DUR Board Meeting
June 1, 2009

Pioneer Room
State Capitol

1pm

North Dakota Medicaid
DUR Board Meeting
Agenda
Pioneer Room
State Capitol
June 1, 2009
1pm

1. Administrative items
    - Travel vouchers
    - Board members sign in

2. Old business
    - Review and approval of minutes of 03/02/09 meeting — Chairman
    - Budget update — Brendan
    - Tablet splitting update — Brendan
    - ADHD first fill quantities update — Brendan
    - Second review of Aczone — HID
    - Yearly PA review — HID
        - Sedative/Hypnotics
        - Qualaquin
        - ACE-I/ARBs/Renin Inhibitors
        - Synagis
        - GH/IGF-1

3. New business
    - Legislative update — Brendan
    - Review of Uloric — HID
    - Review of Moxatag
    - Review of Savella
    - Criteria recommendations — Brendan
    - Upcoming meeting date/agenda — Chairman
    - Adjourn to Executive Session to discuss patient profiles (time permitting) — Chairman

4. Adjourn — Chairman

Please remember to turn all cellular phones and pagers to silent mode during the meeting.

Drug Utilization Review (DUR) Meeting Minutes
March 2, 2009

Members Present: Patricia Churchill, Norman Byers, Carrie Sorenson, Greg Pfister, Steve Irsfeld, Kim Krohn, Jeffrey Hostetter, John Savageau, Scott Setzepfandt, Leeann Ness, Carlotta McCleary, Cheryl Huber and Todd Twogood.
Members Absent: Gary Betting
Medicaid Pharmacy Department: Brendan Joyce
HID Staff Present: Candace Rieth

Chair, C. Sorenson called the meeting to order at 1:09 pm. Chair, C. Sorenson asked for a motion to approve the minutes from the December meeting. N. Byers moved that the minutes be approved and J. Hostetter seconded the motion. Chair, C. Sorenson called for a voice vote to approve the minutes. The motion passed with no audible dissent.

Budget Update
B. Joyce stated that the budget information is going through the legislative process and that he will update the Board at the next meeting.

Tablet Splitting Initiative
Previously, the Board voted to implement a tablet splitting initiative with continuous updates from the State. The State is interested in adding Lipitor and Lexapro to the list of medications that can be split. An educational endeavor, including provider mailings and newsletters will occur prior to implementation.

Yearly PA Review
The Board reviews products annually that have previously been placed on prior authorization. This allows the Board a chance to update the prior authorization forms and criteria. Antihistamines, PPIs, COX-II/NSAIDs, Revatio, Actoplus met, and Azasite/Quixin were reviewed. The following recommendation were made: change the wording of the forms from 'physician' to 'prescriber' to include prescriptions written by nurse practitioners, make the medications listed on the Ophthalmic PA form the same as the medications listed on the Ophthalmic PA Criteria form and to include omeprazole on the PPI criteria form.

Legislative Update
B. Joyce gave a legislative update on HB 1385. The committee reviewing the exempt drug classes from prior authorization received a copy of the DUR Board's recommendations regarding those classes. A vote was taken in the house to maintain the exempt status of these classes. Outcomes of the Senate vote will be presented at the June meeting.

Strattera and Stimulants
The board reviewed patients receiving concurrent prescriptions of Strattera and stimulants. A recommendation was made to limit the initial day's supply of stimulants to decrease waste and increase compliance. The Board would like the State to move forward with an educational endeavor prior to implementation of initial fill quantity limits on stimulants.

Aczone Review
B. Joyce reviewed Aczone with Board members. There was no public comment. N. Byers made a motion to prior authorize Aczone. J. Savageau seconded the motion. This topic will be brought up again at the next Board meeting for finalization.

Criteria Recommendations

The recommended RDUR criteria enclosed in the packet were developed from product information provided by the manufacturers and usually are consistent with new indications, new drugs added, new warnings, etc. These proposed criteria will be added to the current set of criteria, and will be used in future DUR cycles. N. Byers moved to approve the new criteria and C. Huber seconded the motion. Chair, C. Sorenson called for a voice vote. The motion passed with no audible dissent.

The next DUR board meeting will be held June 1, 2009. J. Hostetter made a motion to adjourn the meeting and K. Krohn seconded. Chair C. Sorenson adjourned the meeting at 2:10 pm.

NORTH DAKOTA DEPARTMENT **Medical Services**

John Hoeven, Governor
Carol K. Olson, Executive Director

(701) 328-2321
Fax (701) 328-1544
Toll Free 1-800-755-2604
Provider Relations (701) 328-4030

[TODAY]

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

DEAR [tadrs1]:

In compliance with the OBRA '90 federal legislation, state Medicaid agencies are mandated to have an operating Drug Use Review (DUR) Board. One large part of the DUR Board's duties is to facilitate provider education. Part of this process is to help assure that Medicaid beneficiaries receive appropriate medications in the most cost-effective manner, thus conserving state expenditures for drugs whenever possible.

The North Dakota DUR Board recently requested that Medicaid pharmacy claims be scanned for potential cost savings with implementation of a tablet splitting initiative. According to a report published in the American Journal of Managed Care[1], healthcare plans can realize an average savings of 36 percent (based on average wholesale prices or AWP) on those medications that are not priced based on their dosage strength, but instead are available in two or more strengths with a similar price.

You are receiving this letter because Department records indicate a patient(s), in your care, received a prescription for strength of Lipitor or Lexapro that can be split. We are asking that patients currently receiving Lipitor 10mg tablets be converted to ½ of a Lipitor 20mg tablet, patients currently receiving Lipitor 20mg tablets be converted to ½ of a Lipitor 40mg tablet, patients receiving Lexapro 5mg tablets be converted to ½ of a Lexapro 10mg tablet and patients currently taking Lexapro 10mg tablets be converted to ½ of a Lexapro 20mg tablet. Potential savings for splitting Lipitor and Lexapro are approximately $167,000 annually. Please discuss this option with patients and change Lipitor and Lexapro prescriptions to tablet splitting when possible.

The Department is dedicated to improving the health and well being of our patients. We thank you for your participation in the North Dakota Medicaid Program and hope that you will assist us in making the most effective utilization of our resources as we continue to provide valuable pharmacy benefits to our patients.

Sincerely,

Brendan K. Joyce, PharmD
Administrator, Pharmacy Services
[provid]

[1] Stafford RS, Radley DC. The Potential of Pill Splitting to Achieve Cost Savings. Am J Man Care. 2002 August; 8(8): 706-12.

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DEAR [tadrs1]:

In compliance with the OBRA '90 federal legislation, state Medicaid agencies are mandated to have an operating Drug Use Review (DUR) Board. One large part of the DUR Board's duties is to facilitate provider education. Part of this process is to help assure that Medicaid beneficiaries receive appropriate medications in the most cost-effective manner, thus conserving state expenditures for drugs whenever possible.

The North Dakota DUR Board recently reviewed appropriate treatment of attention deficit hyperactivity disorder (ADHD). Annual expenditures* to the state have increased approximately 27% between 2006 and 2008. Current annual costs* for the medications used to treat ADHD are approximately 2.8 million dollars. In an effort to improve patient care and control pharmacy costs, the DUR Board suggested that the Department undertake an educational endeavor to address combination therapy, duration of therapy and stimulant wastage during the dose titration process.

Research currently available has not shown clear advantages of one stimulant over another, but encourages titration to the highest recommended dosage before switching to another agent. Because evidence is lacking, the combination of two or more ADHD medications is discouraged. Duration of activity should also be taken into consideration when dosing patients. A scan of stimulants and Strattera® pharmacy claims suggests that dosing guidelines for long-acting stimulants are not always followed (patients are dosed more frequently than once a day). Particular attention should be paid to single daily dosing of agents considered to be long-acting.

The initial dose and titration schedule of stimulants must be individualized to each patient and because the patient-clinician communication should be frequent during this initiation phase, it may be prudent to **limit prescription quantities to a 10 day supply** when starting a patient on a new dose or new medication; keeping the prescription quantities low until the patient is stabilized on an effective dose. This will prevent the waste that occurs when a patient fills a prescription for 30 days worth of medication, and then after three days informs the provider that the dose isn't working for them. Since it is not possible to predict the optimal dose based solely on age, weight, or symptom severity, the usual approach is to begin with a very small dose of a stimulant medication and then increase the dose gradually allowing about three to seven days on a dose before trying a larger one.

The Department would also ask that providers consider appropriate **dose optimization** when higher strengths are commercially available. For example, a patient receiving Adderall® XR 10 mg one capsule every morning + Adderall XR 15 mg one capsule every morning should receive the commercially available Adderall XR 25 mg capsule instead. As another example, a patient that receives Concerta® 27 mg two tablets every morning should receive the commercially available Concerta 54 mg.

You are receiving this letter because Department records indicate a patient(s), in your care, received a prescription for an agent used to treat ADHD. In presenting this information to you, the Department recognizes 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. In the future when dose adjusting stimulants, please consider writing each prescription for a small quantity to minimize waste. All stimulant claims will be reviewed in 6 months to determine if this educational endeavor is successful.

*before rebates

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The Department is dedicated to improving the health and well being of our patients. We thank you for your participation in the North Dakota Medicaid Program and hope that you will assist us in making the most effective utilization of our resources as we continue to provide valuable pharmacy benefits to our patients.

Sincerely,

Brendan K. Joyce, PharmD
Administrator, Pharmacy Services

[provid]

Aczone Gel PA FORM

Prior Authorization Vendor for ND Medicaid

Fax Completed Form to:
866-254-0761
For questions regarding this Prior authorization, call
866-773-0695

ND Medicaid requires that patients receiving a new prescription for Aczone gel must try other topical acne agents as first line therapy.

Part I: TO BE COMPLETED BY PHYSICIAN

Recipient Name	Recipient Date of Birth	Recipient Medicaid ID Number	
Physician Name			
Physician Medicaid Provider Number	Telephone Number	Fax Number	
Address	City	State	Zip Code
Requested Drug and Dosage: □ ACZONE GEL	**Diagnosis for this request:**		

Qualifications for coverage:

□ Failed acne therapy Name of medication failed: _____	Start Date	End Date	Dose	Frequency

□ *I confirm that I have considered a generic or other alternative and that the requested drug is expected to result in the successful medical management of the recipient.*

Physician Signature	Date

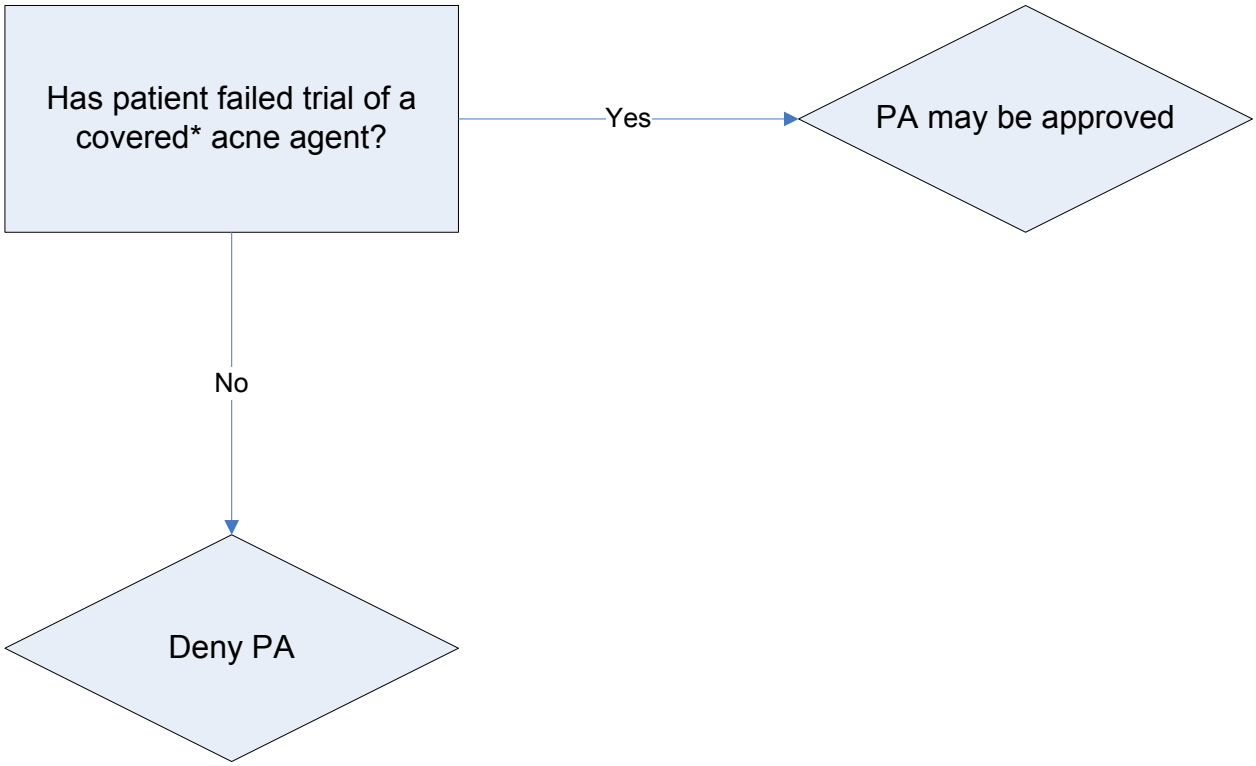
Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:			ND MEDICAID PROVIDER NUMBER:
TELEPHONE NUMBER	FAX NUMBER	DRUG	NDC #

Part III: FOR OFFICIAL USE ONLY

Date Received	Initials:
Approved - Effective dates of PA: From: / / To: / /	Approved by:
Denied: (Reasons)	

North Dakota Department of Human Services
Aczone Authorization Algorithm



*Tretinoin and benzoyl peroxide products do not require a PA

HEALTH INFORMATION DESIGNS

Prior Authorization Vendor for ND Medicaid

Sedative/Hypnotic PA Form

Fax Completed Form to:
866-254-0761
For questions regarding this Prior authorization, call
866-773-0695

ND Medicaid requires that patients receiving a new prescription for a name brand Sedative/Hypnotic must use Ambien® (zolpidem) as first line therapy.

****Note:***

- **The PA will be approved if there is a failed trial of Ambien (zolpidem).**
- **Estazolam, flurazepam, temazepam, triazolam, quazepam and Ambien (zolpidem) do not require a PA.**

Part I: TO BE COMPLETED BY PHYSICIAN

Recipient Name	Recipient Date of Birth	Recipient Medicaid ID Number	
Physician Name			
Physician Medicaid Provider Number	Telephone Number	Fax Number	
Address	City	State	Zip Code
Requested Drug and Dosage:	**Diagnosis for this request:**		
Qualifications for coverage:			
□ Failed Ambien (zolpidem)	Start Date: End Date:	Dose: Frequency:	
□ *I confirm that I have considered a generic or other alternative and that the requested drug is expected to result in the successful medical management of the recipient.*			
Physician Signature		Date	

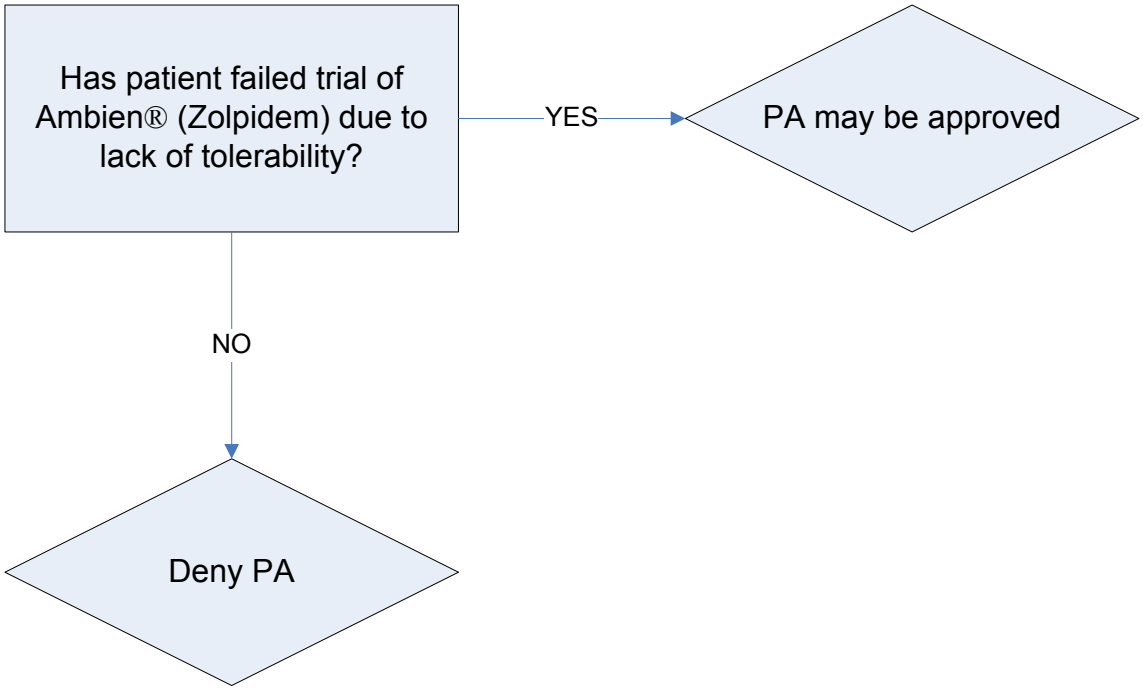
Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:			ND MEDICAID PROVIDER NUMBER:
PHONE NUMBER	FAX NUMBER	DRUG	NDC #

Part III: FOR OFFICIAL USE ONLY

Date Received	Initials:
Approved - Effective dates of PA: From: / / To: / /	Approved by:
Denied: (Reasons)	

North Dakota Department of Human Services
Sedative/Hypnotic Authorization Algorithm



NORTH DAKOTA MEDICAID
Percentage Market Share Within Sub-Classes
Sedative/Hypnotics

	FEB 04	MAY 06	DEC 08
All Sedative/Hypnotics(No Subclass)			
AMBIEN	91.22	56.59	0.00
AMBIEN CR	0.00	17.51	8.12
LUNESTA	0.00	18.71	6.41
ROZEREM	0.00	4.80	2.14
SONATA	8.78	2.40	0.00
ZALEPLON	0.00	0.00	0.43
ZOLPIDEM TARTRATE	0.00	0.00	82.91

Class added to PDL Jun 2006

HEALTH INFORMATION DESIGNS

Qualaquin Form

Clear Fields

Fax Completed Form to:
866-254-0761
For questions regarding this Prior authorization, call
866-773-0695

Prior Authorization Vendor for ND Medicaid

ND Medicaid will cover Qualaquin with a diagnosis of Malaria.

Part I: TO BE COMPLETED BY PHYSICIAN

RECIPIENT NAME:		RECIPIENT MEDICAID ID NUMBER:
Recipient Date of birth:		
PHYSICIAN NAME:		PHYSICIAN MEDICAID ID NUMBER:
Address:		Phone:
City:		FAX:
State: Zip:		

REQUESTED DRUG:	**Requested Dosage:** (must be completed)

Qualifications for coverage:

- ❑ Malaria

.

Physician Signature: Date:

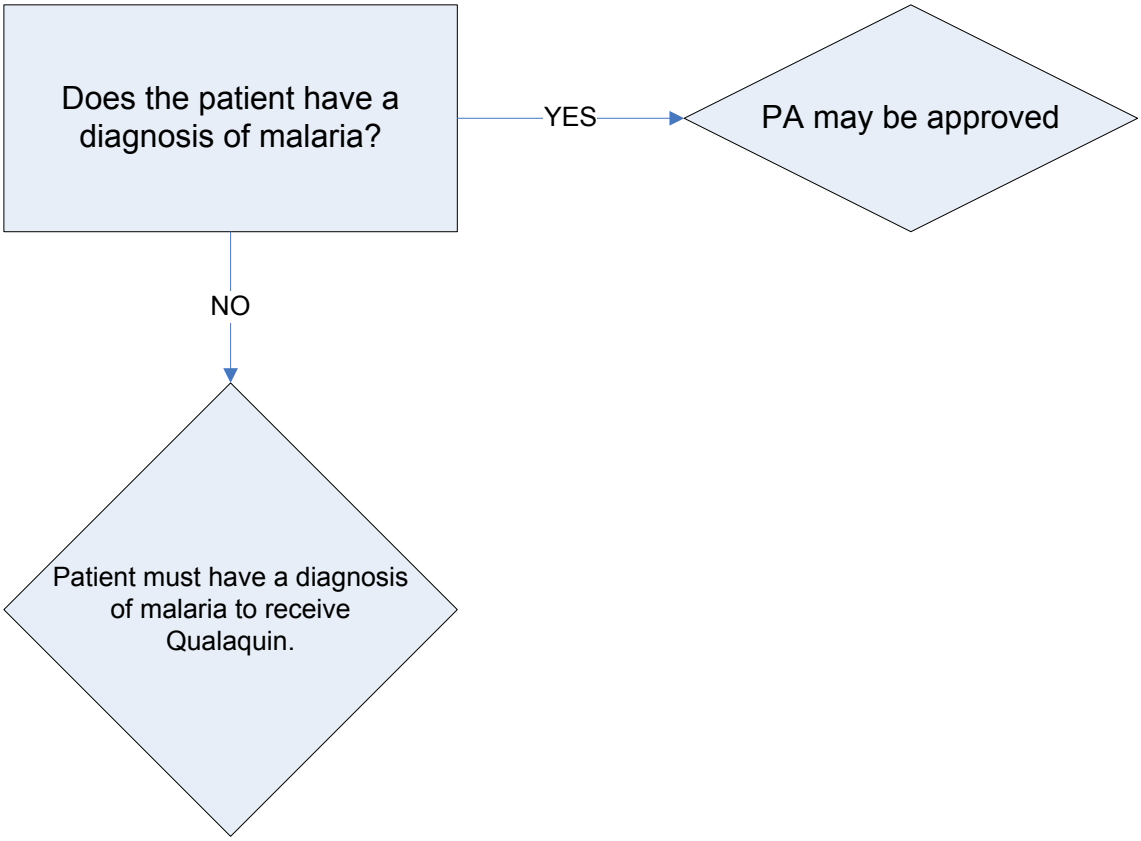
Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:		ND MEDICAID PROVIDER NUMBER:
Phone:		FAX:
Drug:		NDC#:

Part III: FOR OFFICIAL USE ONLY

Date: / /		Initials: _____
Approved - Effective dates of PA: From: / /		To: / /
Denied: (Reasons)		

North Dakota Department of Human Services
Qualaquin Criteria Algorithm



ACE-Inhibitors (ACE-I), Angiotensin II Receptor Blockers (ARB) and Renin Inhibitor PA Form

Fax Completed Form to: 866-254-0761
For questions regarding this Prior authorization, call 866-773-0695

Prior Authorization Vendor for ND

ND Medicaid requires that patients receiving a prescription for Aceon must use at least two generic ACE-Is as first line.
ND Medicaid requires that patients receiving an ARB or Renin Inhibitor must try and fail one ACE-I.

*__Note:__

- **ACE-I: Captopril, enalapril, moexipril, ramipril, lisinopril, trandolapril, quinapril, benazepril, and fosinopril do not require a prior authorization.**
- **Angiotensin II receptor antagonists: Cozaar, Micardis, Teveten, Atacand, Diovan, Avalide, Benicar and their hydrochlorothiazide containing combinations.**
- **Renin Inhibitor: Tekturna and Tekturna HCT.**

Part I: TO BE COMPLETED BY PHYSICIAN

Recipient Name	Recipient Date of Birth	Recipient Medicaid ID Number	
Physician Name			
Physician Medicaid Provider Number	Telephone Number	Fax Number	
Address	City	State	Zip Code
Requested Drug and Dosage:	**Diagnosis for this request:**		

Qualifications for coverage:

□ Failed ACE-I therapy (list two ACE-I to receive Aceon)	Start Date	End Date	Dose	Frequency

□ *I confirm that I have considered a generic or other alternative and that the requested drug is expected to result in the successful medical management of the recipient.*

Physician Signature	Date

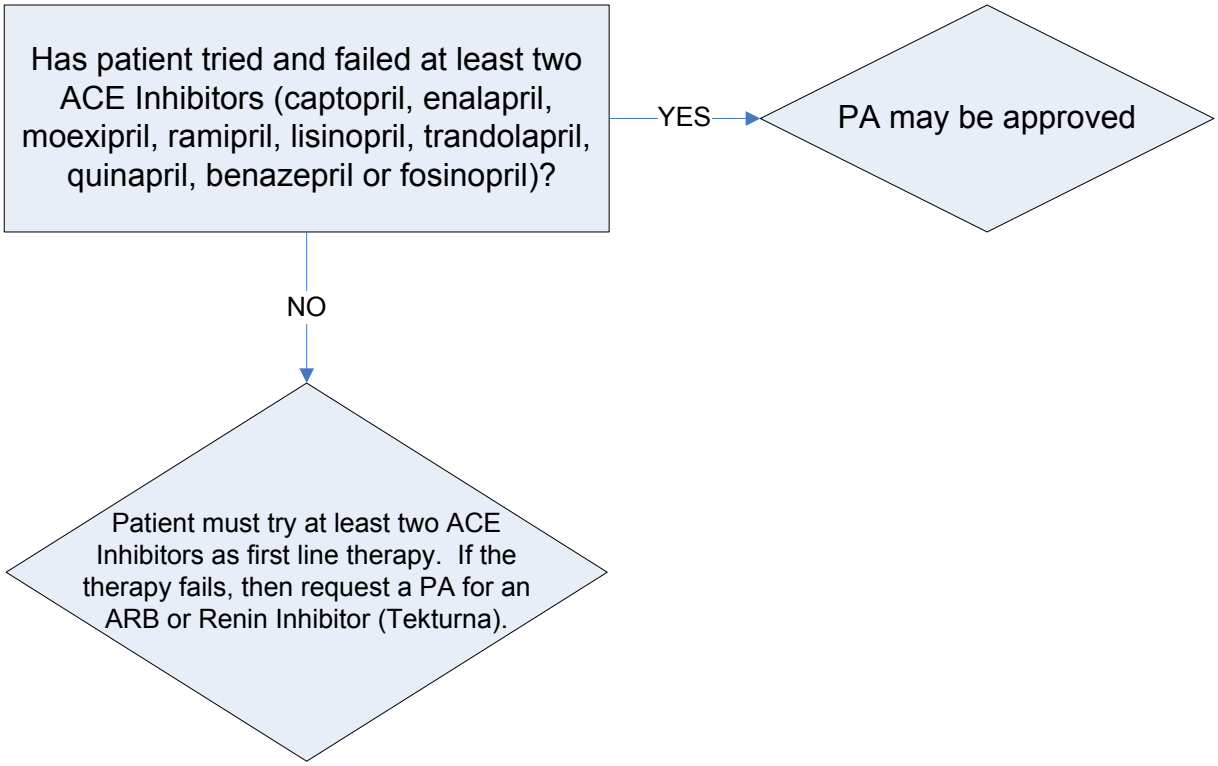
Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:			ND MEDICAID PROVIDER NUMBER:
TELEPHONE NUMBER	FAX NUMBER	DRUG	NDC #

Part III: FOR OFFICIAL USE ONLY

Date Received	Initials:
Approved - Effective dates of PA: From: / / To: / /	Approved by:
Denied: (Reasons)	

North Dakota Department of Human Services
ACE-Is, ARBs and Renin Inhibitor (Tekturna) Authorization Criteria Algorithm



NORTH DAKOTA MEDICAID
Percentage Market Share Within Sub-Classes
ACE Inhibitors

	FEB 04	APR 05	DEC 08
All ACE Inhibitors(No Subclass)			
ACCUPRIL	8.39	0.46	0.00
ACCURETIC	0.33	0.11	0.00
ACEON	0.33	0.42	0.00
ALTACE	7.61	8.61	0.00
BENAZEPRIL HCL	0.29	5.27	2.56
BENAZEPRIL HCL-HCTZ	0.00	0.98	0.60
CAPOTEN	0.00	0.00	0.00
CAPOZIDE	0.00	0.00	0.00
CAPTOPRIL	1.99	1.62	1.51
CAPTOPRIL/HYDROCHLOROTHIAZIDE	0.00	0.00	0.00
ENALAPRIL MALEATE	18.87	18.24	9.94
ENALAPRIL MALEATE-HCTZ	0.81	0.74	0.00
ENALAPRIL MALEATE/HCTZ	0.00	0.00	0.00
FOSINOPRIL SODIUM	1.77	2.57	0.60
FOSINOPRIL-HYDROCHLOROTHIAZIDE	0.00	0.18	0.15
LEXXEL	0.00	0.04	0.00
LISINOPRIL	37.70	41.64	64.01
LISINOPRIL-HCTZ	3.64	4.43	8.89
LOTENSIN	5.22	0.04	0.00
LOTENSIN HCT	1.36	0.07	0.00
LOTREL	4.38	3.97	0.30
MAVIK	0.37	0.60	0.00
MOEXIPRIL HCL	2.83	0.14	0.90
MOEXIPRIL-HYDROCHLOROTHIAZIDE	0.00	0.00	0.45
MONOPRIL	1.58	0.07	0.00
MONOPRIL HCT	0.40	0.11	0.00
PRINIVIL	0.11	0.04	0.00
PRINZIDE	0.00	0.00	0.00
QUINAPRIL	0.00	0.00	0.00
QUINAPRIL HCL	0.00	5.83	5.27
QUINARETIC	0.00	0.18	0.00
RAMIPRIL	0.00	0.00	4.67
TARKA	0.15	0.25	0.00
TRANDOLAPRIL	0.00	0.00	0.00
UNIRETIC	1.58	1.30	0.15
UNIVASC	0.00	2.00	0.00
VASERETIC	0.00	0.00	0.00
VASOTEC	0.07	0.00	0.00
VASOTEC I.V.	0.00	0.00	0.00
ZESTORETIC	0.18	0.11	0.00
ZESTRIL	0.04	0.04	0.00

Class added to PDL May 2005

NORTH DAKOTA MEDICAID
Percentage Market Share Within Sub-Classes
ARBS

	FEB 04	AUG 05	DEC 08
All ARBS(No Subclass)			
ATACAND	12.11	12.05	4.31
ATACAND HCT	1.93	2.45	0.00
AVALIDE	1.68	2.04	0.86
AVAPRO	7.86	8.27	3.45
BENICAR	7.09	8.99	10.34
BENICAR HCT	1.16	4.19	6.03
COZAAR	26.80	24.51	24.14
DIOVAN	21.39	20.84	26.72
DIOVAN HCT	8.63	7.97	12.07
HYZAAR	9.66	5.82	4.31
MICARDIS	1.16	1.43	4.31
MICARDIS HCT	0.13	1.02	3.45
TEKTURNA	0.00	0.00	0.00
TEKTURNA HCT	0.00	0.00	0.00
TEVETEN	0.26	0.41	0.00
TEVETEN HCT	0.13	0.00	0.00

Class added to PDL Sep 2005

Synagis Utilization

NDC USAGE for Synagis from 08/01/08 to 02/24/09				
NDC Code	**Rx Num**	**Total Reimb Amt**	**Total Claim Cost**	**Label Name**
60574411301	124	$214,225.04	$246,571.99	SYNAGIS 100 MG/1 ML VIAL
60574411401	57	$51,045.21	$58,862.66	SYNAGIS 50 MG/0.5 ML VIAL
TOTAL	181	$265,270.25	$305,434.65	50 recipients

NDC USAGE for Synagis from 08/01/07 to 04/30/08				
NDC Code	**Rx Num**	**Total Reimb Amt**	**Total Claim Cost**	**Label Name**
60574411301	224	$377,751.10	$457,914.94	SYNAGIS 100 MG/1 ML VIAL
60574411401	127	$102,929.47	$125,911.44	SYNAGIS 50 MG/0.5 ML VIAL
TOTAL	351	$480,680.57	$583,826.38	76 recipient

NDC USAGE for Synagis from 08/01/06 to 04/30/07				
NDC Code	**Rx Num**	**Total Reimb Amt**	**Total Claim Cost**	**Label Name**
60574411301	295	$435,140.21	$537,324.47	SYNAGIS 100 MG/1 ML VIAL
60574411401	161	$115,087.68	$146,079.93	SYNAGIS 50 MG/0.5 ML VIAL
TOTAL	456	$550,227.89	$683,404.40	97 recipients

Growth Hormone PA Form

Fax Completed Form to:
866-254-0761
For questions regarding this Prior authorization, call
866-773-0695

Prior Authorization Vendor for ND Medicaid

ND Medicaid requires that patients receiving Growth Hormone meet one of the criteria below:

- **Growth Hormone Deficiency in children and adults with a history of hypothalamic pituitary disease**
- **Short stature associated with chronic renal insufficiency before renal transplantation**
- **Short stature in patients with Turner Syndrome (TS) or Prader-Willi Syndrome (PWS)**
- **Human Immunodeficiency Virus (HIV) associated wasting in adults**

Part I: TO BE COMPLETED BY PHYSICIAN

RECIPIENT NAME:	RECIPIENT MEDICAID ID NUMBER:
Recipient Date of birth: / /	
PHYSICIAN NAME:	PHYSICIAN MEDICAID ID NUMBER:
Address:	Phone: ( )
City:	FAX: ( )
State: Zip:	
REQUESTED DRUG:	**Requested Dosage:** (must be completed)

Qualifications for coverage:

Criteria met:	Diagnosis Date: Drug:	Dose: Frequency:
Physician Signature:		Date:

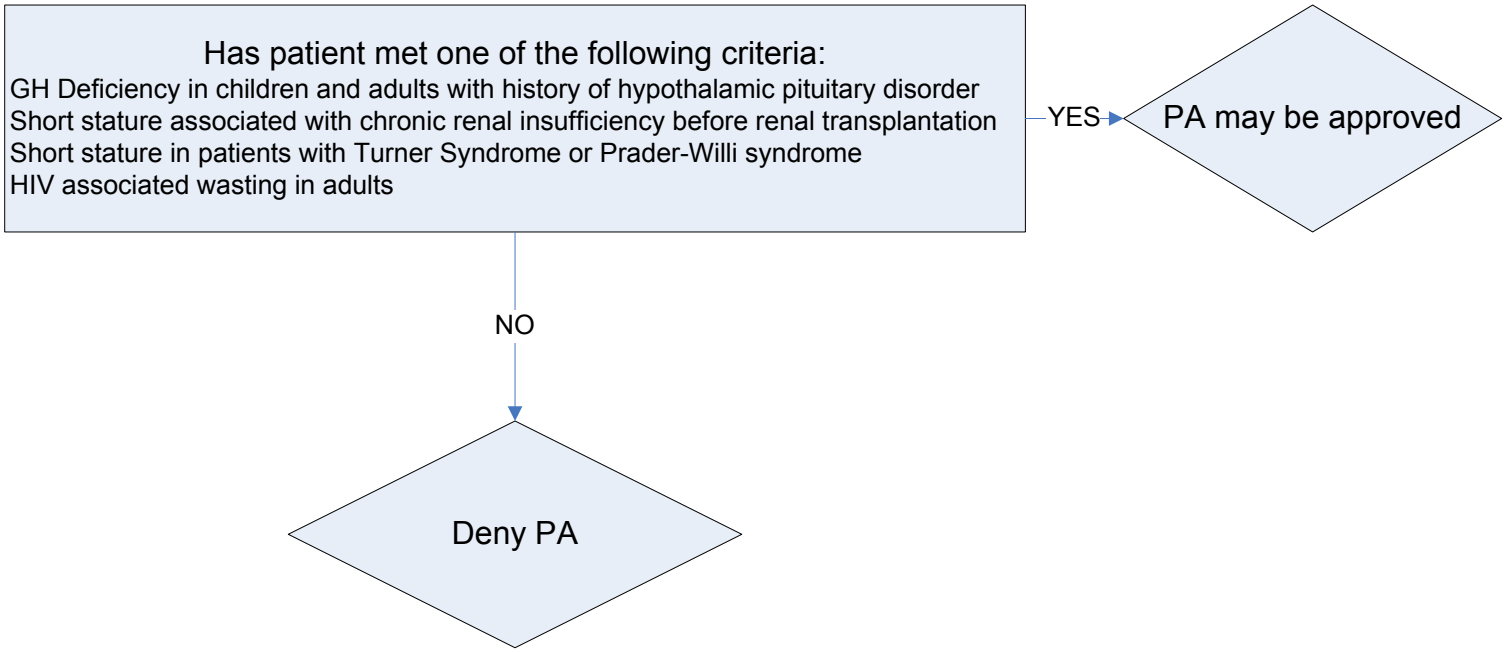
Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:	ND MEDICAID PROVIDER NUMBER:
Phone:	FAX:
Drug:	NDC#:

Part III: FOR OFFICIAL USE ONLY

Date: / /	Initials: _____
Approved - Effective dates of PA: From: / /	To: / /
Denied: (Reasons)	

North Dakota Department of Human Services
Growth Hormone Authorization Algorithm



Growth Hormone Utilization

02/01/08 – 01/31/09

Label Name	Rx Num	Total Reimb Amt
GENOTROPIN MINIQUICK 1 MG	1	$236.43
NUTROPIN AQ 20 MG/2ML PEN CART	1	$393.09
GENOTROPIN MINIQUICK 0.4 MG	6	$3,736.86
GENOTROPIN MINIQUICK 0.6 MG	9	$7,592.19
NORDITROPIN NORDIFLEX 5 MG/1.5	11	$11,157.96
GENOTROPIN 13.8 MG CARTRIDGE	3	$12,372.99
NORDITROPIN NORDIFLX 10 MG/1.5	10	$17,283.46
Total 6 recipients	**41**	**$52,772.98**

North Dakota Department of Human Services
Pharmacotherapy Review
Uloric®
June 1, 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 guideline 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 don't 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.

ULORIC PA FORM

HEALTH INFORMATION DESIGNS

Prior Authorization Vendor for ND Medicaid

Fax Completed Form to:
866-254-0761
For questions regarding this Prior authorization, call
866-773-0695

ND Medicaid requires that patients receiving a new prescription for Uloric must try allopurinol as first line therapy.

- Allopurinol does not require a prior authorization.

Part I: TO BE COMPLETED BY PHYSICIAN

Recipient Name	Recipient Date of Birth	Recipient Medicaid ID Number	
Physician Name			
Physician Medicaid Provider Number	Telephone Number	Fax Number	
Address	City	State	Zip Code
Requested Drug and Dosage: □ ULORIC	**Diagnosis for this request:**		

Qualifications for coverage:

□ Failed allopurinol therapy Serum Urate Level: _____	Start Date	End Date	Dose	Frequency

□ *I confirm that I have considered a generic or other alternative and that the requested drug is expected to result in the successful medical management of the recipient.*

Physician Signature	Date

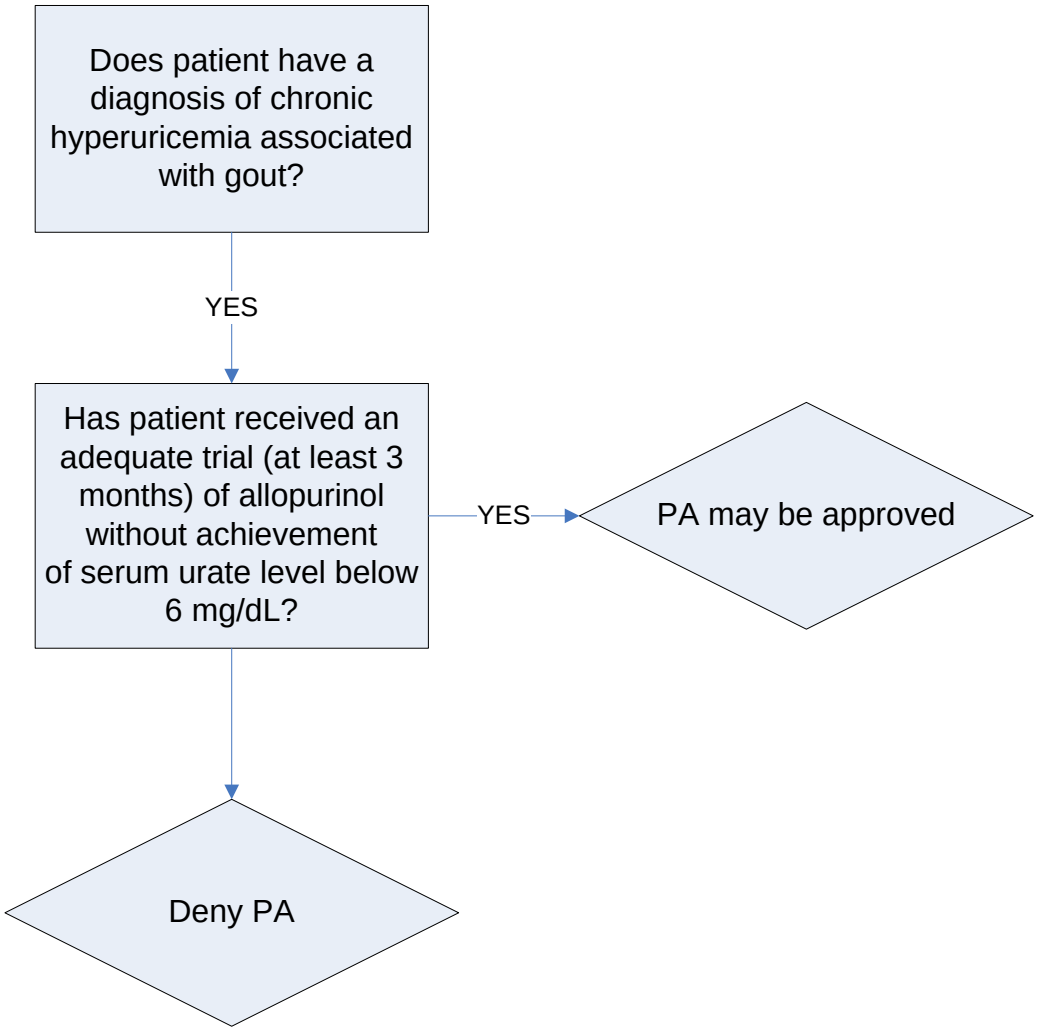
Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:			ND MEDICAID PROVIDER NUMBER:
TELEPHONE NUMBER	FAX NUMBER	DRUG	NDC #

Part III: FOR OFFICIAL USE ONLY

Date Received	Initials:
Approved - Effective dates of PA: From: / / To: / /	Approved by:
Denied: (Reasons)	

North Dakota Department of Human Services
Uloric Authorization Algorithm



Allopurinol does not require a prior authorization.

North Dakota Department of Human Services
Pharmacotherapy Review
Moxatag®
June 1, 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.

MOXATAG PA FORM

Prior Authorization Vendor for ND Medicaid

Fax Completed Form to:
866-254-0761
For questions regarding this Prior authorization, call
866-773-0695

ND Medicaid requires that patients receiving a new prescription for Moxatag must submit documentation of allergies or show a history of intolerable side effects to the inactive ingredients in regular-release amoxicillin.

- Regular-release amoxicillin does not require a prior authorization.

Part I: TO BE COMPLETED BY PHYSICIAN

Recipient Name	Recipient Date of Birth	Recipient Medicaid ID Number	
Physician Name			
Physician Medicaid Provider Number	Telephone Number	Fax Number	
Address	City	State	Zip Code

REQUESTED DRUG : □ MOXATAG	**Dosage**
Qualifications for coverage:	
□ Allergic/intolerable side effects to inactive ingredients of regular-release amoxicillin. Name of inactive ingredient: _____	Diagnosis for this request:
□ *I confirm that I have considered a generic or other alternative and that the requested drug is expected to result in the successful medical management of the recipient.*	
Physician Signature	Date

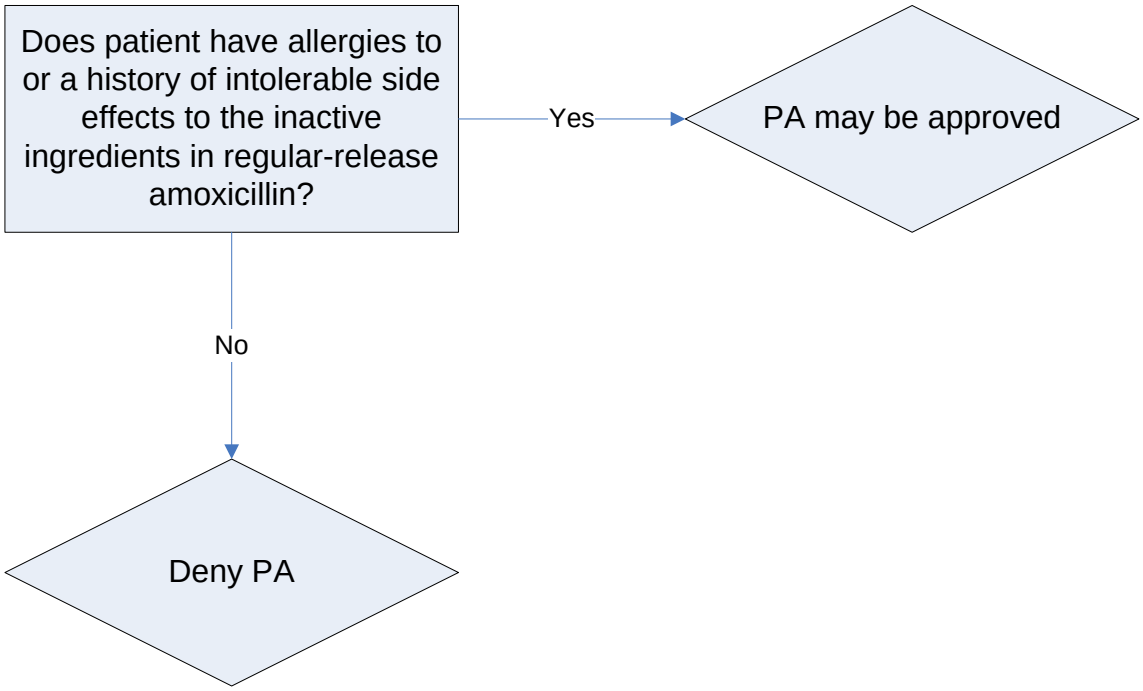
Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:			ND MEDICAID PROVIDER NUMBER:
TELEPHONE NUMBER	FAX NUMBER	DRUG	NDC #

Part III: FOR OFFICIAL USE ONLY

Date Received	Initials:
Approved - Effective dates of PA: From: / / To: / /	Approved by:
Denied: (Reasons)	

North Dakota Department of Human Services
Moxatag Authorization Algorithm



Regular-release amoxicillin does not require a prior authorization and costs approximately $4.40 for a course of therapy compared to $84.40 for a course of Moxatag therapy.

North Dakota Department of Human Services
Pharmacotherapy Review
Savella®
June 1, 2009

I. Overview

Savella (milnacipran) is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) approved by the FDA on January 14, 2009 for the management of fibromyalgia in adults.

II. Fibromyalgia Treatment Guidelines

A. University of Texas, School of Nursing, Family Nurse Practitioner Program: Pharmacological Treatment Guideline for Fibromyalgia; 2005.

1. **Adequate sleep** – It is proposed that sleep disturbance occurs from a variety of reasons. Some of these reasons include serotonin metabolism in the central nervous system (CNS), resulting in low levels of brain serotonin, low levels of growth hormone secretion, and generalized body pain from the disease process. Tricyclic antidepressants (TCAs) help promote restorative sleep and heighten the effects of the body's natural pain-killing substances (endorphins), and increase non-rapid eye movement (non-REM) stage 4 sleep. Low levels of serotonin and norepinephrine are related to depression, muscle pain, and fatigue. Administering TCAs such as amitriptyline helps correct these deficiencies. Recommended dosing is as follows: Amitriptyline 25-50 mg 2 to 3 hours before bedtime, allowing peak sedative effect with minimal carry-over effect. May increase dosing to 50-75 mg over the next weeks if needed for added control. Cyclobenzaprine can be used as an alternative to amitriptyline because of its structural similarity to TCA compounds. The dosage is 10-30 mg at bedtime (QHS). Benzodiazepines are a second alternative, but should be used cautiously at bedtime due to their tendency to stabilize the erratic brain waves that interfere with restorative sleep in patients with fibromyalgia. (Millea & Holloway, 2000) (Level I, Recommendation A)

2. **Treat fatigue and depression** – If no response with TCAs, consider adding selective serotonin reuptake inhibitor (SSRI) in the morning. Dosing for fluoxetine is 20 mg every morning (QAM). This class of drugs works to block the re-uptake of serotonin, which in turn allows the body to utilize greater amounts of serotonin. The exact mechanism of action for fluoxetine in fibromyalgia syndrome is unknown. Since people with fibromyalgia already have decreased levels of serotonin; it is believed that fluoxetine increases the levels of serotonin to the brain. (Note: One research study completed in 2002 found there is a synergistic effect between fluoxetine and

amitriptyline due to the pharmacokinetic interaction between the 2 drugs. Using them together may be more effective for the patient's symptoms than using them alone.) (Arnold et al., 2002) (Level I, Recommendation A)

3. **Treat muscle spasms** – Cyclobenzaprine or low dose benzodiazepines (clonazepam) are used to treat muscle spasms. Cyclobenzaprine also modulates muscle tension at a supraspinal level. Dosing is 10-30 mg every day (QD) or, if greater dosing is needed, divide the doses, with the smaller dose in the morning and the larger dose in the evening (Tofferi, Jackson, & O'Malley, 2004). (Level I, Recommendation A)

4. **Adequate pain control** – The pain component of fibromyalgia is thought to be abnormal CNS processing of pain signals. It is thought that the pain is caused by a complex interaction between neurotransmitter release, external stressors, patient behavior, hormones, and the CNS system. Tramadol 50-100 mg every 4 to 6 hours is recommended for pain control. Non-steroidal anti-inflammatory agents are not recommended because fibromyalgia is not an anti-inflammatory process. Opioids are not recommended due to adverse side effects and regulatory concerns, and no increased benefit has been noted in research studies (Inanici & Yunus, 2002). (Level I, Recommendation A)

B. American Pain Society (APS): Guideline for the management of fibromyalgia syndrome pain (FMS) in adults and children; Pharmacological Therapies 2005.

1. For initial treatment of FMS, prescribe a tricyclic antidepressant for sleep, in particular 10 to 30 mg amitriptyline or cyclobenzaprine at bedtime. **(A)**

2. Use selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, alone or in combination with tricyclics, for pain relief. **(B)** The doses of all antidepressants should be individualized and any concurrent mood disturbances treated. **(Panel consensus)**

3. Do not use non-steroidal anti-inflammatory drugs (NSAIDs) as the primary pain medication for people with FMS. **(A)** There is no evidence that NSAIDs are effective when used alone to treat FMS patients. NSAIDs, including COX-2 selective agents and acetaminophen, may provide some analgesia when used with other medications. **(C)**

4. Use tramadol (50 to 100 mg two or three times daily) for pain relief in people with FMS. The dose of tramadol should be increased slowly over time and should be tapered gradually when discontinued. Tramadol can be used alone or in combination with acetaminophen. **(B)**

5. Use opioids for management of FMS pain only after all other pharmacologic and nonpharmacologic therapies have been exhausted. **(Panel consensus)**

6. Use sleep and anti-anxiety medications such as trazodone, benzodiazepines, nonbenzodiazepine sedatives, or L-dopa and carbidopa in FMS, especially if sleep disturbances such as restless leg syndrome are prominent. **(A)**

7. Do not use corticosteroids in the treatment of FMS unless there is concurrent joint, bursa, or tendon inflammation. **(A)**

8. Ask patients about their use of complementary products and practices and have sufficient knowledge of them to be able to answer questions concerning efficacy and identify possible negative interactions with prescribed treatment. **(C)**

III. Pharmacology and Mechanism of Action

The exact mechanism of the central pain inhibitory action of milnacipran and its ability to improve the symptoms of fibromyalgia in humans are unknown. Preclinical studies have shown that milnacipran is a potent inhibitor of neuronal norepinephrine and serotonin reuptake without directly affecting the uptake of dopamine or other neurotransmitters.

IV. Pharmacokinetics

Milnacipran is well absorbed after oral administration with an absolute bioavailability of approximately 85% to 90%. It is excreted predominantly unchanged in urine (55%) and has a terminal elimination half-life of about 6 to 8 hours. Steady-state levels are reached within 36-48 hours. Milnacipran is absorbed following oral administration with maximum concentrations reached within 2 to 4 hours. Absorption is not affected by food. The mean volume of distribution is approximately 400L. Plasma protein binding is 13%.

V. Warnings/Precautions

1. **Suicidality** – Monitor for worsening depressive symptoms and suicide risk.

2. **Serotonin Syndrome** – Serotonin syndrome has been reported with SNRIs and SSRIs. Concomitant use of serotonergic drugs is not recommended.

3. **Elevated blood pressure and heart rate** – Cases have been reported with milnacipran. Monitor blood pressure and heart rate prior to initiating treatment with milnacipran and periodically throughout treatment.

4. **Seizures** – Cases have been reported with milnacipran therapy. Prescribe milnacipran with care in patients with a history of seizure disorder.

5. **Hepatotoxicity** – More patients treated with milnacipran than with placebo experienced mild elevations of ALT and AST. Rarely, fulminant hepatitis has been reported. Avoid concomitant use of milnacipran with substantial alcohol use or chronic liver disease.

6. **Discontinuation** – Withdrawal symptoms have been reported in patients when discontinuing treatment. A gradual dose reduction is recommended.

7. **Abnormal Bleeding** – Milnacipran may increase the risk of bleeding events. Caution patients about the risk of bleeding associated with the concomitant use of milnacipran and NSAIDs, aspirin, or other drugs that affect coagulation.

8. Male patients with a history of obstructive uropathies may experience higher rates of genitourinary adverse events.

VI. Drug Interactions

1. **Lithium** – Serotonin syndrome may occur when lithium is co-administered with milnacipran and with other drugs that impair metabolism of serotonin.

2. **Epinephrine and norepinephrine** – Milnacipran inhibits the reuptake of norepinephrine. Concomitant use of milnacipran and epinephrine and norepinephrine may be associated with paroxysmal hypertension and possible arrhythmia.

3. **Serotonergic Drugs** – Co-administration of milnacipran with other inhibitors of serotonin re-uptake may result in hypertension and coronary artery vasoconstriction, through additive serotonergic effects.

4. **Digoxin** – Use of milnacipran concomitantly with digoxin may be associated with potentiation of adverse hemodynamic effects. Postural hypotension and tachycardia have been reported in combination therapy with intravenously administered digoxin. Co-administration should be avoided.

5. **Clonidine** – Because milnacipran inhibits norepinephrine reuptake, co-administration with clonidine may inhibit clonidine's anti-hypertensive effect.

6. **Clomipramine** – In a drug-drug interaction study, an increase in euphoria and postural hypotension was observed in patients who switched from clomipramine to milnacipran.

7. **CNS-active drugs** – Given the primary CNS effects of milnacipran, caution should be used when it is taken in combination with other centrally acting drugs, including those with a similar mechanism of action.

VII. Contraindications

1. **Monoamine Oxidase Inhibitors** – Concomitant use of milnacipran in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated. In patients receiving a serotonin reuptake inhibitor in combination with a MAOI, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Therefore, it is recommended that milnacipran should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 5 days should be allowed after stopping milnacipran before starting an MAOI.

2. **Uncontrolled Narrow-Angle Glaucoma** – In clinical trials, milnacipran was associated with increased risk of mydriasis. Therefore, do not use milnacipran in patients with uncontrolled narrow-angle glaucoma.

VIII. Adverse Reactions

The most frequently occurring adverse reactions (≥ 5% and greater than placebo) were nausea, headache, constipation, dizziness, insomnia, hot flush, hyperhidrosis, vomiting, palpitations, heart rate increased, dry mouth, and hypertension.

IX. Dosage and Administration

- Administer milnacipran in two divided doses per day
- Begin dosing at 12.5 mg on the first day and increase to 100 mg/day over a 1-week period:
  Day 1: 12.5 mg once
  Day 2-3: 25 mg/day (12.5 mg twice daily)
  Day 4-7: 50 mg/day (25 mg twice daily)
  After Day 7: 100 mg/day (50 mg twice daily)
- Recommended dose is 100 mg/day
- May be increased to 200 mg/day based on individual patient response
- Dose should be adjusted in patients with severe renal impairment

X. Efficacy

The efficacy of milnacipran for the management of fibromyalgia was established in two double-blind, placebo-controlled, multicenter studies in adult patients (18-74 years of age). Patients enrolled in the studies all had a diagnosis of fibromyalgia based on the American College of Rheumatology (ACR) criteria. Approximately 35% of patients had a history of depression.

A larger proportion of patients treated with milnacipran than with placebo experienced a simultaneous reduction in pain from baseline of at least 30% and also rated

themselves as much improved or very much improved based on the patient global assessment. Analysis of the studies showed that there were more treatment responders among the less depressed patients than the more depressed patients.

There are no head-to-head trials comparing the efficacy of milnacipran to duloxetine or pregabalin in the treatment of fibromyalgia. All three appear to be modestly effective for the management of fibromyalgia based on their individual clinical trial data.

XI. Conclusion

Current guidelines recommend a low-dose tricyclic antidepressant, cyclobenzaprine, SSRI (alone or in combination with a low-dose tricyclic), and cognitive behavioral therapy as initial treatment for fibromyalgia. For additional management of pain and sleep disturbance, tramadol (alone or in combination with acetaminophen), and sleep medications might be beneficial. Use opioids only after all pharmacologic and nonpharmacologic options have been exhausted.

References:

1. Wolters Kluwer Health, Inc, ed. Drug Facts and Comparisons. St. Louis, MO. 2009
2. New drug: Savella (milnacipran). Pharmacist's Letter/Prescriber's Letter 2009;25(3):250310.
3. Savella® [package insert]. New York, NY: Forest Pharmaceuticals, Inc.; January 2009.
4. University of Texas, School of Nursing, Family Nurse Practitioner Program. Fibromyalgia treatment guideline. Austin (TX): University of Texas, School of Nursing; 2005 May.
5. Buckhardt CS, Goldenberg D, et al. Guideline for the management of fibromyalgia syndrome pain in adults and children. Glenview (IL): American Pain Society (APS); 2005.

SAVELLA PA FORM

Fax Completed Form to:
866-254-0761
For questions regarding this Prior authorization, call
866-773-0695

Prior Authorization Vendor for ND Medicaid

ND Medicaid requires that patients receiving a new prescription for Savella must have a diagnosis of fibromyalgia

Part I: TO BE COMPLETED BY PHYSICIAN

Recipient Name	Recipient Date of Birth	Recipient Medicaid ID Number	
Physician Name			
Physician Medicaid Provider Number	Telephone Number	Fax Number	
Address	City	State	Zip Code
Requested Drug and Dosage: □ SAVELLA	**Diagnosis for this request:**		
□ *I confirm that I have considered a generic or other alternative and that the requested drug is expected to result in the successful medical management of the recipient.*			
Physician Signature		Date	

Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:			ND MEDICAID PROVIDER NUMBER:
TELEPHONE NUMBER	FAX NUMBER	DRUG	NDC #

Part III: FOR OFFICIAL USE ONLY

Date Received	Initials:
Approved - Effective dates of PA: From: / / To: / /	Approved by:
Denied: (Reasons)	

North Dakota Department of Human Services
Pharmacotherapy Review
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 withdrew 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.

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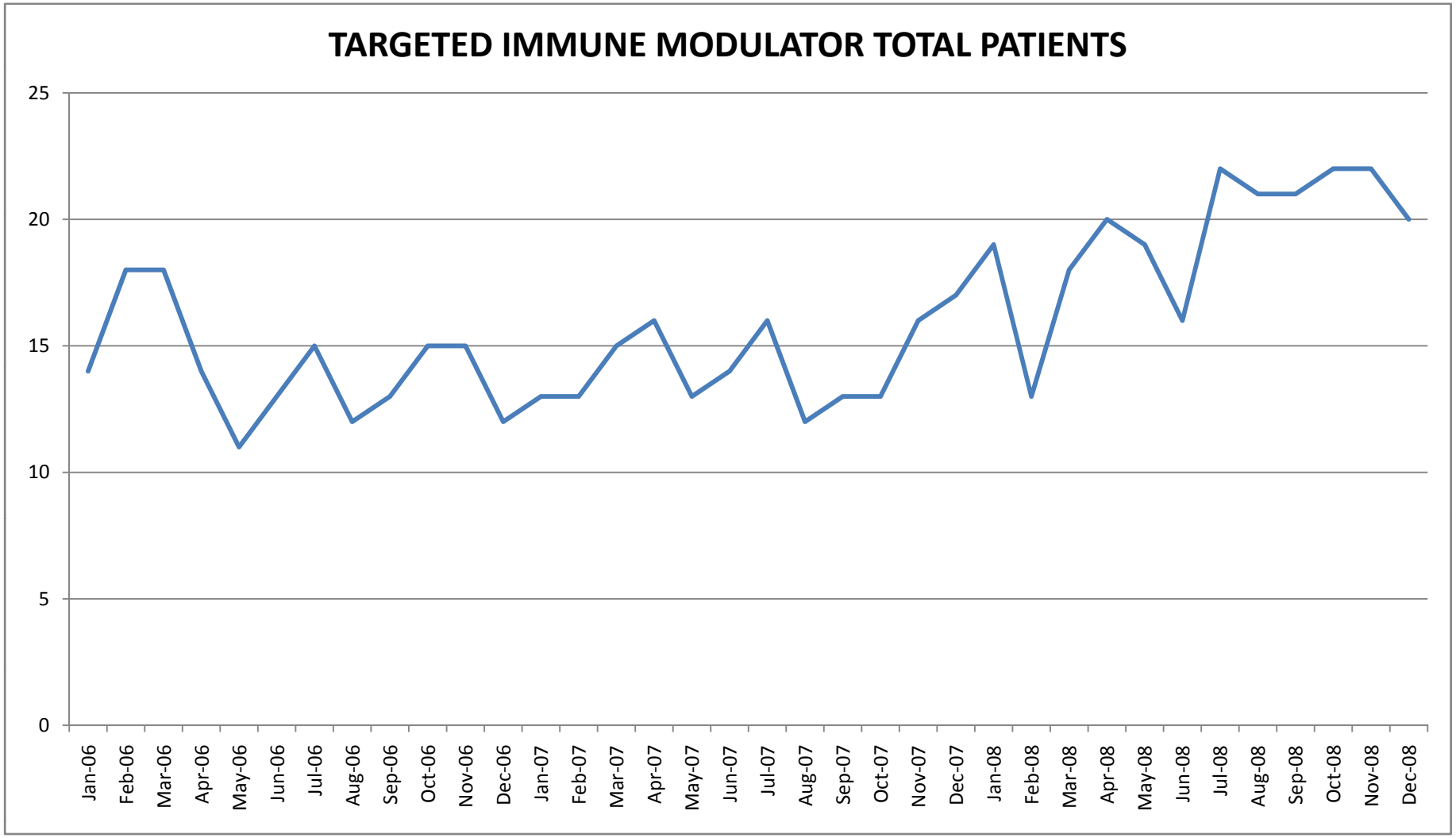
Targeted Immune Modulator Utilization 01/01/08 to 12/31/08		
Generic Name	**Rx Num**	**Total Reimb Amt**
ADALIMUMAB (HUMIRA)	107	$189,846.63
ANAKINRA (KINERET)	11	$9,211.02
ETANERCEPT (ENBREL)	125	$140,691.64
TOTAL 39 Recipients	243	$339,749.29

Summary by Age

Age	Recip Count
3	1
14	1
16	1
17	1
19	2
27	2
28	3
29	1
31	1
34	1
35	2
36	1
37	3
38	1

Summary by Age

Age	Recip Count
40	1
42	2
45	1
46	2
48	1
49	1
50	2
51	1
52	1
54	1
58	1
61	1
62	1
64	2


TARGETED IMMUNE MODULATOR TOTAL PATIENTS
25
20
15
10
5
0
Jan-06
Feb-06
Mar-06
Apr-06
May-06
Jun-06
Jul-06
Aug-06
Sep-06
Oct-06
Nov-06
Dec-06
Jan-07
Feb-07
Mar-07
Apr-07
May-07
Jun-07
Jul-07
Aug-07
Sep-07
Oct-07
Nov-07
Dec-07
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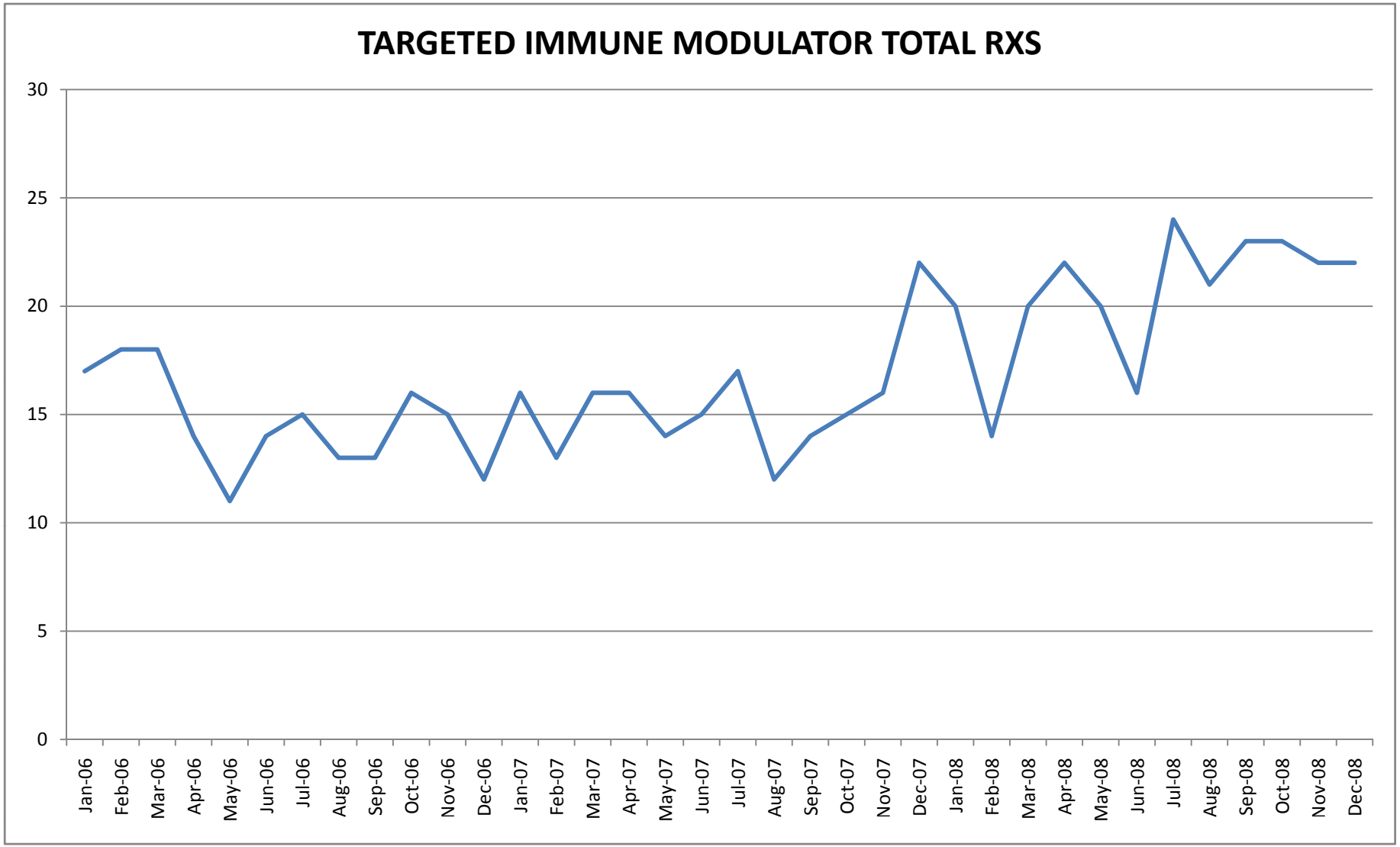
Jul-08
Aug-08
Sep-08
Oct-08
Nov-08
Dec-08


TARGETED IMMUNE MODULATOR TOTAL RXS
30
25
20
15
10
5
0
Jan-06
Feb-06
Mar-06
Apr-06
May-06
Jun-06
Jul-06
Aug-06
Sep-06
Oct-06
Nov-06
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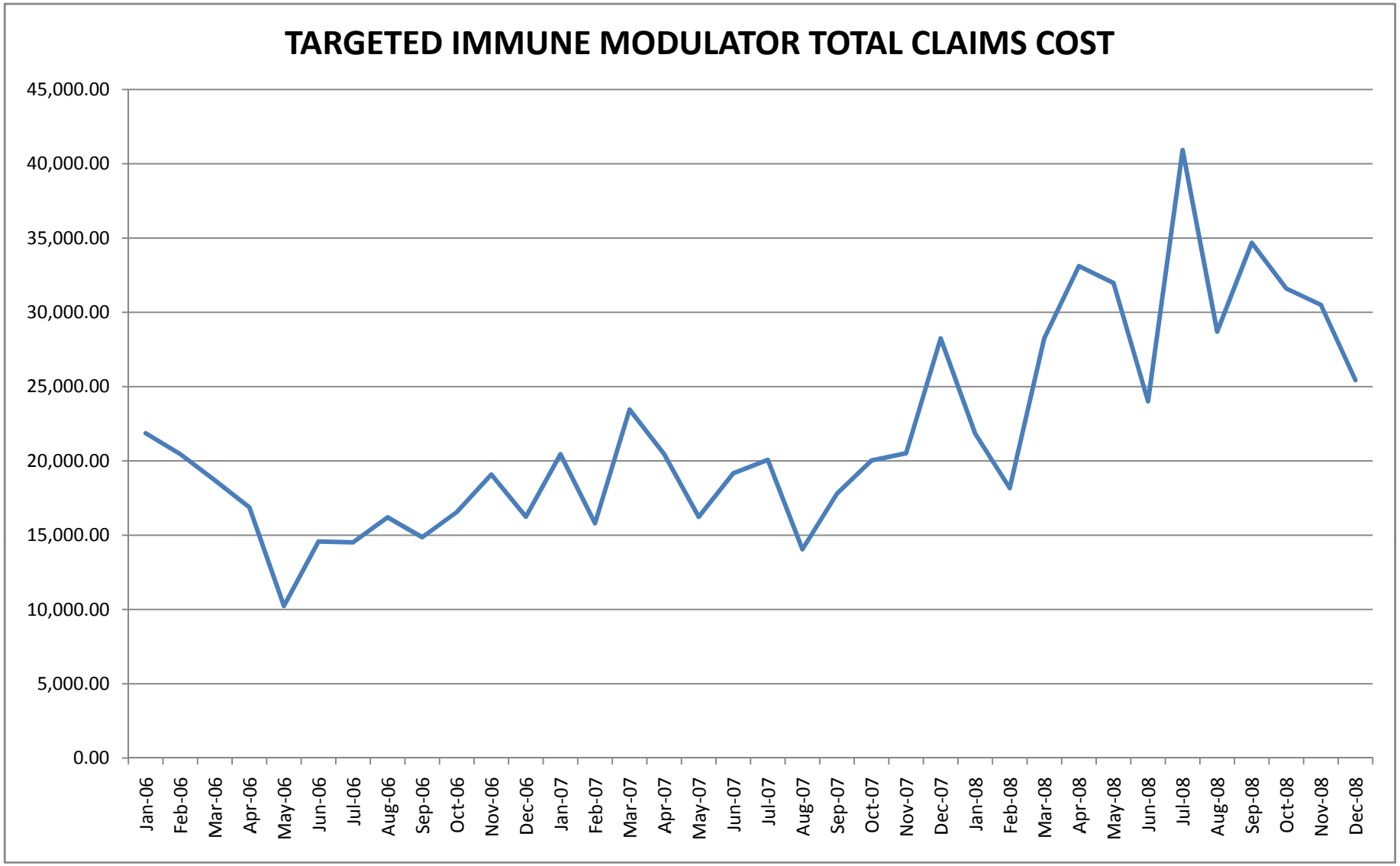
TARGETED IMMUNE MODULATOR TOTAL CLAIMS COST
45,000.00
40,000.00
35,000.00
30,000.00
25,000.00
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10,000.00
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TARGETED IMMUNE MODULATORS PA FORM

Prior Authorization Vendor for ND Medicaid

Fax Completed Form to:
866-254-0761
For questions regarding this Prior authorization, call
866-773-0695

ND Medicaid requires that patients receiving a new prescription for Orencia, Humira, Enbrel, Amevive, Kineret, Cimzia, and Remicade must submit a prior authorization form for coverage.

Part I: TO BE COMPLETED BY PHYSICIAN

Recipient Name	Recipient Date of Birth	Recipient Medicaid ID Number	
Physician Name			
Physician Medicaid Provider Number	Telephone Number	Fax Number	
Address	City	State	Zip Code

Requested Drug:	**Diagnosis for this request:**
□ ORENCIA □ HUMIRA □ ENBREL □ AMEVIVE □ KINERET □ CIMZIA □ REMICADE	

□ *I confirm that I have considered a generic or other alternative and that the requested drug is expected to result in the successful medical management of the recipient.*

Physician Signature	Date

Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:			ND MEDICAID PROVIDER NUMBER:
TELEPHONE NUMBER	FAX NUMBER	DRUG	NDC #

Part III: FOR OFFICIAL USE ONLY

Date Received	Initials:
Approved - Effective dates of PA: From: / / To: / /	Approved by:
Denied: (Reasons)	

NORTH DAKOTA MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS
2ND QUARTER 2009

Criteria Recommendations	*Approved*	*Rejected*

1. Rufinamide / Over-utilization _____ _____

Alert Message: The maximum recommended dose of rufinamide (Banzel) is 3200 mg per day administered in 2 equally divided doses.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Rufinamide		

Max Dose: 3200 mg/day

References:
Facts & Comparisons, 2008 Updates.
Banzel Prescribing Information, November 2008, Novartis Pharma AG

2. Rufinamide / Nonadherence _____ _____

Alert Message: Non-adherence to the prescribed dosing regimen for Banzel (rufinamide) may result in sub-therapeutic effects and loss of seizure control.

Conflict Code: LR – Non-adherence
Drugs/Diseases

Util A	Util B	Util C
Rufinamide		

Less than 75 days in 90 day review.

References:
Facts & Comparisons, 2008 Updates.
Banzel Prescribing Information, November 2008, Novartis Pharma AG.

3. Rufinamide / Triazolam _____ _____

Alert Message: The concurrent use of Banzel (rufinamide) with triazolam may result in decreased exposure to triazolam due to the induction, by rufinamide, of CYP3A4-mediated triazolam metabolism. Based on in-vivo studies the co-administration and pre-treatment with rufinamide (400 mg bid) resulted in a 37% decrease in AUC and 23% decrease in Cmax of triazolam.

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

Util A	Util B	Util C
Rufinamide	Triazolam	

References:
Facts & Comparisons, 2008 Updates.
Banzel Prescribing Information, November 2008, Novartis Pharma AG.

4. Rufinamide / Oral Contraceptives _____ _____

Alert Message: The concurrent use of Banzel (rufinamide) with oral contraceptives (OC) may result in decreased exposure to the OC due to the induction, by rufinamide, of CYP3A4-mediated hormone metabolism. Patients of childbearing age should be warned that the coadministration of these agents may render the OC less effective. Additional non-hormonal forms of contraception are recommended during rufinamide therapy.

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

Util A	Util B	Util C
Rufinamide	Oral Contraceptives	

References:
Facts & Comparisons, 2008 Updates.
Banzel Prescribing Information, November 2008, Novartis Pharma AG.

5. Rufinamide / Carbamazepine _____ _____

Alert Message: Concurrent use of Banzel (rufinamide) with carbamazepine may result in decreased plasma levels of both rufinamide (19% to 26%) and carbamazepine (7% to 13%) with the effects being more marked in the pediatric population.

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

Util A	Util B	Util C
Rufinamide	Carbamazepine	

References:
Facts & Comparisons, 2008 Updates.
Banzel Prescribing Information, November 2008, Novartis Pharma AG.

6. Rufinamide / Phenobarbital _____ _____

Alert Message: Concurrent use of Banzel (rufinamide) with phenobarbital may result in a 25% to 46% decrease in rufinamide plasma concentrations and increased phenobarbital concentrations of 8% - 13%. The effect is usually more marked in the pediatric population.

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

Util A	Util B	Util C
Rufinamide	Phenobarbital	

References:
Facts & Comparisons, 2008 Updates.
Banzel Prescribing Information, November 2008, Novartis Pharma AG.

7. Rufinamide / Phenytoin _____ _____

Alert Message: Concurrent use of Banzel (rufinamide) with phenytoin may result in a 25% to 46% decrease in the rufinamide plasma concentrations. Phenytoin plasma levels may increase by 7% to 21% due to phenytoin's non-linear pharmacokinetics. The effect is usually more marked in the pediatric population.

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

Util A	Util B	Util C
Rufinamide	Phenytoin	

References:
Facts & Comparisons, 2008 Updates.
Banzel Prescribing Information, November 2008, Novartis Pharma AG.

8. Rufinamide / Primidone _____ _____

Alert Message: Concurrent use of Banzel (rufinamide) with primidone may result in a 25% to 46% decrease in rufinamide concentrations independent of dose or concentration of primidone. The effect is usually more marked in the pediatric population.

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

Util A	Util B	Util C
Rufinamide	Primidone	

References:
Facts & Comparisons, 2008 Updates.
Banzel Prescribing Information, November 2008, Novartis Pharma AG.

9. Rufinamide / Valproate _____ _____

Alert Message: Concurrent use of Banzel (rufinamide) with valporate may result in a 16% to 70% increase in rufinamide concentrations with the more marked effect in the pediatric population. Patients stabilized on rufinamide before being prescribed valproate should begin valproate therapy at a low dose, and titrate to a clinically effective dose. Patients on valporate who have rufinamide added to the regimen should begin with a rufinamide dose lower than 400mg.

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

Util A	Util B	Util C
Rufinamide	Valporate	

References:
Facts & Comparisons, 2008 Updates.
Banzel Prescribing Information, November 2008, Novartis Pharma AG.

10. Rufinamide / Lamotrigine _____ _____

Alert Message: Concurrent use of Banzel (rufinamide) and lamotrigine may result in a 7% to 13% decrease in lamotrigine concentrations in a concentration-dependent manner. The effect is usually more marked in the pediatric population.

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

Util A	Util B	Util C
Rufinamide	Lamotrigine	

References:
Facts & Comparisons, 2008 Updates.
Banzel Prescribing Information, November 2008, Novartis Pharma AG.

11. Rufinamide /Short QT Syndrome Inducing Drugs _____ _____

Alert Message: Banzel (rufinamide) is contraindicated in patients with familial short QT syndrome. Formal cardiac ECG studies demonstrated shortening of the QT interval up to 20 msec with rufinamide treatment. Caution should also be used when administering rufinamide with other drugs that shorten the QT interval.

Conflict Code: DC – Inferred Drug Disease Warning
Drugs/Diseases

Util A	Util B		Util C
Rufinamide	Short QT Interval		
	Digoxin	Propafenone	
	Lamotrigine	Moricizine	
	Ranolazine	Lidocaine	
	Magnesium	Carbamazepine	
	Mexiletine	Amitriptyline	
	Procainamide	Imipramine	
	Disopyramide	Haloperidol	
	Phenytoin	Metoclopramide	
	Flecainide		

References:
Facts & Comparisons, 2008 Updates.
Banzel Prescribing Information, November 2008, Novartis Pharma AG.

12. 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.