Division of Medicaid

Office of the Governor

State of Mississippi

DUR Board Meeting

February 15, 2007

2:00 p.m.

Woolfolk Building, Room 117

Jackson, MS

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

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

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

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

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

Troy Griffin
Advanced Healthcare Management
402 5th Avenue SW
Magee, MS 39111
Term Expires: June 30, 2008

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

Lee Montgomery, M.D.
Magnolia Family Medical
P.O. Box 1124
McComb, MS 39649
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

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

Lee Voulters, M.D.
The Vicksburg Clinic
2100 Hwy 61 North
Vicksburg, MS 39183
Term Expires: June 30, 2009

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

Upcoming Mississippi Medicaid DUR Board Meeting Dates

May 17, 2007
August 16, 2007
November 15, 2007
February 21, 2008

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

February 15, 2007

Welcome — **Randy Calvert, RPh**

Old Business

- **Approval of Meeting Minutes**
- **Updates**
  - **Cost Management Analysis** — **Dennis Smith, RPh**
  - **DUR Activity Report** — **Sam Warman, RPh**

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**
- **Carisoprodol – Prescribing Information Update**
- **Cough and Cold Preparations – Children Under Age Two**
- **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.

Minutes of the November 16, 2006
Drug Utilization Review (DUR) Board Meeting

Members Attending: Billy Brown, Pharm D; Harold Blakely, R.Ph.; Randy Calvert, R.Ph.; Frank Marascalco, R.Ph.; Lee Montgomery, M.D.; Andrea Phillips, M.D.

Members Absent: Troy Griffin; Wallace Strickland

Also Present: DOM Staff: Judith Clark, R.Ph., Director of the Medicaid Pharmacy Bureau; Vicky Donaho

HID Staff: Dennis Smith, R.Ph.; Sam Warman, R.Ph.; Kathleen Burns, R.N.

Randy Calvert, R.Ph., acting chair called the meeting to order at 2:15 p.m.

Updates

Cost Management Analysis:
Mr. Smith presented a brief report on the total cost of claims for the top 15 therapeutic classes from July 1, 2006 through August 31, 2006. This list was led by antipsychotic agents and anticonvulsants. The top 25 drugs based on the number of claims from July 1, 2006 thru August 31, 2006 were led by hydrocodone with acetaminophen followed by Zyrtec. The Top 25 drugs based on total claims cost from July 1, 2006 thru August 31, 2006 were led by Risperdal, followed by Seroquel.

Retrospective Drug Utilization Review (RDUR) Activities Update:
Mr. Warman reported on RDUR activities for the periods of October thru December 2005, and November 2005 thru January 2006. The RDUR initiatives reported on included the encouragement of ACE inhibitor or ARB use in patients with diabetes and/or chronic kidney disease, the appropriate use of antihypertensive medications in patients at risk for cardiovascular disease. Another issue reported on was the encouragement of appropriate use of hydroxyurea in patients with sickle cell anemia. The recommendation was made to continue all criteria in place and to report after another 90 days.

Pharmacy Program Updates:
Ms. Clark presented information regarding the new Preferred Drug List (PDL) becoming effective January 1, 2007. She pointed out that the new PDL will be available on the Division of Medicaid website in the near future. Ms. Clark distributed information regarding a new outreach project for chronic obstructive pulmonary disease that may become available through several sources for physicians to distribute to targeted patients. Due to the lack of a quorum, all voting was postponed until the next board meeting.

New Business:
Mr. Smith presented several suggested RDUR intervention modules. The concurrent use of Restasis® and medications with anticholinergic properties was discussed. Information

was presented to reflect the incidence of this concurrent use at approximately 30 percent. Based on these findings, a RDUR criterion was recommended to identify patients who may benefit from a change in therapy that may allow for discontinuation of Restasis®.

The next intervention discussed was the concurrent use of triptans with SSRI or SNRI antidepressants. This is a result of a recent FDA action regarding the risk of serotonin syndrome in patients taking these medications concurrently. Approximately 14 percent of patients who were treated with a triptan also received one or more prescriptions for an SNRI or SSRI during the report period. A RDUR criterion was recommended to identify patients who may be at risk for serotonin syndrome due to the concurrent use of members of these drug classes.

The new inhaled insulin product, Exubera®, was discussed. Mr. Smith highlighted the appropriate use of the product and presented possible concerns, such as potential waste due to complicated dosing regimens. 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. Mr. Smith recommended that in addition to being subject to prior authorization, RDUR criteria are recommended to support the use of Exubera® within the parameters of its approved labeling.

Several other general recommended RDUR criteria were introduced. Due to the lack of a quorum, however, these criteria were held for the next meeting of the board.

Next, Mr. Smith presented a brief synopsis of recent actions surrounding modafinil (Provigil®). Primarily, the recent FDA decision to not allow the marketing of a version of modafinil with an indication for ADHD was discussed. The possible concern for Medicaid is the apparent off-label use of Provigil® for ADHD. A one page Prescribing Information Update document was introduced to the board. The document is intended for use by the HID academic detailers to reinforce with prescribers the appropriate FDA-approved use of this product.

Mr. Smith also presented a study of the relationship between compliance and hospitalizations in children. This study focused on the use of inhaled corticosteroids in children with asthma. In brief, the findings supported the hypothesis that consistent use of inhaled corticosteroids decreases the risk of asthma-related hospitalizations. It was interesting to note that approximately two-thirds of children who had at least one asthma-related hospitalization had no prescription claims for these products.

The last new business topic discussed was the treatment of opioid dependence with buprenorphine and naloxone (Suboxone®). Mr. Smith summarized the treatment recommendations for this product and history of its approval for office-based treatment of patients who had previously had only the option of methadone treatment. The board discussed possible cooperation with the manufacturer in supporting this treatment option for appropriate Medicaid beneficiaries.

Boxed Warning Updates:

Mr. Smith presented the following black box warnings, labeling changes or other actions by the FDA**:**

Coumadin (warfarin sodium)
Audience: Pharmacists, other healthcare professionals, and patients
[Posted 10/06/2006]
FDA and Bristol-Myers Squibb notified pharmacists and physicians of revisions to the labeling for Coumadin, to include a new patient Medication Guide as well as reorganization and highlighting of the current safety information to better inform providers and patients.

Isotretinoin - Accutane and generic isotretinoin
Audience: Dermatological, other healthcare professionals and patients
[Posted 10/06/2006]
FDA and the iPLEDGE program notified healthcare professionals and patients of an update to iPLEDGE, a risk management program to reduce the risk of fetal exposure to isotretinoin, which will eliminate one element of the program, the 23 day lock-out period for males and females of non-child bearing potential. This change does not affect female patients of child-bearing potential.

Lamictal (lamotrigine)
Audience: Neurologists, obstetricians, other healthcare professionals, and patients
[Posted 09/29/2006]
The FDA notified healthcare professionals and patients of new preliminary information from the North American Antiepileptic Drug Pregnancy Registry that suggests that babies exposed to Lamictal, indicated to treat seizures and bipolar disorder, during the first three months of pregnancy may have a higher chance of being born with a cleft lip or cleft palate. More research is needed to be sure about the possibility of the increased chance of cleft lip or cleft palate developing in babies of pregnant women who take Lamictal. Women who take Lamictal and are pregnant or are thinking of becoming pregnant should talk with their doctor. Patients should not start or stop using Lamictal without talking to their doctor.

Ortho Evra (norelgestromin/ethinyl estradiol)
Audience: Gynecologists, other healthcare professionals and consumers
[Posted 09/20/2006]
Ortho-McNeil and FDA notified healthcare professionals and patients about revisions to the prescribing information to inform them of the results of two separate epidemiology studies that evaluated the risk of developing a serious blood clot in women using Ortho Evra compared to women using a different oral contraceptive. The first study found that the risk of non-fatal venous thromboembolism (VTE) associated with the use of Ortho Evra contraceptive patch is similar to the risk associated with the use of oral contraceptive pills containing 35 micrograms of ethinyl estradiol and norgestimate. The second study found an approximate two-fold increase in the risk of medically verified VTE events in users of Ortho Evra compared to users of norgestimate-containing oral contraceptives containing 35 micrograms of estrogen. Although the results of the two studies differ, the results of the second study support FDA's concerns regarding the

potential for Ortho Evra use to increase the risk of blood clots in some women. Prescribing information for Ortho Evra continues to recommend that women with concerns or risk factors for thromboemboli disease talk with their healthcare professionals about using Ortho Evra versus other contraceptive options.

Ibuprofen and Aspirin Taken Together
Audience: Consumers and healthcare professionals
[Posted 09/08/2006]
FDA notified consumers and healthcare professionals that taking Ibuprofen for pain relief and aspirin at the same time may interfere with the benefits of aspirin taken for the heart. Ibuprofen can interfere with the anti-platelet effect of low dose aspirin (81 mg per day), that may render aspirin less effective when used for cardioprotection and stroke prevention. Although it is all right to use Ibuprofen and aspirin together, FDA recommends that consumers contact their healthcare professional for more information on the timing of when to take these two medicines, so that both medicines can be effective.

Dexedrine (dextroamphetamine sulfate)
Audience: Psychiatrists, pediatricians, mental healthcare professionals, pharmacists and consumers
[Posted 08/21/2006]
The FDA and GlaxoSmithKline notified healthcare professionals of changes to the BOXED WARNING, WARNINGS and PRECAUTIONS sections of the prescribing information for Dexedrine (dextroamphetamine sulfate), approved for the treatment of Attention-Deficit Hyperactivity Disorder and narcolepsy. The warnings describe reports of sudden death in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems.

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/ receiving Aptivus capsules in combination antiretroviral therapy in clinical trials 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.

Next Meeting information:
Ms. Clark reminded the Board of the next scheduled meeting on February 15, 2007. Randy Calvert adjourned the meeting at 4:30 p.m.

Respectfully Submitted:
Health Information Designs

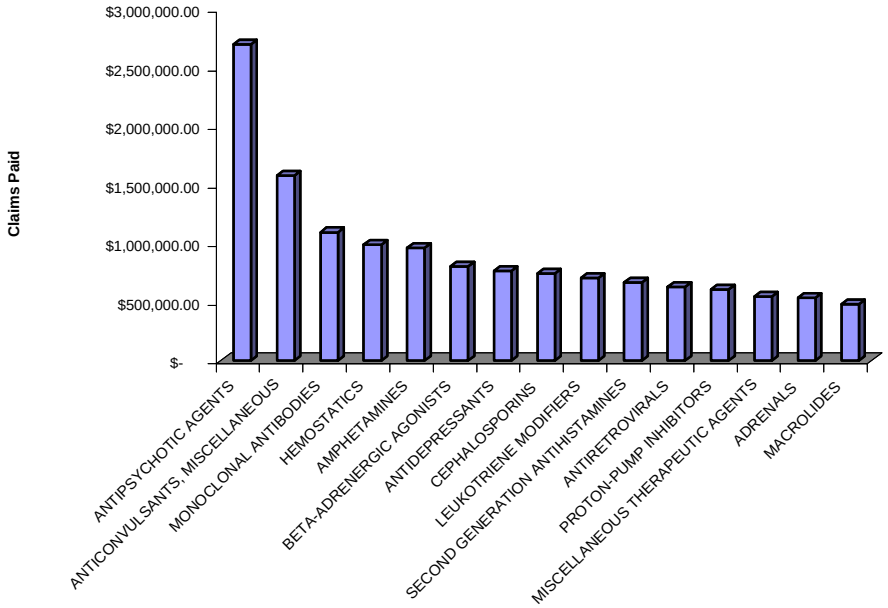
MISSISSIPPI MEDICAID
Cost Management Analysis

TOP 15 THERAPEUTIC CLASSES BY TOTAL COST OF CLAIMS FROM 10/01/06-10/31/06

AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
ANTIPSYCHOTIC AGENTS	9,920	$ 2,698,315.45	$ 272.01	2.62%
ANTICONVULSANTS, MISCELLANEOUS	9,933	$ 1,577,394.98	$ 158.80	2.63%
MONOCLONAL ANTIBODIES	843	$ 1,095,980.79	$ 1,300.10	0.22%
HEMOSTATICS	44	$ 988,719.85	$ 22,470.91	0.01%
AMPHETAMINES	9,198	$ 960,802.77	$ 104.46	2.43%
BETA-ADRENERGIC AGONISTS	12,984	$ 803,049.99	$ 61.85	3.43%
ANTIDEPRESSANTS	13,975	$ 764,745.10	$ 54.72	3.69%
CEPHALOSPORINS	12,707	$ 746,263.81	$ 58.73	3.36%
LEUKOTRIENE MODIFIERS	7,314	$ 706,924.34	$ 96.65	1.93%
SECOND GENERATION ANTIHISTAMINES	13,830	$ 669,046.48	$ 48.38	3.66%
ANTIRETROVIRALS	1,019	$ 630,835.99	$ 619.07	0.27%
PROTON-PUMP INHIBITORS	4,342	$ 605,215.71	$ 139.39	1.15%
MISCELLANEOUS THERAPEUTIC AGENTS	2,109	$ 547,155.20	$ 259.44	0.56%
ADRENALS	9,350	$ 535,219.68	$ 57.24	2.47%
MACROLIDES	12,647	$ 480,648.29	$ 38.00	3.34%
TOTAL TOP 15	120,215	$ 13,810,318.43	$ 114.88	31.78%

Total Rx Claims	378,297
From 10/01/06-10/31/06	

Top 15 Therapeutic Classes
Based on Total Cost of Claims



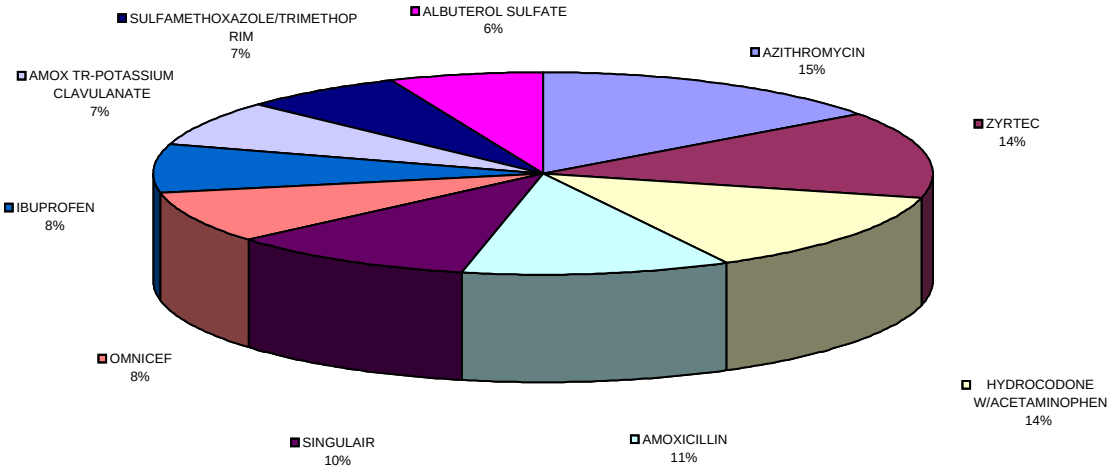
MISSISSIPPI MEDICAID
Cost Management Analysis

TOP 25 DRUGS BASED ON NUMBER OF CLAIMS FROM 10/01/06-10/31/0(

Drug	AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
AZITHROMYCIN	MACROLIDES	10,487	$ 385,216.64	$ 36.73	2.77%
ZYRTEC	SECOND GENERATION ANTIHISTAMINES	9,756	$ 498,888.56	$ 51.14	2.58%
HYDROCODONE W/ACETAMINOPHEN	OPIATE AGONISTS	9,553	$ 93,427.91	$ 9.78	2.53%
AMOXICILLIN	PENICILLINS	7,668	$ 66,347.62	$ 8.65	2.03%
SINGULAIR	LEUKOTRIENE MODIFIERS	7,302	$ 705,975.08	$ 96.68	1.93%
OMNICEF	CEPHALOSPORINS	5,883	$ 525,432.68	$ 89.31	1.56%
IBUPROFEN	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS	5,409	$ 44,778.22	$ 8.28	1.43%
AMOX TR-POTASSIUM CLAVULANATE	PENICILLINS	5,213	$ 277,776.65	$ 53.29	1.38%
SULFAMETHOXAZOLE/TRIMETHOPRIM	SULFONAMIDES (SYSTEMIC)	4,639	$ 51,530.81	$ 11.11	1.23%
ALBUTEROL SULFATE	BETA-ADRENERGIC AGONISTS	4,466	$ 111,744.83	$ 25.02	1.18%
ED A-HIST	PROPYLAMINE DERIVATIVES	4,434	$ 42,194.29	$ 9.52	1.17%
ALPRAZOLAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	4,238	$ 34,266.26	$ 8.09	1.12%
ALBUTEROL	BETA-ADRENERGIC AGONISTS	4,237	$ 95,856.57	$ 22.62	1.12%
CEPHALEXIN	CEPHALOSPORINS	4,077	$ 67,433.49	$ 16.54	1.08%
AMOXICILLIN TRIHYDRATE	PENICILLINS	4,013	$ 52,105.62	$ 12.98	1.06%
PREVACID	PROTON-PUMP INHIBITORS	3,859	$ 543,107.72	$ 140.74	1.02%
ACETAMINOPHEN W/CODEINE	OPIATE AGONISTS	3,447	$ 29,383.04	$ 8.52	0.91%
ADDERALL XR	AMPHETAMINES	3,226	$ 379,744.41	$ 117.71	0.85%
PROMETHAZINE HCL	PHENOTHIAZINE DERIVATIVES	3,187	$ 38,970.56	$ 12.23	0.84%
CLONAZEPAM	BENZODIAZEPINES (ANTICONVULSANTS)	3,007	$ 55,227.39	$ 18.37	0.79%
CONCERTA	AMPHETAMINES	2,792	$ 322,483.33	$ 115.50	0.74%
FERROUS SULFATE	IRON PREPARATIONS	2,758	$ 10,461.38	$ 3.79	0.73%
LORAZEPAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	2,643	$ 72,016.60	$ 27.25	0.70%
RISPERDAL	ANTIPSYCHOTIC AGENTS	2,563	$ 672,821.27	$ 262.51	0.68%
NYSTATIN	POLYENES	2,457	$ 34,518.12	$ 14.05	0.65%
TOTAL TOP 25		121,314	$ 5,211,709.05	$ 42.96	32.07%

Total Rx Claims From 10/01/06-10/31/06	378,297

Top 10 Drugs
Based on Number of Claims



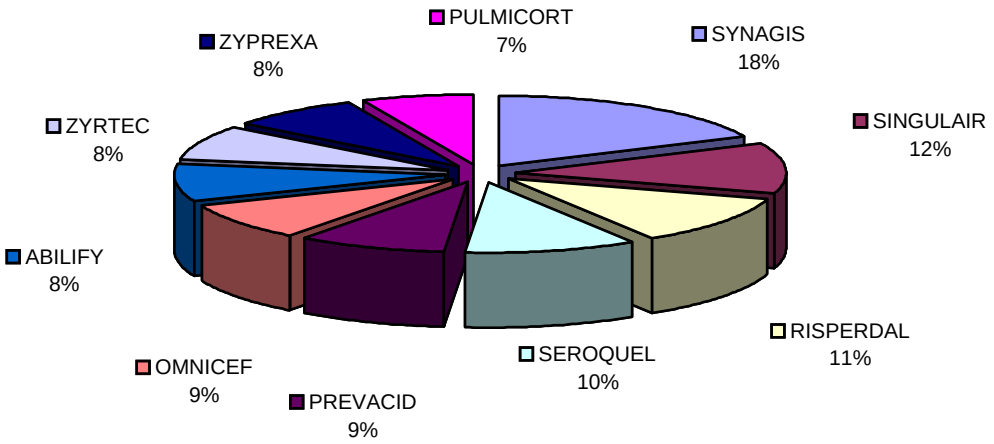
MISSISSIPPI MEDICAID
Cost Management Analysis

TOP 25 DRUGS BASED ON TOTAL CLAIMS COST FROM 10/01/06-10/31/06

Drug	AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
SYNAGIS	MONOCLONAL ANTIBODIES	843	$ 1,095,980.79	$ 1,300.10	0.22%
SINGULAIR	LEUKOTRIENE MODIFIERS	7,302	$ 705,975.08	$ 96.68	1.93%
RISPERDAL	ANTIPSYCHOTIC AGENTS	2,563	$ 672,821.27	$ 262.51	0.68%
SEROQUEL	ANTIPSYCHOTIC AGENTS	2,313	$ 620,535.92	$ 268.28	0.61%
PREVACID	PROTON-PUMP INHIBITORS	3,859	$ 543,107.72	$ 140.74	1.02%
OMNICEF	CEPHALOSPORINS	5,883	$ 525,432.68	$ 89.31	1.56%
ABILIFY	ANTIPSYCHOTIC AGENTS	1,254	$ 509,538.08	$ 406.33	0.33%
ZYRTEC	SECOND GENERATION ANTIHISTAMINES	9,756	$ 498,888.56	$ 51.14	2.58%
ZYPREXA	ANTIPSYCHOTIC AGENTS	1,058	$ 468,918.39	$ 443.21	0.28%
PULMICORT	ADRENALS	1,800	$ 394,883.33	$ 219.38	0.48%
AZITHROMYCIN	MACROLIDES	10,487	$ 385,216.64	$ 36.73	2.77%
ADDERALL XR	AMPHETAMINES	3,226	$ 379,744.41	$ 117.71	0.85%
TOPAMAX	ANTICONVULSANTS, MISCELLANEOUS	1,206	$ 329,142.19	$ 272.92	0.32%
CONCERTA	AMPHETAMINES	2,792	$ 322,483.33	$ 115.50	0.74%
ADVAIR DISKUS	BETA-ADRENERGIC AGONISTS	1,710	$ 282,235.36	$ 165.05	0.45%
AMOX TR-POTASSIUM CLAV.	PENICILLINS	5,213	$ 277,776.65	$ 53.29	1.38%
ADVATE	HEMOSTATICS	11	$ 259,415.05	$ 23,583.19	0.00%
FEIBA VH IMMUNO	HEMOSTATICS	4	$ 240,553.82	$ 60,138.46	0.00%
XOPENEX	BETA-ADRENERGIC AGONISTS	1,573	$ 231,151.14	$ 146.95	0.42%
STRATTERA	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	1,547	$ 225,396.01	$ 145.70	0.41%
GABAPENTIN	ANTICONVULSANTS, MISCELLANEOUS	1,688	$ 200,139.24	$ 118.57	0.45%
TRILEPTAL	ANTICONVULSANTS, MISCELLANEOUS	1,149	$ 194,107.24	$ 168.94	0.30%
EFFEXOR XR	ANTIDEPRESSANTS	1,394	$ 191,292.65	$ 137.23	0.37%
LAMICTAL	ANTICONVULSANTS, MISCELLANEOUS	639	$ 190,230.59	$ 297.70	0.17%
LIPITOR	HMG-COA REDUCTASE INHIBITORS	1,931	$ 185,299.65	$ 95.96	0.51%
TOTAL TOP 25		71,201	$ 9,930,265.79	$ 139.47	18.82%

Total Rx Claims	378,297
From 10/01/06-10/31/06	

Top 10 Drugs
Based on Total Claims Cost



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.

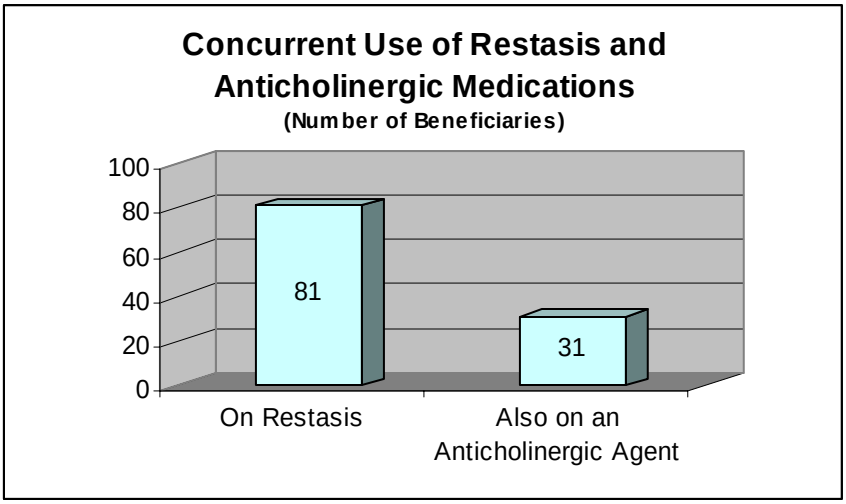
The search parameters were:

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

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 a SSRI or a 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.

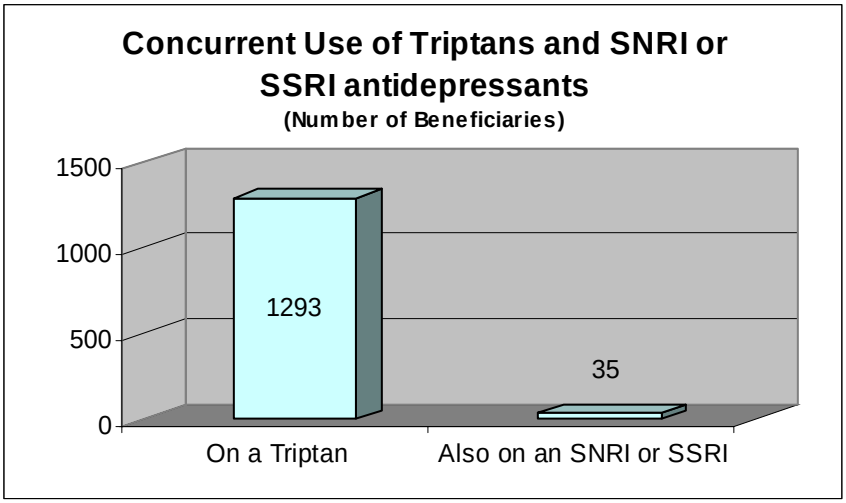
The search parameters were:

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 was introduced last fall. 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. 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
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS

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
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS
FEBRUARY 2007

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.

Carisoprodol (Soma®)

Introduction

During the January 9, 2007 meeting of the Medicaid Pharmacy and Therapeutics Committee, the skeletal muscle relaxants were reviewed. The issues of dependence, abuse, and drug-seeking behavior associated with carisoprodol were mentioned as concerns of the members of the committee.

During this discussion, some members of the committee questioned whether this drug should be covered for Medicaid beneficiaries, given the lack of evidence supporting efficacy for the common uses of the product. The consensus reached by the committee was that although this product is commonly misused, lack of coverage would create an undue burden on providers who routinely use carisoprodol legitimately.

Current Coverage

Carisoprodol products are currently covered by Medicaid, but are limited to 60 tablets per 30 rolling days. These products are not technically considered preferred and do not appear on the preferred drug list (PDL). The net effect of this classification is that prior authorization is not required for coverage.

Utilization

The following chart summarizes the utilization of carisoprodol and carisoprodol-containing products during the fourth quarter of 2006.

Generic Name	Number of Claims	Quantity Dispensed
Carisoprodol	4,057	203,401
Carisoprodol/Aspirin	21	754
Codeine/Carisoprodol/Aspirin	26	936
TOTAL	4,104	205,091

Suggested Action

The suggestion was made that perhaps an attempt should be made to educate providers on appropriate use of carisoprodol products and the potential risks associated with their use. The Medicaid academic detailers, employed and managed by HID, routinely visit with Medicaid prescribers and are available to deliver educational messages and materials to these providers.

As a result of this suggestion, the following document has been created to be distributed to prescribers by the academic detailers. The document is designed to present relevant information in a concise manner.

Prescribing Information Update

CARISOPRODOL (Soma®)

Mississippi Division of Medicaid

- *Carisoprodol (Soma®) is metabolized to meprobamate, a controlled substance with addiction potential.*
- *Long-term use of carisoprodol is not recommended due to the risk of dependence and addiction.*
- *Treatment should be limited to two to three weeks in duration.*
- *Mississippi Medicaid has placed monthly dispensing quantity limits on carisoprodol (Soma®).*

Indications
Carisoprodol is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions.

Efficacy
The skeletal muscle relaxant effects of effects of carisoprodol are minimal and are likely related to its sedative effect. It does not directly relax skeletal muscle and does not depress neuronal conduction, neuromuscular transmission, or muscle excitability.

Abuse Potential
Abuse associated with carisoprodol is well-documented and non-medical use of carisoprodol is an increasing problem. Carisoprodol is used frequently by poly-drug abusers, particularly those dependent on opioids.

According to a study performed in Mississippi and published in 1999, a significant percentage of the physician population is unaware of the potential for abuse associated with carisoprodol use and of its metabolism to meprobamate, a controlled substance. Although awareness has likely increased since that time, it is important that this message continue to be communicated to prescribers. Caution should be exercised when prescribing carisoprodol, especially if the patient has a history of substance abuse.

Risk of Long-term Use
The risk of dependence is increased significantly with long-term use. Treatment with carisoprodol, therefore, should be limited to two to three weeks in duration.

In 2006, the FDA required labeling changes to the package insert of carisoprodol to stress the risk of abuse and dependence. Its use should generally be limited to the acute treatment setting. Caution should be exercised when prescribing carisoprodol, especially if the patient has a history of substance abuse. Long-term use should be avoided.

Appropriate Discontinuation
Patients on high doses of carisoprodol may suffer withdrawal symptoms upon discontinuation. A withdrawal program similar to one used for alcohol withdrawal may be required for these patients. A suggested tapering schedule for such patients is to reduce the dose daily by 25% of the previous day's dose.

Medicaid Dispensing Limitations
The Division of Medicaid has placed the following quantity restrictions on the dispensing of carisoprodol.

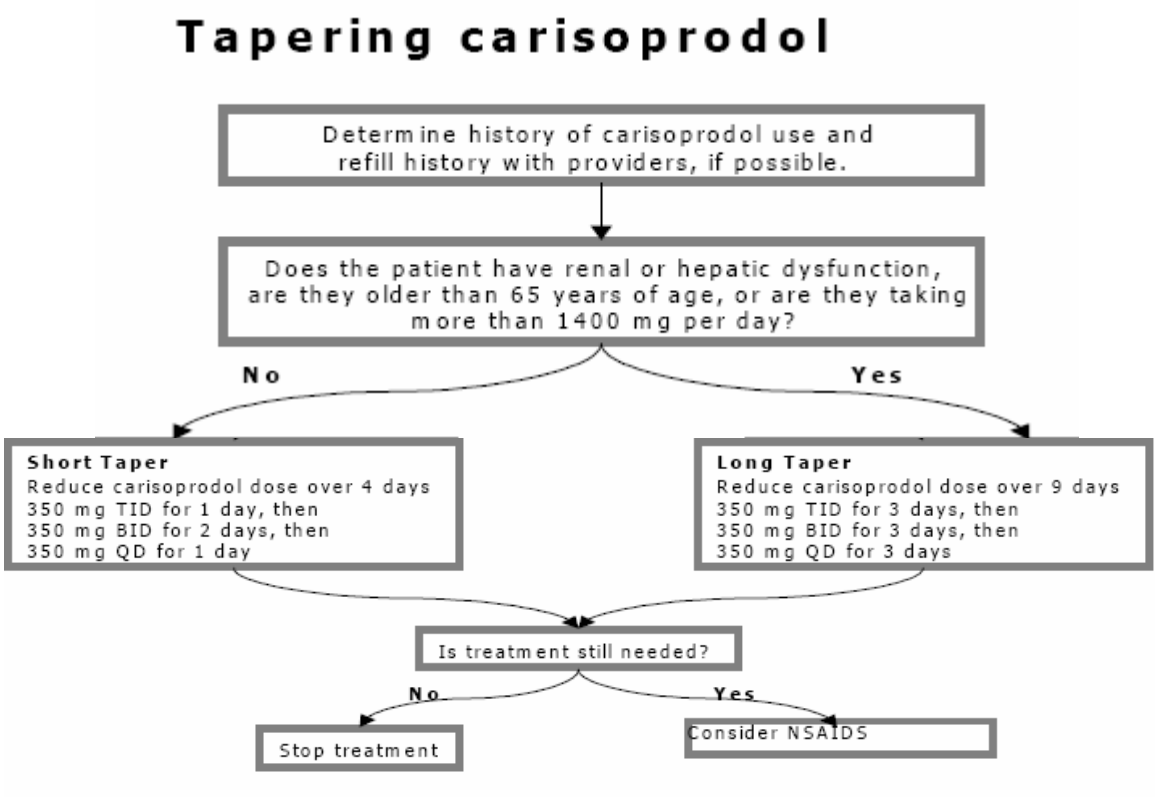
Product	Maximum Quantity Per Fill	Implementation Date
carisoprodol (Soma®) **carisoprodol/ASA (Soma Compound®)** **carisoprodol/ASA/codeine (Soma Compound with Codeine®)**	*These products are limited to a cumulative total of 60 units per 30 rolling days.*	5-8-2006

References:

- Drug Facts and Comparisons. Clinisphere 2.0. Copyright 2006 Wolters Kluwer Health, Inc.
- Reeves RR, Carter OS, Pinkofsky HB, Struve FA, Bennett DM. Carisoprodol (Soma): abuse potential and physician unawareness. G.V. (Sonny) Montgomery VA Medical Center, University of Mississippi School of Medicine, Jackson 39216, USA. J Addict Dis. 1999;18(2):51-6.
- McEvoy GK Ed. American Hospital Formulary Service Drug Information 2006. American Society of Health-System Pharmacists.

Suggested Tapering Schedule

Due to potential dependence, upon discontinuation of high doses of carisoprodol, patients may suffer withdrawal symptoms such as body aches, increased perspiration, anxiety and insomnia. To assist prescribers who wish to discontinue carisoprodol (Soma®), carisoprodol with aspirin (Soma® Compound), and carisoprodol with aspirin and codeine (Soma® Compound with Codeine), the following tapering schedule is available.



Tapering schedule developed by the Department of Veterans Affairs Medical Center, Portland, Oregon, as published in the Oregon DUR Board Newsletter. Oregon DUR Board Newsletter. 2002; 4:1. 28 Dec. 2005. http://pharmacy.oregonstate.edu/drug_policy/news/4_8/4_8.pdf. Permission Pending.

Use of Cough and Cold Medications in Young Children

Introduction

On January 12, 2007, the Centers for Disease Control and Prevention (CDC) issued a Morbidity and Mortality Weekly Report (MMWR) article describing three deaths in U.S. infants aged less than 12 months associated with cough and cold medications. These medications were determined by medical examiners or coroners to be the underlying cause of death. The cases described in this report underscore the need for clinicians to use caution when prescribing and caregivers to use caution when administering cough and cold medications to children aged less than two years.

The full MMWR article is included on the following pages for your study and review.

Utilization

The following table summarizes the use of many of the commonly-prescribed products in this general class in children ages birth through two years. These data reflect utilization during the fourth quarter of 2006.

Age (years)	Number of Claims
0	2,413
1	12,938

As these figures reflect, cough and cold preparations, both over-the-counter and prescription-only are commonly-used in very young beneficiaries. It is important to note that over-the-counter products administered by caregivers are not reflected in this summary.

Recommendations

There are several possible actions that could be taken in response to this issue:

1. A retrospective DUR edit criteria could be implemented; an educational letter would go to prescribers when such products are prescribed to children under two years old.
2. An age edit could be placed on cough and cold products that are not indicated below two years of age.
3. Quantity limits could be imposed on such products to limit the amount of medication available in households of young children.

Summary

In summary, these products are very commonly-prescribed and administered to very young children. While reports of deaths associated with the administration of these agents are very troubling, a balance must be maintained between limiting availability of these products and allowing access to medications that are necessary for appropriate care.

MMWR Weekly

January 12, 2007 / 56(01);1-4

Infant Deaths Associated with Cough and Cold Medications --- Two States, 2005

Cough and cold medications that contain nasal decongestants, antihistamines, cough suppressants, and expectorants commonly are used alone or in combination in attempts to temporarily relieve symptoms of upper respiratory tract infection in children aged <2 years. However, during 2004--2005, an estimated 1,519 children aged <2 years were treated in U.S. emergency departments for adverse events, including overdoses, associated with cough and cold medications.* In response to reports of infant deaths after such events, CDC and the National Association of Medical Examiners (NAME) investigated deaths in U.S. infants aged ≤12 months associated with cough and cold medications. This report describes the results of that investigation, which identified deaths of three infants aged ≤6 months in 2005, for which cough and cold medications were determined by medical examiners or coroners to be the underlying cause. The dosages at which cough and cold medications can cause illness or death in children aged <2 years are not known. Food and Drug Administration (FDA)-approved dosing recommendations for clinicians prescribing cough and cold medications do not exist for this age group. Because of the risks for toxicity, absence of dosing recommendations, and limited published evidence of effectiveness of these medications in children aged <2 years, parents and other caregivers should not administer cough and cold medications to children in this age group without first consulting health-care provider and should follow the provider's instructions precisely (*1*). Clinicians should use caution when prescribing cough and cold medications to children aged <2 years. Moreover, clinicians should always ask caregivers about their use of over-the-counter combination medications to avoid overdose in children from multiple medications that contain the same ingredient.

In January 2006, NAME, in collaboration with CDC, initiated an e-mail inquiry, requesting reports of deaths in infants aged ≤12 months for which cough and cold medications were determined as the underlying cause. To identify additional cases, CDC examined media and medical-journal reports of infant deaths suspected to be linked to cough and cold medications during 2005. A total of 15 local medical examiners in 12 U.S. states and Canada responded to the NAME survey. However, no cases other than those from media and published reports were identified. From these reports, CDC identified three cases of infant deaths in two states during 2005 that were determined by a medical examiner or coroner to have been caused by cough and cold medications (Table 1).

The three infants ranged in age from 1 to 6 months; two were male. All three infants had what appeared to be high levels of pseudoephedrine (a nasal decongestant) in postmortem blood samples. The blood levels of pseudoephedrine ranged from 4,743 ng/mL to 7,100 ng/mL.† One infant (patient 2) had received both a prescription and an over-the-counter cough and cold combination

medication at the same time; both medications contained pseudoephedrine (Table 1). The other two infants also had received pseudoephedrine-containing medications (one prescription and one over the counter). Two of the infants (patients 1 and 2) had been administered prescription medications containing carbinoxamine (an antihistamine), although neither had detectable postmortem blood levels of carbinoxamine. Two of the infants (patients 2 and 3) had detectable blood levels of dextromethorphan (a cough suppressant) and acetaminophen (an antipyretic and analgesic).

All three infants were found dead in their homes. Autopsy and medical investigation records were obtained. A medical examiner or coroner determined that cough and cold medication was the underlying cause of death for each of the three. None of the deaths were determined to be intentional. On autopsy, two of the infants (patients 1 and 2) had evidence of respiratory infection; no abnormalities in cardiac pathology were revealed in any of the infants.

Reported by: *Pediatric Toxicology Committee and Data Committee, National Assoc of Medical Examiners. A Srinivasan, MD, D Budnitz, MD, N Shehab, PharmD, Div of Healthcare Quality Promotion, National Center for Preparedness, Detection, and Control of Infectious Diseases (proposed); A Cohen, MD, EIS Officer, CDC.*

Editorial Note:

Cough and cold medications (Table 2) are in widespread use to treat children, and the overall incidence of reported adverse events has been low. An estimated 1,519 children aged <2 years were treated for adverse events from such medications during 2004--2005; infant deaths, although rare, also have been reported (*2*--*4*). The cases described in this report suggest that such deaths continue to be reported and underscore the need for clinicians to use caution when prescribing and caregivers to use caution when administering cough and cold medications to children aged <2 years.

In children aged ≥2 years, FDA approval of the use of over-the-counter cough and cold medications is based on review of safety and efficacy data by an external advisory review panel. However, in children aged <2 years, systematic reviews of controlled trials of over-the-counter cough and cold medications have concluded they are not more effective than placebo in reducing acute cough (*5*) and other symptoms of upper respiratory tract infection (*6*). Because of the unproven efficacy of the cough suppressants codeine and dextromethorphan in young children and the potential for adverse events, in 1997 the American Academy of Pediatrics issued a policy statement advising that parents should be educated regarding the lack of antitussive effects, risk for adverse events, and potential for overdose in children from these medications (*7*). In 2006, the American College of Chest Physicians released clinical practice guidelines for management of cough, advising health-care providers to refrain from recommending cough suppressants and other over-the-counter cough medications for young children because of associated morbidity and mortality (*8*).

In addition to advising caregivers and health-care providers regarding the risks of administering cough and cold medications to children aged <2 years, public health officials have taken steps to improve the safety of these medications. On June 8, 2006, FDA took enforcement action to stop the manufacture of carbinoxamine-containing medications that had not been approved by the agency; FDA noted that many of the medications were inappropriately labeled for use in infants and young

children despite safety concerns regarding use of carbinoxamine in children aged <2 years (*9*). Although manufacturers were required to cease production by September 6, 2006, some products might still be in distribution. In another action, the availability of pseudoephedrine-containing medications has been affected by the federal Combat Methamphetamine Epidemic Act, which was signed into law March 9, 2006. This act bans over-the-counter sales (but permits behind-the-counter sales in limited amounts) of cold medications that contain pseudoephedrine, which can be used to make methamphetamine. Because of this act, pseudoephedrine has been removed as an ingredient in many cough and cold medications and replaced with other nasal decongestants. However, some pediatric cough and cold medications containing pseudoephedrine still might be sold behind the counter. As an alternative to pseudoephedrine and other nasal decongestants, caregivers might consider clearing nasal congestion in infants with a rubber suction bulb; secretions can be softened with saline nose drops or a cool-mist humidifier.

Few data exist regarding the therapeutic or toxic levels of cough and cold medications in children aged <2 years (*2,3,10*). Blood levels of cough and cold medications revealed in postmortem studies might not reflect levels in the bloodstream at the time of administration (*1*). However, in this report, the blood levels of pseudoephedrine found in the three patients aged 1--6 months were approximately nine to 14 times the levels resulting from administration of recommended doses to children aged 2--12 years.

The findings in this report are subject to at least two limitations. First, because no universally accepted criteria exist for attributing deaths to cough and cold medications, the cause of death in these cases was based on the report of the medical examiner or coroner. However, the actual cause of death might have been overdose of one drug, interaction of different drugs, an underlying medical condition, or a combination of drugs and underlying medical conditions. Second, the findings are limited by the low response rate and absence of identified cases from the NAME survey, which might underestimate the number of deaths in infants attributed to cough and cold medications.

No FDA-approved dosing recommendations exist for administering over-the-counter cough and cold medications to children aged <2 years, and proper dosing for children in this age group has not been studied. Instructions on over-the-counter medications advise consumers to "consult a doctor" for children in this age group (*1*). Suggested dosing for some cough and cold medications can be found in parenting and prescribing guides, and clinicians commonly extrapolate a dose based on the weight or age of children aged <2 years from dosing guidelines for adults and older children (*7*). Such extrapolation is based on the assumption that the pathophysiology of the disease and the effects of the drug are similar in adult and pediatric patients.

Caregivers and clinicians should be aware of the risk for serious illness or fatal overdose from administration of cough and cold medications to children aged <2 years. Caregivers should only administer cough and cold medications to children in this age group when following the exact advice of a clinician. Clinicians should be certain that caregivers understand 1) the importance of administering cough and cold medications only as directed and 2) the risk for overdose if they administer additional medications that might contain the same ingredient. Caregivers should always inform their health-care providers of all medications they are administering to a child.

Acknowledgment
This report is based, in part, on contributions by the Food and Drug Administration.

References

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3. Marinetti L, Lehman L, Casto B, Harshbarger K, Kubiczek P, Davis J. Over-the-counter cold medications---postmortem findings in infants and the relationship to cause of death. J Anal Toxicol 2005;29:738--43.
4. Boland DM, Rein J, Lew EO, Hearn WL. Fatal cold medication intoxication in an infant. J Anal Toxicol 2003;27:523--6.
5. Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. Cochrane Database Syst Rev 2004(4):CD001831.
6. Smith MB, Feldman W. Over-the-counter cold medications. A critical review of clinical trials between 1950 and 1991. JAMA 1993;269: 2258--63.
7. Use of codeine- and dextromethorphan-containing cough remedies in children. American Academy of Pediatrics. Committee on Drugs. Pediatrics 1997;99:918--20.
8. Irwin RS, Baumann MH, Bolser DC, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Chest 2006 Jan;129(1 Suppl):1S--23S.
9. Food and Drug Administration. Carbinoxamine products; enforcement action dates. Federal Register 2006;71:33462.
10. Hanzlick R. National Association of Medical Examiners Pediatric Toxicology (PedTox) Registry Report 3. Case submission summary and data for acetaminophen, benzene, carboxyhemoglobin, dextromethorphan, ethanol, phenobarbital, and pseudoephedrine. Am J Forensic Med Pathol 1995;16:270--7.

* Estimated from the National Electronic Injury Surveillance System--Cooperative Adverse Drug Events Surveillance project, which is jointly operated by CDC, the Food and Drug Administration, and the Consumer Product Safety Commission.

† In pharmacokinetic studies of children aged 2--12 years, the mean maximum plasma concentrations of pseudoephedrine after therapeutic doses ranged from 180 ng/mL to 500 ng/mL and were comparable to adults with current dosing regimens (FDA, unpublished data, 2006).

Table 1

TABLE 1. Reported infant deaths for which cough and cold medications were determined the underlying cause of death* — United States, 2005

Patient	Age (mos)	Sex	Underlying cause of death†	Significant medical conditions, contributing factors, and findings on autopsy	Nasal decongestant postmortem blood levels	Antihistamine postmortem blood levels	Other medication (e.g., cough suppressant or antipyretic) postmortem blood levels
1	1	Male	Pseudoephedrine intoxication	Interstitial pneumonia, recent hospitalization for fever	Pseudoephedrine 4,743 ng/mL	None detected	None detected
2	6	Female	Pseudoephedrine and dextromethorphan intoxication	Bronchopneumonia and empyema on autopsy	Pseudoephedrine 6,832 ng/mL	None detected	Dextromethorphan 1,909 ng/mL, acetaminophen 35 µg/ml
3	3	Male	Drug poisoning	Infant found lying in crib in prone position, reported history of colic, born preterm (33 weeks), small fracture of left distal tibia, acute anoxic encephalopathy on autopsy	Pseudoephedrine 7,100 ng/mL	Doxylamine 1,000 ng/mL	Dextromethorphan 390 ng/mL, acetaminophen 1.9 µg/mL

* As determined by medical examiner or coroner.
† The three infants were known to have received the following medications: patient 1 received a prescription medication containing pseudoephedrine, carbinoxamine, and dextromethorphan; patient 2 received a prescription medication containing pseudoephedrine, carbinoxamine, and dextromethorphan and also received a nonprescription medication containing pseudoephedrine and acetaminophen; patient 3 received a nonprescription medication containing pseudoephedrine and acetaminophen. The nonprescription medications might also have contained other ingredients; exact formulations are unknown.

Table 2

TABLE 2. Examples of common ingredients in cough and cold medications, by class of medication

Class	Examples
Antihistamine (first generation)	Acrivastine, brompheniramine, carbinoxamine, chlorpheniramine, cyproheptadine, diphenhydramine, doxylamine, triprolidine
Antipyretic and analgesic	Acetaminophen, ibuprofen
Cough suppressant (antitussive)	Benzonatate, codeine, dextromethorphan, hydrocodone
Expectorant	Guaifenesin
Nasal decongestant	Ephedrine, phenylephrine, phenylpropanolamine, pseudoephedrine

Date last reviewed: 1/11/2007

Morbidity and Mortality Weekly Report
Centers for Disease Control and Prevention
1600 Clifton Rd, MailStop K-95, Atlanta, GA 30333, U.S.A

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 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.

Tamiflu (oseltamivir phosphate)
Audience: Pediatric and primary care healthcare professionals and patients
Indication: Treatment of uncomplicated acute illness due to influenza infection in patients 1 year and older who have been symptomatic for no more than 2 days.
[Posted 01/04/2007]
Roche notified healthcare professionals of a correction to a Dear Healthcare professional letter issued on November 13, 2006. The original letter referenced changes to the PRECAUTIONS Section of prescribing information for Tamiflu about post marketing reports of self-injury and delirium with the use of Tamiflu in patients with influenza. The prescribing information that accompanied the letter contained an incorrect dosing chart for the Standard Dosage of Tamiflu Oral Suspension for prophylaxis of influenza in pediatric patients. The chart incorrectly specified twice daily instead of once daily dosing under "Recommended Dose" for 10 days. Healthcare professionals should discard the incorrect version of the package insert included in the November 13, 2006 mailing and refer to the new dosing chart included in the December 26, 2006 letter.

Rituxan (Rituximab)
Audience: Oncologists, Rheumatologists, other healthcare professionals, and consumers
Indication: Treatment of CD20-postive, B-cell, non-Hodgkins lymphoma and for moderately-to-severely-active rheumatoid arthritis when there has been inadequate

response to other treatments.
[Posted 12/18/2006]
FDA and Genentech informed healthcare professionals of important emerging safety information about Rituxan. Two patients died after being treated with Rituxan for systemic lupus erythematosus (SLE). Rituxan is approved for the above indication and is prescribed off-label for other serious diseases and conditions such as SLE. The cause of death was a viral infection of the brain called progressive multifocal leukoencephalopathy (PML) that is caused by reactivated JC virus which is present in about 80 percent of adults. Physicians should maintain a high index of suspicion for the development of PML in patients under treatment with Rituxan.

Quinine products
Audience: Pharmacists, other healthcare professionals and consumers
[Posted 12/12/2006]
FDA informed healthcare professionals and consumers that the Agency ordered firms to stop marketing unapproved drug products containing quinine, citing serious safety concerns, including deaths associated with quinine products. There are multiple unapproved products containing quinine currently on the market, used off-label to treat leg cramps and similar conditions. Since 1969, FDA received 665 reports of adverse events with serious outcomes associated with quinine use, including 93 deaths. Quinine drugs are associated with serious side effects, such as cardiac arrhythmias, thrombocytopenia, and severe hypersensitivity reactions. Qualaquin, manufactured by Mutual Pharmaceutical Company, is the only quinine product approved by the FDA.

Heparin Sodium Injection
Audience: Vascular surgeons, ER personnel, pharmacists, and other healthcare professionals
[Posted 12/08/2006]
FDA notified healthcare professionals of revisions to the WARNINGS section of the prescribing information for Heparin to inform clinicians of the possibility of delayed onset of heparin-induced thrombocytopenia (HIT), a serious antibody-mediated reaction resulting from irreversible aggregation of platelets. HIT may progress to the development of venous and arterial thromboses, a condition referred to as heparin-induced thrombocytopenia and thrombosis (HITT). Thrombotic events may be the initial presentation for HITT which can occur up to several weeks after the discontinuation of heparin therapy. Patients presenting with thrombocytopenia or thrombosis after discontinuation of heparin should be evaluated for HIT and HITT.

Compounded topical anesthetic creams
Audience: Consumers, Pharmacists and other healthcare professionals
[Posted 12/06/2006]
FDA notified healthcare professionals and consumers about the serious public health risks related to compounded topical anesthetic creams. FDA issued warning letters to five firms to stop compounding and distributing standardized versions of topical anesthetic creams, marketed for general distribution. Exposure to high concentrations of local anesthetics, like those in compounded topical anesthetic creams, can cause grave

reactions including seizures, irregular heartbeats and death. Compounded topical anesthetic creams are often used to lessen pain in procedures such as laser hair removal, tattoos, and skin treatments. They may be dispensed by clinics and spas that provide these procedures, or by pharmacies and doctors' offices.

Dolophine (methadone hydrochloride)
Audience: Pain management specialists, pharmacists, and other healthcare professionals
Indication: Treatment of moderate to severe pain not responsive to non-narcotic analgesics; detoxification of opioid addiction; and maintenance treatment of opioid addiction
[Posted 11/27/2006]
FDA notified healthcare professionals of reports of death and life-threatening adverse events such as respiratory depression and cardiac arrhythmias in patients receiving methadone. These adverse events are the possible result of unintentional methadone overdoses, drug interactions, and methadone's cardiac toxicities (QT prolongation and Torsades de Pointes). The reports underscore the importance of knowing methadone's toxicities and unique pharmacologic properties, including dosing and monitoring recommendations.

Erythropoiesis Stimulating Agents
Procrit, Epogen, and Aranesp
Audience: Oncologists, nephrologists, and other healthcare professionals
Indication: Treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis.
[Posted 11/17/2006]
FDA notified healthcare professionals of a newly published clinical study showing that patients treated with an erythropoiesis-stimulating agent (ESA) and dosed to a target hemoglobin concentration of 13.5 g/dL are at a significantly increased risk for serious and life threatening cardiovascular complications, as compared to use of the ESA to target a hemoglobin concentration of 11.3 g/dL. The "Correction of Hemoglobin and Outcomes in Renal Insufficiency" study, published November 16, 2006 in the New England Journal of Medicine, reports the adverse cardiovascular complications as a composite of the occurrence of one of the following events: death, myocardial infarction, hospitalization for congestive heart failure, or stroke.
The study findings underscore the importance of following the currently approved prescribing information for Procrit, Epogen, and Aranesp, including the dosing recommendation that the target hemoglobin not exceed 12 g/dL.

Tamiflu (oseltamivir phosphate)
Audience: Pediatric and primary care healthcare professionals and patients
[Posted 11/13/2006]
Roche and FDA notified healthcare professionals of revisions to the PRECAUTIONS/Neuropsychiatric Events and Patient Information sections of the prescribing information for Tamiflu, indicated for the treatment of uncomplicated acute illness due to influenza infection in patients 1 year and older who have been symptomatic for no more than 2 days and for the prophylaxis of influenza in patients 1 year and older.

There have been postmarketing reports (mostly from Japan) of self-injury and delirium with the use of Tamiflu in patients with influenza. People with the flu, particularly children, may be at an increased risk of self-injury and confusion shortly after taking Tamiflu and should be closely monitored for signs of unusual behavior. A healthcare professional should be contacted immediately if the patient taking Tamiflu shows any signs of unusual behavior.

Effexor XR (venlafaxine HCl) Extended-Release Capsules
Effexor (venlafaxine HCl) Tablets
Audience: Neuropsychiatric and other healthcare professionals
[Posted 10/25/2006]
Wyeth and FDA notified healthcare professionals of revisions to the OVERDOSAGE/Human Experience section of the prescribing information for Effexor (venlafaxine HCl), indicated for treatment of major depressive disorder. In postmarketing experience, there have been reports of overdose with venlafaxine, occurring predominantly in combination with alcohol and/or other drugs. Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcome compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Healthcare professionals are advised to prescribe Effexor and Effexor XR in the smallest quantity of capsules consistent with good patient management to reduce the risk of overdose.

Menactra (Meningococcal Conjugate Vaccine A, C, Y, and W135)
Audience: Neurological and Pediatric healthcare professionals, and consumers
[Posted 10/23/2006]
FDA and CDC updated an October 2005 alert to consumers and health care providers regarding reports of Guillain Barre Syndrome (GBS) following administration of Meningococcal Conjugate Vaccine A, C, Y, and W135, manufactured by Sanofi Pasteur. To date a total of 15 confirmed cases of GBS among individuals 11-19 years of age occurring within six weeks of vaccination with Menactra have been reported to the Vaccine Adverse Event Reporting System (VAERS). Two additional cases have been confirmed in persons 20 years of age and older. All individuals are reported to be recovering or have recovered.

While the cases reported suggest a small increased risk of GBS following immunization with Menactra, the limitations in VAERS, and the uncertainty regarding background incidence rates for GBS require that these findings be viewed with caution. At this time, CDC and FDA cannot determine with certainty whether Menactra does increase the risk of GBS in persons who receive the vaccine and, if so, to what degree. At the present time, there are no changes in recommendations for vaccination and individuals should continue to follow their doctors' recommendations. FDA asks any persons with knowledge of possible cases of GBS occurring after receiving Menactra to report them to VAERS at http://www.vaers.hhs.gov or by phone at 1-800-822-7967.

Gleevec (imatinib mesylate)

Audience: Oncology and cardiology healthcare professionals
[Posted 10/19/2006]
Novartis and FDA notified healthcare professionals about revisions to the PRECAUTIONS section of the prescribing information, describing the occasional occurrence of severe congestive heart failure and left ventricular dysfunction in patients taking Gleevec. Most of the patients with reported cardiac events had other co-morbidities and risk factors, including advanced age and previous medical history of cardiac disease. Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully and any patients with signs or symptoms consistent with cardiac failure should be evaluated and treated.