DUR Board Meeting
September 12, 2011
Pioneer Room
State Capitol

North Dakota Medicaid
DUR Board Meeting
Agenda
Pioneer Room
State Capitol
September 12, 2011
1pm

1. Administrative items
    - Travel vouchers

2. Old business

• Review and approval of minutes of 06/06/11 meeting	Chair
• Budget update	Brendan
• Second review of Asacol HD	Brendan
• Second review of Ophthalmic Antihistamines	Brendan
• Second review of Horizant	Brendan
• Second review of Daliresp	Brendan
• Second review of narcotics with high dose APAP	Brendan
• Yearly PA review	HID
o DAW	
o Amrix/Fexmid	
o Xenical	
o Zanaflex caps	
o Ketek	
o Aczone	

3. New business

• Review of Cetraxal	HID
• Review of Dificid	HID
• Review of new oral anticoagulants (Pradaxa, Xarelto, etc.)	HID
• Review of agents used to treat Hereditary Angioedema	HID
• Review of Avandia	HID
• Update simvastatin 80mg products	HID
• Update Hepatitis C prior authorization	HID
• Criteria recommendations	HID
• Upcoming meeting date/agenda	Chair

4. Adjourn — Chair

Please remember to silence all cellular phones and pagers during the meeting.

Drug Utilization Review (DUR) Meeting Minutes
June 6, 2011

Members Present: Norman Byers, Jeffrey Hostetter, John Savageau, David Clinkenbeard, Russ Sobotta, Cheryl Huber, Kim Krohn, Greg Pfister, Patricia Churchill, Steve Irsfeld
Members Absent: James Carlson, Carrie Sorenson, Leann Ness, Todd Twogood, Carlotta McCleary
Medicaid Pharmacy Department: Brendan Joyce, Gary Betting
HID Staff Present: Candace Rieth

Chair, G. Pfister called the meeting to order at 1:06 pm. Chair, G. Pfister asked for a motion to approve the minutes from the March meeting. N. Byers moved that the minutes be approved and P. Churchill seconded the motion. Chair, G. Pfister called for a voice vote to approve the minutes. The motion passed with no audible dissent.

Budget Update
B. Joyce informed the board members that there is no budget update at this time.

Nuedexta Second Review
A motion and second were made at the March meeting to place Nuedexta on prior authorization. The topic was brought up for a second review. There was no public comment. After discussion, Chair, G. Pfister called for a voice vote to approve the motion. The motion passed with no audible dissent.

Nexiclon Second Review
A motion and second were made at the March meeting to place Nexiclon on prior authorization. The topic was brought up for a second review. There was no public comment. After discussion, Chair, G. Pfister called for a voice vote to approve the motion. The motion passed with one audible dissent.

Topical Ketoconazole Products Second Review
A motion and second were made at the December meeting to place topical ketoconazole products on prior authorization. The topic was brought up for a second review. There was no public comment. Chair, G. Pfister called for a voice vote to approve the motion. The motion passed with no audible dissent.

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. Sedative/Hypnotics, Qualaquin, ACE-I/ARB/Renin Inhibitors, Synagis, GH/IGF-1, and Triptan forms and criteria were reviewed. The board recommended that the Triptan form include two steps for new starts. The first step would require failure of sumatriptan. The second step would require failure of naratriptan. There was no public comment. The form will be modified to include new recommendations.

Desoxyn Review
B. Joyce reviewed Desoxyn information with the Board. There was no public comment. After discussion, the board recommended that claims be verified for diagnosis of obesity or ADHD.

Colcrys Review
B. Joyce reviewed Colcrys information with the Board. There was no public comment. After discussion, the board tabled the topic for later review.

Asacol HD Review
B. Joyce reviewed Asacol HD information with the Board. There was no public comment. After discussion, N. Byers made a motion to place Asacol HD on prior authorization. D. Clinkenbeard seconded the motion. This topic will be brought up at the next meeting for finalization.

Ophthalmic Antihistamine Review
B. Joyce reviewed ophthalmic antihistamine information with the Board. There was no public comment. After discussion, J. Hostetter made a motion to place ophthalmic antihistamines on prior authorization and include coverage of over the counter products. J. Savageau seconded the motion. This topic will be brought up at the next meeting for finalization.

Horizant Review
B. Joyce reviewed Horizant with the Board. B. Felt, representing GSK, spoke regarding Horizant. After discussion, J. Hostetter made a motion to place Horizant on prior authorization. P. Churchill seconded the motion. This topic will be brought up at the next meeting for finalization.

Daliresp Review
B. Joyce reviewed Daliresp with the Board. C. McSpadden, representing Forest, spoke regarding Daliresp. After discussion, P. Churchill made a motion to place Daliresp on prior authorization. N. Byers seconded the motion. This topic will be brought up at the next meeting for finalization.

Narcotics with high dose APAP Review
B. Joyce reviewed utilization of narcotics containing high doses of APAP. The FDA is requesting that drug manufacturers limit the amount of acetaminophen in prescription drug products to 325mg per tablet, capsule or other dosage unit. It is expected that the higher-dose formulations will be phased out by 2014. The department prefers to address this change proactively and therefore suggests that hydrocodone (5/325-10/325) and oxycodone (5/325-10/325) products are covered with all other strengths requiring prior authorization. There was no public comment. After discussion, J. Hostetter made a motion to place all strengths of narcotics in combination with acetaminophen except for hydrocodone/oxycodone (5/325-10/325) on prior authorization. J. Savageau seconded the motion. This topic will be brought up at the next 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. P. Churchill moved to approve the new criteria and J. Savageau seconded the motion. Chair, G. Pfister called for a voice vote. The motion passed with no audible dissent.

The next DUR board meeting will be held September 12, 2011. P. Churchill made a motion to adjourn the meeting. J. Savageau seconded. The motion passed with no audible dissent. Chair G. Pfister adjourned the meeting at 2:30 pm.

Asacol HD Prior Authorization

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 Asacol HD must try and fail Asacol.
Note:

- ***Asacol is FDA approved to treat mild to moderate flares and maintain remission of ulcerative colitis.***
- ***Asacol HD is FDA approved to treat flares in patients with moderately active ulcerative colitis.***

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: □ **Asacol HD**	**Diagnosis for this request:**		
Qualifications for coverage:			
□ FAILED ASACOL THERAPY START DATE: DOSE: END DATE: FREQUENCY:			
Physician Signature		Date	

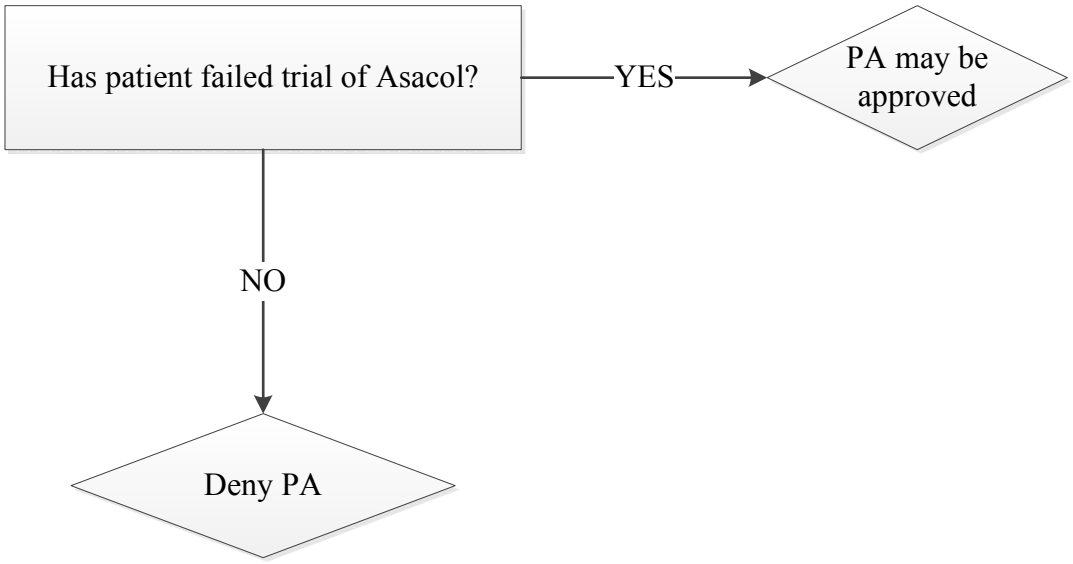
Part II: TO BE COMPLETED BY PHARMACY

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
Asacol HD Authorization Algorithm



For the treatment of moderately active ulcerative colitis: The recommended dose of Asacol HD in adults is two 800 mg tablets to be taken three times daily with or without food, for a total daily dose of 4.8 g for a duration of 6 weeks. $987.84

For the treatment of mildly to moderately active ulcerative colitis: The usual dosage in adults is two 400-mg tablets to be taken three times a day for a total daily dose of 2.4 grams for a duration of 6 weeks. $493.92

For the maintenance of remission of ulcerative colitis: The recommended dosage in adults is 1.6 grams daily, in divided doses.

Ophthalmic Antihistamines
Prior Authorization

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 Lastacaft, Bepreve, and Pataday must first try one of the following:

- ***Ketotifen, Azelastine, Elestat, Emadine, and Patanol do 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: □ **Lastacaft** □ **Bepreve** □ **Pataday**	**Diagnosis for this request:**		
Qualifications for coverage:			
□ FAILED THERAPY START DATE: END DATE:	DOSE: FREQUENCY:		
Physician Signature		Date	

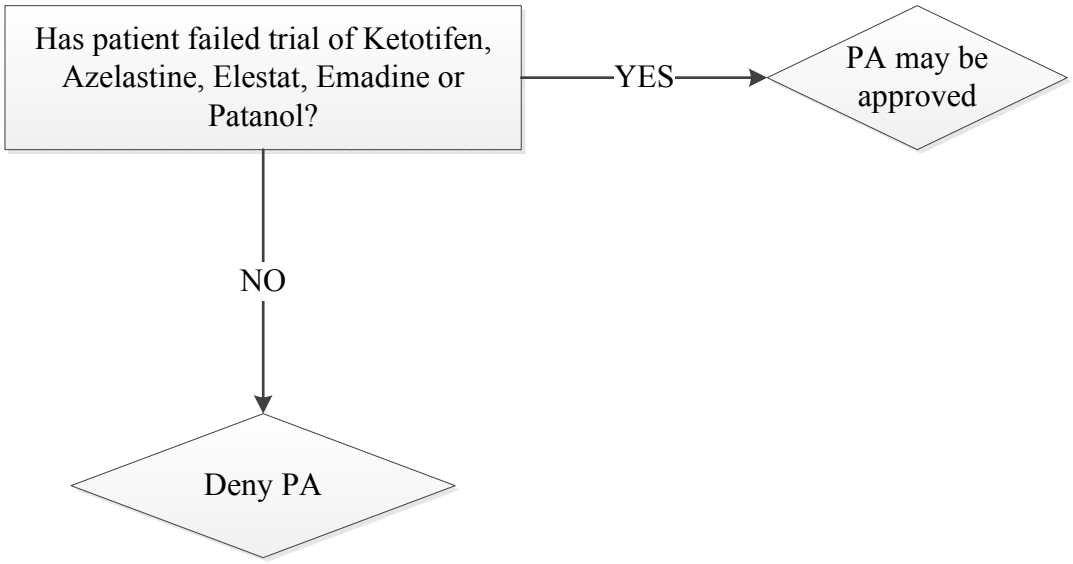
Part II: TO BE COMPLETED BY PHARMACY

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
Ophthalmic Antihistamine Authorization Algorithm



Horizant Prior Authorization

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 Horizant must follow the following guidelines:

- ***Patient must have a diagnosis of Restless Leg Syndrome.***
- ***Patient must have had a trial of gabapentin, pramipexole, or ropinirole.***

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: □ **Horizant**	**Diagnosis for this request:**		
Qualifications for coverage:			
□ FAILED THERAPY START DATE: END DATE:	DOSE: FREQUENCY:		
Physician Signature		Date	

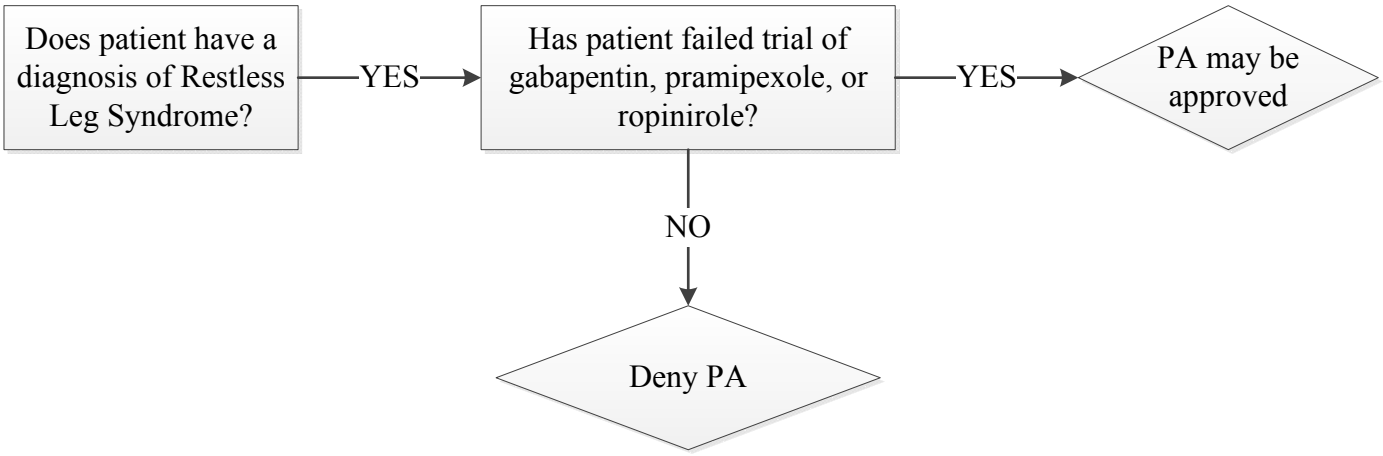
Part II: TO BE COMPLETED BY PHARMACY

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
Horizant Authorization Algorithm



Daliresp Prior Authorization

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 Daliresp must follow the following guidelines:

- ***Patient must be 18 years of age or older.***
- ***Patient must have a diagnosis of severe COPD associated with chronic bronchitis and a history of exacerbations.***

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: □ **Daliresp**	**Diagnosis for this request:**		
Physician Signature		Date	

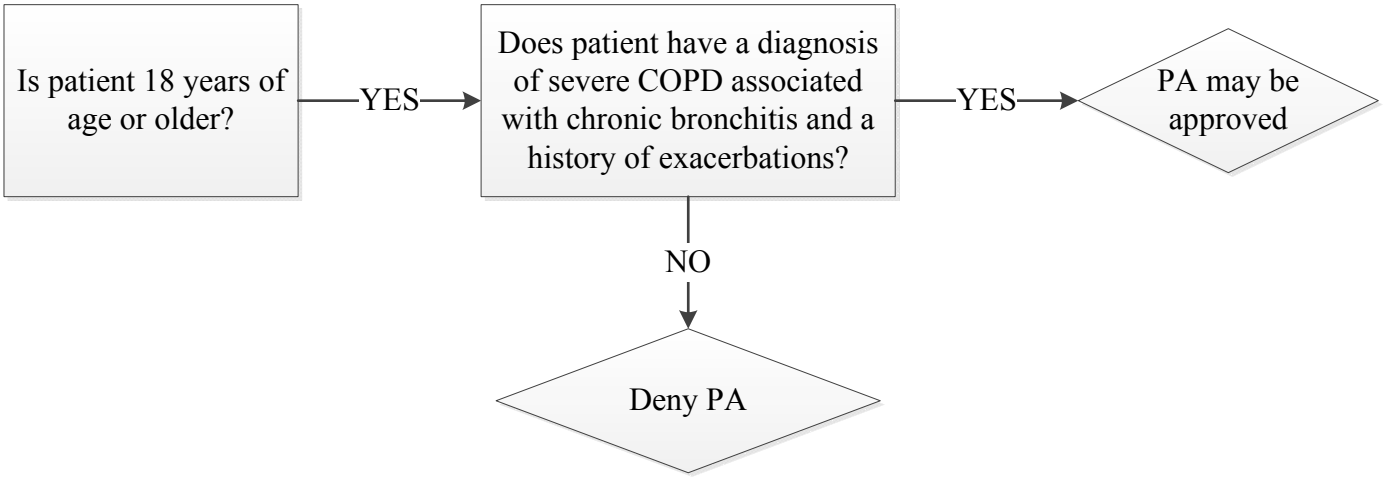
Part II: TO BE COMPLETED BY PHARMACY

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
Daliresp Authorization Algorithm



Narcotics/APAP
Prior Authorization

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 narcotics containing acetaminophen doses greater than 325mg must use hydrocodone/acetaminophen 5/325-10/325 or oxycodone acetaminophen 5/325-10/325.

- ***FDA is requesting that drug manufacturers limit the amount of acetaminophen in prescription drug products to 325mg per dosage unit.***
- ***Higher-dose formulations of hydrocodone/acetaminophen and oxycodone/acetaminophen should be phased out by 2014.***

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 THERAPY START DATE: END DATE:	DOSE: FREQUENCY:		
Physician Signature		Date	

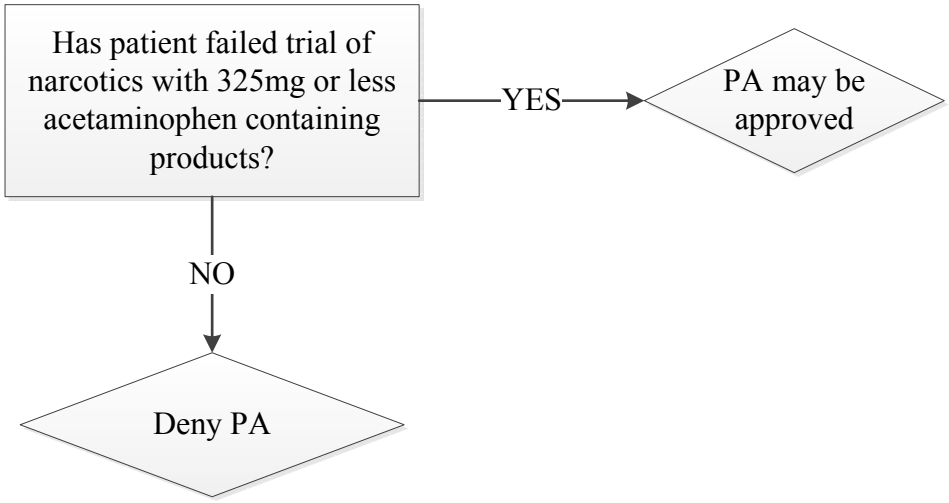
Part II: TO BE COMPLETED BY PHARMACY

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
Narcotics with APAP dose > 325mg
Authorization Algorithm



DISPENSE AS WRITTEN 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

North Dakota Medicaid requires that patients receiving a brand name drug, when there is a generic equivalent available, must first try and fail the generic product for one of the following reasons.

- **The generic product was not effective.**
- **There was an adverse reaction with the generic product,**
- **DAW not allowed for drugs with an authorized generic available.**

Part I: TO BE COMPLETED BY PRESCRIBER

Recipient Name		Recipient Date of Birth		Recipient Medicaid ID Number
Prescriber Name				
Prescriber Medicaid Provider Number		Telephone Number		Fax Number
Address		City	State	Zip Code
Requested Drug:	**DOSAGE:**	**Diagnosis for this request:**		
QUALIFICATIONS FOR COVERAGE: □ FAILED GENERIC EQUIVALENT		**Start Date**	**End Date**	**Dose** / **Frequency**
ADVERSE REACTION TO GENERIC EQUIVALENT (ATTACH FDA MEDWATCH FORM) OR CONTRAINDICATED (PROVIDE DESCRIPTION):				
□ *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.*				
Prescriber 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)	

AMRIX/FEXMID 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 try and fail generic cyclobenzaprine.

**Note:*

- **Cyclobenzaprine does not require PA**
- **Patient must fail therapy on generic cyclobenzaprine before a PA will be considered for Amrix.**

Part I: TO BE COMPLETED BY PRESCRIBER

RECIPIENT NAME:	RECIPIENT MEDICAID ID NUMBER:
Recipient Date of birth: / /	
PRESCRIBER NAME:	PRESCRIBER MEDICAID ID NUMBER:
Address:	Phone: ( )
City:	FAX: ( )
State: Zip:	

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

Qualifications for coverage:

❑ Failed cyclobenzaprine therapy	Start Date:	Dose:
	End Date:	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.*

Prescriber Signature: Date:

Part II: TO BE COMPLETED BY PHARMACY

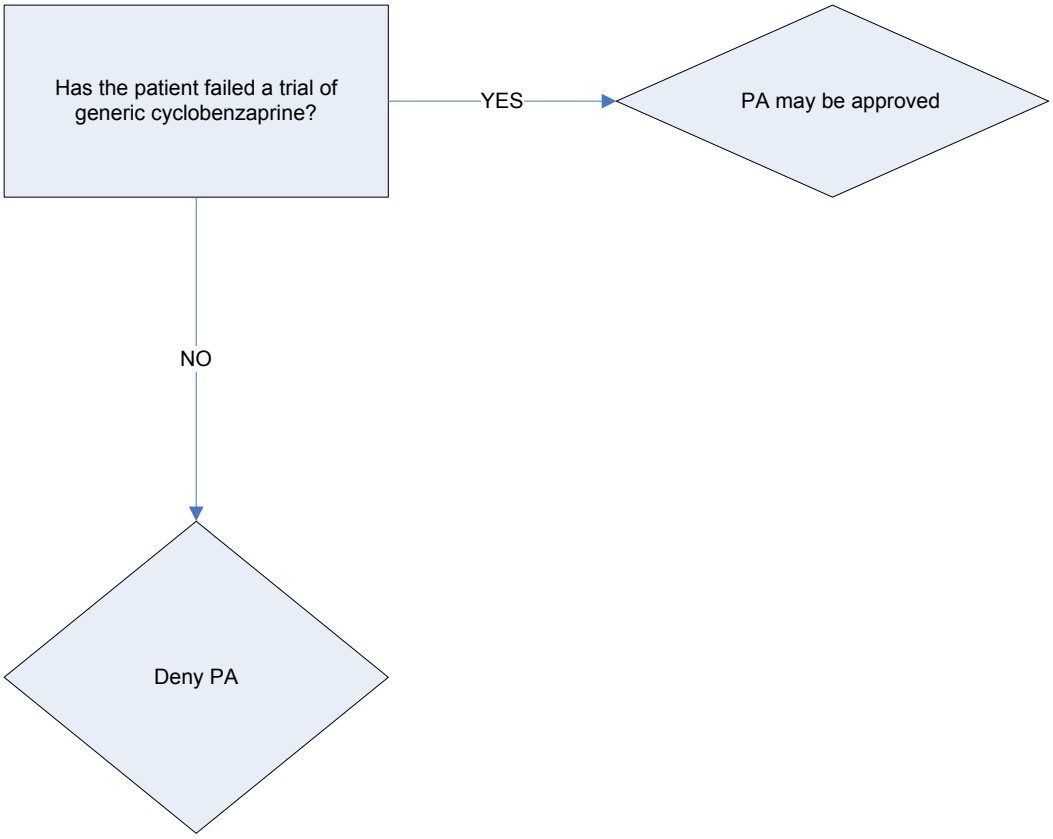
PHARMACY NAME:	ND MEDICAID PROVIDER NUMBER:
Phone:	FAX:
Drug:	NDC#:

Part III: FOR OFFICIAL USE ONLY

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

North Dakota Department of Human Services

Amrix and Fexmid Algorithm



HEALTH INFORMATION DESIGNS

Xenical Prior Authorization

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 prescription for Xenical must be seen by a dietician.
Note:

- ***Patient must have dietician evaluation attached to PA form including height and weight.***
- ***BMI must be equal to or greater than 40.***
- ***5% weight loss must be realized for continued approval (every 6 months).***

Part I: TO BE COMPLETED BY PRESCRIBER

Recipient Name	Recipient Date of Birth	Recipient Medicaid ID Number	
Prescriber Name			
Prescriber Medicaid Provider Number	Telephone Number	Fax Number	
Address	City	State	Zip Code
Requested Drug and Dosage: □ XENICAL	**Diagnosis for this request:**		
Qualifications for coverage:			
□ Dietician evaluation attached	Height:	Weight:	BMI:
Prescriber Signature		Date	

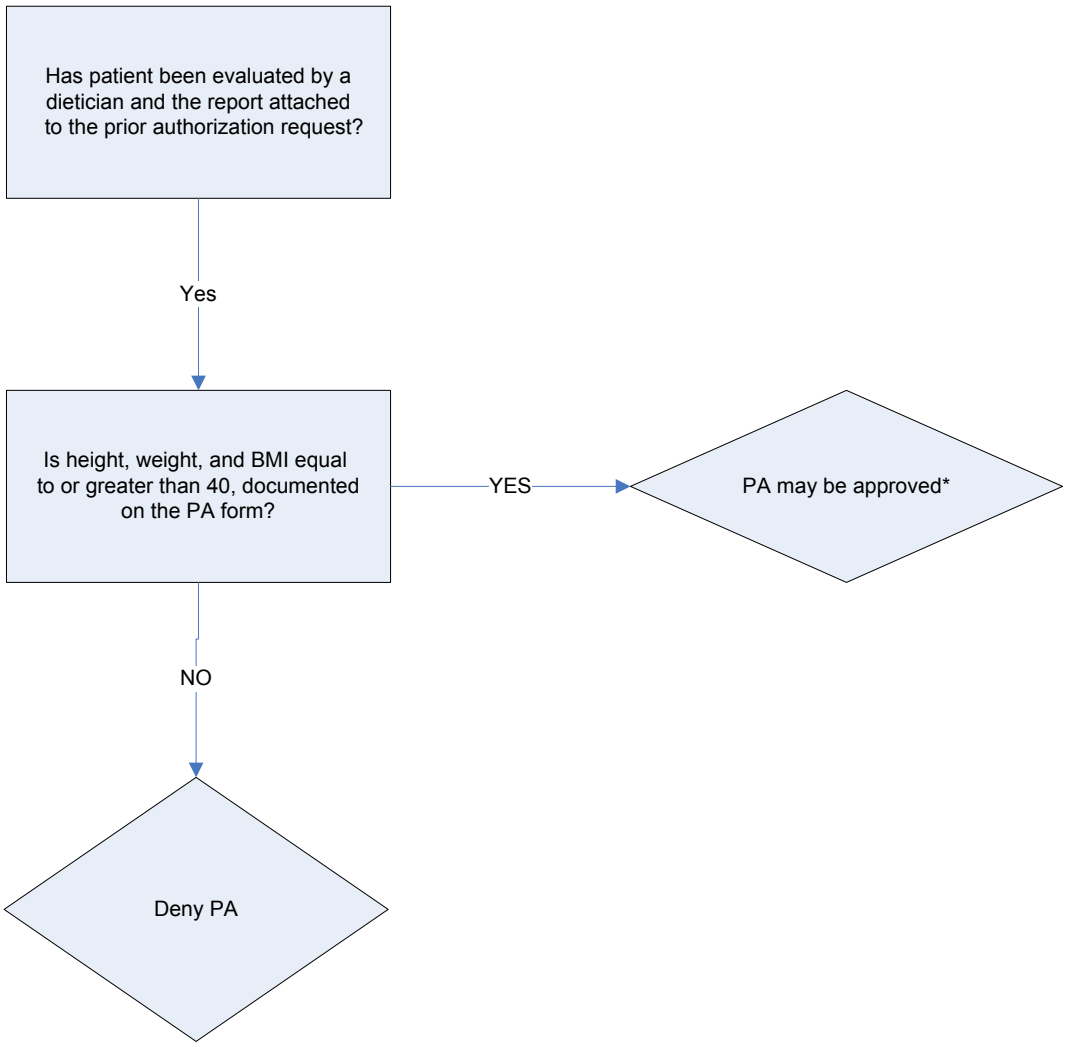
Part II: TO BE COMPLETED BY PHARMACY

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
Xenical Prior Authorization Criteria



*5% weight loss must be realized for continued approval every 6 months.

Prior Authorization Vendor for ND Medicaid

Zanaflex Capsule 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 Zanaflex capsules must use tizanidine tablets first line.
__Note:__

- **Tizanidine tablets do not require a PA.**
- **Patient must fail therapy on tizanidine tablets before a PA may be granted.**

Part I: TO BE COMPLETED BY PRESCRIBER

Recipient Name	Recipient Date of Birth	Recipient Medicaid ID Number	
Prescriber Name			
Prescriber Medicaid Provider Number	Telephone Number	Fax Number	
Address	City	State	Zip Code
Requested Drug and Dosage:	**Diagnosis for this request:**		
Qualifications for coverage:			
□ Failed generic drug	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.*			
Prescriber Signature		Date	

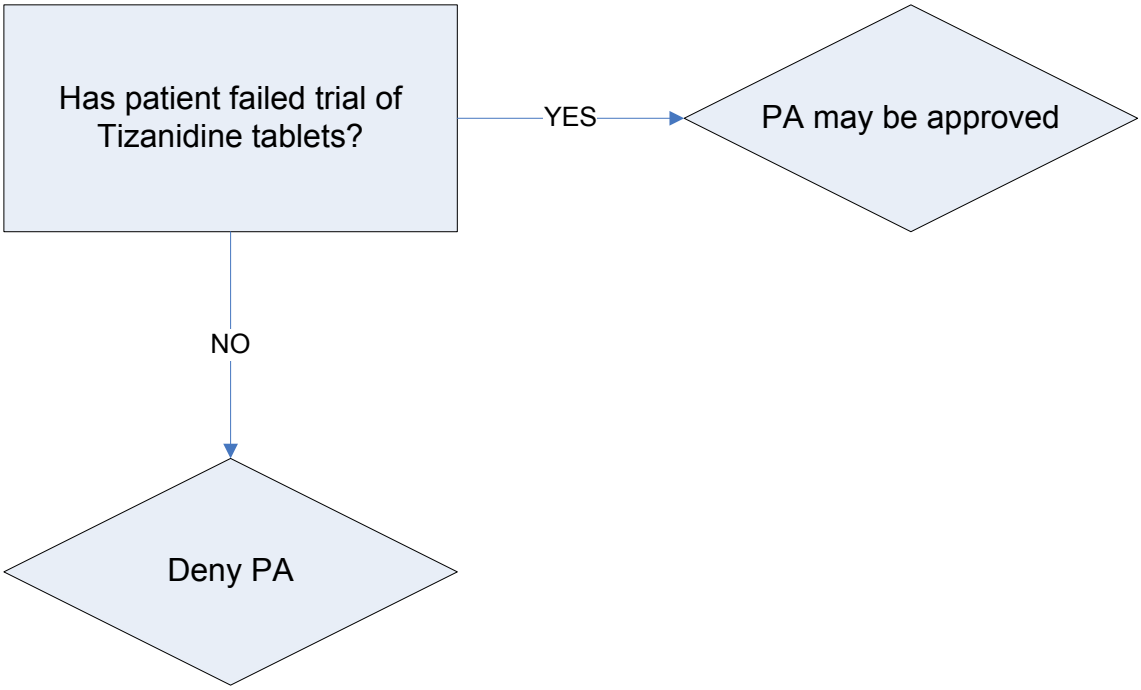
Part II: TO BE COMPLETED BY PHARMACY

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
Zanaflex Authorization Algorithm



HEALTH INFORMATION DESIGNS

KETEK 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 will cover Ketek with a diagnosis of community-acquired pneumonia (of mild to moderate severity) due to Streptococcus pneumoniae for patients 18 years and older.
- ND Medicaid will cover Ketek for patients with an allergy to fluoroquinolones or tetracyclines.

Part I: TO BE COMPLETED BY PRESCRIBER

RECIPIENT NAME:		RECIPIENT MEDICAID ID NUMBER:
Recipient Date of birth: / /		
PRESCRIBER NAME:		PRESCRIBER MEDICAID ID NUMBER:
Address:		Phone: ( )
City:		FAX: ( )
State: Zip:		

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

Qualifications for coverage:

□ Community acquired pneumonia (of mild to moderate severity) due to Streptococcus pneumoniae, (including multi-drug resistant isolates, Haemophilus influenzae, Moraxella catarrhalis, Chlamydophila pneumoniae, or Mycoplasma pneumoniae) for patients 18 years and older.

□ Please list fluoroquinolone or tetracycline that patient is allergic to: _____

□ *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.*

Prescriber Signature: Date:

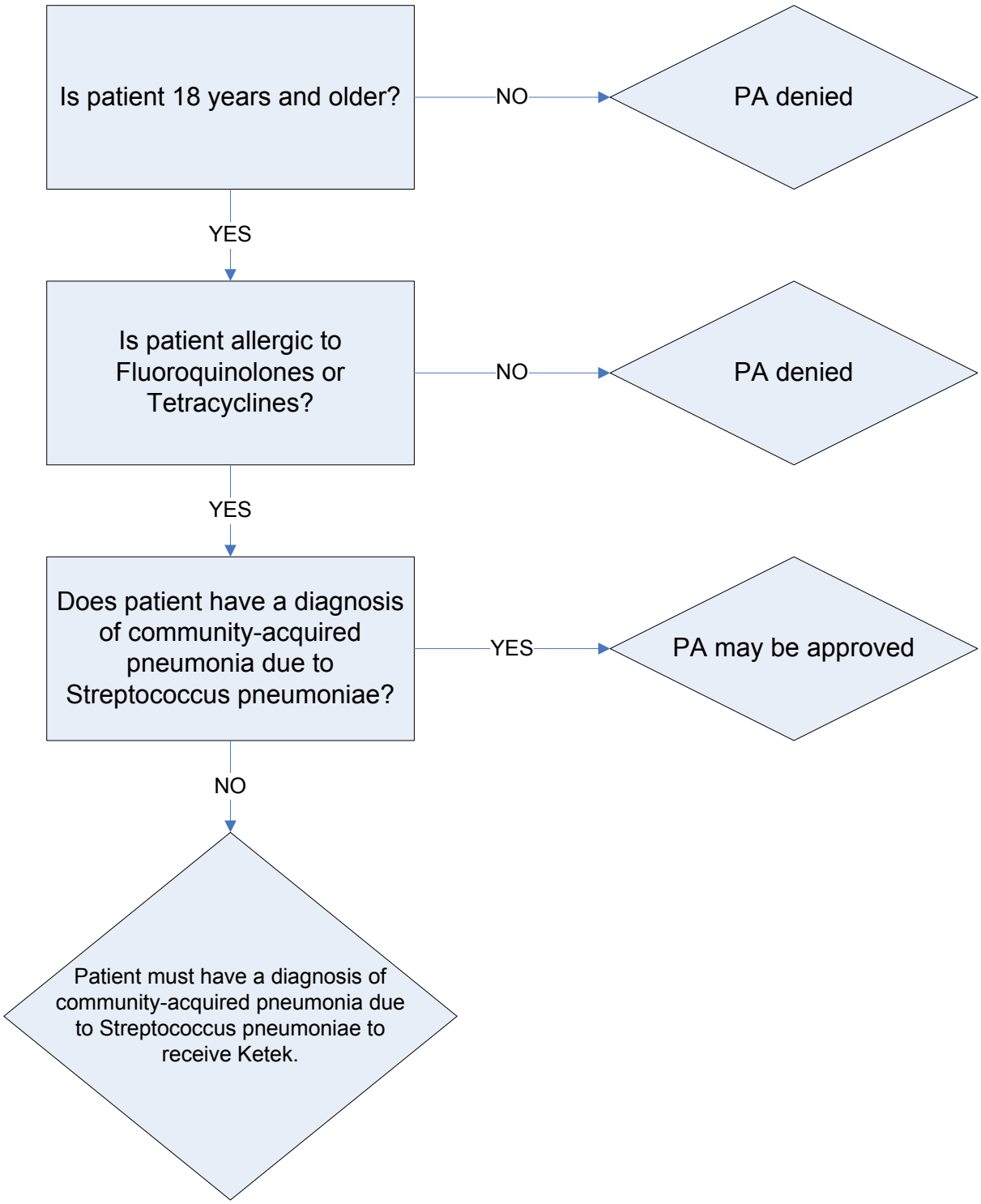
Part II: TO BE COMPLETED BY PHARMACY

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
Ketek Criteria Algorithm



Aczone Gel 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 new prescription for Aczone gel must try other topical acne agents as first line therapy.

Part I: TO BE COMPLETED BY PRESCRIBER

Recipient Name	Recipient Date of Birth	Recipient Medicaid ID Number	
Prescriber Name			
Prescriber 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.*

Prescriber Signature	Date

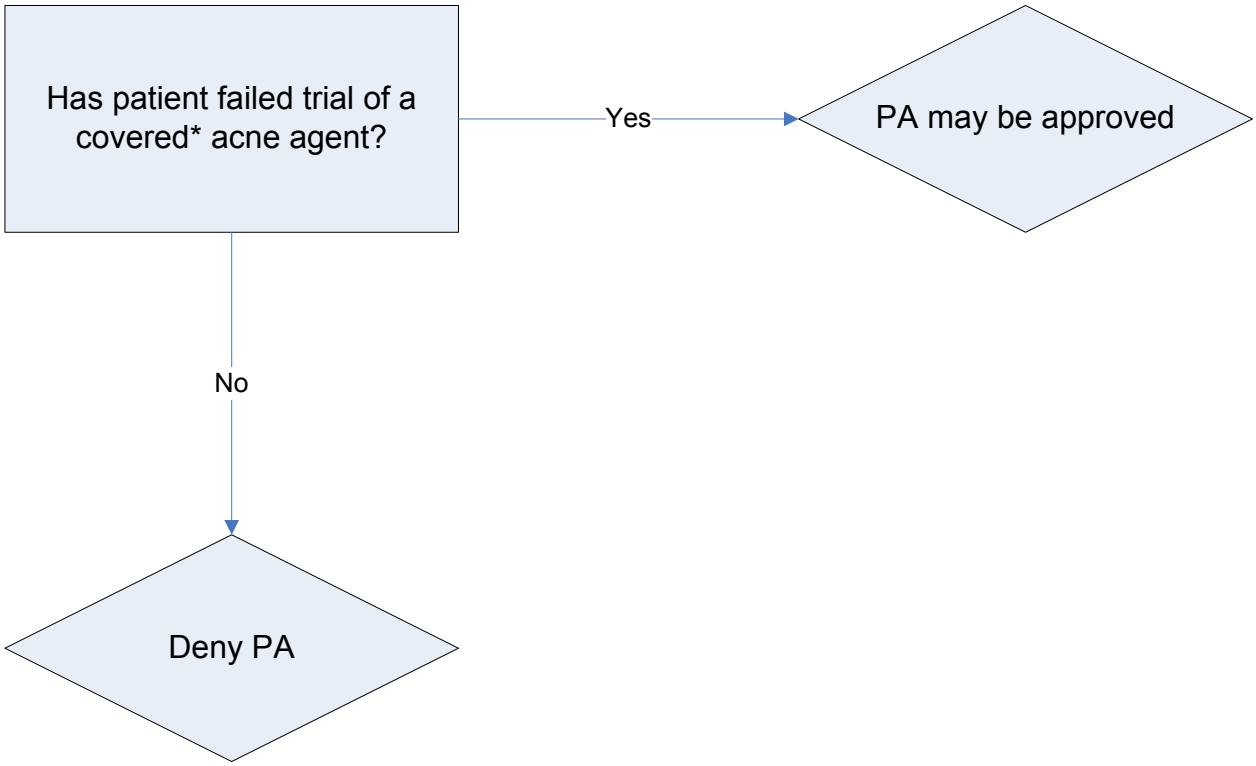
Part II: TO BE COMPLETED BY PHARMACY

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.

North Dakota Medicaid
DUR Board Meeting
Cetraxal® Review

I. Overview

Cetraxal is a quinolone antimicrobial indicated for the treatment of acute otitis externa due to susceptible isolates of *Pseudomonas aeruginosa* or *Staphylococcus aureus*.

II. Dosage and Administration

Contents of one single use container should be instilled into the affected ear twice daily (approximately 12 hours apart) for 7 days.

III. Pharmacology/Pharmacokinetics

Ciprofloxacin is a fluoroquinolone antimicrobial. The bactericidal action of ciprofloxacin results from the interference with the enxyme DNA gyrase, which is needed for the synthesis of bacterial DNA. The maximum plasma concentration of ciprofloxacin is anticipated to be less than 5ng/mL.

IV. Warnings/Precautions

- **Otic Use Only** – Cetraxal should not be used for injection, for inhalation, or for ophthalmic use.
- **Hypersensitivity** – Cetraxal should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.
- **Growth of Resistant Organisms with Prolonged Use** – Cetraxal may result in overgrowth of nonsusceptible organisms, including yeast and fungi. If super-infection occurs, discontinue use and institute alternative therapy.
- **Lack of Clinical Response** – If the infection is not improved after one week of therapy, cultures may help guide further treatment.

V. Adverse Reactions

In a randomized, active-controlled clinical trial, approximately 300 patients with clinical signs and symptoms of otitis externa were treated with Cetraxal. The most frequently reported adverse reactions were application site pain, ear pruritus, fungal ear superinfection, and headache, each reported in approximately 2-3% of patients.

References

1. Cetraxal® [prescribing information]. Ridgeland, MS. Wraser Pharmaceuticals; April 2009.

North Dakota Medicaid
DUR Board Meeting
Dificid® Review

I. Overview

Dificid is a new macrolide antibacterial drug indicated in adults for treatment of *Clostridium difficile*-associated diarrhea.

II. Dosage and Administration

The recommended dose is one 200mg tablet orally twice daily for 10 days with or without food. A ten-day regimen costs approximately $3,000.

III. Warnings/Precautions

- **Not for Systemic Infections**: Since there is minimal systemic absorption of fidaxomicin, Dificid is not effective for treatment of systemic infections.
- **Development of Drug Resistant Bacteria**: Only use Dificid for infection proven or strongly suspected to be caused by *C. difficile*.

IV. Adverse Reactions

The most common adverse reactions are nausea (11%), vomiting (7%), abdominal pain (6%), gastrointestinal hemorrhage (4%), anemia (2%), and neutropenia (2%).

V. Drug Interactions

Fidaxomicin and its main metabolite, OP-1118, are substrates of the efflux transporter, P-glycoprotein (P-gp), which is expressed in the gastrointestinal tract. Cyclosporine is an inhibitor of P-gp, however, concomitant P-gp inhibitor use had no attributable effect on safety or treatment outcome of fidaxomicin-treated patients in controlled clinical trials.

VI. Pharmacology/Pharmacokinetics

Fidaxomicin is bactericidal against *C. difficile* in vitro, inhibiting RNA synthesis by RNA polymerases. Fidaxomicin acts locally in the gastrointestinal tract on *C. difficile*. It has minimal systemic absorption following oral administration.

Fidaxomicin is primarily transformed by hydrolysis at the isobutyryl ester to form its main and microbiologically active metabolite, OP-1118. Metabolism of fidaxomicin and formation of OP-1118 are not dependent on cytochrome P450 enzymes. At the therapeutic dose, OP-1118 was the predominant circulating compound in healthy adults, followed by fidaxomicin.

VII. Treatment Regimens for *Clostridium difficile* Infections

Infection Characteristics	Clinical Status	Treatment Regimen
Initial episode Mild to moderate severity	WBC 15,000 cells/mcL or lower **AND** SCr less than 1.5 times baseline	Metronidazole 500mg PO tid for 10 to 14 days
Initial episode Severe	WBC 15,000 cells/mcL or greater **OR** SCr 1.5 times or greater versus baseline	Vancomycin 125mg PO qid for 10 to 14 days
Initial episode Severe, complicated	WBC 15,000 cells/mcL or greater **OR** SCr 1.5 times or greater versus baseline with hypotension/shock, ileus, megacolon	Vancomycin 500 mg PO/NG qid x 10 to 14 days PLUS metronidazole 500 mg IV q8h If ileus, consider adding rectal vancomycin
First recurrence	-	Same regimen as first episode
Second recurrence	-	Oral vancomycin in tapered regimen

References

1. Dificid® [prescribing information]. San Diego, CA. Optimer Pharmaceuticals, Inc.; May 2011.
2. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: *2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA)*. Accessed online July 2011 at www.idsociety.org.

North Dakota Medicaid
DUR Board Meeting
Pradaxa® Review

I. Overview

Pradaxa is indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

II. Dosage and Administration

Recommended Dose:
For patients with creatinine clearance (CrCl) >30 mL/min, the recommended dose of Pradaxa is 150 mg taken orally, twice daily, with or without food. For patients with CrCl 15-30 mL/min, the recommended dose is 75 mg twice daily. Dosing recommendations for patients with a CrCL <15 mL/min or on dialysis cannot be provided.
Instruct patients to swallow the capsules whole. Breaking, chewing, or emptying the contents of the capsule can result in increased exposure.

Converting from or to Warfarin:
When converting patients from warfarin therapy to Pradaxa, discontinue warfarin and start Pradaxa when the international normalized ratio (INR) is below 2.0. When converting from Pradaxa to warfarin, adjust the starting time of warfarin based on creatinine clearance as follows:
• For CrCl >50 mL/min, start warfarin 3 days before discontinuing Pradaxa.
• For CrCl 31-50 mL/min, start warfarin 2 days before discontinuing Pradaxa.
• For CrCl 15-30 mL/min, start warfarin 1 day before discontinuing Pradaxa.
• For CrCl <15 mL/min, no recommendations can be made.
Because Pradaxa can contribute to an elevated INR, the INR will better reflect warfarin's effect after Pradaxa has been stopped for at least 2 days.

Converting from or to Parenteral Anticoagulants:
For patients currently receiving a parenteral anticoagulant, start Pradaxa 0 to 2 hours before the time that the next dose of the parenteral drug was to have been administered or at the time of discontinuation of a continuously administered parenteral drug (e.g., intravenous unfractionated heparin).
For patients currently taking Pradaxa, wait 12 hours (CrCl ≥30 mL/min) or 24 hours (CrCl <30 mL/min) after the last dose of Pradaxa before initiating treatment with a parenteral anticoagulant.

Surgery and Interventions:
If possible, discontinue Pradaxa 1 to 2 days (CrCl ≥50 mL/min) or 3 to 5 days (CrCl <50 mL/min) before invasive or surgical procedures because of the increased risk of bleeding. Consider longer times for patients undergoing major surgery, spinal puncture, or

placement of a spinal or epidural catheter or port, in who complete hemostasis may be required.
If surgery cannot be delayed, there is an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention. Bleeding risk can be assessed by the ecarin clotting time (ECT). This test is a better marker of the anticoagulant activity of dabigatran than activated partial thromboplastin time (aPTT), prothrombin time (PT)/INR, or thrombin time (TT). If ECT is not available, the aPTT test provides an approximation of Pradaxa's anticoagulant activity.

III. Contraindications

Pradaxa is contraindicated in patients with:

- Active pathological bleeding.
- History of a serious hypersensitivity reaction to Pradaxa.

IV. Warnings/Precautions

Risk of Bleeding:
Pradaxa increases the risk of bleeding and can cause significant and, sometimes, fatal bleeding. Risk factors for bleeding include the use of drugs that increase the risk of bleeding in general (e.g., anti-platelet agents, heparin, fibrinolytic therapy, and chronic use of NSAIDs) and labor and delivery. Promptly evaluate any signs or symptoms of blood loss (e.g., a drop in hemoglobin and/or hematocrit or hypotension). Discontinue Pradaxa in patients with active pathological bleeding.
In the RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) study, a life-threatening bleed (bleeding that met one or more of the following criteria: fatal, symptomatic intracranial, reduction in hemoglobin of at least 5 grams per deciliter, transfusion of at least 4 units of blood, associated with hypotension requiring the use of intravenous inotropic agents, or necessitating surgical intervention) occurred at an annualized rate of 1.5% and 1.8% for PRADAXA 150 mg and warfarin, respectively.

Temporary Discontinuation of Pradaxa:
Discontinuing anticoagulants, including Pradaxa, for active bleeding, elective surgery, or invasive procedures, places patients at an increased risk of stroke. Lapses in therapy should be avoided, and if anticoagulation with Pradaxa must be temporarily discontinued for any reason, therapy should be restarted as soon as possible.

Effect of P-gp Inducers and Inhibitors on Dabigatran Exposure:
The concomitant use of Pradaxa with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided. P-gp inhibitors ketoconazole, verapamil, amiodarone, quinidine, and clarithromycin do not require dose adjustments.

V. Adverse Reactions

The RE-LY study provided safety information on the use of two doses of Pradaxa and warfarin. The rates of adverse reactions leading to treatment discontinuation were 21%

for Pradaxa 150mg and 16% for warfarin. The most frequent adverse reactions leading to discontinuation of Pradaxa were bleeding and gastrointestinal events (e.g., dyspepsia, nausea, upper abdominal pain, gastrointestinal hemorrhage, and diarrhea).

Bleeding:
The risk of major bleeds was similar with Pradaxa 150 mg and warfarin across major subgroups defined by baseline characteristics, with the exception of age, where there was a trend towards a higher incidence of major bleeding on Pradaxa (hazard ratio 1.2, 95% CI: 1.0 to 1.4) for patients ≥75 years of age.
There was a higher rate of major gastrointestinal bleeds in patients receiving Pradaxa 150 mg than in patients receiving warfarin (1.6% vs. 1.1%, respectively, with a hazard ratio vs. warfarin of 1.5, 95% CI, 1.2 to 1.9), and a higher rate of any gastrointestinal bleeds (6.1% vs. 4.0%, respectively).

Gastrointestinal Adverse Reactions:
Patients on Pradaxa 150 mg had an increased incidence of gastrointestinal adverse reactions (35% vs. 24% on warfarin). These were commonly dyspepsia (including abdominal pain upper, abdominal pain, abdominal discomfort, and epigastric discomfort) and gastritis-like symptoms (including GERD, esophagitis, erosive gastritis, gastric hemorrhage, hemorrhagic gastritis, hemorrhagic erosive gastritis, and gastrointestinal ulcer).

Hypersensitivity Reactions:
In the RE-LY study, drug hypersensitivity (including urticaria, rash, and pruritus), allergic edema, anaphylactic reaction, and anaphylactic shock were reported in <0.1% of patients receiving Pradaxa.

VI. Drug Interactions

The concomitant use of Pradaxa with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided. P-gp inhibitors ketoconazole, verapamil, amiodarone, quinidine, and clarithromycin do not require dose adjustments.

VII. Pharmacology/Pharmacokinetics

Dabigatran and its acyl glucuronides are competitive, direct thrombin inhibitors. Because thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of a thrombus. Both free and clot-bound thrombin, and thrombin-induced platelet aggregation are inhibited by the active moieties.
Dabigatran etexilate mesylate is absorbed as the dabigatran etexilate ester. The ester is then hydrolyzed, forming dabigatran, the active moiety. Dabigatran is metabolized to four different acyl glucuronides and both the glucuronides and dabigatran have similar pharmacological activity.

Absorption:
The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate is approximately 3 to 7%. Dabigatran etexilate is a substrate of the efflux transporter P-gp. Pradaxa may be administered with or without food. Pradaxa capsules should not be broken, chewed, or opened before administration.

Distribution:
Dabigatran is approximately 35% bound to human plasma proteins. The volume of distribution of dabigatran is 50 to 70 L.

Elimination:
Dabigatran is eliminated primarily in the urine. After oral administration of radiolabeled dabigatran, 7% of radioactivity is recovered in urine and 86% in feces. The half-life of dabigatran in healthy subjects is 12 to 17 hours.

Metabolism:
After oral administration, dabigatran etexilate is converted to dabigatran. The cleavage of the dabigatran etexilate by esterase-catalyzed hydrolysis to the active principal dabigatran is the predominant metabolic reaction. Dabigatran is not a substrate, inhibitor, or inducer of CYP450 enzymes. Dabigatran is subject to conjugation forming pharmacologically active acyl glucuronides.

References

1. Pradaxa® [prescribing information]. Ridgefield, CT. Boehringer Ingelheim Pharmaceuticals, Inc.; March 2011.

North Dakota Medicaid
DUR Board Meeting
Xarelto® Review

I. Overview

Xarelto (rivaroxaban) is a factor Xa inhibitor indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery.

II. Dosage and Administration

The recommended dose of Xarelto is 10mg taken orally once daily with or without food. The initial dose should be taken at least 6 to 10 hours after surgery once hemostasis has been established.

- For patients undergoing hip replacement surgery, treatment duration of 35 days is recommended.
- For patients undergoing knee replacement surgery, treatment duration of 12 days is recommended.

III. Contraindications

Xarelto is contraindicated in patients with:

- Hypersensitivity to Xarelto
- Active major bleeding

IV. Warnings/Precautions

- **Spinal/Epidural Anesthesia or Puncture**: When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma, which can result in long-term or permanent paralysis.
  An epidural catheter should not be removed earlier than 18 hours after the last administration of Xarelto. The next dose is not to be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, the administration of Xarelto is to be delayed for 24 hours.
- **Risk of Bleeding**: Xarelto increases the risk of bleeding and can cause serious and fatal bleeding. Major hemorrhages including intracranial, epidural hematoma, gastrointestinal, retinal, and adrenal bleeding have been reported. Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include platelet aggregation inhibitors, other antithrombotic agents, fibrinolytic therapy, thienopyridines, and chronic use of non-steroidal anti-inflammatory drugs.

Bleeding can occur at any site during therapy with Xarelto. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site. Promptly evaluate any signs or symptoms of blood loss.

- **Risk of Pregnancy Related Hemorrhage**: Xarelto should be used with caution in pregnant women and only if the potential benefit justifies the potential risk to the mother and fetus. Xarelto dosing in pregnancy has not been studied. The anticoagulant effect of Xarelto cannot be monitored with standard laboratory testing nor readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).
- **Renal Impairment**: Avoid the use of Xarelto in patients with severe renal impairment (creatinine clearance <30 mL/min) due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with moderate renal impairment (CrCl 30 to <50 mL/min). Patients who develop acute renal failure while on Xarelto should discontinue the treatment.
- **Hepatic Impairment**: Clinical data in patients with moderate hepatic impairment indicate a significant increase in rivaroxaban exposure and pharmacodynamic effects. No clinical data are available for patients with severe hepatic impairment. Avoid use of Xarelto in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy.

V. Adverse Reactions

The most common adverse reactions with Xarelto were bleeding complications. The rates of major bleeding events and any bleeding events observed in patients in the RECORD clinical trials are shown below.

	Xarelto 10mg
Total treated patients	**N=4487 n (%)**
Major bleeding event	14 (0.3)
Fatal bleeding	1 (<0.1)
Bleeding into a critical organ	2 (<0.1)
Bleeding that required re-operation	7 (0.2)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	4 (0.1)
Any bleeding event	261 (5.8)
Hip Surgery Study	**N=3281 n (%)**
Major bleeding event	7 (0.2)
Fatal bleeding	1 (<0.1)
Bleeding into a critical organ	1 (<0.1)
Bleeding that required re-operation	2 (0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	3 (0.1)
Any bleeding event	201 (6.1)

Knee Surgery Study	N=1206 n (%)
Major bleeding event	7 (0.6)
Fatal bleeding	0
Bleeding into a critical organ	1 (0.1)
Bleeding that required re-operation	5 (0.4)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	1 (0.1)
Any bleeding event	60 (5.0)

Other adverse reactions reported by ≥1% of Xarelto-Treated Patients in RECORD 1-3 studies

System/Organ Class Adverse Reaction	Xarelto 10mg N=4487 n (%)
Injury, poisoning and procedural complications	
Wound secretion	125 (2.8)
Musculoskeletal and connective tissue disorders	
Pain in extremity	74 (1.7)
Muscle spasm	52 (1.2)
Nervous system disorders	
Syncope	55 (1.2)
Skin and subcutaneous tissue disorders	
Pruritus	96 (2.1)
Blister	63 (1.4)

VI. Drug Interactions

Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Inhibitors and inducers of these CYP450 enzymes or transporters may result in changes in rivaroxaban exposure.

Drugs that inhibit cytochrome P450 3A4 enzymes and drug transport systems:
In drug interaction studies evaluating the concomitant use with drugs that are combined P-gp and CYP3A4 inhibitors, increases in rivaroxaban exposure and pharmacodynamic effects (i.e., factor Xa inhibition and PT prolongation) were observed. Significant increases in rivaroxaban exposure may increase bleeding risk.

- Ketoconazole (combined P-gp and strong CYP3A4 inhibitor): Steady-state rivaroxaban AUC and Cmax increased by 160% and 70%, respectively. Similar increases in pharmacodynamic effects were also observed.
- Ritonavir (combined P-gp and strong CYP3A4 inhibitor): Single-dose rivaroxaban AUC and Cmax increased by 150% and 60%, respectively. Similar increases in pharmacodynamic effects were also observed.
- Clarithromycin (combined P-gp and strong CYP3A4 inhibitor): Single-dose rivaroxaban AUC and Cmax increased by 50% and 40%, respectively. The smaller increases in exposure observed for clarithromycin compared to ketoconazole or ritonavir may be due to the relative difference in P-gp inhibition.
- Erythromycin (combined P-gp and moderate CYP3A4 inhibitor): Both the single-dose rivaroxaban AUC and C_{max} increased by 30%.

Avoid concomitant administration of XARELTO with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan) which cause significant increases in rivaroxaban exposure that may increase bleeding risk. When clinical data suggest a change in exposure is unlikely to affect bleeding risk (e.g., clarithromycin, erythromycin), no precautions are necessary during coadministration with drugs that are combined P-gp and CYP3A4 inhibitors.

Drug-Disease Interactions with Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems:
Based on simulated pharmacokinetic data, patients with renal impairment receiving Xarelto with drugs that are combined P-gp and weak or moderate CYP3A4 inhibitors (e.g., erythromycin, azithromycin, diltiazem, verapamil, quinidine, ranolazine, dronedarone, amiodarone, and felodipine), may have significant increases in exposure compared with patients with normal renal function and no inhibitor use, since both pathways of rivaroxaban elimination are affected. Since these increases may increase bleeding risk, use Xarelto in this situation only if the potential benefit justifies the potential risk.

Drugs that Induce Cytochrome P450 3A4 Enzymes and Drug Transport Systems:
In a drug interaction study, co-administration of Xarelto (20 mg single dose with food) with a drug that is a combined P-gp and strong CYP3A4 inducer (rifampicin titrated up to 600 mg once daily) led to an approximate decrease of 50% and 22% in AUC and Cmax, respectively. Similar decreases in pharmacodynamic effects were also observed. These decreases in exposure to rivaroxaban may decrease efficacy. Avoid concomitant use of Xarelto with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort). Consider increasing the Xarelto dose if these drugs must be coadministered.

Anticoagulants:
In a drug interaction study, single doses of enoxaparin (40 mg subcutaneous) and Xarelto (10 mg) given concomitantly resulted in an additive effect on anti-factor Xa activity. Enoxaparin did not affect the pharmacokinetics of rivaroxaban. In another study, single doses of warfarin (15 mg) and Xarelto (5 mg) resulted in an additive effect on factor Xa inhibition and PT. Warfarin did not affect the pharmacokinetics of rivaroxaban. The safety of long-term concomitant use of these drugs has not been studied. Avoid concurrent use of Xarelto with other anticoagulants due to the increased bleeding risk other than during therapeutic transition periods where patients should be observed closely. Promptly evaluate any signs or symptoms of blood.

NSAIDs/Aspirin:
In a single-dose drug interaction study there were no pharmacokinetic or pharmacodynamic interactions observed after concomitant administration of naproxen or aspirin (acetylsalicylic acid) with Xarelto. The safety of long-term concomitant use of

these drugs has not been studied. NSAIDs/aspirin are known to increase bleeding, and bleeding risk may be increased when these drugs are used concomitantly with Xarelto. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with NSAIDs and/or platelet aggregation inhibitors.

Clopidogrel:
In two drug interaction studies where clopidogrel (300 mg loading dose followed by 75 mg daily maintenance dose) and Xarelto (15 mg single dose) were co-administered in healthy subjects, an increase in bleeding time to 45 minutes was observed in approximately 45% and 30% of subjects in these studies, respectively. The change in bleeding time was approximately twice the maximum increase seen with either drug alone. There was no change in the pharmacokinetics of either drug. Avoid concurrent administration of clopidogrel with Xarelto unless the benefit outweighs the risk of increased bleeding.

VII. Pharmacology/Pharmacokinetics

Xarelto is an orally bioavailable factor Xa inhibitor that selectively blocks the active site of factor Xa and does not require a cofactor (such as anti-thrombin III) for activity. Activation of factor X to factor Xa (FXa) via the intrinsic and extrinsic pathways plays a central role in the cascade of blood coagulation.

Absorption:
The absolute bioavailability of rivaroxaban is high (estimated to be 80% to 100%) for the 10 mg dose. Rivaroxaban is rapidly absorbed with maximum concentrations appearing 2 to 4 hours after tablet intake. Intake with food does not affect rivaroxaban AUC or Cmax at the 10 mg dose.
Absorption of rivaroxaban is dependent on the site of drug release in the GI tract. A 29% and 56% decrease in AUC and Cmax compared to tablet was reported when rivaroxaban granulate is released in proximal small intestine. Exposure is further reduced when drug is released in the distal small intestine, or ascending colon. Avoid administration of rivaroxaban via a method that could deposit drug directly into the proximal small intestine (e.g., feeding tube) which can result in reduced absorption and related drug exposure.

Distribution:
Plasma protein binding of rivaroxaban in human plasma is approximately 92% to 95%, with albumin being the main binding component. The steady-state volume of distribution in healthy subjects is approximately 50 L.

Metabolism:
Approximately 51% of an orally administered [14C]-rivaroxaban dose was recovered as metabolites in urine (30%) and feces (21%). Oxidative degradation catalyzed by CYP3A4/5 and CYP2J2 and hydrolysis are the major sites of biotransformation. Unchanged rivaroxaban was the predominant moiety in plasma with no major or active circulating metabolites.

Excretion:
Following oral administration of a [14C]-rivaroxaban dose, 66% of the radioactive dose was recovered in urine (36% as unchanged drug) and 28% was recovered in feces (7% as unchanged drug). Unchanged drug is excreted into urine, mainly via active tubular secretion and to a lesser extent via glomerular filtration (approximate 5:1 ratio). Rivaroxaban is a low-clearance drug, with a systemic clearance of approximately 10 L/hr in healthy volunteers following intravenous administration. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

References

1. Xarelto® [prescribing information]. Gurabo, PR. Janssen Ortho, LLC; July 2011.

North Dakota Medicaid
DUR Board Meeting
Agents Used to Treat Hereditary Angioedema

I. Overview

Hereditary Angioedema (HAE) is a rare genetic disease caused by a deficiency in the C1 esterase enzyme, which regulates the blood system, including the body's inflammatory and coagulation responses. Defective C1-inhibitor can cause a biochemical imbalance that can produce unwanted peptides, which can induce the capillaries to release fluids into surrounding tissues causing swelling. Patients with HAE suffer periodic, painful attacks of severe swelling in various parts of the body including hands, feet, face, abdomen, and sometimes the throat, which can cause airway restriction.

Currently, two C1 esterase replacement therapies are available in the U.S. Another C1 esterase inhibitor is currently being reviewed by the FDA for approval. An injectable peptide drug targeting the bradykinin pathway is also available in the U.S.

Medications included in this Review

Generic Name	Brand Name	Manufacturer
C1 esterase inhibitor (human)	Cinryze	ViroPharma Biologics
C1 esterase inhibitor (human)	Berinert	CSL Behring
Ecallantide	Kalbitor	Dyax Corp

II. Indications

Brand Name	Indication
Cinryze	Cinyrze is a C1 esterase inhibitor indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE.
Berinert	Berinert is a plasma-derived C1 Esterase Inhibitor (Human) indicated for the treatment of acute abdominal or facial attacks of HAE in adult and adolescent patients. The safety and efficacy of Berinert for prophylactic therapy have not been established.
Kalbitor	Kalbitor is a plasma kallikrein inhibitor indicated for treatment of acute attacks of HAE in patients 16 years of age and older.

III. Dosage and Administration

Brand Name	Dosage and Administration
Cinryze	Routine Prophylaxis Dosing: 1,000 units IV every 3 or 4 days
Berinert	Administer 20 units per kg of body weight by IV injection
Kalbitor	30mg (3mL) administered subcutaneously in three 10mg (1mL) injections. If an attack persists, an additional dose of 30mg may be administered within a 24 hour period.

IV. Contraindications

Do not administer to patients who have manifested life-threatening hypersensitivity reactions, including anaphylaxis, to these products.

V. Warnings/Precautions

Brand Name	Warnings and Precautions
Cinyrze	• Hypersensitivity reactions may occur. Epinephrine should be immediately available to treat any acute severe hypersensitivity reactions. • Thrombotic events have been reported. Monitor patients with known risk factors for thrombotic events. • Made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent.
Berinert	• Severe hypersensitivity reactions may occur. Epinephrine should be immediately available for treatment of acute severe hypersensitivity reaction. • Thrombotic events have been reported in association with Berinert when used off-label and at higher than labeled doses. • Because Berinert is made from human blood, it may contain infectious agents (e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent) that can cause disease.
Kalbitor	• Hypersensitivity reactions including anaphylaxis. Administer Kalbitor in a setting equipped to manage anaphylaxis and hereditary angioedema. • Black Box Warning-Because of the risk of anaphylaxis, Kalbitor should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema.

VI. Adverse Reactions

- Cinryze-The most common adverse reactions observed by ≥5% of subjects after receiving Cinryze were upper respiratory tract infection, sinusitis, rash and headache.

- Berinert-The most serious adverse reaction reported in subjects who received Berinert was an increase in the severity of pain associated with HAE. The most common adverse reactions observed by ≥4% of subjects after Berinert treatment were subsequent HAE attack, headache, abdominal pain, nausea, muscle spasm, pain, diarrhea and vomiting.

- Kalbitor-The most common adverse reactions occurring in ≥3% of Kalbitor treated patients and greater than placebo are headache, nausea, diarrhea, pyrexia, injection site reactions, and nasopharyngitis.

VII. Drug Interactions

No drug interaction studies have been conducted.

VIII. Pharmacology

Cinyrze

C1 inhibitor is a normal constituent of human blood and is one of the serine proteinase inhibitors (serpins). The primary function of C1 inhibitor is to regulate the activation of the complement and intrinsic coagulation (contact system) pathway. C1 inhibitor also regulates the fibrinolytic system. Regulation of these systems is performed through the formation of complexes between the proteinases and the inhibitor, resulting in inactivation of both and consumption of the C1 inhibitor. HAE patients have low levels of endogenous or functional C1 inhibitor. Although the events that induce attacks of angioedema in HAE patients are not well defined, it is thought by some that increased vascular permeability and the clinical manifestation of HAE attacks are primarily mediated through contact system activation. Suppression of contact system activation by C1 inhibitor through the inactivation of plasma kallikrein and factor XIIa is thought to modulate this vascular permeability by preventing the generation of bradykinin1. Administration of Cinyrze increases plasma levels of C1 inhibitor activity.

Berinert

C1 esterase inhibitor is a normal constituent of human plasma and belongs to the group of serine protease inhibitors (serpins) that includes antithrombin III, alpha1-protease inhibitor, alpha2-antiplasmin, and heparin cofactor II. As with the other inhibitors in this group, C1 esterase inhibitor has an important inhibiting potential on several of the major cascade systems of the human body, including the complement system, the intrinsic coagulation (contact) system, the fibrinolytic system, and the coagulation cascade. Regulation of these systems is performed through the formation of complexes between the proteinase and the inhibitor, resulting in inactivation of both and consumption of the C1 esterase inhibitor.

C1 esterase inhibitor, which is usually activated during the inflammatory process, inactivates its substrate by covalently binding to the reactive site. C1 esterase inhibitor is the only known inhibitor for the subcomponent of the complement component 1 (C1r), C1s, coagulation factor XIIa, and kallikrein. Additionally, C1 esterase inhibitor is the main inhibitor for coagulation factor XIa of the intrinsic coagulation cascade.

HAE patients have low levels of endogenous or functional C1 esterase inhibitor. Although the events that induce attacks of angioedema in HAE patients are not well defined, it has been postulated that increased vascular permeability and the clinical manifestation of HAE attacks may be primarily mediated through contact system activation. Suppression of contact system activation by C1 esterase inhibitor through the inactivation of plasma kallikrein and factor XIIa is thought to modulate this vascular permeability by preventing the generation of bradykinin.

Administration of Berinert to patients with C1 esterase inhibitor deficiency replaces the missing or malfunctioning protein in patients. The plasma concentration of C1 esterase inhibitor in healthy volunteers is approximately 270 mg/L.

Kalbitor

HAE is a rare genetic disorder caused by mutations to C1-esterase-inhibitor (C1-INH) located on Chromosome 11q and inherited as an autosomal dominant trait. HAE is characterized by low levels of C1-INH activity and low levels of C4. C1-INH functions to regulate the activation of the complement and intrinsic coagulation (contact system pathway) and is a major endogenous inhibitor of plasma kallikrein. The kallikrein-kinin system is a complex proteolytic cascade involved in the initiation of both inflammatory and coagulation pathways. One critical aspect of this pathway is the conversion of High Molecular Weight (HMW) kininogen to bradykinin by the protease plasma kallikrein. In HAE, normal regulation of plasma kallikrein activity and the classical complement cascade is therefore not present. During attacks, unregulated activity of plasma kallikrein results in excessive bradykinin generation. Bradykinin is a vasodilator which is thought by some to be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain.

Kalbitor is a potent (Ki = 25 pM), selective, reversible inhibitor of plasma kallikrein. Kalbitor binds to plasma kallikrein and blocks its binding site, inhibiting the conversion of HMW kininogen to bradykinin. By directly inhibiting plasma kallikrein, Kalbitor reduces the conversion of HMW kininogen to bradykinin and thereby treats symptoms of the disease during acute episodic attacks of HAE.

IX. Cost

The estimated acquisition cost for each 500-unit vial of Cinryze is $2,251.

The estimated acquisition cost for each 500-unit vial of Berinert is $2,048.

The estimated acquisition cost for three 10mg/ml vials of Kalbitor is $3,006.

References

1. Cinyrze® [prescribing information]. Exton, PA. ViroPharma Biologics, Inc.; January 2011.
2. Berinert® [prescribing information]. Kankakee, IL. CSL Behring LLC; November 2009.
3. Kalbitor® [prescribing information]. Cambridge, MA. Dyax Corp; December 2009.

Safety Announcement: Avandia

On May 18, 2011, the U.S. Food and Drug Administration (FDA) informed the public of new restrictions to the prescribing and use of rosiglitazone-containing products. These medicines to treat type II diabetes are sold under the names Avandia, Avandamet, and Avandaryl. Healthcare providers and patients must enroll in a special program in order to prescribe and receive these drugs.

The new restrictions are part of a Risk Evaluation and Mitigation Strategy (REMS)-a program that manages serious risks of marketed drugs. The restrictions are based on data that suggested an elevated risk of heart attacks in patients treated with rosiglitazone. The decision to restrict access to rosiglitazone was made on September 23, 2010.

FDA has modified the REMS for Avandamet and Avandaryl because previously, the REMS consisted of only a Medication Guide. The REMS, which now includes a restricted access and distribution program, applies to all three rosiglitazone products.

The REMS, called the Avandia-Rosiglitazone Medicines Access Program limits the use of rosiglitazone medicines to:

- Patients already being successfully treated with these medicines.
- Patients whose blood sugar cannot be controlled with other anti-diabetic medicines and who, after consulting with their healthcare provider, do not wish to use pioglitazone-containing medicines (Actos, Actoplus Met, Actoplus Met XR, or Duetact).

Healthcare providers and patients must be enrolled in the Avandia-Rosiglitazone Medicines Access Program in order to prescribe and receive rosiglitazone medicines. After *November 18, 2011*, rosiglitazone medicines will no longer be available through retail pharmacies. Patients who are enrolled in the Avandia-Rosiglitazone Medicines Access Program will receive their medicine by mail order through specially certified pharmacies participating in the program.

Additional Information for Healthcare Professionals

- Healthcare providers should determine whether their patients are appropriate candidates to receive treatment with rosiglitazone medicines based on the risks and benefits of taking rosiglitazone medicines versus other therapies.
- Enrollment in the Avandia-Rosiglitazone Medicines Access Program is required for healthcare providers who wish to prescribe rosiglitazone medicines to outpatients or patients in long-term care facilities. To enroll, healthcare providers are required to:
    - Review the prescriber overview and the full prescribing information, including the Medication Guide, for rosiglitazone medicines.
    - Complete and sign the prescriber enrollment form.
- Healthcare providers must provide a copy of the Medication Guide for the prescribed rosiglitazone medicine and review it with the patient or caregiver.
- Healthcare providers must enroll eligible patients into the Avandia-Rosiglitazone Medicines Access Program by completing and signing a patient enrollment form so that the patient may begin or continue to receive rosiglitazone medicines.
- If a patient who has been taking a rosiglitazone medicine is hospitalized, the patient must be enrolled in the Avandia-Rosiglitazone Medicines Access Program to continue receiving the medicine; however, the patient's healthcare provider in the hospital is not required to be enrolled.
- Rosiglitazone medicines will no longer be available through retail pharmacies after *November 18, 2011*. The drug manufacturer, GlaxoSmithKline, will withdraw rosiglitazone medicines from the current supply chain and will provide pharmacies with instructions on returning the medicines.
- Under the Avandia-Rosiglitazone Medicines Access Program, rosiglitazone medicines will only be available to enrolled patients by mail order from certified pharmacies participating in the program.
- Report any adverse events involving rosiglitazone medicines to the FDA MedWatch program, using the information at the bottom of the page in the "Contact Us" box.

References:
FDA Drug Safety Communication: Updated Risk Evaluation and Mitigation Strategy (REMS) to Restrict Access to Rosiglitazone-containing Medicines including Avandia, Avandamet, and Avandaryl. Accessed online at www.fda.gov.

The U.S. Food and Drug Administration recently announced safety label changes for the cholesterol-lowering medication simvastatin. The highest approved dose of simvastatin (80mg) has been associated with an elevated risk of muscle injury or myopathy, particularly during the first 12 months of use. The FDA recommends that simvastatin 80mg be used only in patients who have been taking this dose for 12 months or more and have not experienced any muscle toxicity. The 80mg dose should not be prescribed to new patients. The FDA also recommends that patients currently taking 40mg of simvastatin that aren't meeting their LDL cholesterol goal be switched to a different statin rather than raising the simvastatin dose to 80mg.

Last year, an estimated 2.1 million people were prescribed a medication containing 80mg of simvastatin. All statins, despite their proven benefit in lowering the risk of heart attacks and strokes, carry some risk of myopathy, characterized by unexplained muscle weakness or pain. But, the risk is greater for those patients taking 80mg doses of simvastatin, especially in the first year of treatment. The muscle damage is often caused by interactions with other medications although some people are genetically predisposed towards simvastatin-related myopathy.

Simvastatin is sold under the brand name Zocor and as a single-ingredient generic drug. It is also sold in combination with ezetimibe as Vytorin, and niacin as Simcor. The FDA has revised the drug labels for simvastatin and Vytorin to include the new 80mg dosing restrictions. The agency also revised the labels for simvastatin, Vytorin, and Simcor to include new dosing recommendations when these drugs are used in combination with certain medications that increase the level of simvastatin in the body, thus increasing the risk of myopathy.

FDA recommends that healthcare professionals:

- Maintain patients on simvastatin 80mg only if they have been taking this dose for 12 or more months without evidence of muscle toxicity.
- Not start new patients on simvastatin 80mg.
- Place patients who do not meet their LDL cholesterol (LDL-C) goal on simvastatin 40mg on alternative LDL-C lowering treatment(s) that provides greater LDL-C lowering.
- Follow the recommendations in the simvastatin-containing medicines labels regarding drugs that may increase the risk for muscle injury when used with simvastatin.
- Switch patients who need to be initiated on a drug that interacts with simvastatin to an alternative statin with less potential for the drug-drug interaction.
- Report adverse events involving simvastatin-containing medications to the FDA MedWatch program.

Relative LDL-lowering Efficacy of the Statin and Statin-based Therapies

Atorvastatin	Fluvastatin	Pitavastatin	Lovastatin	Pravastatin	Rosuvastatin	Vytorin*	Simvastatin	%↓ LDL-C
-----	40 mg	1 mg	20 mg	20 mg	-----	-----	10 mg	30%
10 mg	80 mg	2 mg	40 or 80 mg	40 mg	-----	-----	20 mg	38%
20 mg	-----	4 mg	80 mg	80 mg	5 mg	10/10 mg	40 mg	41%
40 mg	-----		-----	-----	10 mg	10/20 mg	80 mg	47%
80 mg	-----		-----	-----	20 mg	10/40 mg	-----	55%
	-----		-----	-----	40 mg	10/80 mg	-----	63%

*No incremental benefit of Vytorin on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.

References:

1. FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. Available at www.fda.gov. Accessed June 27, 2011.

Hepatitis C Virus (HCV) Medication Prior Authorization

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 prescription for Intron, Infergen, Pegasys, PegIntron, Incivek, or Victrelis must submit a prior authorization form.

Note:

- ***Prior authorization will be granted if the requested product has been approved by the FDA for the indication listed below.***
- ***Current recommended therapy of chronic HCV infection is the combination of pegylated interferon alfa (PEGIntron or Pegasys) and ribavirin.***
- ***Incivek and Victrelis patients must be 18 years of age or older.***
- ***Incivek and Victrelis patients must also be taking ribavirin and peg-interferon.***
- ***Incivek and Victrelis will only be approved for 12 weeks for review of HCV-RNA levels and compliance.***

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: □ **Intron** □ **Pegasys** □ **Infergen** □ **PEGIntron** □ **Incivek** □ **Victrelis**	**Diagnosis for this request:** **Ribavirin dose:** **Peg-interferon dose:**		
Physician Signature		Date	

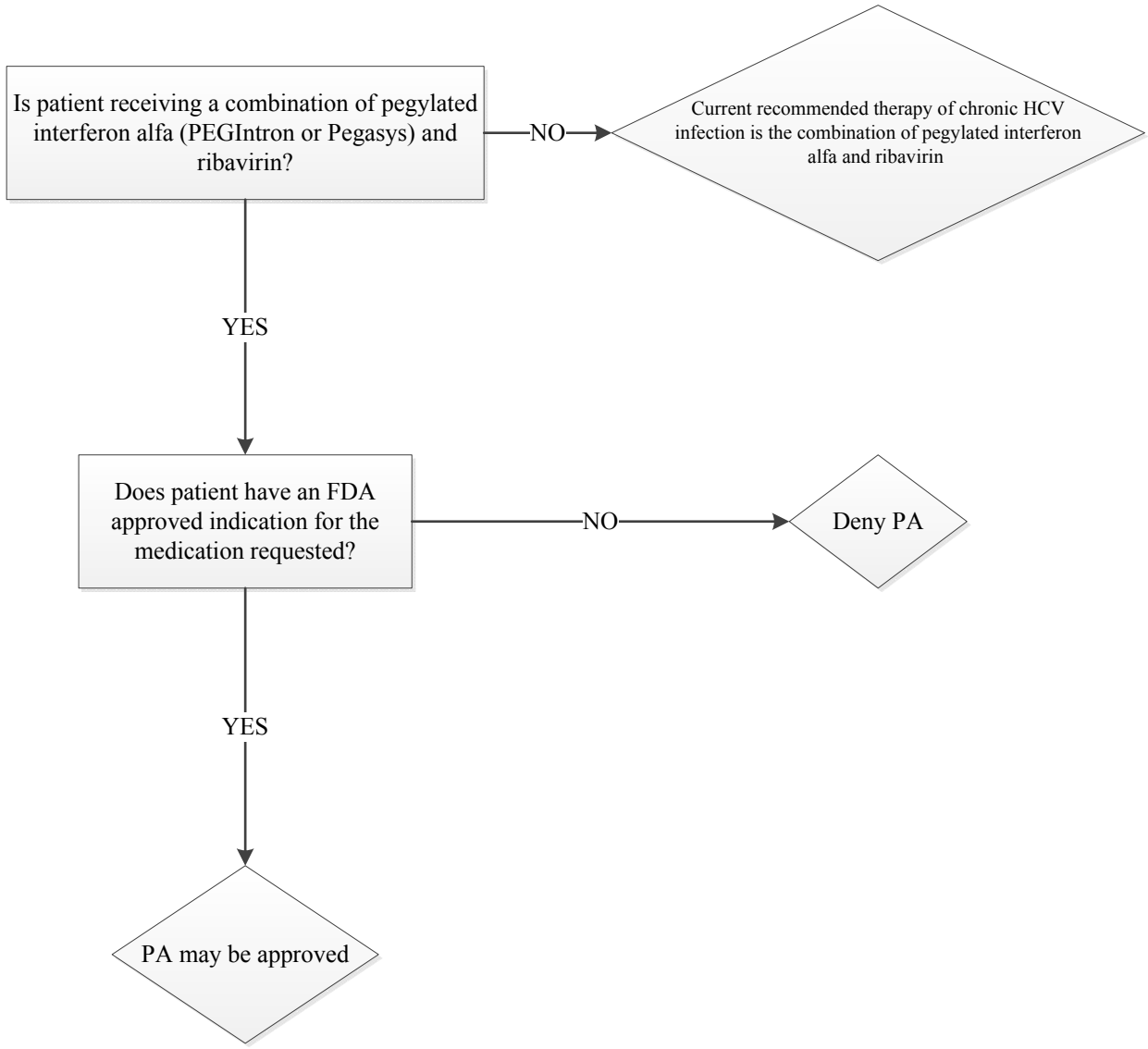
Part II: TO BE COMPLETED BY PHARMACY

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
Hepatitis C Virus (HCV) Medication Authorization Algorithm



NORTH DAKOTA MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS
3RD QUARTER 2011

Criteria Recommendations ***Approved Rejected***

1. Linagliptin / High Dose _____ _____

Alert Message: Tradjenta (linagliptin) may be over-utilized. The recommended dose of linagliptin is 5 mg once daily.

Conflict Code: HD – High Dose
Drugs/Diseases

Util A	Util B	Util C
Linagliptin		

Max Dose: 5mg/day
References:
Tradjenta Prescribing Information, May 2011, Boehringer Ingelheim.

2. Linagliptin / Non-adherence _____ _____

Alert Message: Based on refill history, your patient may be under-utilizing Tradjenta (linagliptin). Non-adherence to the prescribed dosing regimen may result in sub-therapeutic effects, which may lead to decreased patient outcomes and additional healthcare costs.

Conflict Code: LR – Non-adherence
Drugs/Diseases

Util A	Util B	Util C
Linagliptin		

References:
Lau DT, Nau DP, Oral Antihyperglycemic Medication Nonadherence and Subsequent Hospitalization Among Individuals with Type 2 Diabetes, Diabetes Care. 27:2149-2153, 2004.
Miller KE, Medication Nonadherence Affects Diabetes Treatment. Am Family Phys. Vol. 75 No. 6, March 15, 2007.
Ho PM, Rumsfeld JS, Masoudi FA, et al., Effect of Medication Nonadherence in Diabetes Mellitus, Cardiology Review, April 2007.
Tradjenta Prescribing Information, May 2011, Boehringer Ingelheim.

3. Linagliptin / Sulfonylureas _____ _____

Alert Message: The concurrent use of Tradjenta (linagliptin) with a sulfonylurea may result in hypoglycemia. A dose reduction of the sulfonylurea may be necessary to reduce the risk of hypoglycemia.

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

Util A	Util B	Util C
Linagliptin	Sulfonylureas	

References:
Tradjenta Prescribing Information, May 2011, Boehringer Ingelheim.

4. Linagliptin / Type 1 Diabetes & Diabetic Ketoacidosis _____ _____

Alert Message: Tradjenta (linagliptin) should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Conflict Code: MC – Drug/Actual Disease Precaution
Drugs/Diseases

Util A	Util B	Util C
Linagliptin	Type 1 Diabetes	
	Diabetic Ketoacidosis	

References:
Tradjenta Prescribing Information, May 2011, Boehringer Ingelheim.

5. Linagliptin / Strong P-gp or CYP3A4 Inducers _____ _____

Alert Message: Concurrent use of Tradjenta (linagliptin) and a strong P-gp or CYP3A4 inducer may result in decreased linagliptin exposure and reduced efficacy. The manufacturer strongly recommends use of an alternative to linagliptin if therapy with a strong inducer is required.

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

Util A	Util B	Util C
Linagliptin	Rifampin	
	Efavirenz	
	Nevirapine	
	Carbamazepine	
	Dexamethasone	
	Phenytoin	
	Phenobarbital	

References:
Tradjenta Prescribing Information, May 2011, Boehringer Ingelheim.

6. Linagliptin / Pediatric Patients (0-17 yoa) _____ _____

Alert Message: Safety and effectiveness of Tradjenta (linagliptin) in patients below the age of 18 have not been established.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Linagliptin		

Age Range: 0-17 yoa
References:
Tradjenta Prescribing Information, May 2011, Boehringer Ingelheim.

7. Azilsartan / High Dose _____ _____

Alert Message: Edarbi (azilsartan) may be over-utilized. The recommended maximum daily dose is 80 mg taken once daily. If patient is treated with high doses of diuretics consider starting dose of 40 mg per day.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Azilsartan		

Max Dose: 80mg/day
References:
Facts & Comparisons, 2011 Updates.
Edarbi Prescribing Information, March 2011, Takeda Pharms.

8. Rilpivirine / Nonadherence _____ _____

Alert Message: Nonadherence to antiretroviral therapy may result in insufficient plasma levels and partial suppression of viral load leading to the development of resistance, HIV progression, and increased mortality.

Conflict Code: LR - Nonadherence
Drugs/Diseases

Util A	Util B	Util C
Rilpivirine		

References:
Edurant Prescribing Information, May 2011, Tibotec Pharmaceuticals.
Hoffman C, Mulcahy F, Goals and Principles of Therapy, Eradication, Cost, Prevention and Adherence. In: Hoffman C, Rockstroh J, Kamps BS, eds. HIV Medicine, Flying Publishers-Paris, Cagliari, Wuppertal, Sevilla, 2005:167-173.
Cheever LW, Chapter V: Adherence to HIV Therapies. In: A Guide to Clinical Care of Women with HIV/AIDS, 2005 Edition, HIV/AIDS Bureau, US Department of Health and Human Services. http://hab.hrsa.gov/publications/womencare05/WG05chap5.htm
Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents - A Working Group of the Office of AIDS Research Advisory Council. January 10, 2011.

9. Rilpivirine / Contraindicated Drugs _____ _____

Alert Message: Co-administration of Edurant (rilpivirine) is contraindicated with drugs where significant decrease in rilpivirine plasma concentrations may occur due to CYP3A4 enzyme induction or gastric pH increase, which may result in loss of virologic response and possible resistance and cross-resistance.

Conflict Code: Drugs/Diseases

Util A	Util B	Util C
Rilpivirine	Carbamazepine	Omeprazole
	Oxcarbazepine	Esomeprazole
	Phenobarbital	Lansoprazole
	Phenytoin	Pantoprazole
	Rifabutin	Rabeprazole
	Rifampin	Dexamethasone
	Rifapentine	

References:
Edurant Prescribing Information, May 2011, Tibotec Pharmaceuticals.
Micromedex 2.0 Healthcare Series, DrugDex Evaluations, Thomson Reuters, 2011.

10. Rilpivirine / NNRTIs _____ _____

Alert Message: Edurant (rilpivirine) should not be used in combination with other NNRTIs. Concurrent use of rilpivirine with delavirdine may cause increases in rilpivirine plasma concentrations and use with the other NNRTIs, efavirenz, etravirine or nevirapine, may cause a decrease in rilpivirine plasma concentrations.

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

Util A	Util B	Util C
Rilpivirine	Delavirdine	
	Efavirenz	
	Etravirine	
	Nevirapine	

References:
Edurant Prescribing Information, May 2011, Tibotec Pharmaceuticals.

11. Rilpivirine / Antacids _____ _____

Alert Message: Caution should be exercised when Edurant (rilpivirine) is prescribed concomitantly with antacids (e.g., aluminium or magnesium hydroxide, calcium carbonate) as antacids increase gastric pH which may cause significant decreases in rilpivirine plasma concentrations. Rilpivirine requires an acidic environment for optimal absorption. Antacids should be administered either at least 2 hours before or at least 4 hours after rilpivirine.

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

Util A	Util B	Util C
Rilpivirine	Aluminum Hydroxide	
	Magnesium Hydroxide	
	Calcium Carbonate	

References:
Edurant Prescribing Information, May 2011, Tibotec Pharmaceuticals.

12. Rilpivirine / H2-Blockers _____ _____

Alert Message: Concurrent use of Edurant (rilpivirine) and a H2-receptor antagonist may cause significant decreases in rilpivirine plasma concentrations due to H2-receptor antagonist-induced increased gastric pH. Rilpivirine requires an acidic environment for optimal absorption. All H2-receptor antagonists should be administered at least 12 hours before or at least 4 hours after rilpivirine.

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

Util A	Util B	Util C
Rilpivirine	Cimetidine	
	Famotidine	
	Nizatidine	
	Ranitidine	

References:
Edurant Prescribing Information, May 2011, Tibotec Pharmaceuticals.

13. Rilpivirine / Certain Macrolides _____ _____

Alert Message: Concurrent use of Edurant (rilpivirine) with clarithromycin, erythromycin or telithromycin may cause an increase in rilpivirine plasma concentrations due to inhibition by the macrolide of rilpivirine CYP3A4-mediated metabolism. When possible, alternatives such as azithromycin should be considered.

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

Util A	Util B	Util C
Rilpivirine	Erythromycin	
	Clarithromycin	
	Telithromycin	

References:
Edurant Prescribing Information, May 2011, Tibotec Pharmaceuticals.

14. Rilpivirine / Methadone _____ _____

Alert Message: The concurrent use of Edurant (rilpivirine) and methadone may result in decreased methadone plasma concentrations. Methadone maintenance therapy may need to be adjusted in some patients.

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

Util A	Util B	Util C
Rilpivirine	Methadone	

References:
Edurant Prescribing Information, May 2011, Tibotec Pharmaceuticals.

15. Rilpivirine / All Other Antiretrovirals (Negating) _____ _____

Alert Message: Monotherapy with a NNRTI is not recommended in HIV-1-infected patients. Drug resistant virus emerges rapidly when an NNRTI is administered as single agent therapy.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C (Negating)
Rilpivirine		All other Antiretroviral Agents

References:
Edurant Prescribing Information, May 2011, Tibotec Pharmaceuticals.

16. Rilpivirine / Severe Renal Impairment & ESRD _____ _____ _____

Alert Message: Caution should be exercised when using Edurant (rilpivirine) in patients with severe renal impairment or end-stage renal disease. Rilpivirine plasma concentrations may be increased due to alteration in drug absorption, distribution and metabolism, secondary to renal function. Monitor patient for rilpivirine adverse effects.

Conflict Code: MC - Drug (Actual) Disease Precaution
Drugs/Diseases

Util A	Util B	Util C (include)
Rilpivirine		Stage 4 CKD
		Stage 5 CKD
		ESRD

References:
Edurant Prescribing Information, May 2011, Tibotec Pharmaceuticals.

17. Rilpivirine / Azole Antifungals _____ _____ _____

Alert Message: Concurrent use of Edurant (rilpivirine) and an azole antifungal may result in elevated rilpivirine plasma concentrations and/or decreased azole plasma concentrations. Monitor patients for rilpivirine adverse effects as well as breakthrough fungal infections.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Rilpivirine	Ketoconazole	
	Itraconazole	
	Fluconazole	
	Voriconazole	
	Posaconazole	

References:
Edurant Prescribing Information, May 2011, Tibotec Pharmaceuticals.
Brown KC, Sunita P and Kashuba ADM. Drug Interactions with New and Investigational Antiretrovirals. 2009;48(4):211-241.

18. Rilpivirine / Depressive Disorders _____ _____

Alert Message: Severe depressive disorders have been reported with Edurant (rilpivirine). Immediate medical evaluation is recommended if the patient reports severe depressive symptoms to assess the possibility that the symptoms are related to rilpivirine, and if so, to determine whether the risks of continued therapy outweigh the benefits.

Conflict Code: MC – Drug/Actual Disease Precaution/Warning
Drugs/Diseases

Util A	Util B	Util C
Rilpivirine	Major Depressive Disorder	
	Suicidal Ideation (V-code V62.84)	

References:
Edurant Prescribing Information, May 2011, Tibotec Pharmaceuticals.
Micromedex 2.0 Healthcare Series, DrugDex Evaluations, Thomson Reuters, 2011.

19. Pioglitazone / Bladder Cancer _____ _____

Alert Message: The use of pioglitazone for more than one year may be associated with an increased risk of bladder cancer. The FDA recommends the pioglitazone not be used in patients with active bladder cancer and used with caution in patients with a prior history of bladder cancer.

Conflict Code: MC – Drug Actual Disease Precaution
Drugs/Diseases

Util A	Util B	Util C
Pioglitazone	Bladder Cancer	

References:
MedWatch FDA Safety Information and Adverse Event Reporting Program. Actos (pioglitazone): Ongoing Safety Review – Potential Increased Risk of Bladder Cancer. 06-15-2011.

20. Varenicline / Cardiovascular Disease _____ _____

Alert Message: Chantix (varenicline) may be associated with a small, increased risk of certain cardiovascular adverse events, including heart attack, in patients with cardiovascular disease. The known benefits of varenicline should be weighed against its potential risk when deciding to use the drug in smokers with cardiovascular disease.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Varenicline	Myocardial Infarction	
	Hypertension	
	Hear Failure	
	Atherosclerosis	

References:
MedWatch FDA Safety Information and Adverse Event Reporting Program. Chantix (varenicline): Label Change – Risk of Certain Cardiovascular Adverse Events. 06-16-2011.

21. 5-ARI's / Increased Risk of Prostate Cancer _____ _____

Alert Message: The use of 5-alpha reductase inhibitors (5-ARIs) may increase the risk of a more serious form of prostate cancer (high-grade prostate cancer). The risk appears to be low but weigh the known benefits against the potential risks when deciding to start or continue treatment with 5-ARIs in men.

Conflict Code: TA – Therapeutic Appropriateness

Drugs/Diseases

Util A	Util B	Util C
Finasteride		
Dutasteride		
Dutasteride/Tamsulosin		

References:

MedWatch FDA Safety Information and Adverse Event Reporting Program. FDA Drug Safety Communication: 5-Alpha Reductase Inhibitors (5-ARIs) May Increase the Risk of More Serious Form of Prostate Cancer. 06-09-2011.