DUR Board Meeting
March 7, 2011
Heritage Center
State Capitol

North Dakota Medicaid
DUR Board Meeting
Agenda
Heritage Center
612 East Boulevard Avenue
State Capitol Grounds
March 7, 2011
1pm

1. Administrative items
    - Travel vouchers

2. Old business
    - Review and approval of minutes of 12/6/10 meeting — Chair
    - Budget update — Brendan
    - Second review of Statins — Brendan
    - Second review of Gilenya — Brendan
    - Second review of Xyrem — Brendan
    - Yearly PA review — HID
        - Antihistamines
        - PPIs
        - COX-II/NSAIDs
        - Revatio
        - Actoplus Met
        - Azasite/Quixin
        - Carisoprodol
        - Blood Factors
        - Relistor
        - Sancuso
        - Nuvigil
        - Nucynta

3. New business
    - Review of Nuedexta — HID
    - Review of Nexiclon — HID
    - Review of topical ketoconazole products (Extina, Xolegel, Ketocon Plus) — HID
    - Review of Granisol — HID
    - Criteria recommendations — HID
    - Upcoming meeting date/agenda — Chair

4. Adjourn — Chair

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

DUR Board Meeting
December 6, 2010
1:00 pm CST

In attendance: Brendan Joyce, Gary Betting, Russell Sobotta, Pat Churchill, Greg Pfister (Chairman), Cheryl Huber, Carlotta McCleary, Jim Carlson, Norm Byers, Dave Clinkenbeard, John Savageau, Carrie Sorenson, Steve Irsfeld, Jeff Hostetter, Kimberly Krohn, Todd Twogood.
Absent: Leann Ness

Meeting called to order at 1:03 pm. Chairman Pfister asked for a motion to approve the minutes from the September 13, 2010 meeting. Motion to approve was given by Cheryl Huber; Seconded by Pat Churchill; Motion approved; no opposition. Motion carried.

Brendan provided an update on the budget. Discussion was held on the average cost of a prescription; average cost of a generic prescription; and how costs are increasing based mostly on increasing numbers of Medicaid recipients.

John Savageau asked what percentage of population has gone on Medicaid. Brendan stated that he didn't have any recent numbers of unduplicated counts per year.

Second Review of agents used to treat Hepatitis C – Chairman Pfister asked for discussion; no discussion; no public comment; Vote taken: all board members approved; no opposition. Motion carried.

Second Review of ODT Preparations – Chairman Pfister asked for discussion; Brendan provided further explanation; Brendan suggested adding to the form "patient unable to swallow"; A motion to add check box to the form was made by Steve Irsfeld; motion was seconded by Todd Twogood; Vote was taken: all board members in favor, no opposition. Motion carried. Vote was taken on amended form: all board members in favor, no opposition. Motion carried.

Second Review of Oravig – discussion by board members – none; public comment – none; Vote taken: all in favor; no opposition. Motion carried.

Second Review of Zyclara – discussion by Board members-none; there was no public comment; Vote taken: all in favor; no opposition. Motion carried.

Second Review of Clorpres – discussion – none; public comment – none; Vote taken: all in favor; no opposition. Motion carried.

Second Review of Livalo – discussion – none; public comment – none; Vote taken: all in favor; no opposition. Motion carried.

Yearly PA Review of number of agents – Brendan – Question was asked by Carrie Sorenson regarding adding Oxycontin to the brand name products; Brendan asked for any comments or changes on the forms:

Solodyn – no board comments; no public comments;

Oracea – no board comments; no public comments;

Oxycontin CR PA form – board discussion on merging with other brand name narcotics PA form, perhaps still having Oxycontin mentioned separately, but then having a statement saying "see brand name narcotic form" – Chairman asked if there was any public comment? None.

Short Acting Beta Agonists – Public Comment by Barbara Felt asked the Board to consider adding Ventolin HFA to the list of drugs covered without prior authorization due to it having a dose counter; Kimberly Krohn asked what was the cost differential? Brendan could not provide the information due to Federal Rebate Law, however, he did comment that the cost differential was significant. John Savageau asked Barbara Felt questions on the study. Barbara asked the Board to reconsider the number of doses. Dr. Betting asked what percentage was kids? Jeff Hostetter asked Barbara to prove the request. Todd Twogood made a comment on how children use the inhalers and working to educate, to have a counter would be important. Brendan provided comment. Jeff Hostetter commented that he couldn't make a clinical decision with the information provided. Brendan commented that he has spoken with other states and they don't pay for convenience. Steve commented. Dr. Twogood commented. No changes were made.

Soma 250 form – Brendan commented that only two requests have been received; no public comment;

Vusion form – no board comments; no public comments;

Immunomodulators form – no board comments; no public comments.

Moxatag form – no board comments; no public comments.

Uloric form – no board comments; no public comments.

Smoking Cessation criteria – Dr. Twogood asked why this was on the agenda; Brendan explained that it is prior authorized, but the form is not for public distribution to avoid misuse. Steve asked how many used this. Brendan commented 285; other comments were made by Kim Krohn; no public comments.

New Business

Review of Statins – Brendan discussed that any new products would require PA, but that all current products would not require additional PA. Cheryl asked when patents expire. Brendan said 2011, 2014, and 2016. The logic for the PA is to protect current market share just like was done with the triptan class. Chairman asked for board discussion on the statins. No public comment was given; Dr. Byers moved to keep the existing products and any new products would require PA; Motion seconded by Todd Twogood.

Next topic was on Long Acting Beta Agonists – A 15-month look back was suggested by Brendan for the Board to consider, in addition to better approaches for the Board to consider. Steve commented about "red flagging" those people to contact their provider. Kimberly Krohn commented on having to run the scripts so many times before they go through. Todd Twogood commented. Kimberly Krohn commented on the urgent care world. Todd Twogood commented that in children can't always look back 15 months as many of the diagnosis are new. Brendan commented he could put edits in the system to come back with data to the Board. Brendan wants to build the edit properly, and wants to address the compliance issues. It would not impact phone calls or prescription data. John would like to see the trend. The majority of concern is with walk in clinics. Brendan questioned the guidelines in kids and asked for direction/comment. Todd Twogood commented. Steve asked for the same delivery system. Brendan again asked what data would be useful. The "one and done's" would be on a 15 month review to where they have not been on any other inhaler, and no repeats. Can the data identify the physician too? Response by the board was to identify the non compliant for Serevent and look back 75 days. Brendan will collect data for the next six to nine months. Dr. Twogood commented on exacerbation patients and their needs, and how they might change the data. Data will also be collected on the overuse of rescue inhalers, with edits/data collected for those patients who use the inhalers more than twice per week and filling it every month. Edit should be for four times per year. Plotting will be by monthly usage. Barbara Felt made public comment on being opposed to asthma and COPD patients and a proposed PA for combination products. Barbara Felt recommended to the board to put a PA on the LABA alone. However when used in combination, Barbara Felt recommended breaking that out based on the diseases. Barbara Felt provided additional information, bullet points and comments. Barbara recommended reviewing for other parameters. She also asked that the board look in the NIH guidelines for additional recommendations. She asked the Board to consider the "ratio" and the use of controller medication for overall control. Dr. Twogood asked for an explanation of "ratio". Barbara Felt replied that the "ratio" would be 0.5 and above for a 30 day supply.

Review of Gilenya – looking to keep it to the FDA use as the cost is $50,000/year. Dana Maier made public comment – first oral drug for Multiple Sclorosis (MS). Dana commented on the trial data, side effects, pregnancy registry, and 5 other adverse events in the REM program; Trial data recommends that patients should have eye exam, liver tests, etc. during the first six months; It is also recommended that patients be observed for the first 6 hours when taking the drug. Brendan asked about severity

level. Dana commented on the data from the clinical trials. The indication is for relapsing forms of MS. Brendan said the bullet points would be not to use in combination therapy and would clarify the diagnosis to relapsing forms of MS. John Savageau commented that not much data is given and would recommend PA for this drug. John Savageau asked for additional clinical trial data and a two page summary for the product so that the Board can review. Dr. Krohn commented on other PA forms and the monitoring. Brendan replied to these questions. John Savageau made a motion to revise the current PA form for Gilenya for relapsing forms. Cheryl seconded.

All in favor of modifying the form – Vote taken – all in favor; none opposed. Motion carried.

It was moved and seconded to accept the form.

Review of Xyrem – this medication is considered a "date rape" drug which is used for narcolepsy. Brendan stated that the PA would be to ensure appropriate diagnosis. He shared information on a specific case where the medication was prior authorized, and where the doctor didn't have any medical data. It turned out the patient didn't have narcolepsy. Brendan is asking the Board to require a special form for the medication that only a physician's signature would make it valid, and the physician would have to validate the diagnosis of narcolepsy. Dr. Klinkinbeard made the motion to do this. Motion seconded by Cheryl. Vote was taken -- all approved; no opposed. Motion carried.

Todd Twogood moved to go forward; seconded by Carrie.

Discussion was held on Darvocet – Worker's Comp will not cover this medication any longer. Since this item was not on the agenda, Brendan asked for direction from the Board about what to do. Steve Irsfeld indicated it was a voluntary recall and has been taken off the market. The Board recommended that Medicaid encourage other physicians to not use or prescribe the medication. Brendan will put quantity limits on the drug to 1 or ½ per day, and will report back at the next meeting what the utilization has been.

Todd Twogood had one item to ask the Board, and that was to change the edit on the limitation on extended release ADHD medications and change it from 10 days to 14 days, The Board agreed to have the edit changed.

Criteria Recommendations – Cheryl moved to accept criteria recommendations; Steve seconded. There was no discussion by the board; Vote taken – all approved; no opposition; Motion carried.

Next meetings will be March 7th, 2011 and possibly June 13th, 2011.
The meeting was adjourned by the chair.

North Dakota Medicaid
Pharmacotherapy Review
Statin and Statin Combinations

I. Overview

The 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors, also known as statins, are the most effective class of drugs for lowering serum low-density lipoprotein (LDL-C) concentrations. Depending on the agent, the statins can decrease LDL-C by 18% to 60% when used as monotherapy. The statins work by inhibiting HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate in an early step in the biosynthesis of cholesterol. In addition to LDL-C reduction, statins lower total cholesterol as well as triglycerides, and slightly increase high-density lipoprotein (HDL-C).

Lowering total cholesterol and LDL-C and raising HDL-C is important for many reasons. Deposition of cholesterol in the arterial walls is central to the pathogenesis of atherosclerosis in the coronary arteries. A direct correlation exists between total cholesterol, LDL-C, and the risk of developing coronary heart disease (CHD). Each 1% reduction in LDL-C results in approximately a 1% decrease in the risk of a major cardiac event. An inverse relationship exists between HDL-C and the risk of developing CHD; each 1mg/dL decrease in HDL-C results in a 2-3% increase in the risk of CHD.

CHD is the single leading cause of death in America today with over 425,000 deaths in 2006. From 1996 to 2006, the death rate from CVD decreased 29.2 percent and the death rate from CHD decreased 36.4 percent. Advances have been made in the treatment of CVD, CHD and hyperlipidemia, but there is still work to be done. There are approximately 35.7 million adults in the U.S. with a total cholesterol value of 240mg/dL and greater. The direct and indirect healthcare cost for CVD in 2009 is estimated to be at $475.3 billion.

Pharmacotherapy that can lower total cholesterol and LDL-C while raising HDL-C is not only worthwhile, but extremely valuable. HMG-CoA reductase inhibitors are considered first-line agents for treating hyperlipidemia.

Table 1 lists the agents included in this review.

Table 1. Statin and Statin Combinations Included in this Review

Generic Name	Brand Name	Dosage Form/Strength	Generic Availability	Manufacturer
Atorvastatin	Lipitor®	Tablets: 10mg, 20mg, 40mg, and 80mg	No	Pfizer
Atorvastatin/amlodipine	Caduet®	Tablets: 2.5mg/10mg, 2.5mg/20mg, 2.5mg/40mg, 5mg/10mg, 5mg/20mg, 5mg/40mg, 5mg/80mg,	No	Pfizer

Generic Name	Brand Name	Dosage Form/Strength	Generic Availability	Manufacturer
		10mg/10mg, 10mg/20mg, 10mg/40mg, and 10mg/80mg		
Fluvastatin	Lescol®, Lescol XL®	Capsules: 20mg, and 40mg; Extended-release tablets: 80mg	No	Novartis
Lovastatin	Mevacor®, Altoprev®	Tablets: 10mg, 20mg, and 40mg; Extended-release tablets: 20mg, 40mg, and 60mg	Yes-Mevacor No-Altoprev	Merck, Altoprev-First Horizon, various generic companies
Lovastatin/niacin ER	Advicor®	Tablets: 500mg/20mg, 750mg/20mg, 1000mg/20mg, and 1000mg/40mg	No	Abbott
Rosuvastatin	Crestor®	Tablets: 5mg, 10mg, 20mg, and 40mg	No	AstraZeneca
Pitavastatin	Livalo®	Tablets: 1mg, 2mg, and 4mg	No	Kowa Pharmaceuticals
Pravastatin	Pravachol®	Tablets: 10mg, 20mg, 40mg, and 80mg	Yes	Bristol-Myers Squibb, various generic companies
Simvastatin	Zocor®	Tablets: 5mg, 10mg, 20mg, 40mg, and 80mg	Yes	Merck, various generic companies
Simvastatin/ezetimibe	Vytorin®	Tablets:10mg/10mg, 10mg/20mg, 10mg/40mg, and 10mg/80mg	No	Merck/Schering-Plough
Simvastatin/niacin ER	Simcor®	500mg/20mg, 500mg/40mg, 750/20mg, 1,000mg/20mg and 1,000mg/40mg	No	Abbott

II. Current Treatment Guidelines

The decision to treat hyperlipidemia generally follows the treatment guidelines of the Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III, published in 2002 and updated in 2004. The report stresses that the intensity of treatment should be directed by the degree of cardiovascular risk. Because LDL-C is the major atherogenic lipid component, NCEP-ATP III focuses primarily on achieving target LDL-C levels. For most patients who are prescribed a statin, the target is <130 mg/dL or <100 mg/dL. In ATP-III, patients who have type 2 diabetes without CHD; peripheral or carotid vascular disease; and patients who have multiple risk factors and a 10-year risk of CHD > 20% are said to have 'CHD equivalents.' This means that the criteria for using drug therapy and the LDL-C target is the same for patients who have a history of CHD.

The 2006 update of the American Heart Association/American College of Cardiology consensus statement on secondary prevention states that an LDL-C goal of <70 mg/dL for high risk patients is a therapeutic option. Factors that place patients in the category of very high risk are the presence of established CVD plus 1) multiple major risk factors (especially diabetes), 2) severe and poorly controlled risk factors (especially continued smoking), 3) multiple risk factors of the metabolic syndrome (especially high triglycerides >200 mg/dL plus non-HDL-C >130 mg/dL with low HDL-C <40 mg/dL, and 4) patients with acute coronary syndromes. If it is not possible to attain LDL-C <70 mg/dL because of a high baseline LDL-C, it generally is possible to achieve LDL-C reductions of >50% with either statins or LDL-C lowering drug combinations. The optimal goal of <70 mg/dL does not apply to individuals who are not at high risk.

Table 2 summarizes NCEP Treatment Guidelines for LDL-C goals and cutpoints for therapeutic lifestyle changes (TLC), and pharmacotherapy in different risk categories.

Table 2. NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for TLC and Pharmacotherapy

Risk Category	LDL Goal	LDL Level to Initiate TLC	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalent (10-year risk > 20%)	< 100 mg/dL	≥ 100 mg/dL	≥ 130 mg/dL (100-129 mg/dL, drug optional)*
2 or more Risk Factors (10-year risk ≤ 20%)	< 130 mg/dL	≥130 mg/dL	≥ 130 mg/dL (for 10-year risk 10-20%) > 160 mg/dL (for 10-year risk < 10%)
0-1 Risk Factors	< 160 mg/dL	≥ 160 mg/dL	≥ 190 mg/dL (160-189 mg/dL, drug optional)**

*Some authorities recommend use of LDL-C lowering drugs in this category if an LDL-C < 100 mg/dL cannot be achieved by TLC. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment may also call for deferring drug therapy in this subcategory.

**Factors that favor drug therapy after 3 months of TLC include a severe single risk factor (heavy smoking, poorly controlled hypertension, strong family history of premature CHD, or very low HDL-C), multiple life-habit risk factors and emerging risk factors, or 10-year risk approaching 10%.

III. Comparative Indications for HMG-CoA Reductase Inhibitors

The Food and Drug Administration (FDA) has approved HMG-CoA reductase inhibitors for use adjunctively with a diet restricted in saturated fat and cholesterol when diet and other nonpharmacological therapies alone have produced inadequate responses.

Table 3. FDA Approved Indications for the HMG-CoA Reductase Inhibitors

Indication	Atorvastatin	Fluvastatin/ Fluvastatin XL	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
Primary prevention of CV disease in patients with multiple risk factors for CHD, diabetes, peripheral vascular disease, history of stroke, or other cerebrovascular disease to:							
Reduce angina risk	√		√				

Indication	Atorvastatin	Fluvastatin/ Fluvastatin XL	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
Reduce MI risk	√				√	√	√
Reduce stroke risk	√					√	√
Reduce risk for revascularization procedures	√		√		√	√	√
Reduce risk of CV mortality					√		√
Secondary prevention of CV events in patients with clinically evident CHD to:							
Reduce risk of MI	√				√		√
Reduce risk of stroke	√				√		√
Reduce risk for revascularization procedures	√	√			√		√
Reduce risk of hospitalization for CHF	√						
Reduce angina risk	√						
Slow progression of coronary atherosclerosis		√	√		√	√	
Reduce risk of total mortality by reducing coronary death					√		√
Hypercholesterolemia							
Primary hyper-cholesterolemia (heterozygous familial and nonfamilial)	√	√	√	√	√	√	√
Adolescents with heterozygous familial hyper-cholesterolemia	√	√	√		√		√
Homozygous familial hyper-cholesterolemia	√					√	√
Mixed dyslipidemia (Fredrickson types IIa and IIb)	√	√	√	√	√	√	√
Hyper-triglyceridemia (Fredrickson type IV)	√				√	√	√

Indication	Atorvastatin	Fluvastatin/ Fluvastatin XL	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
Primary dysbetalipo-proteinemia (Fredrickson type III)	√				√	√	√

Combination Product Indications:

1. **Amlodipine/Atorvastatin (Caduet)**
   - Amlodipine: For the treatment of hypertension, chronic stable angina, and confirmed or suspected vasospastic angina (Prinzmetal or Variant angina).
   - Atorvastatin: See indications above.

2. **Niacin (Extended Release)/Lovastatin (Advicor)**
   - Primary hypercholesterolemia/mixed dyslipidemia: For the treatment of primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson Types IIa and IIb) in the following: Patients treated with lovastatin who require further TG-lowering or HDL-raising who may benefit from having niacin added to their regimen; patients treated with niacin who require further LDL-lowering who may benefit from having lovastatin added to their regimen.

3. **Niacin (Extended Release)/Simvastatin (Simcor)**
   - Hypercholesterolemia: For the reduction of total cholesterol, LDL-C, APO B, non-HDL-C, or TG, or to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson type IIa and IIb) when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate.
   - Hypertriglyceridemia: For the reduction of triglycerides in patients with hypertriglyceridemia (Fredrickson type IV hyperlipidemia) when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate.

4. **Ezetimibe/Simvastatin (Vytorin)**
   - Homozygous familial hypercholesterolemia: For reducing elevated total cholesterol and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments.
   - Primary hypercholesterolemia: Adjunctive therapy to diet for reducing elevated total cholesterol, LDL-C, apolipoprotein B (apo B), triglycerides, and non-high-density lipoprotein cholesterol (HDL-C), and to increase HDL-C in patients with primary (heterozygous familial and nonfamilial) hypercholesterolemia or mixed hyperlipidemia.

IV. Comparative Pharmacokinetic Parameters of HMG-CoA Reductase Inhibitors

Table 4. Pharmacokinetic parameters of HMG-CoA Reductase Inhibitors

	Atorvastatin	Fluvastatin/ Fluvastatin XL	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
Elimination Half Life	14 hours (20-30 hours for HMG-CoA reductase inhibitory activity)	<3 hours for IR and 9 hours for ER	3 to 4 hours (IR)	12 hours	77 hours (pravastatin plus metabolites)	19 hours	
Absolute Bioavailability	~14%	24%-IR 29%-ER	<5%; BA for ER was 190% compared with IR	51%	17%	20%	<5%
Food Effect	Decreased rate and extent of absorption; not clinically significant	Decreased rate, but not extent of absorption	Decreased bio-availability (ER)	Decreased rate by 43%, but not sig-nificantly reduce extent	Decreased bio-availability; not clinically significant	Decreased rate 20%, but not extent of absorption	
Protein Binding	≥98%	98%	>95%	>99%	50%	88%	95%
Time to peak	1 to 2 hours	<1 hour (IR); 3 hours ER)	2 to 4 hours	1 hour	1 to 1.5 hours	3 to 5 hours	1.3 to 2.4 hours
Main Metabolizing Enzyme	CYP3A4 (hepatic-first pass)	CYP2C9 (75%) (hepatic- first pass)	CYP3A4 (hepatic-extensive first pass)	Marginal CYP2C9	Extensive sulfation	Minor CYP2C9	Extensive CYP3A4
Primary Route of Elimination	Bile; <2% (urine)	5% (urine); 90% (feces)	10% (urine); 83% (feces)	15% (urine); 79% (feces)	20% (urine); 70% (feces)	90% (feces)	13% (urine); 60% (feces)
Effects of Renal/Hepatic Impairment	Plasma levels ↑ in chronic alcoholic liver disease.	Plasma levels ↑ with hepatic insufficiency.	Plasma levels ↑ in severe renal disease.	Plasma concentrations are ↑ in mild to moderate hepatic im-pairment; rate and extent of absorption are increased 60% and 79%	Potential drug accumulation with renal or hepatic insufficiency; mean AUC varied 18-fold in cirrhotic patients, and peak values varied 47-fold.	Increased plasma concentrations with severe renal impairment and hepatic disease.	Higher systemic exposure may occur in hepatic and severe renal in-sufficiency.

	Atorvastatin	Fluvastatin/ Fluvastatin XL	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
				respect-ively, in patients with moderate renal im-pairment.			

V. HMG-CoA Reductase Inhibitor Drug Interactions

Table 5. HMG-CoA Reductase Inhibitor Drug Interactions

Precipitant drug	Object drug		Description
Amiodarone	HMG-CoA reductase inhibitors Atorvastatin Lovastatin Simvastatin	↑	Amiodarone may inhibit the metabolism (CYP3A4) of certain HMG-CoA reductase inhibitors, increasing the risk of toxicity (eg, myopathy). If coadministration cannot be avoided, use the lowest possible H MG-CoA reductase inhibitor dose.
Antacids	HMG-CoA reductase inhibitors Rosuvastatin Atorvastatin	↓	Coadministration with aluminum hydroxide/magnesium hydroxide suspension decreased atorvastatin levels by approximately 35%; LDL-C reduction was not altered. Coadministration of rosuvastatin and an aluminum/magnesium combination antacid decreased rosuvastatin levels by 54%. Administer antacids at least 2 hours after rosuvastatin.
Azole antifungals (eg, fluconazole, itraconazole, ketoconazole)	HMG-CoA reductase inhibitors	↑	Azole antifungal agents may inhibit the metabolism of HMG-CoA reductase inhibitors, increasing the risk of toxicity (eg, myopathy). Itraconazole is contraindicated with HMG-CoA reductase inhibitors metabolized by CYP3A4. If coadministration of other agents cannot be avoided, consider suspending the dose of the HMG-CoA reductase inhibitor during the course of therapy. Pravastatin and rosuvastatin levels are affected the least.
Bile acid sequestrants (eg, cholestyramine, colestipol)	H MG-CoA reductase inhibitors Atorvastatin Pravastatin Fluvastatin	↓	The H MG-CoA reductase inhibitor may adsorb to the bile acid sequestrant, reducing the GI absorption of the HMG-CoA reductase inhibitor. Administer pravastatin I hour before or4 hours after bile acid sequestrants. Administer fluvastatin at least 2 hours after a bile acid sequestrant. Plasma levels of atorvastatin decreased approximately 25% with coadministration with colestipol; however, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone.

Precipitant drug	Object drug		Description
Bosentan	HMG-CoA reductase inhibitors Atorvastatin Lovastatin Simvastatin	↓	Bosentan may induce the metabolism (CYP3A4) of certain H MG-CoA reductase inhibitors, decreasing the therapeutic effect. Monitor closely and adjust dosage as needed.
Carbamazepine	HMG-CoA reductase inhibitors Atorvastatin Lovastatin Simvastatin	↓	Carbamazepine may induce the metabolism (CYP3A4) of certain H MG-CoA reductase inhibitors, decreasing the therapeutic effect. Monitor closely and adjust dosage as needed.
Cilostazole	HMG-CoA reductase inhibitors Atorvastatin Lovastatin Simvastatin	↑	Cilostazole may inhibit the metabolism (CYP3A4) of certain HMG-CoA reductase inhibitors, increasing the risk of toxicity (eg, myopathy). Monitor closely and adjust dosage as needed.
Cisapride	HMG-CoA reductase inhibitors Simvastatin	↑↓	Coadministration may decrease simvastatin levels, and cisapride levels may be elevated.
HMG-CoA reductase inhibitors	Cisapride		
Colchicine	HMG-CoA reductase inhibitors	↑	Coadministration may increase the risk of myopathy or rhabdomyolysis. If coadministration cannot be avoided, then use with caution and closely monitor CK.
HMG-CoA reductase inhibitors	Colchicine		
Cyclosporine	HMG-CoA reductase inhibitors	↑	Coadministration may increase HMG-CoA reductase inhibitor plasma levels and increase the risk of myopathy or rhabdomyolysis. If coadministration cannot be avoided, consider decreasing HMG-CoA reductase inhibitor dose and monitor closely. Lovastatin ER should not be coadministered with cyclosporine; however, reduced dosage of immediate-release lovastatin may be considered. Coadministration with pitavastatin is contraindicated.
Danazol	HMG-CoA reductase inhibitors Lovastatin Simvastatin	↑	Coadministration may cause myopathy or rhabdomyolysis. If coadministration cannot be avoided, consider decreasing the HMG-CoA reductase inhibitor dose and monitor closely.

Precipitant drug	Object drug		Description
Diltiazem	HMG-CoA reductase inhibitors Atorvastatin Lovastatin Simvastatin	↑	Diltiazem may inhibit the metabolism (CYP3A4) of certain HMG-CoA reductase inhibitors, increasing the risk of toxicity (eg, myopathy).
Fibric acid derivatives (ie, fenofibrate, gemfibrozil)	HMG-CoA reductase inhibitors	↑	Severe myopathy or rhabdomyolysis may occur. Avoid concurrent use if possible. If used, consider a reduced dosage of the HMG-CoA reductase inhibitor.
HMG-CoA reductase inhibitors	Fibric acid derivatives (ie, fenofibrate, gemfibrozil)		
Glyburide	HMG-CoA reductase inhibitors Fluvastatin	↑	Coadministration increased glyburide Cmax, AUC, and half-life approximately 50%, 69%, and 121%, respectively. Coadministration also led to an increase in fluvastatin Cmax and AUC by 44% and 51%, respectively. Monitor patients.
HMG-CoA reductase inhibitors Fluvastatin	Glyburide		
Histamine H2 antagonists (ie, cimetidine, ranitidine)	HMG-CoA reductase inhibitors Fluvastatin	↑	Coadministration of fluvastatin with cimetidine and ranitidine resulted in a significant increase in fluvastatin Cmax and AUC by 44% and 51%, respectively. Monitor patients.
Hydantoins (eg, phenytoin)	HMG-CoA reductase inhibitors Atorvastatin Fluvastatin Simvastatin	↑↓	Coadministration may result in decreased plasma levels of certain HMG-CoA reductase inhibitors, producing a decrease in therapeutic effect. Coadministration of fluvastatin and phenytoin increased the levels of both drugs.
HMG-CoA reductase inhibitors Fluvastatin	Hydantoins (eg, phenytoin)		
Imatinib	HMG-CoA reductase inhibitors Atorvastatin Lovastatin Simvastatin	↑	Imatinib may inhibit the metabolism (CYP3A4) of certain HMG-CoA reductase inhibitors, increasing the risk of toxicity (eg, myopathy).
Isradipine	HMG-CoA reductase inhibitors Lovastatin	↓	Isradipine may increase clearance of lovastatin and its metabolites by increasing hepatic blood flow. Monitor the clinical response and adjust the lovastatin dosage as necessary.
Macrolides Clarithromycin Erythromycin	HMG-CoA reductase inhibitors	↑	Certain macrolides may inhibit the metabolism of HMG-CoA reductase inhibitors metabolized by CYP3A4. Coadministration increases the risk of severe myopathy or rhabdomyolysis. If coadministration is unavoidable, suspend therapy with an HMG-CoA reductase inhibitor during the course of macrolide therapy. Do not exceed a dosage of **pitavastatin** 1 mg once daily during coadministration.

Precipitant drug	Object drug		Description
Nefazodone	HMG-CoA reductase inhibitors	↑	Nefazodone may inhibit the metabolism (CYP3A4) of certain HMG-CoA reductase inhibitors, increasing the risk of toxicity (eg, myopathy). Avoid use if possible.
Niacin (nicotinic acid)	HMG-CoA reductase inhibitors	↑	Coadministration of HMG-CoA reductase inhibitors with niacin (dosages of at least 1 g/day) increases the risk of severe myopathy or rhabdomyolysis. If coadministration cannot be avoided, use the lowest possible HMG-CoA reductase inhibitor dose.
HMG-CoA reductase inhibitors	Niacin (nicotinic acid)		
NNRTIs (eg, delavirdine, efavirenz, nevirapine)	HMG-CoA reductase inhibitors Atorvastatin Lovastatin Pravastatin Simvastatin	↑↓	Delavirdine may inhibit the metabolism (CYP3A4) of certain HMG-CoA reductase inhibitors, increasing the risk of toxicity (eg, myopathy). However, efavirenz and nevirapine may induce CYP3A4 and reduce HMG-CoA reductase inhibitor levels.
Omeprazole	HMG-CoA reductase inhibitors Fluvastatin	↑	Coadministration of fluvastatin with omeprazole resulted in a significant increase in fluvastatin Cmax (50%) and AUC (24% to 33%), with an 18% to 23% decrease in plasma clearance.
Propranolol	HMG-CoA reductase inhibitors Simvastatin	↔	Coadministration resulted in a significant decrease in simvastatin Cmax, but no change in AUC. No dosage adjustment is needed.
Protease inhibitors (eg, nelfinavir, ritonavir)	HMG-CoA reductase inhibitors	↑↓	Concomitant use may result in elevated plasma levels of certain HMG-CoA reductase inhibitors, increasing the risk of toxicity (eg, myopathy). Darunavir or nelfinavir is contraindicated in patients taking lovastatin or simvastatin; avoid coadministration with ritonavir or atazanavir. However, concomitant use of a protease inhibitor with pravastatin may decrease pravastatin plasma levels, possibly decreasing efficacy. Avoid use if possible.
Quinine	HMG-CoA reductase inhibitors Atorvastatin	↑	Quinine may inhibit the metabolism (CYP3A4) of atorvastatin, increasing the risk of toxicity (eg, myopathy).
Rifamycins (eg, rifampin)	HMG-CoA reductase inhibitors Atorvastatin Fluvastatin Pitavastatin Pravastatin	↑↓	Coadministration may reduce levels of certain HMG-CoA reductase inhibitors. However, pravastatin and pitavastatin levels may be increased in some patients. Do not exceed a dosage of pitavastatin 2 mg once daily during coadministration
St. John's wort	HMG-CoA reductase inhibitors Atorvastatin Lovastatin Simvastatin	↓	St. John's wort may induce the metabolism (CYP3A4) of certain HMG-CoA reductase inhibitors, decreasing therapeutic effect.
Telithromycin	HMG-CoA reductase inhibitors Atorvastatin Lovastatin Simvastatin	↑	Telithromycin may inhibit the metabolism (CYP3A4) of certain HMG-CoA reductase inhibitors, increasing the risk of toxicity (eg, myopathy).

Precipitant drug	Object drug		Description
Verapamil	HMG-CoA reductase inhibitors Atorvastatin Lovastatin Simvastatin	↑	Verapamil may inhibit the metabolism (CYP3A4) of certain HMG-CoA reductase inhibitors, increasing the risk of toxicity (eg, myopathy). If coadministration cannot be avoided, consider decreasing the HMG-CoA reductase inhibitor dose and monitor closely. Atorvastatin may also increase the levels of verapamil.
HMG-CoA reductase inhibitors Atorvastatin	Verapamil		
HMG-CoA reductase inhibitors Atorvastatin	Benzodiazepines (ie, midazolam)	↑	Atorvastatin may decrease the oxidative metabolism (CYP3A4) of certain benzodiazepines. The effects of the benzodiazepines may be increased and prolonged.
HMG-CoA reductase inhibitors Atorvastatin Fluvastatin Lovastatin Simvastatin	Clopidogrel	↓	Data for this interaction are conflicting. Certain HMG-CoA reductase inhibitors may interfere with clopidogrel platelet inhibition. One case of rhabdomyolysis has been reported. No special precautions are needed based on available data.
HMG-CoA reductase inhibitors Atorvastatin Rosuvastatin	Contraceptives, hormonal	↑	Coadministration with atorvastatin increased the AUC for norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively. Coadministration with rosuvastatin increased the AUC for norgestrel and ethinyl estradiol by approximately 34% and 26%, respectively.
HMG-CoA reductase inhibitors Fluvastatin	Diclofenac	↑	Coadministration increased the mean diclofenac Cmax and AUC by 60% and 25%, respectively.
HMG-CoA reductase inhibitors Atorvastatin Fluvastatin Rosuvastatin Simvastatin	Digoxin	↑	Coadministration may increase digoxin plasma concentrations. Monitor digoxin levels and adjust the dosage as needed.
HMG-CoA reductase inhibitors Fluvastatin Lovastatin Pitavastatin Rosuvastatin Simvastatin	Warfarin	↑	The anticoagulant effect of warfarin may increase. Bleeding also has been reported in a few patients. Monitor anticoagulation parameters when starting, stopping, or adjusting the HMG-CoA reductase inhibitor dosage.

VI. Comparative Adverse Effects of HMG-CoA Reductase Inhibitors

Statins are generally well tolerated with the most common side effects being abdominal pain, constipation, flatulence, and headache. More serious but rare side effects of statins include increases in liver enzymes and myopathy accompanied by elevations in creatine kinase, which can progress to rhabdomyolysis and acute renal failure. Routine liver function monitoring is

recommended with each statin, with only slight variations in this monitoring parameter existing between statins. Increases in hepatic transaminases (> 3x ULN) have been reported with statins (0.5%-2.0%) and appear to be dose-dependent (risk increases as the statin dose increases). Elevations in hepatic transaminases frequently reverse with a reduction in dose or suspension of therapy. Upon re-challenge or initiation of another statin, elevations in liver enzymes do not often occur. Myositis (defined as elevated creatine kinase – generally > 10 times the ULN – plus symptomatic muscle aches/weakness) has also been reported with statins (0.1-0.5%), as has rhabdomyolysis when statins are used as monotherapy (0.04%-0.2%).

With regard to more minor adverse reactions, no clear differences seem to exist between the drugs in this class. Patients who do not tolerate one statin generally may tolerate another (tolerability differences between statins do exist for unknown reasons).

Table 6. Adverse Reactions (%) Reported with the HMG-CoA Reductase Inhibitors

Adverse Effects	Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
Cardiovascular							
Angina pectoris	< 2%	-	-	-	3.1%	-	-
Atrial fibrillation	-	-	-	-	-	-	5.7%
Hypertension	< 2%	-	-	-	-	-	-
CNS							
Asthenia	≤ 3.8%	-	1.2% to 3%	-	PM	2.7%	√
Depression	< 2%	√	-	-	1%	-	PM
Dizziness	≥ 2%	√	0.5% to 2%	-	1% to 2.2%	4%	PM
Headache	2.5% to 16.7%	4.7% to 8.9%	2.1% to 7%	√	1.7% to 1.9%	5.5% to 6.4%	7.4%
Insomnia	≥ 2%	0.8% to 2.7%	0.5% to 1%	-	< 1%	-	4%
Paresthesia	< 2%	√	0.5% to 1%	-	< 1%	-	PM
Vertigo	-	√	√	-	< 1%	-	4.5%
Dermatologic							
Alopecia	< 2%	√	0.5% to 1%	-	< 1%	-	PM
Eczema	< 2%	-	-	-	-	-	4.5%
Pruritus	< 2%	√	0.5% to 1%	-	< 1%	√	PM
Rash	1.1% to 3.9%	-	0.8% to 1.3%	-	1.3% to 2.1%	√	√
GI							
Abdominal pain/cramps	≤ 3.8%	3.7% to 4.9%	2% to 2.5%	-	2% to 2.4%	2.4%	7.3%
Acid regurgitation	-	-	0.5% to 1%	-	-	-	-
Constipation	≤ 2.5%	-	2% to 3.5%	3.6%	1.2% to 2.4%	2.4%	6.6%
Diarrhea	≤ 5.3%	3.3% to 4.9%	2.2% to 3%	2.6%	2%	-	√
Dry mouth	< 2%	-	0.5% to 1%	-	-	-	-
Dysgeusia	< 2%	-	0.8%	-	-	-	-
Dyspepsia	1.3% to 2.8%	3.5% to 7.9%	1% to 1.6%	-	3.5%	-	√
Flatulence	1.1% to 2.8%	1.4% to 2.6%	3.7% to 4.5%	-	1.2% to 2.7%	-	√
Gastroenteritis	< 2%	-	-	-	-	≥ 2%	4.9%
Heartburn	-	-	1.6%	-	2%	-	-

Adverse Effects	Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
Nausea	≥ 2%	2.5% to 3.2%	1.9% to 2.5%	-	1.6% to 2.9%	3.4%	5.4%
Vomiting	< 2%	√	0.5% to 1%	-	1.6% to 2.9%	-	PM
GU							
Albuminuria	≥ 2%	-	-	-	-	-	-
Hematuria	≥ 2%	-	-	-	-	√	-
Urinary abnormality	-	-	-	-	0.7% to 1%	-	-
Urinary tract infection	≥ 2%	1.6% to 2.7%	2% to 3%	-	-	-	3.2%
Lab test abnormalities							
ALT > 3 X ULN	0.2% to 2.3%	0.2% to 4.9%	1.9%	-	≤ 1.2%	2.2%	1%
Elevated CPK	< 2%	√	√	√	√	2.6%	√
Musculoskeletal							
Arthralgia	≤ 5.1%	√	0.5% to 5%	√	PM	10.1%	PM
Arthritis	≥ 2%	1.3% to 2.1%	-	-	√	PM	-
Arthropathy	-	3.2%	-	-	-	-	-
Back pain	≤ 3.8%	-	5%	3.9%	-	-	-
Leg pain	< 2%	-	0.5% to 1%	-	-	-	-
Localized pain	-	-	0.5% to 1%	-	1.4%	-	-
Muscle cramps/pain	-	√	0.6% to 1.1%	-	2% to 6%	12.7%	PM
Myalgia	≤ 5.6%	3.8% to 5%	1.8% to 3%	3.1%	0.6% to 1.4%	2.8%	3.7%
Myopathy	√	√	√	-	PM	√	0.02% to 0.53%
Rhabdomyolysis	PM	√	√	-	PM	√	√
Shoulder pain	-	-	0.5% to 1%	-	-	-	-
Ophthalmic							
Blurred vision	-	-	0.9% to 1.2%	-	-	-	-
Eye irritation	-	-	0.5% to 1%	-	-	-	-
Visual disturbance	-	-	-	-	1.6%	-	-
Respiratory							
Bronchitis	≥ 2%	1.8% to 2.6%	-	-	-	-	6.6%
Cough	-	-	-	-	0.1% to 1%	-	-
Dyspnea	< 2%	-	-	-	1.6%	-	-
Pharyngitis	≤ 2.5%	-	-	-	-	-	-
Rhinitis	≥ 2%	-	-	-	0.1%	-	-
Sinusitis	≤ 6.4%	2.6% to 3.5%	4% to 6%	-	-	-	2.3%
Upper respiratory tract infection	-	-	-	-	1.3%	-	9%
Miscellaneous							
Accidental trauma	≤ 4.2%	4.2% to 5.1%	4% to 6%	-	-	-	-
Allergy/hyper-sensitivity	≤ 2.8%	1% to 2.3%	-	√	< 1%	√	PM
Chest pain	≥ 2%	-	0.5% to 1%	-	0.1% to 2.6%	-	-
Diabetes mellitus	-	-	-	-	-	-	4.2%
Edema/Swelling	< 2%	-	-	-	-	-	2.7%
Fatigue	PM	1.6% to 2.7%	-	-	1.9% to 3.4%	-	-
Flu syndrome	≤ 3.2%	5.1% to 7.1%	5%	-	-	-	-
Infection	2.8% to 10.3%	-	11% to 16%	-	-	-	-

Adverse Effects	Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
Pain	-	-	3% to 5%	-	1.4%	≥ 2%	-
Peripheral edema	≥ 2%	-	-	-	-	≥ 2%	-

√ = reported but no evidence given
PM = postmarketing

VII. Dosing and Administration of HMG-CoA Reductase Inhibitors

Table 7. HMG-CoA Reductase Inhibitor Dosing & Administration

	Initial Dose	Dosing Range	Maximum Dose
Atorvastatin	10mg QD	10-80mg QD	80mg QD
Fluvastatin/ Fluvastatin XL	20mg QD 80mg QD (ER)	20-80mg QD	80mg QD
Lovastatin/ Lovastatin ER	20mg QD	10-80mg QD 10-60mg QD (ER)	80mg QD 60mg QD (ER)
Pitavastatin	2mg QD	1-4mg QD	4mg QD
Pravastatin	40mg QD	10-80mg QD	80mg QD
Rosuvastatin	10mg QD	5-40mg QD	40mg QD
Simvastatin	20mg QD	5-80mg QD	80mg QD

VIII. Conclusion

When clinically evaluating the HMG CoA reductase inhibitor class, it is important to look closely at safety and patient outcomes data. However, because the NCEP ATP III guidelines recommend such strict control of LDL-C, the efficacy and LDL-C lowering capacity must also be considered.

As demonstrated in clinical studies, no clear differences seem to exist between the statins in terms of safety. All of the drugs in this class have beneficial effects on coronary heart disease (CHD) outcomes. Atorvastatin, fluvastatin, pravastatin, and simvastatin have also been shown to reduce cardiovascular events in patients with clinically evident CHD (secondary prevention). In addition, fluvastatin, lovastatin, pravastatin, and rosuvastatin have been shown to slow the progression of coronary atherosclerosis in patients with CHD. Studies have demonstrated that statins (atorvastatin, pravastatin, rosuvastatin, and simvastatin) also decrease the risk of stroke. Studies have also demonstrated that combination products are safe, effective and show therapeutic benefit but offer no clinical advantage over the concurrent administration of the individual components.

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ND Medicaid Utilization				
AHFS Class 240608				
11/24/09 - 11/23/10				
Label Name	**Rx Num**	**Total Reimb Amt**	**Avg Cost per script**	**% Marketshare**
CADUET 10 MG-10 MG TABLET	33	$3,426.06	$103.82	
CADUET 10 MG-20 MG TABLET	3	$481.20	$160.40	
CADUET 10 MG-80 MG TABLET	9	$1,541.96	$171.33	
CADUET 5 MG-10 MG TABLET	37	$4,588.73	$124.02	
CADUET 5 MG-40 MG TABLET	24	$2,016.39	$84.02	
CADUET TOTAL	**106**			**1.24%**
CRESTOR 10 MG TABLET	468	$51,725.13	$110.52	
CRESTOR 20 MG TABLET	134	$14,464.23	$107.94	
CRESTOR 40 MG TABLET	122	$12,120.42	$99.35	
CRESTOR 5 MG TABLET	198	$21,797.81	$110.09	
CRESTOR TOTAL	**922**			**10.82%**
LESCOL 20 MG CAPSULE	1	$17.00	$17.00	
LESCOL TOTAL	**1**			**0.01%**
LIPITOR 10 MG TABLET	257	$20,540.15	$79.92	
LIPITOR 20 MG TABLET	1119	$85,562.64	$76.46	
LIPITOR 40 MG TABLET	789	$60,329.59	$76.46	
LIPITOR 80 MG TABLET	602	$52,190.55	$86.70	
LIPITOR TOTAL	**2767**			**32.48%**
LOVASTATIN 10 MG TABLET	17	$224.00	$13.18	
LOVASTATIN 20 MG TABLET	80	$1,167.13	$14.59	
LOVASTATIN 40 MG TABLET	86	$1,621.99	$18.86	
LOVASTATIN TOTAL	**183**			**2.15%**
PRAVASTATIN SODIUM 10 MG TAB	9	$97.64	$10.85	
PRAVASTATIN SODIUM 20 MG TAB	96	$1,120.21	$11.67	
PRAVASTATIN SODIUM 40 MG TAB	147	$1,833.22	$12.47	
PRAVASTATIN SODIUM 80 MG TAB	28	$493.34	$17.62	
PRAVASTATIN TOTAL	**280**			**3.29%**
SIMCOR 1,000-20 MG TABLET	16	$1,940.44	$121.28	
SIMCOR 500-20 MG TABLET	29	$2,806.24	$96.77	
SIMCOR TOTAL	**45**			**0.53%**
SIMVASTATIN 10 MG TABLET	427	$4,129.09	$9.67	
SIMVASTATIN 20 MG TABLET	1785	$17,998.98	$10.08	
SIMVASTATIN 40 MG TABLET	1388	$17,542.71	$12.64	
SIMVASTATIN 5 MG TABLET	3	$22.86	$7.62	
SIMVASTATIN 80 MG TABLET	612	$7,732.93	$12.64	
SIMVASTATIN TOTAL	**4215**			**49.48%**
Totals 1,252 recipients	**12823**	**$389,532.64**		

HEALTH INFORMATION DESIGNS

Gilenya 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 who are prescribed Gilenya must follow these guidelines:

***Note:**

- ***Must have relapsing forms of multiple sclerosis.***
- ***Must have a current electrocardiogram (within 6 months) for patients taking anti-arrhythmics, beta-blockers, or calcium channel blockers; patients with cardiac risk factors; and patients with a slow or irregular heart beat.***
- ***Must have a recent CBC (within 6 months).***
- ***Must have an adequate ophthalmologic evaluation at baseline and 3-4 months after treatment initiation.***
- ***Must have recent (within 6 months) transaminase and bilirubin levels before initiation of therapy.***
- ***Will not be approved for use in combination 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: □ **Gilenya**	**Diagnosis for this request:**		
Qualifications for coverage:			
Current electrocardiogram **Date:**	**Current CBC** **Date:**	**Ophthalmologic Evaluation** **Date:**	**Transaminase/Bilirubin levels** **Date:**
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)	

HEALTH INFORMATION DESIGNS

Xyrem 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 who are prescribed Xyrem must meet these guidelines:
Note:

- ***Must be 18 years or older.***
- ***Must have a diagnosis of excessive daytime sleepiness and cataplexy in patients with narcolepsy.***
- ***Must be enrolled in the Xyrem Success Program***

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: □ **Xyrem**	**Diagnosis for this request:**		
Qualifications for coverage:			
□ Enrolled in Xyrem Success Program	Enrolled Date:	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)	

ANTIHISTAMINE 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 antihistamines must use loratadine (Claritin generic) and cetirizine (Zyrtec generic) as step therapy.

***Note:**

- ***Loratadine OTC and cetirizine OTC (or prescription generic) may be prescribed WITHOUT prior authorization.***
- ***Loratadine OTC and cetirizine OTC are covered by Medicaid when prescribed by a physician.***
- ***Patients must use loratadine or cetirizine for a minimum of 14 days for the trial to be considered a failure. Patient preference does not constitute a failure. Patients must use fexofenadine as step 2 after loratadine or cetirizine failure.***
- ***Net cost to Medicaid: Loratadine = cetirizine << Allegra (generic) << Clarinex = Xyzal***

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: □ **ALLEGRA (GENERIC)** □ **CLARINEX** □ **XYZAL**	**Requested Dosage:** (must be completed) **Diagnosis for this request:**

Qualifications for coverage:

□ Failed loratadine or cetirizine (include which agent failed)_____	Start Date:	End Date:
□ Failed Allegra (generic) Step 2	Start Date:	End Date:

□ *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:

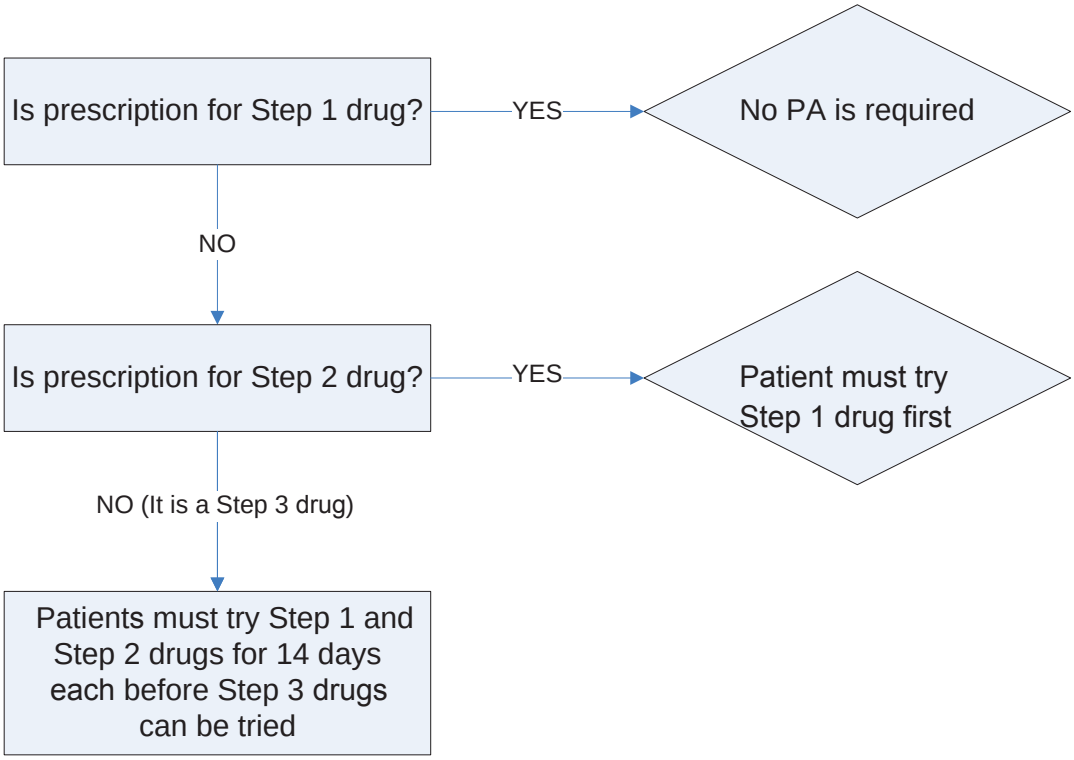
Part II: TO BE COMPLETED BY PHARMACY

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
Antihistamine Authorization Criteria Algorithm



Please Note:

Step 1 drug is defined as Loratadine OTC or Cetirizine
Step 2 drug is defined as Allegra (generic)
Step 3 drug is defined as Clarinex or Xyzal-must try Step 1 and Step 2 drugs before trying Step 3.

Net cost to Medicaid: Loratadine = cetirizine << Allegra (generic) << Clarinex = Xyzal

HEALTH INFORMATION DESIGNS

Prior Authorization Vendor for ND Medicaid

Proton Pump Inhibitor 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 proton pump inhibitors must use Prilosec OTC, Prevacid 24HR, or Omeprazole as first line.
*__Note:__

- **Prilosec OTC, Prevacid 24HR, and Omeprazole may be prescribed WITHOUT prior authorization. Prilosec OTC and Prevacid 24HR are covered by Medicaid when prescribed by a physician.**
- **Prior Authorization is NOT required for patients < 13 years of age.**
- **Patients must use Prilosec OTC, Prevacid 24HR, or omeprazole for a minimum of 14 days for the trial to be considered a failure. Patient preference does not constitute a failure.**
- **Net cost to Medicaid: Prilosec OTC = Prevacid 24HR = Omeprazole <<< Pantoprazole < Lansoprazole << Aciphex < Prilosec RX << Nexium << Zegerid <<< Dexilant.**

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: □ Protonix □ Aciphex □ Prevacid □ Nexium □ Prilosec □ Zegerid □ Dexilant	**Requested Dosage:** (must be completed) **Diagnosis for this request:**

Qualifications for coverage:

❑ Failed Prilosec OTC/Prevacid 24HR/Omeprazole therapy	Start Date:	Dose:
	End Date:	Frequency:
□ Pregnancy – Due Date		
□ Inability to take or tolerate oral tablets (must check a box) □ Tube Fed □ Requires soft food or liquid administration □ Other (provide description)		
□ Adverse reaction (attach FDA Medwatch form) to omeprazole/lansoprazole.		
□ *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:

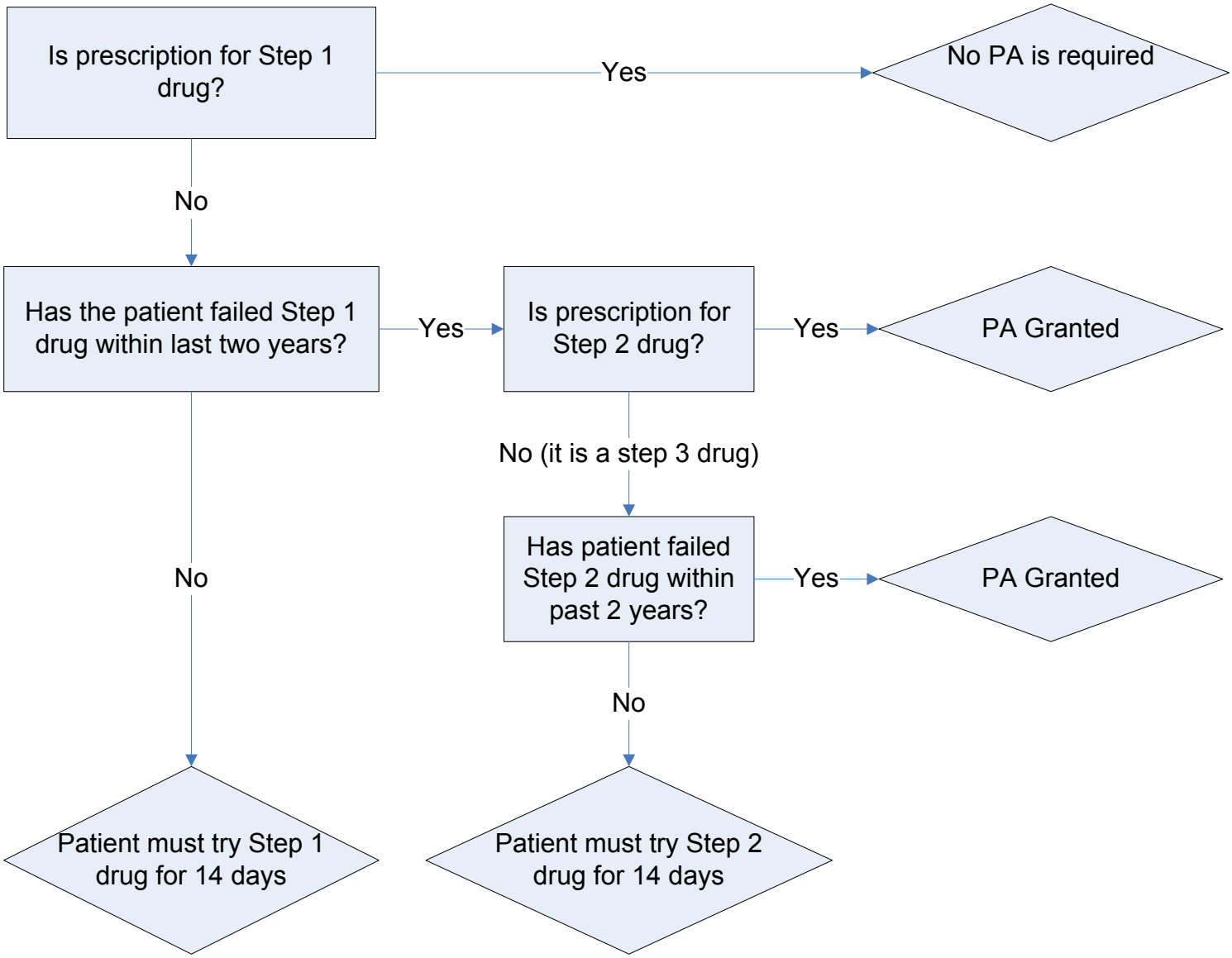
Part II: TO BE COMPLETED BY PHARMACY

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
Proton Pump Inhibitor Authorization Criteria Algorithm



Please Note:

Step 1 drug is defined as Prilosec OTC, Prevacid 24HR, and omeprazole

Step 2 drug is defined as pantoprazole and lansoprazole

Step 3 drug is defined as Nexium, Aciphex, Zegerid, and Dexilant (which is 5-8 times more expensive)

HEALTH INFORMATION DESIGNS

Prior Authorization Vendor for ND Medicaid

BRAND NAME NSAID/COX-II PA FORM

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

ND Medicaid requires that patients using brand name NSAIDs or COX-II drugs must use a generic NSAID as first line.

***Note: The PA will be approved if one of the following criteria is met:**

- **Failed two trials of prescribed oral NSAIDs to receive brand name oral NSAIDs**
- **Failed trial of Voltaren gel to receive brand name topical NSAIDs for inflammation**
- **Recipient is on warfarin or corticosteroid therapy**
- **Recipient has history of gastric or duodenal ulcer or has comorbidities of GI bleed, perforation or obstruction**
- **Recipient has history of endoscopically documented NSAID induced gastritis with GI bleed**
- **Solaraze will be covered for patients with a diagnosis of actinic keratoses**

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:**	
□ Celebrex	□ Warfarin/Corticosteroid therapy	□ GI bleed, perforation or obstruction
□ Other _____	□ Gastric or duodenal ulcer	□ Endoscopically documented NSAID gastritis with GI Bleed
	□ Actinic keratoses **(Solaraze)**	

Qualifications for coverage:

□ Failed NSAID therapy	Start Date	End Date	Dose	Frequency
□ Failed NSAID therapy	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

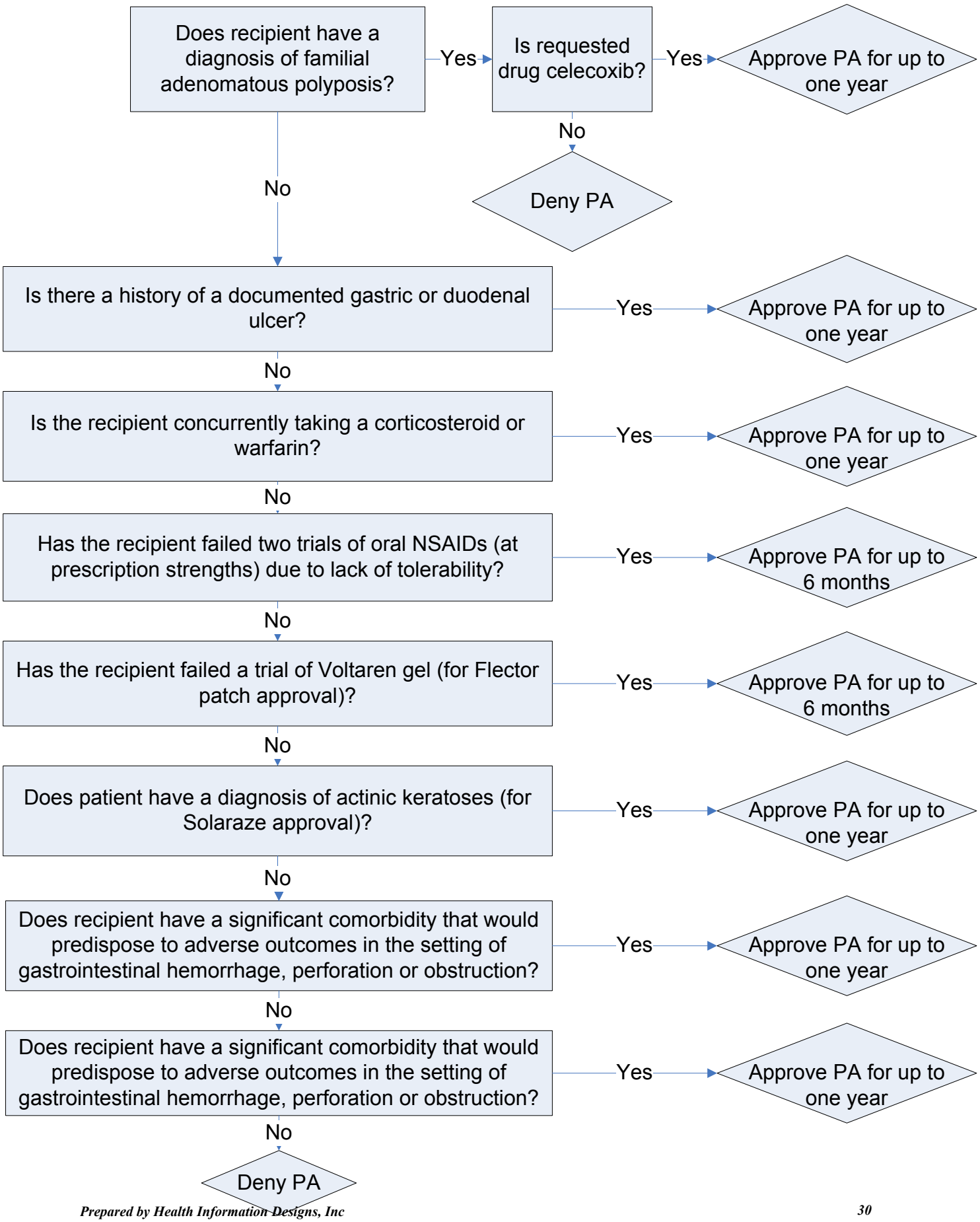
Part II: TO BE COMPLETED BY PHARMACY

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
Name Brand NSAID/COX-II Authorization Algorithm



Revatio/Adcirca
Prior Authorization 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 Revatio or Adcirca must have a diagnosis of Pulmonary Arterial Hypertension based on WHO (Group I) Classification for Pulmonary Hypertension.

****Note:***

- ***Patients taking Bosentan, Nitrates or Viagra/Levitra/Cialis will not receive a PA***

Part I: TO BE COMPLETED BY PRESCRIBER

Recipient Name	Recipient Date of Birth	Recipient Medicaid ID Number	
Prescriber Name			
Prescriber Medicaid Number	Telephone Number	Fax Number	
Address	City	State	Zip Code
Requested Drug and Dosage: □ **Revatio** □ **Adcirca**	**Diagnosis for this request:**		
Qualifications for coverage:			
□ Indication for the treatment of Pulmonary Arterial Hypertension (WHO Group I Classification)			
Prescriber Signature	Date		

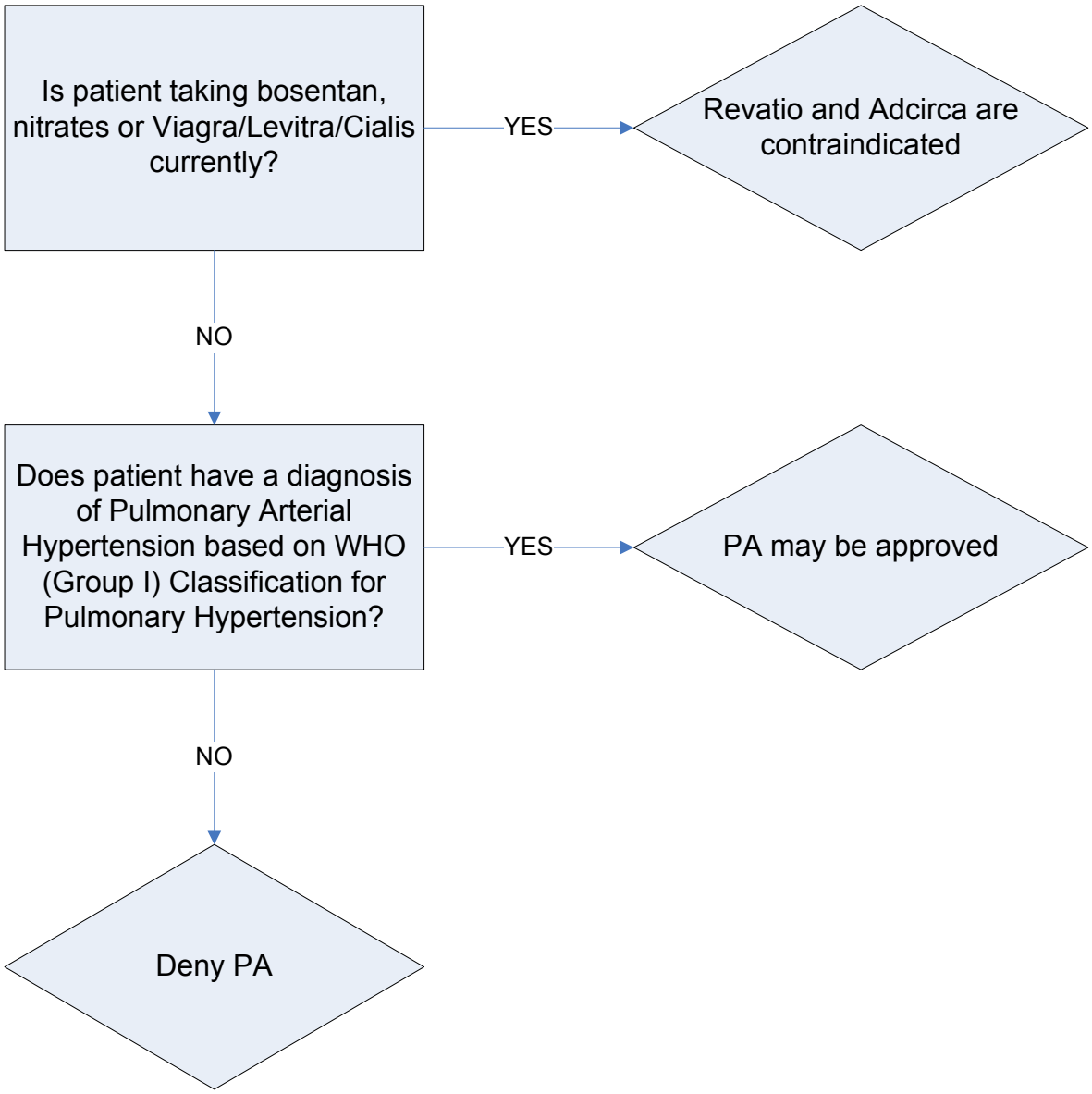
Part II: TO BE COMPLETED BY PHARMACY

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
Revatio/Adcirca Authorization Algorithm



ACTO*plus* met 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 receive Actos and Metformin separately.
Note:

- ***Actos does not require PA***
- ***Metformin does not require PA***
- ***Patients must fail therapy on Actos and Metformin separately 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: □ **ACTO*plus* met**	**Diagnosis for this request:**		
Qualifications for coverage:			
□ Failed both drugs separately	Start Date: End Date:	Dose: Frequency:	
Prescriber Signature		Date	

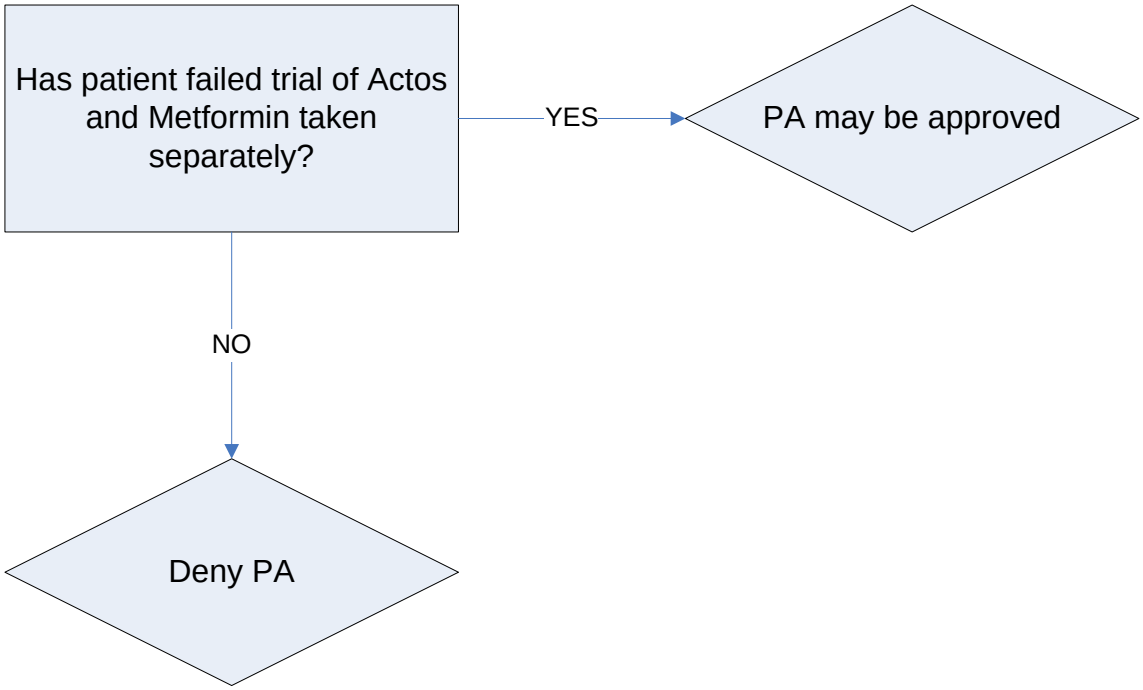
Part II: TO BE COMPLETED BY PHARMACY

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
ACTO*plus met* Authorization Algorithm



OPHTHALMIC ANTI-INFECTIVE
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 will not pay for Azasite or Quixin without documented failure of a first line antibiotic ophthalmic agent.

***Note: First line agents include sulfacetamide (Bleph 10®, etc.), erythromycin, bacitracin-polymixin B (Polysporin®), polymyxin B neomycin-gramicidin (Neosporin®), trimethoprim-polymyxin B (Polytrim®), gentamicin (Garamycin®, etc.), ofloxacin (Ocuflox®) and ciprofloxacin (Ciloxan®).**

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: □ AZASITE □ QUIXIN	**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.*			
Prescriber Signature		Date	

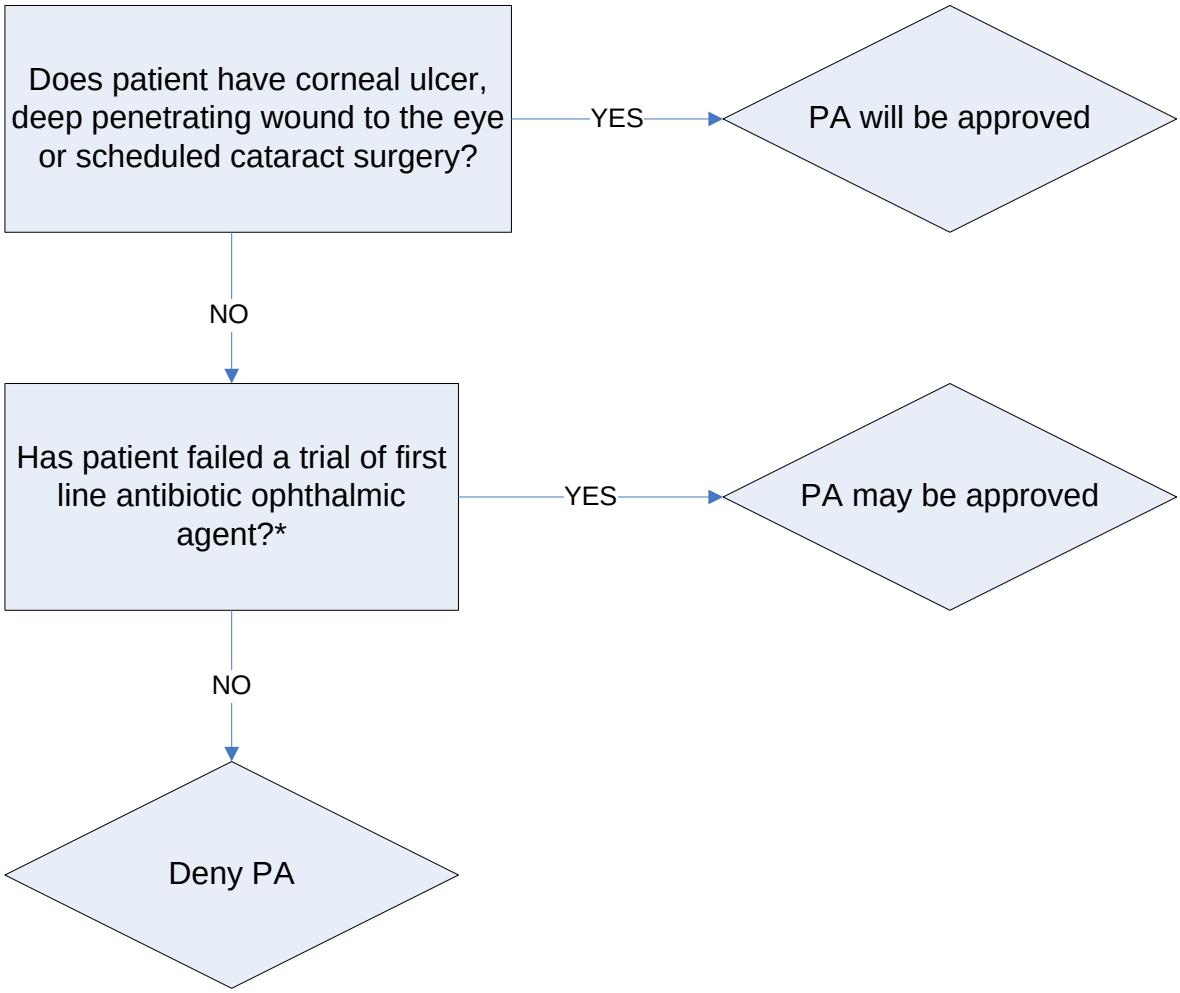
Part II: TO BE COMPLETED BY PHARMACY

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
Ophthalmic Anti-infective Authorization Algorithm



*First line agents include: sulfacetamide (Bleph 10, etc.), erythromycin, bacitracin-polymixin B (Polysporin), polymyxin B-neomycin-gramicidin (Neosporin), trimethoprim-polymyxin B (Polytrim), gentamicin (Garamycin, etc.), ofloxacin (Ocuflox), and ciprofloxacin (Ciloxan).

CARISOPRODOL 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 using carisoprodol 350mg longer than two times per year (272 tablets) must receive a prior authorization. Cyclobenzaprine, chlorzoxazone, methocarbamol and orphenadrine do not require a prior authorization.

***Note:**

- **PA will be approved if recipient is currently taking carisoprodol on a chronic basis and provider is weaning patient.**

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: □ CARISOPRODOL	**Diagnosis for this request:**		
Qualifications for coverage:			
□ CHRONIC CARISOPRODOL RECIPIENT BEING WEANED (PLEASE INCLUDE WEANING SCHEDULE)	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		

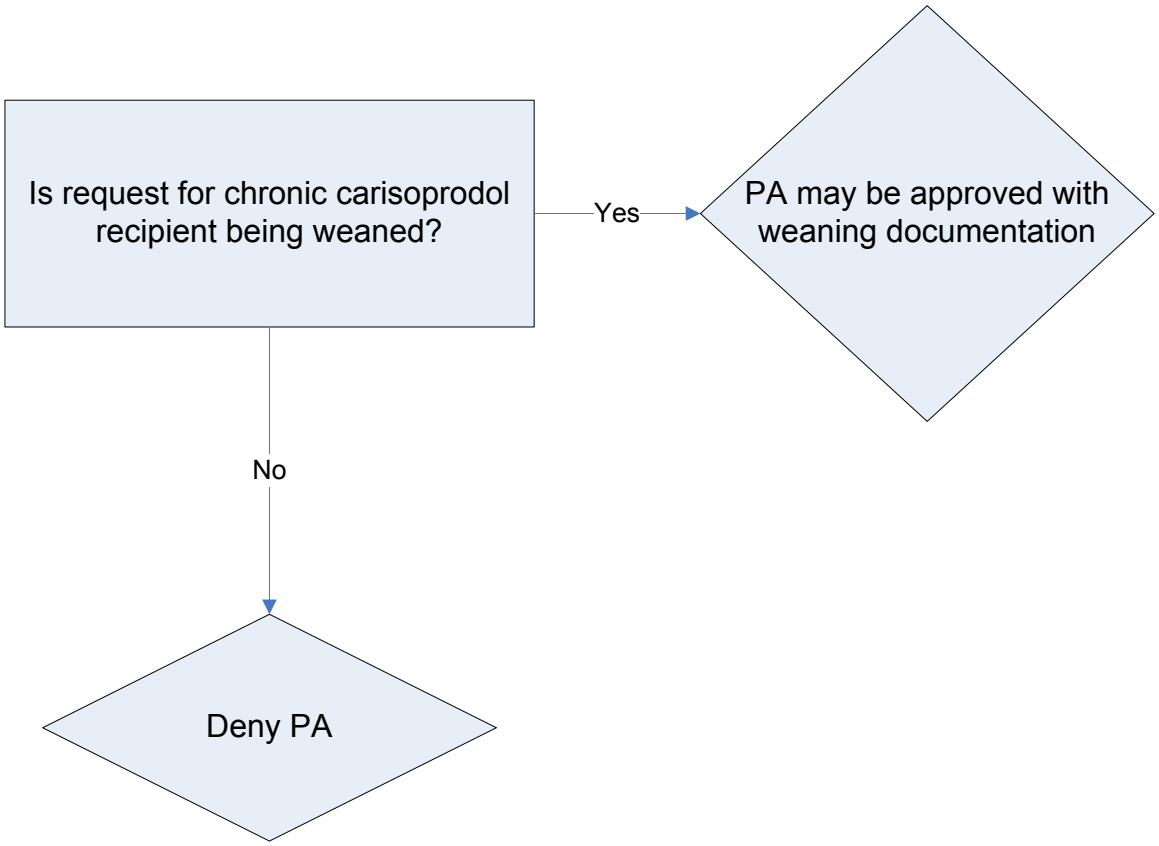
Part II: TO BE COMPLETED BY PHARMACY

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
Carisoprodol Authorization Algorithm



BLOOD FACTOR PRODUCTS 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 blood factor products must provide the following information:

- Visit once per year with an accredited Hemophilia Treatment Center
- Date of last appointment with treatment center
- Contact information for treatment center

Part I: TO BE COMPLETED BY PRESCRIBER

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 :	**DOSAGE:**		
Qualifications for coverage:			
TREATMENT CENTER CONTACT INFORMATION:	DATE OF LAST APPOINTMENT WITH TREATMENT CENTER: _____		
Prescriber Signature:		Date:	

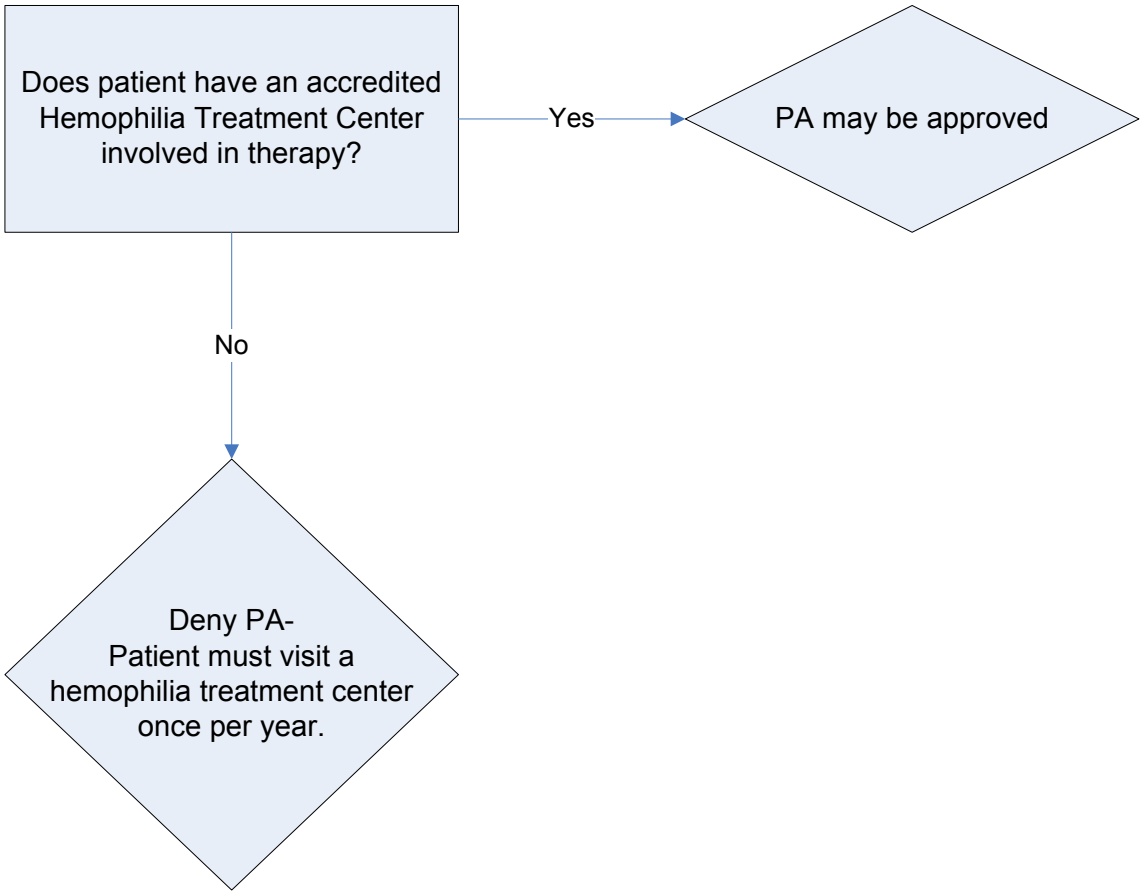
Part II: TO BE COMPLETED BY PHARMACY

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
Blood Factor Products Authorization Algorithm



Relistor 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 Relistor must meet the following guidelines:

- Diagnosis of opioid-induced constipation
- Inability to tolerate oral medications *or*
- Failed two oral medications

Note:
***Polyethylene glycol powder is covered without a prior authorization.**

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: □ **Relistor**	**Diagnosis for this request:**		
Qualifications for coverage:			
FIRST FAILED MEDICATION	START DATE:	END DATE:	
SECOND FAILED MEDICATION	START DATE:	END DATE:	
□ INABILITY TO TOLERATE ORAL MEDICATIONS			
Prescriber Signature		Date	

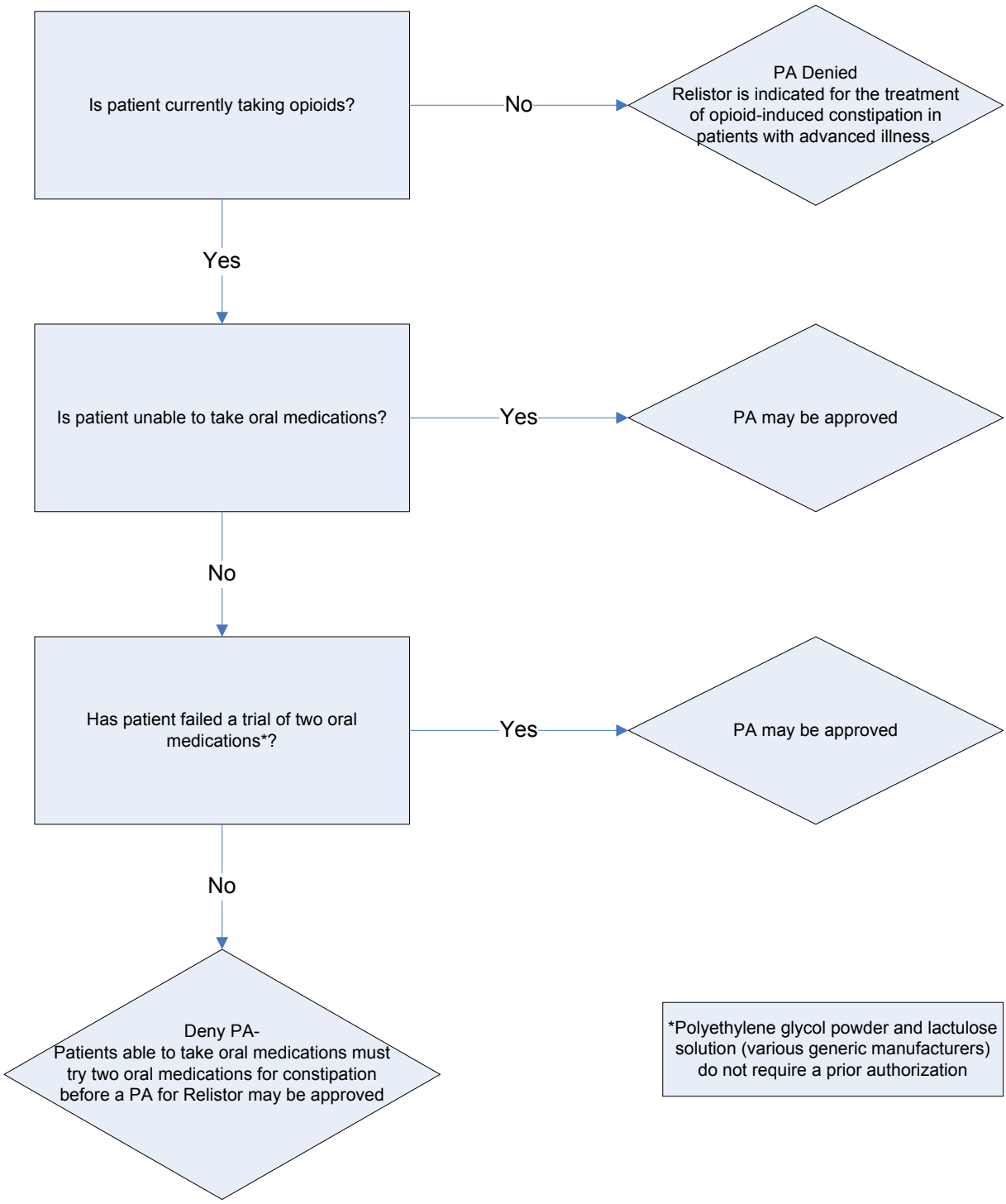
Part II: TO BE COMPLETED BY PHARMACY

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
Relistor Authorization Algorithm



Sancuso 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 Sancuso must be unable to take oral medications.
Note:

- ***Dolasetron, oral granisetron, and ondansetron do not require PA.***
- ***Patients must be unable to take oral medications or***
- ***Patients must fail therapy on ondansetron or oral granisetron 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: □ **Sancuso**	**Diagnosis for this request:**		
Qualifications for coverage:			
□ FAILED MEDICATION	START DATE: END DATE:	DOSE: FREQUENCY:	
□ PATIENT UNABLE TO TAKE ORAL MEDICATIONS			
Prescriber Signature		Date	

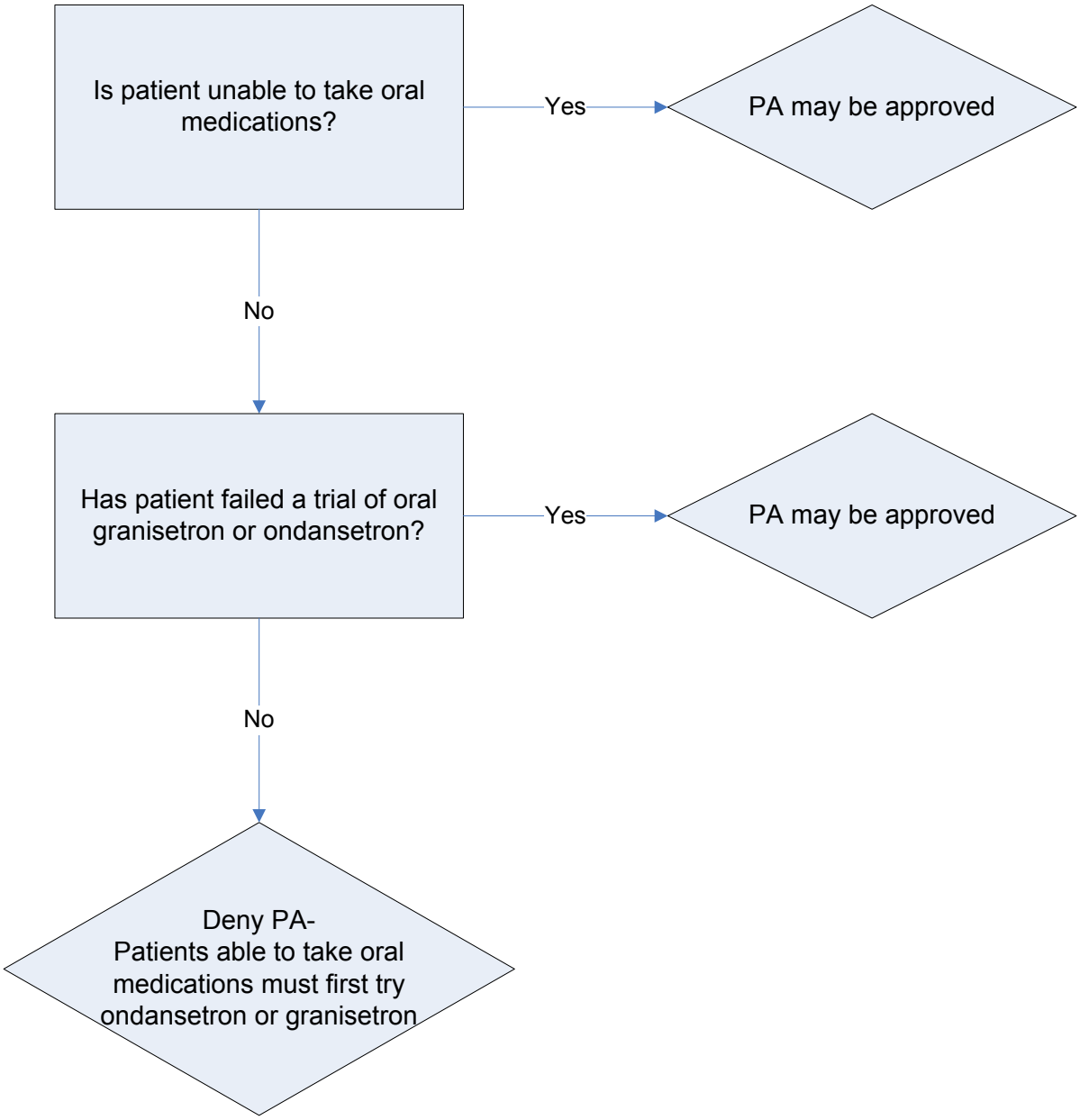
Part II: TO BE COMPLETED BY PHARMACY

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
Sancuso Authorization Algorithm



HEALTH INFORMATION DESIGNS

Prior Authorization Vendor for ND Medicaid

Nuvigil Prior Authorization

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 Nuvigil must suffer from excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome, narcolepsy, or shift work disorder.

- **Provigil is covered without a prior authorization.**

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: □ **Nuvigil**	**Diagnosis for this request:**		
Qualifications for coverage:			
□ FAILED PROVIGIL (MODAFINIL)	START DATE: END DATE:	DOSE: FREQUENCY:	
□ EXCESSIVE SLEEPINESS ASSOCIATED WITH OBSTRUCTIVE SLEEP APNEA/HYPOPNEA SYNDROME □ NARCOLEPSY □ SHIFT WORK SLEEP DISORDER			
Prescriber Signature		Date	

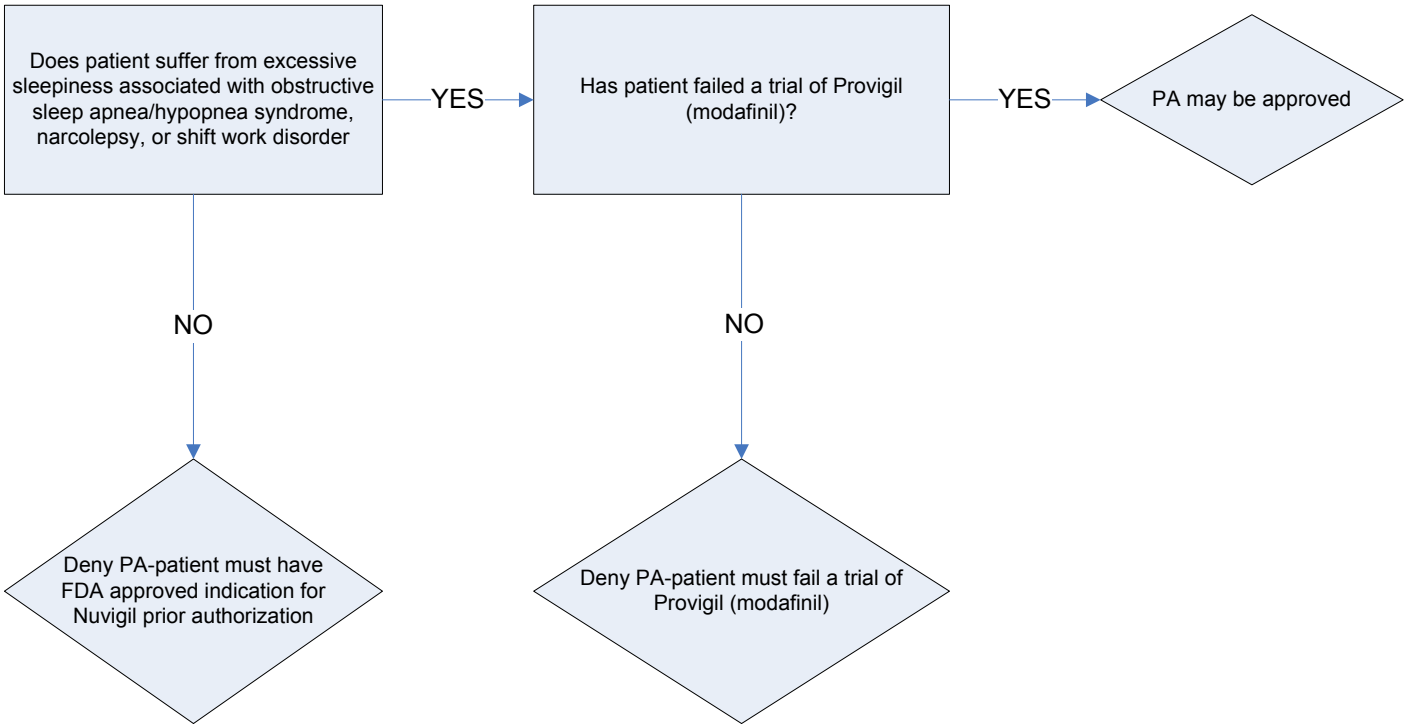
Part II: TO BE COMPLETED BY PHARMACY

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
Nuvigil Authorization Algorithm



Nucynta Prior Authorization

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 Nucynta must be unable to tolerate other opioids due to gastrointestinal side effects.

- **Oxycodone is covered without a prior authorization.**

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: □ **Nucynta**	**Diagnosis for this request:**		
Qualifications for coverage:			
□ UNABLE TO TOLERATE OTHER OPIOIDS DUE TO GASTROINTESTINAL SIDE EFFECTS OPIOID TRIED_____ START DATE: DOSE: END DATE: FREQUENCY:			
Prescriber Signature		Date	

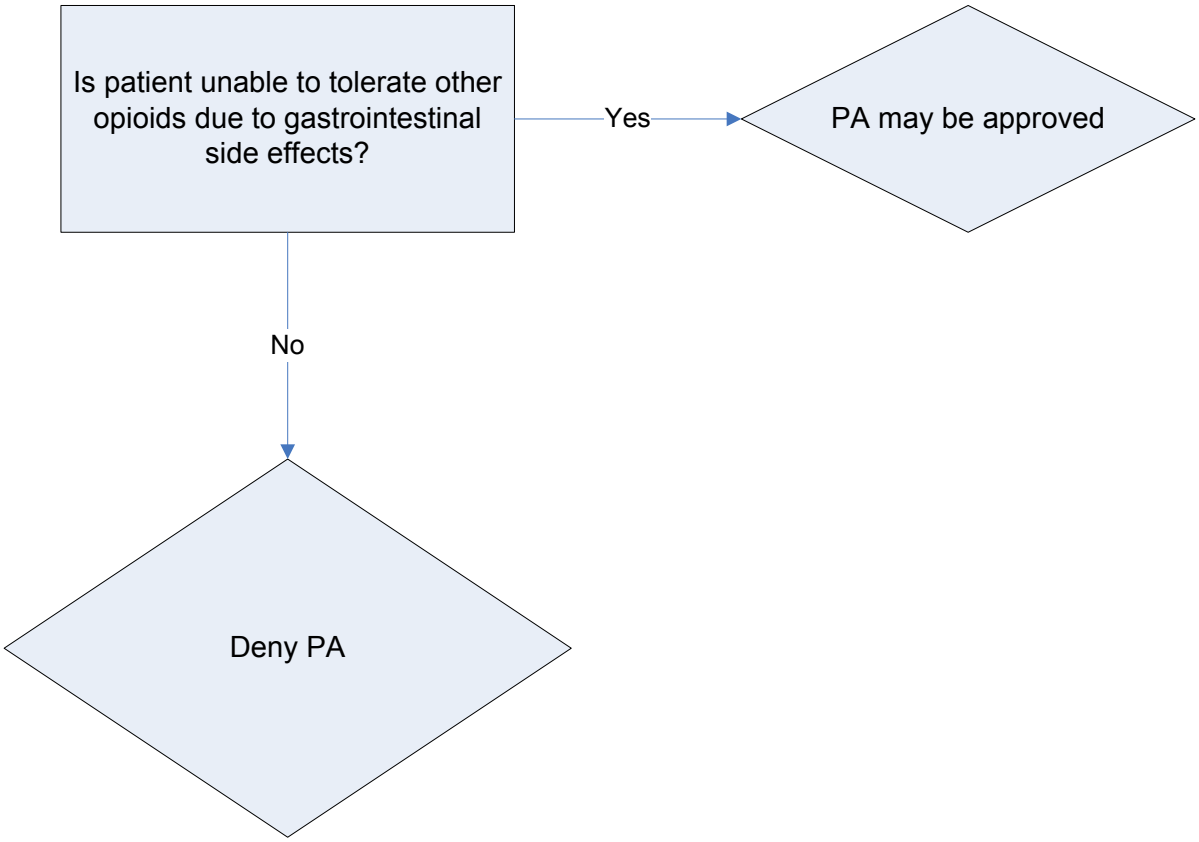
Part II: TO BE COMPLETED BY PHARMACY

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
Nucynta Authorization Algorithm



North Dakota Medicaid
DUR Board Meeting
Nuedexta® Review

I. Overview

Nuedexta is the first drug to be approved for the treatment of people with symptoms of pseudobulbar affect, or the loss of emotional control. Pseudobulbar affect occurs secondary to a variety of neurological conditions and is characterized by involuntary, sudden, and frequent episodes of laughing or crying.

II. Indications and Usage

Nuedexta is a combination product containing dextromethorphan hydrobromide and quinidine sulfate indicated for pseudobulbar affect (PBA). Studies to support the effectiveness of Nuedexta were performed in patients with underlying amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS). Nuedexta has not been shown to be safe or effective in people with other diseases that can be associated with episodic emotional outbursts, such as Alzheimer's disease and other forms of dementia.

III. Dosage and Administration

The recommended starting dose of Nuedexta is one capsule daily by mouth for the initial seven days of therapy. On the eighth day of therapy and thereafter, the daily dose should be a total of two capsules a day, given as one capsule every 12 hours.

The need for continued treatment should be reassessed periodically, as spontaneous improvement of PBA occurs in some patients.

IV. Pharmacology

Dextromethorphan (DM) is a sigma-1 receptor agonist and an uncompetitive NMDA receptor antagonist. Quinidine increases plasma levels of dextromethorphan by competitively inhibiting cytochrome P450 2D6, which catalyzes a major biotransformation pathway for dextromethorphan. The mechanism by which dextromethorphan exerts therapeutic effects in patients with PBA is unknown.

V. Pharmacokinetics

Both dextromethorphan and quinidine are metabolized primarily by liver enzymes. Quinidine's primary pharmacological action in Nuedexta is to competitively inhibit the metabolism of dextromethorphan catalyzed by CYP2D6 in order to increase and prolong plasma concentrations of dextromethorphan.

- Following single and repeated combination doses of dextromethorphan hydrobromide 30mg/quinidine sulfate 10mg, dextromethorphan hydrobromide/quinidine sulfate-treated subjects had an approximately 20-fold increase in dextromethorphan exposure compared to dextromethorphan given without quinidine.

- Maximal plasma concentrations of dextromethorphan are reached approximately 3 to 4 hours after dosing and maximal plasma concentrations of quinidine are reached approximately 1 to 2 hours after dosing.

- Dextromethorphan is approximately 60-70% protein bound and quinidine is approximately 80-89% protein bound.

- Dextromethorphan is metabolized by CYP2D6 and quinidine is metabolized by CYP3A4. In extensive metabolizers, the elimination half-life of dextromethorphan was approximately 13 hours and the elimination half-life of quinidine was approximately 7 hours.

VI. Contraindications

- Nuedexta should not be used concomitantly with other drugs containing quinidine, quinine, or mefloquine.

- Nuedexta is contraindicated in patients with a history of quinine, mefloquine or quinidine-induced thrombocytopenia, hepatitis, bone marrow depression or lupus-like syndrome. Nuedexta is also contraindicated in patients with a known hypersensitivity to dextromethorphan.

- Nuedexta is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious and possibly fatal drug interactions, including serotonin syndrome. Allow at least 14 days after stopping Nuedexta before starting and MAOI.

- Nuedexta is contraindicated in patients with a prolonged QT interval, congenital long QT syndrome or a history suggestive of torsades de pointes, and in patients with heart failure. Nuedexta is contraindicated in patients receiving drugs that both prolong QT interval and are metabolized by CYP2D6 (e.g., thioridazine and pimozide) as effects on QT interval may be increased.

- Nuedexta is contraindicated in patients with complete atrioventricular (AV) block without implanted pacemakers, or in patients who are at high risk of complete AV block.

VII. Warnings/Precautions

- **Thrombocytopenia and Other Hypersensitivity Reactions** – Quinidine can cause immune-mediated thrombocytopenia that can be severe or fatal. Non-specific symptoms, such as lightheadedness, chills, fever, nausea, and vomiting, can precede or occur with thrombocytopenia. Quinidine-associated thrombocytopenia usually, but not always, resolves within a few days of discontinuation of the sensitizing drug.

- **Hepatotoxicity** – Hepatitis, including granulomatous hepatitis, has been reported in patients receiving quinidine, generally during the first few weeks of therapy. Fever may be a presenting symptom, and thrombocytopenia or other signs of hypersensitivity may also occur. Most cases remit when quinidine is withdrawn.

- **Cardiac Effects** – Nuedexta causes dose-dependent QT_c prolongation. OT prolongation can cause torsades de pointes-type ventricular tachycardia, with the risk increasing as the degree of prolongation increases. When initiating Nuedexta in patients at risk of QT prolongation and torsades de pointes, electrocardiographic (ECG) evaluation of QT interval should be conducted at baseline and 3-4 hours after the first dose. This includes patients concomitantly taking/initiating drugs that prolong the QT interval or that are strong or moderate CYP3A4 inhibitors, and patients with left ventricular hypertrophy (LVH) or left ventricular dysfunction (LVD). LVH and LVD are more likely to be present in patients with chronic hypertension, known coronary artery disease, or history of stroke.

- **Concomitant use of CYP2D6 Substrates** – The quinidine in Nuedexta inhibits CYP2D6 in patients in whom CYP2D6 is not otherwise genetically absent or its activity otherwise pharmacologically inhibited. (poor metabolizers) Because of this effect on CYP2D6, accumulation of parent drug and /or failure of active metabolite formation may decrease the safety and/or the efficacy of drugs used concomitantly with Nuedexta that are metabolized by CYP2D6.

- **Dizziness** – Nuedexta may cause dizziness. Precautions to reduce the risk of falls should be taken, particularly for patients with motor impairment affecting gait or a history of falls.

- **Serotonin Syndrome** – When used with SSRIs or tricyclic antidepressants, Nuedexta may cause serotonin syndrome, with changes including altered mental status, hypertension, restlessness, myoclonus, hyperthermia, hyperreflexia, diaphoresis, shivering, and tremor.

- **Anticholinergic Effects of Quinidine** – Monitor for worsening clinical condition in myasthenia gravis and other conditions that may be adversely affected by anticholinergic effects.

- **CYP2D6 Poor Metabolizers** – The quinidine component of Nuedexta is intended to inhibit CYP2D6 so that higher exposure to dextromethorphan can be achieved compared to when dextromethorphan is given alone. Approximately 7-10% of Caucasians and 3-8% of African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers. The quinidine component of Nuedexta is not expected to contribute to the effectiveness of Nuedexta in poor metabolizers, but adverse effects of the quinidine are still possible. In those patients who may be at risk of significant toxicity due to quinidine, genotyping to determine if they are poor metabolizers should be considered prior to making the decision to treat with Nuedexta.

VIII. Adverse Reactions

Adverse Drug Reactions with an Incidence of ≥ 3% of Patients and ≥ 2x Placebo in Nuedexta-treated Patients

	Nuedexta	**Placebo**
	N=107	N=109
Diarrhea	13	6
Dizziness	10	5
Cough	5	2
Vomiting	5	1
Asthenia	5	2
Peripheral edema	5	1
Urinary tract infection	4	1
Influenza	4	1
Increased gamma-glutamyltransferase	3	0
Flatulence	3	1

IX. Drug Interactions

- MAOIs
- Drugs that Prolong QT and are Metabolized by CYP2D6
- Drugs that Prolong QT and Concomitant CYP3A4 Inhibitors
- SSRIs and Tricyclic Antidepressants
- CYP2D6 Substrate
- Digoxin
- Alcohol

References

1. Nuedexta [prescribing information]. Aliso Viejo, CA: Avanir Pharmaceuticals; October 2010.

North Dakota Medicaid
DUR Board Meeting
Nexiclon XR® Review

I. Indication

Nexiclon XR is indicated in the treatment of hypertension.

II. Dosage and Administration

The dose of Nexiclon XR should be initiated at 0.17mg once daily. Initial dose is recommended to be administered at bedtime.

Further increments of 0.09mg once daily may be made at weekly intervals if necessary until the desired response is achieved. The therapeutic doses most commonly employed have ranged from 0.17mg to 0.52mg once daily. Doses higher than 0.52mg per day were not evaluated and are not recommended.

III. Pharmacology

Clonidine stimulates alpha-adrenoreceptors in the brain system. This action results in reduced sympathetic outflow from the central nervous system and in decreases in peripheral resistance, renal vascular resistance, heart rate, and blood pressure.

IV. Pharmacokinetics

Following single doses of Nexiclon XR 0.17mg, clonidine mean peak plasma concentrations of 0.49ng/mL occurred at 7.8 hours. The plasma half-life of clonidine was 13.7 hours. The half-life may increase up to 41 hours in patients with severe impairment of renal function. Following oral administration of clonidine, about 40-60% of the absorbed dose is recovered in the urine as unchanged drug in 24 hours. About 50% of the absorbed dose is metabolized in the liver.

V. Warnings/Precautions

- **Withdrawal** – Instruct patients not to discontinue therapy without consulting their physician. Sudden cessation of clonidine treatment has resulted in symptoms such as nervousness, agitation, headache and tremor accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma. When discontinuing therapy, reduce the dose gradually over 2 to 4 days to avoid withdrawal symptoms.

- **General Precautions** – In patients who have developed localized sensitization or an allergic reaction to a clonidine transdermal system, substitution of oral clonidine therapy may be associated with the development of a generalized skin

rash. Monitor carefully and up-titrate slowly in patients with severe coronary insufficiency, conduction disturbances, recent myocardial infarction, cerebrovascular disease, or chronic renal failure. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of a possible sedative effect of clonidine. The sedative effect may be increased by concomitant use of alcohol, barbiturates, or other sedating drugs.

- **Perioperative Use** – Nexiclon XR may be administered up to 28 hours prior to surgery and resumed the following day. Blood pressure should be carefully monitored during surgery and additional measures to control blood pressure should be available if required.

VI. Adverse Reactions

Most adverse reactions are mild and tend to diminish with continued therapy. The most frequent (which also appear to be dose-related) are dry mouth (approximately 40%); drowsiness (approximately 33%); dizziness (approximately 16%); constipation and sedation (approximately 10% each).

VII. Drug Interactions

No drug interaction studies have been conducted with Nexiclon XR. The following have been reported with other oral formulations of clonidine.

- Clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates, or other sedating drugs. If a patient receiving clonidine is also taking tricyclic antidepressants, the hypotensive effect of clonidine may be reduced, necessitating an increase in the clonidine dose.
- Monitor heart rate in patients receiving clonidine concomitantly with agents know to affect sinus node function or AV nodal conduction, e.g., digitalis, calcium channel blockers, and beta-blockers. Sinus bradycardia resulting in hospitalization and pacemaker insertion has been reported in association with the use of clonidine concomitantly with diltiazem or verapamil.
- Amitriptyline in combination with clonidine enhances the manifestation of corneal lesions in rats.
- Based on *in vitro* studies, high concentrations of alcohol may increase the rate of release of Nexiclon XR.

References

1. Nexiclon XR [prescribing information]. Cupertino, CA: NextWave Pharmaceuticals, Inc; October 2010.

North Dakota Medicaid
DUR Board Meeting
Topical Ketoconazole Agents

I. Description

Ketoconazole is an imidazole antifungal agent. It was approved by the FDA in 1981 and is available in oral tablets, 2% topical cream, 2% shampoo, 2% foam, and a 2% gel.

II. Indications/Dosage

For the treatment of seborrheic dermatitis:
Topical dosage (2% gel, Xolegel):
Adults, adolescents, and children ≥ 12 years: Apply a sufficient amount to the affected areas once daily for 2 weeks.

Topical dosage (2% foam, Extina):
Adults, adolescents, and children ≥ 12 years: Apply a sufficient amount to the affected areas twice daily for 4 weeks.

Topical dosage (2% cream co-packaged with hydrocortisone 1% gel, Ketocon Plus)
Apply a sufficient amount to the affected areas once to twice daily for two – six weeks.

III. Pharmacology

Like other azole antifungals, ketoconazole exerts its effect by altering the fungal cell membrane. Ketoconazole inhibits ergosterol synthesis by interacting with 14-alpha demethylase, a cytochrome P-450 enzyme that is necessary for the conversion of lanosterol to ergosterol, an essential component of the membrane.

IV. Warnings/Precautions

- Combination products containing corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression if applied over large surface areas, associated with prolonged use, used under occlusive dressings, or used in combination with other topical corticosteroids. If HPA suppression is noted, reduce application frequency or discontinue the drug.

- Due to the alcohol content of Xolegel and the alcohol, butane, and propane content of Extina foam, avoid fire, flame, or tobacco smoking during and immediately after the use of these products.

V. Adverse Reactions

After topical application of ketoconazole cream, the most commonly reported adverse reaction is skin irritation (i.e., pruritus, burning, and stinging), while rare reports of contact dermatitis have been noted in post-marketing reports.

Ketoconazole topical foam (Extina) was associated with an increased incidence of contact sensitization, including photosensitivity in dermal safety studies. Application site reaction (6%) and burning (10%) were reported with ketoconazole foam. Dryness, erythema, pruritus, rash, and warmth were all noted in ≤ 1% of patients using ketoconazole foam.

The most common adverse reactions associated with the ketoconazole topical gel (Xolegel) include application site burning (4%), dermatitis (< 1%), discharge (< 1%), dryness (< 1%), erythema (< 1%), irritation (< 1%), pain (< 1%), pruritus (< 1%), pustules (< 1%), impetigo (< 1%), pyogenic granuloma (< 1%), acne (< 1%), and nail discoloration (< 1%).

VI. Drug Interactions

Significant drug interactions with the topical agents have not been noted.

VII. Cost Comparison

The average cost per script for ketoconazole cream and shampoo is $26.00. The average cost per script of Extina is $344.39 (100gm) and $184.86 (50gm). The average cost per script of Xolegel is $334.24 (45gm) and $105.53 (15gm). The average cost per script of Ketocon Plus is $253.79 (102.53gm).

References

1. Xolegel[prescribing information]. Research Triangle Park, NC: Steifel Laboratories, Inc.; November 2010.
2. Extina [prescribing information]. Research Triangle Park, NC: Steifel Laboratories, Inc.; November 2008.
3. Wolters Kluwer Health, Inc. Drug Facts and Comparisons. St. Louis, MO. 2010.
4. Clinical Pharmacology, 2011 Gold Standard.

North Dakota Medicaid
DUR Board Meeting
Granisol® Review

I. Overview

Granisetron is an oral, parenteral, and transdermal antiemetic agent. It is commonly used to offset nausea and vomiting from highly emetogenic cancer chemotherapy. Granisetron is similar to ondansetron in activity, efficacy, and adverse effects. Despite its effectiveness, granisetron is not recommended for the routine treatment of nausea due to its significant cost relative to other anti-nauseants.

II. Indications and Usage

Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy including high-dose cisplatin. Prevention of nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation.

III. Dosage and Administration

The recommended adult dosage is 2mg once daily or 1mg twice daily. In the 2mg once-daily regimen, 10mL of oral solution (2 teaspoonfuls, equivalent to 2mg) is given up to 1 hour before chemotherapy. In the 1mg twice-daily regimen, the first teaspoonful (5mL) of solution is given up to 1 hour before chemotherapy, and the second teaspoonful (5mL), 12 hours after the first. Either regimen is administered only on the day(s) chemotherapy is given.

Measure dose with a calibrated oral syringe or other calibrated container.

IV. Pharmacology

Granisetron is a selective 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT$_1$; 5-HT$_{1A}$; 5-HT$_{1B/C}$; 5-HT$_2$; for alpha1-, alpha2-, or beta-adrenoreceptors; for dopamine-D2; or for histamine-H1; benzodiazepine; picrotoxin or opioid receptors.

Serotonin receptors of the 5-HT$_3$ type are located peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. During chemotherapy that induces vomiting, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT3 receptors. This evokes vagal afferent discharge, inducing vomiting. Animal studies demonstrate that, in binding to 5-HT3 receptors, granisetron blocks serotonin stimulation and subsequent vomiting after emetogenic stimuli such as cisplatin.

V. Pharmacokinetics

Granisetron distributes freely between plasma and erythrocytes. Approximately 65% of the drug is protein bound.

Granisetron metabolism involves N-demethylation and aromatic ring oxidation followed by conjugation. Because in vitro studies have shown that the primary route of metabolism of granisetron is inhibited by ketoconazole, the cytochrome P-450 system is probably a metabolic pathway of the drug.

VI. Warnings/Precautions

- Because QT prolongation has been reported, Granisol should be used with caution in patients with pre-existing arrhythmias or cardiac conduction disorders.

- The use of granisetron in patients after abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may make a progressive ileus, GI obstruction, and/or gastric distension.

- Patients with hepatic disease, hepatitis, and elevated hepatic enzymes should be observed closely while receiving granisetron since the primary route of metabolism is via hepatic pathways.

VII. Drug Interactions

Granisetron has been associated with QT prolongation. According to the manufacturer, the use of granisetron in patients concurrently treated with drugs known to prolong the QT interval and/or are arrhythmogenic, may result in clinical consequences.

VIII. Adverse Reactions

	Granisol (%)
Hepatic function abnormalities	5-6
Headache	14-21
Hypotension	≤ 1
Hypertension	1-2
Diarrhea	4-9
Constipation	18
Asthenia	14
Abdominal pain	6
Dizziness	5
Insomnia	5
Anxiety	2
Agitation	<2
CNS stimulation	<2
Drowsiness	1

IX. Cost Comparison

The average cost per script for granisetron tablets is $232.51 (10-14 1mg doses). The average cost per script for Granisol is $322.89 (6-1mg doses).

References

1. Kytril [prescribing information]. Nutley, NJ: Roche Laboratories Inc.; March 2010.
2. Wolters Kluwer Health, Inc. Drug Facts and Comparisons. St. Louis, MO. 2010.
3. Clinical Pharmacology, 2011 Gold Standard.

NORTH DAKOTA MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS
1ST QUARTER 2011

Criteria Recommendations ***Approved Rejected***

1. Lurasidone / Overutilization _____ _____

Alert Message: Latuda (lurasidone) may be over-utilized. The manufacturer's maximum recommended dose is 80 mg once daily. Exceeding the recommended dose may increase the risk of adverse effects (e.g., akathisia, somnolence, dystonia, and parkinsonism).

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C (Negating)
Lurasidone		Moderate Renal Impairment
		Severe Renal Impairment
		Diltiazem
		Verapamil
		Aprepitant
		Fluconazole
		Erythromycin
		Chronic Liver Disease and Cirrhosis

Max Dose: 80 mg/day

References:
Latuda Prescribing Information, Oct. 2010, Sunovion Pharma, Inc.

2. Lurasidone / Moderate & Severe Renal and Hepatic Impairment _____ _____

Alert Message: Latuda (lurasidone) may be over-utilized. The manufacturer's recommends that the lurasidone dose should not exceed 40 mg once daily in patients with moderate to severe renal or hepatic impairment.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C (Include)
Lurasidone 80mg		Moderate Renal Impairment
		Severe Renal Impairment
		Chronic Liver Disease and Cirrhosis

Max Dose: 40 mg/day

References:
Latuda Prescribing Information, Oct. 2010, Sunovion Pharma, Inc.

3. Lurasidone / Non-adherence _____ _____

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

Conflict Code: LR - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Lurasidone		

References:
Latuda Prescribing Information, Oct. 2010, Sunovion Pharma, Inc.

4. Lurasidone / Strong CYP3A4 Inhibitors _____ _____

Alert Message: The concurrent use of Latuda (lurasidone) with a strong CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin and nefazodone) is contraindicated. Coadministration of lurasidone with ketoconazole was shown to significantly increase the Cmax and AUC of lurasidone (6.9 and 9 times, respectively).

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

Util A	Util B		Util C
Lurasidone	Ketoconazole	Atazanavir	
	Itraconazole	Saquinavir	
	Indinavir	Clarithromycin	
	Nelfinavir	Nefazodone	
	Ritonavir	Telithromycin	

References:
Latuda Prescribing Information, Oct. 2010, Sunovion Pharma, Inc.
Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine. Available at: http://medicine.iupui.edu/clinpharm/ddos/table.asp.
FDA: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.

5. Lurasidone / Strong 3A4 Inducers _____ _____

Alert Message: The concurrent use of Latuda (lurasidone) with a strong CYP3A4 inducer (e.g., rifampin, carbamazepine, and phenobarbital) is contraindicated. Coadministration of lurasidone with rifampin was shown to significantly decrease the Cmax and AUC of lurasidone as compared to that of lurasidone alone (1/7th and 1/5th, respectively).

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

Util A	Util B		Util C
Lurasidone	Rifampin	Nevirapine	
	Carbamazepine	Efavirenz	
	Phenytoin		
	Rifabutin		
	Phenobarbital		
	Dexamethasone		

References:
Latuda Prescribing Information, Oct. 2010, Sunovion Pharma, Inc.
Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine. Available at: http://medicine.iupui.edu/clinpharm/ddos/table.asp.

6. Lurasidone / Moderate 3A4 Inhibitors _____ _____

Alert Message: The dose of Latuda (lurasidone) should not exceed 40 mg/day when it is co-administered with a moderate CYP3A4 inhibitor (e.g., diltiazem, verapamil, aprepitant, erythromycin, fluconazole). Lurasidone is a CYP3A4 substrate and metabolic inhibition of this isozyme may result in increased lurasidone plasma concentrations and risk of adverse effects.

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

Util A	Util B		Util C
Lurasidone 80mg	Diltiazem	Erythromycin	
	Verapamil	Fluconazole	
	Aprepitant		

Max Dose: 40 mg/day

References:
Latuda Prescribing Information, Oct. 2010, Sunovion Pharma, Inc.

7. Lurasidone / Therapeutic Appropriateness _____ _____

Alert Message: The safety and effectiveness of Latuda (lurasidone) in pediatric patients have not been established.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Lurasidone		

Age Range: 0 – 17 yoa
References:
Latuda Prescribing Information, Oct. 2010, Sunovion Pharma, Inc.

8. Kapvay / Overuse _____ _____

Alert Message: Kapvay (clonidine extended-release) may be over-utilized. The manufacturer's recommended maximum daily dose is 0.4 mg/day.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Kapvay		

Age Range: 10 – 999 yoa
Max Dose: 0.4mg/day

References:
Kapvay Prescribing Information, 2010, Shionogi Pharma, Inc.

9. Kapvay / Non-adherence _____ _____

Alert Message: Based on refill history, your patient may be underutilizing Kapvay (clonidine extended-release). Non-adherence to the prescribed dosing regimen may result in sub-therapeutic effects, which may lead to decreased patient outcomes and additional healthcare costs. Also, abrupt discontinuation of clonidine may result in withdrawal effects.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Kapvay		

References:
Kapvay Prescribing Information, 2010, Shionogi Pharma, Inc.

10. Kapvay / Therapeutic Duplication _____ _____

Alert Message: Kapvay (clonidine extended-release) should not be used with other clonidine-containing products (e.g., Catapres, Catapres TTS) due to the potential for additive adverse effects (e.g., hypotension, syncope).

Conflict Code: TD - Therapeutic Duplication
Drugs/Diseases

Util A	Util B	Util C
Kapvay	Clonidine IR	
	Clonidine Transdermal	

References:
Kapvay Prescribing Information, 2010, Shionogi Pharma, Inc.

11. Silenor / Overuse _____ _____

Alert Message: Silenor (doxepin) may be over-utilized. The manufacturer's recommended maximum daily dose is 6 mg, 30 minutes before bedtime.

Conflict Code: ER - Overutilization
Drugs/Diseases
Util A Util B Util C
Silenor

Max Dose: 6mg/day

References:
Facts & Comparisons, 2010 Updates.
Silenor Prescribing Information, March 2010, Somaxon Pharmaceuticals.

DUR Board Meeting
June 6, 2011
Heritage Center
State Capitol

North Dakota Medicaid
DUR Board Meeting
Agenda
Pioneer Room
State Capitol
June 6, 2011
1pm

1. Administrative items
    - Travel vouchers

2. Old business
    - Review and approval of minutes of 03/07/11 meeting — Chair
    - Budget update — Brendan
    - Second review of Nuedexta — Brendan
    - Second review of Nexiclon — Brendan
    - Second review of topical ketoconazole products (Extina, Xolegel, Ketocon Plus) — Brendan
    - Yearly PA review — HID
        - Sedative/Hypnotics
        - Qualaquin
        - ACE-I/ARB/Renin Inh
        - Synagis
        - GH/IGF-1
        - Triptans

3. New business
    - Review of Desoxyn — HID
    - Review of Colcrys — HID
    - Review of Asacol HD — HID
    - Review of Ophthalmic Antihistamines — HID
    - Review of Horizant — HID
    - Review of Daliresp
    - Review of Narcotics with high dose APAP — 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
March 7, 2011

Members Present: Norman Byers, Carrie Sorenson, Jeffrey Hostetter, John Savageau, David Clinkenbeard, Russ Sobotta, Cheryl Huber, Kim Krohn, Greg Pfister, Patricia Churchill, Steve Irsfeld
Members Absent: James Carlson, 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 1:08 pm. Chair, G. Pfister asked for a motion to approve the minutes from the December meeting. J. Hostetter moved that the minutes be approved and C. Huber 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. The budget is currently going through the legislative process.

Statin Second Review
A motion and second were made at the December meeting to place any new statin products 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.

Gilenya Second Review
A motion and second were made at the December meeting to place Gilenya 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.

Xyrem Second Review
A motion and second were made at the December meeting to place Xyrem 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. Antihistamines, PPIs, COX-II/NSAIDs, Revatio, Actoplus Met, Azasite/Quixin, Carisoprodol, Blood factors, Relistor, Sancuso, Nuvigil and Nucynta forms and criteria were reviewed. No changes were made to the forms or criteria that were reviewed.

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

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

Topical Ketoconazole Products Review
B. Joyce reviewed topical ketoconazole product information with the Board. There was no public comment. After discussion, S. Irsfeld made a motion to place topical ketoconazole products on prior authorization. C. Sorenson seconded the motion. This topic will be brought up at the next meeting for finalization.

Granisol Review
B. Joyce reviewed Granisol information with the Board. There was no public comment. After discussion, J. Hostetter made a motion to place Granisol on prior authorization and include it on the Sancuso form. C. Huber 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. S. Irsfeld 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 June 6, 2011. J. Hostetter made a motion to adjourn the meeting. C. Huber seconded. The motion passed with no audible dissent. Chair G. Pfister adjourned the meeting at 2:15 pm.

Nuedexta 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 Nuedexta must have a diagnosis of amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS) and exhibit signs of pseudobulbar affect.

Note:

- ***Nuedexta is indicated for the treatment of pseudobulbar affect (PBA).***
- ***Nuedexta has not been shown to be safe or effective in other types of emotional lability that can commonly occur, for example, in Alzheimer's disease and other dementias.***
- ***Nuedexta is contraindicated in patients with a prolonged QT interval, heart failure, or complete atrioventricular (AV) block.***

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: □ **Nuedexta**	**Diagnosis for this request (must check at least 2):** □ **PBA** □ **ALS** □ **MS**		
Physician Signature		Date	

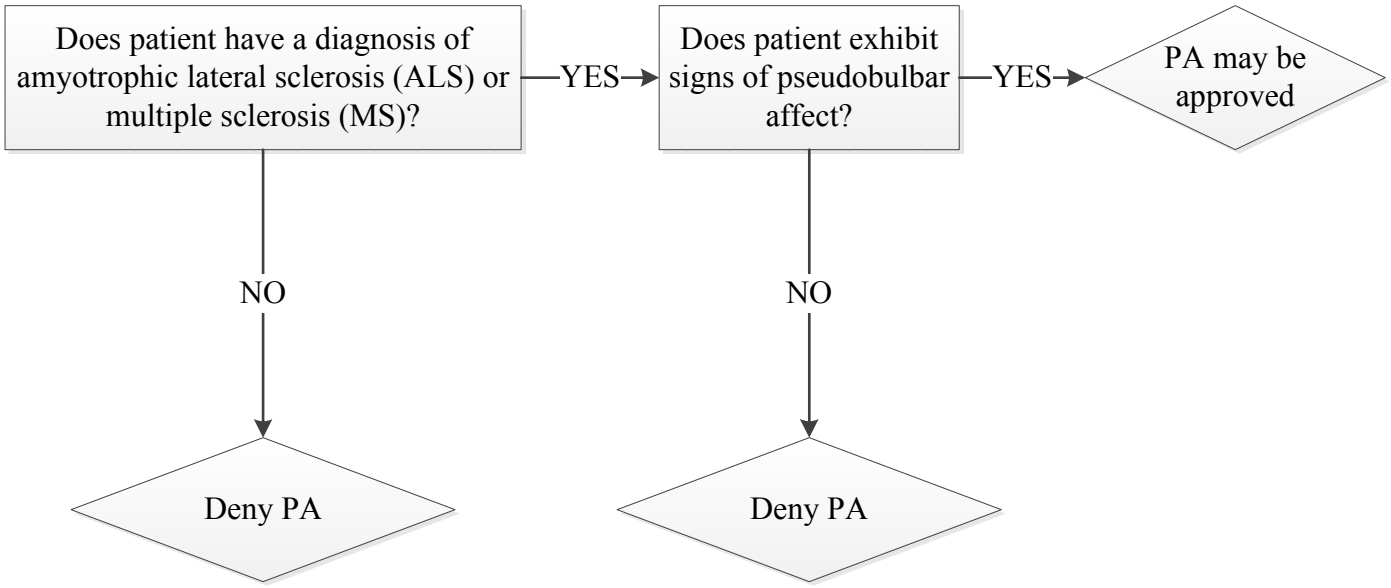
Part II: TO BE COMPLETED BY PHARMACY

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
Nuedexta Authorization Algorithm



Nexiclon 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 Nexiclon must try and fail clonidine.
Note:

- ***Clonidine does not require 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: □ **Nexiclon**	**Diagnosis for this request:**		
Qualifications for coverage:			
□ FAILED CLONIDINE THERAPY START DATE: END DATE:	DOSE: FREQUENCY:		
Physician Signature		Date	

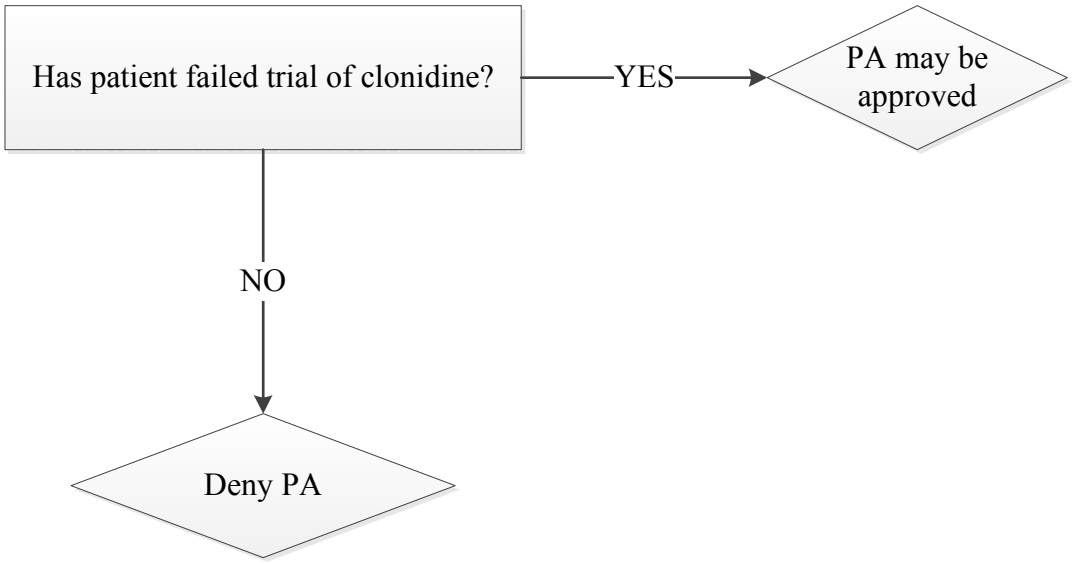
Part II: TO BE COMPLETED BY PHARMACY

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
Nexiclon Authorization Algorithm



Topical Ketoconazole Products
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 who are prescribed Extina, Xolegel, and Ketocon Plus must first try a covered ketoconazole medication.

Note:

- ***Ketoconazole creams and ketoconazole shampoos 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: □ **Extina** □ **Xolegel** □ **Ketocon Plus**	**Diagnosis for this request:**		
Qualifications for coverage:			
□ Medication Failed _____	Start Date: End Date:	Dose: Frequency:	
Physician Signature		Date	

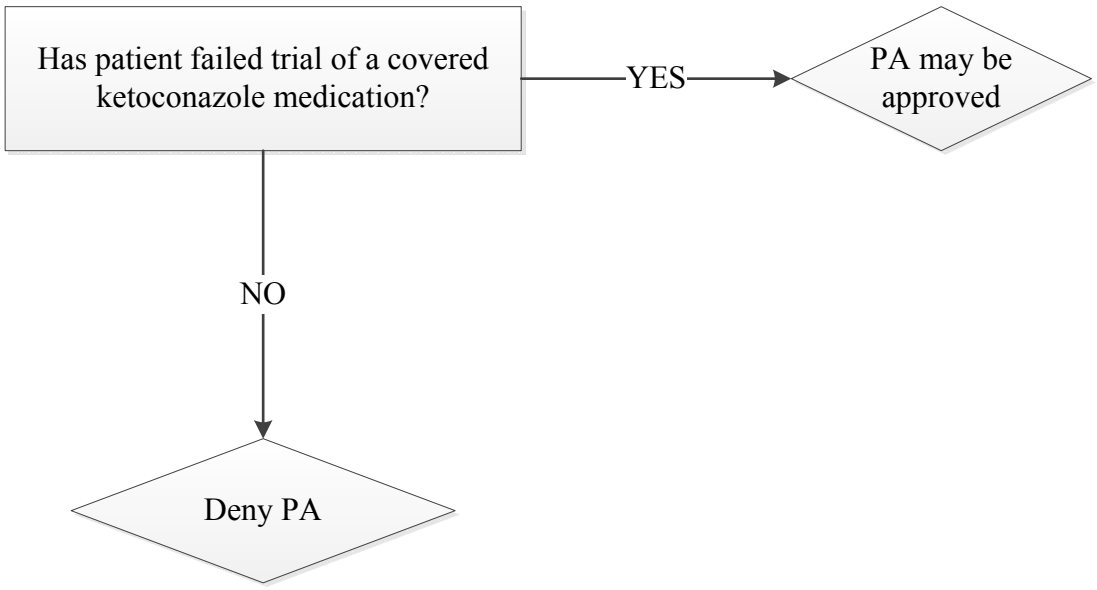
Part II: TO BE COMPLETED BY PHARMACY

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
Topical Ketoconazole Products Authorization Algorithm



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 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 AMBIEN (ZOLPIDEM)	Start Date: End Date:	Dose: Frequency:	
□ HIGH RISK FOR ADDICTION			
□ *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	

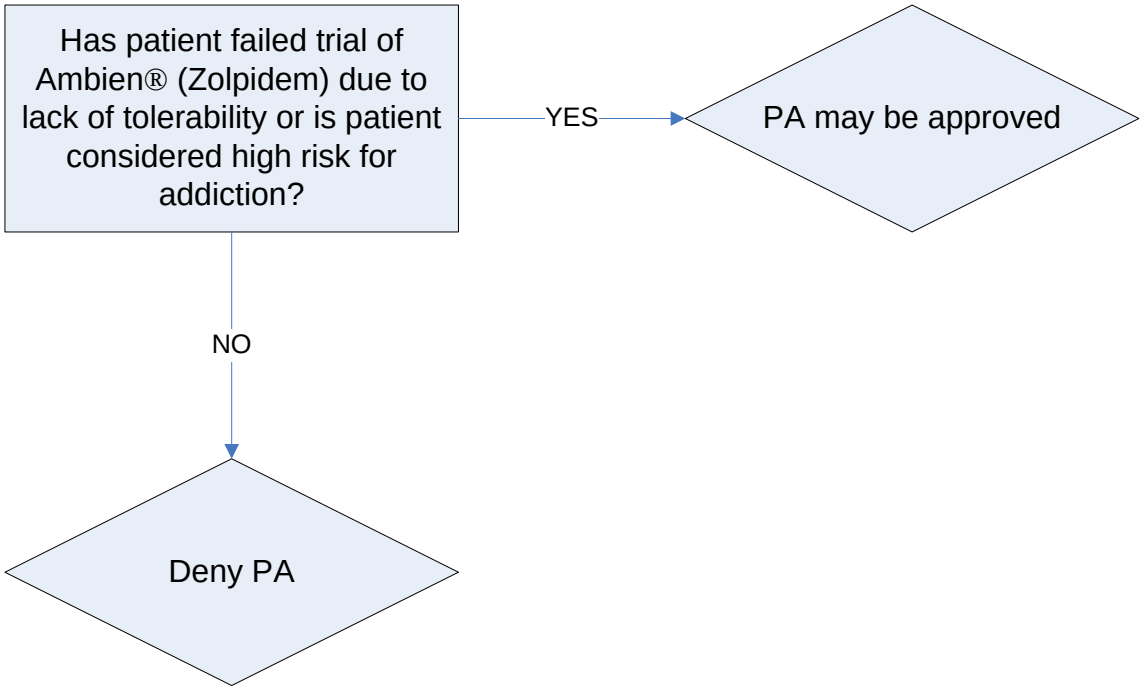
Part II: TO BE COMPLETED BY PHARMACY

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
Sedative/Hypnotic Authorization Algorithm



QUALAQUIN 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 Qualaquin with a diagnosis of Malaria.

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: □ **QUALAQUIN**	**Requested Dosage:** (must be completed)

Qualifications for coverage:

□ Diagnosis of malaria

□ *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:

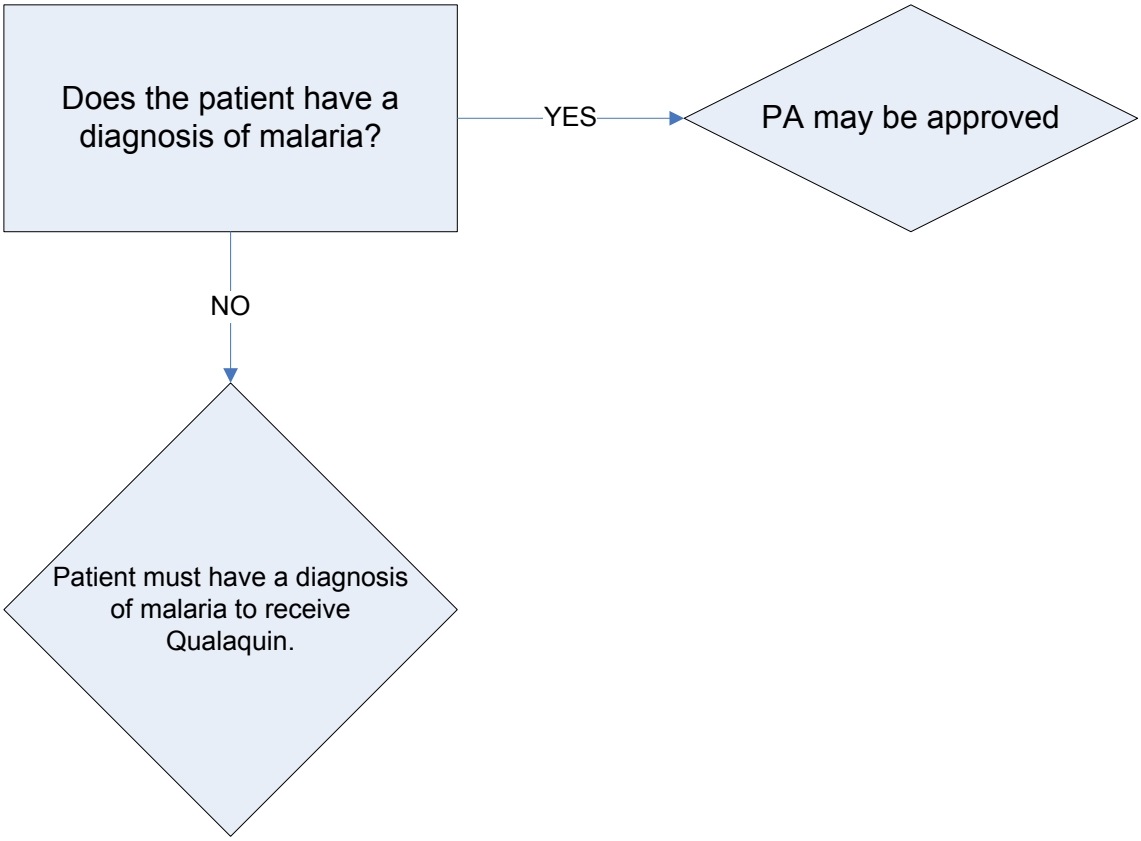
Part II: TO BE COMPLETED BY PHARMACY

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
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 try 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 and their hydrochlorothiazide containing combinations do not require a prior authorization.**
- **Angiotensin II receptor antagonists: Cozaar, Micardis, Teveten, Atacand, Diovan, Avapro, Benicar, Edarbi and their hydrochlorothiazide containing combinations.**
- **Renin Inhibitor: Tekturna and Tekturna HCT.**

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 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.*

Prescriber Signature	Date

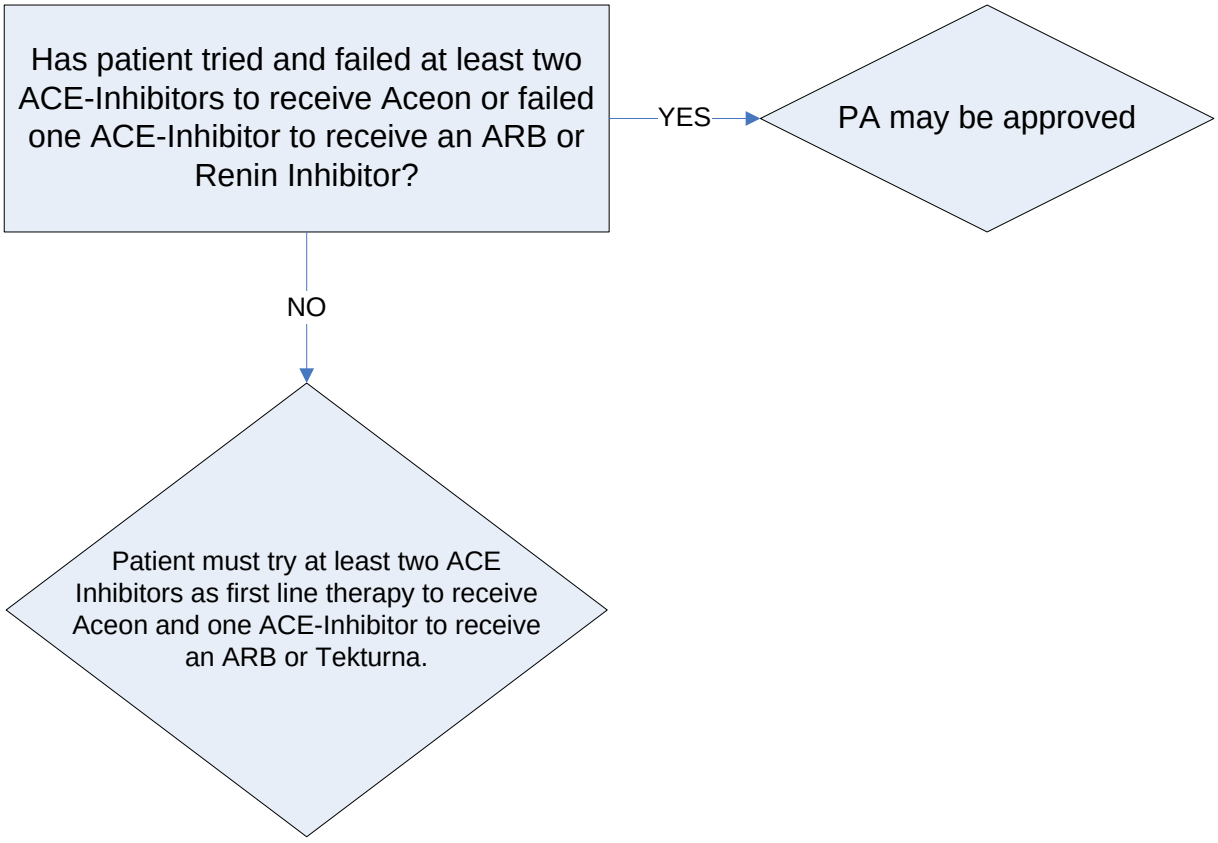
Part II: TO BE COMPLETED BY PHARMACY

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
ACE-Is, ARBs and Renin Inhibitor (Tekturna) Authorization Criteria Algorithm



ACE-I: Captopril, enalapril, moexipril, ramipril, lisinopril, trandolapril, quinapril, benazepril or fosinopril and hydrochlorothiazide combinations

ARB: Micardis, Teveten, Atacand, Avapro, Benicar, Cozaar, Diovan, Edarbi, and hydrochlorothiazide combinations

Renin Inhibitor: Tekturna and hydrochlorothiazide combination

HEALTH INFORMATION DESIGNS

SYNAGIS WEB BASED FORM

For questions regarding this Prior Authorization Call 701-328-4023

Prior Authorization Vendor for ND Medicaid

Note:

- Synagis season will be October 19th through April 21st
- Based on the 2009 American Academy of Pediatrics *Policy Statement – Modified Recommendations for Use of Palivizumab for Prevention of Respiratory Syncytial Virus Infections**, a maximum of 5 or 3 doses will be allowed during the Synagis season determined by gestational age.
- Providers will choose when to start dosing Synagis based on prevalence of RSV in the community

TO BE COMPLETED BY PRESCRIBER

Recipient Medicaid ID Number	Recipient Date of Birth	Prescriber NPI	Prescriber Fax Number

Diagnosis (qualification for Synagis)

___ Prematurity

≤28 weeks, 6 days gestational age – Synagis allowed if younger than 12 months of age at start of RSV season (max of 5 doses)

29-31 weeks, 6 days gestational age – Synagis allowed if younger than 6 months of age at start of RSV season (max of 5 doses)

32-34 weeks, 6 days gestational age – Synagis allowed during RSV season up to 6 months of life (max of 3 doses)

Gestational Age (e.g. 32 weeks, 4 days)

Weeks _____ **Days** _____

Risk Factor(s) (for those 32-34 weeks, 6 days)

___ Daycare attendance

___ Sibling younger than 5 years of age

___ Chronic Lung Disease of Prematurity (CLD)

Must be less than 24 months of age and receive medical therapy within six months before start of RSV season

___ Supplemental Oxygen

___ Bronchodilator

___ Diuretic

___ Chronic corticosteroid therapy

___ Congenital Heart Disease (CHD)

Must be less than 24 months of age and requiring medical therapy for CHD

Medical Therapy Required _____

___ Neuromuscular disease

___ Congenital abnormalities of the airways

*Accessed online at http://aappolicy.aappublications.org/cgi/reprint/pediatrics;124/6/1694.pdf.

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 Turners Syndrome (TS) or Prader-Willi Syndrome (PWS)**
- **Human Immunodeficiency Virus (HIV) associated wasting in adults**

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:		
Criteria met:	Diagnosis Date: Drug:	Dose: Frequency:
PRESCRIBER SIGNATURE	DATE:	

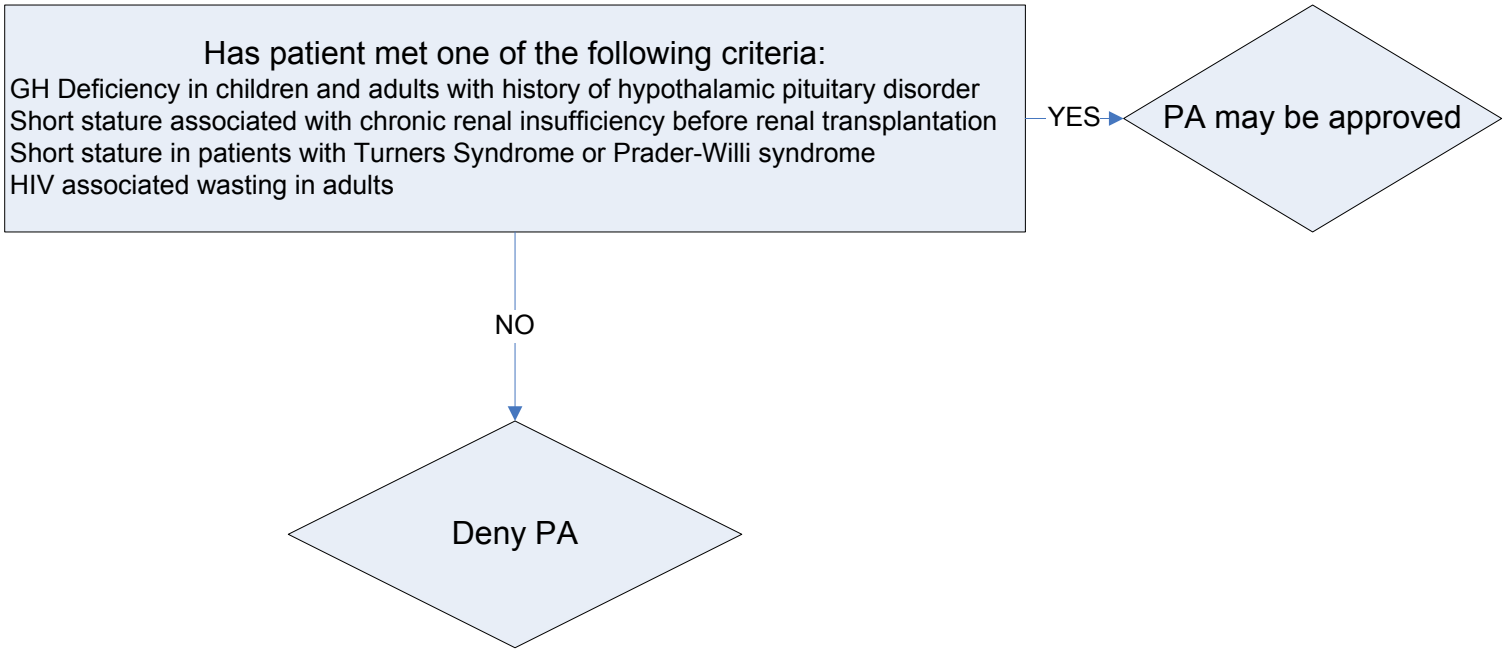
Part II: TO BE COMPLETED BY PHARMACY

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
Growth Hormone Authorization Algorithm



Serotonin (5-HT$_1$) Receptor Agonists - Triptan 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 Amerge, Axert, Frova, Maxalt, Relpax, Treximet, or Zomig must try Imitrex (sumatriptan) as first line therapy.

***Note:**

- **Imitrex (sumatriptan) does not require a PA.**
- **Injectables are not subject to a prior authorization at this time.**

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:**
□ AMERGE □ RELPAX □ AXERT □ TREXIMET □ FROVA □ ZOMIG □ MAXALT	

Qualifications for coverage:

	Start Date	End Date	Dose	Frequency
□ Failed sumatriptan therapy				

□ *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

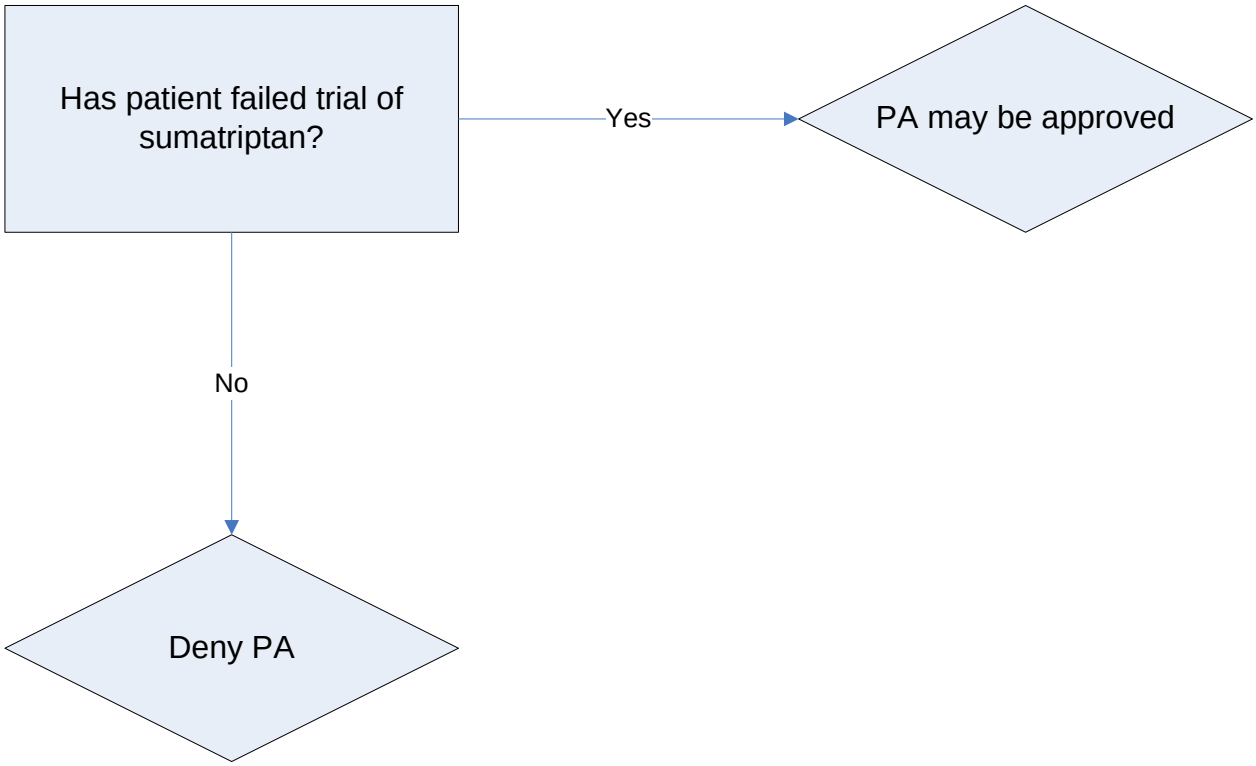
Part II: TO BE COMPLETED BY PHARMACY

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
Serotonin (5-HT_1) Receptor Agonists
Triptan Prior Authorization Algorithm



North Dakota Medicaid
DUR Board Meeting
Desoxyn® Review

I. Overview

Desoxyn is indicated for treatment of attention-deficit hyperactivity disorder (ADHD) characterized by moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. Desoxyn is also indicated for adjunctive, short-term (e.g., a few weeks) treatment of exogenous obesity in patients whose obesity is refractory to repeated diets, group programs, and other drugs. Desoxyn is sometimes used to treat narcolepsy, although this is a non-FDA approved indication.

II. Dosage and Administration

For treatment of ADHD the initial dose is 5mg once or twice daily. Increase by increments of 5mg at weekly intervals. Usual effective dose is 20-25mg daily divided into two doses; administer the lowest effective dose and, if possible, occasionally interrupt drug administration to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

For treatment of exogenous obesity the dose is 5mg 30 minutes before each meal for only a few weeks.

III. Pharmacology/Pharmacokinetics

Desoxyn (methamphetamine) is a schedule C-II controlled substance. Methamphetamine is a sympathomimetic amine with CNS stimulant activity.

In humans, methamphetamine is rapidly absorbed from the GI tract. The primary site of metabolism is in the liver by aromatic hydroxylation, N-dealkylation and deamination. At least 7 metabolites have been identified in the urine. The biological half-life has been reported in the range of 4 to 5 hours. Excretion occurs primarily in the urine and is dependent on urine pH. Alkaline urine will significantly increase the drug half-life. Approximately 62% of an oral dose is eliminated in the urine within the first 24 hours with about one-third as intact drug and the remainder as metabolites.

IV. Contraindications

Methamphetamine tablets are contraindicated during or within 14 days following the administration of monoamine oxidase (MAO) inhibitors; hypertensive crisis may result. It is also contraindicated in patients with glaucoma, advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, or known hypersensitivity or idiosyncrasy to sympathomimetic amines.

Methamphetamine should not be given to patients who are in an agitated state or who have a history of drug abuse.

V. Warnings/Precautions

- **Black Box Warning:** Methamphetamine has a high potential for abuse. It should thus be tried only in weight reduction programs for patients in whom alternative therapy has been ineffective. Administration of methamphetamine for prolonged periods of time in obesity may lead to drug dependence and must be avoided. Particular attention should be paid to the possibility of subjects obtaining methamphetamine for nontherapeutic use or distribution to others, and the drug should be prescribed or dispensed sparingly.
- **Tolerance:** Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect; rather, the drug should be discontinued.
- **Growth inhibition:** Decrements in the predicted growth (i.e., weight gain or height) rate have been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.
- **Fatigue:** Methamphetamine should not be used to combat fatigue or to replace rest in healthy persons.
- **Prescribing/dispensing:** Prescribing or dispensing of methamphetamine should be limited to the smallest amount that is feasible at one time in order to minimize the possibility of overdosage.
- **Special risk patients:** Methamphetamine tablets should be used with caution in patients with even mild hypertension.
- **Drug abuse and dependence:** Methamphetamine has been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. Abrupt cessation following prolong high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with methamphetamine include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis often clinically indistinguishable from schizophrenia.

VI. Drug Interactions

- **Insulin:** Insulin requirements in diabetes mellitus may be altered in association with the use of methamphetamine and the concomitant dietary regimen.
- **Guanethidine:** Methamphetamine may decrease the hypotensive effect of guanethidine.
- **MAO inhibitors:** Methamphetamine tablets are contraindicated during or within 14 days following the administration of MAO inhibitors; hypertensive crisis may result.
- **Tricyclic antidepressants and indirect-acting sympathomimetic amines:** Concurrent administration of tricyclic antidepressants and indirect-acting

sympathomimetic amines such as the amphetamines should be closely supervised and dosage carefully adjusted.

- **Phenothiazines:** Phenothiazines are reported in the literature to antagonize the CNS stimulant action of the amphetamines.
- **Urinary acidifiers:** Urinary acidifiers decrease the half-life and shorten the duration of action of amphetamines, possibly decreasing the pharmacologic effects. A higher amphetamine dose may be necessary.
- **Urinary alkalinizers:** Urinary alkalinizers increase the half-life and prolong the duration of amphetamines, possibly increasing the pharmacologic and toxic effects (e.g., cardiovascular, excessive CNS stimulation). A lower amphetamine dose may be necessary.
- **Drug/Lab test interactions:** Literature reports suggest that amphetamines may be associated with significant elevation of plasma corticosteroids. This should be considered if determination of plasma corticosteroid levels is desired in a person receiving amphetamines.

VII. Adverse Reactions

The following are adverse reactions in decreasing order of severity within each category that have been reported:

- **Cardiovascular:** Elevation of blood pressure, tachycardia, and palpitation.
- **CNS:** Psychotic episodes have rarely been reported at recommended doses. Dizziness, dysphoria, overstimulation, euphoria, insomnia, tremor, restlessness, and headache. Exacerbation of motor and phonic tics and Tourette's syndrome.
- **GI:** Diarrhea, constipation, dryness of mouth, unpleasant taste, and other GI disturbances.
- **Hypersensitivity:** Urticaria.
- **Endocrine:** Impotence and changes in libido.
- **Miscellaneous:** Suppression of growth has been reported with the long-term use of stimulants in children.

References

1. Wolters Kluwer Health, Inc. Drug Facts and Comparisons. St. Louis, MO. 2010.
2. Clinical Pharmacology, 2011 Gold Standard.

North Dakota Medicaid
DUR Board Meeting
Colcrys® Review

I. Overview

Colcrys tablets are indicated for prophylaxis and treatment of acute gout flares and the treatment of familial Mediterranean fever (FMF) in adults and children 4 years or older.

II. Dosage and Administration

- **Prophylaxis of Gout Flares:** The recommended dosage of Colcrys for prophylaxis of gout flares for adults and adolescents older than 16 years of age is 0.6mg once or twice daily. The maximum recommended dose for prophylaxis of gout flares is 1.2mg/day.
- **Treatment of Gout Flares:** The recommended dose of Colcrys for treatment of a gout flare is 1.2mg at the first sign of the flare followed by 0.6mg one hour later. Higher doses have not been found to be more effective. The maximum recommended dose for treatment of gout flares is 1.8mg over a 1 hour period. Colcrys may be administered for treatment of a gout flare during prophylaxis at doses not to exceed 1.2mg at the first sign of the flare followed by 0.6mg one hour later. Wait 12 hours and then resume prophylactic dose.
- **FMF:** The recommended dosage of Colcrys for FMF in adults is 1.2mg to 2.4mg daily. Colcrys should be increased as needed to control disease and as tolerated in increments of 0.3mg/day to a maximum recommended daily dose. If intolerable side effects develop, the dose should be decreased in decrements of 0.3mg/day. The total daily Colcrys dose may be administered in one to two divided doses. The recommended dosage of Colcrys for FMF in pediatric patients 4 years of age and older is based on age. The following daily doses may be given as a single or divided dose twice daily:

  Children 4-6 years: 0.3mg to 1.8mg daily
  Children 6-12 years: 0.9mg to 1.8mg daily
  Adolescents older than 12 years: 1.2mg to 2.4mg daily

III. Pharmacology/Pharmacokinetics

Gout:
The exact mechanism of action of colchicine, an anti-inflammatory agent, in gout is not completely known, but it involves a reduction in lactic acid production by leukocytes, which results in a decrease in uric acid deposition and a reduction in phagocytosis, with abatement of the inflammatory response.

Colchicine is not an analgesic, though it relieves pain in acute attacks of gout. It is not a uricosuric agent and will not prevent progression of gout to chronic gouty arthritis. It does have a prophylactic, suppressive effect that helps to reduce the incidence of acute

attacks and to relieve the residual pain and mild discomfort that patients with gout occasionally feel.

FMF:
The mechanism by which colchicines exerts its beneficial effect in patients with FMF has not been fully elucidated; however, recent data suggests that colchicine may interfere with the intracellular assembly of the inflammasome complex present in neutrophils and monocytes that mediates activation of interleukin-1 beta. Additionally, colchicine disrupts cytoskeletal functions through inhibition of beta-tubulin polymerization into microtubules, and, consequently, prevents the activation, degranulation, and migration of neutrophils.

Mean (% Coefficient of Variation) Pharmacokinetic Parameters in Healthy Adults

$C_{max\ (colchicines\ ng/mL)}$	T_{max} (h)	Vd/F (L)	CL/F (L/hr)	$t_{1/2}$ (h)
Colcrys 0.6mg Single Dose (n=13)				
2.5 (28.7)	1.5 (1.0 – 3.0)	341.5 (54.4)	54.1 (31.0)	-
Colcrys 0.6mg BID x 10 days (n=13)				
3.6 (23.7)	1.3 (0.5 – 3.0)	1150 (18.7)	30.3 (19)	26.6 (16.3)

IV. Contraindications

Patients with renal or hepatic impairment should not be given Colcrys in conjunction with P-gp or strong CYP3A4 inhibitors. In these patients, life-threatening and fatal colchicines toxicity has been reported with colchicine taken in therapeutic doses.

V. Warnings/Precautions

- **Fatal overdoses** have been reported with colchicine in adults and children.
- **Blood dyscrasias:** Myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, and aplastic anemia have been reported.
- **Monitor for toxicity** and if present consider temporary interruption or discontinuation of colchicine.
- **Drug interaction P-gp and/or CYP3A4 inhibitors:** Co-administration of colchicine with P-gp and/or strong CYP3A4 inhibitors has resulted in life-threatening interactions and death.
- **Neuromuscular toxicity:** Myotoxicity including rhabdomyolysis may occur, especially in combination with other drugs known to cause this effect.

VI. Drug Interactions

Co-administration of P-gp and/or CYP3A4 inhibitors (*e.g.,* clarithromycin or cyclosporine) has been demonstrated to alter the concentration of colchicine.
The potential for drug-drug interactions must be considered prior to and during therapy.

VII. Adverse Reactions

Prophylaxis of Gout Flares: The most common adverse reaction in clinical trials for the prophylaxis of gout was diarrhea.

Treatment of Gout Flares: The most common adverse reactions reported in the clinical trial for gout were diarrhea (23%) and pharyngolaryngeal pain (3%).

FMF: The most common adverse reactions (up to 20%) are abdominal pain, diarrhea, nausea, and vomiting. These effects are usually mild, transient, and reversible upon lowering the dose.

VIII. Utilization

ND Medicaid Colcrys Utilization			
01/01/10 - 12/31/10			
Label Name	**Rx Num**	**Total Reimb Amt**	**Average cost/script**
COLCRYS 0.6 MG TABLET	4	$952.24	$238.06
TOTAL 3 recipients	4	$952.24	

References

1. Colcrys® [prescribing information]. Philadelphia, PA: Mutual Pharmaceutical Company, Inc.; September 2010.
2. Wolters Kluwer Health, Inc. Drug Facts and Comparisons. St. Louis, MO. 2010.
3. Clinical Pharmacology, 2011 Gold Standard.

North Dakota Medicaid
DUR Board Meeting
Asacol® HD Review

I. Overview

Asacol HD is a locally acting aminosalicylate indicated for the treatment of moderately active ulcerative colitis. The mechanism of action of mesalamine is unknown, but it appears to be topical rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase pathways (i.e., prostanoids) and through the lipoxygenase pathways (i.e., leukotrienes) and hydroxyeicosatetraenoic acids, is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon. Recent data also suggest that mesalamine can inhibit the activation of NFKB, a nuclear transcription factor that regulates the transcription of many genes for proinflammatory proteins.

II. Dosage and Administration

Adults: Two 800mg tablets three times daily with or without food, for a total daily dose of 4.8g. Treatment duration is up to 6 weeks. Safety and effectiveness beyond 6 weeks have not been established.

III. Pharmacokinetics

Asacol tablets are coated with an acrylic-based resin that delays release of mesalamine until it reaches the terminal ileum and beyond. Approximately 28% of the mesalamine in Asacol tablets is absorbed after oral ingestion, leaving the remainder available for topical action and excretion in the feces.

IV. Warnings/Precautions

- Renal impairment may occur. Monitor renal function at the beginning of treatment and periodically during therapy.
- Acute exacerbation of colitis symptoms can occur.
- Patients with pyloric stenosis may have prolonged gastric retention of Asacol HD tablets.
- Use caution with pre-existing liver disease.

V. Adverse Reactions

The most common adverse reactions (observed in >2% of patients) were headache, nausea, nasopharyngitis, abdominal pain, and worsening of ulcerative colitis.

VI. Utilization

North Dakota Medicaid Asacol Utilization			
01/01/10 – 12/31/10			
Label Name	**Rx Num**	**Total Reimb Amt**	**Avg Cost/Script**
ASACOL HD DR 800 MG TABLET	1	$334.35	$334.35
ASACOL EC 400 MG TABLET	58	$15,794.30	$272.32

References

1. Asacol® HD [prescribing information]. Rockway, NJ: Warner Chilcott (US), LLC; October 2010.
2. Wolters Kluwer Health, Inc. Drug Facts and Comparisons. St. Louis, MO. 2010.
3. Clinical Pharmacology, 2011 Gold Standard.

North Dakota Medicaid
DUR Board Meeting
Ophthalmic Antihistamines Review

I. Overview

Conjunctivitis is defined as an inflammation of the conjunctiva, which is a thin membrane that lines the inner surface of the eyelids and the whites of the eye (sclera) and helps keep the eyelid and eyeball moist. Allergic conjunctivitis is caused by airborne allergens that come in contact with the eye. Symptoms may be sudden in onset (acute), seasonal, or present year-round (perennial).

The most common symptoms of allergic conjunctivitis include redness in the white of the eye or inner eyelid, watery discharge, itching of both eyes, swelling of the eyelid, and blurred vision. Both eyes are usually affected, although symptoms may be worse in one eye.

Ophthalmic Antihistamines Included in this Review

Generic Name	Brand Name
Alcaftadine	Lastacaft®
Azelastine	Optivar®
Bepotastine	Bepreve®
Emedastine	Emadine®
Epinastine	Elestat®
Ketotifen	Alaway® OTC, Zaditor® OTC, Zyrtec® Itchy Eye OTC
Olopatadine	Patanol®, Pataday®

II. Indications

Generic Name	FDA Approved Indications
Alcaftadine	• Prevention of itching associated with allergic conjunctivitis.
Azelastine	• Treatment of itching of the eye associated with allergic conjunctivitis.
Bepotastine	• For the treatment of itching associated with signs and symptoms of allergic conjunctivitis.
Emedastine	• For the temporary relief of the signs and symptoms of allergic conjunctivitis.
Epinastine	• For the prevention of itching associated with allergic conjunctivitis
Ketotifen	• For the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander.
Olopatadine	• For the treatment of the signs and symptoms of allergic conjunctivitis. (Patanol) • For the treatment of ocular itching associated with allergic conjunctivitis. (Pataday)

III. Dosage and Administration

Drug	Dosing and Administration
Alcaftadine	Adults: Instill one drop in each eye once daily. Children 2 years of age and older: Instill one drop in each eye once daily.
Azelastine	Adults: One drop instilled into each affected eye twice a day Children 3 years of age and older: One drop instilled into each affected eye twice a day.
Bepotastine	Adults: Instill one drop into the affected eye(s) twice a day. Children 2 years of age and older: Instill one drop into the affected eye(s) twice a day.
Emedastine	Adults: Instill one drop in the affected eye up to four times daily. Children 3 years of age and older: Instill one drop in the affected eye up to four times daily.
Epinastine	Adults: Instill one drop in each eye twice a day. Children 3 years of age and older: Instill one drop in each eye twice a day.
Ketotifen	Adults: One drop in the affected eye(s) every eight to 12 hours. Children 3 years of age and older: One drop in the affected eye(s) every eight to twelve hours.
Olopatadine 0.1%	Adults: One to two drops in each affected eye two times per day at an interval of six to eight hours. Children 3 years of age and older: One to two drops in each affected eye two times per day at an interval of six to eight hours.
Olapatadine 0.2%	Adults: One drop in each affected eye once a day. Children 3 years of age and older: One drop in each affected eye once a day.

IV. Pharmacology

Ophthalmic Antihistamine	Antihistamine	Mast Cell Stabilizer
Alcaftadine	√	√
Azelastine	√	√
Bepotastine	√	√
Emedastine	√	
Epinastine	√	√
Ketotifen	√	√
Olopatadine	√	√

V. Pharmacokinetics

Alcaftadine – no indication of systemic accumulation or changes in plasma exposure following daily topical ocular administration. The protein binding of alcaftadine and the active metabolite is 39.2% and 62.7% respectively. The carboxylic acid metabolite is primarily eliminated unchanged in the urine.

Azelastine – absorption following ocular administration relatively low. Azelastine is oxidatively metabolized to the principal metabolite, N-desmethylazelastine, by the cytochrome P450 enzyme system. The plasma protein binding of azelastine and the active metabolite are approximately 88% and 97% respectively.

Bepotastine – the extent of protein binding is approximately 55%. In vitro studies demonstrated that bepotastine is minimally metabolized by cytochrome P450 isozymes. The main route of elimination is urinary excretion with approximately 75% to 90% excreted unchanged in the urine.

Emedastine – low systemic exposure. The elimination half-life of oral Emedastine in plasma is 3 to 4 hours. Approximately 44% of the oral dose is recovered in the urine over 24 hours with only 3.6% of the dose excreted as parent drug. Two primary metabolites, 5- and 6- hydroxyemedastine are excreted in the urine as both free and conjugated forms.

Epinastine – low systemic exposure. Epinastine is 64% bound to plasma proteins. Epinastine is mainly excreted unchanged with about 55% of an intravenous dose recovered unchanged in the urine and 30% in feces. Less than 10% is metabolized. Renal elimination is mainly via active tubular secretion.

Ketotifen – 75% bound to plasma proteins. Ketotifen undergoes glucuronidation to the inactive metabolite ketotifen-*N*-glucuronide and demethylation to *nor*-ketotifen, which has similar activity as the parent compound. The distribution and elimination half-lives following oral administration of ketotifen are 2 and 22 hours, respectively. About 60 – 70% of ketotifen, primarily as the *N*-glucuronide metabolite, is eliminated in the urine within 48 hours

Olopatadine – low systemic exposure. The half-life in plasma is approximately 3 hours, and elimination is predominantly through renal excretion. Approximately 60% to 70% of the dose is recovered in the urine as parent drug. Two metabolites, the mono-desmethyl and the N-oxide, were detected at low concentrations in the urine.

VI. Warnings/Precautions

- Alcaftadine, bepotastine, and epinastine should not be used to treat contact lens-related irritation.
- Patients should be advised not to wear contact lens if their eye is red.
- The preservative in alcaftadine, bepotastine, and epinastine (benzalkonium chloride) may be absorbed by soft contact lenses. Lenses may be reinserted 10 minutes after administration of alcaftadine.

- Instruct patients to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections.

VII. Drug Interactions

Due to the route of administration of these products, clinically significant drug interactions are not well identified.

VIII. Adverse Reactions

Alcaftadine – the most frequent ocular adverse reactions, occurring in less than 4% of alcaftadine-treated eyes, were eye irritation, burning and/or stinging upon instillation, eye redness, and eye pruritus.

Azelastine – the most frequently reported adverse reactions were transient eye burning/stinging, headaches, and bitter taste.

Bepotastine – the most significant reported adverse reaction occurring in approximately 25% of subjects was a mild taste following instillation.

Emedastine – the most frequent adverse reaction is headache.

Epinastine – the most frequently reported ocular adverse events were burning sensation in the eye, folliculosis, hyperemia, and pruritus.

Ketotifen – conjunctival injection, headaches, and rhinitis were reported at an incidence of 10% to 25%.

Olopatadine – burning or stinging, dry eye, foreign body sensation, hyperemia, keratitis, lid edema, and pruritus.

IX. Utilization

ND Medicaid Ophthalmic Antihistamine Utilization			
01/01/10 - 12/31/10			
Label Name	**Rx Num**	**Total Reimb Amt**	**Average Cost/Script**
OPTIVAR 0.05% DROPS	3	$322.46	$107.49
BEPREVE 1.5% EYE DROPS	3	$196.05	$65.35
AZELASTINE HCL 0.05% DROPS	10	$958.85	$95.89
ELESTAT 0.05% EYE DROPS	35	$3,572.25	$102.06
PATADAY 0.2% EYE DROPS	139	$13,310.46	$95.76
PATANOL 0.1% EYE DROPS	403	$36,512.61	$90.60
Totals 317 recipients	593	$54,872.68	

References

1. Wolters Kluwer Health, Inc, ed. Drugs Facts & Comparisons. St. Louis, MO. 2010.
2. Bepreve® Prescribing Information, January 2010, ISTA Pharmaceuticals, Inc.
3. Optivar® Prescribing Information, April, 2009, MEDA Pharmaceuticals, Inc.
4. Elestat® Prescribing Information, August, 2008, Allergan, Inc.
5. Pataday® Prescribing Information, Alcon Laboratories, Inc.
6. Patanol® Prescribing Information, January 2007, Alcon Laboratories, Inc.

North Dakota Medicaid
DUR Board Meeting
Horizant® Review

I. Overview

On April 6, 2011, the FDA approved Horizant (gabapentin enacarbil) extended release tablets, a once-daily treatment for moderate-to-severe restless legs syndrome (RLS). RLS is a disorder in which there is an urge or need to move the legs to stop unpleasant sensations.

II. Dosage and Administration

The recommended dose of Horizant is 600mg once daily taken with food at about 5pm. A dose of 1,200mg once daily provided no additional benefit compared with the 600mg dose, but caused an increase in adverse reactions.

III. Pharmacology/Pharmacokinetic

Gabapentin enacarbil is a prodrug of gabapentin and its therapeutic effects in RLS are attributable to gabapentin. The precise mechanism by which gabapentin is efficacious in RLS is unknown.

- **Absorption:** Mean bioavailability of gabapentin for Horizant in the fed state is about 75%. Bioavailability under fasting conditions has been estimated to be 42% to 65%. The T_{max} of gabapentin after administration of 600mg of Horizant was 5.0 hours in fasted subjects and 7.3 hours in fed subjects. Steady state is reached in 2 days with daily administration.
- **Distribution:** Plasma protein binding of gabapentin has been reported to be <3%. The apparent volume of distribution of gabapentin in subjects receiving Horizant is 76L.
- **Metabolism:** After oral administration, gabapentin enacarbil undergoes extensive first-pass hydrolysis by non-specific carboxylesterases primarily in enterocytes and to a lesser extent in the liver, to form gabapentin, carbon dioxide, acetaldehyde, and isobutyric acid.
- **Elimination:** Following hydrolysis of gabapentin enacarbil, the released gabapentin is excreted unchanged by the kidney. Renal clearance ranged from 5 to 7 L/hr. The elimination half-life of gabapentin ranges from 5.1 to 6.0 hours and is unaltered by dose.

IV. Warnings/Precautions

- **Driving impairment:** Warn patients not to drive until they have gained sufficient experience with HORIZANT to assess whether it will impair their ability to drive.
- **Somnolence/sedation and dizziness:** May impair the patient's ability to operate complex machinery.

- Horizant is not interchangeable with other gabapentin products.
- **Suicidal thoughts or behaviors:** Monitor for suicidal thoughts or behaviors.

V. Adverse Reactions

Most common adverse reactions (≥10% and at least 2 times the rate of placebo) were somnolence/sedation and dizziness.

References

1. Horizant® [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; April 2011.
2. Clinical Pharmacology, 2011 Gold Standard.

North Dakota Medicaid
DUR Board Meeting
Daliresp® Review

I. Overview

Daliresp (roflumilast) is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Daliresp is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

II. Dosage and Administration

The recommended dosage for patients with COPD is one 500mcg tablet per day, with or without food.

III. Pharmacology/Pharmacokinetics

Roflumilast and its active metabolite (roflumilast N-oxide) are selective inhibitors of phosphodiesterase 4 (PDE4). Roflumilast and roflumilast N-oxide inhibition of PDE4 (a major cyclic-3',5'-adenosine monophosphate (cyclic AMP)-metabolizing enzyme in lung tissue) activity leads to accumulation of intracellular cyclic AMP. While the specific mechanism by which Daliresp exerts its therapeutic action in COPD patients is not well defined, it is thought to be related to the effects of increased intracellular cyclic AMP in lung cells.

- **Absorption:** The absolute bioavailability of roflumilast following a 500mcg oral dose is approximately 80%. Maximum plasma concentrations typically occur one hour after dosing while plateau-like maximum concentrations of the N-oxide metabolite are reached in approximately 8 hours.
- **Distribution:** Plasma protein binding of roflumilast and its N-oxide metabolite is approximately 99% and 97%, respectively. Volume of distribution for single dose 500mcg roflumilast is about 2.9L/kg.
- **Metabolism:** Roflumilast is extensively metabolized via Phase 1 (cytochrome P450) and Phase II (conjugation) reactions. The N-oxide metabolite is the only major metabolite observed in the plasma of humans.
- **Elimination:** The plasma clearance after short-term intravenous infusion of roflumilast is on average about 9.6L/h. Following an oral dose, the median plasma effective half-life of roflumilast and its N-oxide metabolite are approximately 17 and 30 hours, respectively. Steady state plasma concentrations of roflumilast and its N-oxide metabolite are reached after approximately 4 days for roflumilast and 6 days for N-oxide following once daily dosing.

IV. Contraindications

- Moderate to severe liver impairment.

V. Warnings/Precautions

- **Acute bronchospasm:** Do not use for the relief of acute bronchospasm.
- **Psychiatric Events including Suicidality:** Advise patients, caregivers, and families to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Carefully weigh the risks and benefits of treatment with Daliresp in patients with a history of depression and/or suicidal thoughts or behavior.
- **Weight Decrease:** Monitor weight regularly. If unexplained or clinically significant weight loss occurs, evaluate weight loss and consider discontinuation of Daliresp.
- **Drug Interactions:** Use with strong cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended.

VI. Drug Interactions

Use with inhibitors of CYP3A4 or dual inhibitors of CYP3A4 and CYP1A2 (e.g., erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine) will increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit.

VII. Adverse Reactions

Most common adverse reactions (≥2%) are diarrhea, weight decrease, nausea, headache, back pain, influenza, insomnia, dizziness and decreased appetite.

References

1. Daliresp® [prescribing information]. St. Louis, MO: Forest Pharmaceuticals, Inc.; February 2011.
2. Clinical Pharmacology, 2011 Gold Standard.

Changes for Acetaminophen-Containing Products

In June 2009, the safety of acetaminophen was discussed at a Joint Meeting of the Food and Drug Administration (FDA) Drug Safety and Risk Management Advisory Committee, Nonprescription Drugs Advisory Committee, and Anesthetic and Life Support Drugs Advisory Committee.

The Advisory Committee recommended, and 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. In addition, a boxed warning detailing the potential for severe liver injury and a warning highlighting the potential for allergic reactions will be added to the label. OTC medications containing acetaminophen will not be affected by this action.

A number of studies have detailed the incidence of liver toxicity in patients using acetaminophen and clearly indicate reason for concern. A 2007 Centers for Disease Control and Prevention (CDC) report estimates that of 1600 cases of acute liver failure (ALF) each year, acetaminophen was the most common cause. This same study found that most of the cases of acetaminophen-related ALF were caused by unintentional overdose, where a patient accidentally took too much acetaminophen. It is the hope that by limiting the maximum amount of acetaminophen in prescription products, patients will be less likely to overdose.

Information for providers:

- Advise patients not to exceed the acetaminophen maximum total daily dose (4 grams/day)
- Severe liver injury, including cases of acute liver failure resulting in liver transplant and death, has been reported with the use of acetaminophen
- Advise patients not to drink alcohol while taking acetaminophen
- Remind patients of the importance of reading all prescription and OTC labels to ensure they are not taking multiple acetaminophen-containing products
- Rare cases of anaphylaxis and other hypersensitivity reactions have occurred with the use of acetaminophen
- Patients should seek medical attention immediately if they have taken too much acetaminophen or if they experience symptoms of hypersensitivity

References:

1. Changes for acetaminophen-containing prescription products. Pharmacist's Letter/Prescriber's Letter 2011;27(2):270203.
2. Bower WA, Johns M, Margolis HS, et al. Population-based surveillance for acute liver failure. Am J Gastroenterol 2007;102:2459-63.
3. Food and Drug Administration drug safety communication concerning changes to prescription acetaminophen-containing products. January 13, 2011. www.fda.gov/Drugs/DrugSafety/ucm239821. Accessed February 2011.

ND Medicaid Combination APAP Utilization		
01/01/10 - 12/31/10		
Label Name	**Rx Num**	**Total Reimb Amt**
ACETAMINOPHEN-COD #2 TABLET	46	$430.16
ACETAMINOPHEN-COD #3 TABLET	3,460	$95,415.66
ACETAMINOPHEN-COD #4 TABLET	25	$512.84
HYDROCODON-ACETAMINOPH 2.5-500	12	$64.45
HYDROCODON-ACETAMINOPH 7.5-325	114	$2,110.88
HYDROCODON-ACETAMINOPH 7.5-500	814	$7,726.24
HYDROCODON-ACETAMINOPH 7.5-650	33	$354.52
HYDROCODON-ACETAMINOPH 7.5-750	297	$2,370.17
HYDROCODON-ACETAMINOPHEN 5-325	1,623	$36,571.43
HYDROCODON-ACETAMINOPHEN 5-500	7,556	$71,691.91
HYDROCODON-ACETAMINOPHN 10-325	2,010	$86,541.77
HYDROCODON-ACETAMINOPHN 10-500	470	$9,013.59
HYDROCODON-ACETAMINOPHN 10-650	5,155	$55,112.85
HYDROCODON-ACETAMINOPHN 10-660	16	$352.39
OXYCODON-ACETAMINOPHEN 2.5-325	3	$98.83
OXYCODON-ACETAMINOPHEN 7.5-325	98	$3,029.96
OXYCODON-ACETAMINOPHEN 7.5-500	109	$2,325.33
OXYCODONE-ACETAMINOPHEN 10-325	603	$21,457.44
OXYCODONE-ACETAMINOPHEN 10-650	173	$4,793.92
OXYCODONE-ACETAMINOPHEN 5-325	4,370	$42,163.70
OXYCODONE-ACETAMINOPHEN 5-500	846	$9,683.67
Totals 10,312 Recipients	**27,833**	**$451,821.71**
55.62% of current utilization has a dose of APAP that will be phased out by 2014		

NORTH DAKOTA MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS
2ND QUARTER 2011

Criteria Recommendations ***Approved Rejected***

1. Topiramate / Therapeutic Appropriateness _____ _____

Alert Message: The use of Topamax (topiramate) during the first trimester of pregnancy has been shown to increase the risk for the development of oral clefts in infants. Data from the AED Pregnancy Registry shows that infants exposed to topiramate as a single therapy experienced a 1.4% prevalence of oral clefts as compared to 0.39% to 0.55% in infants exposed to other antiepileptic drugs. Females of childbearing age receiving topiramate should be warned of the potential hazard to the fetus if a woman becomes pregnant while using the drug. Topiramate is pregnancy category D.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Topiramate		

Gender: Females
Age Range: 12 – 50 yoa
References:
MedWatch FDA Drug Safety Communication: Risk of Oral Clefts in Children Born to Mothers Taking Topamax (topiramate). 03-04-2011.
Facts & Comparisons, 2011 Updates.

2. Vilazodone / Overutilization _____ _____

Alert Message: The recommended dose of Viibryd (vilazodone) is 40 mg once daily. Vilazodone should be titrated to the 40 mg dose starting with an initial dose of 10 mg/day for 7 days, followed by 20 mg/day for 7 days then 40 mg daily. Vilazodone should be taken with food to insure adequate drug concentrations.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Vilazodone		

References:
Viibryd Prescribing Information. Jan. 2010, Torvis Pharms.
Facts & Comparisons, 2011 Updates.
Micromedex Healthcare Series, DrugDex Drug Evaluations, 2011 Thomson Reuters.

3. Vilazodone / MAO Inhibitors _____ _____

Alert Message: The use of Viibryd (vilazodone) is contraindicated with an MAO inhibitor or within 14 days of stopping or starting an MAOI due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs.

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

Util A	Util B		Util C
Vilazodone	Isocarboxazid	Selegiline	
	Phenelzine	Rasagiline	
	Tranylcypromine	Linezolid	

References:
Viibryd Prescribing Information. Jan. 2010, Torvis Pharms.
Facts & Comparisons, 2011 Updates.
Micromedex Healthcare Series, DrugDex Drug Evaluations, 2011 Thomson Reuters.

4. Vilazodone 20 & 40 mg / Strong CYP3A4 Inhibitors _____ _____

Alert Message: The dose of Viibryd (vilazodone) should not exceed 20 mg/day when co-administered with a strong CYP3A4 inhibitor (e.g., ketoconazole, ritonavir, clarithromycin and nefazodone). Vilazodone is a CYP3A4 substrate and concurrent use with a strong 3A4 inhibitor may result in a significant increase in vilazodone plasma concentrations.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B		Util C
Vilazodone 20 & 40	Ketoconazole	Indinavir	
	Itraconazole	Nelfinavir	
	Ritonavir	Telithromycin	
	Saquinavir	Clarithromycin	
	Atazanavir	Nefazodone	

References:
Viibryd Prescribing Information. Jan. 2010, Torvis Pharms.
Facts & Comparisons, 2011 Updates.
Micromedex Healthcare Series, DrugDex Drug Evaluations, 2011 Thomson Reuters.

5. Vilazodone / CPY3A4 Inducers _____ _____

Alert Message: The concurrent use of Viibryd (vilazodone) with a CYP3A4 inducer (e.g., carbamazepine, phenobarbital and phenytoin) may result in inadequate drug concentrations of vilazodone and diminished effectiveness.

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

Util A	Util B			Util C
Vilazodone	Carbamazepine	Barbiturates	Prednisone	
	Phenytoin	Rifabutin	Oxcarbazepine	
	Efavirenz	Rifampin	Modafinil	
	Nevirapine	Dexamethasone		

References:
Viibryd Prescribing Information. Jan. 2010, Torvis Pharms.
Micromedex Healthcare Series, DrugDex Drug Evaluations, 2011 Thomson Reuters.
Facts & Comparisons, 2011 Updates.

6. Vilazodone / Non-adherence _____ _____

Alert Message: Based on refill history, your patient may be underutilizing Viibryd (vilazodone). Non-adherence to the prescribed dosing regimen may result in sub-therapeutic effect, which may lead to decreased patient outcomes and additional healthcare costs.

Conflict Code: LR – Non-Adherence
Drugs/Diseases

Util A	Util B	Util C
Vilazodone		

References:
Viibryd Prescribing Information. Jan. 2010, Torvis Pharms.
Micromedex Healthcare Series, DrugDex Drug Evaluations, 2011 Thomson Reuters.
Facts & Comparisons, 2011 Updates.

7. Vilazodone / Therapeutic Appropriateness _____ _____

Alert Message: The safety and effectiveness of Viibryd (vilazodone) in the pediatric population have not been established.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Vilazodone		

Age Range: 0-17 yoa
References:
Facts & Comparisons, 2011 Updates.
Micromedex Healthcare Series, DrugDex Drug Evaluations, 2011 Thomson Reuters.
Viibryd Prescribing Information. Jan. 2010, Torvis Pharms.

8. Terbutaline / Pregnancy (Black Box Warning) _____ _____

Alert Message: Injectable terbutaline should not be used in pregnant women for prevention or prolonged treatment (beyond 48-72 hours) of preterm labor in either the hospital or outpatient setting because of the potential for serious maternal heart problems and death. Oral terbutaline should not be used for prevention or any treatment of preterm labor because it has not been shown to be effective and has similar safety concerns.

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

Util A	Util B	Util C (Negating)
Terbutaline	Pregnancy	Miscarriage/Delivery/Abortion

References:
MedWatch: The FDA Safety Information and Adverse Event Reporting Program, Terbutaline: Label Change-Warning Against Use for Treatment of Preterm Labor. 2/17/2011.
Facts & Comparisons, 2011 Updates.
Micromedex Healthcare Series, DrugDex Drug Evaluations, 2011 Thomson Reuters.

9. TNF Blockers, Azathioprine, Mercaptopurine / Therapeutic Appropriateness _____ _____

Alert Message: The FDA continues to receive reports of the occurrence of a rare cancer of the white blood cells (Heptaosplenic T-Cell Lymphoma-HSTCL), primarily in adolescents and young adults being treated for Crohn's disease and ulcerative colitis with tumor necrosis factor blockers, as well as azathioprine and mercaptopurine. Educate patients about signs and symptoms of malignancies such as HSTCL and monitor for emergence of malignancies during therapy with these agents.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Azathioprine		
Mercaptopurine		
Infliximab		
Etanercept		
Adalimumab		
Certolizumab		
Golimumab		

References:
MedWatch: The FDA Safety information and Adverse Event Reporting Program. Tumor Necrosis Factor (TNF) blockers, Azathioprine and/or Mercaptopurine: Update on Reports of Hepatosplenic T-Cell Lymphoma in Adolescents and Young Adults. 4/14/2011.

10. Saquinavir / Ritonavir _____ _____

Alert Message: The concurrent use of saquinavir (Invirase) and ritonavir (Norvir) may cause prolongation of the QT and PR intervals. QT prolongation can lead to torsades de pointes which can progress to life-threatening ventricular fibrillation and PR prolongation may lead to complete heart block. Patients at particular risk are those with underlying heart conditions. Inform patients on this antiretroviral combination of the potential risks and counsel them concerning appropriate actions if they experience related symptoms.

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

Util A	Util B	Util C
Saquinavir	Ritonavir	

References:
FDA: Drug Safety Communication: Invirase Labels Now Contain Updated Risk Information on Abnormal Heart Rhythms. Oct. 21, 2010.

11. Dabigatran / Overutilization _____ _____

Alert Message: Pradaxa (Dabigatran) may be over utilized. The manufacturer's recommended maximum dose for patients with CrCl > 30mL/min is 150 mg twice daily. Exceeding the recommended daily dose may result in adverse effects including major bleeds.

Conflict Code: - ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C **(Negating)**
Dabigatran		Severe Kidney Disease Stage 4 & 5

Max Dose: 300mg/day

References:
Pradaxa Prescribing Information, October 2010, Boehringer Ingelheim Pharmaceuticals, Inc.
Facts & Comparisons, 2011 Updates.

12. Dabigatran / Overutilization _____ _____

Alert Message: Pradaxa (Dabigatran) may be over utilized. The manufacturer's recommended maximum dose for patients with CrCl 15-30 mL/min is 75 mg twice daily. Exceeding the recommended daily dose may result in adverse effects including major bleeds.

Conflict Code: - ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Dabigatran		Severe Kidney Disease Stage 4 & 5

Max Dose: 150mg/day

References:
Pradaxa Prescribing Information, October 2010, Boehringer Ingelheim Pharmaceuticals, Inc.
Facts & Comparisons, 2011 Updates.

13. Dabigatran / Non-adherence _____ _____

Alert Message: Non-adherence to Pradaxa (dabigatran) therapy may result in sub-therapeutic effects increasing the risk stroke and systemic embolism. If dabigatran must be temporarily discontinued for any reason, therapy should be restarted as soon as possible.

Conflict Code: LR – Non-adherence
Drugs/Diseases

Util A	Util B	Util C
Dabigatran		

References:
Pradaxa Prescribing Information, October 2010, Boehringer Ingelheim Pharmaceuticals, Inc.
Facts & Comparisons, 2011 Updates.

14. Dabigatran / Drugs that Increase Bleeding _____ _____

Alert Message: Pradaxa (dabigatran) increases the risk of bleeding and can cause significant and, sometimes, fatal bleeding. Risk factors for bleeding include use of drugs that increase the risk of bleeding in general (e.g., antiplatelet agents, heparin, fibrinolytic therapy, and chronic use of NSAIDS) and labor and delivery. Dabigatran is contraindicated in patients with active pathological bleeding.

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

Util A	Util B	Util C
Dabigatran	NSAIDS	
	Aspirin	
	Heparin	
	Warfarin	
	Antiplatelet Agents	

References:
Pradaxa Prescribing Information, October 2010, Boehringer Ingelheim Pharmaceuticals, Inc.
Facts & Comparisons, 2011 Updates.

15. Dabigatran / Active Bleeds _____ _____

Alert Message: Pradaxa (dabigatran) increases the risk of bleeding and can cause significant and, sometimes, fatal bleeding. Dabigatran is contraindicated in patients with active pathological bleeding.

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

Util A	Util B	Util C
Dabigatran	GI Bleeds	
	Intracranial Hemorrhage	

References:
Pradaxa Prescribing Information, October 2010, Boehringer Ingelheim Pharmaceuticals, Inc.
Facts & Comparisons, 2011 Updates.

16. Dabigatran / P-gp Inducers _____ _____

Alert Message: Concurrent use of Pradaxa (dabigatran) and P-gp inducers should generally be avoided. In clinical studies the co-administration of rifampin with dabigatran decreased dabigatran AUC and Cmax by 66% and 67% respectively.

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

Util A	Util B	Util C
Dabigatran	Rifampin	
	Carbamazepine	
	Tipranavir	
	Ritonavir	
	Dexamethasone	
	Doxorubicin	
	Nefazodone	
	Prazosin	
	Trazodone	
	Vinblastine	
	Nelfinavir	

References:
Pradaxa Prescribing Information, October 2010, Boehringer Ingelheim Pharmaceuticals, Inc.
Clinical Pharmacology, 2010 Gold Standard.
Hartshorn EA and Tatro DS. Principles of Drug Interactions. Facts & Comparisons E Answers. 2010 Updates.
Facts & Comparisons, 2011 Updates.

17. Dabigatran / Therapeutic Appropriateness _____ _____

Alert Message: Remind patients that Pradaxa (dabigatran) capsules should always be swallowed whole, never broken, chewed or opened before administration. The oral bioavailability of dabigatran increases by 75% when the pellets are taken without the capsule shell resulting in increased systemic exposure and risk of bleeding.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Dabigatran		

References:
Pradaxa Prescribing Information, 2011, Boehringer Ingelheim Pharmaceuticals, Inc.
Facts & Comparisons, 2011 Updates.
Clinical Pharmacology, 2011 Gold Standard.

18. Lurasidone / Overutilization _____ _____

Alert Message: Latuda (lurasidone) may be over-utilized. The manufacturer's maximum recommended dose is 80 mg once daily. Exceeding the recommended dose may increase the risk of adverse effects (e.g., akathisia, somnolence, dystonia, and parkinsonism).

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C (Negating)
Lurasidone		Moderate Renal Impairment
		Severe Renal Impairment
		Diltiazem
		Verapamil
		Aprepitant
		Fluconazole
		Erythromycin
		Chronic Liver Disease and Cirrhosis

Max Dose: 80 mg/day

References:
Latuda Prescribing Information, Oct. 2010, Sunovion Pharma, Inc.
Facts & Comparisons, 2011 Updates.

19. Lurasidone / Moderate & Severe Renal and Hepatic Impairment _____ _____

Alert Message: Latuda (lurasidone) may be over-utilized. The manufacturer's recommends that the lurasidone dose should not exceed 40 mg once daily in patients with moderate to severe renal or hepatic impairment .

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C (Include)
Lurasidone 80mg		Moderate Renal Impairment
		Severe Renal Impairment
		Chronic Liver Disease and Cirrhosis

Max Dose: 40 mg/day

References:
Latuda Prescribing Information, Oct. 2010, Sunovion Pharma, Inc.
Facts & Comparisons, 2011 Updates.

20. Lurasidone / Non-adherence _____ _____

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

Conflict Code: LR - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Lurasidone		

References:
Latuda Prescribing Information, Oct. 2010, Sunovion Pharma, Inc.
Perkins DO, Predictors of Noncompliance in Patients with Schizophrenia, J Clin Psychiatry, 2002;63:1121-1128.
Weiden PJ, Zygmunt A, Medication Noncompliance in Schizophrenia: Part 1: Assessment, Jrnl Prac Psych and Behav Hlth, March 1997.
Weiden PJ, Olfson M, Cost of Relapse in Schizophrenia, Schizophrenia Bulletin, 1995;21(3):419-29.
Theida P, et.al., An Economic Review of Compliance with Medication Therapy in the Treatment of Schizophrenia, Psychiatric Services, 2003;54:508-516.
National Institute of Mental Health, Schizophrenia, NIH Publication No. 02-3517, 1999.

21. Lurasidone / Strong CYP3A4 Inhibitors _____ _____

Alert Message: The concurrent use of Latuda (lurasidone) with a strong CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin and nefazodone) is contraindicated. Coadministration of lurasidone with ketoconazole was shown to significantly increase the Cmax and AUC of lurasidone (6.9 and 9 times, respectively).

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

Util A	Util B		Util C
Lurasidone	Ketoconazole	Atazanavir	
	Itraconazole	Saquinavir	
	Indinavir	Clarithromycin	
	Nelfinavir	Nefazodone	
	Ritonavir	Telithromycin	

References:
Latuda Prescribing Information, Oct. 2010, Sunovion Pharma, Inc.
Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine. Available at: http://medicine.iupui.edu/clinpharm/ddos/table.asp.
FDA: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.
Facts & Comparisons, 2011 Updates.

22. Lurasidone / Strong 3A4 Inducers _____ _____

Alert Message: The concurrent use of Latuda (lurasidone) with a strong CYP3A4 inducer (e.g., rifampin, carbamazepine, and phenobarbital) is contraindicated. Coadministration of lurasidone with rifampin was shown to significantly decrease the Cmax and AUC of lurasidone as compared to that of lurasidone alone (1/7th and 1/5th, respectively).

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

Util A	Util B		Util C
Lurasidone	Rifampin	Nevirapine	
	Carbamazepine	Efavirenz	
	Phenytoin		
	Rifabutin		
	Phenobarbital		
	Dexamethasone		

References:
Latuda Prescribing Information, Oct. 2010, Sunovion Pharma, Inc.
Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine. Available at: http://medicine.iupui.edu/clinpharm/ddos/table.asp.
Facts & Comparisons, 2011 Updates.

23. Lurasidone / Moderate 3A4 Inhibitors _____ _____

Alert Message: The dose of Latuda (lurasidone) should not exceed 40 mg/day when it is co-administered with a moderate CYP3A4 inhibitor (e.g., diltiazem, verapamil, aprepitant, erythromycin, fluconazole). Lurasidone is a CYP3A4 substrate and metabolic inhibition of this isozyme may result in increased lurasidone plasma concentrations and risk of adverse effects.

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

Util A	Util B		Util C
Lurasidone 80mg	Diltiazem	Erythromycin	
	Verapamil	Fluconazole	
	Aprepitant		

Max Dose: 40 mg/day
References:
Latuda Prescribing Information, Oct. 2010, Sunovion Pharma, Inc.
Facts & Comparisons, 2011 Updates.

24. Lurasidone / Therapeutic Appropriateness _____ _____

Alert Message: The safety and effectiveness of Latuda (lurasidone) in pediatric patients have not been established.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Lurasidone		

Age Range: 0 – 17 yoa
References:
Latuda Prescribing Information, Oct. 2010, Sunovion Pharma, Inc.
Facts & Comparisons, 2011 Updates.

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	

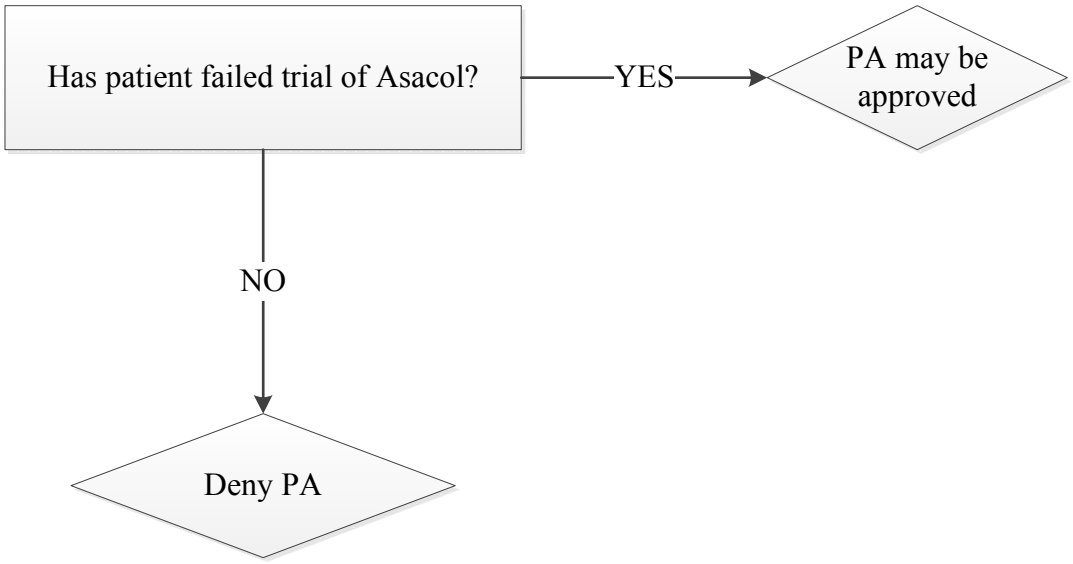
Part II: TO BE COMPLETED BY PHARMACY

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	

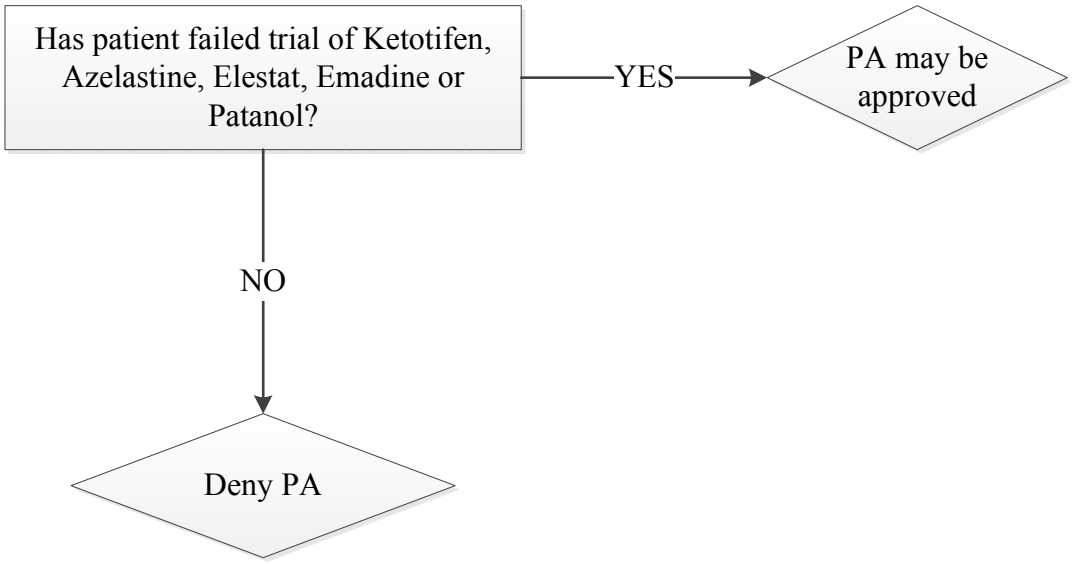
Part II: TO BE COMPLETED BY PHARMACY

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	

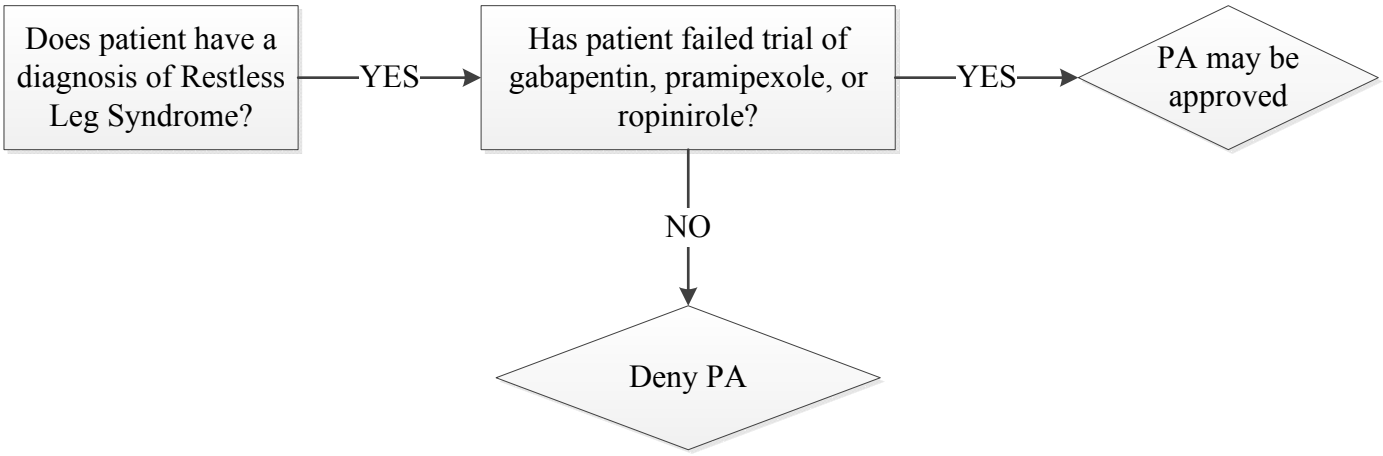
Part II: TO BE COMPLETED BY PHARMACY

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	

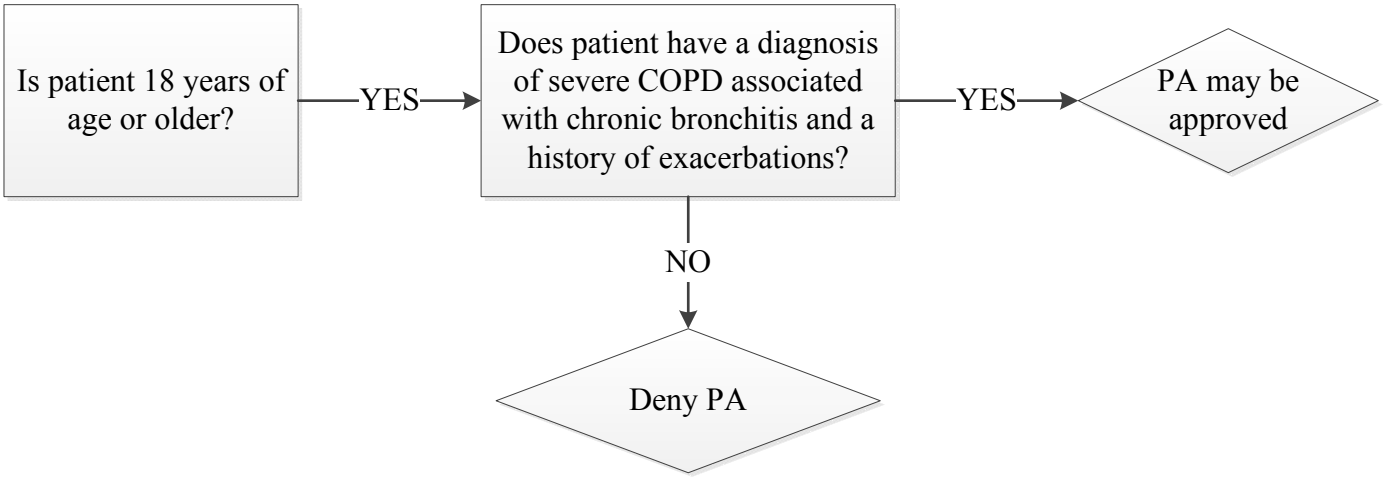
Part II: TO BE COMPLETED BY PHARMACY

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	

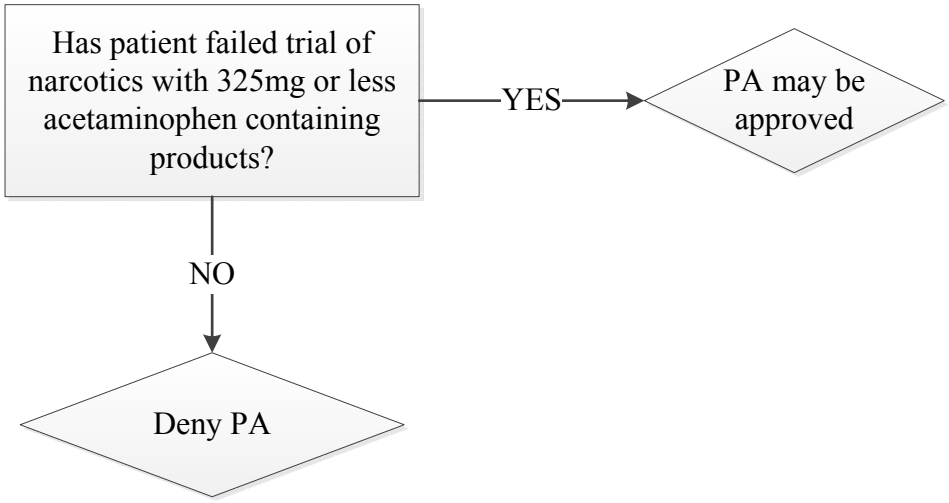
Part II: TO BE COMPLETED BY PHARMACY

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

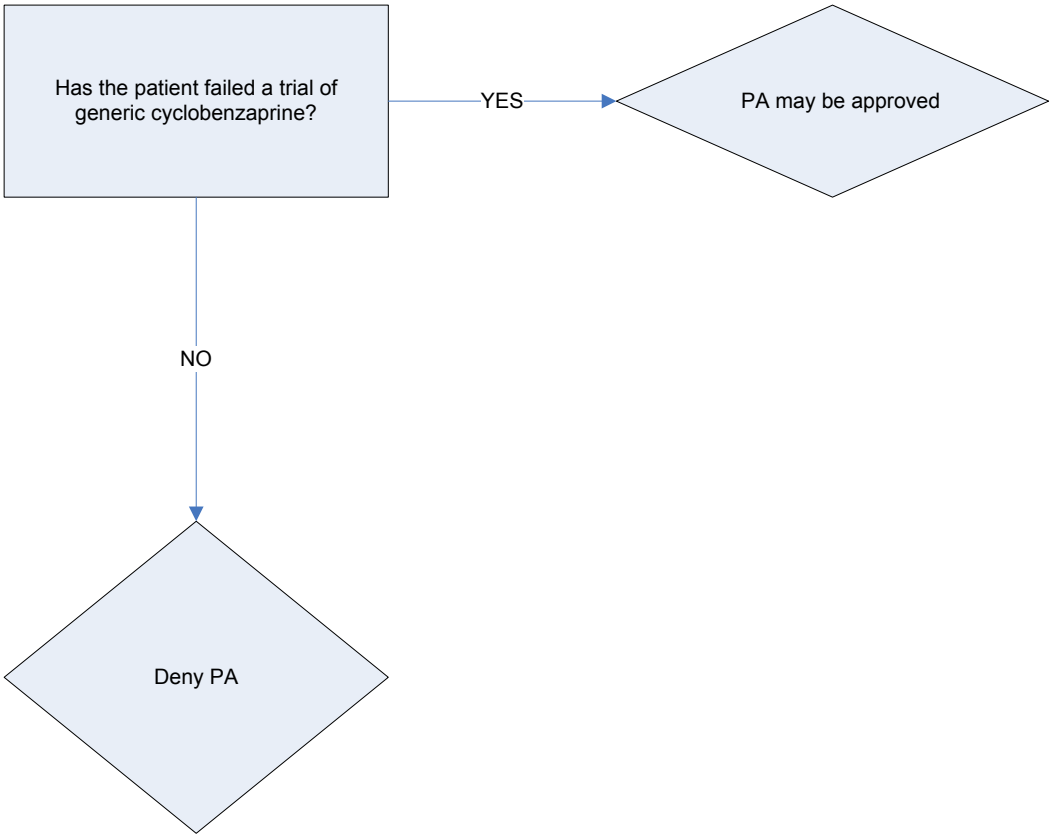
PHARMACY NAME:	ND MEDICAID PROVIDER NUMBER:
Phone:	FAX:
Drug:	NDC#:

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	

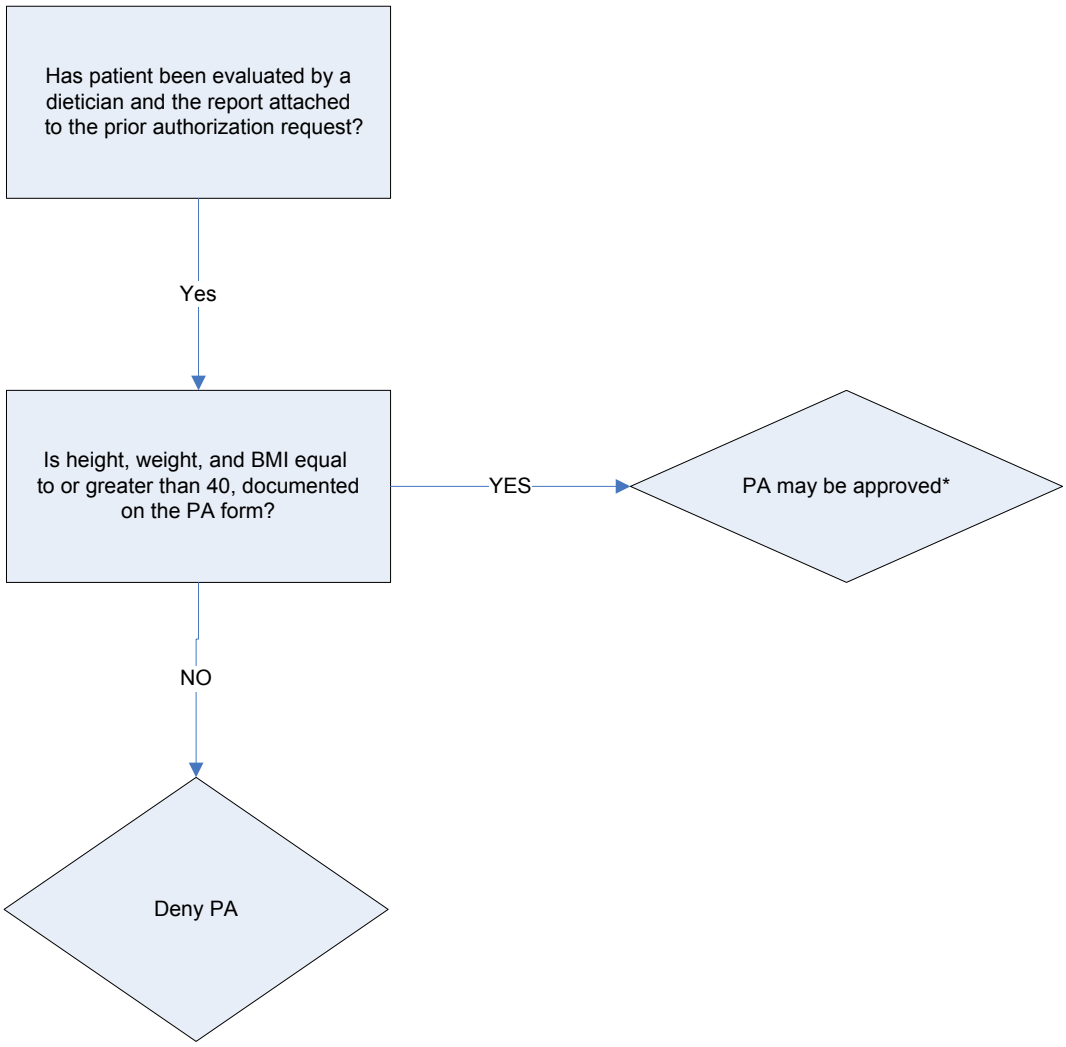
Part II: TO BE COMPLETED BY PHARMACY

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	

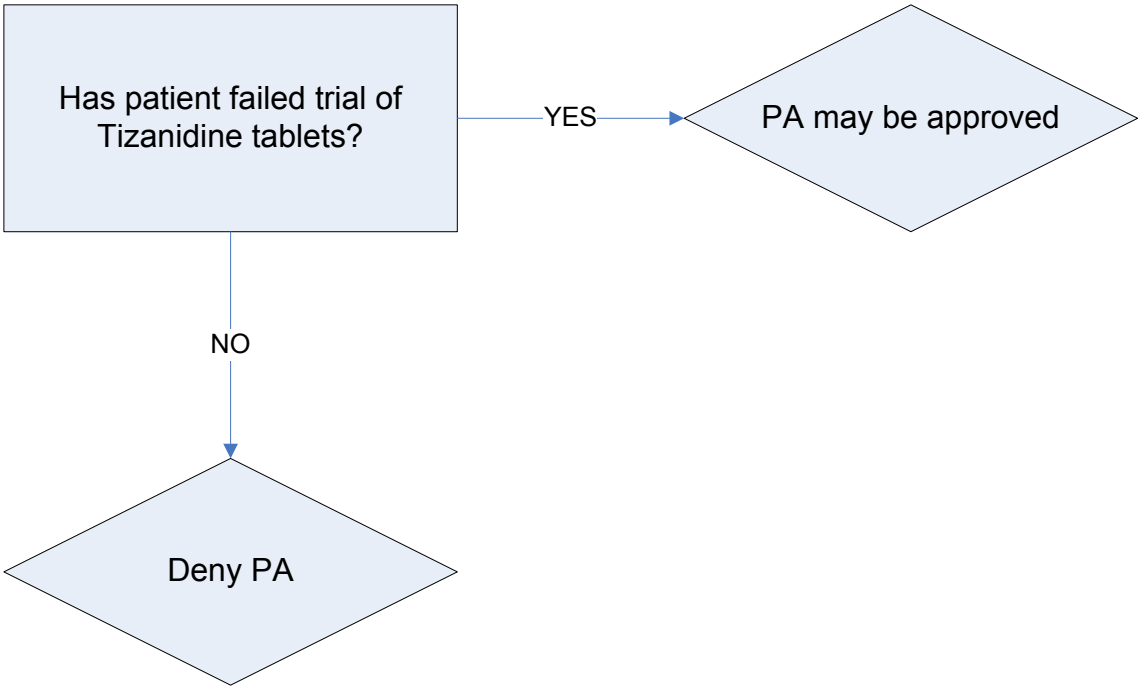
Part II: TO BE COMPLETED BY PHARMACY

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:

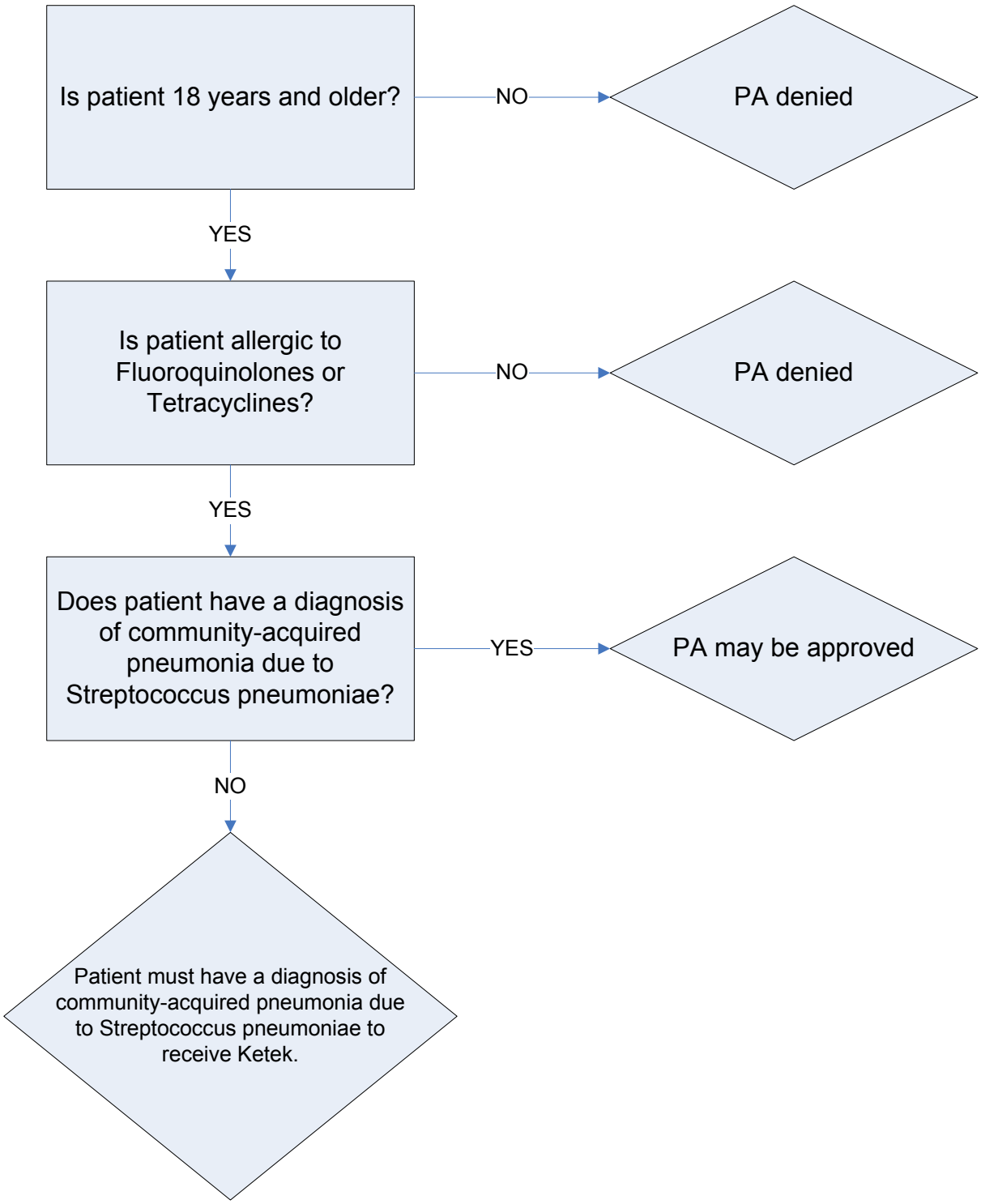
Part II: TO BE COMPLETED BY PHARMACY

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

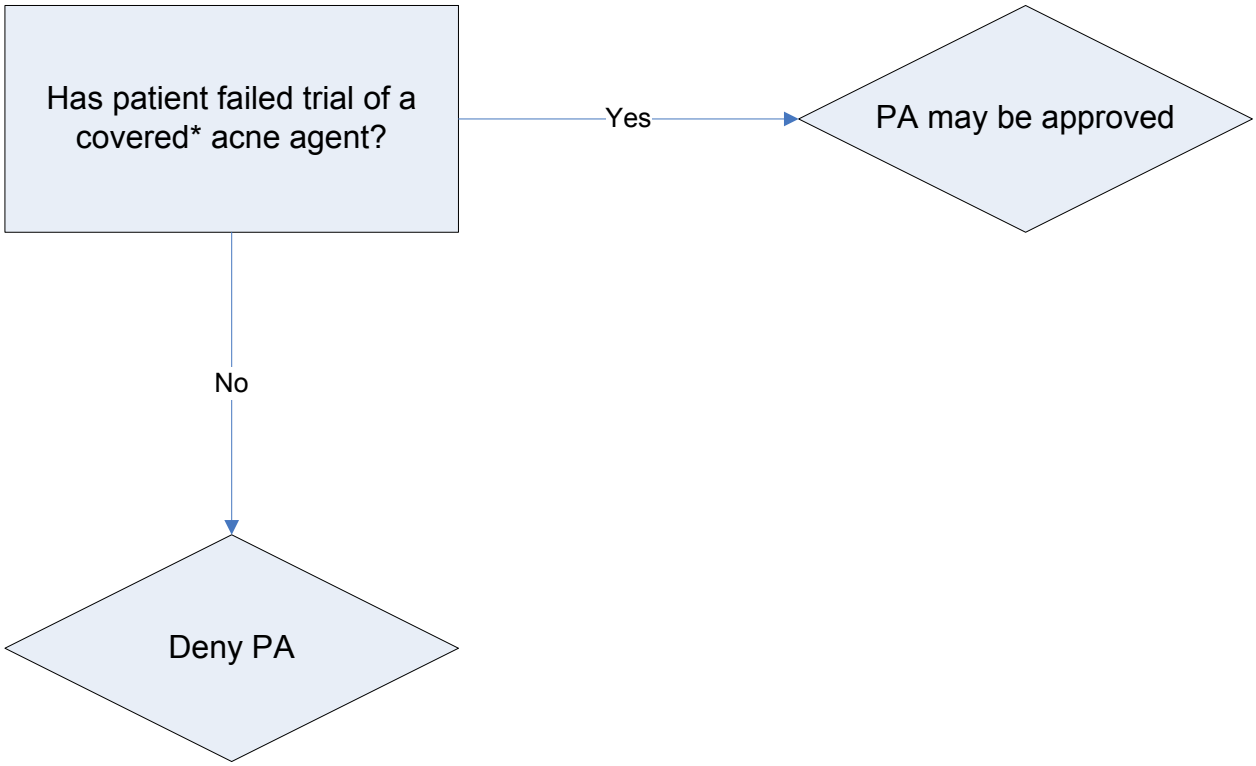
Part II: TO BE COMPLETED BY PHARMACY

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	

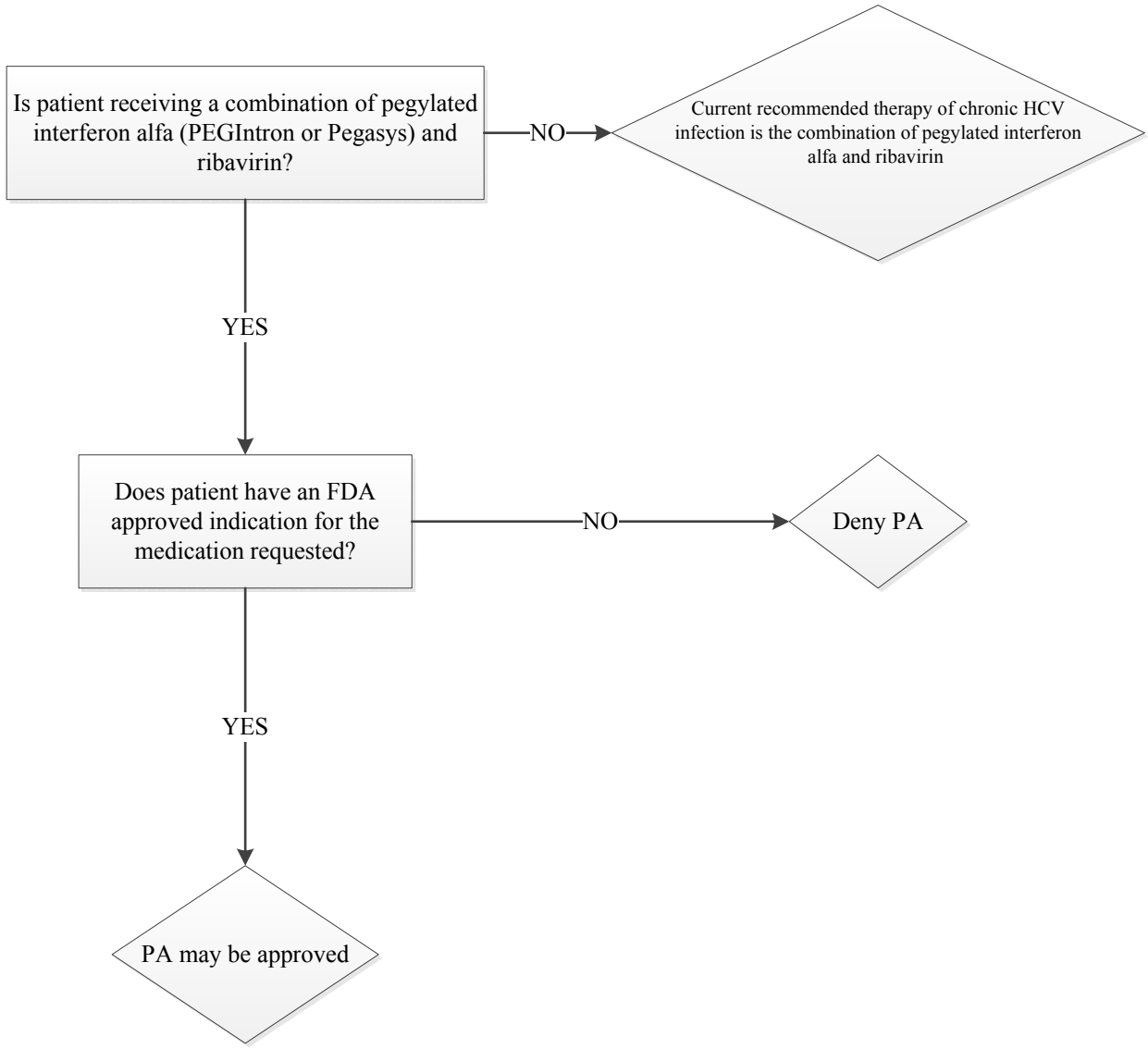
Part II: TO BE COMPLETED BY PHARMACY

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.

DUR Board Meeting
December 5, 2011
Pioneer Room
State Capitol

North Dakota Medicaid
DUR Board Meeting
Agenda
Pioneer Room
State Capitol
December 5, 2011
1pm

1. Administrative items
    - Travel vouchers

2. Old business
    - Review and approval of minutes of 09/12/11 meeting — Chair
    - Budget update — Brendan
    - Second review of Dificid — Brendan
    - Second review of New Oral Anticoagulants (Pradaxa, Xarelto, etc) — Brendan
    - Second review of agents used to treat Hereditary Angioedema — Brendan
    - Yearly PA review — HID
        - Solodyn
        - Oracea
        - Oxycontin
        - Short-Acting $Beta_2$ Agonists
        - Soma 250
        - Vusion
        - Targeted Immunomodulators
        - Moxatag
        - Uloric
        - Smoking Cessation
        - Topical Anesthetic Agents
        - Name Brand Narcotics
        - Ribapak
        - Metozolv
        - Suboxone/Subutex
        - Ampyra
        - Ultram/Rybix/Ryzolt
        - Xolair

3. New business
    - Review of Pulmonary Arterial Hypertension Agents — HID
    - Review of Topical Acne Agents — HID
    - Review of Benign Prostatic Hyperplasia — HID
    - Review of Juvisync — HID
    - Review of Gralise — 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
September 12, 2011

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

Chair, G. Pfister called the meeting to order at 1:03 pm. Chair, G. Pfister asked for a motion to approve the minutes from the September 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 are approximately 64,500 recipients eligible for Medicaid benefits. Approximately 19,200 receive prescriptions. There are approximately 58,160 pharmacy claims per month with a cost of approximately 2.9 million dollars.

Asacol HD Second Review
A motion and second were made at the June meeting to place Asacol HD 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.

Ophthalmic Antihistamines Second Review
A motion and second were made at the June meeting to place Ophthalmic Antihistamines on prior authorization. The topic was brought up for a second review. There was no public comment. Brendan will determine if OTC manufacturers of ophthalmic antihistamines provide federal rebates. If they do, OTC products will be covered. After discussion, Chair, G. Pfister called for a voice vote to approve the motion. The motion passed with no audible dissent.

Horizant Second Review
A motion and second were made at the June meeting to place Horizant 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.

Daliresp Second Review
A motion and second were made at the June meeting to place Daliresp 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.

Narcotics with high dose acetaminophen Second Review
A motion and second were made at the June meeting to place narcotics with acetaminophen (other than 5/325 and 10/325) 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. DAW,

Amrix/Fexmid, Xenical, Zanaflex, Ketek, and Aczone forms and criteria were reviewed. No changes were made.

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

Dificid Review
B. Joyce reviewed Dificid information with the Board. There was no public comment. After discussion, T. Twogood made a motion to place Dificid on prior authorization. G. Pfister seconded the motion. This topic will be brought up at the next meeting for finalization.

New Oral Anticoagulants Review
B. Joyce reviewed new oral anticoagulants information with the Board. J. Robinson, representing Boehringer Ingelheim, spoke regarding Pradaxa. J. Stoffel, representing Janssen Scientific Affairs, spoke regarding Xarelto. After discussion, J. Savageau made a motion to place Pradaxa on prior authorization. G. Pfister seconded the motion. This topic will be brought up at the next meeting for finalization.

Hereditary Angioedema Review
B. Joyce reviewed products used to treat Hereditary Angioedema with the Board. L. Smith, representing Shire, spoke regarding Firazyr. After discussion, C. Huber made a motion to place these agents on prior authorization. P. Churchill seconded the motion. This topic will be brought up at the next meeting for finalization.

Avandia Update
B. Joyce updated the board on the recent FDA safety announcement regarding Avandia. Because Avandia will only be available through a Risk Evaluation and Mitigation Strategy (REMS) system, the board chose to not make any changes to Avandia coverage.

Simvastatin Update
B. Joyce updated the board on the recent FDA safety announcement regarding high dose simvastatin.

Hepatitis C Update
B. Joyce reviewed the current PA form for Hepatitis C including the two new agents on the market, Victrelis and Incivek. Board members recommended that the form have a space for genotype.

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 N. Byers 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 December 5, 2011. P. Churchill made a motion to adjourn the meeting. N. Byers seconded. The motion passed with no audible dissent. Chair G. Pfister adjourned the meeting at 3:00 pm.

DIFICID 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 Dificid must meet the following criteria:

- **Patient must have diagnosis of *Clostridium difficile*-associated diarrhea (CDAD)**
- **Patient must be ≥ 18 years of age**
- **Patient must have been treated per the current guidelines and failed**
- **Compounded oral vancomycin is covered without prior authorization**
- **Metronidazole is covered without 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: □ DIFICID	**Diagnosis for this Request:**	**Failed therapy:** **Start Date:** **End Date:**
□ *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

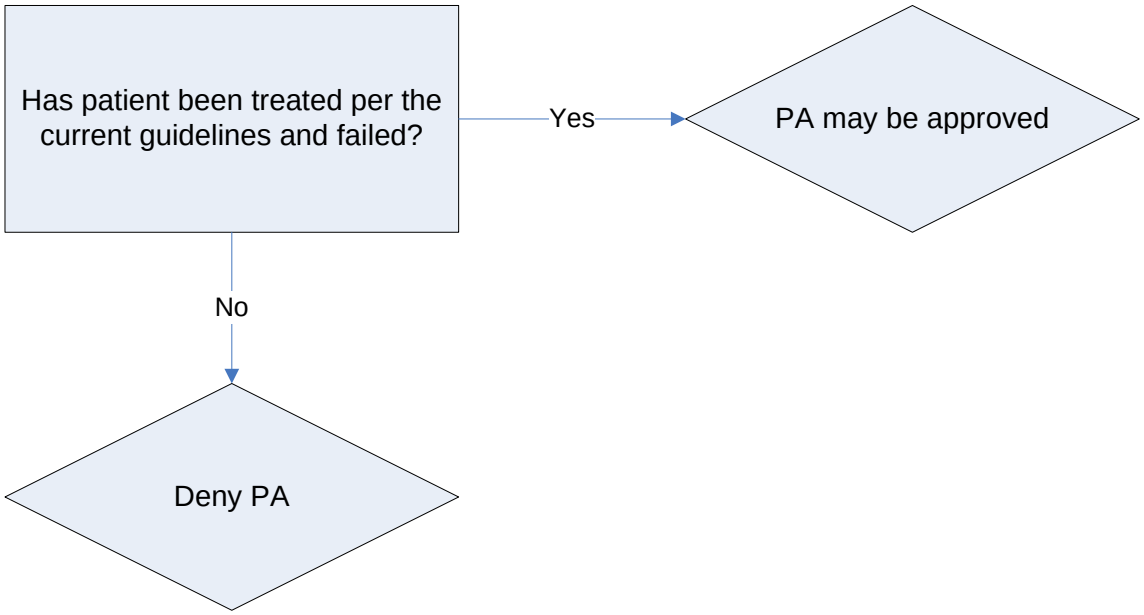
Part II: TO BE COMPLETED BY PHARMACY

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
Dificid Prior Authorization Algorithm



- Patient must have diagnosis of *Clostridium difficile*-associated diarrhea (CDAD)
- Patient must be ≥ 18 years of age
- Patient must have been treated per the current guidelines and failed
- Compounded oral vancomycin is covered without prior authorization
- Metronidazole is covered without prior authorization

ORAL ANTICOAGULANTS
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 Pradaxa must meet the following criteria:

- **Patient must have diagnosis of atrial fibrillation**

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: □ PRADAXA	**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.*			
Prescriber Signature		Date	

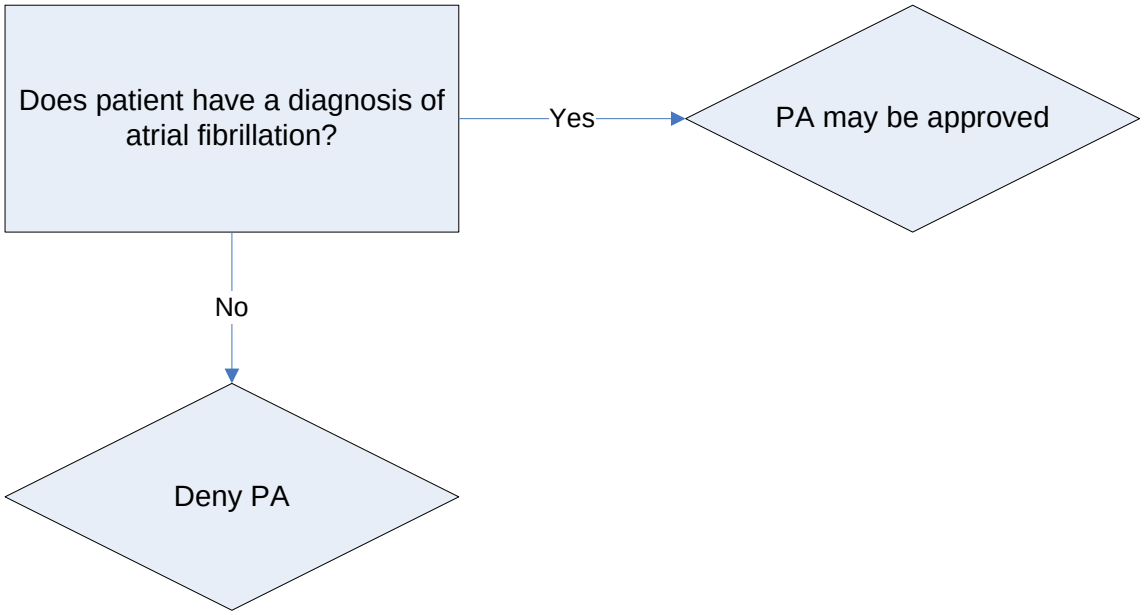
Part II: TO BE COMPLETED BY PHARMACY

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
Oral Anticoagulants Prior Authorization Algorithm



HEREDITARY ANGIOEDEMA
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 an agent used to treat hereditary angioedema must meet the following criteria:

- **Patient must have diagnosis of hereditary angioedema confirmed by a specialist**

Part I: TO BE COMPLETED BY PHYSICIAN

Recipient Name	**Recipient Date of Birth**	Recipient Medicaid ID Number	
Physician Name	Specialist Involved in therapy:		
Physician Medicaid Provider Number	Telephone Number	Fax Number	
Address	City	State	Zip Code
Requested Drug and Dosage: □ BERINERT □ FIRAZYR □ CINRYZE □ KALBITOR	**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.*			
Prescriber Signature		Date	

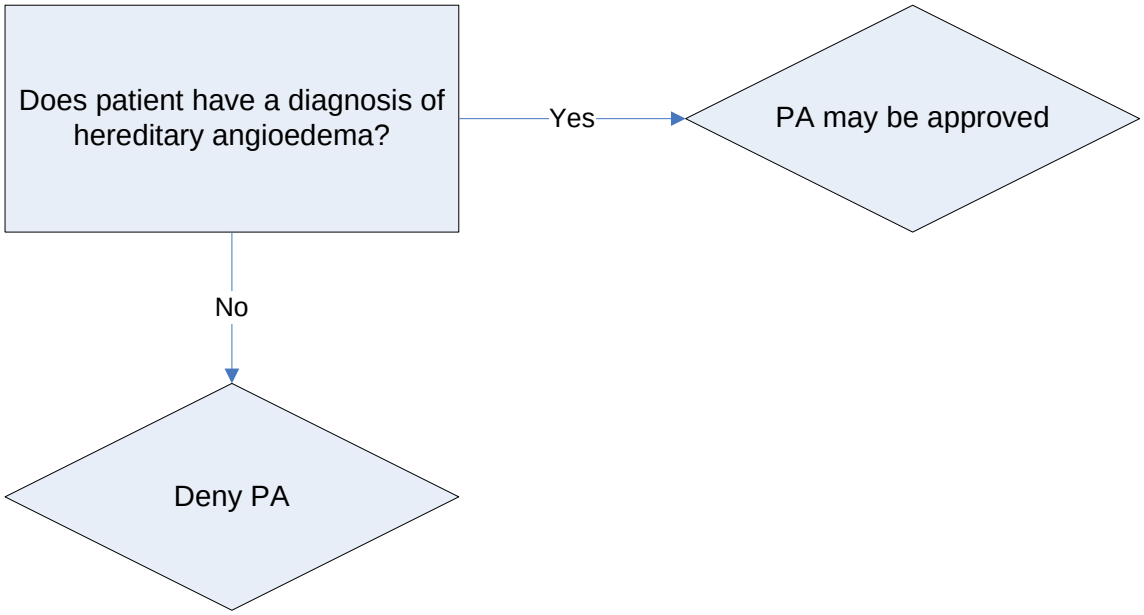
Part II: TO BE COMPLETED BY PHARMACY

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
Hereditary Angioedema Prior Authorization Algorithm



SOLODYN 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

Note: ND Medicaid will not pay for Solodyn without documented failure of a first line tetracycline agent.

- First line agents include: doxycycline, minocycline, and tetracycline.

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: □ **SOLODYN**	**Requested Dosage:** (must be completed)

Qualifications for coverage:

□ Patient has failed a 90 day trial of which first line agent _____

□ *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:

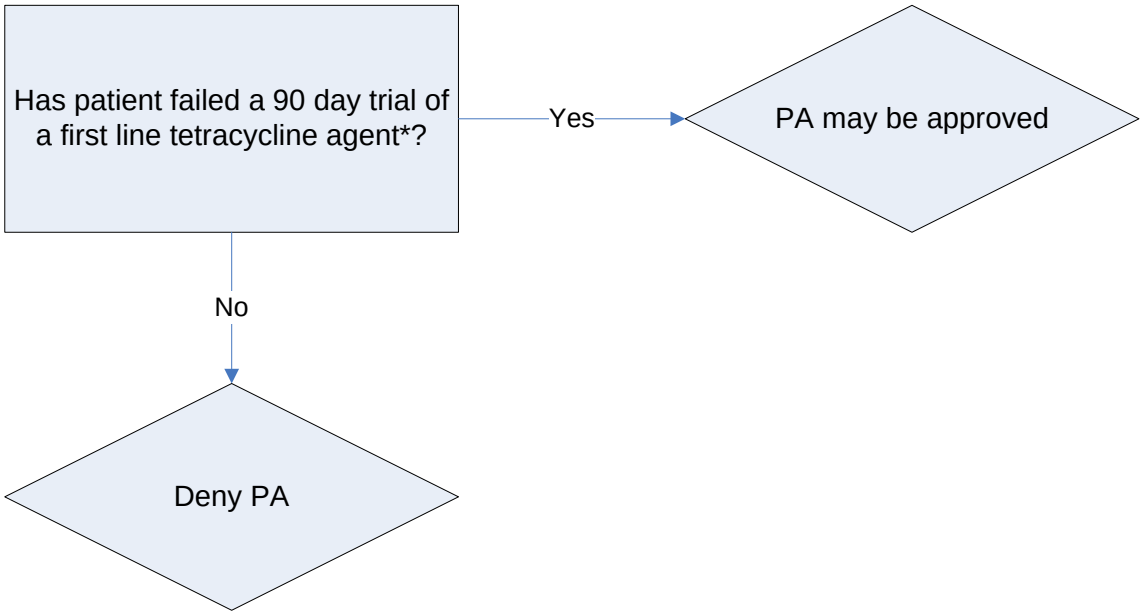
Part II: TO BE COMPLETED BY PHARMACY

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
Solodyn Prior Authorization Algorithm



*Doxycycline, minocycline, and tetracycline do not require a PA and cost approximately $3 - $40 for a course of therapy compared to $775 dollars for Solodyn.

DORYX and ORACEA 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

Note: ND Medicaid will not pay for Oracea without documented failure of a first line tetracycline agent.

- First line agents include: doxycycline, minocycline, and tetracycline.

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: □ **ORACEA** □ **DORYX**	**Requested Dosage:** (must be completed)

Qualifications for coverage:

□ Patient has failed a 90 day trial of which first line agent _____

□ *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:

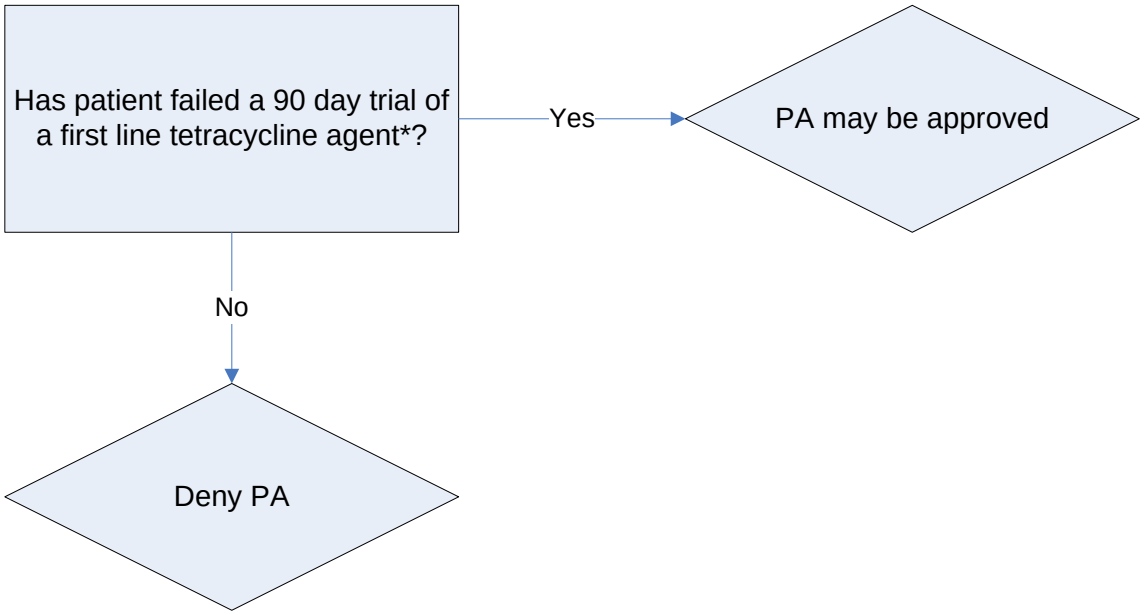
Part II: TO BE COMPLETED BY PHARMACY

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
Doryx and Oracea Prior Authorization Algorithm



**Doxycycline, minocycline, and tetracycline do not require a PA and cost approximately $3 - $40 for a course of therapy compared to $353 dollars for Oracea and $331 dollars for Doryx.

HEALTH INFORMATION DESIGNS

Prior Authorization Vendor for ND Medicaid

OXYCODONE CR
PA FORM

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

***Note: The PA may be approved if all of the following criteria are met.**

- **Patient has a chronic pain indication (includes cancer).**
- **Patient has taken an immediate release narcotic for the past 90 days or is switching from another sustained release opioid analgesic.**

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: □ OXYCODONE CR	**DOSAGE:**	**Diagnosis for this request:**		
QUALIFICATIONS FOR COVERAGE: □ CHRONIC MALIGNANT PAIN INDICATION □ CHRONIC NON-MALIGNANT PAIN INDICATION		**LIST IMMEDIATE RELEASE MEDICATION TAKEN:**		
LIST OTHER SUSTAINED RELEASE OPIOID ANALGESIC PATIENT IS SWITCHING FROM:				
□ *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	

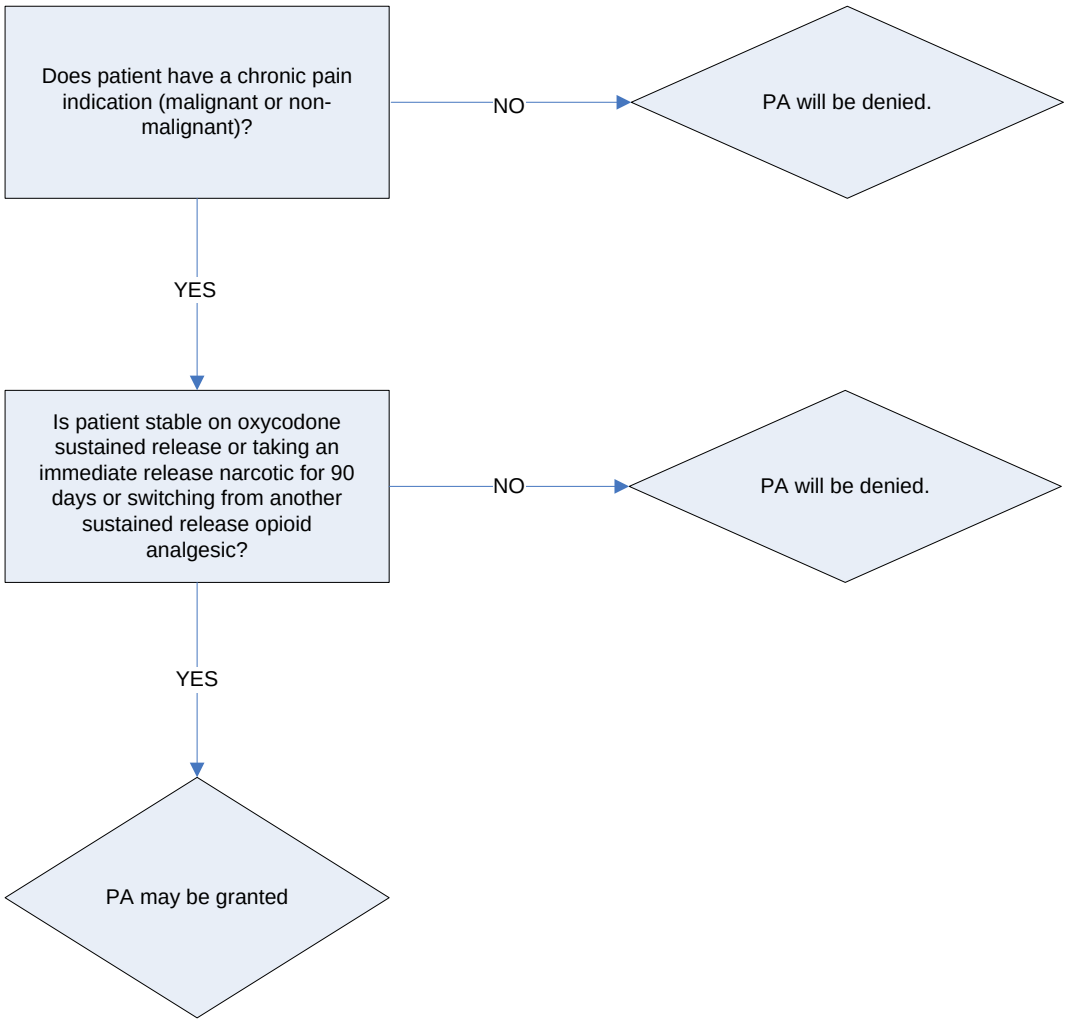
Part II: TO BE COMPLETED BY PHARMACY

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
Oxycodone CR Prior Authorization Criteria Algorithm



Short-Acting HFA Beta$_2$ Agonist 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 ProAir HFA, Ventolin HFA, or Xopenex HFA must use Proventil HFA as first line therapy.

***Note: Proventil HFA does not require a prior authorization.**

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: □ XOPENEX HFA □ VENTOLIN HFA □ PROAIR HFA	**Diagnosis for this request:**		

Qualifications for coverage:

□ Failed Proventil HFA therapy	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

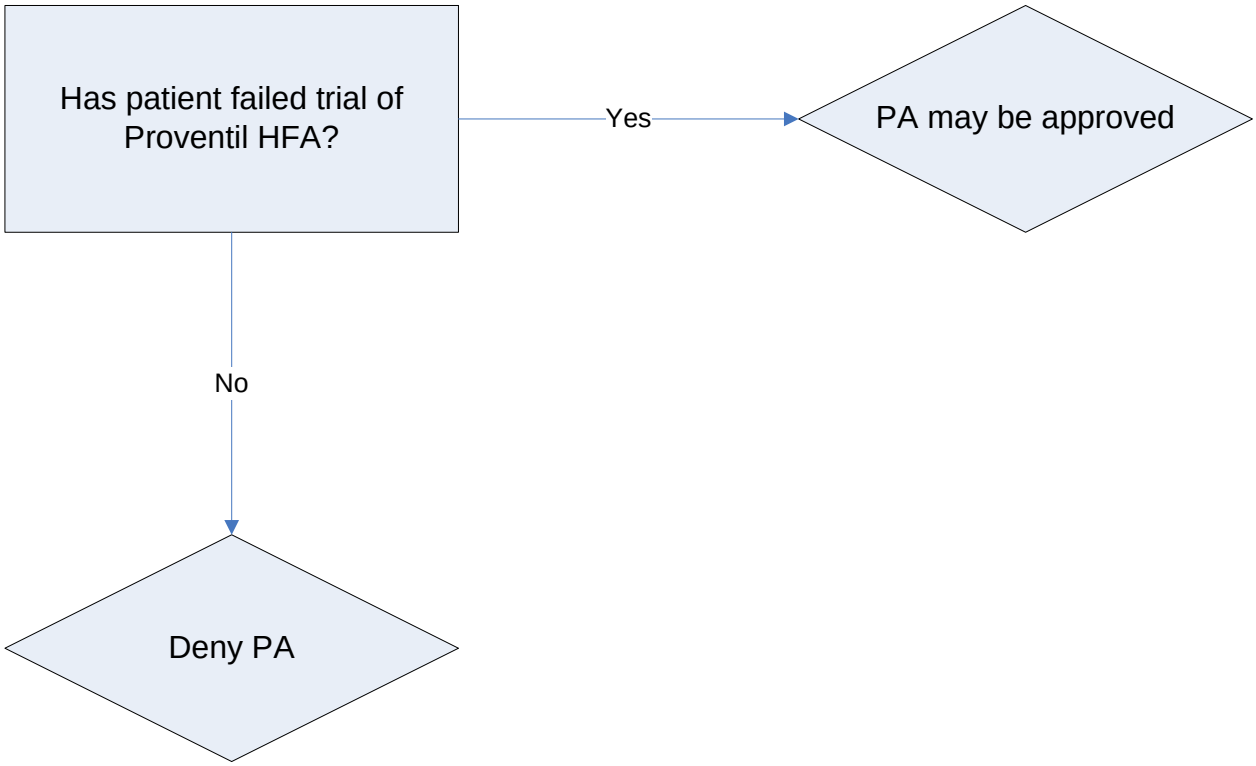
Part II: TO BE COMPLETED BY PHARMACY

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 Short-Acting Beta$_2$ Agonist Authorization Algorithm



SOMA 250mg 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 using brand name Soma 250mg must use generic carisoprodol 350mg first line.

***Note: The PA will be approved if recipient fails a trial of carisoprodol 350mg.**

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: □ SOMA 250MG	**Diagnosis for this request:**		

Qualifications for coverage:

□ Failed skeletal muscle relaxant therapy	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

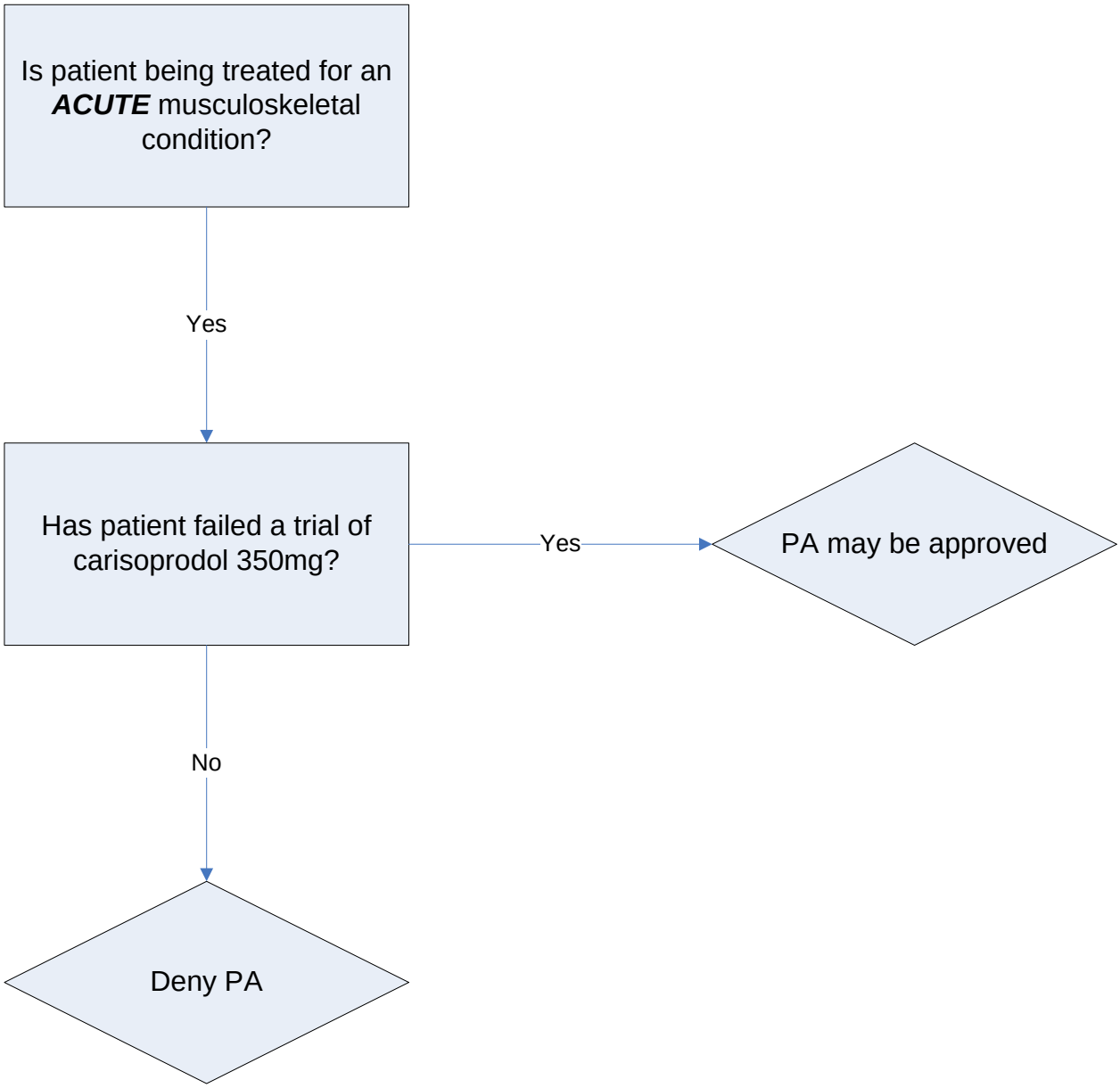
Part II: TO BE COMPLETED BY PHARMACY

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
Soma 250mg Authorization Algorithm



Vusion 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 Vusion must try other topical antifungal products as first line therapy.

***Note: Nystatin and clotrimazole do not require a prior authorization.**

Part I: TO BE COMPLETED BY PRESCRIBER

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: □ VUSION	**Diagnosis for this request:**		

Qualifications for coverage:

□ Failed antifungal 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

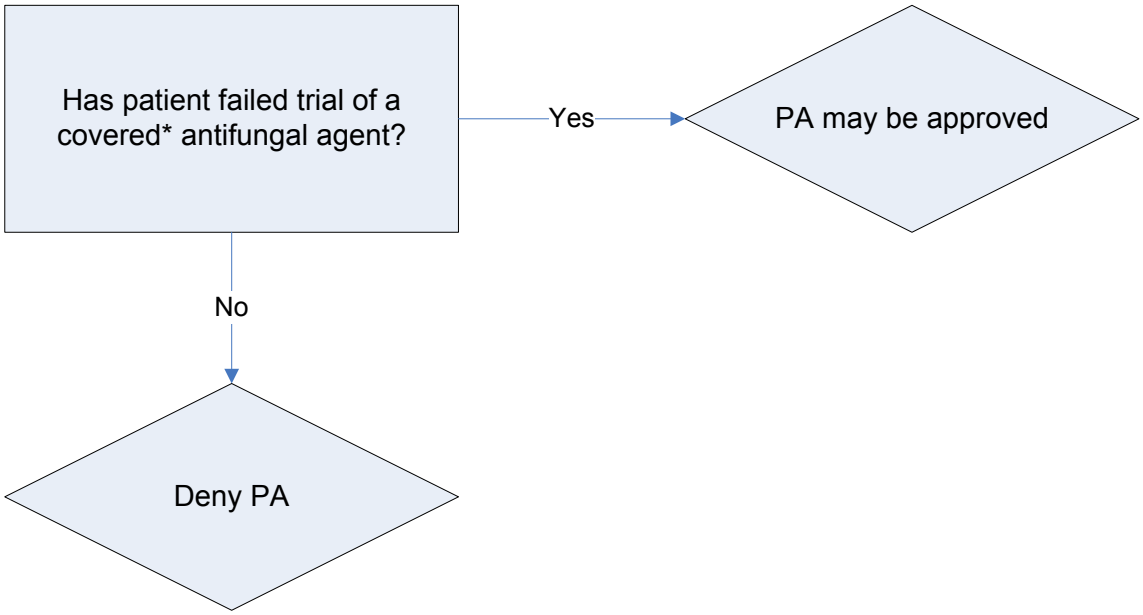
Part II: TO BE COMPLETED BY PHARMACY

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
Vusion Prior Authorization Algorithm



*Nystatin and clotrimazole do not require a PA and cost approximately $6 - $36 for a course of therapy compared to $246 for a course of Vusion therapy.

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 Actemra, Orencia, Humira, Enbrel, Amevive, Kineret, Cimzia, Remicade, Simponi and Stelara must submit a prior authorization form.

- Prior authorization will be granted if the requested product has been approved by the FDA for the indication listed below.

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:		**FDA Approved Indication for this request:**
□ ORENCIA	□ AMEVIVE	
□ ENBREL	□ CIMZIA	
□ KINERET	□ REMICADE	
□ HUMIRA	□ SIMPONI	
□ STELARA	□ ACTEMRA	

□ *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

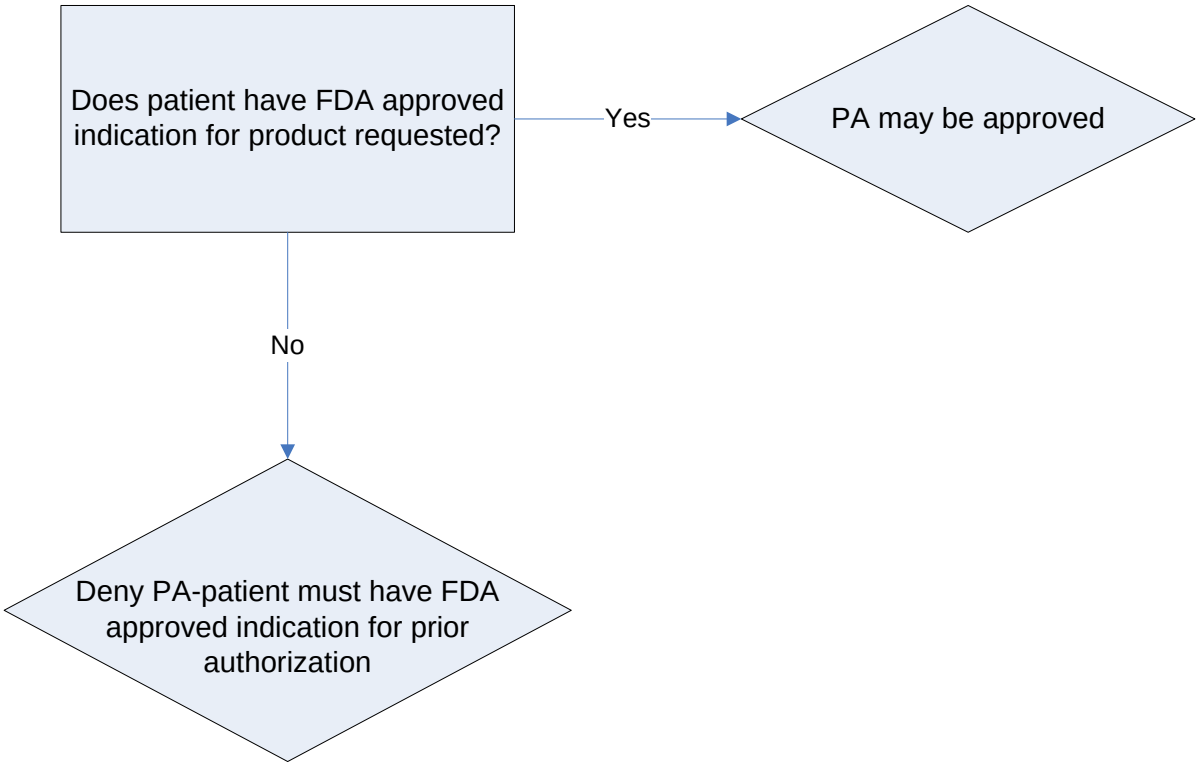
Part II: TO BE COMPLETED BY PHARMACY

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
Targeted Immune Modulators Authorization Algorithm



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

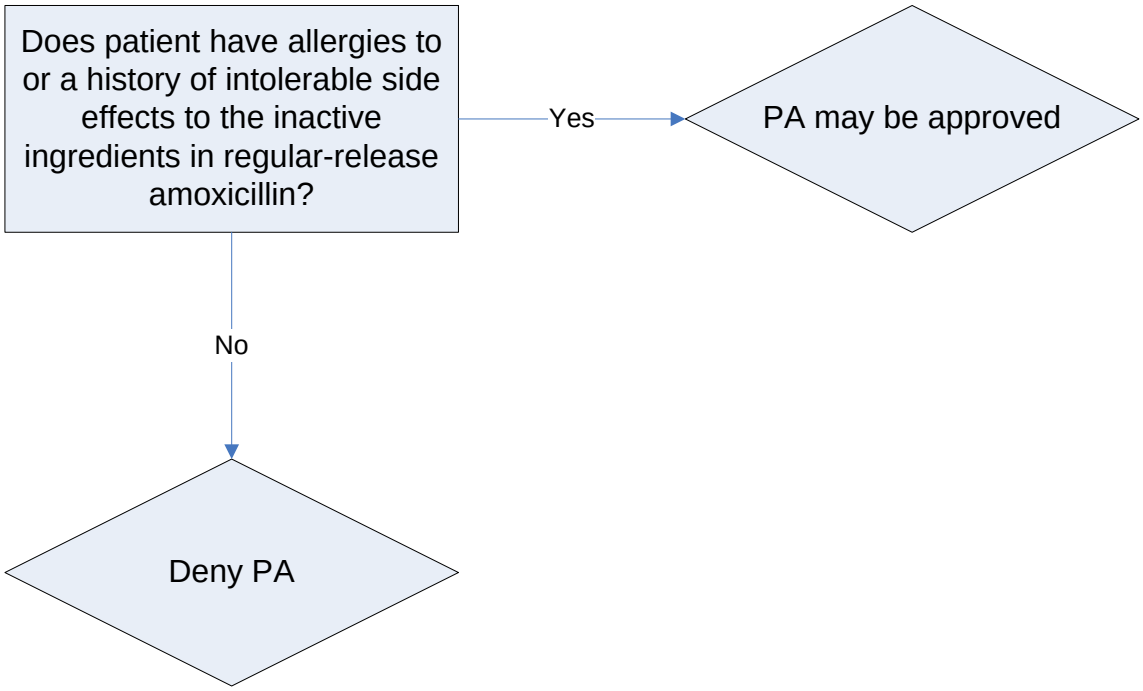
Part II: TO BE COMPLETED BY PHARMACY

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.

ULORIC 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 Uloric must try allopurinol as first line therapy or have documented renal/hepatic dysfunction.

- Allopurinol does not require a prior authorization.
- Allopurinol doses must be 300 mg or greater to be considered failed 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: □ ULORIC	**Diagnosis for this request:**		

Qualifications for coverage:

□ FAILED ALLOPURINOL THERAPY	Start Date	End Date	Dose	Frequency
□ RENAL OR HEPATIC IMPAIRMENT				
□ *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	

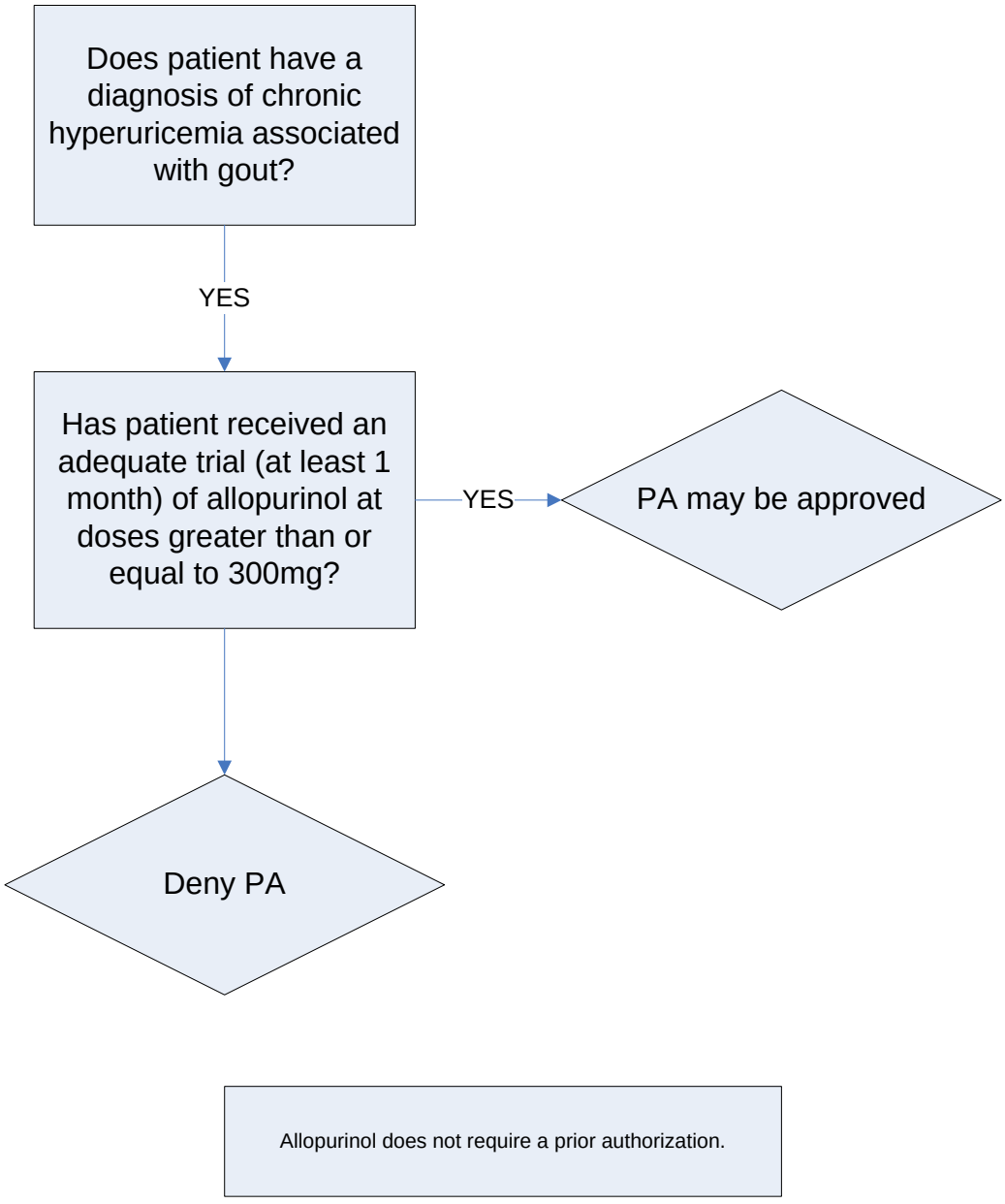
Part II: TO BE COMPLETED BY PHARMACY

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



Smoking Cessation Program

North Dakota Quitline

1-800-QUIT-NOW

Prior Authorization Vendor for ND Medicaid

North Dakota Medicaid has recently joined forces with the Department of Health to provide free, confidential, telephone-based cessation counseling to recipients interested in quitting tobacco. Beginning November 15, 2008, in order to receive smoking cessation products (patches, gum, lozenges, bupropion, or Chantix®), Medicaid recipients must be signed up with the North Dakota Tobacco Quitline (1-800-QUIT-NOW or 1-800-784-8669). Once a recipient is enrolled in counseling, they will work with their counselor to determine which medications they wish to use. The complete process is described below:

1. Patient calls ND Quitline and enrolls in counseling.
2. Quitline counselors guide patient through quitting process.
3. Individualized treatment plan developed.
4. If medications are used, the patient will receive an enrollment letter which will include the Quitline's standing orders for the specific medication(s).
5. The HID Prior Authorization form will be included with the letter
6. The client must contact their physician and obtain the prescription.
7. The patient, physician or pharmacy must fax the Prior Authorization form and enrollment letter to HID.
8. Patient takes prescription to pharmacy.
9. Pharmacy fills prescription and the claim is paid.

Patients will be limited to a 90 day supply of therapy for patches, gum, lozenges, and bupropion, every two years. Combination therapy with these medications is allowed.

Chantix is limited to the initial 12 weeks of therapy with an additional 12 weeks (24 consecutive weeks) allowed if the patient has continuously quit for a minimum of one month (since day 56 of therapy). The Chantix regimen will be allowed once every two years.

Prior authorizations will be entered based upon the recipient's Quit Date. This means that the approval date range will be sufficient to allow recipients to pick up medications at least one week prior to their Quit Date. Compliance will be an important aspect of the patient's success.

Please contact Health Information Designs, Inc. at (334) 502-3262 or toll free at 1-800-225-6998, with questions regarding the smoking cessation prior authorization process.

LOCAL ANESTHETICS (TOPICAL) 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 a topical local anesthetic must meet the following criteria:

- **These medications will only be covered when prescribed for use prior to certain procedures (e.g., placement of a peripheral or central line or injections through an implanted port). Medical procedure must be listed on PA form.**
- **PA not required for patients 12 years of age and younger.**

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: □ EMLA □ SYNERA	**Medical Procedure:**		
Physician Signature		Date	

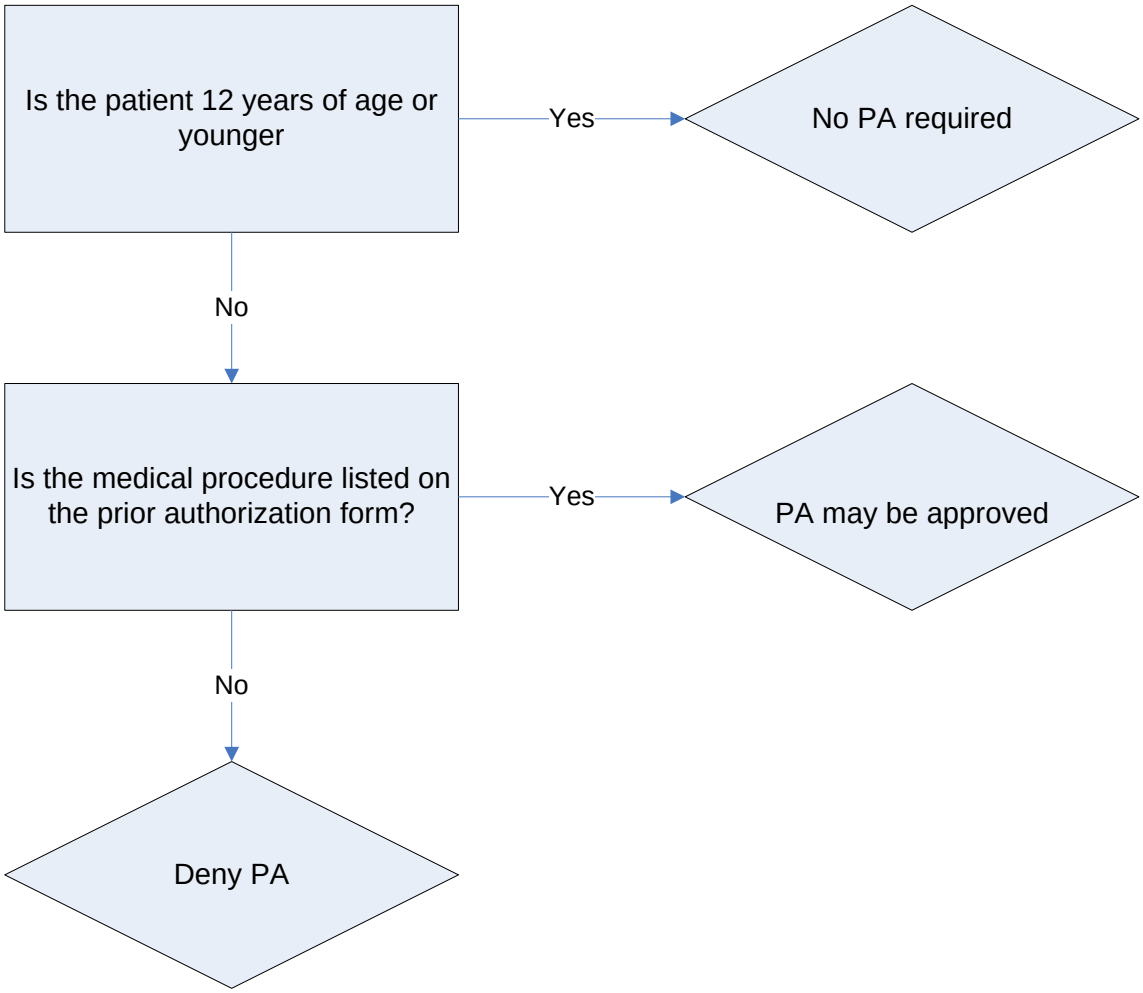
Part II: TO BE COMPLETED BY PHARMACY

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
Local Anesthetics (Topical) Prior Authorization Algorithm



BRAND-NAME NARCOTICS 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 a brand-name narcotic must meet the following criteria:

- **Documented failure of a 30-day trial of a generic narcotic.**

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:

□ EMBEDA □ OPANA ER □ KADIAN □ AVINZA □ EXALGO □ FENTORA □ ONSOLIS □ MAGNACET □ BUTRANS

□ OTHER BRAND NAME PRODUCT _____

FAILED THERAPY	**START DATE**	**END DATE**	**DOSE**	**FREQUENCY**

Physician Signature	Date

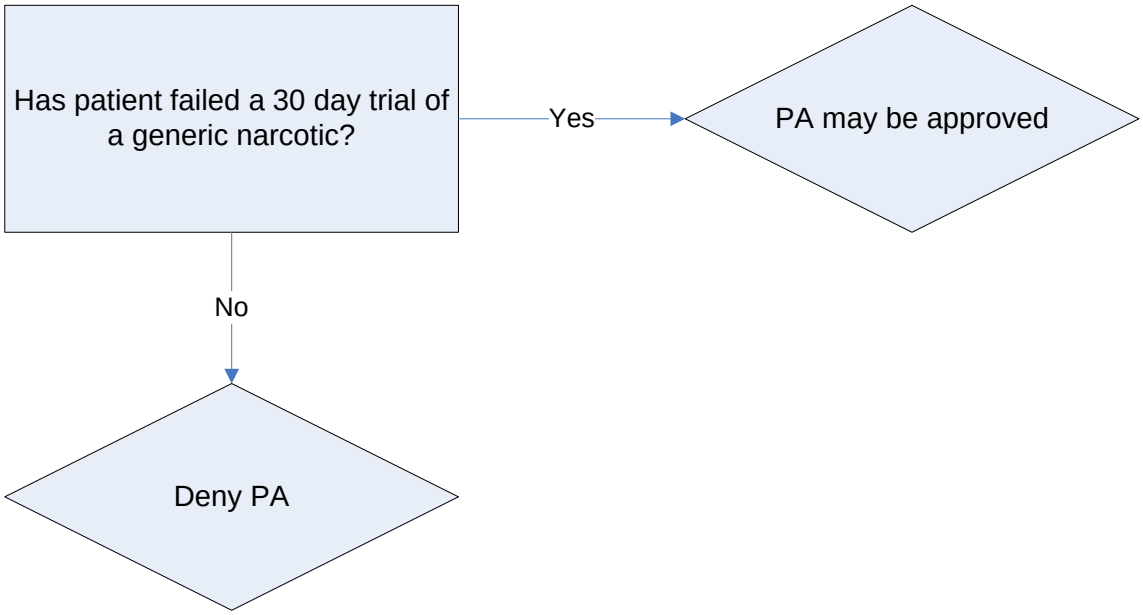
Part II: TO BE COMPLETED BY PHARMACY

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
Name-brand Narcotics Prior Authorization Algorithm



RIBAPAK 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 RibaPak must meet the following criteria:

- **Patient must first try Ribavirin or Ribasphere.**

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: □ RIBAPAK	**FDA Approved Indication for this request:**		

□ **Failed therapy with Ribavirin or Ribasphere**	**Start Date**	**End Date**	**Dose**
WHAT IS THE HCV GENOTYPE? (I-IV)			
***TREATMENT WILL BE COVERED FOR 24 TO 48 WEEKS BASED UPON GENOTYPE AND DIAGNOSIS.**			
□ Treatment regimen for Hepatitis C will include pegylated or non-pegylated interferon in combination with oral ribavirin.			
Physician Signature		Date	

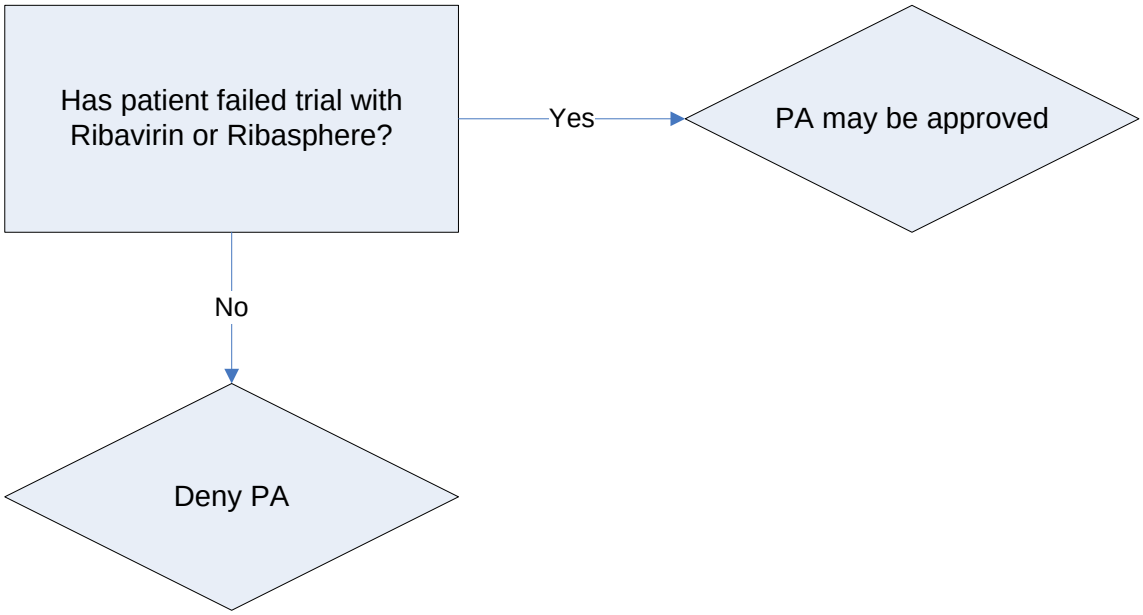
Part II: TO BE COMPLETED BY PHARMACY

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
Ribapak Prior Authorization Algorithm



METOZOLV ODT 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 Metozolv must meet the following criteria:

- **Patient must try metoclopramide.**

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: □ METOZOLV		**Diagnosis for this request:**	
□ **FAILED METOCLOPRAMIDE THERAPY**	**START DATE**	**END DATE**	**DOSE**
□ *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	

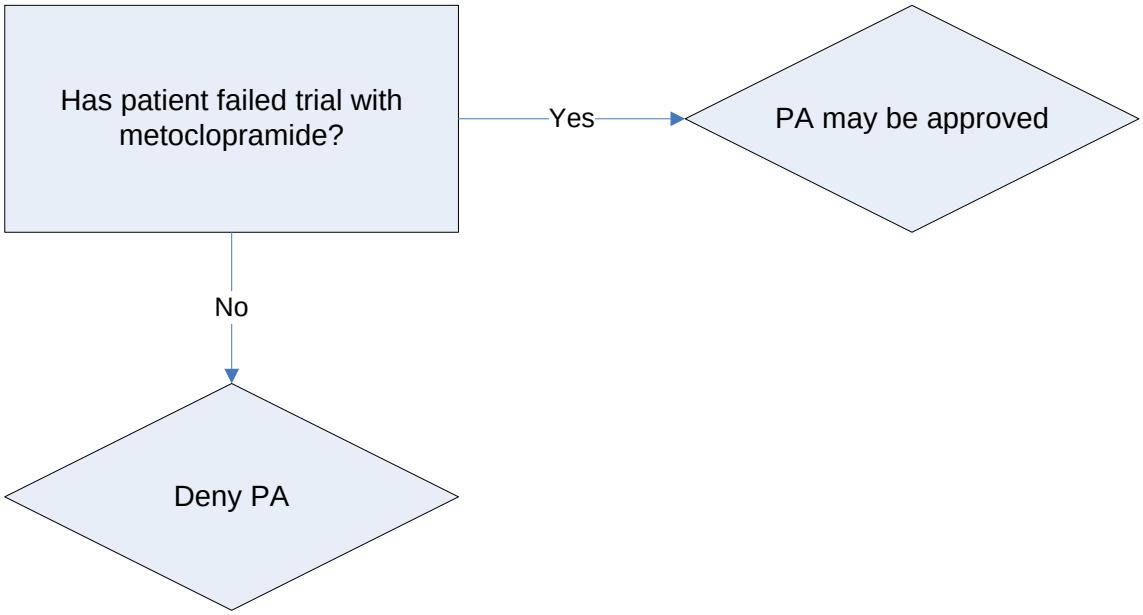
Part II: TO BE COMPLETED BY PHARMACY

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
Metozolv Prior Authorization Algorithm



SUBOXONE/SUBUTEX 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 Suboxone and Subutex must meet the following criteria:

- **Patient must be 16 years or older.**
- **Indicated for use in treatment of documented opioid dependence.**
- **Must not be taking other opioids, tramadol, or carisoprodol concurrently.**
- **Prescriber must be registered to prescribe Suboxone/Subutex under the Substance Abuse and Mental Health Services Administration (SAMHSA).**

Part I: TO BE COMPLETED BY PHYSICIAN

Recipient Name	**Recipient Date of Birth**	Recipient Medicaid ID Number	
Physician Name	**(SAMHSA ID)**		
Physician Medicaid Provider Number	Telephone Number	Fax Number	
Address	City	State	Zip Code
Requested Drug and Dosage: □ SUBOXONE □ SUBUTEX	**FDA Approved Indication for this request:**		
□ Patient is not taking other opioids, tramadol, or carisoprodol concurrently with Suboxone or Subutex.			
Physician Signature	Date		

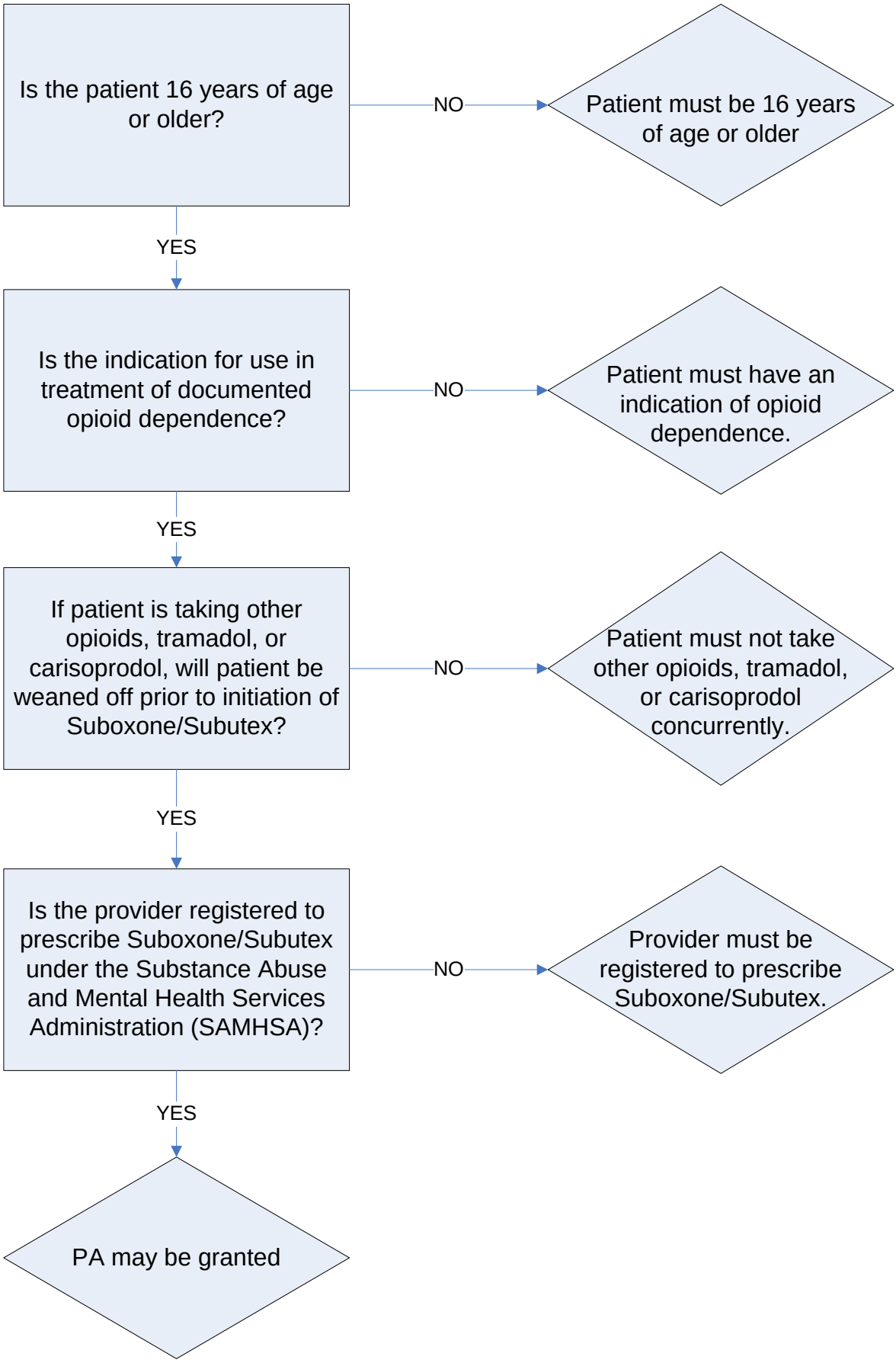
Part II: TO BE COMPLETED BY PHARMACY

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
Suboxone/Subutex Authorization Algorithm



AMPYRA 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 Ampyra must meet the following criteria:

- **Patient must be 18 years or older.**
- **Patient must have a specialist (neurologist or physiatrist) involved in therapy.**
- **Patient must have a confirmed diagnosis of multiple sclerosis.**
- **Patient must not have a history of seizures**
- **Patient's CrCl (creatinine clearance) must be greater than 50mL/min**

Part I: TO BE COMPLETED BY PHYSICIAN

Recipient Name	**Recipient Date of Birth**	Recipient Medicaid ID Number	
Physician Name	Specialist involved in therapy (if not treating physician)		
Physician Medicaid Provider Number	Telephone Number	Fax Number	
Address	City	State	Zip Code
Requested Drug and Dosage: □ AMPYRA	**FDA approved indication for this request:**		
Does the patient have a CrCL greater than 50mL/min?	□ YES	□ NO	
Does the patient have a history of seizures?	□ YES	□ NO	
What is the patient's baseline Timed 25-foot Walk (T25FW)?			
Physician Signature		Date	

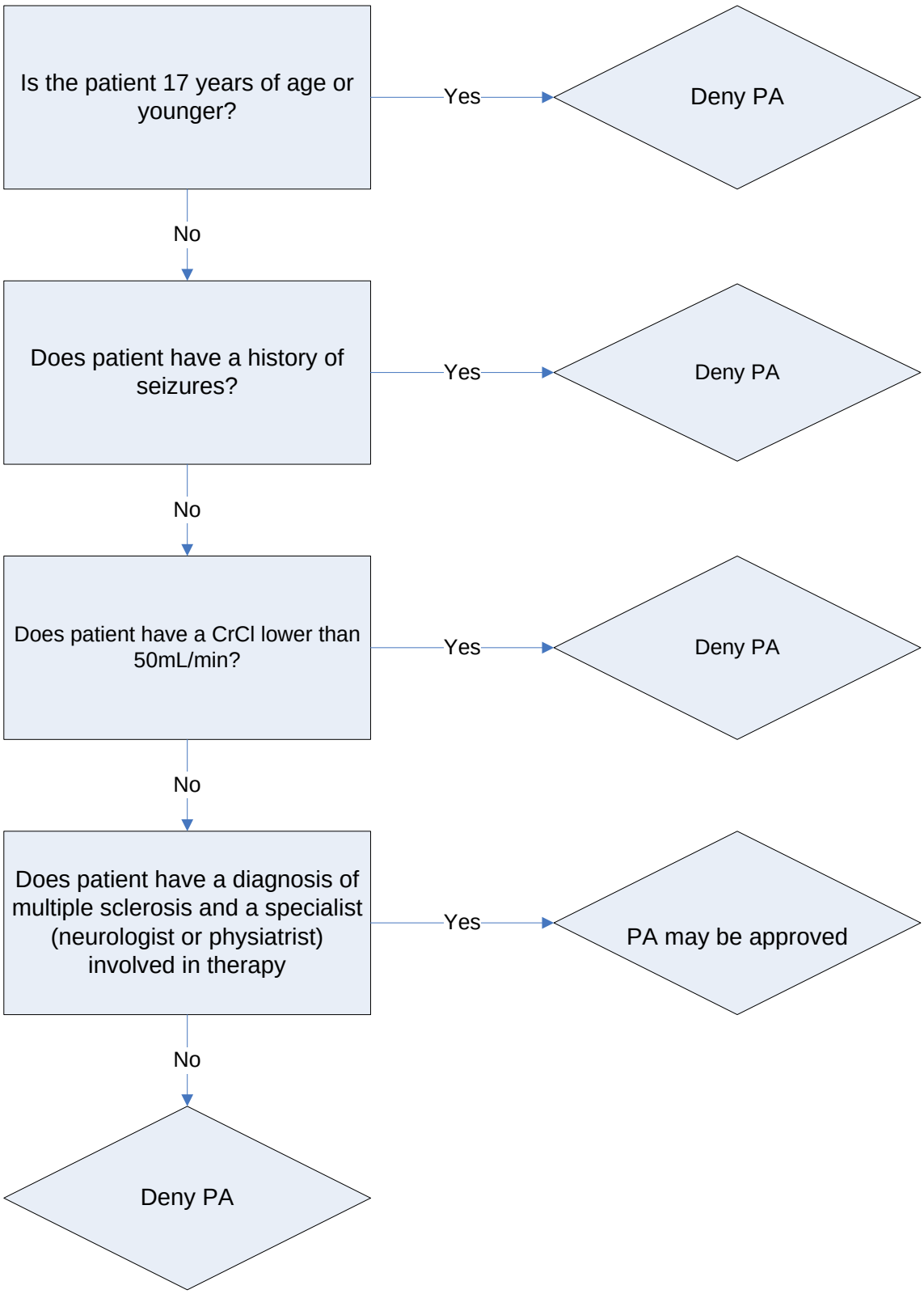
Part II: TO BE COMPLETED BY PHARMACY

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
Ampyra Prior Authorization Algorithm



TRAMADOL ER 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 tramadol ER (Ultram ER/Ryzolt) or tramadol ODT (Rybix) must meet the following criteria:

- **Documented failure of a 30-day trial of generic immediate release tramadol at maximum daily dosage of 400mg per day.**

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: □ ULTRAM ER OR GENERIC □ RYZOLT □ RYBIX	**Diagnosis for this request:**

FAILED THERAPY	**START DATE**	**END DATE**	**DOSE**	**FREQUENCY**

Physician Signature	Date

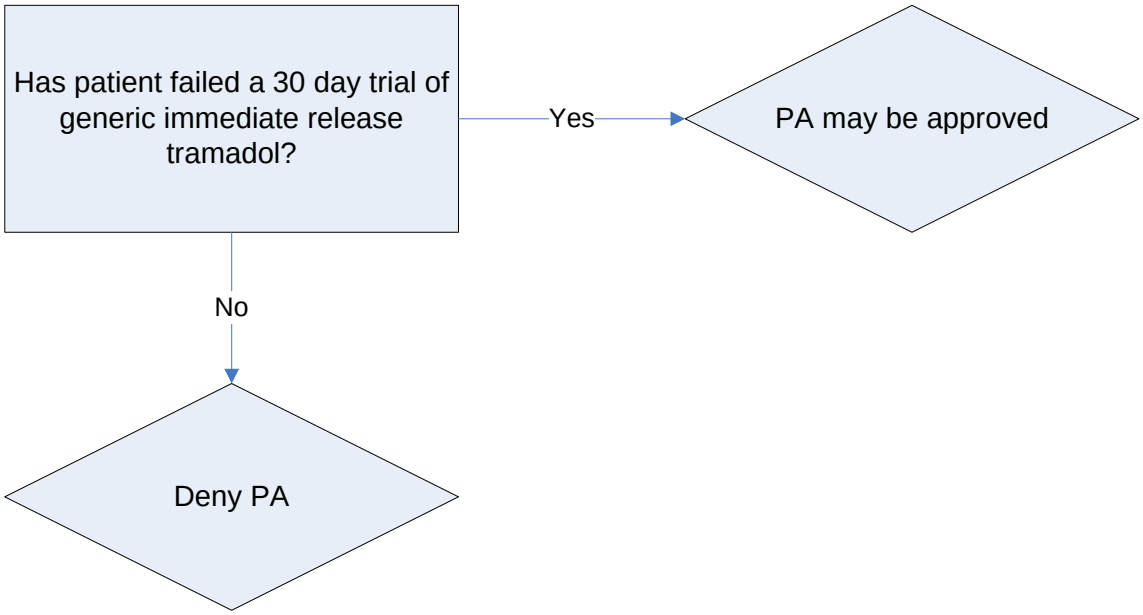
Part II: TO BE COMPLETED BY PHARMACY

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
Tramadol ER Prior Authorization Algorithm



XOLAIR 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 Xolair must meet the following criteria:

- **Patient must have moderate to severe persistent asthma**
- **Patient must have serum IgE level between 30 and 700 IU/mL**

Part I: TO BE COMPLETED BY PHYSICIAN

Recipient Name	**Recipient Date of Birth**	Recipient Medicaid ID Number	
Physician Name	Specialist Involved in Therapy (if not treating physician)		
Physician Medicaid Provider Number	Telephone Number	Fax Number	
Address	City	State	Zip Code

Requested Drug and Dosage: □ XOLAIR	**Diagnosis for this Request:**	**Serum IgE Level:**
Physician Signature		Date

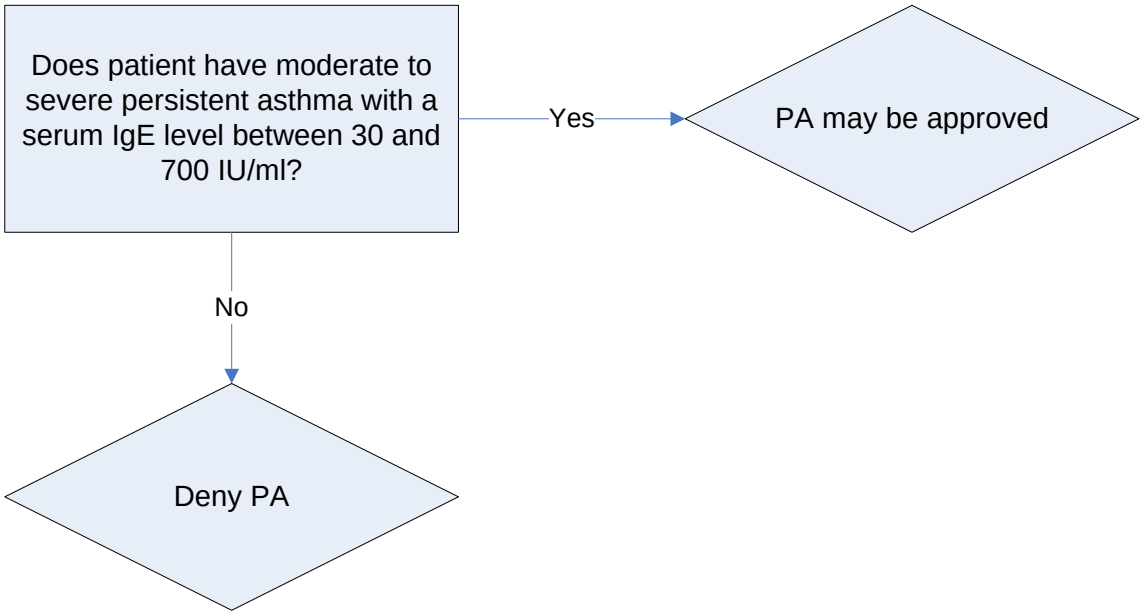
Part II: TO BE COMPLETED BY PHARMACY

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
Xolair Prior Authorization Algorithm



North Dakota Medicaid
DUR Meeting
Pulmonary Arterial Hypertension Agents (PAH) Review

I. Overview

PAH is a rare disorder caused by the constriction of the pulmonary arteries that leads to elevation of pulmonary vascular resistance, right ventricular failure, cardiac remodeling, and death. PAH is defined as a sustained elevation of mean pulmonary arterial pressure to more than 25mmHg at rest or to more than 30mmHg while exercising, with a normal pulmonary wedge pressure (<15mmHg). Symptoms of PAH include dyspnea (especially with physical activity), fatigue, dizziness, syncope, peripheral edema and chest pain. These symptoms are often attributed to more common conditions such as asthma, general fatigue, or lack of physical fitness.

PAH has an estimated prevalence of 30-50 cases per million, although the prevalence in certain at-risk groups (HIV-infected patients, sickle cell patients, systemic sclerosis patients) is substantially higher. Due to the non-specific nature of the symptoms, PAH is most frequently diagnosed when patients have reached an advanced stage of disease, suggesting that prevalence may be higher than documented.

Oral and Inhaled PAH Agents Included in this Review

Generic Name	Brand Name
Ambrisentan	Letairis®
Bosentan	Tracleer®
Sildenafil	Revatio®
Tadalafil	Adcirca®
Iloprost	Ventavis®
Treprostinil	Tyvaso®

II. Current Treatment Guidelines

Clinical Guideline	Recommendation
Updated Evidence-Based Treatment Algorithm in Pulmonary Arterial Hypertension, 2009	• Oral anticoagulant drugs, if no contraindication exists, diuretics in cases of fluid retention, and supplemental oxygen in cases of hypoxemia, even though RCTs with these compounds are lacking. • Referral to centers experienced in acute vasoreactivity testing and the treatment of pulmonary vascular diseases. • Acute vasoreactivity testing should be performed in all patients with PAH, although patients with IPAH, HPAH, and PAH associated with anorexigen use are the most likely to exhibit a positive response. • Vasoreactive patients should be treated with optimally tolerated doses of CCBs; maintenance of response, defined as WHO functional class I or II with near-normal hemodynamic status should be confirmed by repeat right

Clinical Guideline	Recommendation
	heart catheterization and clinical assessment after 3 to 6 months of treatment. • Nonresponders to acute vasoreactivity testing or responders who remain in WHO functional class III should be considered candidates for treatment with either a PDE5 inhibitor or an ERA. • WHO Class II: ambrisentan, bosentan, and sildenafil (Grade A for all); tadalafil (Grade B). • WHO Class III: ambrisentan, bosentan, epoprostenol IV, iloprost inh, sildenafil (Grade A for all); tadalafil, treprostinil (Grade B). • Continuous IV epoprostenol remains first-line therapy for PAH patients in WHO functional class IV, because of its demonstrated survival benefit in IPAH/HPAH, with extrapolation to associated PAH patients in WHO functional class IV (Grade A); Iloprost inh (Grade B). • Combination therapy should be considered for patients who fail to show improvement or who deteriorate with monotherapy. • The goal in treating PAH patients is to improve WHO functional class III and IV patients to functional class I or II and to improve all functional class II patients to functional class I or at least to maintain functional class II in patients presenting in that functional class. • Both atrial septostomy and lung transplantation are indicated in carefully selected patients for refractory PAH or in cases where medical treatments are unavailable. These procedures should be performed only in experienced centers.

III. FDA Approved Indications

Generic Name	FDA Approved Indications
Ambrisentan	• Endothelin receptor antagonist indicated for the treatment of PAH (WHO Group 1) to improve exercise ability and delay clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (32%).
Bosentan	• Endothelin receptor antagonist indicated for the treatment of PAH (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%).
Sildenafil	• Phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of PAH (WHO Group 1) to improve exercise ability and delay clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%).
Tadalafil	• PDE5 inhibitor indicated for the treatment of PAH (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II – III symptoms and etiologies of

Generic Name	FDA Approved Indications
	idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).
Iloprost	• Synthetic analog of prostacyclin indicated for the treatment of PAH (WHO Group I) in patients with NYHA Class III or IV symptoms. In controlled trials, it improved a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration.
Treprostinil	• Prostacyclin vasodilator indicated for the treatment of PAH (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominantly patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

IV. Pharmacokinetics

Drug	Bioavailability (%)	Serum Half-Life (hours)	Metabolites	Excretion (%)
Ambrisentan	Unknown	9	Unknown	Renal: minor Non-renal: major
Bosentan	50	5	Two inactive and one active that contributes 10-20 percent of parent drug activity	Renal: 3 Feces: 97
Sildenafil	41	4	N-desmethyl metabolite with *in vitro* potency for PDE5 approximately 50% of the parent drug	Renal: 13 Feces:80
Tadalafil	Unknown	15	Predominantly metabolized to a catechol metabolite which is considered inactive	Renal: 36 Feces: 61
Iloprost	Unknown	20-30 mins	Main metabolite is tetranor-iloprost	Feces: 12 Renal: 68
Treprostinil	64 to 72	4 hours	Five inactive metabolites	Feces: 13 Renal:79

V. Drug Interactions

PAH Agents Drug Interactions	
Ambrisentan	• Cyclosporine: Multiple dose co-administrations of ambrisentan and cyclosporine resulted in an approximately 2-fold increase in ambrisentan exposure in healthy volunteers; therefore, limit the dose of ambrisentan to 5mg once daily when co-administered with cyclosporine.
Bosentan	• Hormonal contraceptives: Use with bosentan decreases exposure and reduces contraceptive effectiveness. • Cyclosporine A, glyburide: Concomitant administration of each drug with bosentan is contraindicated. • Simvastatin and other CYP3A-metabolized statins: Combination use decreases statin levels and may reduce efficacy. • Rifampin: Alters bosentan levels. Monitor hepatic function weekly for 4 weeks, followed by normal monitoring.
Sildenafil	• Nitrates: Concomitant use of sildenafil with nitrates in any form is contraindicated.

PAH Agents Drug Interactions	
	• Ritonavir and other Potent CYP3A inhibitors: Concomitant use of sildenafil with ritonavir and other potent CYP3A inhibitors is not recommended. • Alpha-blockers: Use caution when co-administering alpha-blockers with sildenafil because of additive blood pressure-lowering effects. • Amlodipine: When sildenafil 100mg oral was co-administered with amlodipine, 5mg or 10mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8mmHg/systolic and 7mmHg/diastolic.
Tadalafil	• Nitrates: Do not use tadalafil in patients who are using any form of organic nitrate. In clinical pharmacology studies, tadalafil potentiated the hypotensive effect of nitrates. When deemed medically necessary, at least 48 hours should elapse after the last dose of tadalafil before nitrate administration is considered. In such circumstances, nitrates should be administered under close medical supervision with appropriate hemodynamic monitoring. • Alpha-blockers: PDE5 inhibitors and alpha-adrenergic blocking agents are both vasodilators with blood pressure lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. • Antihypertensives: Small reductions in blood pressure occurred in clinical pharmacology studies following co-administration of tadalafil with PDE5 inhibitors. • Alcohol: Both alcohol and tadalafil act as mild vasodilators. When mild vasodilators are taken in combination, blood pressure lowering effects of each individual compound may be increased. Substantial consumption of alcohol in combination with tadalafil can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache. • Ritonavir: Ritonavir initially inhibits and later induces CYP3A, the enzyme involved in the metabolism of tadalafil. At steady state of ritonavir (about 1 week), the exposure to tadalafil is similar as in the absence of ritonavir. • Potent inhibitors of CYP3A: Tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole, and itraconazole, avoid use of tadalafil. • Potent inducers of CYP3A: For patients chronically taking potent inducers of CYP3A, such as rifampin, avoid use of tadalafil.
Iloprost	• Antihypertensive agents: Iloprost has the potential to increase the hypotensive effect of vasodilators and antihypertensive agents. • Anticoagulants: There is a potential for increased risk of bleeding, particularly in patients maintained on anticoagulants.
Treprostinil	• Concomitant diuretics, antihypertensives or other vasodilators: May increase the risk of systemic hypotension.

VI. Contraindications/Warnings/Precautions

PAH Agents Warnings/Precautions	
Ambrisentan	• **Black Box Warning: Contraindicated in Pregnancy.** • Fluid retention may require intervention. • Decreases in sperm count have been observed in patients taking endothelin receptor antagonists. • Decreases in hemoglobin have been observed within the first few weeks; measure hemoglobin at initiation, at 1 month, and periodically thereafter. • If patients develop acute pulmonary edema during initiation of therapy, consider the possibility of underlying pulmonary veno-occlusive disease and discontinue treatment if necessary.

PAH Agents Warnings/Precautions	
Bosentan	• **Black Box Warning: Risks of Liver Injury and Teratogenicity.** • Contraindications: Pregnancy, use with cyclosporine, use with glyburide. • Pre-existing hepatic impairment: Avoid use in moderate and severe impairment. Use with caution in mild impairment. • Fluid retention may require intervention. • It cannot be excluded that endothelin receptor antagonists such as bosentan have an adverse effect on spermatogenesis. • Monitor hemoglobin levels after 1 and 3 months of treatment, then every 3 months thereafter. • If signs of pulmonary edema occur, consider the possibility of underlying pulmonary veno-occlusive disease and discontinue treatment if necessary.
Sildenafil	• Contraindication: Use with organic nitrates. • Carefully consider whether patients with certain underlying conditions (e.g., resting hypotension, fluid depletion) could be adversely affected by vasodilatory effects of sildenafil. Not recommended in patients with pulmonary veno-occlusive disease. • Note additive blood pressure-lowering effects with alpha-blockers. • In patients with PAH secondary to connective tissue disease (CTD), higher rates of epistaxis with sildenafil than placebo, including with concomitant oral vitamin K antagonists. • Use with ritonavir and other potent CYP3A inhibitors not recommended. • Consider discontinuing sildenafil if sudden loss of vision occurs, which could be non-arteritic ischemic optic neuropathy (NAION). • Discontinue sildenafil if sudden decrease or loss of hearing occurs. • Avoid use with Viagra or other PDE5 inhibitors. • Advise patients to seek emergency treatment if an erection lasts > 4 hours. Use sildenafil with caution in patients predisposed to priapism. • Sildenafil may cause serious vaso-occlusive crises.
Tadalafil	• Contraindication: Concomitant organic nitrates. • Carefully consider whether patients with certain underlying conditions (e.g., cardiovascular disease, impaired autonomic control of blood pressure, aortic stenosis) could be adversely affected by vasodilatory effects of tadalafil. Not recommended in patients with pulmonary veno-occlusive disease. • Note additive blood pressure-lowering effects with concomitant alpha-blocker or alcohol use. • Requires dosage adjustment when used with Ritonavir. • Avoid use with other potent CYP3A inhibitors. • Avoid use in patients chronically taking potent inducers of CYP3A (e.g., rifampin). • Patients should seek immediate medical attention if sudden loss of vision occurs, which could be a sign of NAION. • Advise patients to seek immediate medical attention if sudden decrease or loss of hearing occurs. • Avoid use with Cialis or other PDE5 inhibitors. • Advise patients to seek emergency treatment if an erection lasts > 4 hours.
Iloprost	• Hypotension leading to syncope has been observed. Iloprost should not be administered in patients with systolic blood pressure below 85 mmHg. • Discontinue if pulmonary edema is present. • Patients with a history of hyper-reactive airway disease may be more sensitive to bronchospasm.
Treprostinil	• Safety and efficacy have not been established in patients with significant underlying lung disease (such as asthma or chronic obstructive pulmonary

PAH Agents Warnings/Precautions	
	disease) • In patients with low systemic arterial pressure, treprostinil may cause symptomatic hypotension. • Treprostinil may increase the risk of bleeding, particularly in patients receiving anticoagulants. • Treprostinil dosage adjustments may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn. • Hepatic or renal insufficiency may increase exposure and decrease tolerability.

VII. Adverse Effects

PAH Agents Adverse Effects	
Ambrisentan	• Most common placebo-adjusted adverse reactions are peripheral edema, nasal congestion, sinusitis, flushing, palpitations, nasopharyngitis, abdominal pain, and constipation.
Bosentan	• Most common (≥3%) placebo-adjusted adverse reactions are respiratory tract infection and anemia.
Sildenafil	• Most common adverse reactions (≥ 3% and more frequent than placebo) include epistaxis, headache, dyspepsia, flushing, insomnia, erythema, dyspnea, and rhinitis.
Tadalafil	• The most common adverse reaction is headache.
Iloprost	• Most common (≥3% placebo adjusted) adverse reactions are vasodilation (flushing), cough increased, headache, trismus, insomnia, nausea, hypotension, vomiting, alkaline phosphatase increased, flu syndrome, back pain, tongue pain, palpitations, syncope, GGT increased, muscle cramps, hemoptysis, and pneumonia
Treprostinil	• Most common adverse reactions (≥ 10%) are cough, headache, nausea, dizziness, flushing, throat irritation, pharyngolaryngeal pain and diarrhea.

VIII. Dosing and Administration

Drug	Dosing and Administration	Availability
Ambrisentan	• Initiate treatment at 5mg once daily with or without food, and consider increasing the dose to 10mg once daily if 5mg is tolerated.	5mg and 10mg tablets
Bosentan	• Initiate at 62.5mg twice daily with or without food for 4 weeks, and then increase to 125mg twice daily. • Patients with low body weight (<40kg) and >12 years old: Initial and maintenance dose is 62.5mg twice daily. • Reduce the dose and closely monitor patients developing aminotransferase elevations >3 ULN. • Discontinue 36 hours prior to initiation of ritonavir. Patients on ritonavir: Initiate bosentan at 62.5mg once daily or every other day.	62.5mg and 125mg tablets
Sildenafil	• Take 20mg three times a day, approximately 4-6 hours apart, with or without food. Higher doses not recommended. • Inject 10mg (12.5mL) three times a day.	20mg tablets 10mg (12.5mL) single use vial

Drug	Dosing and Administration	Availability
Tadalafil	• Take 40mg once daily, with or without food. • Dividing the dose over the course of the day is not recommended. • Use with ritonavir requires dosage adjustments.	20mg tablets
Iloprost	• Patients should receive 6-9 doses (inhalations) per day (minimum of 2 hours between doses during waking hours). • Starting dose 2.5mcg. • Uptitrate to 5mcg if 2.5mcg is well tolerated. • Maintenance dose 5mcg.	1mL ampules
Treprostinil	• Administer undiluted, as supplied. A single breath of Tyvaso delivers approximately 6mcg of treprostinil. • Administer in 4 separate treatment sessions each day approximately four hours apart, during waking hours. • Initial dosage: 3 breaths (18mcg) per treatment session. If 3 breaths are not tolerated, reduce to 1 or 2 breaths. • Dosage should be increased by an additional 3 breaths at approximately 1-2 week intervals, if tolerated. • Titrate to target maintenance dosage of 9 breaths or 54mcg per treatment session as tolerated.	2.9mL ampule containing 1.74 treprostinil (0.6mg per mL)

IX. Utilization

07/01/10 to 06/30/11			
Label Name	**Rx Num**	**Total Reimb Amt**	**Average Cost per Script**
REVATIO 20 MG TABLET	13	$3,294.56	$253.43
TRACLEER 62.5 MG TABLET	3	$4,388.25	$1,462.75
TRACLEER 125 MG TABLET	11	$64,187.36	$5,835.21
ADCIRCA 20 MG TABLET	13	$10,825.15	$832.70
7 recipients	**40**	**$82,695.32**	
Summary by Age			
Age	**Recip Count**	**Rx Count**	**Total Dollars**
2	1	6	$0.00
3	2	5	$372.76
26	1	1	$1,460.90
27	1	1	$1,460.90
36	1	11	$9,226.17
37	1	16	$70,174.59

References

1. Wolters Kluwer Health, Inc, ed. Drugs Facts & Comparisons. St. Louis, MO. 2011.
2. Barst R et al. Updated Evidence-Based Treatment Algorithm in Pulmonary Arterial Hypertension. JACC. 2009;54;S78-S84. Accessed online April 22, 2011.
3. Letairis® [prescribing information]. Foster City, CA: Gilead Sciences, Inc.; March 2011.
4. Tracleer® [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc.; February 2011.
5. Revatio® [prescribing information]. New York, NY: Pfizer Labs; November 2010.
6. Adcirca® [prescribing information]. Indianapolis, IN: Eli Lilly and Company; April 2011.
7. Ventavis® [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc.; June 2010.
8. Tyvaso® [prescribing information]. Research Triangle Park, NC: United Therapeutics Corp.; February 2011.

Agents used to treat PAH-ND Medicaid Utilization

07/01/10 to 06/30/11			
Label Name	**Rx Num**	**Total Reimb**	**Average Cost per Script**
REVATIO 20 MG TABLET	13	$3,294.56	$253.43
TRACLEER 62.5 MG TABLET	3	$4,388.25	$1,462.75
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37	1	16	$70,174.59

North Dakota Medicaid
DUR Meeting
Acne Agents, Topical

I. Overview

Acne vulgaris is a common skin disease that affects 60-70% of Americans at some time during their lives. Twenty percent will have severe acne, which results in permanent scarring. Acne vulgaris is characterized by noninflammatory, open or closed comedones and by inflammatory papules, pustules, and nodules. Acne vulgaris may be present in newborns, adolescents (with onset of puberty) and to a lesser degree in adults.

There are different types of lesions associated with acne. Whiteheads or closed comedones are clogged follicles that stay beneath the skin and appear as round white bumps. Blackheads are open comedones that reach the surface of the skin and have a blackish appearance. Papules are small solid lesions that are slightly inflamed and elevated above the surface of the skin. Pustules are inflamed pus-filled lesions. Nodules and cysts are large, inflamed, pus-filled lesions and are likely to cause scarring.

Medications included in this Review

Generic Name	Brand Name	Manufacturer	Availability
Adapalene	Differin	Galderma	0.1% cream, gel (generic)
		Various generic manufacturers	0.1% lotion (brand only) 0.3% gel (brand only)
Azelaic acid	Azelex	Allergan	20% cream
Benzoyl peroxide/adapalene	Epiduo	Galderma	0.1% (adapalene)-2.5% (benzoyl peroxide) gel
Benzoyl peroxide	Benzac AC	Galderma	10% gel, cleanser 5% gel, cleanser
	Benzac W Wash	Galderma	10% cleanser 5% cleanser
	Benzefoam	Onset Therapeutics	5.3% foam
	Brevoxyl	Stiefel	4% gel 8% gel
	Clinac BPO	Ferndale	7% gel
	Desquam X	Ranbaxy	10% cleanser 5% cleanser
	Inova	JSJ	4%-5% (vit E) combo 8%-5% (vit E) combo
	Lavoclen	Prasco	4% cleanser 8% cleanser
	Neobenz Micro	Intendis	5.5% cream
	Oscion	Prasco	3% cleanser, med. pad 6% cleanser, med. pad 9% cleanser, med. pad
	Pacnex	Medimetriks	4.25% med. pad 7% med. pad
	SE BPO	Seton	3% towelette 6% towelette 7% cleanser 9% towelette
			3% cleanser, med. pad,

Generic Name	Brand Name	Manufacturer	Availability
	Triaz	Medicis	towelette 6% cleanser, med. pad, towelette 9% cleanser, med. pad, towelette 4% lotion
	Zaclir	Hawthorn	8% lotion
	Zoderm	Doak	4.5%-10% (urea) cream, gel, cleanser, med. pad 5.75%-10% (urea) cleanser 6.5%-10% (urea) cream, gel, cleanser, med. pad 8.5%-10% (urea) cream, gel, cleanser, med. pad
		Various generic manufacturers	
Benzoyl peroxide/clindamycin	Acanya BenzaClin	Valeant Dermik Mylan (generic)	1.2%-2.5% gel 1%-5% gel
Benzoyl peroxide/erythromycin	Benzamycin	Sanofi-Aventis Various generic manufacturers	3%-5% gel
Benzoyl peroxide/hyaluronate sodium	Zacare	Hawthorne	4%-0.2% combo 8%-0.2% combo
Benzoyl peroxide/salicylic acid/tocopherol	Inova 4/1, 8/2	JSJ	1%-4%-5% combo 2%-8%-5% combo
Benzoyl peroxide/sulfur	NuOx	Gentex Breckenridge (generic)	6%-3% gel
Clindamycin	Cleocin T	Pharmacia	1% solution, med. swab, lotion, gel
	Clindagel	Galderma	1% gel
	Evoclin	Stiefel	1% foam
		Various generic manufacturers	
Dapsone	Aczone	Allergan	5% gel
Erythromycin	Akne-Mycin	Valeant Various generic manufacturers	2% ointment
Sodium sulfacetamide	Klaron	Dermik	10% suspension
Sodium sulfacetamide/sulfur	Avar LS	Tiber	10%-2% cleanser
	Avar-E LS	Tiber	10%-2% cream
	Cerisa	Stratus	10%-1% cleanser
	Clarifoam EF	Onset Therapeutics	10%-5% foam
	Rosac	Stiefel	10%-1% cleanser 10%-5% cream
	Plexion	Medicis	10%-5% med. pad, cream
	Prascion	Prasco	10%-5% med. pad, cream
		Various generic manufacturers	
Tazarotene	Tazorac	Allergan	0.05% gel, cream 0.1% gel, cream
Tretinoin	Atralin	Valeant	0.05% gel

Generic Name	Brand Name	Manufacturer	Availability
	Avita Retin-A Micro Retin-A Various generic manufacturers	Mylan Ortho Ortho	0.025% gel, cream 0.04% gel 0.1% gel 0.01% gel 0.025% cream, gel 0.05% cream 0.01% cream
Clindamycin/tretinoin	Veltin Ziana	Stiefel Medicis	1.2-0.025% gel 1.2-0.025% gel

II. Indications

All products included in this review are indicated for the topical treatment of acne vulgaris. Some of the products have additional indications of plaque psoriasis, acne rosacea and seborrheic dermatitis.

III. Guidelines

The American Academy of Dermatology updated guidelines for the management of acne vulgaris in 2007.

- Topical therapy is a standard of care in acne treatment.
- Topical retinoids are important in acne treatment.
- Benzoyl peroxide and combinations with erythromycin and clindamycin are effective acne treatments.
- Topical antibiotics are effective acne treatments. However, the use of these agents along can be associated with the development of bacterial resistance.
- Salicylic acid is moderately effective in the treatment of acne.
- Azelaic acid has been shown to be effective in clinical trials, but its clinical use, compared to other agents, has limited efficacy according to experts.
- Data from peer-reviewed literature regarding the efficacy of sulfur, resorcinol, sodium sulfacetamide, aluminum chloride, and zinc are limited.
- Employing multiple topical agents that affect different aspects of acne pathogenesis can be useful. However, it is the opinion of the work group that such agents not be applied simultaneously unless they are known to be compatible.

IV. Pharmacology

- Adapalene: Adapalene binds to specific retinoic acid nuclear receptors but does not bind to the cytosolic receptor protein. Although the exact mode of action of adapalene is unknown, it is suggested that topical adapalene may normalize the differentiation of follicular epithelial cells resulting in decreased microcomedone formation.

- Azelaic acid: The exact mechanism of action of azelaic acid is not known. Azelaic acid has been shown to possess antimicrobial activity against *Propionibacterium acnes* and *Staphylococcus epidermidis*. The antimicrobial action may be attributable to inhibition of microbial cellular protein synthesis. A normalization of keratinization leading to an anticomedonal effect of azelaic acid may also contribute to its clinical activity. Electron microscopic and immunohistochemical evaluation of skin biopsies from human subjects treated with azelaic acid demonstrated a reduction in the thickness of the stratum corneum, a reduction in number and size of keratohyalin granules, and a reduction in the amount and distribution of filaggrin (a protein component of keratohyalin) in epidermal layers. This is suggestive of the ability to decrease microcomedone formation.

- Benzoyl peroxide: Benzoyl peroxide is an antibacterial agent and has been shown to be effective against *Propionibacterium acnes*, an anaerobe found in sebaceous follicles and comedones. The antibacterial action of benzoyl peroxide is believed to be due to the release of active oxygen: it also has a keratolytic and desquamative effect, which may also contribute to its efficacy. When benzoyl peroxide is applied to the skin, it is absorbed and converted to benzoic acid. It is available in combination with other agents such as antibiotics and sulfur, which contributes a mild keratolytic action. Salicylic acid causes desquamation of hyperkeratotic epithelium.

- Dapsone: The exact mechanism of action of dapsone in the treatment of acne vulgaris is unknown, but in vitro studies suggest that it may suppress neutrophil recruitment oxidation, which may help prevent the production of toxic respiratory and secretory products. It may also have antimicrobial activity.

- Erythromycin/Clindamycin: Erythromycin and clindamycin are antibiotics that reduce lesions of acne vulgaris in part due to the antibacterial activity; however, the exact mechanism is not fully known. Erythromycin and clindamycin act by inhibition of protein synthesis in susceptible organisms by reversibly binding to 50 S ribosomal subunits, thereby inhibiting translocation of aminoacyl transfer-RNA and inhibiting polypeptide synthesis. Antagonism has been demonstrated in vitro between erythromycin, lincomycin, chloramphenicol, and clindamycin.

- Sodium sulfacetamide: Sulfonamides act as a competitive inhibitor of para-aminobenzoic acid (PABA) utilization, an essential component for bacterial growth.

- Tazarotene: A retinoid prodrug that, when activated, has antihyperproliferative, differentiation normalizing, and anti-inflammatory effects. The exact mechanism of action is unknown. Tretinoin, another retinoid, works by decreasing cohesiveness of follicular epithelial cells and decreasing microcomedone

formation. It may also stimulate mitotic activity and increase turnover of follicular epithelial cells, causing extrusion of the comedones.

- Tretinoin: Decreases cohesiveness and stimulates mitotic activity and turnover of follicular epithelial cells, resulting in decreased formation and increased extrusion of comedones.

V. Pharmacokinetics

Clindamycin is only one percent available systemically when administered topically. The low levels seen in the plasma are excreted unchanged in the urine.

Topically administered erythromycin is not detectable in the plasma.

Less than two percent of benzoyl peroxide is absorbed in the systemic circulation. Due to the lipophilic nature, benzoyl peroxide concentrates in the lipid-rich sebaceous follicles. The small amount that is systemically absorbed is converted to benzoic acid, which is further metabolized to benzoate. Benzoate is then excreted in the urine.

The systemic exposure to dapsone 5% gel versus oral dapsone 100 mg was studied for 14 days. The results indicated that twice daily topical application of the agent leads to less systemic exposure to the drug than the 100 mg once daily oral administration of the drug. Patients applying the drug topically had approximately 100-times less exposure to the active drug, as measured by the area-under-the curve (AUC), than patients taking the drug orally.

Tazarotene is converted by ester hydrolysis to its active metabolite, tazarotenic acid. There is little parent compound absorbed in the plasma, and the small amount is highly plasma protein-bound. Tazarotenic acid is eliminated by the urinary and fecal routes. Its half-life is about 18 hours.

Tretinoin has only been found in trace amounts in plasma when applied topically. It is a metabolite of Vitamin A.

Sulfacetamide is approximately four percent bioavailable and is excreted in the urine unchanged. The half-life of sulfacetamide varies between 7 and 13 hours. Absorption through intact skin has not been determined for sodium sulfacetamide. Approximately one percent of topical sulfur is systemically absorbed.

Pharmacokinetic studies with adapalene and the combination product with benzoyl peroxide have only found trace amounts of adapalene in plasma when administered topically. Excretion is primarily by the biliary route. Azelaic acid is approximately 4% bioavailable, and any absorbed drug is excreted unchanged in the urine. Its half-life is about 12 hours.

VI. Contraindications/Warnings

Products containing clindamycin or erythromycin are contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.

Sulfacetamide is contraindicated in patients with hypersensitivity to sulfonamides.

Sodium sulfacetamide/sulfur is not to be used by patients with kidney disease.

Tazarotene is contraindicated in pregnant women or women who may become pregnant. Do not use retinoids on eczematous skin, as they may cause severe irritation.

Some glucose-6-phosphate dehydrogenase (G6PD) deficient patients using dapsone gel developed laboratory changes suggestive of mild hemolysis. Medication should be discontinued if suggestive signs and symptoms of hemolytic anemia occur. Topical administration of dapsone gel did not demonstrate peripheral neuropathy or skin reactions as reported with oral administration.

For patients using adapalene, tretinoin, or benzoyl peroxide-containing products, excessive or prolonged exposure to sunlight should be limited. Patients taking other photosensitizing medications should use additional caution. Weather extremes such as wind or cold may also be irritating. Patients should use caution to avoid contamination of hair, fabrics, and carpet with benzoyl peroxide products as bleaching and/or discoloration may result.

Erythema, scaling, dryness, and stinging/burning may be experienced with the use of adapalene/benzoyl peroxide gel. These reactions are most likely to occur during the first four weeks of treatment. Reactions are generally mild to moderate in intensity and typically lessen with continued use. Depending upon severity, patients should be advised to use a moisturizer and/or reduce the frequency of application. Adapalene/benzoyl peroxide gel should not be applied to cuts, abrasions, eczematous or sunburned skin. As with other retinoids, the use of 'waxing' as a depilatory method should be avoided on skin surfaces treated with adapalene/benzoyl peroxide gel.

Pseudomembranous colitis has been reported with bacterial agents such as clindamycin and erythromycin, ranging in severity from mild to life-threatening, when administered orally or parenterally. Absorption of these antibiotics through the skin is minimal, however.

Concomitant topical acne treatment, as well as cosmetic products with drying effects, should be used with caution, as possible cumulative irritancy may occur.

During the early weeks of therapy, apparent exacerbations of acne may occur. This is caused by the product's action on previously unseen lesions and should not be viewed as a reason to discontinue therapy.

Fatalities have rarely occurred due to severe reactions to sulfonamides such as sulfacetamide. Sulfacetamide also contains sodium metabisulfite, which may cause allergic-type reactions in patients.

Azelaic acid can cause hypopigmentation.

Contact with eyes, eyelids, lips, and mucous membranes should be avoided. Breaks in the skin should also not come into contact with these products.

Avoid fire, flame, and smoking following use of any gel; they are flammable.

Tretinoin gel contains soluble fish proteins and should be used with caution in patients with known sensitivity or allergy to fish.

VII. Adverse Effects

Adapalene

Gel: Some adverse effects such as erythema, scaling, dryness, pruritus, and burning will occur in 10% to 40% of patients with adapalene gel. Pruritus or burning immediately after application also occurs in approximately 20% of patients with adapalene gel. The following additional adverse experiences were reported in 1% or less of patients: Skin irritation, burning/stinging, erythema, sunburn, and acne flares. These are most commonly seen during the first month of therapy and decrease in frequency and severity thereafter. All adverse effects with use of adapalene during clinical trials were reversible upon discontinuation of therapy.

Cream: Patients noted mild to moderate effects in the following: erythema (10-38%), scaling (6-35%), dryness (9-42%), persistent pruritis (4-21%), and burning/stinging (4-24%). Other reported local cutaneous adverse events in patients who used adapalene cream once daily included: sunburn (2%), skin discomfort-burning and stinging (1%), and skin irritation (1%).

Azelaic acid

Cream: The most common adverse reactions occurring in approximately 1% to 5% of patients were pruritus, burning, stinging and tingling. Other adverse reactions such as erythema, dryness, rash, peeling, irritation, dermatitis, and contact dermatitis were reported in less than 1% of subjects. In patients using azelaic acid formulations, the following additional adverse reactions have been reported rarely: Worsening of asthma, vitiligo depigmentation, small depigmented spots, hypertichosis, reddening (signs of keratosis pilaris), and exacerbation of recurrent herpes labialis.

Gel: Patients using the gel formulation noted mild to moderate effects in the following: burning/stinging/tingling (9-20%), pruritis (4-7%), scaling/dry sking/xerosis (2-6%), and erythema/irritation (2%).

Benzoyl peroxide
Adverse effects may include excessive drying manifested by marked peeling, erythema, possible edema, and allergic contact sensitization/dermatitis.

Clindamycin
Cases of diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported as adverse reactions in patients treated with oral and parenteral formulations of clindamycin and, rarely, with topical clindamycin. Abdominal pain and GI disturbances, as well as gram-negative folliculitis, have been reported in association with the use of topical formulations of clindamycin.

Erythromycin
Peeling, dryness, burning, itching, desquamation, erythema, and oiliness have been reported occasionally. Irritation of the eyes and tenderness of the skin have also been reported with the topical use of erythromycin. A generalized urticarial reaction, possibly related to the use of erythromycin, which required systemic steroid therapy has been reported.

Gel: In controlled clinical trials, the incidence of burning associated with erythromycin topical gel was approximately 25 percent.

Ointment: In clinical trials, there was one report of a possible contact sensitization, which could not be confirmed. There were isolated reports of skin irritation, such as erythema and peeling.

Sodium Sulfacetamide
It has been reported that sodium sulfacetamide may cause local irritation or sensitization with long term therapy – if such irritation occurs, therapy should be discontinued. Sulfacetamide sodium occasionally may cause reddening and scaling of the skin.

Sulfur
Contact sensitization reactions are associated with the use of topical benzoyl peroxide and sulfur products and may be expected to occur in 10 to 25 of 1000 patients. The most frequent adverse reactions associated with benzoyl peroxide and sulfur use are excessive erythema and peeling which may be expected to occur in five of 100 patients. Excessive erythema and peeling most frequently appear during the initial phase of drug use and may normally be controlled by reducing frequency of use.

Tazarotene
Gel: Desquamation, burning/stinging, dry skin, erythema, pruritus (10% to 30%); irritation, skin pain, fissuring, localized edema, skin discoloration (1% to 10%).

Cream: Desquamation, dry skin, erythema, burning sensation (10% to 30%); pruritus, irritation, face pain, stinging (1% to 5%).

Tretinoin

Almost all patients reported 1 or more local reactions such as peeling, dry skin, burning, stinging, erythema, and pruritus during therapy with tretinoin. Sensitive skin may become excessively red, edematous, blistered, or crusted. If these effects occur, discontinue medication until skin integrity is restored or adjust to a tolerable level. True contact allergy is rare. Temporary hyperpigmentation or hypopigmentation has been reported with repeated application. Some individuals have a heightened susceptibility to sunlight while under treatment. All adverse effects have been reversible upon discontinuation.

References

1. Wolters Kluwer Health, Inc, ed. Drugs Facts & Comparisons. St. Louis, MO. 2011.
2. Strauss J et al. Guidelines of Care for Acne Vulgaris Management. Available online at www.aad.org. ccessed online August 3, 2011.

Topical Acne Agents-ND Medicaid Utilization			
07/01/10 - 06/30/11			
Label Name	**Rx Num**	**Total Reimb**	**Average Cost per Script**
ACANYA GEL	6	$856.52	$142.75
ACANYA GEL PUMP	5	$835.28	$167.06
ACZONE 5% GEL	16	$2,635.92	$164.75
ADAPALENE 0.1% CREAM	113	$19,187.96	$169.80
ADAPALENE 0.1% GEL	222	$28,841.20	$129.92
ATRALIN 0.05% GEL	10	$1,823.12	$182.31
AZELEX 20% CREAM	50	$8,580.94	$171.62
BENZAC AC WASH 5% LIQUID	2	$309.76	$154.88
BENZACLIN GEL	225	$20,245.21	$89.98
BENZACLIN GEL 50G PUMP	246	$36,604.56	$148.80
BENZAMYCINPAK GEL	6	$817.90	$136.32
BENZOYL PEROX 4% CREAMY WASH	5	$216.26	$43.25
BENZOYL PEROXIDE 10% GEL	24	$374.00	$15.58
BENZOYL PEROXIDE 10% WASH	32	$837.20	$26.16
BENZOYL PEROXIDE 2.5% GEL	5	$100.65	$20.13
BENZOYL PEROXIDE 2.5% WASH	11	$282.48	$25.68
BENZOYL PEROXIDE 5% GEL	51	$1,086.25	$21.30
BENZOYL PEROXIDE 5% WASH	115	$8,492.28	$73.85
BPO 4% GEL	13	$1,002.43	$77.11
CLEOCIN 75 MG/5 ML GRANULES	72	$12,628.71	$175.40
CLINDAGEL 1% GEL	3	$118.96	$39.65
CLINDAMYCIN 75 MG/5 ML SOLN	109	$13,868.51	$127.23
CLINDAMYCIN PH 1% GEL	282	$9,118.91	$32.34
CLINDAMYCIN PH 1% SOLUTION	183	$4,670.68	$25.52
CLINDAMYCIN PHOS 1% PLEDGET	102	$4,047.69	$39.68
CLINDAMYCIN PHOSP 1% LOTION	169	$5,708.06	$33.78
CLINDAMYCIN PHOSPHATE 1% FOAM	1	$160.87	$160.87
CLINDAMYCIN-BENZOYL PEROX GEL	202	$25,741.85	$127.43
DESQUAM-X 5% WASH	6	$1,754.00	$292.33
DIFFERIN 0.1% CREAM	31	$6,001.77	$193.61
DIFFERIN 0.1% GEL	36	$8,279.44	$229.98
DIFFERIN 0.1% LOTION	2	$400.67	$200.34
DIFFERIN 0.3% GEL	149	$25,540.66	$171.41
EPIDUO GEL	117	$20,694.05	$176.87
ERY 2% PADS	4	$176.22	$44.06
ERYTHROMYCIN 2% GEL	36	$682.83	$18.97
ERYTHROMYCIN 2% SOLUTION	98	$1,407.89	$14.37
ERYTHROMYCIN-BENZOYL GEL	118	$5,726.73	$48.53
LAVOCLEN-4 CREAMY WASH	1	$50.17	$50.17
RE BENZOYL PEROXIDE 5.5% CREAM	2	$191.84	$95.92
RETIN-A MICRO 0.04% GEL	63	$7,059.53	$112.06
RETIN-A MICRO 0.1% GEL	35	$6,105.45	$174.44
RETIN-A MICRO PUMP 0.04% GEL	29	$4,883.29	$168.39
RETIN-A MICRO PUMP 0.1% GEL	14	$2,888.11	$206.29

Label Name	Rx Num	Amt	Average Cost per Script
SOD SULFACETAMIDE-SULFUR LOTN	3	$181.59	$60.53
TAZORAC 0.05% CREAM	21	$3,582.10	$170.58
TAZORAC 0.05% GEL	20	$3,813.92	$190.70
TAZORAC 0.1% CREAM	50	$8,686.45	$173.73
TAZORAC 0.1% GEL	35	$4,961.21	$141.75
TRETINOIN 0.01% GEL	23	$2,146.04	$93.31
TRETINOIN 0.025% CREAM	111	$5,037.93	$45.39
TRETINOIN 0.025% GEL	39	$2,027.20	$51.98
TRETINOIN 0.05% CREAM	76	$4,256.97	$56.01
TRETINOIN 0.1% CREAM	55	$4,285.67	$77.92
TRI-LUMA CREAM	2	$360.44	$180.22
VELTIN GEL	1	$164.44	$164.44
ZIANA GEL	1	$198.06	$198.06
1,385 recipients	**3459**	**$340,738.83**	

Summary by Age

Age	Recip Count	Rx Count	Total Dollars
0	3	3	$247.61
1	15	17	$1,371.02
2	24	27	$3,348.50
3	30	31	$3,577.34
4	24	25	$3,100.68
5	19	20	$2,805.37
6	22	22	$3,450.14
7	18	21	$2,408.83
8	16	17	$2,766.25
9	13	18	$2,109.28
10	5	5	$676.77
11	13	21	$1,971.54
12	30	58	$5,554.47
13	50	95	$9,821.81
14	79	228	$21,805.68
15	115	290	$30,483.34
16	134	412	$39,330.63
17	138	406	$42,499.93
18	109	304	$32,761.50
19	49	123	$10,646.92
20	47	121	$10,308.45
21	24	47	$6,533.24
22	20	58	$7,338.77
23	24	51	$4,078.46
24	24	84	$5,291.11
25	30	58	$4,252.16
26	24	46	$3,202.34
27	29	86	$8,721.16

Age	Recip Count	Rx Count	Total Dollars
28	26	41	$4,373.89
29	25	72	$7,555.54
30	20	45	$5,612.14
31	19	49	$4,468.08
32	17	44	$3,820.99
33	21	62	$4,715.97
34	9	24	$3,451.27
35	9	23	$1,574.57
36	19	50	$5,094.65
37	13	63	$4,915.50
38	10	46	$3,894.12
39	7	21	$1,577.20
40	7	18	$673.95
41	2	6	$715.32
42	7	25	$713.78
43	6	15	$1,272.73
44	2	13	$1,171.24
45	6	18	$1,271.17
46	3	9	$515.61
47	3	4	$774.71
48	5	24	$1,774.08
49	2	3	$497.40
50	2	6	$421.36
51	4	45	$5,769.59
52	3	5	$93.96
53	1	5	$771.31
54	2	6	$65.57
55	2	2	$333.23
57	1	1	$503.41
58	1	2	$102.70
59	1	16	$1,567.00
60	1	1	$14.60
66	1	1	$198.89

North Dakota Medicaid
DUR Board Meeting
Agents Used to Treat Benign Prostatic Hyperplasia

I. Overview

Benign Prostatic Hyperplasia (BPH) is a noncancerous enlargement of the prostrate that restricts the flow of urine from the bladder. Patients with BPH may present with lower urinary tract symptoms (LUTS) resulting from irritation (urinary frequency, nocturia, urgency, urge incontinence) and/or obstruction (difficulty initiating urination or passing urine, weak stream, involuntary postvoid dripping of urine and sensation of incomplete bladder emptying). Drugs used in the treatment of BPH relieve LUTS and prevent complications.

Medications included in this Review

Alpha-Blockers	
Brand Name	**Generic Name**
Cardura, Cardura XL	doxazosin
Flomax	tamsulosin
Hytrin	terazosin
Rapaflo	silodosin
Uroxatral	alfuzosin ER
5-Alpha Reductase (5AR) Inhibitors and combinations	
Avodart	dutasteride
Jalyn	dutasteride/tamsulosin
Proscar	finasteride
Phosphodiesterase 5 (PDE5) inhibitor	
Cialis	tadalafil

II. Indications

Drug	Indication
Avodart	• Treatment of symptomatic BPH in men with an enlarged prostate.
Cardura	• Treatment of both the urinary outflow obstruction and obstructive and irritative symptoms associated with BPH. • Treatment of hypertension.
Cardura XL	• Treatment of the signs and symptoms of BPH.
Cialis	• Erectile dysfunction. • Signs and symptoms of BPH. • Erectile dysfunction and the signs and symptoms of BPH.
Flomax	• Treatment of the signs and symptoms of BPH.
Hytrin	• Treatment of symptoms of BPH. • Treatment of mild to moderate hypertension (HTN).

Drug	Indication
Jalyn	• Treatment of symptomatic BPH in men with an enlarged prostate.
Proscar	• Treatment of symptomatic BPH in men with an enlarged prostate.
Rapaflo	• Treatment of the signs and symptoms of BPH.
Uroxatral	• Treatment of signs and symptoms of BPH.

III. Dosage and Administration

Drug	Dosages
Avodart	• Monotherapy: 0.5mg once daily. • Combination with tamsulosin: 0.5mg daily and tamsulosin 0.4mg once daily.
Cardura	• Initial dosage in patients with HTN and/or BPH is 1mg given once daily. • BPH: Dosage may be increased to 2mg and thereafter to 4mg and 8mg once daily. The recommended titration interval is 1-2 weeks. • HTN: Dosage may be increased to 2mg and thereafter if necessary to 4mg, 8mg and 16mg once daily.
Cardura XL	• Recommended starting dose (initial therapy or switching from immediate release): 4mg once daily with breakfast. • Dose range: 4 to 8mg once daily.
Cialis	• BPH: 5mg, taken at approximately the same time every day. • ED and BPH: 5mg, taken at approximately the same time every day.
Flomax	• 0.4mg once daily taken approximately one-half hour following the same meal each day. • Can be increased to 0.8mg once daily for patients who fail to respond to the 0.4mg dose after 2 to 4 weeks of dosing.
Hytrin	• BPH: 1mg at bedtime increased incrementally (2mg, 5mg, 10mg) to maximum maintenance dose of 20mg daily. • HTN: 1mg at bedtime increased slowly. Doses over 20mg do not appear to provide further blood pressure effect.
Jalyn	• One capsule (0.5mg dutasteride and 0.4mg tamsulosin) taken once daily.
Proscar	• One tablet (5mg) taken once a day. • Combination with alpha-blocker: One tablet (5mg) taken once a day in combination with the alpha-blocker doxazosin.
Rapaflo	• One capsule (8mg) once daily.
Uroxatral	• One tablet (10mg) once daily.

IV. Contraindications

Drug	Contraindications
Avodart	• Pregnancy and women of childbearing potential. • Pediatric patients. • Patients with previously demonstrated, clinically significant hypersensitivity (e.g., serious skin reactions, angioedema) to dutasteride or other 5 alpha-reductase inhibitors.
Cardura	• Patients with a known sensitivity to quinazolines (e.g., prazosin, terazosin), doxazosin, or any of the inert ingredients.
Cardura XL	• Patients with a known sensitivity to quinazolines (e.g., prazosin, terazosin), doxazosin, or any of the inert ingredients.
Cialis	• Administration to patients receiving any form of organic nitrate is contraindicated.
Flomax	• Patients known to be hypersensitive to tamsulosin or any component of tamsulosin capsules.
Hytrin	• Patients with a known sensitivity to terazosin.
Jalyn	• Pregnancy and women of child-bearing age. • Pediatric patients. • Patients with previously demonstrated, clinically significant hypersensitivity (e.g., serious skin reactions, angioedema) to dutasteride, other 5 alpha-reductase inhibitors, tamsulosin, or any component of this product.
Proscar	• Hypersensitivity to any components of this product. • Women who are or may potentially be pregnant.
Rapaflo	• Patients with severe renal impairment. • Patients with severe hepatic impairment. • Concomitant administration with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, itraconazole, ritonavir).
Uroxatral	• Moderate to severe hepatic impairment • Coadministration with potent CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir) • Known hypersensitivity to alfuzosin or any of the ingredients

V. Warnings/Precautions

Drug	Warnings and Precautions
Avodart	• Dutasteride reduces serum prostate-specific (PSA) concentration by approximately 50%. However, any confirmed increase in PSA while on dutasteride may signal the presence of prostate cancer and should be evaluated, even if those values are still within the normal range for

Drug	Warnings and Precautions
	untreated men. • May increase the risk of high-grade prostate cancer. • Assess patients to rule out other urological diseases, including prostate cancer, prior to prescribing dutasteride. • Women who are pregnant or could become pregnant should not handle dutasteride capsules due to potential risk to a male fetus. • Patients should not donate blood until 6 months after their last dose of dutasteride.
Cardura	• Syncope and 'First-dose' Effect • Priapism • Carcinoma of the prostate should be ruled out prior to commencing therapy with doxazosin. • Cataract Surgery-Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in some patients or or previously treated with alpha blockers. • Orthostatic Hypotension
Cardura XL	• Postural hypotension with or without syncope may occur in the first few hours after administration. • IFIS has been observed during cataract surgery in some patients. • Caution should be used when administering to patients with preexisting severe gastrointestinal narrowing or coronary insufficiency. • Screen for the presence of prostate cancer prior to treatment and at regular intervals afterwards.
Cialis	• Use with alpha blockers, antihypertensives or substantial amounts of alcohol may lead to hypotension. • Not recommended in combination with alpha blockers for the treatment of BPH because efficacy of the combination has not been adequately studied and because of the risk of blood pressure lowering. • If taking potent inhibitors of CYP3A4, dose should be adjusted. • Patients should seek emergency treatment if an erection lasts >4 hours. • Patients should seek medical care if a sudden loss of vision occurs in one or both eyes, which could be a sign of Non Arteritic Ischemic Optic Neuropathy (NAION). • Patients should seek prompt medical attention in the event of sudden decrease or loss of hearing. • Prior to initiating treatment for BPH, consideration should be given to other urological conditions that may cause similar symptoms.

Drug	Warnings and Precautions
Flomax	• Advise patients about the possibility of symptoms related to postural hypotension and to avoid situations where injury could result, should syncope occur. • Should not be used in combination with strong inhibitors of CYP3A4. Use with caution in combination with moderate inhibitors of CYP3A4, with strong or moderate inhibitors of CYP2D6, in patients known to be CYP2D6 poor metabolizers, or in combination with other cytochrome P450 inhibitors. • Should not be used in combination with other alpha adrenergic blocking agents. • Exercise caution with concomitant administration of warfarin. • Advise patients about the possibility and seriousness of priapism. • IFIS has been observed during cataract surgery in some patients. • Advise patients to be screened for the presence of prostate cancer prior to treatment and at regular intervals afterwards.
Hytrin	• Terazosin can cause orthostatic hypotension and syncope, which can be hazardous for patients in occupations that require alertness. • The addition of terazosin to other antihypertensive agents can cause a rapid decrease in blood pressure. • Use with caution in patients with angina pectoris because severe hypotension may cause or worsen angina. • Patients with renal impairment and geriatric patients should be monitored carefully for exaggerated hypotensive effects (e.g., first dose effect). • Should be used during pregnancy only if the benefits to the mother outweigh the risks to the fetus. • Patients receiving or who have previously received treatment with alpha-1 blockers may be at risk for IFIS during surgery for cataracts.
Jalyn	• Orthostatic hypotension and/or syncope can occur. Advise patients of symptoms related to postural hypotension and to avoid situations where injury could result if syncope occurs. • Do not use with other alpha adrenergic antagonists, as this may increase the risk of hypotension. • Any confirmed increase in PSA while on dutasteride/tamsulosin may signal the presence of prostate cancer and should be evaluated, even if those values are still within the normal range for untreated men. • Do not use with strong inhibitors of CYP3A4 (e.g.,

Drug	Warnings and Precautions
	ketoconazole). Use caution in combination with moderate CYP3A4 inhibitors (e.g., erythromycin) or strong (e.g., paroxetine) or moderate CYP2D6 inhibitors, or known poor metabolizers of CYP2D6. Concomitant use with known inhibitors can cause a marked increase in drug exposure. • Exercise caution with concomitant use of PDE-5 inhibitors, as this may increase the risk of hypotension. • Drugs that contain dutasteride may increase the risk of high-grade prostate cancer. • Assess patients to rule out other urological diseases, including prostate cancer, prior to therapy. • Women who are pregnant or could become pregnant should not handle capsules due to potential risk to a male fetus. • Advise patients about the possibility and seriousness of priapism. • Patients should not donate blood until 6 months after their last dose. • IFIS has been observed during cataract surgery after alpha adrenergic antagonist exposure. • Exercise caution with concomitant use of warfarin.
Proscar	• Any confirmed increase in PSA may signal the presence of prostate cancer and should be evaluated, even if those values are still within the normal range for men. • May increase the risk of high-grade prostate cancer. • Appropriate evaluation should be performed to rule out other urological conditions, including prostate cancer, that might mimic BPH. • Women should not handle crushed or broken tablets when they are pregnant or may potentially be pregnant due to potential risk to a male fetus. • Not indicated for use in pediatric patients or women.
Rapaflo	• Postural hypotension, with or without symptoms, may develop when beginning therapy. • Dose should be decreased in patients with moderate renal impairment. • Should not be used in combination with other alpha-blockers. • Rule out the presence of carcinoma of the prostate prior to initiating therapy. • Possibility of IFIS during cataract surgery.
Uroxatral	• Postural hypotension/syncope. • Severe renal impairment. • Mild hepatic impairment. • Should not be used in combination with other alpha

Drug	Warnings and Precautions
	adrenergic antagonists. • Prostate carcinoma should be ruled out prior to treatment. • IFIS during cataract surgery may require modifications to the surgical technique. • Discontinue if symptoms of angina pectoris appear or worsen. • Use with caution in patients with a history of QT prolongation or who are taking medications which prolong the QT interval.

VI. Adverse Reactions

Drug	Adverse Reactions
Avodart	• The most common adverse reactions, reported in ≥1% of patients treated with dutasteride and more commonly than in patients treated with placebo, are impotence, decreased libido, ejaculation disorders, and breast disorders.
Cardura	• No significant difference in the incidence of adverse events compared to placebo was seen except for dizziness, fatigue, hypotension, edema, and dyspnea.
Cardura XL	• The most commonly reported adverse reactions from clinical trials are asthenia, headache, hypotension, and dizziness.
Cialis	• Most common adverse reactions (≥2%) include dyspepsia, back pain, myalgia, nasal congestion, flushing and pain in limb.
Flomax	• The most common adverse events (≥2% of patients and at a higher incidence than placebo) with the 0.4mg dose or 0.8mg dose were headache, dizziness, rhinitis, infection, abnormal ejaculation, asthenia, back pain, diarrhea, pharyngitis, chest pain, cough increased, somnolence, nausea, sinusitis, insomnia, libido decreased, tooth disorder, and blurred vision.
Hytrin	• The most common adverse effects of terazosin therapy are lightheadedness, dizziness, headache, drowsiness, asthenia, lethargy, nausea, vomiting, peripheral edema, nasal congestion, and palpitations.
Jalyn	• The most common adverse reactions, reported in ≥1% of patients treated with dutasteride/tamsulosin are ejaculation disorders, impotence, decreased libido, dizziness, and breast disorders.
Proscar	• The drug-related adverse reactions, reported in ≥1% of patients and greater than in patients treated with placebo over a 4-year study are: impotence, decreased libido,

Drug	Adverse Reactions
	decreased volume of ejaculate, breast enlargement, breast tenderness and rash.
Rapaflo	• Most common adverse reactions (incidence ≥2%) are retrograde ejaculation, dizziness, diarrhea, orthostatic hypotension, headache, nasopharyngitis, and nasal congestion.
Uroxatral	• Most common adverse reactions in clinical studies (incidence ≥2% and at a higher incidence than placebo): dizziness, upper respiratory tract infection, headache, fatigue.

VII. Drug Interactions

Drug	Drug Interactions
Avodart	• Use with caution in patients taking potent, chronic CYP3A4 enzyme inhibitors (e.g., ritonavir).
Cardura	• Concomitant administration with a phosphodiesterase-5 (PDE-5) inhibitor can result in additive blood pressure lowering effects and symptomatic hypotension.
Cardura XL	• Caution should be exercised with concomitantly administering doxazosin with a strong cytochrome P450 (CYP3A4) inhibitor. • Concomitant administration with a phosphodiesterase-5 (PDE-5) inhibitor can result in additive blood pressure lowering effects and symptomatic hypotension.
Cialis	• Can potentiate the hypotensive effects of nitrates, alpha blockers, antihypertensives, or alcohol. • CYP3A4 inhibitors (e.g., ketoconazole, ritonavir) increase exposure. Dose adjustment needed. • CYP3A4 inducers (e.g., rifampin) decrease exposure.
Flomax	• Should not be used with strong inhibitors of CYP3A4 (e.g., ketoconazole). Should be used with caution in combination with moderate inhibitors of CYP3A4 (e.g., erythromycin), in combination with strong (e.g., paroxetine) or moderate (e.g., terbinafine) inhibitors of CYP2D6, or in patients known to be CYP2D6 poor metabolizers, particularly at a dose higher than 0.4mg. • Concomitant use of PDE5 inhibitors with tamsulosin can potentially cause symptomatic hypotension.
Hytrin	• The administration of terazosin with diuretics, monoamine oxidase inhibitors (MAOIs), or antihypertensive agents can result in additive hypotensive effects. • Terazosin has been reported to increase peak concentrations of finasteride by 16% and AUC by 31% when the two

Drug	Drug Interactions
	agents are coadministered. • Concurrent use of phosphodiesterase inhibitors and alpha-blockers may lead to symptomatic hypotension in some patients.
Jalyn	• Dutasteride is extensively metabolized in humans by the CYP3A4 and CYP3A5 isoenzymes. Use caution when prescribing to patients taking potent, chronic CYP3A4 enzyme inhibitors (e.g., ritonavir). • Tamsulosin is extensively metabolized, mainly by CYP3A4 or CYP2D6. There is a significant increase in tamsulosin exposure when coadministered with a combination of both CYP3A4 and CYP2D6 inhibitors. • Caution should be exercised with concomitant administration of warfarin and tamsulosin-containing products.
Proscar	• No clinically significant adverse interactions.
Rapaflo	• Strong P-glycoprotein inhibitors (e.g., cyclosporine) coadministration may increase plasma silodosin concentration. Concomitant use is not recommended. • Concomitant use with alpha-blockers is not recommended. • Concomitant use of PDE5 inhibitors with alpha-blockers can potentially cause symptomatic hypotension.
Uroxatral	• Concomitant use of PDE5 inhibitors with alpha adrenergic antagonists can potentially cause symptomatic hypotension.

VIII. Utilization

ND Medicaid Utilization			
Agents used to treat BPH			
07/01/10 - 06/30/11			
Label Name	**Rx Num**	**Total Reimb Amt**	**Average Cost per Script**
FLOMAX 0.4 MG CAPSULE	3	$577.53	$192.51
UROXATRAL 10 MG TABLET	7	$862.68	$123.24
JALYN 0.5-0.4 MG CAPSULE	3	$340.67	$113.56
AVODART 0.5 MG SOFTGEL	38	$4,233.30	$111.40
FINASTERIDE 5 MG TABLET	69	$3,442.38	$49.89
TAMSULOSIN HCL 0.4 MG CAPSULE	439	$11,959.56	$27.24
DOXAZOSIN MESYLATE 4 MG TAB	76	$1,691.62	$22.26
TERAZOSIN 10 MG CAPSULE	8	$95.33	$11.92
DOXAZOSIN MESYLATE 8 MG TAB	24	$264.71	$11.03
TERAZOSIN 2 MG CAPSULE	51	$512.20	$10.04
DOXAZOSIN MESYLATE 1 MG TAB	19	$177.61	$9.35
TERAZOSIN 5 MG CAPSULE	25	$225.57	$9.02

ND Medicaid Utilization			
Agents used to treat BPH			
07/01/10 - 06/30/11			
Label Name	**Rx Num**	**Total Reimb Amt**	**Average Cost per Script**
DOXAZOSIN MESYLATE 2 MG TAB	52	$451.66	$8.69
TERAZOSIN 1 MG CAPSULE	14	$114.27	$8.16
169 recipients	**828**	**$24,949.09**	

Cialis approximate cost per month - $121.80

References

1. Clinical Pharmacology, 2011 Gold Standard.
2. Cardura® [prescribing information]. New York, NY. Roerig Division of Pfizer, Inc.; July 2009.
3. Cardura XL® [prescribing information]. New York, NY. Roerig Division of Pfizer, Inc; July 2011.
4. Flomax® [prescribing information]. Boehringer Ingelheim Pharmaceuticals, Inc.; January 2011.
5. Rapaflo® [prescribing information]. Morristown, NJ. Watson Laboratories, Inc.; November 2009.
6. Uroxatral® [prescribing information]. Bridgewater, NJ. Sanofi-Aventis; December 2010.
7. Avodart® [prescribing information]. Research Triangle Park, NC. GlaxoSmithKline; June 2011.
8. Jalyn® [prescribing information]. Research Triangle Park, NC. GlaxoSmithKline; June 2011.
9. Proscar® [prescribing information]. Whitehouse Station, NJ. Merck & Co., Inc.; June 2011.
10. Cialis® [prescribing information]. Indianapolis, IN. Lilly USA; October 2011.

North Dakota Medicaid
DUR Board Meeting
Juvisync® Review

I. Overview

The U.S. Food and Drug Administration recently approved Juvisync, the first combination pill to treat Type 2 diabetes and high cholesterol. Juvisync contains sitagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor. Sitagliptin enhances the body's own ability to lower elevated blood sugar and is approved for use in combination with diet and exercise to improve glycemic control in adults with type 2 diabetes. Simvastatin is an HMG-CoA reductase inhibitor approved for use with diet and exercise to reduce cholesterol.

II. Dosage and Administration

Doses are 100mg/10mg, 100mg/20mg, and 100mg/40mg per day. Recommended usual starting dose is 100mg/40mg once a day in the evening. Patients already taking simvastatin (10, 20, or 40mg) can initiate Juvisync at a dose of 100mg sitagliptin and the dose of simvastatin already being taken.

III. Contraindications

- History of a serious hypersensitivity reaction, such as anaphylaxis or angioedema, to any component of this medication.
- Concomitant administration of strong CYP3A4 inhibitors.
- Concomitant administration of gemfibrozil, cyclosporine, danazol.
- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels.
- Women who are pregnant or may become pregnant.
- Nursing mothers.

IV. Warnings/Precautions

- Postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis.
- Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase with higher doses and concomitant use of certain medicines. Predisposing factors include advanced age (≥65), female gender, uncontrolled hypothyroidism, and renal impairment. Patients should be advised to report any symptoms of myopathy.
- Persistent elevations in hepatic transaminase can occur. Check liver enzyme tests before initiating therapy and as clinically indicated thereafter.

- Increased risk of hypoglycemia when added to an insulin secretagogue (e.g., sulfonylurea) or insulin therapy. Consider lowering the dose of the sulfonylurea or insulin to reduce the risk of hypoglycemia.
- Postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with sitagliptin such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. In such cases, promptly stop medication, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment.

V. Adverse Reactions

Most common adverse reactions (incidence ≥5%) with simvastatin are: upper respiratory infection, headache, abdominal pain, constipation, and nausea. Adverse reactions reported in ≥5% of patients treated with sitagliptin and more commonly than in patients treated with placebo are: upper respiratory tract infection, nasopharyngitis and headache. In the add-on to sulfonylurea and add-on to insulin studies, hypoglycemia was also more commonly reported in patients treated with sitagliptin compared to placebo.

VI. Drug Interactions

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, danazol	Contraindicated with Juvisync
Verapamil, diltiazem	Do not exceed 100mg/10mg Juvisync daily
Amiodarone, amlodipine, ranolazine	Do not exceed 100mg/20mg Juvisync daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

Coumarin anticoagulants: Concomitant use with simvastatin prolongs INR. Achieve stable INR prior to starting Juvisync. Monitor INR frequently until stable upon initiation or alteration of Juvisync therapy.

Other Lipid-lowering Medications: Use with other fibrate products or lipid-modifying doses (≥1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with Juvisync.

References

1. Juvisync® [prescribing information]. Whitehouse Station, NJ. Merck & Co., Inc.; October 2011.

North Dakota Medicaid
DUR Meeting
Gralise® Review

I. Overview

Gralise is a once-daily gabapentin approved for the management of postherpetic neuralgia (PHN).

II. Dosage and Administration

Gralise should be titrated to an 1800 mg dose taken orally, once-daily, with the evening meal.

Gralise recommended Titration Schedule

	Day 1	Day 2	Days 3-6	Days 7-10	Days 11-14	Day 15
Daily Dose	300 mg	600 mg	900 mg	1200 mg	1500 mg	1800 mg

III. Warnings/Precautions

- Gralise has differing pharmacokinetic profiles from gabapentin that affects the frequency of administration.
- The safety and effectiveness of Gralise in patients with epilepsy has not been studied.
- Antiepileptic drugs, including gabapentin, the active ingredient in Gralise, increase the risk of suicidal thoughts or behavior.
- Increased seizure frequency may occur in patients with seizure disorders if Gralise is rapidly discontinued. Withdraw Gralise gradually over a minimum of 1 week.

IV. Adverse Reactions

The most common adverse reaction (greater than or equal to 5% and twice placebo) is dizziness.

V. Drug Interactions

- An increase in gabapentin AUC values have been reported when administered with hydrocodone.
- An increase in gabapentin AUC values have been reported when administered with morphine.
- An antacid containing aluminum hydroxide and magnesium hydroxide reduced the bioavailability of gabapentin immediate release by about approximately 20%, but by only 5% when gabapentin was taken 2 hours after antacids. It is recommended that Gralise be taken at least 2 hours following antacid administration.

VI. Pharmacology/Pharmacokinetics

The mechanism of action by which gabapentin exerts its analgesic action is unknown but in animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). Gabapentin prevents pain-related responses in several models of neuropathic pain in rats and mice (e.g., spinal nerve ligation models, spinal cord injury model, acute herpes zoster infection model). Gabapentin also decreases pain-related responses after peripheral inflammation (carrageenan footpad test, late phase of formulin test), but does not alter immediate pain-related behaviors (rat tail flick test, formalin footpad acute phase). The relevance of these models to human pain is not known.

Gabapentin is absorbed from the proximal small bowel by a saturable L-amino transport system. Gabapentin bioavailability is not dose proportional; as the dose is increased, bioavailability decreases. Time to reach maximum plasma concentration for Gralise is 8 hours, which is about 4-6 hours longer compared to gabapentin immediate release.

Table 5: Mean (SD) Steady-State Pharmacokinetics for GRALISE and Gabapentin Immediate Release in Plasma of Healthy Subjects (Day 5, n = 21)

Pharmacokinetic Parameters (Mean ± SD)	**GRALISE 1800 mg QD**	**Gabapentin Immediate Release 600 mg TID**
AUC0-24 (ng • hr/mL)	132,808 ± 34,701	141,301 ± 29,759
C_{max} (ng/mL)	9,585 ± 2,326	8,536 ± 1,715
C_{min} (ng/mL)	1,842 ± 654	2,588 ± 783
T_{max} (hr) median (range)	8 (3-12)	2 (1-5)*

*relative to most recent dose

Gabapentin is eliminated by renal excretion as unchanged drug. Dosage adjustment in patients with compromised renal function is necessary.

VII. Gabapentin Utilization

07/01/10 - 06/30/11		
Label Name	**Rx Num**	**Total Reimb Amt**
GABAPENTIN 100 MG CAPSULE	656	$8,698.97
GABAPENTIN 250 MG/5 ML SOLN	12	$1,513.16
GABAPENTIN 300 MG CAPSULE	2028	$37,016.57
GABAPENTIN 400 MG CAPSULE	367	$8,181.80
GABAPENTIN 600 MG TABLET	1098	$31,323.82
GABAPENTIN 800 MG TABLET	254	$9,646.80
NEURONTIN 250 MG/5 ML SOLN	77	$4,984.62
985 recipients	**4492**	**$101,365.74**

References

1. Gralise® [prescribing information]. Menlo Park, CA. Depomed, Inc.; April 2011.

NORTH DAKOTA MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS
4TH QUARTER 2011

Criteria Recommendations ***Approved Rejected***

1. Ketorolac Nasal Spray / High Dose _____ _____

Alert Message: The recommended maximum daily dose of Sprix (ketorolac nasal spray), for adult patients less than 65 years of age, is 126 mg (one 15.75mg spray in each nostril q 6 to 8 hours). The nasal spray should be discarded within 24 hours of taking the first dose, even if the bottle still contains medication.

Conflict Code: HD – High Dose
Drugs/Diseases

Util A	Util B	Util C (Negate)
Ketorolac Nasal Spray		Renal Impairment

Max Dose: 126mg/day
Age Range: 18 – 64 yoa

References:
Sprix Prescribing Information, Jan. 2011, Luitpold Pharmaceuticals, Inc.
Facts & Comparisons, 2011 Updates.

2. Ketorolac Nasal Spray / High Dose (≥ 65 yoa) _____ _____

Alert Message: The recommended maximum daily dose of Sprix (ketorolac nasal spray), for adult patients: 65 years of age or older, renally impaired and less than 50 kg is 63 mg (one 15.75mg spray in only one nostril q 6 to 8 hours). The nasal spray should be discarded within 24 hours of taking the first dose, even if the bottle still contains medication.

Conflict Code: HD – High Dose
Drugs/Diseases

Util A	Util B	Util C
Ketorolac Nasal Spray		

Max Dose: 63 Mg/day
Age Range: ≥ 65 yoa
References:
Sprix Prescribing Information, Jan. 2011, Luitpold Pharmaceuticals, Inc.
Facts & Comparisons, 2011 Updates.

3. Ketorolac Nasal Spray / Renal Impairment High Dose _____ _____

Alert Message: Sprix (ketorolac nasal spray) can cause renal injury and is contraindicated in patients with advanced renal disease or patients ar risk for renal failure due to volume depletion. The recommended maximum daily dose of ketorolac nasal spray, for adult patients with mild renal impairment is 63 mg (one 15.75mg spray in only one nostril q 6 to 8 hours).

Conflict Code: HD – High Dose
Drugs/Diseases

Util A	Util B	Util C (include)
Ketorolac Nasal Spray		Renal Impairment

Max Dose: 63 mg/day
References:
Sprix Prescribing Information, Jan. 2011, Luitpold Pharmaceuticals, Inc.
Facts & Comparisons, 2011 Updates.

4. Ketorolac Nasal Spray / Duration _____ _____

Alert Message: Sprix (ketorolac) may be over-utilized. The manufacturer recommends a maximum duration (alone or sequentially with other formulations of ketorolac) of 5 days because of the potential for increasing the frequency and severity of adverse reactions.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Ketorolac Nasal Spray		

Day supply: > 5 days
References:
Sprix Prescribing Information, Jan. 2011, Luitpold Pharmaceuticals, Inc.
Facts & Comparisons, 2011 Updates.

5. Ketorolac Nasal Spray / Therapeutic Appropriateness _____ _____

Alert Message: Sprix (ketorolac nasal spray) has not been shown to be safe and effective in patients 17 years of age and younger.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Ketorolac Nasal Spray		

Age Range: 0 – 17 yoa
References:
Sprix Prescribing Information, Jan. 2011, Luitpold Pharmaceuticals, Inc.
Facts & Comparisons, 2011 Updates.

6. Ezogabine / High Dose (18-65 yoa) _____ _____

Alert Message: Potiga (ezogabine) may be over-utilized. The optimal effective dosing range for ezogabine is 600 mg to 1,200 mg per day (in 3 divided doses daily). In clinical trials 400 mg 3 times daily showed limited evidence of additional improvement in seizure reduction but an increase in adverse events and discontinuation, compared to the 300 mg 3 times daily.

Conflict Code: HD – High Dose
Drugs/Diseases

Util A	Util B	Util C (Negate)
Ezogabine		ESRD
		Stage 3, 4 & 5 CKD

Max Dose: 1200mg/day
Age Range: 18-65 yoa
References:
Potiga Prescribing Information, June 2011, Valeant Pharma.
Facts & Comparisons, 2011 Updates.

7. Ezogabine / High Dose (Elderly > 65yoa) _____ _____

Alert Message: Potiga (ezogabine) may be over-utilized. The maximum recommended daily dose of ezogabine in patients over 65 years of age is 750 mg (250 mg 3 times daily). Exceeding the dosing range may increase the risk of adverse effects, including psychosis, hallucinations, confusional state, vertigo and memory impairment.

Conflict Code: HD – High Dose
Drugs/Diseases

Util A	Util B	Util C
Ezogabine		

Max Dose: 750mg/day
Age Range: 66 - 999 yoa

References:
Potiga Prescribing Information, June 2011, Valeant Pharma.

8. Ezogabine / High Dose Renal impairment _____ _____

Alert Message: Potiga (ezogabine) may be over-utilized. The maximum recommended daily dose of ezogabine in patients with moderate to severe renal impairment (CrCL < 50 mL /min or ESRD on dialysis) is 600 mg per day (200 mg 3 times daily). Exceeding the dosing range may increase the risk of adverse effects, including psychosis, hallucinations, confusional state, vertigo and memory impairment.

Conflict Code: HD – High Dose
Drugs/Diseases

Util A	Util B	Util C (Include)
Ezogabine		End Stage Renal Disease Stage 3, 4 & 5 CKD

Max Dose: 600mg/day
References:
Potiga Prescribing Information, June 2011, Valeant Pharma.

9. Ezogabine / High Dose Hepatic impairment _____ _____

Alert Message: Potiga (ezogabine) may be over-utilized. The maximum recommended daily dose of ezogabine in patients with moderate hepatic impairment (Child-Pugh >7-9) is 750 mg per day or severe hepatic impairment (Child-Pugh > 9) is 600 mg per day. Exceeding the recommended dose may cause a significant increase in ezogabine exposure resulting in the risk of adverse effects including dizziness, psychosis, hallucination and confusional state.

Conflict Code: HD – High Dose
Drugs/Diseases

Util A	Util B	Util C (Include)
Ezogabine		Hepatic Impairment

Max Dose: 600mg/day
References:
Potiga Prescribing Information, June 2011, Valeant Pharma.

10. Ezogabine / Non-adherence _____ _____

Alert Message: Based on refill history, your patient may be under-utilizing Potiga (ezogabine). 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
Ezogabine		

References:
Potiga Prescribing Information, June 2011, Valeant Pharma.

11. Ezogabine / Therapeutic Appropriateness (0-17 yoa) _____ _____

Alert Message: Safety and effectiveness of Potiga (ezogabine) in patients under 18 years of age have not been established

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Ezogabine		

Age Range: 0-17 yoa
References:
Potiga Prescribing Information, June 2011, Valeant Pharma.

12. Ezogabine / Phenytoin & Carbamazepine _____ _____

Alert Message: The concurrent use of Potiga (ezogabine) with phenytoin or carbamazepine may result in reduced ezogabine plasma levels. An increase in dosage of ezogabine should be considered when adding phenytoin or carbamazepine.

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

Util A	Util B	Util C
Ezogabine	Phenytoin	
	Carbamazepine	

References:
Potiga Prescribing Information, June 2011, Valeant Pharma.

13. Ezogabine / Digoxin _____ _____

Alert Message: The concurrent use of Potiga (ezogabine) with digoxin may result in increased digoxin serum concentrations. Serum levels of digoxin should be monitored during concomitant administration with ezogabine.

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

Util A	Util B	Util C
Ezogabine	Digoxin	

References:
Potiga Prescribing Information, June 2011, Valeant Pharma.

14. Ezogabine / QT Prolongation _____ _____

Alert Message: Potiga (ezogabine) use has been shown to produce QT prolongation. The QT interval should be monitored when ezogabine is prescribed with medications known to increase the QT interval and in patients with known prolonged QT interval, congestive heart failure, ventricular hypertrophy, hypokalemia or hypomagnesemia.

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

Util A	Util B	Util C
Ezogabine	QT Prolongation	
	Heart Failure	
	Ventricular hypertrophy	
	Hypokalemia	
	Hypomagnesemia	

References:
Potiga Prescribing Information, June 2011, Valeant Pharma.

15. Ezogabine / Drugs Causing QT Prolongation _____ _____

Alert Message: Potiga (ezogabine) use has been shown to produce QT prolongation. The QT interval should be monitored when ezogabine is prescribed with medications known to increase the QT interval and in patients with known prolonged QT interval, congestive heart failure, ventricular hypertrophy, hypokalemia or hypomagnesemia.

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

Util A	Util B					Util C
Ezogabine	Albuterol	Disopyramide	Imipramine	Pazopanib	Thioridazine	
	Alfuzosin	Dofetilide	Indapamide	Pentamidine	Tizanidine	
	Amantadine	Dolasetron	Isradipine	Pimozide	Tolterodine	
	Amiodarone	Doxepin	Itraconazole	Posaconazole	Trazodone	
	Amitriptyline	Dronedarone	Ketoconazole	Procainamide	TMP/SMZ	
	Amphetamine	Droperidol	Lapatinib	Propafenone	Trimipramine	
	Arsenic Trioxide	Ephedrine	Levalbuterol	Protriptyline	Vandetanib	
	Asenapine	Epinephrine	Levofloxacin	Quetiapine	Vardenafil	
	Atazanavir	Erythromycin	Lithium	Quinidine	Venlafaxine	
	Atomoxetine	Escitalopram	Metaproterenol	Ranolazine	Ziprasidone	
	Azithromycin	Felbamate	Methadone	Risperidone	Zolmitriptan	
	Chloral Hydrate	Flecainide	Moexipril/HCTZ	Ritonavir		
	Chloroquine	Fluconazole	Moxifloxacin	Salmeterol		
	Chlorpromazine	Fluoxetine	Nicardipine	Saquinavir		
	Ciprofloxacin	Foscarnet	Nilotinib	Sertraline		
	Citalopram	Fosphenytoin	Norfloxacin	Solifenacin		
	Clarithromycin	Galantamine	Nortriptyline	Sotalol		
	Clomipramine	Gemifloxacin	Octreotide	Sunitinib		
	Clozapine	Granisetron	Ofloxacin	Tacrolimus		
	Dasatinib	Haloperidol	Ondansetron	Tamoxifen		
	Desipramine	Ibutilide	Paliperidone	Telithromycin		
	Diphenhydramine	Iloperidone	Paroxetine	Terbutaline		

References:
Potiga Prescribing Information, June 2011, Valeant Pharma.
ArizonaCERT: Drugs That Prolong the QT Interval and/or Induce Torsades de\Pointes. Available at: http://www.azcert.org/medical-pros/drug-lists/list-03.cfm?sort=Generic_name

16. Anticonvulsants / Suicidal Behavior and Ideation _____ _____

Alert Message: Anticonvulsants increase the risk of suicidal thoughts or behavior in patients taking these medications for any indication. All patients currently taking or starting on any antiepileptic agent should be closely monitored for notable changes in behavior that could indicate the emergence or worsening of depression, suicidal thoughts or behaviors, and/or any unusual changes in mood or behavior.

Conflict Code: TA therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Carbamazepine		
Phenytoin		
Felbamate		
Gabapentin		
Lacosamide		
Lamotrigine		
Levetiracetam		
Oxcarbazepine		
Pregabalin		
Primidone		
Rufinamide		
Ethosuximide		
Methsuximide		
Zonisamide		
Tiagabine		
Topiramate		
Valproic Acid		
Vigabatrin		
Ezogabine		

References:
Potiga Prescribing Information, June 2011, Valeant Pharma.
Facts & Comparisons, 2011 Updates.

17. Ticagrelor / Overutilization _____ _____

Alert Message: Brilinta (ticagrelor) may be over utilized. The manufacturer's recommended maintenance dose is 90 mg twice daily in conjunction with 75-100 mg of aspirin. Exceeding the recommended daily dose of ticagrelor may result in adverse effects including major bleeds.

Conflict Code: - ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C (Negating)
Ticagrelor		Cirrhosis

Max Dose: 180mg/day

References:
Brilinta Prescribing Information, July 2011, AstraZeneca.
Micromedex Healthcare Series, DrugDex Drug Evaluations, 2011 Thomson Reuters.

18. Ticagrelor / Severe Hepatic Impairment _____ _____

Alert Message: Brilinta (ticagrelor) is contraindicated in patients with severe hepatic impairment. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins.

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

Util A	Util B	Util C
Ticagrelor	Cirrhosis	

References:
Brilinta Prescribing Information, July 2011, AstraZeneca.
Micromedex Healthcare Series, DrugDex Drug Evaluations, 2011 Thomson Reuters.

19. Ticagrelor / Non-adherence _____ _____

Alert Message: Based on refill history, your patient may be under-utilizing Brilinta (ticagrelor). 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
Ticagrelor		

References:
Brilinta Prescribing Information, July 2011, AstraZeneca.
Steen H, Review: Evidence-based Prescribing and Adherence to Antiplatelet Therapy – How Much Difference do They Make to Patients with Atherothrombosis? Intern Jrnl Card. Vol. 134, Issue 2, 15 May 2009, pp 150-159.

20. Ticagrelor / Drugs that Increase Bleeding _____ _____

Alert Message: Brilinta (ticagrelor) increases the risk of bleeding and can cause significant and, sometimes, fatal bleeding. Risk factors for bleeding include use of drugs that increase the risk of bleeding in general (e.g., antiplatelet agents, heparin, fibrinolytic therapy, and chronic use of NSAIDS), older age and history of bleeding disorders. Ticagrelor is contraindicated in patients with active pathological bleeding.

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

Util A	Util B	Util C
Ticagrelor	NSAIDS	
	Aspirin > 100mg	
	Heparin	
	LMWHS	
	Warfarin	
	Antiplatelet Agents	
	Dabigatran	

References:
Brilinta Prescribing Information, July 2011, AstraZeneca.
Clinical Pharmacology, 2011 Gold Standard.

21. Ticagrelor / Active Bleeds _____ _____

Alert Message: Brilinta (ticagrelor) increases the risk of bleeding and can cause significant and, sometimes, fatal bleeding. Ticagrelor is contraindicated in patients with active pathological bleeding.

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

Util A	Util B	Util C
Ticagrelor	GI Bleeds	
	Intracranial Hemorrhage	

References:
Brilinta Prescribing Information, July 2011, AstraZeneca.
Micromedex Healthcare Series, DrugDex Drug Evaluations, 2011 Thomson Reuters.

22. Ticagrelor / Strong CYP3A4 Inhibitors and Inducers _____ _____

Alert Message: Concurrent use of Brilinta (ticagrelor) and strong CYP3A4 inhibitors or inducers should be avoided. Ticagrelor is predominantly metabolized by CYP3A4 (and to a lesser extent 3A5) and the inhibition or induction of metabolism may significantly alter ticagrelor plasma concentrations.

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

Util A	Util B		Util C
Ticagrelor	Atazanavir	Phenobarbital	
	Clarithromycin	Rifampin	
	Indinavir	Carbamazepine	
	Itraconazole	Dexamethasone	
	Ketoconazole	Phenytoin	
	Nefazodone		
	Nelfinavir		
	Ritonavir		
	Saquinavir		
	Telithromycin		
	Voriconazole		

References:
Brilinta Prescribing Information, July 2011, AstraZeneca.
Micromedex Healthcare Series, DrugDex Drug Evaluations, 2011 Thomson Reuters.

23. Ticagrelor / Simvastatin & Lovastatin _____ _____

Alert Message: Concurrent use of Brilinta (ticagrelor) and simvastatin or lovastatin may result in higher serum concentrations of simvastatin or lovastatin resulting in the increase risk of statin-related adverse effects (e.g., myopathy and/or rhabdomyolysis). Avoid doses of simvastatin or lovastatin greater than 40 mg per day.

Conflict Code: ER – Overutilization
Drugs/Diseases

Util A	Util B	Util C (Include)
Simvastatin		Ticagrelor
Lovastatin		

Max Dose of Simvastatin: 40mg/day
Max Dose of Lovastatin: 40mg/day

References:
Brilinta Prescribing Information, July 2011, AstraZeneca.
Micromedex Healthcare Series, DrugDex Drug Evaluations, 2011 Thomson Reuters

24. Ticagrelor / Aspirin > 100mg _____ _____

Alert Message: Concurrent use of Brilinta (ticagrelor) and aspirin doses above 100 mg decreases the effectiveness of ticagrelor. Therefore, after the initial loading dose of aspirin (usually 325 mg), the maintenance aspirin dose with ticagrelor should be 75-100 mg.

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

Util A	Util B	Util C
Ticagrelor	Aspirin > 100mg	

References:
Brilinta Prescribing Information, July 2011, AstraZeneca.
Micromedex Healthcare Series, DrugDex Drug Evaluations, 2011 Thomson Reuters

25. Ticagrelor / Digoxin _____ _____

Alert Message: Due to the inhibition of the p-glycoprotein (P-gp) transporter by Brilinta (ticagrelor), concomitant use of digoxin (a P-gp substrate) and ticagrelor may increase digoxin serum concentrations. Monitor digoxin levels with initiation of or any change in ticagrelor therapy.

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

Util A	Util B	Util C
Ticagrelor	Digoxin	

References:
Brilinta Prescribing Information, July 2011, AstraZeneca.
Micromedex Healthcare Series, DrugDex Drug Evaluations, 2011 Thomson Reuters

26. Ticagrelor / Therapeutic Appropriateness _____ _____

Alert Message: The safety and effectiveness of Brilinta (ticagrelor) in pediatric patients have not been established.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Ticagrelor		

Age Range; 0-18
References:
Brilinta Prescribing Information, July 2011, AstraZeneca.

27. Simvastatin-Containing Agents / Amlodipine _____ _____

Alert Message: The dose of a simvastatin-containing agent should not exceed 20 mg per day in patients also receiving an amlodipine-containing product due to the increased risk of simvastatin-related myopathy and/or rhabdomyolysis. If the dose of simvastatin needs to be increased beyond 20 mg per day consider switching to an alternative statin with less potential for interaction.

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

Util A	Util B	Util C
Simvastatin > 20mg	Amlodipine	

References:
Zocor Prescribing Information, June 2011, Merck & Co., Inc.
Vytorin Prescribing Information, June 2011, Merck & Co., Inc.
Simcor Prescribing Information, Abbott Laboratories.
MedWatch FDA Drug Safety Communication: New Restrictions, Contraindications, and Dose Limitations for Zocor (simvastatin) to Reduce the Risk of Muscle Injury. 06-08-2011.

28. Zocor & Vytorin / Contraindicated Drugs _____ _____

Alert Message: The concurrent use of a simvastatin-containing agent and a potent CYP3A4 inhibitor, gemfibrozil, cyclosporine or danazol is contraindicated due to the risk of simvastatin-related myopathy and rhabdomyolysis.

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

Util A	Util B	Util C
Simvastatin	Itraconazole	
Simvastatin/Ezetimibe	Ketoconazole	
	Posaconazole	
	Erythromycin	
	Clarithromycin	
	Telithromycin	
	Nefazodone	
	Gemfibrozil	
	Cyclosporine	
	Danazol	

References:
Zocor Prescribing Information, June 2011, Merck & Co., Inc.
Vytorin Prescribing Information, June 2011, Merck & Co., Inc.
MedWatch FDA Drug Safety Communication: New Restrictions, Contraindications, and Dose Limitations for Zocor (simvastatin) to Reduce the Risk of Muscle Injury. 06-08-2011.

29. Simcor / Contraindicated Drugs _____ _____

Alert Message: The concurrent use of a Simcor (simvastatin/niacin ER) and a potent CYP3A4 inhibitor, gemfibrozil, cyclosporine, danazol, amiodarone, verapamil or diltiazem is contraindicated due to the risk of simvastatin-related myopathy and rhabdomyolysis.

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

Util A	Util B		Util C
Simcor	Itraconazole	Amiodarone	
	Ketoconazole	Verapamil	
	Posaconazole	Diltiazem	
	Erythromycin		
	Clarithromycin		
	Telithromycin		
	Nefazodone		
	Gemfibrozil		
	Cyclosporine		
	Danazol		

References:
Simcor Prescribing Information, June 2011, Abbott Pharmaceuticals.

*Simcor separated from Zocor and Vytorin because the product is contraindicated with additional drugs (amiodarone, verapamil and diltiazem) because it does not come in a dose (10mg simvastatin) which can be safely used with these agents.

30. Protease Inhibitors / Simvastatin & Lovastatin _____ _____

Alert Message: Concurrent use of a protease inhibitor and lovastatin or simvastatin is contraindicated due to the increased risk of statin-related myopathy including rhabdomyolysis. Protease inhibitors inhibit the CYP3A4-mediated metabolism of these two statins, significantly increasing plasma levels. Alternative statins which have the lowest potential for drug-drug interactions include pravastatin or fluvastatin. Atorvastatin may be used with caution, starting with the lowest possible dose and monitoring closely.

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

Util A	Util B	Util C
Saquinavir	Simvastatin	
Ritonavir	Lovastatin	
Darunavir		
Nelfinavir		
Indinavir		
Atazanavir		
Tipranavir		
Fosamprenavir		

References:
Simcor Prescribing Information, June 2011, Abbott Pharmaceuticals.
Zocor Prescribing Information, June 2011, Merck & Co., Inc.
Vytorin Prescribing Information, June 2011, Merck & Co., Inc.
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.
Drug Interaction Charts. Liverpool HIV Pharmacology Group, University of Liverpool. Accessed: August 2011. Available at: http://www.hiv-druginteractions.org.

31. Citalopram / CYP 2C19 Inhibitors _____ _____

Alert Message: Citalopram 20 mg per day is the maximum recommended dose for patients taking a concomitant CYP2C19 inhibitor (e.g., cimetidine, omeprazole and fluvoxamine) due to the risk of QT prolongation and torsades de pointes.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C (Include)
Citalopram		Cimetidine
		Fluvoxamine
		Lansoprazole
		Omeprazole
		Pantoprazole
		Rabeprazole
		Fluoxetine
		Indomethacin
		Ketoconazole
		Modafinil
		Oxcarbazepine
		Probenecid
		Ticlopidine
		Topiramate

Max Dose: 20 mg/day

References:
Celexa Prescribing Information, Aug. 2011, Forest Pharmaceuticals, Inc.
MedWatch The FDA Safety Information and Adverse Event Reporting Program, Celexa (citalopram hydrobromide): Drug Safety Communication – Abnormal Heart Rhythms Associated with High Doses. 08/24/2011.
Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table.\Indiana University School of Medicine. Available at: http://medicine.iupui.edu/clinpharm/ddos/table.asp.

31. Citalopram / Hepatic impairment _____ _____

Alert Message: The recommended dose of citalopram in patients with hepatic impairment is 20 mg once daily, with titration to 40 mg per day in nonresponsive patients only. Citalopram should not be dosed above 40 mg per day due to the risk of QT prolongation which can lead to torsades de pointes, a potentially life-threatening arrhythmia. Citalopram is contraindicated in patients with congenital long QT syndrome.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C(Include)
Citalopram		Hepatic Impairment

Max Dose: 40 mg/day

References:
Celexa Prescribing Information, Aug. 2011, Forest Pharmaceuticals, Inc.
MedWatch The FDA Safety Information and Adverse Event Reporting Program, Celexa (citalopram hydrobromide): Drug Safety Communication – Abnormal Heart Rhythms Associated with High Doses. 08/24/2011.