South Dakota

Department of Social Services

Medicaid P&T Committee Meeting

June 12, 2009

DEPARTMENT OF SOCIAL SERVICES
MEDICAL SERVICES
700 Governors Drive
Pierre, South Dakota 57501-2291
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SOUTH DAKOTA
MEDICAID P&T COMMITTEE MEETING
AGENDA

Friday, June 12, 2009
1:00 – 3:00 PM

DDN Locations:
Sioux Falls
University Center Room 282S
2205 Career Avenue

Pierre
Capitol Building Room B12
500 E Capitol

Rapid City
School of Mines
Classroom Building Room 109

Call to Order

Approval of Minutes of Previous Meeting

Prior Authorization Update

Review of Top 15 Therapeutic Categories/Top 25 Drugs

Old Business
- **Psychotropic Mailing Update**
- **Antidepressant Mailing Update**
- **Xopenex® Update**

New Business

Drug Product and Utilization Review
- **Targeted Immunomodulators Review (Enbrel®, Kineret®, Orencia®, Humira®, Remicade®, Cimzia®, Raptiva® and Amevive®**

Newer Products to Market Review
- **Moxatag, Uloric, Bystolic, Fexmid, Amrix**

Oral Presentations and Comments by Manufacturers' Representatives

Next Meeting Date/Adjournment

Minutes of the March 13, 2009
Pharmacy & Therapeutics (P&T) Committee Meeting
SD Department of Social Services, Medical Services Division

Members present
Verdayne Brandenburg, M.D.; Galen Goeden, R.Ph.; William Ladwig, R.Ph.; Dennis Hedge, PharmD.; Rick Holm, M.D.; Debra Farver, PharmD.; Timothy Soundy, M.D.

Members absent
Dana Darger, R.Ph.; James Engelbrecht, M.D.; Willis Sutliff, M.D.

DSS staff present
Mike Jockheck, R.Ph.; Revi Warne, DSS; Larry Iversen, Director, Division of Medical Services.

HID staff present
Candace Rieth, Pharm.D.

Administrative Business
The P&T meeting was called to order by V. Brandenburg at approximately 1:08pm. The minutes of the December 12, 2008 meeting were presented. R. Holm made a motion to approve as written, with a second by B. Ladwig. The motion was approved unanimously.

Prior Authorization Statistics
C. Rieth presented an overview of the prior authorization (PA) activity for January 2009. There were a total of 1,690 PAs processed in the month of January, with 99.76% of those requests responded to in less than 8 hours. There were 1,502 (89%) requests received electronically and 188 (11%) requests received by fax. In response to a request from the committee, C. Rieth presented the number of approvals and denials, by form type, for the faxed (manual) PA requests.

Analysis of the Top 15 Therapeutic Classes
C. Rieth reviewed the Top 15 Therapeutic Classes by total cost of claims from 10/01/2008 – 12/31/2008. The top five classes were antipsychotics, anticonvulsants, cerebral stimulants, amphetamines, and antidepressants. The top 15 therapeutic classes make up 42.28% of total claims.

Duplicate Antipsychotic Therapy Update
At the December P&T meeting, T. Soundy made a motion to recommend that the State investigate duplicate antipsychotic therapy. T. Soundy suggested that this be done through an internal peer review process. D. Hedge mentioned that the DUR Board reviewed patient profiles and sent letters on those patients receiving duplicate antipsychotic therapy. D. Hedge stated that those letters were mailed and that the Board is waiting to receive the surveys back from the practitioners. An update will be given at a future P&T meeting.

T. Soundy made a motion to send letters to the top 100 prescribers of psychotropic medications. The letter should include information regarding average cost per prescription of at least the top 10 medications showing less expensive options. B. Ladwig seconded the motion. There was no public comment. The motion was approved unanimously. This letter will be drafted and reviewed by the Department and an update will be given at the next P&T meeting.

Future Agenda Item

B. Ladwig made a motion that new drugs coming to market be reviewed at each P&T meeting. G. Goeden seconded the motion. L. Iversen informed the committee that all products must be covered by Medicaid if a rebate agreement is signed between the manufacturer of the product and CMS. The P&T committee may review products for prior authorization as long as public notice and the opportunity for public comment are given. There was no public comment. The motion passed unanimously.

Antidepressant Mailing Update

C. Rieth informed the committee that the final draft of the antidepressant letter to be mailed has been sent to the Department for approval. This letter should be mailed prior to the next committee meeting.

Quantity Limits Update

C. Rieth informed the committee that the quantity limits approved at the last meeting are in the process of being implemented.

Singulair Review

At the December meeting, V. Brandenburg made a motion to place Singulair on prior authorization with an automatic approval on the first prescription received by a recipient. This would allow providers time to submit a diagnosis for their patients. The motion was tabled pending review of data submitted by Merck, manufacturer of Singulair. After review of the data, B. Ladwig made a motion to send an educational letter to prescribers of Singulair informing them of costs as well as the guidelines for use. R. Holm seconded the motion. M. Daniels, representing Merck, spoke against prior authorization of Singulair. The motion passed unanimously. A sample letter will be brought to the next meeting.

Xopenex Review

C. Rieth reviewed the sample letter that will be sent informing prescribers of comparative costs of short acting beta agonists.

Lyrica Review

C. Rieth reviewed Lyrica and Gabapentin utilization. G. Goeden made a motion to place Lyrica on prior authorization. D. Farver seconded the motion. J. Blow, a local practitioner, spoke against prior authorization of Lyrica. C. Hoffman, representing Pfizer, spoke against prior authorization of Lyrica. Roll call was taken; Farver, yes; Hedge, no; Goeden, yes; Ladwig, no; Soundy, no; Holm, no; Brandenburg, no. Motion failed. Lyrica will not require a prior authorization.

Targeted Immunomodulator Review

Because of time restraints, V. Brandenburg made a motion to defer the Targeted Immunomodulator Review until the next meeting. B. Ladwig seconded the motion. Motion passed unanimously.

Xolair Review

C. Rieth reviewed Xolair utilization. B. Ladwig made a motion to place Xolair on prior authorization. D. Farver seconded the motion. There was no public comment. Motion passed unanimously.

The next meeting date is June 12, 2009. The location will be sent to members and interested parties as soon as possible. A motion was made by V. Brandenburg at 3:00pm to adjourn the SD Medicaid P&T. B. Ladwig seconded. Motion passed unanimously and the meeting was adjourned.

South Dakota Medicaid
Monthly Prior Authorization Report
April 1, 2009 – April 30, 2009

PA Response Time Ratio

Total PAs	Response Under 8 Hours	Response Over 8 Hours	% Under 8 Hours	% Over 8 Hours
1,781	1,779	2	99.89%	0.11%

By Form Type

Form Type	Description	Approve	Deny
ALT	Altabax	0	33
AMB	Ambien CR	1	1
ANT	Antihistamines	35	69
ARB	ARBS	26	27
DAW	Dispense As Written	13	22
GRH	Growth Hormone	8	0
HLM	Head Lice Medication	0	3
MAX	Max Units Override	159	1,041
PPI	Proton Pump Inhibitors	93	223
VUS	Vusion	0	27
Totals		335	1,446

By Request Type

04/01/09 - 04/30/09	# of	Electronic Requests		Faxed Requests		Mailed Requests		Phone Requests	
	Requests	#	%	#	%	#	%	#	%
Prior Authorizations:									
Altabax	33	33	100%	0	0%	0	0%	0	0%
Ambien CR	2	2	100%	0	0%	0	0%	0	0%
Antihistamines	104	81	78%	23	22%	0	0%	0	0%
ARBS	53	45	85%	8	15%	0	0%	0	0%
Dispense As Written	35	18	51%	17	49%	0	0%	0	0%
Growth Hormone	8	0	0%	8	100%	0	0%	0	0%
Head Lice Medication	3	0	0%	3	100%	0	0%	0	0%
Max Units Override	1,200	1,054	88%	146	12%	0	0%	0	0%
Proton Pump Inhibitors	316	223	71%	93	29%	0	0%	0	0%
Vusion	27	26	96%	1	4%	0	0%	0	0%
Prior Authorization Totals	1,781	1,482	83%	299	17%	0	0%	0	0%

South Dakota Medicaid
Monthly PA Report
April 1, 2009 – April 30, 2009

Electronic PAs (unique)

04/01/09 - 4/30/09	# Unique Approved	# Unique Denied	# Unique Incomplete	Unique Total	Approval %	Total Transactions
Prior Authorizations:						
Altabax	0	31	0	31	0.00%	33
Ambien CR	1	1	0	2	50.00%	2
Antihistamines	12	69	0	81	14.80%	81
ARBS	19	24	0	43	44.20%	45
Dispense As Written	0	18	0	18	0.00%	18
Max Units Override	40	976	0	1,016	3.90%	1,054
Proton Pump Inhibitors	25	185	0	210	11.90%	223
Vusion	0	26	0	26	0.00%	26
Prior Authorization Totals:	97	1,330	0	1,427	6.8%	1,482

Manual Approvals and Denials

04/01/09 - 04/30/09	# Requests	# Approved	# Denied
Prior Authorizations:			
Antihistamines	23	23	0
ARBS	8	7	1
Dispense as Written	17	13	4
Growth Hormone	8	8	0
Head Lice	3	0	3
Max Units	146	117	29
Proton Pump Inhibitors	93	68	25
Vusion	1	0	1
Prior Authorization Totals:	299	236	63

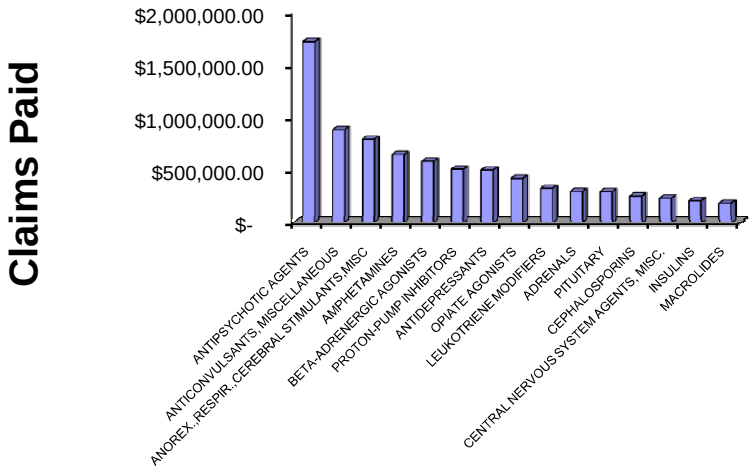
SOUTH DAKOTA MEDICAID
Cost Management Analysis

TOP 15 THERAPEUTIC CLASSES BY TOTAL COST OF CLAIMS FROM 01/01/2009 - 03/25/2009

AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
ANTIPSYCHOTIC AGENTS	6,556	$ 1,718,395.15	$ 262.11	3.48%
ANTICONVULSANTS, MISCELLANEOUS	6,105	$ 882,827.70	$ 144.61	3.24%
ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	5,697	$ 793,330.96	$ 139.25	3.02%
AMPHETAMINES	4,085	$ 648,222.51	$ 158.68	2.17%
BETA-ADRENERGIC AGONISTS	9,277	$ 583,914.79	$ 62.94	4.92%
PROTON-PUMP INHIBITORS	5,406	$ 509,039.73	$ 94.16	2.87%
ANTIDEPRESSANTS	12,811	$ 500,727.97	$ 39.09	6.79%
OPIATE AGONISTS	11,889	$ 421,816.52	$ 35.48	6.30%
LEUKOTRIENE MODIFIERS	3,029	$ 326,418.03	$ 107.76	1.61%
ADRENALS	4,964	$ 296,840.79	$ 59.80	2.63%
PITUITARY	504	$ 295,210.73	$ 585.74	0.27%
CEPHALOSPORINS	6,610	$ 253,597.65	$ 38.37	3.51%
CENTRAL NERVOUS SYSTEM AGENTS, MISC.	1,250	$ 234,359.51	$ 187.49	0.66%
INSULINS	1,567	$ 209,923.26	$ 133.97	0.83%
MACROLIDES	8,078	$ 185,034.98	$ 22.91	4.28%
TOTAL TOP 15	87,828	$ 7,859,660.28	$ 89.49	46.57%

Total Rx Claims From 01/01/2009 - 03/25/2009	188,577

Top 15 Therapeutic Classes
Based on Total Cost of Claims

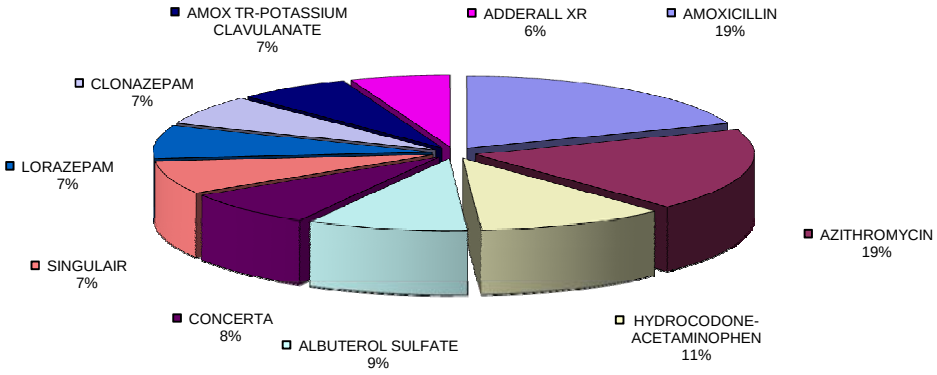


TOP 25 DRUGS BASED ON NUMBER OF CLAIMS FROM 01/01/2009 - 03/25/2009

Drug	AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
AMOXICILLIN	PENICILLINS	7,838	$ 73,187.52	$ 9.34	4.16%
AZITHROMYCIN	MACROLIDES	7,485	$ 169,100.04	$ 22.59	3.97%
HYDROCODONE-ACETAMINOPHEN	OPIATE AGONISTS	4,439	$ 45,424.68	$ 10.23	2.35%
ALBUTEROL SULFATE	BETA-ADRENERGIC AGONISTS	3,774	$ 73,212.13	$ 19.40	2.00%
CONCERTA	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	3,165	$ 475,239.53	$ 150.15	1.68%
SINGULAIR	LEUKOTRIENE MODIFIERS	3,013	$ 324,913.38	$ 107.84	1.60%
LORAZEPAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	2,987	$ 25,889.64	$ 8.67	1.58%
CLONAZEPAM	BENZODIAZEPINES (ANTICONVULSANTS)	2,707	$ 23,801.70	$ 8.79	1.44%
AMOX TR-POTASSIUM CLAVULANATE	PENICILLINS	2,647	$ 77,064.86	$ 29.11	1.40%
ADDERALL XR	AMPHETAMINES	2,325	$ 464,310.56	$ 199.70	1.23%
CEFDINIR	CEPHALOSPORINS	2,307	$ 131,601.64	$ 57.04	1.22%
OMEPRAZOLE	PROTON-PUMP INHIBITORS	2,253	$ 46,771.53	$ 20.76	1.19%
FLUOXETINE HCL	ANTIDEPRESSANTS	2,244	$ 20,133.41	$ 8.97	1.19%
SERTRALINE HCL	ANTIDEPRESSANTS	1,986	$ 18,999.97	$ 9.57	1.05%
CEPHALEXIN	CEPHALOSPORINS	1,800	$ 22,004.94	$ 12.22	0.95%
IBUPROFEN	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS	1,773	$ 12,983.02	$ 7.32	0.94%
LORATADINE	SECOND GENERATION ANTIHISTAMINES	1,763	$ 14,211.63	$ 8.06	0.93%
LEVOTHYROXINE SODIUM	THYROID AGENTS	1,680	$ 15,744.53	$ 9.37	0.89%
RISPERIDONE	ANTIPSYCHOTIC AGENTS	1,679	$ 146,906.69	$ 87.50	0.89%
PREVACID	PROTON-PUMP INHIBITORS	1,623	$ 273,226.31	$ 168.35	0.86%
TRAZODONE HCL	ANTIDEPRESSANTS	1,615	$ 11,071.98	$ 6.86	0.86%
CETIRIZINE HCL	SECOND GENERATION ANTIHISTAMINES	1,601	$ 36,839.22	$ 23.01	0.85%
SEROQUEL	ANTIPSYCHOTIC AGENTS	1,581	$ 395,475.21	$ 250.14	0.84%
CLONIDINE HCL	CENTRAL ALPHA-AGONISTS	1,517	$ 11,182.52	$ 7.37	0.80%
CEFPROZIL	CEPHALOSPORINS	1,415	$ 58,125.37	$ 41.08	0.75%
TOTAL TOP 25		67,217	$ 2,967,422.01	$ 44.15	35.64%

Total Rx Claims From 01/01/2009 - 03/25/2009	188,577

Top 10 Drugs
Based on Number of Claims

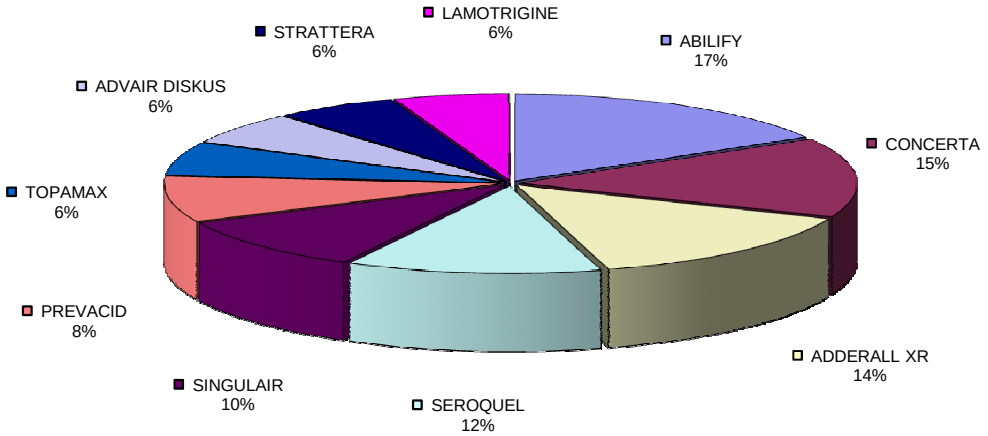


TOP 25 DRUGS BASED ON TOTAL CLAIMS COST FROM 01/01/2009 - 03/25/2009

Drug	AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
ABILIFY	ANTIPSYCHOTIC AGENTS	1,390	$ 536,386.11	$ 385.89	0.74%
CONCERTA	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	3,165	$ 475,239.53	$ 150.15	1.68%
ADDERALL XR	AMPHETAMINES	2,325	$ 464,310.56	$ 199.70	1.23%
SEROQUEL	ANTIPSYCHOTIC AGENTS	1,581	$ 395,475.21	$ 250.14	0.84%
SINGULAIR	LEUKOTRIENE MODIFIERS	3,013	$ 324,913.38	$ 107.84	1.60%
PREVACID	PROTON-PUMP INHIBITORS	1,623	$ 273,226.31	$ 168.35	0.86%
TOPAMAX	ANTICONVULSANTS, MISCELLANEOUS	612	$ 200,875.60	$ 328.23	0.32%
ADVAIR DISKUS	BETA-ADRENERGIC AGONISTS	1,037	$ 195,701.49	$ 188.72	0.55%
STRATTERA	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	1,213	$ 189,176.29	$ 155.96	0.64%
LAMOTRIGINE	ANTICONVULSANTS, MISCELLANEOUS	864	$ 179,320.40	$ 207.55	0.46%
AZITHROMYCIN	MACROLIDES	7,485	$ 169,100.04	$ 22.59	3.97%
ZYPREXA	ANTIPSYCHOTIC AGENTS	314	$ 168,949.56	$ 538.06	0.17%
VYVANSE	AMPHETAMINES	1,203	$ 166,416.72	$ 138.33	0.64%
OXYCONTIN	OPIATE AGONISTS	461	$ 162,204.74	$ 351.85	0.24%
FOCALIN XR	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	1,053	$ 150,751.02	$ 143.16	0.56%
RISPERIDONE	ANTIPSYCHOTIC AGENTS	1,679	$ 146,906.69	$ 87.50	0.89%
XOPENEX	BETA-ADRENERGIC AGONISTS	988	$ 137,351.53	$ 139.02	0.52%
CEFDINIR	CEPHALOSPORINS	2,307	$ 131,601.64	$ 57.04	1.22%
NUTROPIN AQ	PITUITARY	52	$ 128,334.93	$ 2,467.98	0.03%
RISPERDAL CONSTA	ANTIPSYCHOTIC AGENTS	163	$ 123,278.03	$ 756.31	0.09%
NEXIUM	PROTON-PUMP INHIBITORS	577	$ 110,617.85	$ 191.71	0.31%
CYMBALTA	ANTIDEPRESSANTS	719	$ 102,770.39	$ 142.94	0.38%
EFFEXOR XR	ANTIDEPRESSANTS	652	$ 100,891.36	$ 154.74	0.35%
GEODON	ANTIPSYCHOTIC AGENTS	287	$ 100,442.30	$ 349.97	0.15%
HELIXATE FS	HEMOSTATICS	3	$ 96,269.82	$ 32,089.94	0.00%
TOTAL TOP 25		34,766	$ 5,230,511.50	$ 150.45	18.44%

Total Rx Claims From 01/01/2009 - 03/25/2009	188,577

Top 10 Drugs
Based on Total Claims Cost



South Dakota Department of Social Services
Pharmacy and Therapeutics Committee Meeting
Targeted Immune Modulators Review

I. Overview

Targeted immune modulators (TIMs) are used in the treatment of certain types of immunologic and inflammatory diseases, including ankylosing spondylitis (AS), Crohn's disease, juvenile idiopathic arthritis, plaque psoriasis, psoriatic arthritis (PsA), rheumatoid arthritis (RA), and ulcerative colitis (UC). The drugs work by selectively blocking steps in the inflammatory and immune cascades by either interfering with the activation of T cells, by targeting the inflammatory mediator TNF-α or by competitively blocking the Interleukin-1 (IL-1) receptor.

Table 1 summarizes the TIMs included in this review.

Table 1. Targeted Immune Modulators

Generic Name	Brand Name	Manufacturer
Abatacept	Orencia®	Bristol-Myers Squibb
Adalimumab	Humira®	Abbott
Alefacept	Amevive®	Astellas
Anakinra	Kineret®	Amgen
Certolizumab	Cimzia®	UCB
Efalizumab	Raptiva®*	Genentech
Etanercept	Enbrel®	Immunex
Infliximab	Remicade®	Centocor

* Genentech voluntarily withdrawing Raptiva from the U.S. Market (April 8, 2009)

II. Pharmacology

TNF is a naturally occurring cytokine that is involved in normal anti-inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of RA, including juvenile idiopathic arthritis, psoriatic arthritis, and ankylosing spondylitis patients and play an important role in the pathological inflammation and joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis plaques.

TNF inhibitors block these specific proinflammatory mediators. Adalimumab, etanercept, certolizumab and infliximab target TNF-α. Adalimumab binds specifically to TNF-α, blocking its interaction with both the p55 and p75 cell surface TNF receptor. Etanercept binds circulating TNF-α and lymphotoxin-α preventing them from interacting with a cell surface receptor. Infliximab binds both circulating and transmembrane forms of TNF-α, thereby preventing binding with the receptor. Certolizumab binds to human TNF-α selectively neutralizing it.

IL-1, another naturally occurring cytokine, has both immune and pro-inflammatory actions. Anakinra competitively blocks the IL-1 receptor, thus blocking various inflammatory and immunological responses.

The immunosuppressant agents abatecept, alefacept and efalizumab produce their immune response by inhibiting T-cell activation. Abatecept suppresses inflammation, decreases anticollagen antibody production and reduces antigen-specific production of interferon-gamma. Treatment with alefacept results in a reduction in circulating total CD4+ and CD8+ T-lymphocyte counts. CD2 is also expressed at low levels on the surface of killer cells and certain bone marrow B lymphocytes. Efalizumab inhibits the binding of leukocyte function antigen-1 (LFA-1) to intercellular adhesion molecule-1 (ICAM-1), thereby inhibiting the adhesion of leukocytes to other cell types.

III. Indications

Table 2. FDA approved indications for the agents included in this review

Generic Name	FDA Approved Indications
Abatecept	• Moderately to severely active RA in adults. Orencia may be used as monotherapy or concomitantly with disease-modifying-antirheumatic drugs (DMARDs) other than TNF antagonists. • Moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 6 and older. Orencia may be used as monotherapy or concomitantly with MTX.
Adalimumab	• Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active disease. Humira can be used alone or in combination with methotrexate or other DMARDs. • Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 4 years of age and older. Humira can be used alone or in combination with methotrexate. • Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis. Humira can be used alone or in combination with DMARDS. • Reducing signs and symptoms in patients with active ankylosing spondylitis. • Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab. • The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. Humira should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician.
Alefacept	• Treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.
Anakinra	• Reducing signs and symptoms and slowing the progression of structural damage in moderately to severely active rheumatoid arthritis, in patients 18 years of age or older who have failed 1 or more disease modifying antirheumatic drugs (DMARDs).
Certolizumab	• Reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
Efalizumab	• Treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
Etanercept	• Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis. Enbrel can be initiated in combination with methotrexate or used alone. • Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients ages 2 and older. • Reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis. Enbrel can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone. • Reducing signs and symptoms in patients with active ankylosing spondylitis. • Treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
Infliximab	• In combination with methotrexate for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis. • Reducing signs and symptoms and inducing and maintaining clinical remission in adult and pediatric patients with moderately to severely active Crohn's disease who have had an inadequate

Generic Name	FDA Approved Indications
	response to conventional therapy. • Reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease. • Reducing signs and symptoms in patients with active ankylosing spondylitis. • Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis. • Treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate. • Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

IV. Dosing and Administration

Table 3. Dosing recommendations for the agents included in this review

Drug	Dosing and Administration	Availability
Abatacept	• <60 kg 500 mg • 60 – 100 kg 750 mg • >100 kg 1,000 mg • Pediatric patients weighing less than 75 kg receive 10 mg/kg. • Administer as a 30-minute intravenous infusion. • Following initial dose, give at 2 and 4 weeks, then every 4 weeks.	• 250 mg single-use vial
Adalimumab	• RA, PsA, AS – 40 mg every other week. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDSs), analgesics or other DMARDs may be continued during treatment. Some patients with RA not receiving methotrexate may benefit from increasing the frequency to 40 mg every week. • Juvenile idiopathic arthritis – Patients 4 to 17 years of age - 15 kg to < 30 kg: 20 mg every other week. ≥ 30 kg: 40 mg every other week. Methotrexate, glucocorticoids, salicylates, NSAIDs, analgesics or other DMARDs may be continued during treatment. • Crohn's Disease – Initial dose is 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg every other week. Aminosalicylates, corticosteroids, and/or immunomodulatory agents (e.g., 6-mercaptopurine and azathioprine) may be continued during treatment.	• 40 mg/0.8 ml in a single-use prefilled pen • 40 mg/0.8 ml in a single-dose prefilled glass syringe • 20 mg/0.4 ml in a single-dose prefilled glass syringe

Drug	Dosing and Administration	Availability
	• Plaque psoriasis – 80 mg initial dose followed by 40 mg every other week starting one week after initial dose.	
Alefacept	• 7.5 mg given once weekly as an IV bolus or 15 mg given once weekly as an IM injection. • Recommended regimen is a course of 12 weekly injections. • Retreatment with an additional 12-week course may be initiated provided that CD4+ T lymphocyte counts are within the normal range, and a minimum of a 12-week interval has passed since the previous course of treatment.	• 7.5 mg single-use vial for IV administration • 15 mg single-use vial for IM administration
Anakinra	• Recommended dose for the treatment of patients with rheumatoid arthritis is 100mg/day administered by subcutaneous injection. Higher doses did not result in a higher response. • Dose should be administered at approximately the same time every day. • Consider a dose of 100mg every other day for RA patients who have severe renal insufficiency or end stage renal disease.	• Single-use preservative free, prefilled glass syringes containing 100mg of anakinra.
Certolizumab	• 400 mg subcutaneously initially and at weeks 2 and 4. • If response occurs, follow with 400 mg subcutaneously every four weeks.	• Two single-use glass vials each containing 200 mg of lyophilized Cimzia for reconstitution.
Efalizumab	• Single 0.7 mg/kg subcutaneously conditioning dose followed by weekly subcutaneous doses of 1 mg/kg not to exceed 200mg.	• Single-use vial designed to deliver 125 mg of efalizumab.
Etanercept	• A 50 mg dose should be given as one subcutaneous injection using either a 50 mg single-use prefilled syringe or a single-use prefilled SureClick autoinjector. • A 50 mg dose can also be given as two 25 mg subcutaneous injections using 25 mg single-use prefilled syringes or multiple-use vials. • When administering Enbrel as two injections in adults or children, the injections should be given either on the same day or 3 or 4 days apart. • Adult RA, AS, and PsA – 50 mg per week. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with Enbrel. • Adult plaque psoriasis – 50 mg dose given twice weekly (administered 3 or 4 days apart) for 3 months followed by a reduction to a maintenance dose of 50 mg	• 25 mg single-use prefilled syringe • 50 mg single-use prefilled syringe • 50 mg single-use prefilled SureClick autoinjector • 25 mg multiple-use vial

Drug	Dosing and Administration	Availability
	per week. • Juvenile idiopathic arthritis – pediatric patients ages 2 to 17 years is 0.8 mg/kg per week (max of 50 mg per week). Glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with Enbrel. Concurrent use with methotrexate and higher doses of Enbrel have not been studied in pediatric patients.	
Infliximab	• RA - 3 mg/kg given as an intravenous infusion followed with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. • Crohn's Disease (adults) – 5mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter. For adult patients who respond and then lose their response, consideration may be given to treatment with 10 mg/kg. Patients who do not respond by week 14 are unlikely to respond with continued dosing and consideration should be given to discontinuation. • Crohn's Disease (children) - The recommended dose is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. • AS , PsA– 5mg/kg given as an intravenous infusion followed with additional similar doses at 2 and 6 weeks after the first infusion, then every 6 weeks thereafter. • UC – 5 mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter.	• 100mg single-use vials

V. Pharmacokinetics

Table 4. Pharmacokinetics of the agents included in this review

Drug	C_{max} (mcg/ml)	t ½	Onset of action	Systemic clearance	Volume of distribution
Abatacept	171 - 398	8 – 25 days	> 12 days	0.13 - 0.47 ml/h/kg	0.02 - 0.13 (L/kg)
Adalimumab	4.7 ± 1.6	10 – 20 days	1 – 14 days	12 ml/h	4.7 – 6 L
Alefacept	1.4	11 – 12 days	30 – 60 days	0.25 ml/h/kg	94 ml/kg
Anakinra	3.1 – 29	7 - 8 hours	7 – 21 days	137 ± 21 ml/min	3.6 – 15 L
Certolizumab	0.5 – 90	14 days	8 weeks	17 ml/h	6.4 L
Efalizumab	9 - 12	6.2 days	14 days	24 ± 18 ml/kg/day	58 ml/kg (10mg/kg dose)
Etanercept	4.7 ± 1.6	10 – 20 days	1 – 28 days	12 ml/hr	4.7 – 6.0 L
Infliximab	118	7.7 – 9.5 days	2 – 14 days	0.012 – 0.032 L/h	3 L

VI. Drug Interactions

Abatacept (Orencia)

- Concurrent administration of a TNF antagonist with Orencia has been associated with an increased risk of serious infections and no significant additional efficacy over use of the TNF antagonists alone.
- There is insufficient experience to assess the safety and efficacy of Orencia administered concurrently with other biologic RA therapy and therefore such use is not recommended.
- Parenteral drug products containing maltose can interfere with the readings of blood glucose monitors that use test strips with glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) resulting in falsely elevated blood glucose readings on the day of infusion. Patients should be advised to consider methods of glucose monitoring that do not react with maltose.

Adalimumab (Humira)

- Concurrent administration of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent has been associated with a risk of serious infections, an increased risk of neutropenia and no additional benefit compared to these medicinal products alone. Therefore, the combination of anakinra with other TNF-blocking agents, including Humira, may also result in similar toxicities.
- Live vaccines should not be given concurrently with Humira.
- Humira has been studied in RA patients taking concomitant methotrexate. Although methotrexate reduced the apparent Humira clearance, the data do not suggest the need for dose adjustment of either Humira or methotrexate.

Alefacept (Amevive) – no formal drug interaction studies have been performed.

Anakinra (Kineret)

- No drug-drug interaction studies in human subjects have been conducted.
- Toxicologic and toxicokinetic studies in rats did not demonstrate any alteration in the clearance or toxicologic profile of either methotrexate or Kineret when the two agents were administered together.
- In a study in which patients with active RA were treated for up to 24 weeks with concurrent Kineret and etanercept therapy, a 7% rate of serious infections was observed, which was higher than that observed with etanercept alone.
- Two percent of patients treated concurrently with Kineret and etanercept developed neutropenia.

Certolizumab (Cimzia)

- Concurrent administration of anakinra and another TNF blocker has shown an increased risk of serious infections, an increased risk of neutropenia, and no added benefit compared to these medicinal products alone. Therefore, the combination of anakinra with other TNF blockers, including Cimzia, may also result in similar toxicities.
- Do not give live (including attenuated) vaccines concurrently with Cimzia.
- Interference with certain coagulation assays has been detected in patients treated with Cimzia. Cimzia may cause erroneously elevated aPTT assay results in patients without coagulation abnormalities. This effect has been observed with the PTT-LA test from Diagnostica Stago, and the HemosIL APTT-SP liquid and HemosIL lyophilized silica tests from Instrumentation Laboratories. Other aPTT assays may be affected as well. Interference with thrombin time (TT) and prothrombin time (PT) assays have not been observed. There is no evidence that Cimzia therapy has an effect on *in vivo* coagulation.

Efalizumab (Raptiva)

- No formal drug interaction studies have been performed with Raptiva. Raptiva should not be used with other immunosuppressive drugs.
- Live (including live-attenuated) vaccines should not be administered during Raptiva treatment.
- Increases in lymphocyte counts related to the pharmacologic mechanism of action are frequently observed during Raptiva treatment.

Etanercept (Enbrel)

- Specific drug interaction studies have not been conducted with Enbrel. However, it was observed that the pharmacokinetics of Enbrel was unaltered by concomitant methotrexate in rheumatoid arthritis patients.
- In a study in which patients with active RA were treated for up to 24 weeks with concurrent Enbrel and anakinra therapy, a 7% rate of serious infections was observed, which was higher than that observed with Enbrel alone. Two percent of patients treated concurrently with Enbrel and anakinra developed neutropenia.
- Two percent of patients treated with Enbrel and anakinra concurrently developed neutropenia.
- In a study of patients with Wegener's granulomatosis, the addition of Enbrel to standard therapy (including cyclophosphamide) was associated with a higher incidence of non-cutaneous solid malignancies. The use of Enbrel in patients receiving concurrent cyclophosphamide therapy is not recommended.
- Patients in a clinical study who were on established therapy with sulfasalazine, to which Enbrel was added, were noted to develop a mild decrease in mean neutrophil counts in comparison to groups treated with either Enbrel or sulfasalazine alone.

Infliximab (Remicade)

- Concurrent administration of etanercept (another TNFα-blocking agent) and anakinra (an interleukin-1 receptor antagonist) has been associated with an increased risk of serious infections and increased risk of neutropenia and no additional benefit compared to these medicinal products alone. Other TNFα-blocking agents (including Remicade) used in combination with anakinra may also result in similar toxicities.
- Specific drug interaction studies, including interactions with methotrexate, have not been conducted.

VII. Adverse Events

Table 5. Adverse Events > 2% for the agents included in this review

Adverse Event	Abatacept n=1,955 %	Adalimumab n=705 %	Alefacept n=1,869 %	Anakinra n=1,565 %	Certolizumab n=620 %	Efalizumab n=1,213 %	Etanercept n=349 %	Infliximab n=1,129 %
↓ CD4+ T lymphocyte counts below normal	-	-	48	-	-	-	-	-
↓ CD8+ T lymphocyte counts below normal	-	-	59	-	-	-	-	-
↓ Lymphocytes below normal	-	-	22	-	-	-	-	-
Abdominal pain	-	7	-	5	-	-	5	12
Accidental injury	-	10	-	-	-	-	-	-
Acne	-	-	-	-	-	4	-	-
Alkaline phosphatase ↑	-	5	-	-	-	-	-	-
Arthralgia	-	-	-	6	6	-	-	8
Asthenia	-	-	-	-	-	-	5	-
Back pain	7	6	-	-	-	4	-	8
Bronchitis	-	-	-	-	-	-	-	10
Chills	-	-	-	-	-	13	-	-
Cough	8	-	-	-	-	-	6	12
Diarrhea	-	-	-	7	-	-	-	12
Dizziness	9	-	-	-	-	-	7	-

Adverse Event	Abatacept n=1,955 %	Adalimumab n=705 %	Alefacept n=1,869 %	Anakinra n=1,565 %	Certolizumab n=620 %	Efalizumab n=1,213 %	Etanercept n=349 %	Infliximab n=1,129 %
Dyspepsia	6	-	-	-	-	-	4	10
Fatigue	-	-	-	-	-	-	-	9
Fever	-	-	-	-	-	7	-	7
Flu syndrome	-	7	-	6	-	7	-	-
Headache	18	12	-	12	-	32	17	18
Hematuria	-	5	-	-	-	-	-	-
Hyper-cholesterolemia	-	6	-	-	-	-	-	-
Hyperlipidemia	-	7	-	-	-	-	-	-
Hypertension	7	5	-	-	-	-	-	7
Injection site pain	-	12	-	-	-	-	-	-
Injection site reaction	-	8	16	71	-	-	37	-
Lab test abnormal	-	8	-	-	-	-	-	-
Low-titer antibodies	-	5	3	-	4	-	-	-
Moniliasis	-	-	-	-	-	-	-	5
Mouth Ulcer	-	-	-	-	-	-	2	-
Myalgia	-	-	-	-	-	8	-	-
Nasopharyngitis	12	-	-	-	-	-	-	-
Nausea	-	9	-	8	-	11	9	21
Pain	3	-	-	-	-	10	-	8
Pharyngitis	-	-	-	-	-	-	7	12
Pruritus	-	-	-	-	-	-	-	7
Rash	4	12	-	-	-	-	5	10
Respiratory disorder	-	-	-	-	-	-	5	-
Rhinitis	-	-	-	-	-	-	12	8
Serious infection (bacterial, viral, pneumonia, and pyelonephritis)	-	-	-	-	3	29	35	-
Sinusitis	-	11	-	7	-	-	3	14
URI	-	17	-	14	20	-	29	32
UTI	6	8	-	-	7	-	-	8
Vomiting	-	-	-	-	-	-	3	-
Worsening of RA	-	-	-	19	-	-	-	-

VIII. Black Box Warnings

<u>Adalimumab (Humira)</u>

- Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infection due to other opportunistic pathogens.
- Humira should be discontinued if a patient develops a serious infection or sepsis during treatment.
- Perform test for latent TB; if positive, start treatment for TB prior to starting Humira.

- Monitor all patients for active TB during treatment, even if initial latent TB test is negative.

Certolizumab (Cimzia)

- Increased risk of serious infections leading to hospitalization or death including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens.
- Cimzia should be discontinued if a patient develops a serious infection or sepsis.
- Perform test for latent TB; if positive, start treatment for TB prior to starting Cimzia.
- Monitor all patients for active TB during treatment, even if initial latent TB test is negative.

Efalizumab (Raptiva)-voluntary U.S. market withdrawal began April 8, 2009

- Infections, including serious infections leading to hospitalizations or death, have been observed in patients treated with Raptiva. These infections have included bacterial sepsis, viral meningitis, invasive fungal disease and other opportunistic infections. Patients should be educated about the symptoms of infection and be closely monitored for signs and symptoms of infection during and after treatment with Raptiva. If a patient develops a serious infection, Raptiva should be discontinued and appropriate therapy instituted.
- Raptiva increases the risk for Progressive Multifocal Leukoencephalopathy (PML), a rapidly progressive viral infection of the central nervous system that has no known treatment and that leads to death or severe disability. The risk of PML may markedly increase with longer duration of Raptiva exposure. The time dependent threshold when the risk for PML increases is unknown. Patients on Raptiva should be monitored frequently to ensure they are receiving significant clinical benefit, to ensure they understand the significance of the risk of PML, and for any sign or symptom that may be suggestive of PML. Raptiva dosing should be withheld immediately at the first sign or symptom suggestive of PML. For diagnosis, brain magnetic resonance imaging (MRI) and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended.

Etanercept (Enbrel)

- Patients treated with Enbrel are at increased risk for developing serious infections that may lead to hospitalization or death.
- Most patients who developed these infections were taking concomitant immunosuppresants such as methotrexate or corticosteroids.
- Enbrel should be discontinued if a patient develops a serious infection or sepsis.
- Reported infections include: active TB, including reactivation of latent TB. Patients with tuberculosis have frequently presented with disseminated or extra pulmonary disease. Patients should be tested for latent TB before Enbrel use and during therapy. Treatment for latent infection should be initiated prior to Enbrel use.
- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacterial, viral and other infections due to opportunistic pathogens.
- The risks and benefits of treatment with Enbrel should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.
- Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Enbrel, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

Infliximab (Remicade)

- Patients treated with Remicade are at increased risk for developing serious infections that may lead to hospitalization or death.
- Most patients who developed these infections were taking concomitant immunosuppresants such as methotrexate or corticosteroids.
- Remicade should be discontinued if a patient develops a serious infection or sepsis.
- Reported infections include: active TB, including reactivation of latent TB; invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis; bacterial, viral and other infections due to opportunistic pathogens.
- Rare postmarketing cases of hepatosplenic T-cell lymphoma have been reported in adolescent and young adult patients with Crohn's disease on concomitant treatment with azathioprine or 6-mercaptopurine. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal.

References

1. Wolters Kluwer Health, Inc, ed. Drugs Facts & Comparisons. St. Louis, MO. 2008.
2. Evidence-based Practice Center; Drug Class Review on Targeted Immune Modulators; Final Report January 2007. Accessed online February 2009 www.ohsu.edu.
3. Remicade® Prescribing Information, December 2008, Centocor, Inc.
4. Cimzia® Prescribing Information, December 2008, UCB, Inc.
5. Amevive® Prescribing Information, October 2006, Astellas Pharma US, Inc.
6. Humira® Prescribing Information, March 2009, Abbott Laboratories.
7. Enbrel® Prescribing Information, April 2009, Immunex Corporation.
8. Kineret® Prescribing Information, October 2002, Amgen.
9. Orencia® Prescribing Information, April 2008, Bristol-Myers Squibb.
10. Raptiva® Prescribing Information, March 2009, Genentech.

Targeted Immune Modulators Utilization
01/01/2008 – 12/31/2008

Label Name	Rx Num	Total Reimb Amt	Average cost per script
ENBREL 25 MG KIT	38	$53,223.13	$1,400.61
ENBREL 50 MG/ML SYR	32	$52,808.93	$1,650.28
ENBREL 50 MG/ML SURECLICK SYR	66	$111,242.81	$1,685.50
HUMIRA 40 MG/0.8 ML PEN	121	$191,509.58	$1,582.72
HUMIRA CROHN'S STARTER PACK	1	$4,877.67	$4,877.67
KINERET 100 MG/0.67 ML SYR	10	$14,141.30	$1,414.13
RAPTIVA 125 MG KIT	3	$5,323.68	$1,774.56
TOTAL	271	$433,127.10	54 Recipients

Market Share 2008

Label Name	Percentage
ENBREL	50.18%
HUMIRA	45.02%
KINERET	3.69%
RAPTIVA	1.11%

Summary by Age
01/01/2008 – 12/31/2008

Age	Recip Count	Rx Count
11	1	5
16	2	4
19	2	10
20	2	8
22	1	9
26	1	8
28	2	4
29	2	3
30	1	3
31	1	7
32	1	1
33	2	6
34	2	19
35	1	10
38	2	6
39	2	13

Age	Recip Count	Rx Count
40	1	2
41	2	9
43	4	12
45	3	20
46	3	12
47	1	13
48	1	4
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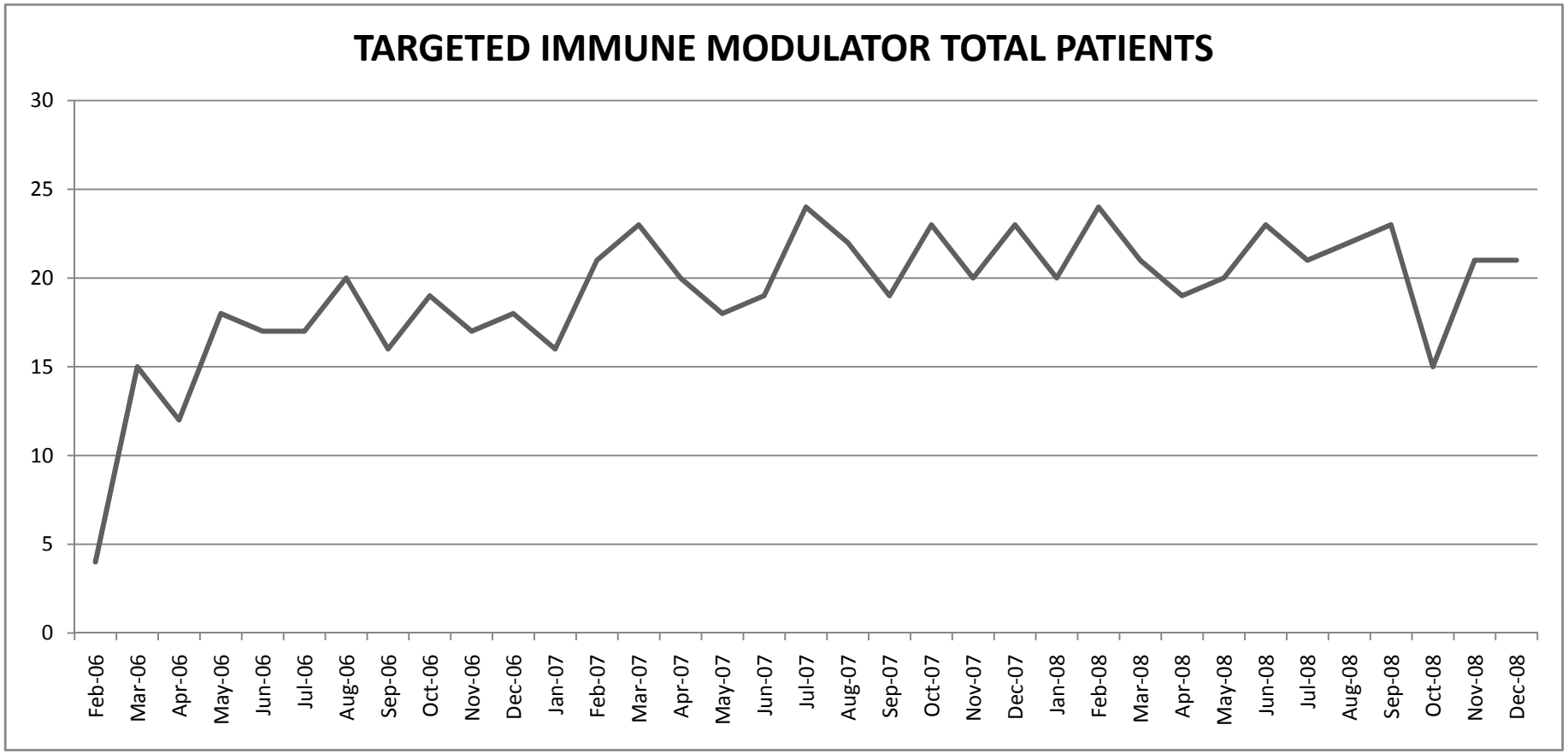
57	1	5
58	3	22
59	2	18
62	1	5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15
10
5
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Feb-06
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Apr-06
May-06
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Aug-06
Sep-06
Oct-06
Nov-06
Dec-06
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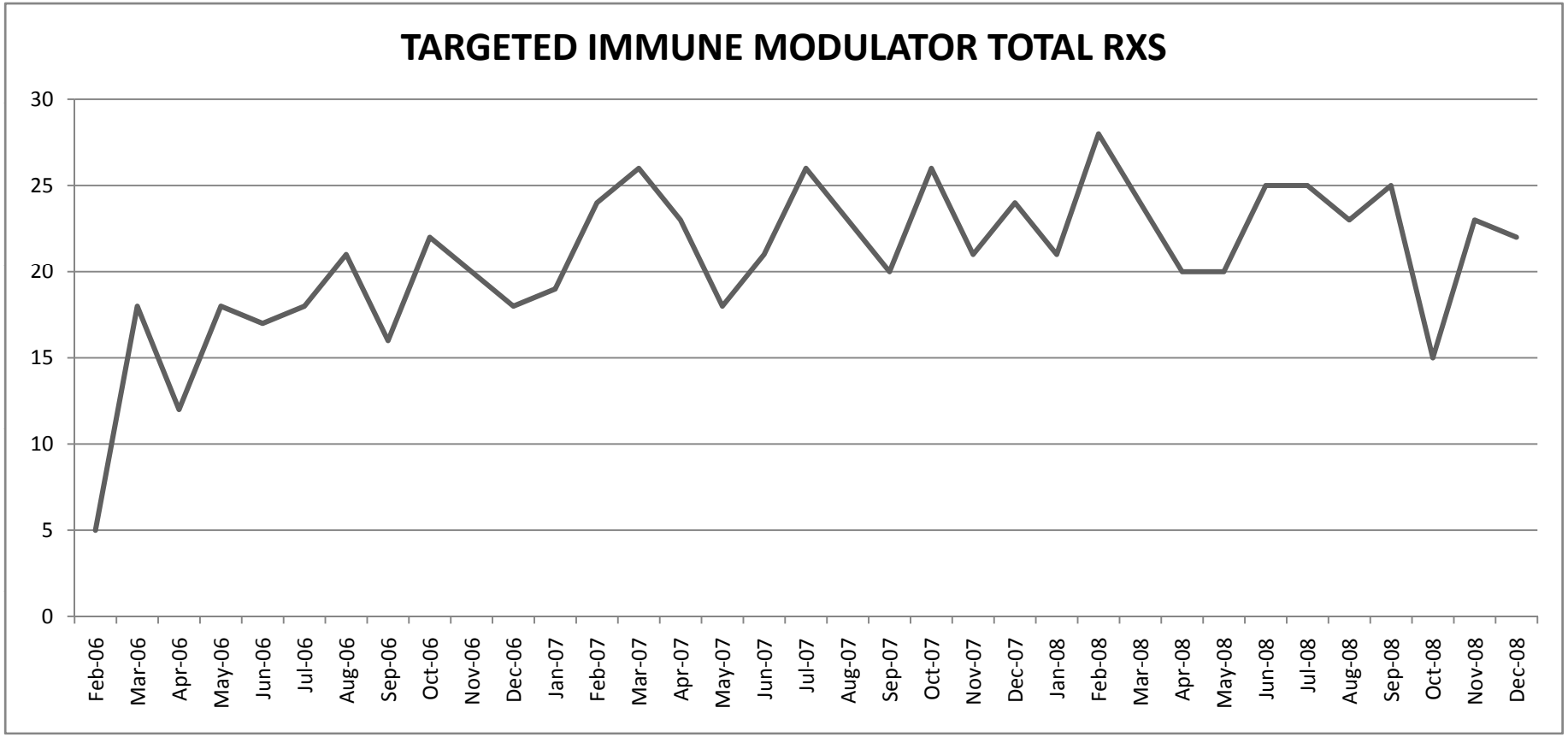
TARGETED IMMUNE MODULATOR TOTAL RXS
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25
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Jul-06
Aug-06
Sep-06
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Nov-06
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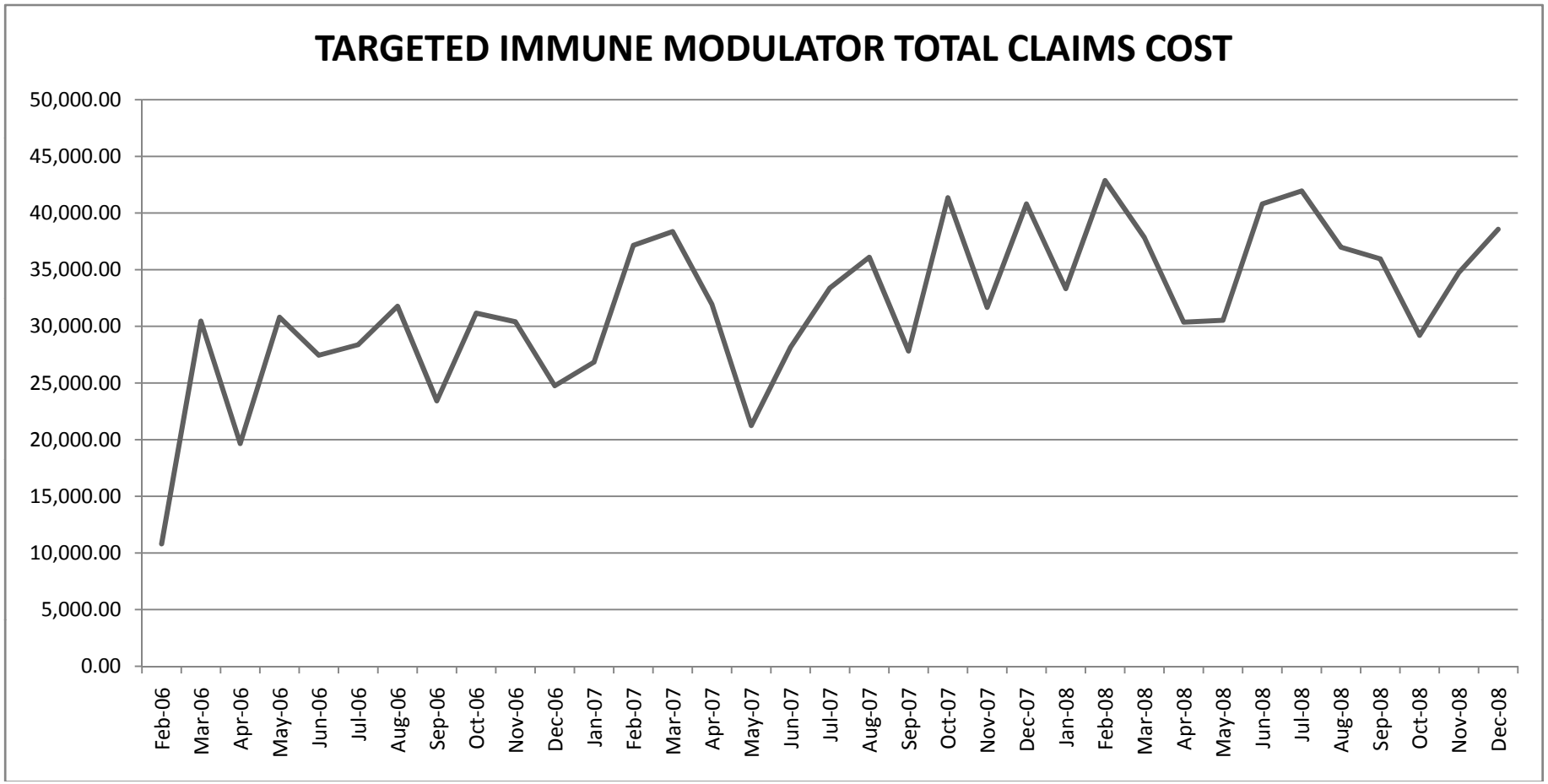
TARGETED IMMUNE MODULATOR TOTAL CLAIMS COST
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45,000.00
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20,000.00
15,000.00
10,000.00
5,000.00
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South Dakota Department of Social Services
Pharmacotherapy Review
Moxatag®
June 12, 2009

I. Overview

Moxatag is a once-daily extended-release formulation of amoxicillin approved in January, 2008.

II. Indications and Usage

Moxatag is a penicillin-class antibacterial for the treatment of tonsillitis and/or pharyngitis secondary to *Streptococcus pyogenes* in adults and pediatric patients 12 years or older.

III. Pharmacology and Mechanism of Action

Amoxicillin is a semi-synthetic antimicrobial belonging to the penicillin-class of antimicrobials with activity against gram-positive bacteria. Amoxicillin exerts its bactericidal action against susceptible organisms during the stage of multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide.

IV. Pharmacokinetics

Following the administration of Moxatag with a low-fat meal in healthy subjects, mean amoxicillin AUC, C_{max}, and T_{max} values were 29.8 ug-h/mL, 6.6 ug/mL and 3.1 hours, respectively. Amoxicillin is approximately 20% protein bound in human serum. Amoxicillin is primarily cleared by renal excretion. The half-life of amoxicillin after oral administration of Moxatag is approximately 1.5 hours, similar to that of immediate-release amoxicillin.

V. Warnings/Precautions

1. **Anaphylaxis and Hypersensitivity Reactions** – Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins. Before initiating therapy with Moxatag, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, Moxatag should be discontinued and appropriate

therapy instituted. **Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.**

2. ***Clostridium difficile* Associated Diarrhea (CDAD)** – *Clostridium difficile* Associated Diarrhea has been reported with nearly all antibacterial agents, including amoxicillin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile. C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

3. **Superinfections –** The possibility of super infections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur, amoxicillin should be discontinued and appropriate therapy instituted.

4. **Mononucleosis Rash** – A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin-class antibiotics should not be administered to patients with mononucleosis.

5. **Development of Drug-Resistant Bacteria** – Prescribing amoxicillin in the absence of proven or strongly suspected bacterial infection or treating prophylactically is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

6. **False-Positive Urinary Glucose Tests** – High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinitest®, Benedict's Solution, or Fehling's Solution. Since this effect may also occur with amoxicillin, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix®) be used.

VI. Drug Interactions

1. **Probenecid** – Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use of Moxatag and probenecid may result in increased and

prolonged blood levels of amoxicillin. The clinical relevance of this finding has not been evaluated.

2. **Other Antibiotics** – Chloramphenicol, macrolides, sulfonamides, and tetracyclines may interfere with bactericidal effects of penicillin. This has been demonstrated in vitro; however, the clinical significance of this interaction is not well documented.

3. **Oral Contraceptives** – As with other antibiotics, amoxicillin may affect the gut flora, leading to lower estrogen reabsorption and potentially resulting in reduced efficacy of combined oral estrogen/progesterone contraceptives.

VII. Adverse Reactions

Drug-Related Treatment-Emergent Adverse Reactions by System Organ Class		
	Moxatag (N=302)	**Pen VK (N=306)**
Patients with at least one drug-related treatment-emergent adverse event	32 (10.6%)	45 (14.7%)
Infections and infestations		
Vulvovaginal mycotic infection	6 (2.0%)	8 (2.6%)
Gastrointestinal disorders		
Diarrhea	5 (1.7%)	6 (2.0%)
Nausea	4 (1.3%	2 (0.7%)
Vomiting	2 (0.7%)	5 (1.6%)
Abdominal pain	1 (0.3%)	3 (1.0%)
Nervous system disorders		
Headache	3 (1.0%)	3 (1.0%)

VIII. Dosage and Administration

The recommended dose of Moxatag is 775 mg once daily taken within 1 hour of finishing a meal for 10 days. The full 10 day course of therapy should be completed for effective treatment of tonsillitis and/or pharyngitis secondary to *S. pyogenes*. Do not chew or crush tablet.

VIII. Cost Comparisons

A course of Moxatag for treatment of strep throat will cost about $90, compared with $10 or less for a course of amoxicillin or penicillin.

IX. Efficacy

In a randomized, parallel-group, multi-center, double-blind, double-dummy study in adults and pediatrics (age ≥ 12 years) with tonsillitis and/or pharyngitis secondary to *S. pyogenes*, Moxatag 775 mg QD for 10 days was non-inferior to penicillin VK 250 mg QID for 10 days.

X. Conclusion

Effective treatments currently available for strep throat include penicillin, amoxicillin, cephalosporins, macrolides and clindamycin. Penicillin is the drug of choice because of proven efficacy, narrow spectrum and low cost. The efficacy of amoxicillin is similar to that of penicillin and is usually preferred for young children because the suspension has a better taste.

Some experts are concerned about giving amoxicillin (immediate- or extended-release) once daily for strep throat. This is because the blood levels of either formulation are less likely to remain above the minimum inhibitory concentration (MIC) of group A strep for the majority of the dosing interval (the amount of time blood levels are above MIC with Moxatag is about 4 hours longer than with immediate-release amoxicillin).

Because of expense and the lack of guidelines suggesting once daily amoxicillin as an option for first line therapy for strep throat, Moxatag represents a suitable second- or third-line therapy for those patients that are intolerant to the inactive ingredients in immediate release amoxicillin.

References:

1. Wolters Kluwer Health, Inc, ed. Drug Facts and Comparisons. St. Louis, MO. 2009
2. New formulation: Moxatag (amoxicillin extended release). Pharmacist's Letter/Prescriber's Letter 2009;25(2):250206.
3. Moxatag® [package insert]. Germantown, MD: Middlebrook Pharmaceuticals, Inc.; June 2008.

South Dakota Department of Social Services
Pharmacotherapy Review
Uloric®
June 12, 2009

I. Overview

Uloric (febuxostat) is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout. Uloric is not recommended for the treatment of asymptomatic hyperuricemia.

II. Current Treatment Guidelines for Gout

National Institute for Health and Clinical Excellence: Febuxostat for the management of hyperuricemia in people with gout.

1. Febuxostat is recommended as an option for the management of chronic hyperuricemia in gout only for people who are intolerant of allopurinol or for whom allopurinol is contraindicated.
2. For the purpose of this guidance, intolerance of allopurinol is defined as adverse effects that are sufficiently severe to warrant its discontinuation, or to prevent full dose escalation for optimal effectiveness as appropriate.
3. People currently receiving febuxostat should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

British Society for Rheumatology and British Health Professionals in Rheumatology: Guidelines for the management of gout.

1. Affected joints should be rested (C) and analgesic, anti-inflammatory drug therapy commenced immediately, and continued for 1-2 weeks (A).
2. Fast-acting oral non-steroidal anti-inflammatory drugs (NSAIDs) at maximum doses are the drugs of choice when there are no contraindications (A).
3. In patients with increased risk of peptic ulcers, bleeds or perforations, co-prescription of gastro-protective agents should follow standard guidelines for the use of NSAIDs and Cox-IIs (A).
4. Colchicine can be an effective alternative but is slower to work than NSAIDs (A).
5. Allopurinol should not be commenced during an acute attack (B) but in patients already established on allopurinol, it should be continued and the acute attack should be treated conventionally (A).
6. Opiate analgesics can be used as adjuncts (C).
7. Corticosteroids can be effective in patients unable to tolerate NSAIDs, and in patients refractory to other treatments (A).
8. If diuretics are being used to treat hypertension, an alternative antihypertensive agent should be considered, but in patients with heart failure, diuretic therapy should not be discontinued (C).

III. Pharmacology

Febuxostat achieves its therapeutic effect by decreasing serum uric acid. Febuxostat is not expected to inhibit other enzymes involved in purine and pyrimidine synthesis and metabolism at therapeutic concentrations.

IV. Pharmacokinetics

Febuxostat has an apparent mean terminal elimination half-life ($t_{1/2}$) of approximately 5 to 8 hours. The absorption of febuxostat following oral dose administration was estimated to be at least 49%. Maximum plasma concentrations of febuxostat occurred between 1 to 1.5 hours post-dose. The mean apparent steady state volume of distribution of febuxostat was approximately 50L. The plasma protein binding is approximately 99.2% (primarily to albumin). Febuxostat is eliminated by both hepatic and renal pathways.

V. Warnings/Precautions

1. **Gout Flare** – After initiation of febuxostat, an increase in gout flares is frequently observed. This increase is due to reduction in serum uric acid levels resulting in mobilization of urate from tissue deposits. In order to prevent gout flares, concurrent prophylactic treatment with an NSAID or colchicine is recommended.

2. **Cardiovascular Events –** In the randomized controlled studies, there was a higher rate of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions (MI), and non-fatal strokes) in patients treated with febuxostat. A causal relationship has not been established. Monitor for signs and symptoms of MI and stroke.

3. **Liver Enzyme Elevations –** During randomized controlled studies, transaminase elevations greater than 3 times the upper limit of normal were observed (AST: 2%, 2%, and ALT: 3%, 2% in febuxostat and allopurinol-treated patients, respectively). No dose-effect relationship for these transaminase elevations was noted. Laboratory assessment of liver function is recommended at, for example, 2 and 4 months following initiation of febuxostat and periodically thereafter.

VI. Drug Interactions

1. **Xanthine Oxidase (XO) Substrate Drugs-Azathioprine, Mercaptopurine, and Theophylline**: Febuxostat is an XO inhibitor. Drug interaction studies with drugs that are metabolized by XO have not been conducted. Inhibition of XO by febuxostat may cause increased plasma concentrations of these drugs leading to toxicity. Febuxostat is contraindicated in patients being treated with azathioprine, mercaptopurine, and theophylline.

2. **P450 Substrate Drugs**: Pharmacokinetic interactions between febuxostat and drugs metabolized by the CYP enzymes are unlikely.

3. **Colchicine**: No dose adjustment is necessary for either febuxostat or colchicine when the two drugs are co-administered.

4. **Naproxen**: No dose adjustment is necessary for febuxostat or naproxen when the two drugs are co-administered.

5. **Indomethacin**: No dose adjustment is necessary for febuxostat or indomethacin when these two drugs are co-administered.

6. **Hydrochlorothiazide:** No dose adjustment is necessary for febuxostat when co-administered with hydrochlorothiazide.

7. **Warfarin**: No dose adjustment is necessary for warfarin when co-administered with febuxostat.

8. **Desipramine**: Co-administration of drugs that are CYP2D6 substrates (such as desipramine) with febuxostat are not expected to require dosage adjustment.

VII. Adverse Reactions

In three randomized, controlled clinical studies which were 6 to 12 months in duration, the following adverse reactions were reported by the treating physician as related to the study drug.

Adverse reactions reported > 1% in febuxostat treatment groups and at least 0.5% greater than placebo				
	Placebo	**Febuxostat**		**Allopurinol***
Adverse Reactions	**N=134**	**40 mg daily N=757**	**80 mg daily N=1279**	**N=1277**
Liver Function Abnormalities	0.7%	6.6%	4.6%	4.2%
Nausea	0.7%	1.1%	1.3%	0.8%
Arthralgia	0%	1.1%	0.7%	0.7%
Rash	0.7%	0.5%	1.6%	1.6%

*Of the subjects who received allopurinol, 10 received 100mg, 145 received 200mg, and 1,122 received 300mg, based on level of renal impairment.

VIII. Dosage and Administration

- The recommended starting dose of febuxostat is 40 mg once daily. For patients who do not achieve a serum uric acid (sUA) less than 6 mg per dL after 2 weeks with 40 mg, febuxostat 80 mg is recommended.
- Febuxostat can be administered without regard to food or antacid use.
- No dose adjustment is necessary when administering febuxostat to patients with mild to moderate renal or hepatic impairment.

VIII. Cost Comparisons

Cost of therapy differs significantly between febuxostat and allopurinol. Febuxostat 40 mg and 80 mg cost about $160.00 per month. Allopurinol, on the other hand, is available generically and costs under $16.00 for a month's supply of 300 mg tablets.

IX. Efficacy

Febuxostat has been compared to allopurinol in three studies. In the chart below, febuxostat 40 mg daily is comparable to allopurinol 300 mg daily. Febuxostat 80 mg daily is more effective than allopurinol 300 mg daily in reducing uric acid levels to goal <6 mg/dL. (While febuxostat 80 mg significantly lowers uric acid more than allopurinol in the studies below, it should be noted that these studies only used allopurinol doses up to 300 mg daily.)

Comparison of Uloric to Allopurinol Patients (%) with Serum Uric Acid Levels Less than 6 mg/dL at Final Visit						
Study	**Uloric 40 mg daily**	**Uloric 80 mg daily**	**Allopurinol 300 mg daily***	**Placebo**	**Percent difference (95% CI)**	
					Uloric 40 mg vs allopurinol	**Uloric 80 mg vs allopurinol**
Study #1 (6 months) (N=2268)	45%	67%	42%		3% (-2%-8%)	25% (20%-30%)
Study #2 (6 months) (N=643)		72%	39%	1%		33% (26%-42%)
Study #3 (12 months) (N=491)		74%	36%			38% (30%-46%)

* The majority of patients received allopurinol 300 mg daily in these trials. In study #1, 145 of 2,268 allopurinol subjects were dosed at 200 mg daily. In study #2, ten of 643 allopurinol subjects were dosed at 100 mg daily.

X. Conclusion

Guidelines suggest that allopurinol be tried first for most patients with gout. In the past, allopurinol has been underutilized by providers because of concerns about its adverse effects (GI intolerance, rash, rare but frequently fatal hypersensitivity syndrome), conservative renal dosage adjustment, and inadequate published randomized controlled trials of efficacy and safety of allopurinol above 300 mg daily. While the majority of prescribers only use allopurinol up to 300 mg daily, it is approved by the FDA for doses up to 800 mg per day (in divided doses). Consider Uloric for patients who do not tolerate or respond well to maximum doses of allopurinol.

References:

1. New drug: Uloric (febuxostat). Pharmacist's Letter/Prescriber's Letter 2009;25(4):250413
2. Uloric® [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; February 2009.
3. National Institute for Health and Clinical Excellence: Febuxostat for the management of hyperuricemia in people with gout. December, 2008. Accessed online at www.nice.org.uk, April, 2009.
4. Jordan K., Cameron J, et al. British Society for Rheumatology and British Health Professionals in Rheumatology: Guideline for the Management of Gout. Rheum 2007 46(8):1372-1374. Accessed online at www.rheumatology.oxfordjournals.org, April, 2009.

South Dakota Department of Social Services
Pharmacotherapy Review
Bystolic®
June 12, 2009

I. Overview

Bystolic (nebivolol) is a beta-adrenergic receptor blocking agent used to treat high blood pressure. Bystolic is dosed once a day and can be used alone or in combination with other hypertension treatments. About 73.6 million people in the United States age 20 or older have high blood pressure.

II. Indication

Bystolic is indicated for the treatment of hypertension.

III. Pharmacology

In extensive metabolizers (most of the population) and at doses less than or equal to 10 mg, nebivolol is preferentially β_1 selective. In poor metabolizers and at higher doses, nebivolol inhibits both β_1 – and β_2 – adrenergic receptors. The mechanism of action of the antihypertensive response has not been definitively established but possible factors may involve decreased heart rate, decreased myocardial contractility, diminution of tonic sympathetic outflow to the periphery from cerebral vasomotor centers, suppression of renin activity, and vasodilation and decreased peripheral vascular resistance.

IV. Pharmacokinetics

Nebivolol is metabolized by a number of routes, including glucuronidation and hydroxylation. The active isomer has an effective half-life of about 12 hours in extensive metabolizers and 19 hours in poor metabolizers. Metabolites also contribute to β-blocking activity.

Mean peak plasma concentrations occur approximately 1.5 to 4 hours post-dosing and food does not alter the pharmacokinetic profile. Nebivolol is approximately 98% protein bound, mostly to albumin.

V. Drug Interactions

When Bystolic is co-administered with an inhibitor or an inducer of CYP2D6, patients should be closely monitored and the nebivolol dose adjusted according to blood pressure response. Drugs that inhibit CYP2D6 can be expected to increase plasma levels of nebivolol.

Bystolic should be used with care when myocardial depressants or inhibitors of AV conduction or antiarrhythmic agents are used concurrently. Both digitalis glycosides and

β-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

Bystolic should not be combined with other β-blockers. Patients receiving catecholamine-depleting drugs should be closely monitored because the added β-blocking action of Bystolic may produce excessive reduction of sympathetic activity. In patients who are receiving Bystolic and clonidine, Bystolic should be discontinued for several days before the gradual tapering of clonidine.

VI. Contraindications/Warnings

Bystolic is contraindicated in patients with severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), or severe hepatic impairment (Child-Pugh > 5), and in patients who are hypersensitive to any component of this product.

Patients with coronary artery disease should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in patients with coronary artery disease following the abrupt discontinuation of therapy with β-blockers.

In patients who have compensated congestive heart failure, Bystolic should be administered cautiously. If heart failure worsens, discontinuation should be considered.

In general, patients with bronchospastic diseases should not receive β-blockers.

If Bystolic is to be continued perioperatively, patients should be closely monitored when anesthetic agents which depress myocardial function (ether, cyclopropane, and trichloroethylene) are used.

β-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be advised about these possibilities and nebivolol should be used with caution.

β-blockers may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of β-blockers may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate a thyroid storm.

β-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in these patients.

Because of the significant negative inotropic and chronotropic effects in patients treated with β-blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be used in patients treated concomitantly with these agents and ECG and blood pressure should be monitored.

VII. Precautions

- Use with CYP2D6 Inhibitors
- Impaired Renal Function
- Impaired Hepatic Function
- Risk of Anaphylactic Reactions

VIII. Adverse Reactions

Treatment-Emergent Adverse Events with an Incidence ≥ 1%

	Placebo (n = 205)	**Nebivolol 5 mg (n = 459)**	**Nebivolol 10 mg (n = 461)**	**Nebivolol 20-40 mg (n = 677)**
Headache	6	9	6	7
Fatigue	1	2	2	5
Dizziness	2	2	3	4
Diarrhea	2	2	2	3
Nausea	0	1	3	2
Insomnia	0	1	1	1
Chest pain	0	0	1	1
Bradycardia	0	0	0	1
Dyspnea	0	0	1	1
Rash	0	0	1	1
Peripheral Edema	0	1	1	1

IX. Dosage and Administration

For most patients, the recommended starting dose is 5 mg once daily, with or without food, as monotherapy or in combination with other agents. For patients requiring further reduction in blood pressure, the dose can be increased at 2-week intervals up to 40 mg. A more frequent dosing regimen is unlikely to be beneficial.

X. How Supplied

Bystolic is available as tablets for oral administration containing 2.5, 5, 10, and 20 mg of nebivolol.

XI. Cost Comparisons

Pricing for cardioselective agents, with only β_1 antagonist activity, ranges from under five dollars a month (atenolol 50 mg once daily) to approximately fifty-four dollars a month (Bystolic 10mg once daily).

XII. Conclusion

Bystolic is an option for treatment of uncomplicated mild-to-moderate hypertension. For heart failure, carvedilol, extended-release metoprolol, and bisoprolol have studies that show improved survival. For hypertension, generic versions of more established beta-blockers, such as atenolol and metoprolol, are still excellent first line options.

References:

1. Bystolic® [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; August 2008.
2. American Heart Association. High Blood Pressure Statistics. Accessed online at www.americanheart.org May 2009.
3. Comparison of oral beta-blockers. Pharmacist's Letter/Prescriber's Letter 2008;24(2):240203.

Reference Card From the

Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)

EVALUATION

Classification of Blood Pressure (BP)*

Category	SBP mmHg		DBP mmHg
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Hypertension, Stage 1	140–159	or	90–99
Hypertension, Stage 2	≥160	or	≥100

* See *Blood Pressure Measurement Techniques* (reverse side)

Key: SBP = systolic blood pressure DBP = diastolic blood pressure

Diagnostic Workup of Hypertension

- Assess risk factors and comorbidities.
- Reveal identifiable causes of hypertension.
- Assess presence of target organ damage.
- Conduct history and physical examination.
- Obtain laboratory tests: urinalysis, blood glucose, hematocrit and lipid panel, serum potassium, creatinine, and calcium. Optional: urinary albumin/creatinine ratio.
- Obtain electrocardiogram.

Assess for Major Cardiovascular Disease (CVD) Risk Factors

- Hypertension
- Obesity (body mass index ≥30 kg/m^2)
- Dyslipidemia
- Diabetes mellitus
- Cigarette smoking
- Physical inactivity
- Microalbuminuria, estimated glomerular filtration rate <60 mL/min
- Age (>55 for men, >65 for women)
- Family history of premature CVD (men age <55, women age <65)

Assess for Identifiable Causes of Hypertension

- Sleep apnea
- Drug induced/related
- Chronic kidney disease
- Primary aldosteronism
- Renovascular disease
- Cushing's syndrome or steroid therapy
- Pheochromocytoma
- Coarctation of aorta
- Thyroid/parathyroid disease

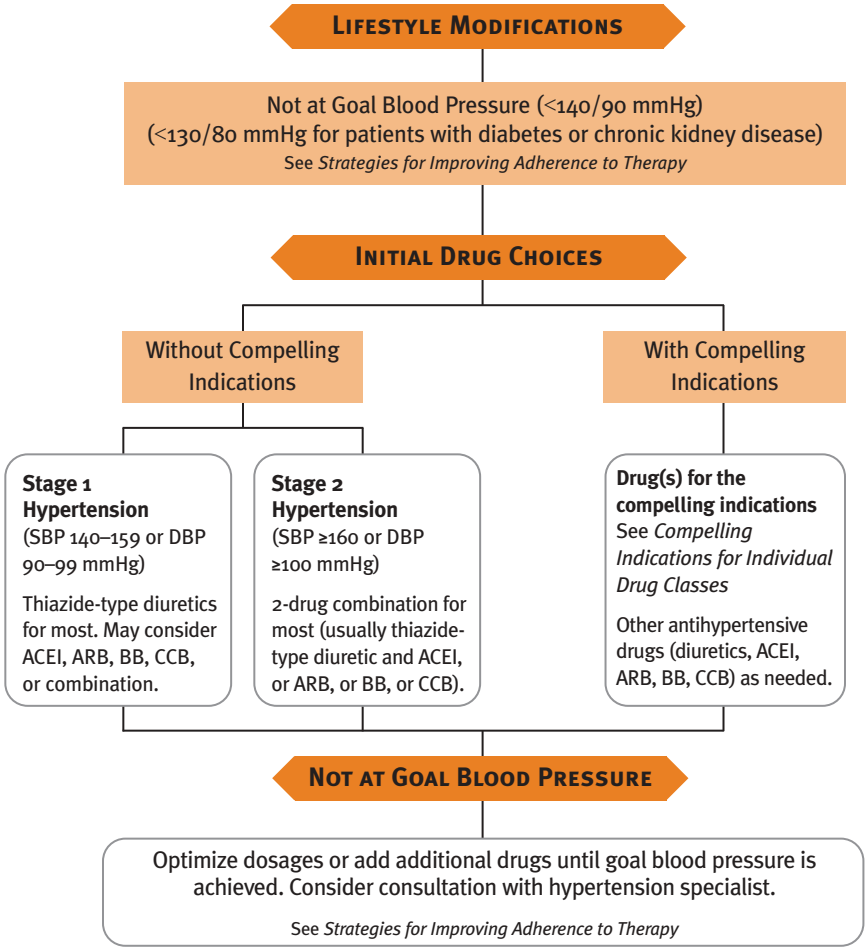
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Heart, Lung, and Blood Institute

TREATMENT

Principles of Hypertension Treatment

- Treat to BP <140/90 mmHg or BP <130/80 mmHg in patients with diabetes or chronic kidney disease.
- Majority of patients will require two medications to reach goal.

Algorithm for Treatment of Hypertension



Blood Pressure Measurement Techniques

Method	Notes
In-office	Two readings, 5 minutes apart, sitting in chair. Confirm elevated reading in contralateral arm.
Ambulatory BP monitoring	Indicated for evaluation of "white coat hypertension." Absence of 10–20 percent BP decrease during sleep may indicate increased CVD risk.
Patient self-check	Provides information on response to therapy. May help improve adherence to therapy and is useful for evaluating "white coat hypertension."

Causes of Resistant Hypertension

- Improper BP measurement
- Excess sodium intake
- Inadequate diuretic therapy
- Medication
  - Inadequate doses
  - Drug actions and interactions (e.g., nonsteroidal anti-inflammatory drugs (NSAIDs), illicit drugs, sympathomimetics, oral contraceptives)
  - Over-the-counter (OTC) drugs and herbal supplements
- Excess alcohol intake
- Identifiable causes of hypertension (see reverse side)

Compelling Indications for Individual Drug Classes

Compelling Indication	Initial Therapy Options
• Heart failure	THIAZ, BB, ACEI, ARB, ALDO ANT
• Post myocardial infarction	BB, ACEI, ALDO ANT
• High CVD risk	THIAZ, BB, ACEI, CCB
• Diabetes	THIAZ, BB, ACEI, ARB, CCB
• Chronic kidney disease	ACEI, ARB
• Recurrent stroke prevention	THIAZ, ACEI

Key: THIAZ = thiazide diuretic, ACEI= angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BB = beta blocker, CCB = calcium channel blocker, ALDO ANT = aldosterone antagonist

Strategies for Improving Adherence to Therapy

- Clinician empathy increases patient trust, motivation, and adherence to therapy.
- Physicians should consider their patients' cultural beliefs and individual attitudes in formulating therapy.

The National High Blood Pressure Education Program is coordinated by the National Heart, Lung, and Blood Institute (NHLBI) at the National Institutes of Health. Copies of the JNC 7 Report are available on the NHLBI Web site at **http://www.nhlbi.nih.gov** or from the NHLBI Health Information Center, P.O. Box 30105, Bethesda, MD 20824-0105; Phone: 301-592-8573 or 240-629-3255 (TTY); Fax: 301-592-8563.

Principles of Lifestyle Modification

- Encourage healthy lifestyles for all individuals.
- Prescribe lifestyle modifications for all patients with prehypertension and hypertension.
- Components of lifestyle modifications include weight reduction, DASH eating plan, dietary sodium reduction, aerobic physical activity, and moderation of alcohol consumption.

Lifestyle Modification Recommendations

Modification	Recommendation	Avg. SBP Reduction Range†
Weight reduction	Maintain normal body weight (body mass index 18.5–24.9 kg/m^2).	5–20 mmHg/10 kg
DASH eating plan	Adopt a diet rich in fruits, vegetables, and lowfat dairy products with reduced content of saturated and total fat.	8–14 mmHg
Dietary sodium reduction	Reduce dietary sodium intake to ≤100 mmol per day (2.4 g sodium or 6 g sodium chloride).	2–8 mmHg
Aerobic physical activity	Regular aerobic physical activity (e.g., brisk walking) at least 30 minutes per day, most days of the week.	4–9 mmHg
Moderation of alcohol consumption	Men: limit to ≤2 drinks* per day. Women and lighter weight persons: limit to ≤1 drink* per day.	2–4 mmHg

* 1 drink = 1/2 oz or 15 mL ethanol (e.g., 12 oz beer, 5 oz wine, 1.5 oz 80-proof whiskey).

† Effects are dose and time dependent.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Heart, Lung, and Blood Institute
National High Blood Pressure Education Program

NIH Publication No. 03-5231
May 2003

South Dakota Department of Social Services
Pharmacotherapy Review
Fexmid®
June 12, 2009

I. Overview

Fexmid (cyclobenzaprine) is a skeletal muscle relaxant which relieves muscle spasm of local origin without interfering with muscle function.

II. Indication

Fexmid is indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions. Improvement is manifested by relief of muscle spasm and its associated signs and symptoms, namely, pain, tenderness, limitation of motion, and restriction in activities of daily living.

Fexmid should be used only for short periods (up to two or three weeks) because adequate evidence of effectiveness for more prolonged use is not available and because muscle spasm associated with acute, painful musculoskeletal conditions is generally of short duration and specific therapy for longer periods is seldom warranted.

*Fexmid has not been found effective in the treatment of spasticity associated with cerebral or spinal cord disease or in children with cerebral palsy.

III. Pharmacokinetics

Estimates of mean oral bioavailability of cyclobenzaprine range from 33% to 55%. It is highly bound to plasma proteins. Drug accumulates when dosed three times a day, reaching steady-state within 3-4 days. At steady state in healthy subjects receiving 10 mg three times a day, peak plasma concentration was 25.9 ng/mL, and area under the concentration-time curve over an 8-hour dosing interval was 177 ng.hr/mL.

Cyclobenzaprine is extensively metabolized and is excreted primarily as glucuronides via the kidney. Cyclobenzaprine has an effective half-life of 18 hours. The plasma concentration of cyclobenzaprine is usually higher in the elderly and in patients with hepatic impairment.

IV. Contraindications/Warnings

- Hypersensitivity to any component of this product.
- Concomitant use of monoamine oxidase inhibitors or within 14 days after discontinuation.
- Hyperpyretic crisis seizures and deaths have occurred in patients receiving cyclobenzaprine (or structurally similar tricyclic antidepressants) concomitantly with MAO inhibitor drugs.

- During the acute recovery phase of myocardial infarction and in patients with arrhythmias, heart block or conduction disturbances, or congestive heart failure.
- Hyperthyroidism.
- Fexmid is closely related to the tricyclic antidepressants and in short term studies at doses somewhat greater than recommended for skeletal muscle spasm, some of the more serious central nervous system reactions noted with the tricyclics have occurred.
- Tricyclic antidepressants have been reported to produce arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke.
- Fexmid is not recommended in subjects with mild, moderate or severe hepatic impairment.
- Fexmid may enhance the effects of alcohol, barbiturates, and other CNS depressants.
- Therapy with cyclobenzaprine in the elderly should be initiated with a 5 mg dose and titrated slowly upward due to the increased plasma concentration in this population.

V. Precautions

Because of its atropine-like action, Fexmid should be used with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure and in patients taking anticholinergic medication.

VI. Drug Interactions

Fexmid may have life-threatening interactions with MAO inhibitors. Fexmid may enhance the effects of alcohol, barbiturates, and other CNS depressants. Tricyclic antidepressants may block the antihypertensive action of guanethidine and similarly acting compounds. Tricyclic antidepressants may enhance the seizure risk in patients taking tramadol.

VII. Pregnancy

Fexmid is Pregnancy Category B. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

VIII. Adverse Reactions

The most common adverse reactions were dry mouth, dizziness, fatigue, constipation, somnolence, nausea, dyspepsia, headache, blurred vision, dysgeusia, palpitations, tremor, dry throat, acne and disturbance in attention.

IX. Drug Abuse and Dependence

Pharmacologic similarities among the tricyclic drugs require that certain withdrawal symptoms be considered when Fexmid is administered, even though they have not been reported to occur with this drug. Abrupt cessation of treatment after prolonged administration rarely may produce nausea, headache, and malaise. These are not indicative of addiction.

X. Dosage and Administration

The recommended adult dose for most patients is cyclobenzaprine 5 mg three times a day. Based on individual patient response, the dose may be increased to either 7.5 mg or 10 mg three times a day. Use of Fexmid for periods longer than two or three weeks is not recommended.

XI. How Supplied

Fexmid tablets are 7.5 mgs in strength.

XII. Cost Comparisons

The approximate cost (estimated acquisition price) for a 30 day supply ranges from $9.90 for cyclobenzaprine generic (30 mg/day) to $302.40 for Fexmid (22.5 mg/day).

XIII. Conclusion

Relatively few high-quality studies provide evidence of the effectiveness of skeletal muscle relaxants in the treatment of acute, uncomplicated musculoskeletal disorders. Because it is not clear as to which agent is best, side-effect profiles and cost become the significant considerations when choosing which skeletal muscle relaxant to prescribe.

References:

1. Fexmid® [package insert]. San Diego, CA: Victory Pharma, Inc.; October 2007.
2. Oral muscle relaxants. Pharmacist's Letter/Prescriber's Letter 2006;22(12):221206.

South Dakota Department of Social Services
Pharmacotherapy Review
Amrix®
June 12, 2009

I. Overview

Amrix (cyclobenzaprine extended release) is a skeletal muscle relaxant which relieves muscle spasm of local origin without interfering with muscle function.

II. Indication

Amrix is indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions. Improvement is manifested by relief of muscle spasm and its associated signs and symptoms, namely, pain, tenderness, and limitation of motion.

Amrix should be used only for short periods (up to two or three weeks) because adequate evidence of effectiveness for more prolonged use is not available and because muscle spasm associated with acute, painful musculoskeletal conditions is generally of short duration and specific therapy for longer periods is seldom warranted.

*Amrix has not been found effective in the treatment of spasticity associated with cerebral or spinal cord disease or in children with cerebral palsy.

III. Pharmacokinetics

Summary of Pharmacokinetic Parameters in Healthy Adult Subjects		
	Amrix 15mg	**Amrix 30mg**
AUC (ng hr/ml)	318.3 ± 114.7	736.6 ± 259.4
C_{max} (ng/ml)	8.3 ± 2.2	19.9 ± 5.9
T_{max} (hrs)	8.1 ± 2.9	7.1 ± 1.6
$t_{1/2}$ (hrs)	33.4 ± 10.3	32.0 ± 10.1

IV. Contraindications/Warnings

- Hypersensitivity to any component of this product.
- Concomitant use of monoamine oxidase inhibitors or within 14 days after discontinuation.
- Hyperpyretic crisis seizures and deaths have occurred in patients receiving cyclobenzaprine (or structurally similar tricyclic antidepressants) concomitantly with MAO inhibitor drugs.
- During the acute recovery phase of myocardial infarction and in patients with arrhythmias, heart block or conduction disturbances, or congestive heart failure.
- Hyperthyroidism.
- Amrix is closely related to the tricyclic antidepressants and in short term studies at doses somewhat greater than recommended for skeletal muscle spasm, some of

the more serious central nervous system reactions noted with the tricyclics have occurred.

- Tricyclic antidepressants have been reported to produce arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke.
- Amrix is not recommended in subjects with mild, moderate or severe hepatic impairment.
- Amrix may enhance the effects of alcohol, barbiturates, and other CNS depressants.
- Use of Amrix is not recommended in elderly patients as a result of a 40% increase in cyclobenzaprine plasma levels and a 56% increase in plasma half-life following administration.

V. Precautions

Because of its atropine-like action, Amrix should be used with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure and in patients taking anticholinergic medication.

VI. Drug Interactions

Amrix may have life-threatening interactions with MAO inhibitors. Amrix may enhance the effects of alcohol, barbiturates, and other CNS depressants. Tricyclic antidepressants may block the antihypertensive action of guanethidine and similarly acting compounds. Tricyclic antidepressants may enhance the seizure risk in patients taking tramadol or tramadol/acetaminophen.

VII. Pregnancy

Amrix is Pregnancy Category B. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

VIII. Adverse Reactions

The most common adverse reactions were dry mouth, dizziness, fatigue, constipation, somnolence, nausea, dyspepsia, headache, blurred vision, dysgeusia, palpitations, tremor, dry throat, acne and disturbance in attention.

IX. Drug Abuse and Dependence

Pharmacologic similarities among the tricyclic drugs require that certain withdrawal symptoms be considered when Amrix is administered, even though they have not been reported to occur with this drug. Abrupt cessation of treatment after prolonged administration rarely may produce nausea, headache, and malaise. These are not indicative of addiction.

X. Dosage and Administration

The recommended adult dose for most patients is one Amrix 15 mg capsule taken once daily. Some patients may require up to 30 mg/day. It is recommended that doses be taken at approximately the same time each day.

XI. How Supplied

Amrix extended-release capsules are available in 15 and 30 mg strengths. Amrix 15 mg capsules are orange/orange and Amrix 30 mg are blue/orange.

XII. Cost Comparisons

The approximate cost (estimated acquisition price) for a 30 day supply ranges from $9.90 for cyclobenzaprine generic (30 mg/day) to $273.30 for Amrix (30 mg/day).

XIII. Conclusion

Relatively few high-quality studies provide evidence of the effectiveness of skeletal muscle relaxants in the treatment of acute, uncomplicated musculoskeletal disorders. Because it is not clear as to which agent is best, side-effect profiles and cost become the significant considerations when choosing which skeletal muscle relaxant to prescribe.

References:

1. Amrix® [package insert]. Frazer, PA: Cephalon, Inc.; December 2008.
2. Oral muscle relaxants. Pharmacist's Letter/Prescriber's Letter 2006;22(12):221206.