Division of Medicaid

Office of the Governor

State of Mississippi

DUR Board Meeting

May 21, 2009

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

Laura Gray, M.D.
905 Garfield Street
Tupelo, MS 38801
Term Expires: June 30, 2009

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

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

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

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

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

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

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

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

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

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

Upcoming Mississippi DUR Board Meeting Dates

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

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

May 21, 2009

Welcome	**Laura Gray, M.D.**
Old Business	**Laura Gray, M.D.**
Approval of Meeting Minutes	
Cost Management Analysis	**Ashleigh Holeman, Pharm.D.**
Pharmacy Program Update	**Paige Clayton, Pharm.D.**
New Business	**Ashleigh Holeman, Pharm.D.**
Concurrent Use of ACE Inhibitors and Angiotension-Receptor Blockers	
Pharmalogical Interventions for Dyslipidemia in Children	
New Box Warning for Metoclopramide	
Plavix and Proton Pump Inhibitors	
Potential Overutilization of Strattera	
Other Criteria Recommendations	
FDA Updates	
Next Meeting Information	**Laura Gray, M.D.**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Respectfully Submitted:
Health Information Designs, Inc.

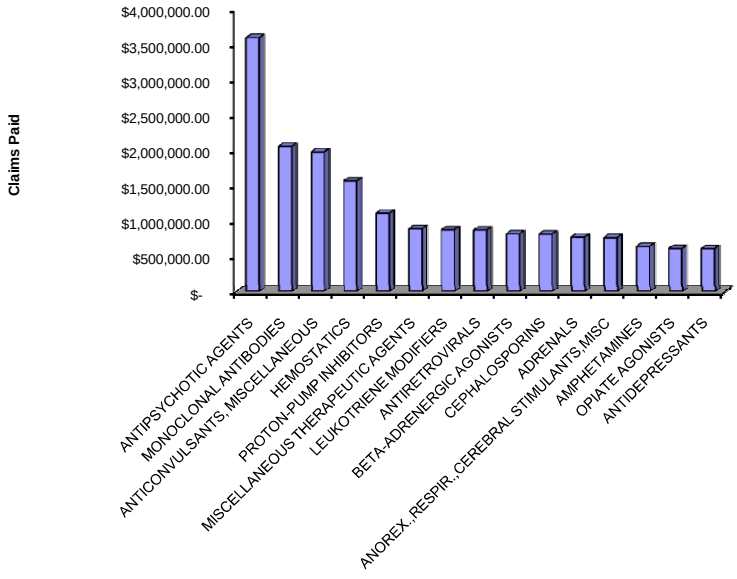
MISSISSIPPI MEDICAID
Cost Management Analysis

TOP 15 THERAPEUTIC CLASSES BY TOTAL COST OF CLAIMS FROM 12/01/08-12/31/08

AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
ANTIPSYCHOTIC AGENTS	11,164	$ 3,597,073.17	$ 322.20	2.70%
MONOCLONAL ANTIBODIES	1,339	$ 2,054,833.11	$ 1,534.60	0.32%
ANTICONVULSANTS, MISCELLANEOUS	12,115	$ 1,972,677.38	$ 162.83	2.93%
HEMOSTATICS	47	$ 1,562,638.06	$33,247.62	0.01%
PROTON-PUMP INHIBITORS	7,230	$ 1,106,920.88	$ 153.10	1.75%
MISCELLANEOUS THERAPEUTIC AGENTS	2,415	$ 883,259.93	$ 365.74	0.58%
LEUKOTRIENE MODIFIERS	7,725	$ 869,579.69	$ 112.57	1.87%
ANTIRETROVIRALS	1,151	$ 868,134.98	$ 754.24	0.28%
BETA-ADRENERGIC AGONISTS	14,415	$ 811,248.00	$ 56.28	3.49%
CEPHALOSPORINS	13,948	$ 806,677.98	$ 57.83	3.38%
ADRENALS	11,672	$ 766,843.67	$ 65.70	2.83%
ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	5,928	$ 757,178.76	$ 127.73	1.44%
AMPHETAMINES	4,660	$ 634,140.62	$ 136.08	1.13%
OPIATE AGONISTS	27,537	$ 604,735.58	$ 21.96	6.67%
ANTIDEPRESSANTS	14,367	$ 603,110.61	$ 41.98	3.48%
TOTAL TOP 15	135,713	$ 17,899,052.42	$ 131.89	32.87%

Total Rx Claims	412,906
From 12/01/08-12/31/08	

Top 15 Therapeutic Classes
Based on Total Cost of Claims



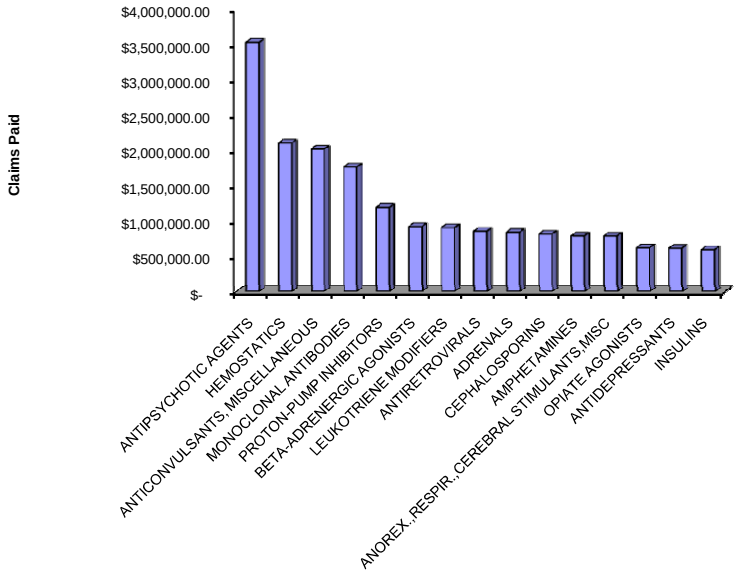
MISSISSIPPI MEDICAID
Cost Management Analysis

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

AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
ANTIPSYCHOTIC AGENTS	11,010	$ 3,530,898.15	$ 320.70	2.59%
HEMOSTATICS	50	$ 2,103,045.66	$42,060.91	0.01%
ANTICONVULSANTS, MISCELLANEOUS	12,231	$ 2,015,204.86	$ 164.76	2.87%
MONOCLONAL ANTIBODIES	1,126	$ 1,761,101.17	$ 1,564.03	0.26%
PROTON-PUMP INHIBITORS	7,646	$ 1,188,837.22	$ 155.48	1.80%
BETA-ADRENERGIC AGONISTS	15,397	$ 914,330.55	$ 59.38	3.62%
LEUKOTRIENE MODIFIERS	8,001	$ 899,595.66	$ 112.44	1.88%
ANTIRETROVIRALS	1,113	$ 850,858.82	$ 764.47	0.26%
ADRENALS	12,450	$ 833,610.65	$ 66.96	2.93%
CEPHALOSPORINS	14,280	$ 808,602.54	$ 56.62	3.36%
AMPHETAMINES	5,190	$ 784,407.77	$ 151.14	1.22%
ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	6,060	$ 782,193.35	$ 129.07	1.42%
OPIATE AGONISTS	28,210	$ 615,017.21	$ 21.80	6.63%
ANTIDEPRESSANTS	14,536	$ 609,750.20	$ 41.95	3.42%
INSULINS	3,846	$ 588,542.81	$ 153.03	0.90%
TOTAL TOP 15	141,146	$ 18,285,996.62	$ 129.55	33.16%

Total Rx Claims	425,605
From 01/01/09-01/31/09	

Top 15 Therapeutic Classes
Based on Total Cost of Claims



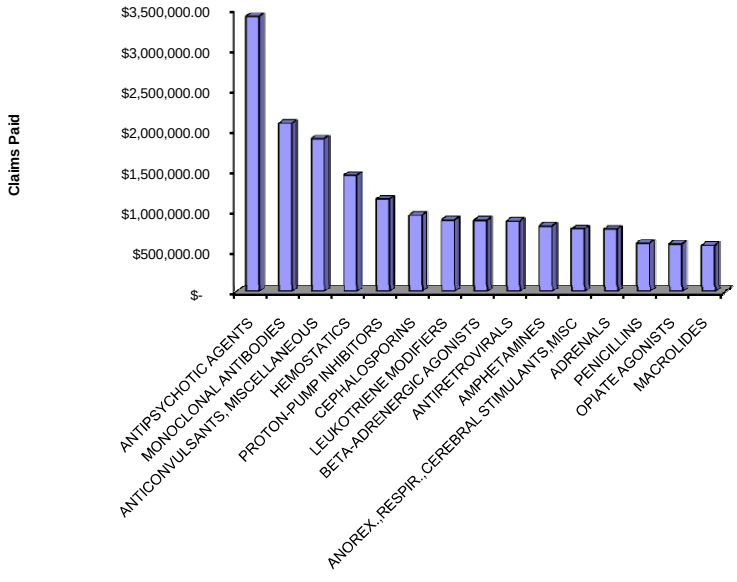
MISSISSIPPI MEDICAID
Cost Management Analysis

TOP 15 THERAPEUTIC CLASSES BY TOTAL COST OF CLAIMS FROM 02/01/09-02/28/09

AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
ANTIPSYCHOTIC AGENTS	10,539	$ 3,411,803.34	$ 323.73	2.45%
MONOCLONAL ANTIBODIES	1,329	$ 2,083,493.87	$ 1,567.72	0.31%
ANTICONVULSANTS, MISCELLANEOUS	11,587	$ 1,891,139.70	$ 163.21	2.70%
HEMOSTATICS	42	$ 1,438,624.32	$34,252.96	0.01%
PROTON-PUMP INHIBITORS	7,395	$ 1,143,899.03	$ 154.69	1.72%
CEPHALOSPORINS	16,021	$ 942,002.65	$ 58.80	3.73%
LEUKOTRIENE MODIFIERS	7,707	$ 882,513.18	$ 114.51	1.80%
BETA-ADRENERGIC AGONISTS	14,622	$ 881,440.88	$ 60.28	3.41%
ANTIRETROVIRALS	1,138	$ 869,850.74	$ 764.37	0.27%
AMPHETAMINES	5,195	$ 807,739.04	$ 155.48	1.21%
ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	5,827	$ 774,123.54	$ 132.85	1.36%
ADRENALS	11,920	$ 769,767.32	$ 64.58	2.78%
PENICILLINS	25,558	$ 595,340.58	$ 23.29	5.95%
OPIATE AGONISTS	27,105	$ 585,832.85	$ 21.61	6.31%
MACROLIDES	18,432	$ 569,127.21	$ 30.88	4.29%
TOTAL TOP 15	164,417	$ 17,646,698.25	$ 107.33	38.30%

Total Rx Claims	429,317
From 02/01/09-02/28/09	

Top 15 Therapeutic Classes
Based on Total Cost of Claims



MISSISSIPPI MEDICAID
Cost Management Analysis

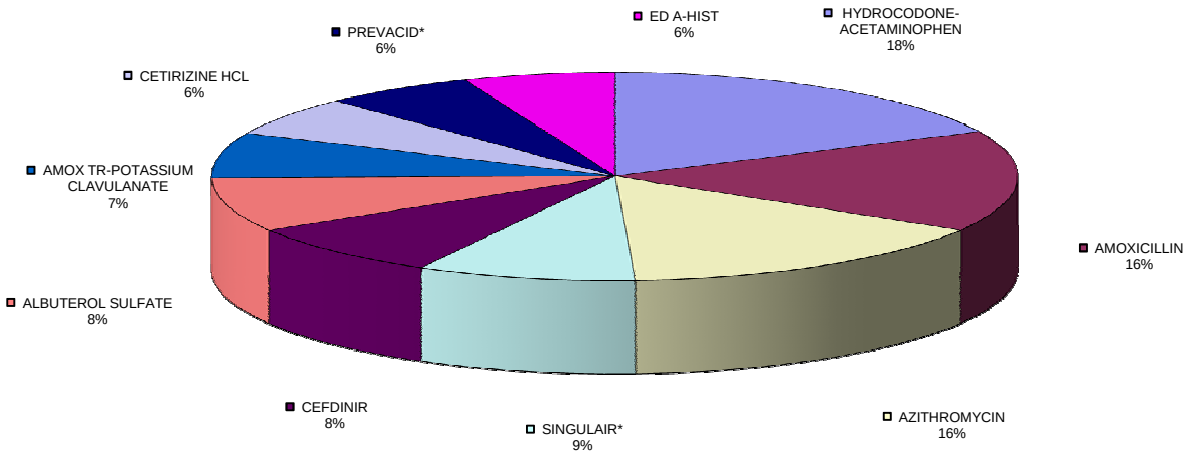
TOP 25 DRUGS BASED ON NUMBER OF CLAIMS FROM 12/01/08-12/31/08

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
HYDROCODONE-ACETAMINOPHEN	OPIATE AGONISTS	15,815	$ 227,954.25	1
AMOXICILLIN	PENICILLINS	13,783	$ 130,258.77	3
AZITHROMYCIN	MACROLIDES	13,615	$ 398,354.59	6
SINGULAIR*	LEUKOTRIENE MODIFIERS	7,715	$ 868,023.23	2
CEFDINIR	CEPHALOSPORINS	7,360	$ 543,337.72	105
ALBUTEROL SULFATE	BETA-ADRENERGIC AGONISTS	7,355	$ 226,567.16	67
AMOX TR-POTASSIUM CLAVULANATE	PENICILLINS	6,181	$ 318,572.04	26
CETIRIZINE HCL	SECOND GENERATION ANTIHISTAMINES	5,395	$ 85,323.91	~
PREVACID*	PROTON-PUMP INHIBITORS	5,353	$ 888,889.03	8
ED A-HIST	PROPYLAMINE DERIVATIVES	5,323	$ 46,874.78	~
IBUPROFEN	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS	5,024	$ 40,126.69	14
ALPRAZOLAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	5,005	$ 41,608.20	9
SULFAMETHOXAZOLE-TRIMETHOPRIM	SULFONAMIDES (SYSTEMIC)	4,381	$ 50,576.10	62
CLONAZEPAM	BENZODIAZEPINES (ANTICONVULSANTS)	3,914	$ 73,734.59	25
PROMETHAZINE HCL	PHENOTHIAZINE DERIVATIVES	3,879	$ 44,627.94	55
RISPERIDONE	ANTIPSYCHOTIC AGENTS	3,364	$ 760,388.69	~
ACETAMINOPHEN-CODEINE	OPIATE AGONISTS	3,262	$ 26,419.89	41
CEPHALEXIN	CEPHALOSPORINS	3,253	$ 49,254.76	18
ADDERALL XR*	AMPHETAMINES	3,162	$ 524,095.47	36
FERROUS SULFATE	IRON PREPARATIONS	2,950	$ 11,919.30	113
PREDNISOLONE SODIUM PHOSPHATE	ADRENALS	2,943	$ 39,234.21	136
LORAZEPAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	2,883	$ 20,973.41	23
VAZOBID	PROPYLAMINE DERIVATIVES	2,841	$ 154,543.41	~
AMLODIPINE BESYLATE	DIHYDROPYRIDINES	2,743	$ 19,019.90	15
RANITIDINE HCL	HISTAMINE H2-ANTAGONISTS	2,675	$ 67,953.32	47
TOTAL TOP 25		140,174	$ 5,658,631.36	

Total Rx Claims From 12/01/08-12/31/08	412,906

** Indicates preferred products on Preferred Drug List*

Top 10 Drugs
Based on Number of Claims



MISSISSIPPI MEDICAID
Cost Management Analysis

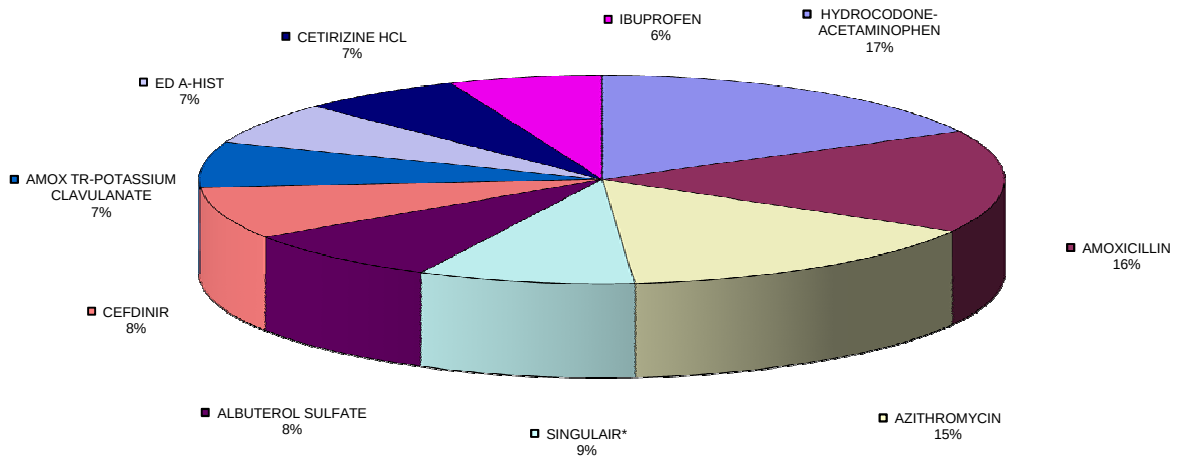
TOP 25 DRUGS BASED ON NUMBER OF CLAIMS FROM 01/01/09-01/31/09

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
HYDROCODONE-ACETAMINOPHEN	OPIATE AGONISTS	16,000	$ 231,707.75	1
AMOXICILLIN	PENICILLINS	14,622	$ 137,306.19	3
AZITHROMYCIN	MACROLIDES	14,184	$ 416,478.10	6
SINGULAIR*	LEUKOTRIENE MODIFIERS	7,995	$ 898,843.56	2
ALBUTEROL SULFATE	BETA-ADRENERGIC AGONISTS	7,641	$ 244,173.52	67
CEFDINIR	CEPHALOSPORINS	7,432	$ 550,255.38	105
AMOX TR-POTASSIUM CLAVULANATE	PENICILLINS	6,505	$ 344,933.56	26
ED A-HIST	PROPYLAMINE DERIVATIVES	6,042	$ 55,166.44	~
CETIRIZINE HCL	SECOND GENERATION ANTIHISTAMINES	5,968	$ 94,267.51	~
IBUPROFEN	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS	5,627	$ 44,451.52	14
PREVACID*	PROTON-PUMP INHIBITORS	5,533	$ 940,873.33	8
ALPRAZOLAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	4,833	$ 40,013.68	9
SULFAMETHOXAZOLE-TRIMETHOPRIM	SULFONAMIDES (SYSTEMIC)	4,757	$ 55,470.81	62
PROMETHAZINE HCL	PHENOTHIAZINE DERIVATIVES	3,957	$ 44,899.17	55
CLONAZEPAM	BENZODIAZEPINES (ANTICONVULSANTS)	3,903	$ 48,806.65	25
PROAIR HFA*	BETA-ADRENERGIC AGONISTS	3,661	$ 158,567.50	24
CEPHALEXIN	CEPHALOSPORINS	3,442	$ 53,519.25	18
ACETAMINOPHEN-CODEINE	OPIATE AGONISTS	3,408	$ 28,763.21	41
RISPERIDONE	ANTIPSYCHOTIC AGENTS	3,332	$ 656,688.48	~
ADDERALL XR*	AMPHETAMINES	3,274	$ 616,949.33	36
FERROUS SULFATE	IRON PREPARATIONS	2,986	$ 12,528.96	113
PREDNISOLONE SODIUM PHOSPHATE	ADRENALS	2,924	$ 38,422.53	136
LORAZEPAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	2,799	$ 20,272.52	23
AMLODIPINE BESYLATE	DIHYDROPYRIDINES	2,760	$ 19,116.23	15
RANITIDINE HCL	HISTAMINE H2-ANTAGONISTS	2,709	$ 69,402.43	47
TOTAL TOP 25		146,294	$ 5,821,877.61	

Total Rx Claims From 01/01/09-01/31/09	425,605

** Indicates preferred products on Preferred Drug List*

Top 10 Drugs
Based on Number of Claims



MISSISSIPPI MEDICAID
Cost Management Analysis

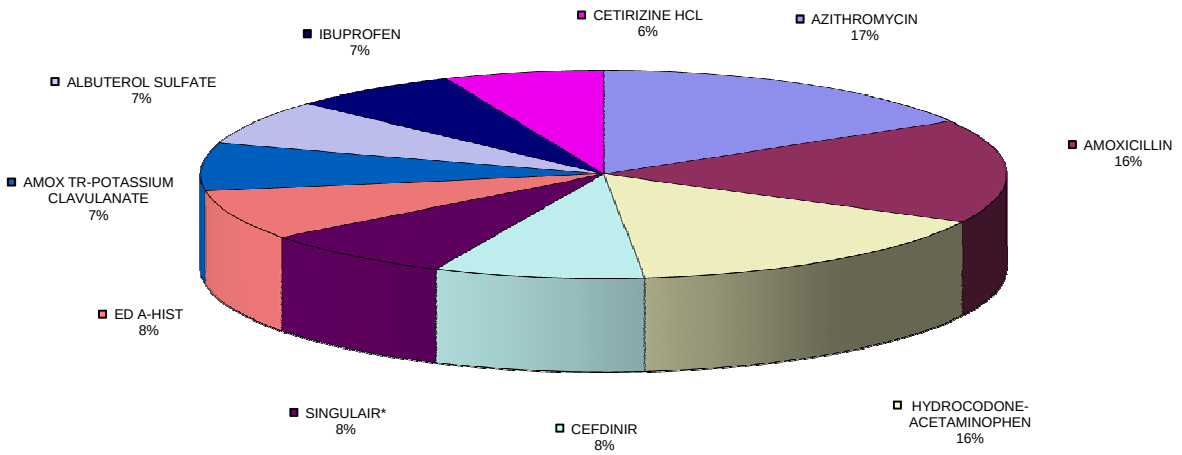
TOP 25 DRUGS BASED ON NUMBER OF CLAIMS FROM 02/01/09-02/28/09

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
AZITHROMYCIN	MACROLIDES	16,187	$ 470,419.98	6
AMOXICILLIN	PENICILLINS	15,809	$ 151,901.18	3
HYDROCODONE-ACETAMINOPHEN	OPIATE AGONISTS	15,488	$ 224,694.67	1
CEFDINIR	CEPHALOSPORINS	8,267	$ 628,326.45	105
SINGULAIR*	LEUKOTRIENE MODIFIERS	7,697	$ 880,923.79	2
ED A-HIST	PROPYLAMINE DERIVATIVES	7,643	$ 69,162.22	~
AMOX TR-POTASSIUM CLAVULANATE	PENICILLINS	7,258	$ 392,385.51	26
ALBUTEROL SULFATE	BETA-ADRENERGIC AGONISTS	6,904	$ 224,273.06	67
IBUPROFEN	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS	6,643	$ 55,070.31	14
CETIRIZINE HCL	SECOND GENERATION ANTIHISTAMINES	6,262	$ 97,922.34	~
PREVACID*	PROTON-PUMP INHIBITORS	5,275	$ 894,982.00	8
ALPRAZOLAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	4,620	$ 38,433.30	9
SULFAMETHOXAZOLE-TRIMETHOPRIM	SULFONAMIDES (SYSTEMIC)	4,549	$ 52,086.73	62
PROMETHAZINE HCL	PHENOTHIAZINE DERIVATIVES	4,417	$ 48,857.71	55
TAMIFLU	NEURAMINIDASE INHIBITORS	4,170	$ 352,684.21	161
CLONAZEPAM	BENZODIAZEPINES (ANTICONVULSANTS)	3,727	$ 28,606.86	25
PROAIR HFA*	BETA-ADRENERGIC AGONISTS	3,710	$ 159,950.89	24
CEPHALEXIN	CEPHALOSPORINS	3,693	$ 56,909.03	18
ACETAMINOPHEN-CODEINE	OPIATE AGONISTS	3,501	$ 29,636.20	41
RISPERIDONE	ANTIPSYCHOTIC AGENTS	3,196	$ 630,207.45	~
ADDERALL XR*	AMPHETAMINES	3,061	$ 606,761.09	36
FERROUS SULFATE	IRON PREPARATIONS	2,754	$ 11,656.68	113
CHERATUSSIN AC	ANTITUSSIVES	2,753	$ 14,145.40	140
AMLODIPINE BESYLATE	DIHYDROPYRIDINES	2,682	$ 18,553.01	15
LORAZEPAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	2,663	$ 18,926.18	23
TOTAL TOP 25		152,929	$ 6,157,476.25	

Total Rx Claims From 02/01/09-02/28/09	429,317

** Indicates preferred products on Preferred Drug List*

Top 10 Drugs
Based on Number of Claims



MISSISSIPPI MEDICAID
Cost Management Analysis

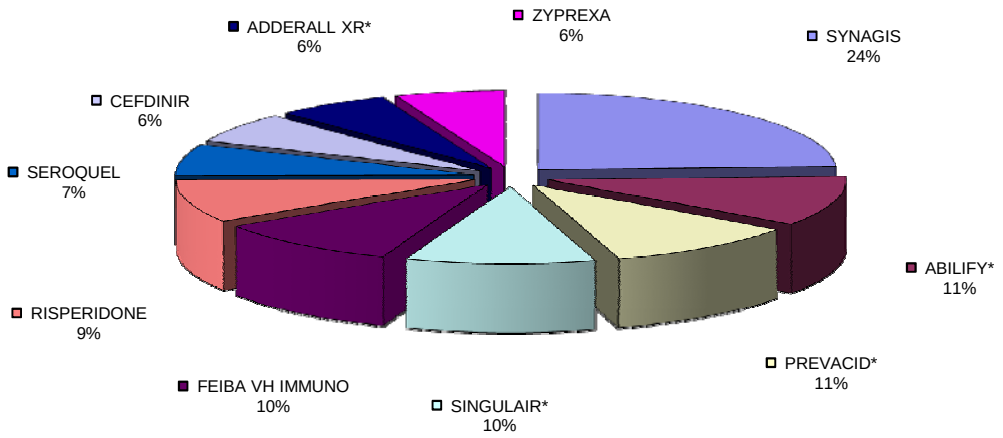
TOP 25 DRUGS BASED ON TOTAL CLAIMS COST FROM 12/01/08-12/31/08

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
SYNAGIS	MONOCLONAL ANTIBODIES	1,339	$ 2,054,833.11	~
ABILIFY*	ANTIPSYCHOTIC AGENTS	1,789	$ 895,774.60	15
PREVACID*	PROTON-PUMP INHIBITORS	5,353	$ 888,889.03	4
SINGULAIR*	LEUKOTRIENE MODIFIERS	7,715	$ 868,023.23	6
FEIBA VH IMMUNO	HEMOSTATICS	13	$ 863,910.70	~
RISPERIDONE	ANTIPSYCHOTIC AGENTS	3,364	$ 760,388.69	~
SEROQUEL	ANTIPSYCHOTIC AGENTS	1,530	$ 555,551.93	7
CEFDINIR	CEPHALOSPORINS	7,360	$ 543,337.72	31
ADDERALL XR*	AMPHETAMINES	3,162	$ 524,095.47	27
ZYPREXA	ANTIPSYCHOTIC AGENTS	860	$ 502,660.06	18
TOPAMAX*	ANTICONVULSANTS, MISCELLANEOUS	1,370	$ 450,700.24	13
AZITHROMYCIN	MACROLIDES	13,615	$ 398,354.59	2
ADVATE H	HEMOSTATICS	6	$ 377,441.41	~
CONCERTA*	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	2,621	$ 367,904.41	34
PULMICORT*	ADRENALS	1,282	$ 364,093.51	64
AMOX TR-POTASSIUM CL	PENICILLINS	6,181	$ 318,572.04	9
ADVAIR DISKUS*	BETA-ADRENERGIC AGONISTS	1,512	$ 296,390.81	3
GEODON*	ANTIPSYCHOTIC AGENTS	730	$ 271,456.52	58
LAMOTRIGINE	ANTICONVULSANTS, MISCELLANEOUS	915	$ 265,288.74	181
HYDROCODONE-ACETAM	OPIATE AGONISTS	15,815	$ 227,954.25	1
ALBUTEROL SULFATE	BETA-ADRENERGIC AGONISTS	7,355	$ 226,567.16	59
PLAVIX*	PLATELET-AGGREGATION INHIBITORS	1,520	$ 219,060.65	5
KEPPRA*	ANTICONVULSANTS, MISCELLANEOUS	768	$ 216,709.95	57
STRATTERA*	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	1,273	$ 216,647.64	73
EFFEXOR XR*	ANTIDEPRESSANTS	1,171	$ 208,538.56	8
TOTAL TOP 25		88,619	$ 12,883,145.02	

Total Rx Claims From 12/01/08-12/31/08	412,906

** Indicates preferred products on Preferred Drug List*

Top 10 Drugs
Based on Total Claims Cost



MISSISSIPPI MEDICAID
Cost Management Analysis

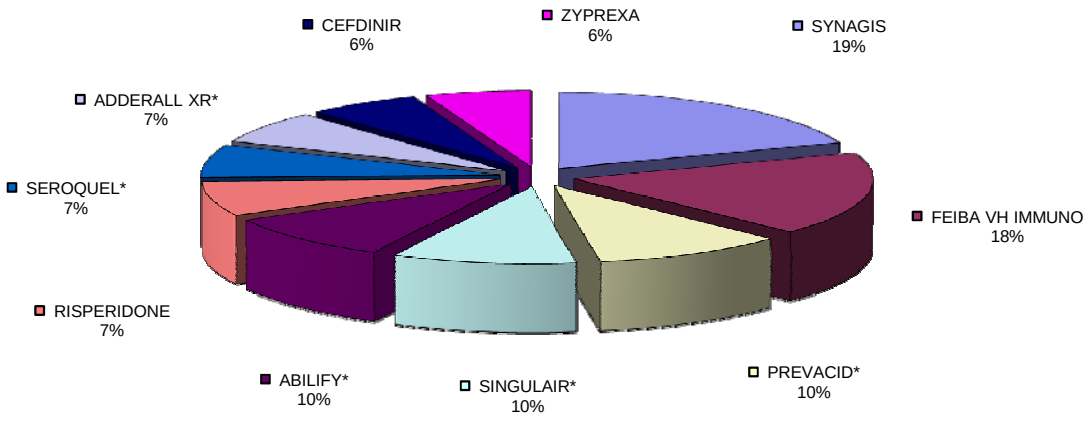
TOP 25 DRUGS BASED ON TOTAL CLAIMS COST FROM 01/01/09-01/31/09

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
SYNAGIS	MONOCLONAL ANTIBODIES	1,126	$ 1,761,101.17	~
FEIBA VH IMMUNO	HEMOSTATICS	18	$ 1,591,794.71	~
PREVACID*	PROTON-PUMP INHIBITORS	5,533	$ 940,873.33	4
SINGULAIR*	LEUKOTRIENE MODIFIERS	7,995	$ 898,843.56	6
ABILIFY*	ANTIPSYCHOTIC AGENTS	1,758	$ 873,934.65	15
RISPERIDONE	ANTIPSYCHOTIC AGENTS	3,332	$ 656,688.48	~
SEROQUEL*	ANTIPSYCHOTIC AGENTS	1,664	$ 619,420.09	7
ADDERALL XR*	AMPHETAMINES	3,274	$ 616,949.33	27
CEFDINIR	CEPHALOSPORINS	7,432	$ 550,255.38	31
ZYPREXA	ANTIPSYCHOTIC AGENTS	855	$ 514,907.86	18
TOPAMAX*	ANTICONVULSANTS, MISCELLANEOUS	1,393	$ 489,208.86	13
AZITHROMYCIN	MACROLIDES	14,184	$ 416,478.10	2
CONCERTA*	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	2,691	$ 382,739.75	34
PULMICORT*	ADRENALS	1,107	$ 346,008.06	64
AMOX TR-POTASSIUM CL	PENICILLINS	6,505	$ 344,933.56	9
ADVAIR DISKUS*	BETA-ADRENERGIC AGONISTS	1,677	$ 325,933.26	3
GEODON*	ANTIPSYCHOTIC AGENTS	743	$ 288,210.08	58
LAMOTRIGINE	ANTICONVULSANTS, MISCELLANEOUS	916	$ 259,792.06	181
BUDESONIDE	ADRENALS	1,242	$ 257,838.79	~
ALBUTEROL SULFATE	BETA-ADRENERGIC AGONISTS	7,641	$ 244,173.52	59
HYDROCODONE-ACETAM	OPIATE AGONISTS	16,000	$ 231,707.75	1
FOCALIN XR*	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	1,691	$ 230,028.02	133
PLAVIX*	PLATELET-AGGREGATION INHIBITORS	1,544	$ 222,599.23	5
EFFEXOR XR*	ANTIDEPRESSANTS	1,216	$ 218,734.88	8
STRATTERA*	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	1,241	$ 211,125.66	73
TOTAL TOP 25		92,778	$ 13,494,280.14	

Total Rx Claims From 01/01/09-01/31/09	425,605

** Indicates preferred products on Preferred Drug List*

Top 10 Drugs
Based on Total Claims Cost



MISSISSIPPI MEDICAID
Cost Management Analysis

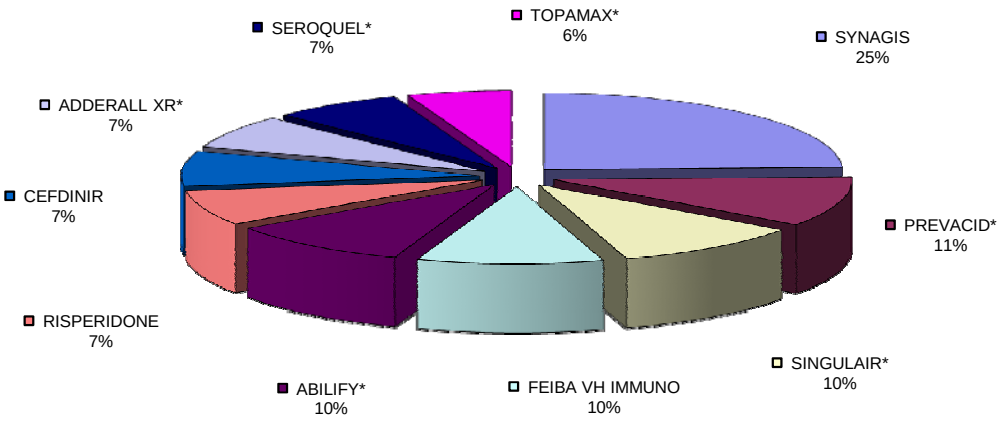
TOP 25 DRUGS BASED ON TOTAL CLAIMS COST FROM 02/01/09-02/28/09

Drug	AHFS Therapeutic Class	Rx	Paid	Top 200 Rank
SYNAGIS	MONOCLONAL ANTIBODIES	1,329	$ 2,083,493.87	~
PREVACID*	PROTON-PUMP INHIBITORS	5,275	$ 894,982.00	4
SINGULAIR*	LEUKOTRIENE MODIFIERS	7,697	$ 880,923.79	6
FEIBA VH IMMUNO	HEMOSTATICS	14	$ 857,607.08	~
ABILIFY*	ANTIPSYCHOTIC AGENTS	1,702	$ 854,002.26	15
RISPERIDONE	ANTIPSYCHOTIC AGENTS	3,196	$ 630,207.45	~
CEFDINIR	CEPHALOSPORINS	8,267	$ 628,326.45	31
ADDERALL XR*	AMPHETAMINES	3,061	$ 606,761.09	27
SEROQUEL*	ANTIPSYCHOTIC AGENTS	1,613	$ 601,973.95	7
TOPAMAX*	ANTICONVULSANTS, MISCELLANEOUS	1,353	$ 478,588.57	13
ZYPREXA	ANTIPSYCHOTIC AGENTS	776	$ 474,549.07	18
AZITHROMYCIN	MACROLIDES	16,187	$ 470,419.98	2
AMOX TR-POTASSIUM CL	PENICILLINS	7,258	$ 392,385.51	9
ACTHAR H.P.	ADRENOCORTICAL INSUFFICIENCY	5	$ 380,467.70	~
CONCERTA*	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	2,635	$ 377,254.12	34
TAMIFLU	NEURAMINIDASE INHIBITORS	4,170	$ 352,684.21	~
ADVAIR DISKUS*	BETA-ADRENERGIC AGONISTS	1,599	$ 311,258.59	3
GEODON*	ANTIPSYCHOTIC AGENTS	709	$ 281,654.68	58
BUDESONIDE	ADRENALS	1,286	$ 280,715.94	~
PULMICORT*	ADRENALS	831	$ 268,685.96	64
LAMOTRIGINE	ANTICONVULSANTS, MISCELLANEOUS	839	$ 232,111.53	181
FOCALIN XR*	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	1,619	$ 226,246.18	133
HYDROCODONE-ACETAM	OPIATE AGONISTS	15,488	$ 224,694.67	1
ALBUTEROL SULFATE	BETA-ADRENERGIC AGONISTS	6,904	$ 224,273.06	59
PLAVIX*	PLATELET-AGGREGATION INHIBITORS	1,483	$ 213,396.21	5
TOTAL TOP 25		95,296	$ 13,227,663.92	

Total Rx Claims From 02/01/09-02/28/09	429,317

** Indicates preferred products on Preferred Drug List*

Top 10 Drugs
Based on Total Claims Cost



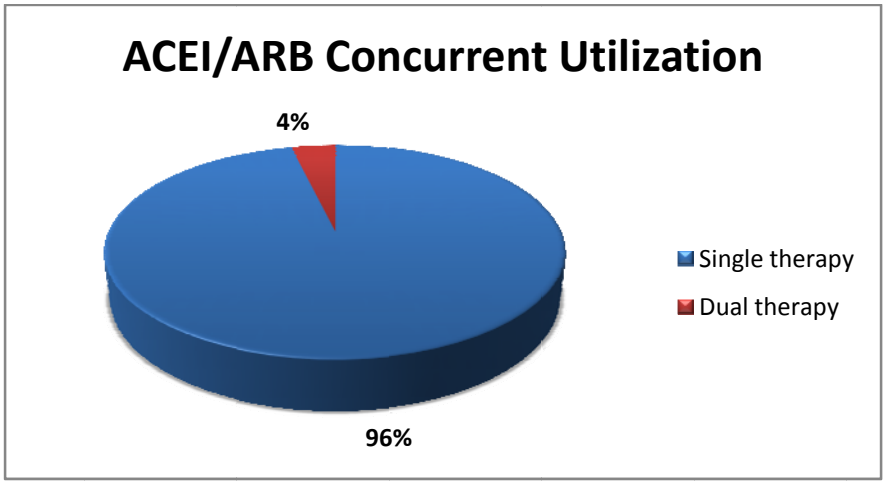
Dual Renin-Angiotensin-Aldosterone System (RAS) Blockade with ACE Inhibitors and Angiotensin Receptor Blockers

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

Mississippi Medicaid

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

Medication	Beneficiary Count
ACEI	15058
ARB	6762
Dual therapy	813



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

Recommendation

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

MISSISSIPPI MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS

Criteria Recommendations ***Approved Rejected***

1. ACE Inhibitors / ARBs _____ _____

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

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

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

References:

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

Pharmalogical Interventions for Dyslipidemia in Children

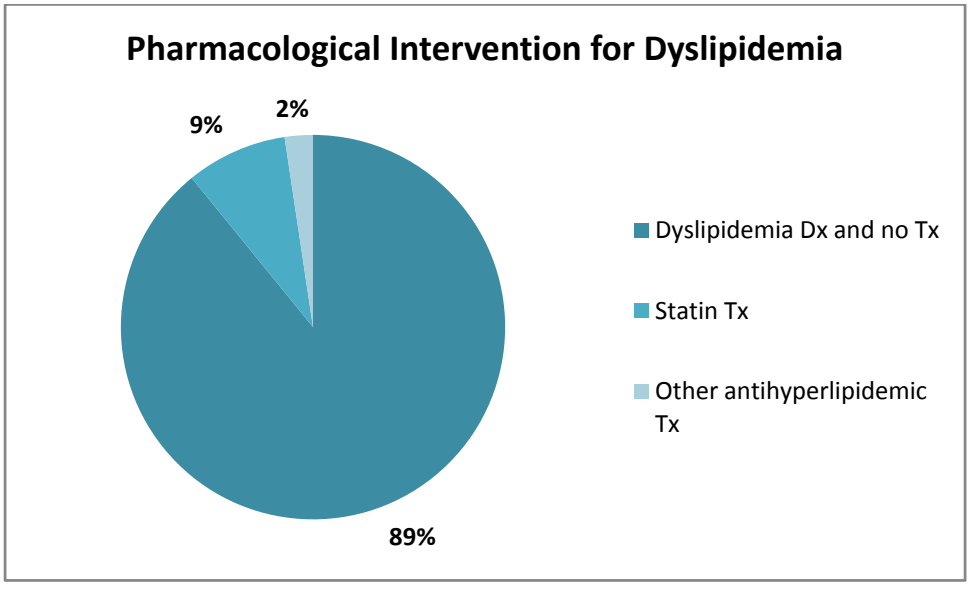
Due to the growing epidemic of obesity, type 2 diabetes mellitus, hypertension and cardiovascular disease in children, the American Academy of Pediatrics felt an urgent need to address the issue of dyslipidemia in the pediatric population. As a result, the AAP revised their guidelines regarding lipid screening and treatment in children in July 2008. These guidelines recommend pharmacological intervention in children ages 8 and older under the following conditions:

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

Autopsy studies have shown that the atherosclerotic process begins in childhood. Therefore, it stands to reason that elevated cholesterol concentrations in childhood and adolescence are associated with an increased risk of atherosclerosis and cardiovascular disease in adulthood for these children.

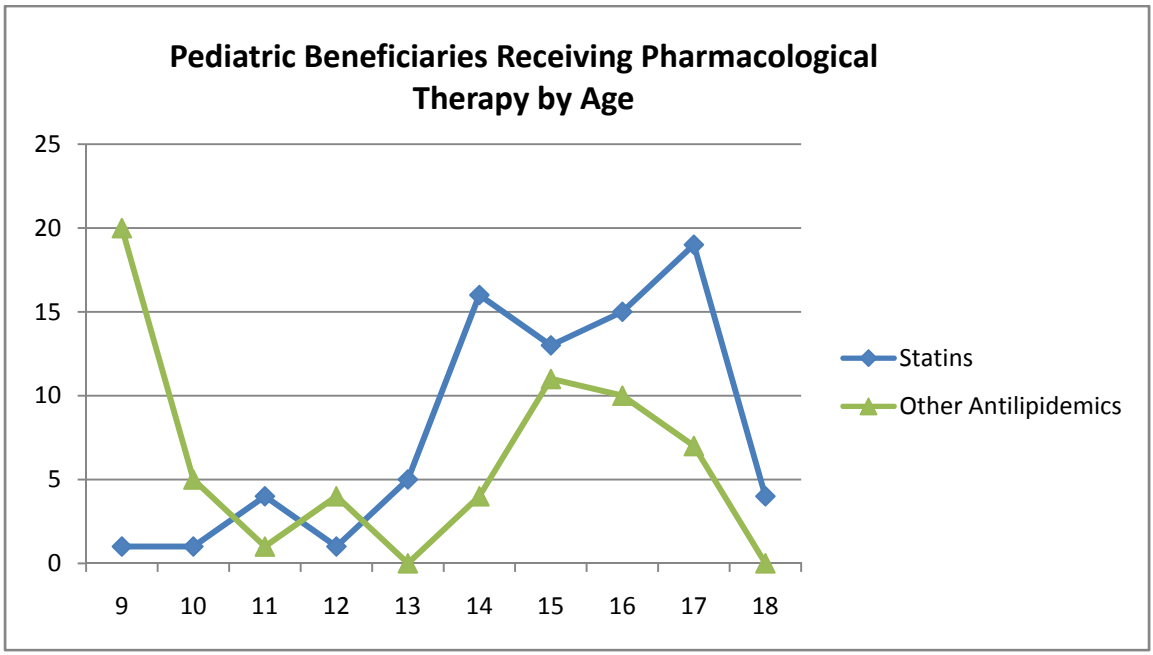
Mississippi Medicaid

HID conducted a claims analyses to determine the rate of pharmacological intervention in pediatric Mississippi Medicaid beneficiaries for dyslipidemia. Two searches were conducted; one for the statins, and one for the other antilipidemics. These searches were conducted for calendar year 2008 for beneficiaries ages 8 through 18. The results are shown below.



Of the 930 beneficiaries ages 8 through 18 identified with a lipid disorder diagnosis in 2008, only 11% received pharmacological treatment of some type for this disorder (9% with a statin and 2% with one of the other antilipidemics). Since the specific LDL levels for these beneficiaries are not known, a

determination of whether this absence of pharmacological treatment is appropriate based on the AAP guidelines cannot be made. Still, such a high percentage of untreated beneficiaries is concerning.



From this chart, one can see that the largest group of beneficiaries receiving either type of pharmacological treatment are those above the age of 13. Another interesting observation to be made from this chart is that more young beneficiaries appear to be started on other antilipidemics (fibric acid derivatives, cholesterol absorption inhibitors, etc) rather than a statin.

Conclusion

As the number of children diagnosed with obesity, diabetes mellitus, and cardiovascular disease increases, the need to develop appropriate and effective treatment guidelines for these children becomes imperative. Increases in cholesterol early in life predispose these children to significant cardiovascular disease as adults; aggressive treatment may be required to lower cholesterol in these patients when diet and exercise fail.

Recommendation

HID recommends the development of a RDUR criterion identifying those pediatric beneficiaries 8 years old and older with any diagnosis of lipid disorder not receiving pharmacological therapy. This criterion may result in an educational letter to the physician informing him/her of the AAP treatment guideline recommendations for this population, providing him/her with valuable information to help determine the most appropriate therapy for the beneficiary.

MISSISSIPPI MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS

Criteria Recommendations ***Approved Rejected***

1. Antihyperlipidemic Agents / Hyperlipidemia Diagnosis _____ _____

Alert Message: The patient has a diagnosis of dyslipidemia and may benefit from the addition of an antihyperlipidemic agent if lifestyle modifications in nutrition and physical activity have been unsuccessful. For patients 8 years and older, depending on LDL levels and number of risk factors, pharmacological intervention with a bile acid sequestrant, statin or cholesterol-absorption blocker may be considered in order to reach target LDL levels and decrease risk of cardiovascular disease.

Conflict Code: AU – Absence of Use
Drugs/Diseases

Util A	Util B	Util C
HMG-CoA Reductase Inhibitors	Hyperlipidemia icd-9s	
Bile Acid Sequestrants		
Cholesterol Absorption Blocker		

Age Range: 8 - 17 years of age

References:

Daniels SR, Greer FR and the Committee on Nutrition, Lipid Screening and Cardiovascular Health in Childhood. Pediatric 2008;122:198-208.
Ford ES, Li C, Zhao G, et al. Concentrations of Low-Density Lipoprotein Cholesterol and Total Cholesterol Among Children and Adolescents in the United States. Circulation. 2009;119:1108-1115.
Kwiterovich PO. Recognition and Management of Dyslipidemia in Children and Adolescents. Jrnl Clinc Endcrinol & Metab. Nov 2008;93:4200-4209.

*This Absence of Use (800) Letter is sent to the physician who is associated with the icd-9 code.

[TODAY]

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

DEAR [tadrs1]:

Health Information Designs, Inc. (HID) is the pharmacy benefits management/drug utilization review organization contracted with the Mississippi Division of Medicaid (DOM) to review pharmacy services provided to Medicaid beneficiaries. Under this contract, we seek to ensure that Medicaid beneficiaries receive appropriate and cost effective drug therapy. One way to achieve this goal is to identify potential drug therapy problems that may place patients at risk, particularly if multiple providers are identified. **This letter is educational in nature and allows you to incorporate the information provided into your continuing assessment of the patient's drug therapy.**

A recent drug history review was conducted on your patient, **[t1d0-recip-fst-nm] [t1d0-recip-lst-nm]**. *The patient has a diagnosis of dyslipidemia and may benefit from the addition of an antihyperlipidemic agent if lifestyle modifications in nutrition and physical activity have been unsuccessful. For patients 8 years and older, depending on LDL levels and number of risk factors, pharmacological intervention with a bile acid sequestrant, statin or cholesterol-absorption blocker may be considered in order to reach target LDL levels and decrease risk of cardiovascular disease.* In presenting this information to you, we recognize that the management of each patient's drug therapy depends upon an assessment of the patient's entire clinical situation about which we are not fully aware.

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

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

RX #(s): [rx_no_a]

Sincerely,

W. Murray Yarbrough M.D.

W. Murray Yarbrough, M.D.
Medical Director
Health Information Designs, Inc.

Case#: [case_no]
Enclosures

PRESCRIBER RESPONSE

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

1. This patient **is** under my care:

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

2. This patient **is not** under my care:

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

3. I have reviewed the enclosed information and found it:
_____ very useful_____ useful_____ neutral_____ somewhat useful_____ not useful.

4. Please check here if you wish to receive reference information on the identified problem___. (Please provide a fax number if available_____-_____-_____.)

Comments: _____
_____
_____
_____

[adrs1] Case# [case_no]
Letter Type [letter_type]
[alert_msg]
[criteria]

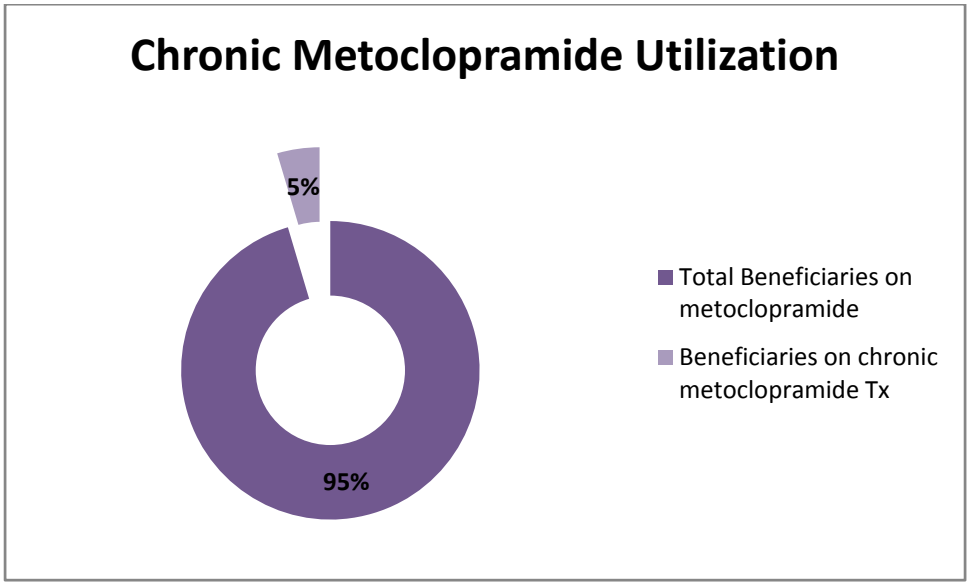
Metoclopramide: New Boxed Warning

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

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

Mississippi Medicaid

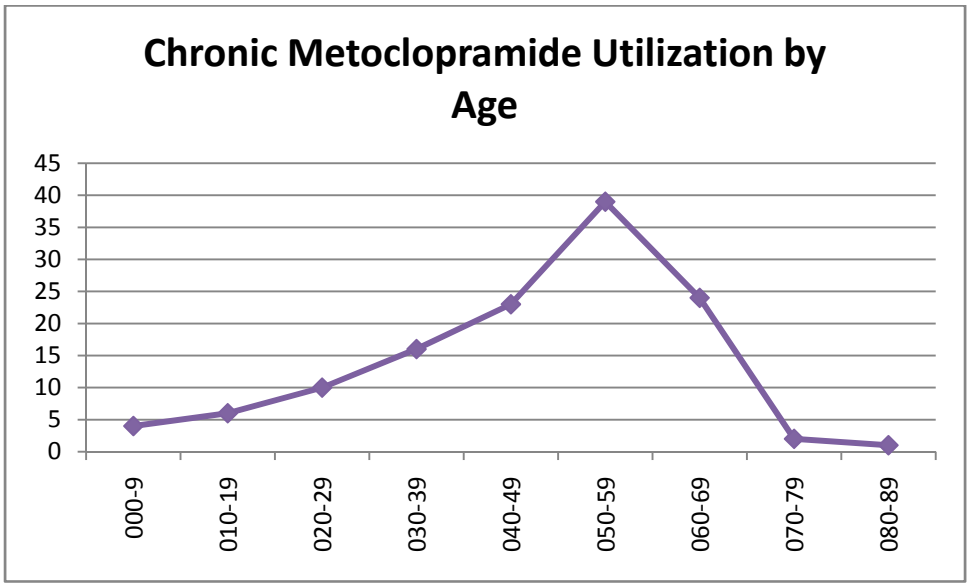
HID conducted claims analyses to determine the extent of chronic use of metoclopramide in the Mississippi Medicaid population. Three searches were conducted over a 6 month time span to identify those beneficiaries who were using metoclopramide continually. The results are included below.



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

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

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



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

Conclusion

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

Recommendation

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

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

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

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

MISSISSIPPI MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS

Criteria Recommendations ***Approved Rejected***

1. Metoclopramide / Over-utilization _____ _____

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

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

Duration: 90 days or greater

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

2. Metoclopramide /Therapeutic Appropriateness _____ _____

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

Age Range: 0 – 17 years of age

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

Criteria Recommendations ***Approved Rejected***

3. Metoclopramide / Meds Causing Extrapyramidal Symptoms _____ _____

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

Conflict Code: DD – Drug Interaction
Drugs/Diseases

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

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

4. Metoclopramide / Seizure Disorders _____ _____

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

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

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

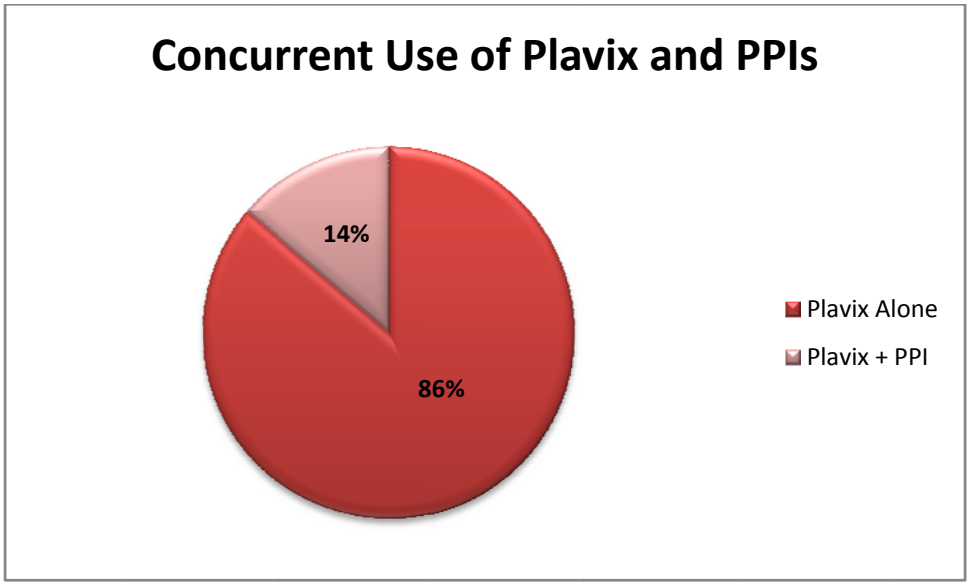
References:
Facts & Comparisons, 2009 Updates.
Reglan Prescribing Information, Feb. 2004, Schwarz Pharma.
Micromedex Healthcare Series, DrugDex Drug Evaluations, 2009.
AHFS Drug Information 2009.

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

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

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

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



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

Conclusion

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

MISSISSIPPI MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS

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

1. Clopidogrel / Proton Pump Inhibitors _____ _____

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

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

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

References:

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

Potential for Overutilization of Strattera®

Strattera® is a selective norepinephrine reuptake inhibitor (SNRI) and is the first nonstimulant drug approved for attention deficit hyperactivity disorder (ADHD). It does not have the potential for abuse and is not classified as a controlled substance, unlike the other medications used for ADHD. Clinical guidelines recommend the use of the stimulants methylphenidate, dextroamphetamine, or amphetamine salts, in combination with behavioral therapy as first line treatment of ADHD. However, Strattera® may be considered an alternate therapy in patients where stimulants are not an option or if initially preferred by the parents and/or health care provider.

During recent conversations with personnel from other Medicaid pharmacy departments, it was brought to DOM's attention that overutilization of Strattera® is a problem in many states. In addition, the manufacturer has also reported awareness of this issue. Some states report that the norm for their ADHD population is twice daily dosing with Strattera®. While the product labeling does provide instructions for twice daily dosing, the potential exists for total daily doses well over the 100-mg maximum recommended dose set by the manufacturer, particularly when using different strengths of the medication. Based on these reports, the Division of Medicaid asked HID to conduct claims analyses to determine if this was a problem in the Mississippi Medicaid population.

HID conducted claims searches for the 2008 calendar year, addressing specific questions presented by DOM. The questions and the results are detailed below.

1) How many beneficiaries receive more than 62 capsules per month of a given strength of Strattera®?

With utilization of all strengths combined, 75 (2.1%) of the 3,525 total beneficiaries in 2008 who received Strattera® received more than 62 capsules per month of Strattera®.

Utilization	Claims	Beneficiaries
Total utilization	14,488	3,525
Claims >62 caps	255	75
% Claims >62 caps	1.70%	2.10%

HID then looked at utilization of each strength to determine which strength saw the most utilization for >62 capsules per month. While the 25mg capsules had the largest claim volume for more than 62 capsules per month, the 40mg capsules was the only strength found with total daily doses exceeding 100mg with 7 (50%) of the claims for 40mg capsules exceeding the maximum daily recommended dose.

Label Name	Rx Num	Qty Dispensed	Total DOM Cost	Number of Claims For >100mg/Day
STRATTERA® 25 MG CAPSULE	105	10352	$43,545.13	0
STRATTERA® 18 MG CAPSULE	74	7623	$32,485.31	0
STRATTERA® 10 MG CAPSULE	62	6752	$26,353.78	0
STRATTERA® 40 MG CAPSULE	14	1075	$4,920.06	7
Totals	**255**	**25802**	**$107,304.28**	**7**

2) How many beneficiaries receive more than one strength of Strattera® in a given month?

November 2008 - December 2008							
Strength	**10**	**18**	**25**	**40**	**60**	**80**	**100**
10		10	17	3	4	0	0
18	10		27	4	3	0	0
25	17	27		33	5	0	1
40	3	4	33		22	2	1
60	4	3	5	22		4	0
80	0	0	0	2	4		0
100	0	0	1	1	0	0	

From the chart above, it is obvious that there are many beneficiaries receiving multiple strengths of Strattera® in a given month. When looking at November and December 2008, the strength combinations with the largest numbers of beneficiaries are 18mg-25mg, 25mg-40mg, and 40mg-60mg.

3) How many beneficiaries receive more than 100mg/day?

After looking at each of the prescription profiles of the beneficiaries who received more than one strength of Strattera® in November and December, only one beneficiary was found to be taking both strengths concurrently. It was discovered that most of the beneficiaries who were identified as receiving more than one strength either:

- Started off with a lower strength for 3-14 days and then were increased to a higher strength for maintenance.
- Were changed from one strength to another during the time period analyzed

When looking at the data for the entire calendar year, there were 7 beneficiaries who received more than 62 capsules of Strattera® 40mg, putting them over the recommended maximum dose of 100mg/day.

4) **Of those beneficiaries on more than one strength, how many are receiving both strengths from the same prescriber?**

After looking at each of the prescription profiles of the beneficiaries who received more than one strength of Strattera® in November and December, HID determined that a vast majority of these beneficiaries are receiving both strengths from the same prescriber.

Conclusion

The issue of overutilization of Strattera® has been brought to the Division of Medicaid's attention by other state Medicaid agencies as well as the manufacturer. Based on claims analyses of the Mississippi Medicaid population, this does not appear to be a significant problem for our state yet. But, as a proactive measure, the Division is contemplating on implementation of cumulative quantity limits of 62 capsules per month for all strengths of Strattera beginning July 1, 2009. Any prescribers who are caring for a beneficiary that they feel need more than this limit may submit a Maximum Unit Override request for review by the HID clinical staff.

MISSISSIPPI MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS
2ND QUARTER 2009

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

1. Milnacipran / Over-utilization _____ _____

Alert Message: The recommended dose of Savella (milnacipran) is 100 mg per day given in two divided doses. Milnacipran therapy should always begin with dosing at 12.5 mg and increase to 100 mg per day over a 1-week period. The daily dose may be increased to 200 mg per day based on individual response.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Milnacipran		

Max Dose: 200 mg per day

References:
Savella Prescribing Information, Jan. 2009, Cypress Bioscience, Inc.

2. Milnacipran / Nonadherence _____ _____

Alert Message: Non-adherence to the prescribed dosing regimen for Savella (milnacipran) may result in loss of therapeutic effect.

Conflict Code: LR – Non-adherence
Drugs/Diseases

Util A	Util B	Util C
Milnacipran		

Less than 75 days in 90 day review.

References:
Savella Prescribing Information, Jan. 2009, Cypress Bioscience, Inc.

3. Milnacipran / Monoamine Oxidase Inhibitors _____ _____

Alert Message: The concurrent use of Savella (milnacipran) and a monoamine oxidase inhibitor (MAOI) is contraindicated. Milnacipran has serotonin reuptake inhibitor activity and the use of this agent with a MAOI may cause a rapid, excessive accumulation of serotonin resulting in serious, sometimes, fatal reactions. Milnacipran should not be used within 14 days of discontinuing an MAOI and at least 5 days should elapse after stopping milnacipran before starting an MAOI.

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

Util A	Util B	Util C
Milnacipran	Isocarboxazid Tranylcypromine Phenelzine	

References:
Savella Prescribing Information, Jan. 2009, Cypress Bioscience, Inc.

Criteria Recommendations ***Approved Rejected***

4. Milnacipran / Risk of Suicide (Black Box Warning) _____ _____

Alert Message: Savella (milnacipran) is a selective serotonin and norepinephrine reuptake inhibitor (SNRI), similar to some drugs used for the treatment of depression and other psychiatric disorders. SNRIs may increase the risk compared to placebo of suicidal thinking and behavior in children, adolescents, and young adults with major depressive disorder and other psychiatric disorders. Monitor patients closely for unusual changes in behavior.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Milnacipran		

References:
Savella Prescribing Information, Jan 2009, Cypress Bioscience, Inc.
Facts & Comparisons, 2009 Updates.

5. Milnacipran / Uncontrolled Narrow Angle Glaucoma _____ _____

Alert Message: The use of Savella (milnacipran) is contraindicated in patients with uncontrolled narrow angle glaucoma. In clinical trials, milnacipran was associated with an increased risk of mydriasis. Milnacipran is a selective serotonin/norepinephrine reuptake inhibitor and mydriasis has been reported with other dual reuptake inhibitors agents.

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

Util A	Util B	Util C
Milnacipran	Narrow Angle Glaucoma	

References:
Savella Prescribing Information, Jan. 2009, Cypress Bioscience, Inc.
Facts & Comparisons, 2009 Updates.

6. Milnacipran / Serotonergic Drugs _____ _____

Alert Message: The concurrent use of Savella (milnacipran) and a serotonergic drug is not recommended. Milnacipran is a selective serotonin/norepinephrine reuptake inhibitor and concomitant therapy with other serotonergic drugs may cause accumulation of serotonin and increase the risk of serotonin syndrome (e.g., mental status changes, hypertension, vasoconstriction, and neuronal aberrations).

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

Util A	Util B		Util C
Milnacipran	Triptans	TCAs	
	Tramadol	Mirtazapine	
	SSRIs	Bupropion	
	SNRIs	Trazodone	
	Nefazodone	Codeine	
	Fentanyl	Zyvox	
	Lithium		

References:
Savella Prescribing Information, Jan. 2009, Cypress Bioscience, Inc.
Facts & Comparisons, 2009 Updates.

Criteria Recommendations ***Approved Rejected***

7. Milnacipran / Clonidine _____ _____

Alert Message: Concurrent use of Savella (milnacipran) and clonidine may result in the loss of blood pressure control. Clonidine acts to decrease norepinephrine (NE) release in the brain which leads to a reduction in arterial blood pressure. Milnacipran inhibits NE reuptake, thereby increasing NE levels and inhibiting the effects of clonidine.

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

Util A	Util B	Util C
Milnacipran	Clonidine	

References:
Savella Prescribing Information, Jan. 2009, Cypress Bioscience, Inc.
Facts & Comparisons, 2009 Updates.

8. Milnacipran / Seizures _____ _____

Alert Message: Savella (Milnacipran) should be used with caution in patients with a history of seizure disorders. Seizures have been reported, infrequently, in patients treated with milnacipran for disorders other than fibromyalgia.

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

Util A	Util B	Util C
Milnacipran	Seizures	
	Epilepsy	
	Convulsions	

References:
Savella Prescribing Information, Jan. 2009, Cypress Bioscience, Inc.
Facts & Comparisons, 2009 Updates.

9. Milnacipran / Hypertension _____ _____

Alert Message: Savella (milnacipran) may cause elevated blood pressure and heart rate. Monitor blood pressure and heart rate prior to initiating milnacipran therapy and periodically throughout treatment.

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

Util A	Util B	Util C
Milnacipran	Hypertension ICD-9	
	Beta Blockers	
	ACE Inhibitors	
	ARBs	
	Diuretics	
	Calcium Channel Blockers	
	Antiadrenergic Agents - Centrally Acting & Peripherally	
	Peripheral Vasodilators	

References:
Savella Prescribing Information, Jan. 2009, Cypress Bioscience, Inc.
Facts & Comparisons, 2009 Updates.

Criteria Recommendations ***Approved Rejected***

10. Febuxostat / Over utilization _____ _____

Alert Message: The recommended starting dose of Uloric (febuxostat) is 40 mg once daily and may be increased to 80 mg once daily in patients who do not achieve a serum uric acid (sUA) less than 6 mg per dL after 2 weeks with the 40 mg. Exceeding the recommended daily dose may cause a risk of adverse effects (e.g., rash, arthralgia, nausea, and liver function abnormalities).

Conflict Code: ER – Overutilization
Drugs/Diseases

Util A	Util B	Util C
Febuxostat		

Max Dose: 80 mg per day

References:
Uloric Prescribing Information, Feb. 2009, Takeda Pharmaceuticals America, Inc.

11. Febuxostat / Nonadherence _____ _____

Alert Message: Non-adherence to the prescribed dosing regimen for Uloric (febuxostat) may result in loss of therapeutic effect.

Conflict Code: LR – Underutilization
Drugs/Diseases

Util A	Util B	Util C
Febuxostat		

Less than a 75 day supply in 90 days

References:
Uloric Prescribing Information, Feb. 2009, Takeda Pharmaceuticals America, Inc.

12. Febuxostat / Azathioprine, Mercaptopurine & Theophylline _____ _____

Alert Message: Uloric (febuxostat) is contraindicated in patients being treated with drugs metabolized by xanthine oxidase (i.e., azathioprine, mercaptopurine, and theophylline). Febuxostat is a xanthine oxidase (XO) inhibitor and concurrent use of febuxostat with drugs metabolized by XO may cause substantially increased plasma concentrations of the XO metabolized drug leading to severe toxicity.

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

Util A	Util B	Util C
Febuxostat	Azathioprine	
	Mercaptopurine	
	Theophylline	

References:
Uloric Prescribing Information, Feb. 2009, Takeda Pharmaceuticals America, Inc.

Criteria Recommendations ***Approved Rejected***

13. Febuxostat / Cardiovascular Events (Warning) _____ _____
Alert Message: In clinical trials, patients treated with Uloric (febuxostat) had a higher rate of cardiovascular thromboembolic events than allopurinol-treated patients. Monitor patients for signs and symptoms of MI or stroke.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases
Util A Util B Util C
Febuxostat

References:
Uloric Prescribing Information, Feb. 2009, Takeda Pharmaceuticals America, Inc.

14. Febuxostat / Liver Enzyme Elevation (Warning) _____ _____
Alert Message: It is recommended that patients receiving Uloric (febuxostat) receive laboratory assessment of liver function at 2 and 4 months following Initiation of febuxostat and periodically thereafter. In controlled studies, elevated transaminase elevations were observed and were the most common adverse event that led to discontinuation of the drug.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases
Util A Util B Util C
Febuxostat

References:
Uloric Prescribing Information, Feb. 2009, Takeda Pharmaceuticals America, Inc.

FDA Updates

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

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

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

Plavix (Clopidogrel bisulfate)
FDA notified healthcare professionals that the makers of Plavix have agreed to work with FDA to conduct studies to obtain additional information that will allow a better understanding and characterization of the effects of genetic factors and other drugs (especially the proton pump inhibitors (PPIs)) on the effectiveness of clopidogrel. FDA is aware of published reports that clopidogrel is less effective in some patients than it is in others. Differences in effectiveness may be due to genetic differences in the way the body metabolizes clopidogrel or that using certain other drugs with clopidogrel can interfere with how the body metabolizes clopidogrel. These studies should lead to a better understanding about how to optimize the use of clopidogrel. The FDA recognizes the importance of obtaining these data promptly. The drug manufacturers have agreed to a timeline for completing the studies and FDA will review the new information expeditiously and will communicate its conclusions and any recommendations to the public at that time. It could take several months to complete the studies and analyze the results. Until further information is available FDA recommends the following:

- Healthcare providers should continue to prescribe and patients should continue to take clopidogrel as directed, because clopidogrel has demonstrated benefits in preventing blood clots that could lead to a heart attack or stroke.
- Healthcare providers should re-evaluate the need for starting or continuing treatment with a PPI, including Prilosec OTC, in patients taking clopidogrel.
- Patients taking clopidogrel should consult with their healthcare provider if they are currently taking or considering taking a PPI, including Prilosec OTC. \

Ethex Corporation Product Recall
FDA notified pharmacists and consumers that ETHEX Corporation has expanded two previous 2008 recalls to include over 60 generic drug products recalled to wholesalers, and two generic drug products, Hydromorphone HCl and Metoprolol Succinate, recalled to retailer level. These generic products may have been manufactured under conditions that did not sufficiently comply with current Good Manufacturing Practices. Some of these products have had specific lots recalled earlier due to defects found, including oversized tablets delivering higher than labeled doses. These additional products are being removed to assure that no other defective products remain in the marketplace. Patients who may have these medicines in their possession should continue to take them in accordance with their prescriptions, as the risk of suddenly stopping needed medication may place patients at risk. Patients should contact their physician or healthcare provider if they have experienced any problems that may be related to taking or using these products, or to obtain replacement medications or prescriptions.

Xigris (Drotrecogin alfa [activated])
FDA is aware of a recently published study, a retrospective medical record review of 73 patients who receive Drotrecogin alfa (activated), marketed as Xigris, indicated for the reduction of mortality in adult patients with severe sepsis who have a high risk of death (Gentry et al.; Crit Care Med 2009).The study reported an increased risk of serious bleeding events and of death in patients with sepsis and baseline bleeding risk factors who received this product. Serious bleeding events occurred in 7 of 20 patients (35%) who had a bleeding risk factor vs. only 2 of 53 (3.8%) patients without any bleeding risk factors. The finding by Gentry et al. of an increased risk of death and serious bleeding events in patients treated with Xigris who also have baseline bleeding risk factors is consistent with the information in the current product label. Prescribers should refer to the product label for the specific contraindications, warnings, and, precautions and carefully weigh the increased risk of bleeding against the benefits of Xigris.

FDA is working with the manufacturer to further evaluate the incidence of serious bleeding events and mortality in patients who received Xigris. FDA will communicate its conclusions and any resulting recommendations to the public when the review is completed, which may take several months. The FDA urges both healthcare professionals and patients to report side effects from the use of Xigris to the FDA's MedWatch Adverse Event Reporting program.

Raptiva (Efalizumab)
FDA issued a Public Health Advisory to notify healthcare professionals of three confirmed, and one possible report of progressive multifocal leukoencephalopathy (PML), a rare brain infection, in patients using the psoriasis drug Raptiva. In October 2008, the labeling for Raptiva was changed to highlight, in a Boxed Warning, the risks of life-threatening infections, including PML. In addition, FDA directed Genentech, the manufacturer of Raptiva, to develop a Risk Evaluation and Mitigation Strategy, or REMS, to ensure that patients receive risk information about Raptiva. The FDA is reviewing this latest information. The agency will take appropriate steps to ensure that the risks of Raptiva do not outweigh

its benefits, that patients prescribed Raptiva are clearly informed of the signs and symptoms of PML, and that health care professionals carefully monitor patients for the possible development of PML. The Public Health Advisory provides recommendations for healthcare providers and patients when treatment with this product is considered.

Zonisamide
FDA notified healthcare professionals that updated clinical data has determined that treatment with zonisamide, indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy, can cause metabolic acidosis in some patients. Patients with predisposing conditions or therapies may be at greater risk for developing metabolic acidosis and the risk of zonisamide-induced metabolic acidosis appears to be more frequent and severe in younger patients. FDA recommends that healthcare professionals measure serum bicarbonate before starting treatment and periodically during treatment with zonisamide, even in the absence of symptoms and is working with the makers of zonisamide to revise the product labeling to reflect this new safety information. The notification includes recommendations for healthcare providers, information for patients, and a data summary.

Metoclopramide
FDA notified healthcare professionals that manufacturers of metoclopramide, a drug used to treat gastrointestinal disorders, must add a boxed warning to their drug labels about the risk of its long-term or high-dose use. Chronic use of metoclopramide has been linked to tardive dyskinesia, which may include involuntary and repetitive movements of the body, even after the drugs are no longer taken. These symptoms are rarely reversible and there is no known treatment. Metoclopramide is available in a variety of formulations including tablets, syrups and injections. Names of metoclopramide-containing products include Reglan Tablets, Reglan Oral Disintegrating Tablets, Metoclopramide Oral Solution, and Reglan Injection. Manufacturers will be required to implement a risk evaluation and mitigation strategy [REMS] to ensure patients are provided with a medication guide that discusses this risk. Current product labeling warns of the risk of tardive dyskinesia with chronic metoclopramide treatment.

Transdermal patches
FDA notified healthcare professionals and patients that certain transdermal patches (medicated patches applied to the skin), containing aluminum or other metals in the backing of the patches, can overheat during an MRI scan and cause skin burns in the immediate area of the patch. FDA is in the process of reviewing the labeling and composition of all medicated patches to ensure that those made with materials containing metal provide a warning about the risk of burns to patients who wear the patches during an MRI scan. Until this review is complete, FDA recommends that healthcare professionals referring patients to have an MRI scan identify those patients who are wearing a patch before the patients have the MRI scan. The healthcare professional should advise these patients about the procedures for removing and disposing of the patch before the MRI scan, and replacing the patch after the MRI scan. MRI facilities should follow published safe practice recommendations concerning patients who are wearing patches.

Propafenone Tablets
FDA and Watson Pharmaceuticals notified healthcare professionals and patients of a recall of Propafenone HCL 225 mg tablets, a drug product used to treat cardiac arrhythmias. The drug is being recalled because some tablets may contain slightly higher levels of the active ingredient than specified. Because it has a narrow therapeutic index, some patients who are particularly sensitive to small variations in dose may experience potentially serious side effects, including arrhythmias (irregular heartbeat) or low blood pressure. The affected lot [lot number 112680A, expiration date July 31, 2010]

of Propafenone HCL tablets was shipped to customers between October 15, 2008 and November 26, 2008.

Digoxin Tablets
Caraco Pharmaceutical Laboratories and FDA notified healthcare professionals of a consumer-level recall of Caraco brand Digoxin, USP, 0.125 mg, and Digoxin, USP, 0.25 mg, distributed prior to March 31, 2009, which are not expired and are within the expiration date of September, 2011. The tablets are being recalled because they may differ in size and therefore could have more or less of the active ingredient, digoxin, a drug product used to treat heart failure and abnormal heart rhythms. The drug has a narrow therapeutic index and the existence of higher than labeled dose may pose a risk of digoxin toxicity in patients with renal failure. Digoxin toxicity can cause nausea, vomiting, dizziness, low blood pressure, cardiac instability, and bradycardia. Death can also result from excessive digoxin intake. A lower than labeled dose may pose a risk of lack of efficacy potentially resulting in cardiac instability. Consumers with the recalled product should return these products to their pharmacy or place of purchase.

Raptiva (efalizumab)
Genentech and FDA notified healthcare professionals of the voluntary, phased withdrawal of Raptiva, a medication for treatment of psoriasis, from the U.S. market due to a potential risk to patients of developing progressive multifocal leukoencephalopathy (PML). By June 8, 2009, Raptiva will no longer be available in the United States. Prescribers are being asked not to initiate Raptiva treatment for any new patients. Prescribers should immediately begin discussing with patients currently using Raptiva how to transition to alternative therapies. The FDA strongly recommends that patients work with their health care professional to transition to alternative therapies for psoriasis.

Ceftriaxone (marketed at Rocephin and generics)
FDA notified healthcare professionals of an update to a previous alert that addresses the interaction of ceftriaxone with calcium-containing products, based on previously reported fatal cases in neonates. At the request of FDA, the manufacturer of ceftriaxone (Roche) conducted two in vitro studies to assess the potential for precipitation of ceftriaxone-calcium when ceftriaxone and calcium-containing products are mixed in vials and in infusion lines. These two in vitro studies were conducted in neonatal and adult plasma to assess the potential for precipitation of ceftriaxone-calcium using varying ceftriaxone and calcium concentrations, including concentrations in excess of those achieved in vivo. Based on the results from these studies, FDA now recommends that ceftriaxone and calcium-containing products may be used concomitantly in patients >28 days of age, using the precautionary recommendations noted because the risk of precipitation is low in this population. FDA had previously recommended, but no longer recommends, that in all age groups ceftriaxone and calcium-containing products should not be administered within 48 hours of one another.