSPECITVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS
AUGUST 2006

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

1. Exubera / Therapeutic Appropriateness _____ _____

Alert Message: Exubera (inhalation insulin) is not indicated for use in patients 18 years of age or younger. Long-term safety and efficacy of inhaled insulin in children have not been established.
Conflict Code: TA – Therapeutic Appropriateness
Drugs/Disease:

Util A	Util B	Util C
Inhalation Human Insulin		

Age Range: 0 – 18 years of age
References:
Facts & Comparisons, 2006 Updates.
Exubera Prescribing Information, May 2006, Pfizer Labs.

2. Exubera / Tobacco Smoking _____ _____

Alert Message: Exubera (inhalation insulin) is contraindicated in patients who smoke or who have discontinued smoking less than 6 months prior to initiating inhaled insulin therapy. If a patient starts or resumes smoking, inhaled insulin must be discontinued and an alternative treatment must be utilized.
Conflict Code: TA – Therapeutic Appropriateness
Drugs/Disease:

Util A	Util B	Util C
Inhalation Human Insulin	Tobacco Use/Abuse ICD-9s	

References:
Facts & Comparisons, 2006 Updates.
Exubera Prescribing Information, May 2006, Pfizer Labs.

3. Exubera / Lung Disease _____ _____

Alert Message: Exubera (inhalation insulin) is contraindicated in patients with unstable or poorly controlled lung disease, because wide variations in lung function may effect the absorption of inhaled insulin increasing the risk of hypoglycemia or hyperglycemia. The use of inhaled insulin is also not recommended in patients with underlying lung disease because safety and efficacy have not been proven in this population.
Conflict Code: TA – Therapeutic Appropriateness
Drugs/Disease:

Util A	Util B	Util C
Inhalation Human Insulin	Asthma ICD-9s	
	COPD ICD-9s	
	Emphysema	
	Cystic Fibrosis	
	Pulmonary Fibrosis	
	Bronchiectasis	

References:
Facts & Comparisons, 2006 Updates.
Exubera Prescribing Information, May 2006, Pfizer Labs.

Recommendations	*Approved*	*Rejected*

4. Exubera / Type I Diabetics _____ _____

Alert Message: A recent review of the patient's drug history profile showed the use of Exubera (inhaled insulin) without the presence of a long-acting insulin product. Inhaled insulin only has a duration of approximately 6 hours and a long-acting insulin is required to maintain adequate glucose control.
Conflict Code: TA – Therapeutic Appropriateness
Drugs/Disease:

Util A	Util B	Util C (Negating)
Inhalation Human Insulin	Type I Diabetes ICD-9s	Long-Acting Insulin

References:
Facts & Comparisons, 2006 Updates.
Exubera Prescribing Information, May 2006, Pfizer Labs.

5. Exubera / Drugs that May Reduce Insulin Effect _____ _____

Alert Message: Certain medications may reduce the glucose-lowering effect of Exubera (inhaled insulin) and thereby increase the risk of hyperglycemia. Concurrent use of these agents with inhaled insulin may require dosage adjustment of the insulin and close blood glucose monitoring.
Conflict Code: DD – Drug/Drug Interaction
Drugs/Disease:

Util A	Util B	Util C
Inhalation Human Insulin	Atypical Antipsychotics	Somatropin
	Corticosteroids	Sympathomimetics
	Danazol	Thyroid Hormones
	Diuretics	
	Glucagon	
	Isoniazid	
	Phenothiazine Derivatives	
	Protease Inhibitors	

References:
Facts & Comparisons, 2006 Updates.
Exubera Prescribing Information, May 2006, Pfizer Labs.

*Separate criteria for Oral Contraceptives and Insulins already exist and turned on for MS.

6. Exubera / Drugs that Increase Inhaled Insulin Effect _____ _____

Alert Message: Certain medications may increase the blood glucose-lowering effect of Exubera (inhaled insulin) and increase the risk of hyperglycemia. Concurrent use of these agents with inhaled insulin may require dosage adjustment of the insulin and close blood glucose monitoring.
Conflict Code: DD – Drug/Drug Interaction
Drugs/Disease:

Util A	Util B	Util C
Inhalation Human Insulin	Disopyramide	
	Fibrates	
	Fluoxetine	
	Pentoxifylline	
	Sulfonamide Antibiotics	

References:
Facts & Comparisons, 2006 Updates.
Exubera Prescribing Information, May 2006, Pfizer Labs.

*Separate criteria for ACE Inhibitors, MAO Inhibitors, and salicylate with insulins already exist and are turned on for MS.

Recommendations	*Approved*	*Rejected*

7. Exubera / Therapeutic Appropriateness _____ _____

Alert Message: Certain substances may increase or decrease the blood glucose-lowering effect of Exubera (inhaled insulin). Concurrent use of these agents with inhaled insulin may require dosage adjustment of the insulin and close blood glucose monitoring.
Conflict Code: DD – Drug/Drug Interaction
Drugs/Disease:

Util A	Util B	Util C
Inhalation Human Insulin	Clonidine	
	Lithium	
	Alcohol Use ICD-9s	

References:
Facts & Comparisons, 2006 Updates.
Exubera Prescribing Information, May 2006, Pfizer Labs.

* Separate criteria for Beta-blockers and insulin already exist and are turned on for MS.

8. Exubera /Bronchodilator & Other Inhaled Products _____ _____

Alert Message: Bronchodilators and other inhaled products may alter the absorption of Exubera (inhaled human insulin). Consistent timing of the dosing of bronchodilators, relative to inhaled insulin administration, close monitoring of blood glucose concentrations, and dose titration as appropriate, are recommended.
Conflict Code: DD – Drug/Drug Interaction
Drugs/Disease:

Util A	Util B	Util C
Inhalation Human Insulin	Bronchodilators	
	Inhaled Corticosteroids	
	Cromolyn Inhalation	
	Nedocromil	
	Acetylcysteine (Mucomyst)	
	Dornase Alfa (Pulmozyme)	
	Pentamidine Inhalation	

*Pentamidine Inhalation not included here but is in separate pentamidine criteria.

References:
Facts & Comparisons, 2006 Updates.
Exubera Prescribing Information, May 2006, Pfizer Labs.

9. Exubera /First Line Therapy _____ _____

Alert Message: Exubera (inhaled insulin) is not indicated as first-line therapy for the treatment of diabetes. Injectable insulin therapy is considered first-line therapy in Type I diabetes. Type II diabetic therapy should begin with a proper diet and exercise program and if blood glucose is not controlled oral hypoglycemic medication(s) should be added followed by insulin therapy in hard-to-control type II patients.
Conflict Code: DD – Drug/Drug Interaction
Drugs/Disease:

Util A	Util B	Util C (Negating)
Inhalation Human Insulin		Insulins
		Oral Antidiabetic Agents

References:
Facts & Comparisons, 2006 Updates.
Exubera Prescribing Information, May 2006, Pfizer Labs.

MISSISSIPPI MEDICAID
RETROSPECITVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS
AUGUST 2006

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

1. Combunox / Duration _____ _____

Alert Message: Combunox (oxycodone/ibuprofen) may be over-utilized. This medication is indicated for short-term (no more than 7 days) management of acute moderate to severe pain.
Conflict Code: ER – Overutilization
Drugs/Diseases

Util A	Util B	Util C
Oxycodone/ibuprofen		

Days supply: 8 days

Reference:
Facts & Comparisons, 2006 Updates.
Combunox Prescribing Information, March 2006, Forest Laboratories.
Micromedex Healthcare Series, Drugdex Drug Evaluations, 2006.

2. Combunox / High Dose _____ _____

Alert Message: Combunox (oxycodone/ibuprofen) may be over-utilized. The manufacturer's recommended maximum dosage is 4 tablets in a 24-hour period, with use not to exceed 7 days.
Conflict Code: ER – Overutilization
Drugs/Diseases

Util A	Util B	Util C
Oxycodone/ibuprofen		

Max Dose: 20 mg of oxycodone

Reference:
Facts & Comparisons, 2006 Updates.
Combunox Prescribing Information, March 2006, Forest Laboratories.
Micromedex Healthcare Series, Drugdex Drug Evaluations, 2006.

3. Duloxetine / Hepatic Insufficiency _____ _____

Alert Message: It is recommended that Cymbalta (duloxetine) not be administered to patients with any hepatic insufficiency. These patients experience decreased duloxetine metabolism and elimination. After a single 20 mg dose of duloxetine cirrhotic patients with moderate liver impairment had a mean plasma clearance about 15% that of age-and gender-matched healthy subjects, a 5-fold increase in AUC, and a half-life approximately three times longer.
Conflict Code: MC – Drug (Actual) Disease Precaution
Severity: Major
Drugs:

Util A	Util B	Util C
Duloxetine	Hepatic Insufficiency	

References:
Cymbalta Product Information, 2005, Eli Lilly and Company.

Criteria Recommendations *Approved* *Rejected*

4. Duloxetine / End Stage Renal Disease _____ _____

Alert Message: Cymbalta (duloxetine) is not recommended in patients with end stage renal disease. A single 60 mg dose of duloxetine resulted in Cmax and AUC values approximately 100% greater in patients with end stage renal disease receiving intermittent hemodialysis than in patients with normal renal function.
Conflict Code: DB - Drug-Drug Marker and/or Diagnosis
Drugs:

Util A	Util B	Util C
Duloxetine	End Stage Renal Disease	
	Sevelamer	
	Paricalcitol	
	Calcitriol	
	Lanthanum	

References:
Cymbalta Product Information, 2005, Eli Lilly and Company.

5. Duloxetine / MAO Inhibitors _____ _____

Alert Message: The concurrent use of Cymbalta (duloxetine) and monoamine oxidase inhibitors is contraindicated due to the risk for developing serotonin syndrome, which may include hyperthermia, tremor, myoclonus, and irritability. It is recommended that duloxetine not be used within 14 days of discontinuing treatment with an MAOI, and at least 5 days should be allowed after discontinuing duloxetine before starting an MAOI.
Conflict Code: DD – Drug/Drug Interaction
Severity: Major
Drugs:

Util A	Util B	Util C
Duloxetine	Phenelzine	
	Isocarboxazid	
	Tranylcypromine	

References:
Cymbalta Product Information, 2005, Eli Lilly and Company.

6. Duloxetine / Thioridazine _____ _____

Alert Message: Cymbalta (duloxetine) and thioridazine should not be co-administered. Duloxetine is a moderate inhibitor of CYP 2D6 and concurrent use with thioridazine, a CYP 2D6 substrate, may increase the risk of serious ventricular arrhythmias and sudden death associated with elevated plasma levels of thioridazine.
Conflict Code: DD – Drug/Drug Interaction
Severity: Major

Util A	Util B	Util C
Duloxetine	Thioridazine	

References:
Cymbalta Product Information, 2005, Eli Lilly and Company.

7. Duloxetine / Narrow-Angle Glaucoma _____ _____

Alert Message: Cymbalta (duloxetine) should be used with caution in patients with controlled narrow-angle glaucoma and is contraindicated in patients with uncontrolled narrow-angle glaucoma. In clinical trials, duloxetine has been shown to increase the risk of mydriasis.
Conflict Code: MC – Drug (Actual) Disease Precaution
Severity: Moderate
Drugs:

Util A	Util B	Util C
Duloxetine	Narrow Angle Glaucoma	

References:
Cymbalta Product Information, 2005, Eli Lilly and Company.

Criteria Recommendations	*Approved*	*Rejected*

8. Duloxetine / Fluvoxamine _____ _____

Alert Message: Cymbalta (duloxetine) should be used with caution in patients receiving Luvox (fluvoxamine), a potent CYP 1A2 inhibitor. Elimination of duloxetine is mainly through hepatic metabolism involving P450 isozymes, CYP2D6 and CYP1A2. Concurrent use of these agents resulted in an approximate 6 fold increase in the AUC and a 2.5 fold increase in the Cmax of duloxetine.
Conflict Code: DD – Drug/Drug Interaction
Severity: Moderate
Drugs:

Util A	Util B	Util C
Duloxetine	Fluvoxamine	

References:
Cymbalta Product Information, 2005, Eli Lilly and Company.

9. Duloxetine / Potent 2D6 Inhibitors _____ _____

Alert Message: Cymbalta (duloxetine) should be used with caution in patients receiving potent CYP 2D6 inhibitors, (paroxetine, fluoxetine and quinidine). The concurrent use of these agents may result in elevated concentrations of duloxetine.
Conflict Code: DD – Drug/Drug Interactions
Severity: Moderate
Drugs:

Util A	Util B	Util C
Duloxetine	Paroxetine	
	Fluoxetine	
	Quinidine	

References:
Cymbalta Product Information, 2005, Eli Lilly and Company.

10. Duloxetine / Certain Tricyclic Antidepressants. _____ _____

Alert Message: Cymbalta (duloxetine) should be used with caution in patients receiving certain tricyclic antidepressants (desipramine, amitriptyline, nortriptyline and imipramine). Duloxetine is a moderate inhibitor of CYP2D6 and concurrent use with these agents may result in elevated TCA plasma concentrations. TCA plasma levels may need to be monitored and TCA dose reduction may be necessary.
Conflict Code: DD – Drug/Drug Interaction
Severity: Moderate
Drugs:

Util A	Util B	Util C
Duloxetine	Nortriptyline	
	Imipramine	
	Amitriptyline	
	Desipramine	

References:
Cymbalta Product Information, 2005, Eli Lilly and Company.

Criteria Recommendations	*Approved*	*Rejected*

11. Duloxetine / CYP2D6 Metabolized Drugs _____ _____

Alert Message: Cymbalta (duloxetine) should be used with caution in patients receiving drugs that are extensively metabolized by the CYP2D6 isozyme and which have a narrow therapeutic index (Type 1C antiarrhythmics and phenothiazines). Duloxetine is a moderate inhibitor of CYP2D6 and concurrent use with these agents may result in elevated plasma concentrations of the CYP2D6 substrate.
Conflict Code: DD – Drug/Drug Interaction
Severity: Moderate
Drugs:

Util A	Util B	Util C
Duloxetine	Propafenone	
	Flecainide	
	Chlorpromazine	
	Fluphenazine	
	Mesoridazine	
	Perphenazine	
	Prochlorperazine	
	Trifluoperazine	

*Excluded thioridazine – has individual criteria

References:
Cymbalta Product Information, 2005, Eli Lilly and Company.

12. Duloxetine / High Dose _____ _____

Alert Message: Cymbalta (duloxetine) may be over-utilized. The recommended dosing range is 40 mg to 60 mg a day. There is no evidence that doses greater than 60 mg/day confer any additional benefit.
Conflict Code: HD – High Dose
Severity: Major
Drugs:

Util A	Util B	Util C
Duloxetine		

Max Dose: 60mg/day
References:
Cymbalta Product Information, 2005, Eli Lilly and Company.

13. Duloxetine / Underuse _____ _____

Alert Message: After reviewing your patient's refill frequency for Cymbalta (duloxetine) we are concerned that they may be non-adherent to the prescribed dosing regimen which may lead to sub-therapeutic effects.
Conflict Code: LR – Underuse Precaution
Severity: Major
Drugs:

Util A	Util B	Util C
Duloxetine		

*Receive 65 day supply or less in 90 days.
References:
Cymbalta Product Information, 2005, Eli Lilly and Company.

Criteria Recommendations	*Approved*	*Rejected*

14. Proton Pump Inhibitors / Warfarin _____ _____

Alert Message: There have been reports of increases in INR and prothrombin time in patients receiving proton pump inhibitors and warfarin concurrently. Monitor PT/INR when a proton pump inhibitor is added to, changed during, or discontinued from concomitant treatment with warfarin. Adjustment of the warfarin dose may be necessary in order to maintain the desired level of anticoagulation.
Conflict Code: DD – Drug/Drug Interaction
Severity: Moderate
Drugs:

Util A	Util B	Util C
Omeprazole	Warfarin	
Lansoprazole		
Rabeprazole		
Pantoprazole		
Esomeprazole		

References:
Prevacid Prescribing Information, July 2006, TAP Pharmaceuticals, Inc.
Aciphex Prescribing Information, August 2003, Eisai, Co., Ltd.
Prilosec Prescribing Information, July 2005, AstraZeneca, L.P.
Nexium Prescribing Information, 2006, AstraZeneca L.P.
Protonix Prescribing Information, December 2005, Wyeth Pharmaceuticals, Inc.

Modafinil (Provigil®)
100 mg and 200 mg oral tablets
Cephalon, Inc.

Recent FDA Action
The manufacturer applied to the FDA to manufacturer another modafinil trade name (Sparlon®) with an indication for ADHD. On August 9, 2006, the FDA issued a non-approvable letter for this product. As a result of this action, the manufacturer has discontinued development of Sparlon®. During clinical trials, one suspected case of Stevens-Johnson syndrome occurred. No additional explanation was available at the time this document was written.

Indications
Modafinil is indicated to improve wakefulness in patients with excessive sleepiness (ES) associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), or shift work sleep disorder (SWSD).

Dosing and Administration
The recommended dose of Provigil® is 200 mg once daily. For patients with narcolepsy, it should be administered in the morning. For patients with SWSD, Provigil® should be taken approximately one hour prior to the start of their work shift.

Doses up to 400 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond that of the 200 mg dose.

Adverse Effects
The most commonly-experienced side effect of modafinil in clinical trials was headache, which occurred in up to 34% of patients taking the medication as compared to 23% among patients taking placebo.

Abuse Potential
Modafinil produces psychoactive and euphoric effects, alterations in mood, perception, thinking and feelings typical of other CNS stimulants. Because of these effects, this agents is a schedule IV controlled substance. Prescribers should follow patients closely, especially those with a history of drug and/or stimulant (e.g., methylphenidate, amphetamine, or cocaine) abuse. Patients should be observed for signs of misuse or abuse (e.g., incrementation of doses or drug-seeking behavior). When the abuse potential of modafinil was compared to that of methylphenidate, individuals experienced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants.

Utilization
During the period from 1/1/2006 through 7/21/2006, there were 795 claims for this agent. Based on requests for prior authorization among children, many prescribers are employing modafinil in the treatment of ADHD. In fact, paid pharmacy claims show that

there were 74 claims among 20 unique beneficiaries with a documented diagnosis of ADHD.

Medicaid Limitations

The Division of Medicaid recently added Provigil® to the list of products with quantity limits. An age restriction was also added. The table below details these limits.

Brand Name	Maximum Quantity per 31 Days[2]	Restrictions	Implementation Date
Provigil®100 mg and 200mg	*100mg :* limit of 1.5 tablets daily *200mg:* limit of 1 tablet daily. If a higher quantity is billed, the claim will deny with NCPDP reject code of E7-INV QUANTITY DISPENSED	If age is < **16**, the claim will deny with NCPDP Reject Code of 75-PRIOR AUTH REQUIRED	6-21-2006

Recommendation

In an effort to inform prescribers of the recent findings regarding modafinil, the Division of Medicaid has recommended the development of an information piece on this agent. This document is intended for distribution to and discussion with prescribers by the Medicaid academic detailing staff. A draft of this page is included here for review and approval by the DUR board.

Prescribing Information Update

Modafanil

Mississippi Division of Medicaid

- *Provigil® is not FDA-approved for the treatment of ADHD.*
- *Provigil ® is a Schedule IV controlled substance due to the abuse potential associated with modafinil.*
- *Mississippi Medicaid has placed monthly dispensing quantity limits on Provigil®.*
- *Safety and effectiveness in individuals below 16 years of age have not been established.*

Indications
Modafinil is indicated to improve wakefulness in patients with excessive sleepiness (ES) associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), or shift work sleep disorder (SWSD).

Dosing and Administration
The recommended dose of Provigil® is 200 mg once daily. For patients with narcolepsy, it should be administered in the morning. For patients with SWSD, Provigil® should be taken approximately one hour prior to the start of their work shift.

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Recent FDA Action
The manufacturer applied to the FDA to market modafinil under the trade name Sparlon® with an indication for ADHD. On August 9, 2006, the FDA issued a non-approvable letter for this product. As a result of this action, the manufacturer has discontinued development of Sparlon®. During clinical trials, one suspected case of Stevens-Johnson syndrome occurred. No additional explanation was available at the time this document was written.

Medicaid Dispensing Limitations
The Division of Medicaid has placed the following quantity and age restrictions on the dispensing of Provigil.

Brand Name	Maximum Quantity per 31 Days[2]	Restrictions	Implementation Date
Provigil®100 mg and 200mg	*100mg :* limit of 1.5 tablets daily *200mg:* limit of 1 tablet daily. If a higher quantity is billed, the claim will deny with NCPDP reject code of E7-INV QUANTITY DISPENSED	If age is < **16**, the claim will deny with NCPDP Reject Code of 75-PRIOR AUTH REQUIRED	6-21-2006

Boxed Warning Update

Code of Federal Regulations definition for Black Box:

Citation: Title 21 CFR 201.57 Section E

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

Aptivus (tipranavir)
Audience: Infectious disease specialists, pharmacists, and other healthcare professionals [Posted 06/30/2006] Boehringer Ingelheim and FDA informed healthcare professionals of important new safety information for Aptivus (tipranavir) capsules, co-administered with ritonavir (500mg/200mg), that includes an addition to the drug's Black Box Warning regarding reports of both fatal and non-fatal intracranial hemorrhage (ICH). Boehringer Ingelheim identified 14 reports of intracranial hemorrhage events, including 8 fatalities, in 6,840 HIV-1 infected individuals receiving Aptivus capsules in combination antiretroviral therapy in clinical trials.

Many of the patients experiencing ICH in the Aptivus clinical development program had other medical conditions (CNS lesions, head trauma, recent neurosurgery, coagulopathy, hypertension or alcohol abuse) or were receiving concomitant medications, including anticoagulants and antiplatelet agents, that may have caused or contributed to these events.

No pattern of abnormal coagulation parameters were observed in patients receiving Aptivus in general, or preceding the development of ICH. Routine measurement of coagulation parameters is not currently indicated in the management of patients on Aptivus. An increased risk of ICH was previously observed in patients with advanced

HIV-1 disease/AIDS. Further investigations are ongoing to assess the role of Aptivus in ICH.

Ketek (telithromycin)
Audience: Infectious disease, hepatology and other healthcare professionals
[Posted 06/29/2006] The Food and Drug Administration notified healthcare professionals and patients that it completed its safety assessment of Ketek (telithromycin), indicated for the treatment of acute exacerbation of chronic bronchitis, acute bacterial sinusitis and community acquired pneumonia of mild to moderate severity, including pneumonia caused by resistant strep infections. The drug has been associated with rare cases of serious liver injury and liver failure with four reported deaths and one liver transplant after the administration of the drug. FDA determined that additional warnings are required and the manufacturer is revising the drug labeling to address this safety concern. FDA is advising both patients taking Ketek and their doctors to be on the alert for signs and symptoms of liver problems. Patients experiencing such signs or symptoms should discontinue Ketek and seek medical evaluation, which may include tests for liver function.

Paxil (paroxetine hydrochloride) Tablets and Oral Suspension
Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets
Audience: Neuropsychiatric and other healthcare professionals
[Posted 05/12/2006] GlaxoSmithKline (GSK) and FDA notified healthcare professionals of changes to the Clinical Worsening and Suicide Risk subsection of the WARNINGS section in the prescribing Information for Paxil and Paxil CR. These labeling changes relate to adult patients, particularly those who are younger adults.

A recent meta-analysis conducted of suicidal behavior and ideation in placebo-controlled clinical trials of paroxetine in adult patients with psychiatric disorders including Major Depressive Disorder (MDD), other depression and non-depression disorders. Results of this analysis showed a higher frequency of suicidal behavior in young adults treated with paroxetine compared with placebo. Further, in the analysis of adults with MDD (all ages), the frequency of suicidal behavior was higher in patients treated with paroxetine compared with placebo. This difference was statistically significant; however, as the absolute number and incidence of events are small, these data should be interpreted with caution. All of the reported events of suicidal behavior in the adult patients with MDD were non-fatal suicide attempts, and the majority of these attempts (8 of 11) were in younger adults aged 18-30. These MDD data suggest that the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24.

It is important that all patients, especially young adults and those who are improving, receive careful monitoring during paroxetine therapy regardless of the condition being treated.