DUR Board Meeting
June 14, 2010
Wyeth/Rockwell Room
Radisson Hotel

1pm

north dakota
department of
human services

North Dakota Medicaid
DUR Board Meeting
Agenda
Wyeth/Rockwell Room
Radisson Hotel
605 East Broadway
June 14, 2010
1pm

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

2. Old business

• Review and approval of minutes of 03/08/10 meeting	Chairman
• Budget update	Brendan
• Review of Intuniv	Brendan
• Review of Xolair and other commonly prior authorized medications	Brendan
• Review of Suboxone/Subutex	Brendan
• Yearly PA review	HID
o Sedative/Hypnotics	
o Qualaquin	
o ACE-I/ARBS/Renin Inhibitors	
o Synagis	
o Growth Hormone/IGF-1 Products	
o Triptans	

3. New business

• Review of Ampyra	HID
• Review of Ribapak	HID
• Review of Emla	HID
• Review of Narcotics	HID
• Review of Metozolv	HID
• Criteria recommendations	HID
• Upcoming meeting date/agenda	Chairman

4. Adjourn — Chairman

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

Drug Utilization Review (DUR) Meeting Minutes
March 8, 2010

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

Chair, J. Hostetter called the meeting to order at 1:07 pm. Chair, J. Hostetter asked for a motion to approve the minutes from the December meeting. N. Byers moved that the minutes be approved and C. Sorenson seconded the motion. Chair, J. Hostetter called for a voice vote to approve the minutes. The motion passed with no audible dissent.

Budget Update
B. Joyce informed the board that the budget remains flat from last quarter.

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. Antihistamine, PPI, COX-II/NSAID, Revatio/Adcirca, Actoplus Met and Ophthalmic Anti-infective forms and criteria were reviewed. Changes were made to the PPI and COX-II/NSAID forms and criteria. The PPI form/criteria will reflect the addition of Prevacid 24 to the list of step one medications and the addition of lansoprazole and pantoprazole to the list of step two medications. The NSAID form/criteria will reflect that Solaraze be approved with an indication of actinic keratosis and that a trial of Voltaren gel will be required prior to approval of Flector. All other forms and criteria will remain the same.

Intuniv Review
Brendan reviewed Intuniv utilization in North Dakota. Currently, there are several edits in place regarding Intuniv; quantity limits, drug-drug (with IR tablets) and age limit of 6-17. The board asked that additional information be brought to the next meeting including the specialty of providers currently prescribing Intuniv as well as any studies of guanfacine IR in children that are available. There was no public comment.

Xolair Review
Brendan reviewed Xolair utilization. The board suggested that Xolair have a patient safety model similar to hemophilia to ensure compliance. The board asked that a review of all specialty medications suitable for criteria based prior authorizations be reviewed and presented with Xolair at the next board meeting. L. Ding of Genentech spoke on behalf of Xolair.

Suboxone/Subutex Review
Brendan reviewed Suboxone and Subutex utilization with the board. After discussion, J. Savageau made a motion to place Suboxone and Subutex on prior authorization. K. Krohn seconded the motion. This topic will be brought up at the next meeting for finalization. There was no public comment.

Elidel/Protopic Review
Brendan reviewed Elidel and Protopic utilization. Currently, there is an edit in place to prevent use of both products consecutively. L. Pukrabek of Astellas spoke on behalf of Protopic. Board members tabled the discussion of Elidel and Protopic.

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. C. Huber moved to approve the new criteria and G. Pfister seconded the motion. Chair, J. Hostetter called for a voice vote. The motion passed with no audible dissent.

The next DUR board meeting will be held June 14, 2010. C. Huber made a motion to adjourn the meeting. C. Sorenson seconded. The motion passed with no audible dissent. Chair J. Hostetter adjourned the meeting at 3:15 pm.

North Dakota Department of Human Services
DUR Board Meeting
Intuniv® Review
June 14, 2010

I. Overview

Most medications for Attention Deficit Hyperactivity Disorder (ADHD) are CNS stimulants, which are thought to work by blocking reuptake of norepinephrine and dopamine in the presynaptic neurons and increasing release of these neurotransmitters into the extraneural space. There are two non-stimulant medications for ADHD, atomoxetine (Strattera®) and guanfacine (Intuniv®). Atomoxetine is classified as a norepinephrine reuptake inhibitor and works by selectively inhibiting presynaptic norepinephrine transporters. Guanfacine is currently used off-label to treat children with ADHD who also have tics, sleep problems and/or aggression. Intuniv is an extended release form of guanfacine recently approved by the FDA to treat ADHD.

ADHD is a pervasive childhood problem, affecting approximately 3 to 7% of school age children. As of 2006, approximately 4.5 million children (5-17 years of age) have been diagnosed with ADHD. Diagnosis of ADHD increased an average of 3% per year from 1997 to 2006. As of 2003, 2.5 million children (56% of those with a diagnosis) were receiving medication.

A diagnosis of ADHD is subjective in nature, with the provider looking for symptoms of inattention, hyperactivity, and impulsivity; symptoms that are frequent and severe enough to interfere with the child's, and often the family's, ability to lead a normal life. ADHD creates a significant financial burden due to the cost of medical care and work loss for patients and family members. These children, left undiagnosed or untreated, are at higher risk of self-injury, depression, low self-esteem, and a host of other societal disorders.

Pharmacotherapy, along with behavior therapy and counseling, can help those patients diagnosed with ADHD lead a normal and productive life. For many years, CNS stimulants have been considered first-line therapy for the treatment of ADHD. With the approval of atomoxetine in late 2002, and extended release guanfacine in 2009, patients now have other treatment options.

II. Pharmacology

Guanfacine is a selective alpha$_{2A}$-adrenergic receptor agonist. By stimulating alpha$_{2A}$-adrenergic receptors, guanfacine reduces sympathetic nerve impulses from the vasomotor center to the heart and blood vessels. This results in a decrease in peripheral vascular resistance and a reduction in heart rate. The mechanism of action of guanfacine in ADHD is not known.

III. Pharmacokinetics

Pharmacokinetic Parameters in Adults		
Parameter	**Intuniv 1mg once daily (n=52)**	**Immediate-release guanfacine 1mg once daily (n=12)**
C_{max} (ng/mL)	1.0 ± 0.3	2.5 ± 0.6
$AUC_{0-\infty}$ (ng.h/mL)	32 ± 9	56 ± 15
t_{max} (h)	6.0 (4.0 – 8.0)	3.0 (1.5-4.0)
$t_{1/2}$ (h)	18 ± 4	16 ± 3

IV. Warnings/Precautions

1. Hypotension, Bradycardia, and Syncope
2. Sedation and Somnolence
3. Other Guanfacine-Containing Products used concomitantly

V. Drug Interactions

1. CYP3A4/5 Inhibitors

Use caution when Intuniv is administered to patients taking ketoconazole and other strong CYP3A4/5 inhibitors, since elevation of plasma guanfacine concentration increases the risk of adverse events such as hypotension, bradycardia, and sedation. There was a substantial increase in the rate and extent of guanfacine exposure when administered with ketoconazole; the guanfacine exposure increased 3-fold.

2. CYP3A4 Inducers

When patients are taking Intuniv concomitantly with a CYP3A4 inducer, an increase in the dose of Intuniv within the recommended dose range may be considered. There was a significant decrease in the rate and extent of guanfacine exposure when co-administered with rifampin, a CYP3A4 inducer. The exposure to guanfacine decreased 70%.

3. Valproic Acid

Co-administration of guanfacine and valproic acid can result in increased concentrations of valproic acid. When Intuniv is co-administered with valproic acid, monitor patients for potential additive CNS effects, and consider monitoring serum valproic acid concentrations. Adjustments in the dose of valproic acid may be indicated.

4. Antihypertensive Drugs

Use caution when Intuniv is administered concomitantly with antihypertensive drugs due to the potential for additive pharmacodynamics (e.g., hypotension, syncope).

5. CNS Depressant Drugs

Caution should be exercised when Intuniv is administered concomitantly with CNS antidepressant drugs (e.g., alcohol, sedative/hypnotics, benzodiazepines, barbiturates, and antipsychotics.

VI. Adverse Events ≥ 2% in short term studies

Adverse Reaction	Placebo (n=149)	All doses of Intuniv (n=513)
Somnolence	12%	38%
Headache	19%	24%
Fatigue	3%	14%
Abdominal pain (upper)	7%	10%
Nausea	2%	6%
Lethargy	3%	6%
Dizziness	4%	6%
Irritability	4%	6%
Hypotension	4%	6%
Decreased appetite	3%	5%
Dry mouth	1%	4%
Constipation	1%	3%

VII. Dosage and Administration

Intuniv is an extended-release tablet and should be dosed once daily. Tablets should not be crushed, chewed or broken before swallowing because this will increase the rate of guanfacine release. Do not administer with high fat meals, due to increased exposure.

Do not substitute for immediate-release guanfacine tablets on a mg-mg basis, because of differing pharmacokinetic properties. If switching from immediate-release guanfacine, discontinue that treatment and titrate with Intuniv according to the recommended schedule. Begin at a dose of 1 mg/day and adjust in increments of no more than 1 mg/week. Maintain the dose within the range of 1-4 mg once daily, depending on clinical response and tolerability.

The effectiveness of Intuniv for longer-term use (more than 9 weeks) has not been systematically evaluated in control trials. Therefore the physician electing to use Intuniv for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

VIII. Utilization and Physician Specialty

ND Medicaid Intuniv Utilization		
02/24/09 to 02/23/10		
Label Name	**Rx Num**	**Total Remb Amt**
INTUNIV ER 1 MG TABLET	67	$5,500.78
INTUNIV ER 2 MG TABLET	70	$7,853.13
INTUNIV ER 3 MG TABLET	55	$6,424.54
INTUNIV ER 4 MG TABLET	9	$1,347.24
TOTAL 81 recipients	201	$21,125.69

ND Medicaid Guanfacine Utilization		
02/24/09 to 02/23/10		
Label Name	**Rx Num**	**Total Reimb Amt**
GUANFACINE 2 MG TABLET	10	$248.00
GUANFACINE 1 MG TABLET	1174	$15,795.25
TOTAL 231 recipients	1184	$16,043.25

The table below shows the specialty of each prescriber and the number of Intuniv prescriptions each prescriber has written.

Specialty of Physicians Prescribing Intuniv	
Psychiatry	18
Psychiatry	30
Psychiatry	1
Psychiatry	15
Psychiatry	1
Psychiatry	5
Pediatrician	1
Endocrinologist	2
Psychiatry	1
Psychiatry	7
Pediatrician	2
Pediatrician	5
Pediatrician	1
Psychiatry	1
Psychiatry	5
Psychiatry	51
Pediatrician	2

Specialty of Physicians Prescribing Intuniv	
Pediatrician	3
Psychiatry	2
Pediatrician	6
Family Practice	1
Psychiatry	8
Pediatrician	2
NP	3
NP	2
NP	2
NP	5
NP	1
Internal medicine	4
PA	2
CRNA	2
Psychiatry	3
CNS	1

IX. Conclusion

Guanfacine is an alpha-2 agonist that has been used off-label for years for ADHD but at doses up to 3 times a day. Intuniv is given once daily. It can improve hyperactivity and inattention, but at the cost of increased drowsiness and fatigue. Intuniv might be best reserved for children who don't tolerate stimulants due to insomnia, anorexia, tics, etc. or as add-on therapy for more severe ADHD symptoms or ADHD with aggression.
Intuniv costs approximately $150 per month compared to less than $50 per month for the generic short-acting guanfacine or certain stimulants.

References

1. Intuniv® Prescribing Information, August 2009, Shire US, Inc.
2. Centers for Disease Control and Prevention. CDC: Attention-Deficit/Hyperactivity Disorder (ADHD) Data and Statistics. Accessed online at http://www.cdc.gov.
3. U.S. Department of Health and Human Services. NIMH: Attention Deficit Hyperactivity Disorder (ADHD). NIH Publication No. 08-3572. Revised 2008. Accessed online at http://www.nimh.nih.gov.
4. Drug treatment for attention-deficit/hyperactivity disorder. Pharmacist's Letter/Prescriber's Letter 2009;25(11):251106.
5. American Academy of Child and Adolescent Psychiatry. Practice parameter for assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. July 2007. Accessed online at http://www.aacap.org.
6. ICSI Health Care Guideline: Diagnosis and Management of ADHD in Primary Care for School-Age Children and Adolescents. 7th Ed. March 2007. Accessed online at http://www.icsi.org.
7. Committee on Quality Improvement, Subcommittee on ADHD (2000), Clinical Practice Guideline: Treatment of the School-Aged Child with ADHD. Pediatrics 108, No.4, October 2001: 1033-1044. Accessed online at http://aappolicy.aappublications.org.

INTUNIV 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 Intuniv must meet the following criteria:

- **Patient must be between 6-17 years of age.**
- **Patient must first try guanfacine.**

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:

□ INTUNIV

□ FAILED GUANFACINE	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
DUR Board Meeting
Xolair® Review
June 14, 2010

I. Overview

Allergic asthma is a chronic disorder in which exposure to allergens such as dust, mold, and pollen triggers airway inflammation and obstruction. Allergic asthma is the most common form of asthma, affecting over 50% of the 20 million asthma sufferers. Over 2.5 million children under the age of 18 suffer from allergic asthma. Although many of the symptoms of allergic asthma and non-allergic asthma are the same (coughing, wheezing, shortness of breath or rapid breathing) allergic asthma is triggered by inhaled allergens. Common inhaled allergens include dust mites, pet dander, pollen, and mold.

Bronchodilators (e.g., anti-cholinergic agents and inhaled beta2-agonists) are generally used for patients with acute exacerbations of asthma. The preferred therapy for patients with moderate persistent asthma is regular treatment with a combination of inhaled corticosteroids and a long-acting inhaled beta2-agonsist. For patients with severe persistent asthma, the primary therapy includes inhaled corticosteroid at higher doses plus a long-acting beta2-agonist.

Xolair is the first monoclonal antibody treatment for allergy related asthma. It is indicated for adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.

II. Pharmacology

Xolair inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. Reduction in surface-bound IgE on FcεRI-bearing cells limits the degree of release of mediators of the allergic response. Treatment with Xolair also reduces the number of FcεRI receptors on basophils in atopic patients.

III. Pharmacokinetics

Drug	Absolute Bioavailability	Peak Serum Concentrations	Serum Elimination t 1/2
Xolair	62%	7-8 days	26 days

IV. Black Box Warning

Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of Xolair. Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond 1 year after beginning regularly administered treatment. Because of the risk of anaphylaxis, observe patients closely for an appropriate period of time after Xolair administration. Health care providers administering Xolair should be prepared to manage anaphylaxis that can be life-threatening. Inform patients of the signs and symptoms of anaphylaxis and instruct them to seek immediate medical care should symptoms occur.

V. Warnings/Precautions

- Anaphylaxis (see Black Box Warning)
- Malignancy – malignant neoplasms were observed in 20 of 4127 (0.5%) Xolair-treated patients compared with 5 of 2236 (0.2%) control patients in clinical studies of adults and adolescents (≥ 12 years of age) with asthma and other allergic disorders. The observed malignancies in Xolair-treated patients were a variety of types, with breast, non-melanoma skin, prostrate, melanoma, and parotid occurring more than once, and five other types occurring once each. The majority of the patients were observed for less than 1 year. The impact of longer exposure to Xolair or use in patients at higher risk of malignancy (e.g., elderly, current smokers) is not known.
- Xolair has not been shown to alleviate asthma exacerbations acutely. Do not use Xolair to treat acute bronchospasm or status asthmaticus.
- Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of Xolair therapy. Decrease corticosteroids gradually under the direct supervision of a physician.
- In rare cases, patients with asthma on therapy with Xolair may present with serious systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between Xolair and these underlying conditions has not been established.
- Monitor patients at high risk of geohelminth infection while on Xolair therapy.
- Serum total IgE levels increase following administration of Xolair due to formation of Xolair:IgE complexes. Elevated serum total IgE levels may persist for up to 1 year following discontinuation of Xolair. Do not use serum total IgE levels obtained less than 1 year following discontinuation to reassess the dosing regimen because these levels may not reflect steady state free IgE levels.

VI. Drug Interactions

No formal drug interaction studies have been performed with Xolair. The concomitant use of Xolair and allergen immunotherapy has not been evaluated.

VII. Adverse Events ≥ 1% More Frequent in Xolair-Treated Patients

Adverse Event	Xolair n=738 %	Placebo n=717 %
Pain	7	5
Fatigue	3	2
Arthralgia	8	6
Fracture	2	1
Leg pain	4	2
Arm pain	2	1
Dizziness	3	2
Pruritus	2	1
Dermatitis	2	1
Earache	2	1
Injection site reactions	45	43
Severe injection site reactions	12	9

VIII. Dosage and Administration

Xolair 150 to 375 mg is administered SC every 2 or 4 weeks. Because the solution is slightly viscous, the injection may take 5-10 seconds to administer. Doses and dosing frequency are determined by serum total IgE level (IU/ml), measured before the start of treatment, and body weight (kg). Doses more than 150 mg are divided among more than one injection site. Total IgE levels are elevated during treatment and remain elevated for up to one year after the discontinuation of treatment. Therefore, re-testing of IgE levels during Xolair treatment cannot be used as a guide for dose determination.

IX. Treatment Guidelines

National Heart Lung and Blood Institute

Stepwise Approach for Managing Asthma in Youths ≥ 12 years of age and adults

- **Intermittent Asthma**
  Step 1 – Preferred: Inhaled short-acting beta2-agonist (SABA) PRN

- **Persistent Asthma: Daily Medication (consult with asthma specialist if step 4 care or higher is required). Consider consultation at step 3.**
  Step 2 – Preferred: Low-dose inhaled corticosteroid (ICS)
  Alternative: Cromolyn, leukotriene receptor antagonist (LTRA), Nedocromil, or Theophylline

Step 3 – Preferred: Low-dose ICS + long-acting inhaled beta2-agonist (LABA) OR medium-dose ICS
Alternative: Low-dose ICS + either LTRA, Theophylline, or Zileuton

Step 4 – Preferred: Medium-dose ICS + LABA
Alternative: Medium-dose ICS + either LTRA, Theophylline, or Zileuton

Step 5 – Preferred: High-dose ICS + LABA AND consider Omalizumab for patients who have allergies

Step 6 – Preferred: High-dose ICS + LABA + oral corticosteroid AND consider Omalizumab for patients who have allergies

- Each step: Patient education, environmental control and management of comorbidities.
- Quick relief medication for all patients. (SABA as needed for symptoms)
- Short course of oral systemic corticosteroids may be needed.
- Use of SABA > 2 days a week for symptom relief generally indicates inadequate control and the need to step up treatment.

Global Initiative for Asthma (2009 update)

Role in therapy – Anti-IgE (omalizumab) is a treatment option limited to patients with elevated serum levels of IgE. Its current indication is for patients with severe allergic asthma who are uncontrolled on inhaled glucocorticosteroids, although the dose of concurrent treatment has varied in different studies. Improved asthma control is reflected by fewer symptoms, less need for reliever medications, and fewer exacerbations. Further investigations will likely provide additional clarification of the role of anti-IgE in other clinical settings.

X. Utilization

Xolair Utilization			
02/24/09 to 02/23/10			
NDC Code	**Rx Num**	**Total Reimb Amt**	**Label Name**
50242004062	11	$3,672.78	XOLAIR 150 MG VIAL
TOTAL	11	$3,672.78	1 recipient

XI. Conclusion

Xolair is a subcutaneously administered monoclonal anti-IgE antibody that reduces free IgE concentrations and promotes down regulation of IgE receptors on basophils. Xolair can be useful as adjunctive therapy with inhaled corticosteroids in patients with step 5 or 6 persistent asthma. Continued studies are required to determine which patients may most benefit from Xolair.

References

1. Wolters Kluwer Health, Inc, ed. Drug Facts and Comparisons. St Louis, MO. 2009.
2. Xolair® Prescribing Information, January 2010, Genentech, Inc.
3. National Heart Lung and Blood Institute. U.S. Department of Health and Human Services. NIH Publication 08-5846, Oct. 2007. Accessed online at www.nhlbi.nih.gov Jan. 2010.
4. Asthma and Allergy Foundation of America. Accessed online at www.aafa.org Jan. 2010.
5. Global Strategy for Asthma Management and Prevention 2009 (update) Accessed online at www.ginasthma.org. Jan. 2010.

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 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			
Physician Medicaid Provider Number	Telephone Number	Fax Number	
Address	City	State	Zip Code

Requested Drug and Dosage: □ XOLAIR	**DIAGNOSIS FOR THIS REQUEST:**	**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)	

Blue Cross Blue Shield of North Dakota
Restricted Use List

Restricted Use Drug - A Prescription Medication or Drug that may require Prior Approval and/or be subject to a limited dispensing amount.

Key Definitions		
F	Formulary Drug	A Brand Name or Generic Prescription Drug that has been determined to be safe, therapeutically effective, high quality, and cost-effective as determined by a committee of Physicians and Pharmacists based on current data.
NF	Non-Formulary Drug	A Prescription Medication or Drug that is not a Formulary Drug

CONTRACEPTIVES: Oral contraceptives, if covered, are covered for females only. Prior approval (PA) required for males. Oral contraceptives may be excluded from coverage under the drug benefit. In all cases, plan inclusions/exclusions determine specific coverage.

The following List of Drugs represents the drugs requiring Prior Approval (PA)

- Specific criteria must be met before medication is covered under the pharmacy benefit. If a prior approval is granted, the drug will be allowed at the Formulary benefit level.
- Both brand name drugs and generic equivalents require Prior Approval.

CATEGORY	BRAND DRUG NAME	GENERIC DRUG NAME
ACNE & SKIN: Prior approval (PA) required for age >35	ATRALIN, AVITA , RETIN-A, TRETINOIN	TRETINOIN
	DIFFERIN	ADAPALENE
	TAZORAC	TAZAROTENE
	ZIANA	CLINDAYMYCIN-TRETINOIN
ANTIBIOTICS	ZYVOX*	LINEZOLID*
	*Initial therapy of 14 doses will be covered to ensure that therapy is not delayed while the prior approval request is being reviewed.	
ANTIFUNGALS	NOXAFIL	POSACONAZOLE
	VFEND	VORICONAZOLE
AUTOIMMUNE INFLAMMATORY DISORDERS	AMEVIVE	ALEFACEPT
	ARCALYST	RILONACEPT
	CIMZIA	CERTOLIZUMAB
	ENBREL	ETANERCEPT
	HUMIRA	ADALIMUMAB
	KINERET	ANAKINRA
	ORENCIA	ABATACEPT
	REMICADE	INFLIXIMAB
	RITUXAN	RITUXIMAB
	SIMPONI	GOLIMUMAB
	STELARA	USTEKINUMAB
CANCER— ORALLY ADMINISTERED	AFINITOR	EVEROLIMUS
	GLEEVEC	IMATINIB MESYLATE
	HERCEPTIN	TRASTUZUMAB
	HYCAMTIN	TOPOTECAN
	IRESSA	GEFITINIB
	NEXAVAR	SORAFENIB
	REVLIMID	LENALIDOMIDE
	SPRYCEL	DASATINIB
	SUTENT	SUNITINIB
	TARCEVA	ERLOTINIB

Blue Cross Blue Shield of North Dakota
Restricted Use List

CATEGORY	BRAND DRUG NAME	GENERIC DRUG NAME
CANCER—ORALLY ADMINISTERED	TASIGNA	NILOTINIB
	THALOMID	THALIDOMIDE
	TYKERB	LAPATINIB
	VOTRIENT	PAZOPANIB
	ZOLINZA	VORINOSTAT
CANCER—INJECTABLE	RITUXAN	RITUXIMAB
ENZYME DEFICIENCIES	KUVAN	SAPROPTERIN
	ORFADIN	NITISINONE
GROWTH HORMONES	GENOTROPIN, HUMATROPE, NORDITROPIN, NUTROPIN, NUTROPIN AQ, OMNITROPE, SAIZEN, SEROSTIM, TEV-TROPIN, ZORBTIVE	SOMATROPIN
	INCRELEX	MECASERMIN
IDIOPATHIC IMMUNE THROMBOCYTOPENIC PURPURA	NPLATE	ROMIPLOSTIM
	PROMACTA	ELTROMBOPAG
LUNG DISORDERS	ACTIMMUNE	INTERFERON GAMMA-1B
	SYNAGIS	PALIVIZUMAB
	XOLAIR	OMALIZUMAB
MEN'S HEALTH: Prior approval (PA) required for females.	AVODART	DUTASTERIDE CAP
	CAVERJECT, EDEX	ALPROSTADIL FOR INJ
	CIALIS	TADALAFIL
	ELIGARD	LEUPROLIDE ACETATE (6 MONTH) FOR SUBCUTANEOUS INJ KIT
	LEVITRA	VARDENAFIL
	MUSE	ALPROSTADIL URETHRAL PELLET
	PROSCAR	FINASTERIDE TAB 5 MG
	STRIANT	TESTOSTERONE BUCCAL MUCOADHESIVE SYSTEM 30 MG
	VANTAS	HISTRELIN ACETATE IMPLANT KIT
	VIAGRA	SILDENAFIL CITRATE
PULMONARY HYPERTENSION	ADCIRCA	TADALAFIL
	FLOLAN	EPOPROSTENOL
	LETAIRIS	AMBRISENTAN
	REMODULIN	TREPROSTINIL
	REVATIO	SILDENAFIL
	TRACLEER	BOSENTAN
	TYVASO	TREPOSTINOL
	VENTAVIS	ILOPROST
WEIGHT LOSS	ADIPEX-P	PHENTERMINE HCL
	BONTRIL PDM, BONTRIL SLOW-RELEASE	PHENDIMETRAZINE
	DIDREX	BENZPHETAMINE
	IONAMIN	PHENTERMINE RESIN
	MERIDIA	SIBUTRAMINE

Blue Cross Blue Shield of North Dakota
Restricted Use List

CATEGORY	BRAND DRUG NAME	GENERIC DRUG NAME
WEIGHT LOSS	TENUATE, TENUATE DOSPAN	DIETHYLPROPION
	XENICAL	ORLISTAT
OTHERS	APOKYN	APOMORPHINE
	BANZEL	RUFINAMIDE
	FORTEO	TERIPARATIDE
	RELISTOR	METHYLNALTREXONE
	RITUXAN	RITUXIMAB
	SENSIPAR	CINACALCET
	SUPPRELIN LA	HISTRELIN ACETATE
	XENAZINE	TETRABENAZINE

Drugs with Quantity Limits
The following list represents the drugs subject to a limited dispensing amount.

BRAND DRUG NAME	GENERIC DRUG NAME	FORMULARY STATUS	Quantity Limit: A Combined Total of 18 tablets per 90 days
VIAGRA	SILDENAFIL CITRATE	NF	A member can receive **up to** a combined total of 18 tablets per 90 days. The claims system **will not allow** any quantity >18 in **any** 90-day claims period.
CIALIS	TADALAFIL	NF	
LEVITRA	VARDENAFIL	NF	
ZYVOX	LINEZOLID	F	Initial therapy of 14 doses will be covered to ensure that therapy is not delayed while the prior approval request is being reviewed.

Blue Cross Blue Shield of North Dakota
Specialty Drug List

Specialty Drug – medications or drugs that are generally high cost and may have other considerations such as special drug administration, limited availability, unique delivery and dispensing or unique and/or required patient support or monitoring.

Use of some products identified by [PA] may be approved only after certain criteria are met. If prior approval is not obtained, benefits may be denied if criteria are not met. A physician (or clinic personnel) should submit a written request to the address shown below for prior approval consideration. **Both brand name drugs and generic equivalents require Prior Approval.**

Pharmacy and Therapeutics Committee
Provider Services
4510 13th Avenue SW
Fargo, ND 58121

CATEGORY	BRAND NAME	GENERIC NAME	
AUTOIMMUNE INFLAMMATORY DISORDERS	AMEVIVE	ALEFACEPT	[PA]
	ARCALYST	RILONACEPT	[PA]
	ENBREL	ETANERCEPT	[PA]
	HUMIRA	ADALIMUMAB	[PA]
	ILARIS	CANAKINUMAB	[PA]
	KINERET	ANAKINRA	[PA]
	SIMPONI	GOLIMUMAB	[PA]
BLOOD MODIFIERS	ARANESP	DARBEPOETIN ALFA	
	EPOGEN	EPOETIN ALFA	
	LEUKINE	SARGRAMOSTIM	
	NEULASTA	PEGFILGRASTIM	
	NEUMEGA	OPRELVEKIN	
	NEUPOGEN	FILGRASTIM	
	NPLATE	ROMIPLOSTIM	[PA]
	PROCRIT	EPOETIN ALFA	
	PROMACTA	ELTROMBOPAG	[PA]
CANCER-ORAL	AFINITOR	EVEROLIMUS	[PA]
	GLEEVEC	IMATINIB	[PA]

CATEGORY	BRAND NAME	GENERIC NAME	
CANCER-ORAL	HEXALEN	ALTRETAMINE	
	HYCAMTIN	TOPOTECAN	[PA]
	IRESSA	GEFITINIB	[PA]
	LYSODREN	MITOTANE	
	MATULANE	PROCARBAZINE	
	NEXAVAR	SORAFENIB	[PA]
	OFORTA	FLUDARABINE	
	REVLIMID	LENALIDOMIDE	[PA]
	SPRYCEL	DASATINIB	[PA]
	SUTENT	SUNITINIB	[PA]
	TARCEVA	ERLOTINIB	[PA]
	TARGRETIN	BEXAROTENE	[PA]
	TASIGNA	NILOTINIB	[PA]
	TEMODAR	TEMOZOLOMIDE	
	THALOMID	THALIDOMIDE	[PA]
	TYKERB	LAPATINIB	[PA]
	VESANOID	TRETINOIN	
	VOTRIENT	PAZOPANIB	[PA]
	XELODA	CAPECITABINE	
	ZOLINZA	VORINOSTAT	[PA]
CYSTIC FIBROSIS	PULMOZYME	DORNASE ALFA	
	TOBI	TOBRAMYCIN NEBU SOLN	
ENZYME DEFICIENCIES	KUVAN	SAPROPTERIN	[PA]
	ZAVESCA	MIGLUSTAT	
GROWTH HORMONES	GENOTROPIN	SOMATROPIN	[PA]
	HUMATROPE	SOMATROPIN	[PA]
	INCRELEX	MECASERMIN	[PA]
	NORDITROPIN	SOMATROPIN	[PA]
	NUTROPIN	SOMATROPIN	[PA]
	NUTROPIN AQ	SOMATROPIN	[PA]
	OMNITROPE	SOMATROPIN	[PA]

CATEGORY	BRAND NAME	GENERIC NAME	
GROWTH HORMONES	SAIZEN	SOMATROPIN	[PA]
	SEROSTIM	SOMATROPIN	[PA]
	TEV-TROPIN	SOMATROPIN	[PA]
	ZORBTIVE	SOMATROPIN	[PA]
HEPATITIS C	COPEGUS	RIBAVIRIN	
	INFERGEN	INTERFERON ALFACON	
	INTRON A	INTERFERON ALFA-2B	
	PEGASYS	PEGINTERFERON ALFA-2A	
	PEG-INTRON	PEGINTERFERON ALFA-2B	
	REBETOL	RIBAVIRIN	
	RIBAPAK	RIBAVIRIN	
	RIBASPHERE	RIBAVIRIN	
HIV	FUZEON	ENFUVIRTIDE	
INFERTILITY	BRAVELLE	UROFOLLITROPIN	
	CETROTIDE	CETRORELIX ACETATE	
	FOLLISTIM AQ	FOLLITROPIN BETA	
	GANIRELIX ACETATE	GANIRELIX ACETATE	
	GONAL-F	FOLLITROPIN ALFA	
	LUVERIS	LUTROPIN ALFA	
	MENOPUR	MENOTROPINS	
	NOVAREL	CHORIONIC GONADOTROPIN	
	OVIDREL	CHORIONIC GONADOTROPIN	
	PREGNYL	CHORIONIC GONADOTROPIN	
	REPRONEX	MENOTROPINS	
LUNG DISORDERS	ACTIMMUNE	INTERFERON GAMMA-1B	[PA]
MULTIPLE SCLEROSIS	AMPYRA	DALFAMPRIDINE	
	AVONEX	INTERFERON BETA-1A	
	BETASERON	INTERFERON BETA-1B	
	COPAXONE	GLATIRAMER ACETATE	

CATEGORY	BRAND NAME	GENERIC NAME	
MULTIPLE SCLEROSIS	EXTAVIA	INTERFERON BETA-1B	
	REBIF	INTERFERON BETA-1A	
PULMONARY HYPERTENSION	ADCIRCA	TADALAFIL	[PA]
	LETAIRIS	AMBRISENTAN	[PA]
	REVATIO	SILDENAFIL CITRATE	[PA]
	TRACLEER	BOSENTAN	[PA]
	TYVASO	TREPROSTINIL	[PA]
	VENTAVIS	ILOPROST	[PA]
OTHERS	ALFERON N	INTERFERON ALFA-N3	
	APOKYN	APOMORPHINE	
	CHENODAL	CHENODIOL	
	EXJADE	DEFERASIROX	
	FORTEO	TERIPARATIDE	
	LEUPROLIDE ACETATE	LUPRON	
	LUPRON DEPOT	LEUPROLIDE ACETATE	
	RELISTOR	METHYLNALTREXONE	
	SAMSCA	TOLVAPTAN	
	XENAZINE	TETRABENAZINE	
	XYREM	SODIUM OXYBATE	

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		

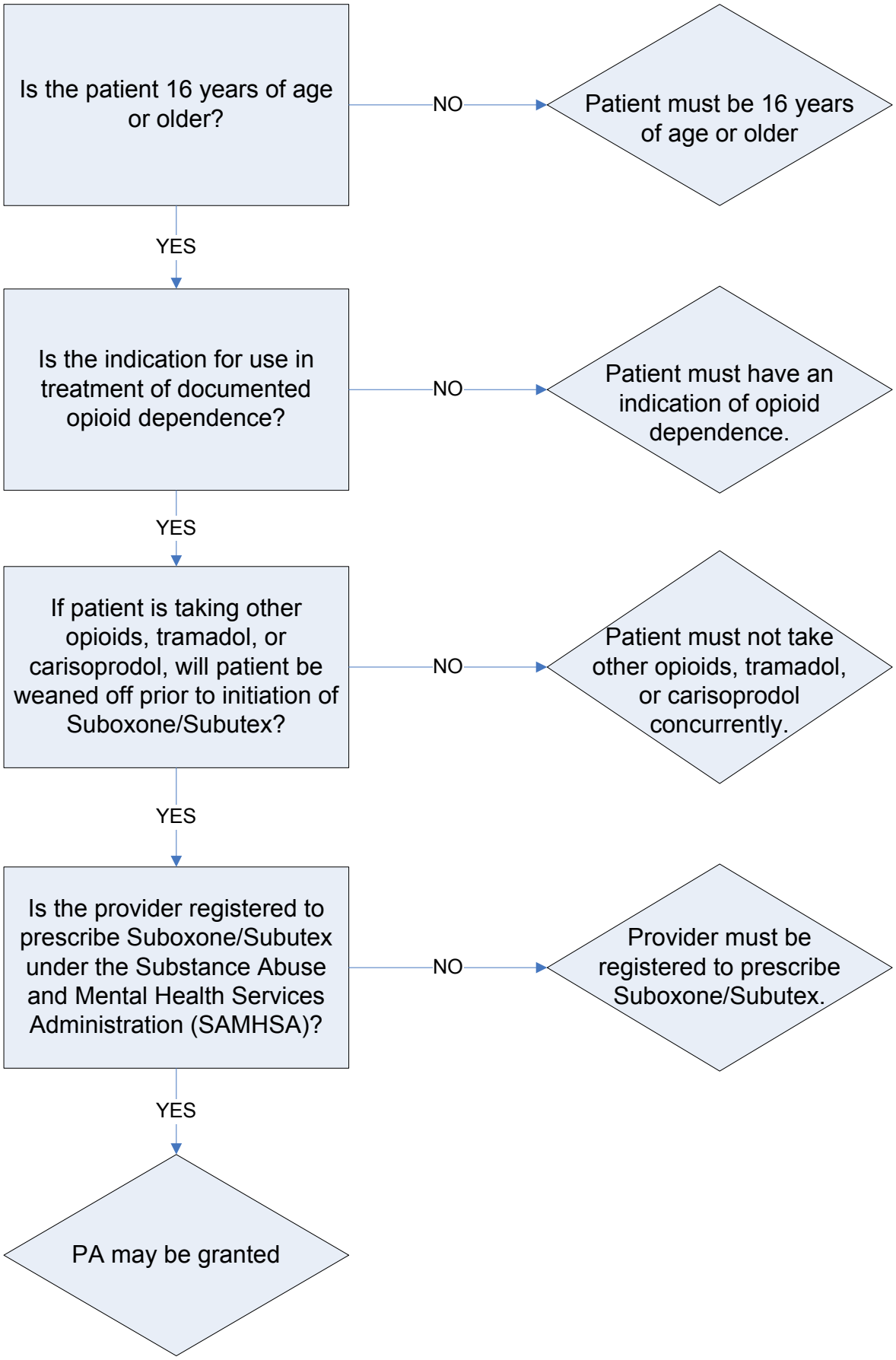
Part II: TO BE COMPLETED BY PHARMACY

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



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	

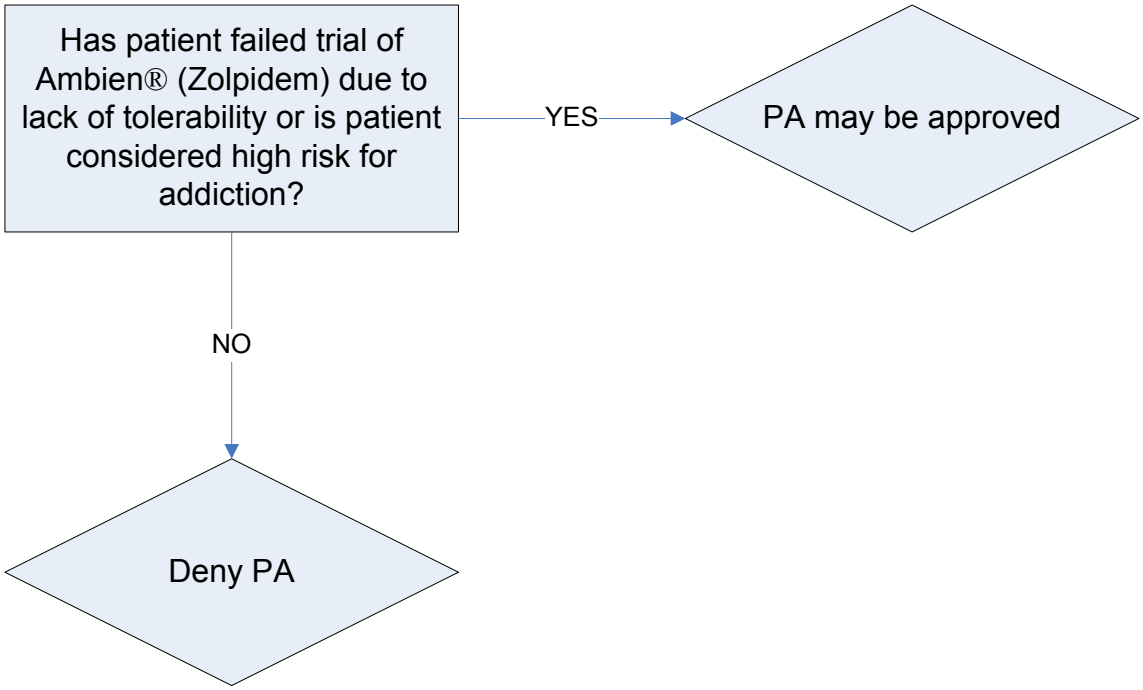
Part II: TO BE COMPLETED BY PHARMACY

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



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

	FEB 04	MAY 06	JAN 10
All Sedative/Hypnotics(No Subclass)			
AMBIEN	91.22	56.59	0.00
AMBIEN CR	0.00	17.51	7.95
LUNESTA	0.00	18.71	6.36
ROZEREM	0.00	4.80	1.19
SONATA	8.78	2.40	0.00
ZALEPLON	0.00	0.00	0.40
ZOLPIDEM TARTRATE	0.00	0.00	84.10

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:

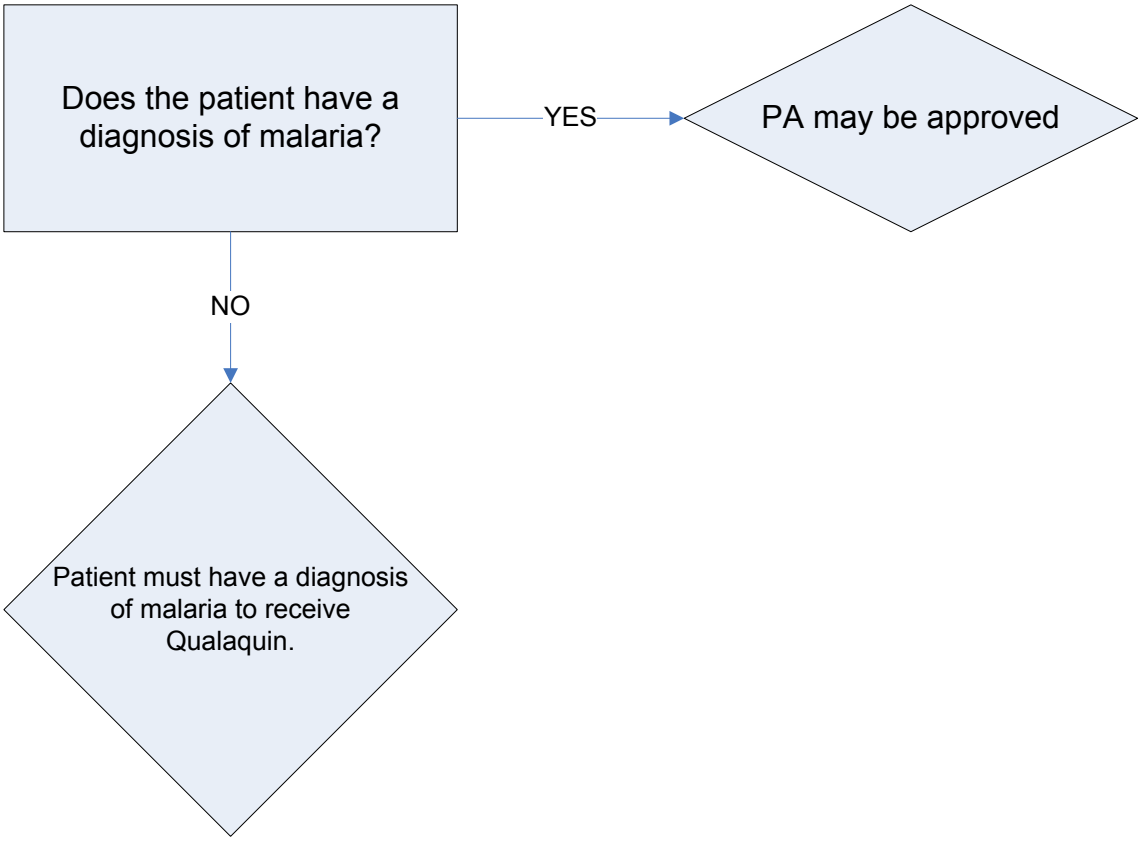
Part II: TO BE COMPLETED BY PHARMACY

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 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

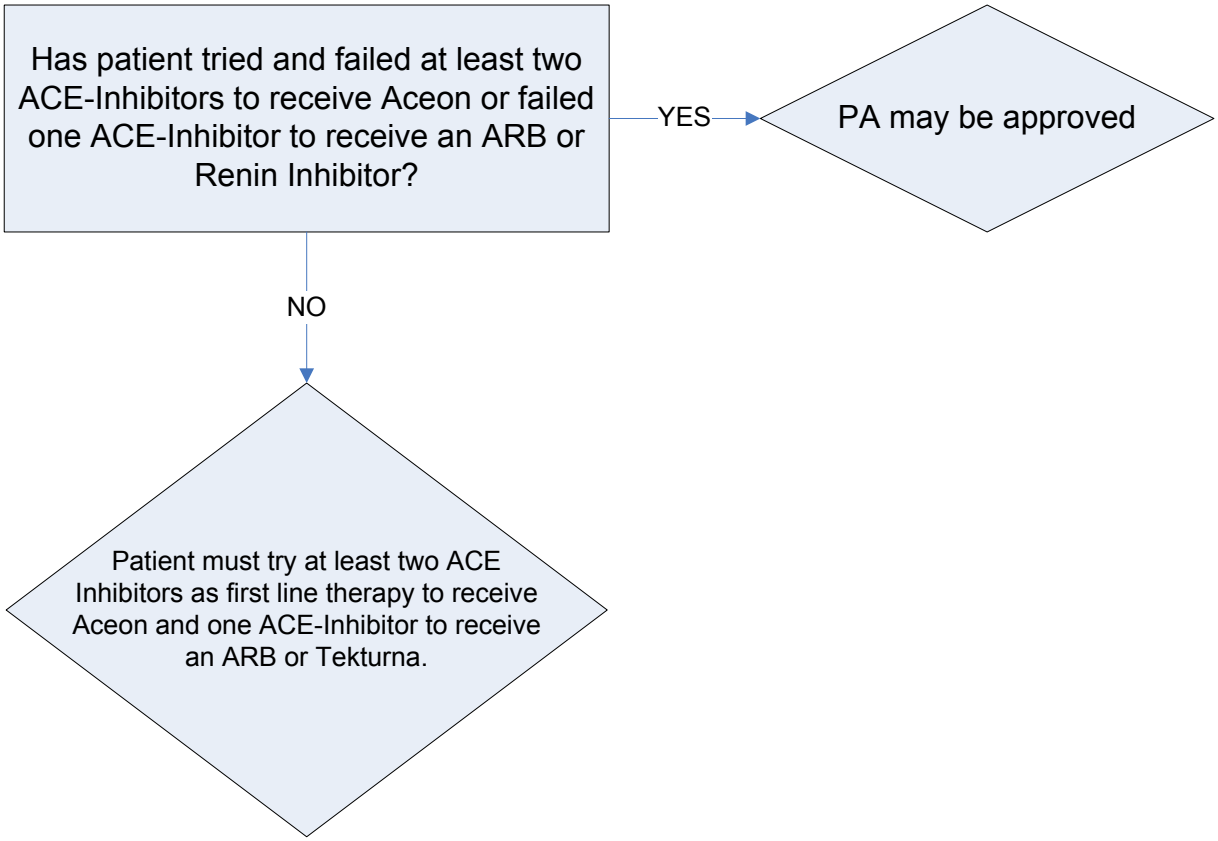
Part II: TO BE COMPLETED BY PHARMACY

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 and hydrochlorothiazide combinations

Renin Inhibitor: Tekturna and hydrochlorothiazide combination

NORTH DAKOTA MEDICAID
Percentage Market Share Within Sub-Classes
ACE-Inhibitors, ARBs and Renin Inhibitors

	FEB 04	APR 05	JAN 10
All ACE-Inhibitors, ARBs and Renin Inhibitors(No Subclass)			
ACCUPRIL	6.52	0.34	0.00
ACCURETIC	0.26	0.08	0.00
ACEON	0.26	0.32	0.00
ALTACE	5.92	6.47	0.00
ATACAND	2.69	3.22	0.12
ATACAND HCT	0.43	0.50	0.00
AVALIDE	0.37	0.55	0.25
AVAPRO	1.75	1.93	0.37
AZOR	0.00	0.00	0.12
BENAZEPRIL HCL	0.23	3.96	2.71
BENAZEPRIL HCL-HCTZ	0.00	0.74	0.37
BENICAR	1.57	2.14	1.11
BENICAR HCT	0.26	0.87	0.74
CAPOTEN	0.00	0.00	0.00
CAPOZIDE	0.00	0.00	0.00
CAPTOPRIL	1.55	1.22	1.23
CAPTOPRIL/HYDROCHLOROTHIAZIDE	0.00	0.00	0.00
COZAAR	5.95	5.78	4.56
DIOVAN	4.75	5.39	2.59
DIOVAN HCT	1.92	1.98	1.35
ENALAPRIL MALEATE	14.68	13.71	8.62
ENALAPRIL MALEATE-HCTZ	0.63	0.55	0.12
ENALAPRIL MALEATE/HCTZ	0.00	0.00	0.00
EXFORGE	0.00	0.00	0.00
FOSINOPRIL SODIUM	1.37	1.93	0.62
FOSINOPRIL-HYDROCHLOROTHIAZIDE	0.00	0.13	0.25
HYZAAR	2.15	1.69	1.11
LEXXEL	0.00	0.03	0.00
LISINOPRIL	29.33	31.30	55.91
LISINOPRIL-HCTZ	2.83	3.33	7.64
LOTENSIN	4.06	0.03	0.00
LOTENSIN HCT	1.06	0.05	0.00
LOTREL	3.40	2.98	0.25
MAVIK	0.29	0.45	0.00
MICARDIS	0.26	0.40	0.62
MICARDIS HCT	0.03	0.24	0.74
MOEXIPRIL HCL	2.20	0.11	0.62
MOEXIPRIL-HYDROCHLOROTHIAZIDE	0.00	0.00	0.62
MONOPRIL	1.23	0.05	0.00
MONOPRIL HCT	0.31	0.08	0.00
PRINIVIL	0.09	0.03	0.00
PRINZIDE	0.00	0.00	0.00
QUINAPRIL	0.00	0.00	0.00
QUINAPRIL HCL	0.00	4.38	3.82
QUINARETIC	0.00	0.13	0.00
RAMIPRIL	0.00	0.00	3.57

TARKA	0.11	0.18	0.00
TEKTURNA	0.00	0.00	0.00
TEKTURNA HCT	0.00	0.00	0.00
TEVETEN	0.06	0.11	0.00
TEVETEN HCT	0.03	0.03	0.00
TRANDOLAPRIL	0.00	0.00	0.00
TWYNSTA	0.00	0.00	0.00
UNIRETIC	1.23	0.98	0.00
UNIVASC	0.00	1.51	0.00
VALTURNA	0.00	0.00	0.00
VASERETIC	0.00	0.00	0.00
VASOTEC	0.06	0.00	0.00
VASOTEC I.V.	0.00	0.00	0.00
ZESTORETIC	0.14	0.08	0.00
ZESTRIL	0.03	0.03	0.00

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, 2009 through April 21, 2010
- Based on the 2009 American Academy of Pediatrics recommendations, 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	Prescriber NPI

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

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:	

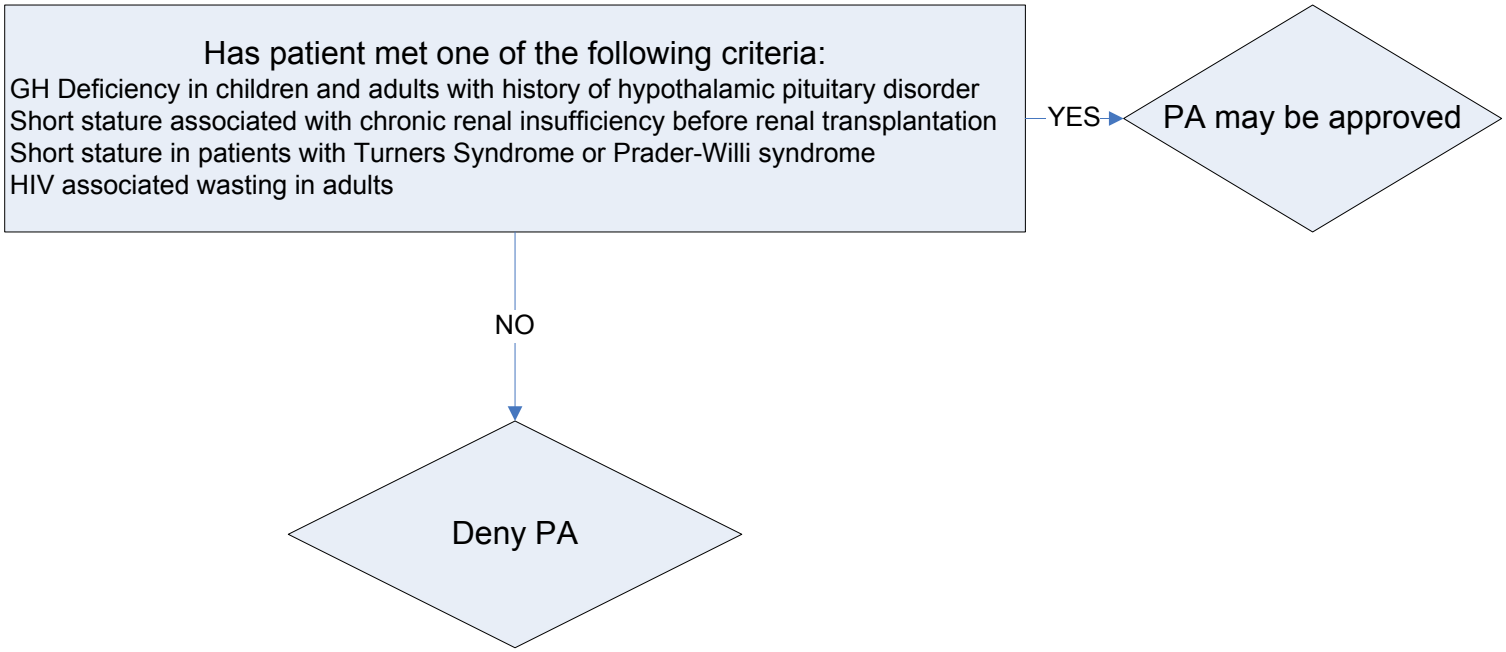
Part II: TO BE COMPLETED BY PHARMACY

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:

□ AMERGE □ RELPAX

□ AXERT □ TREXIMET

□ FROVA □ ZOMIG

□ MAXALT

Diagnosis for this request:

Qualifications for coverage:

□ Failed sumatriptan 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

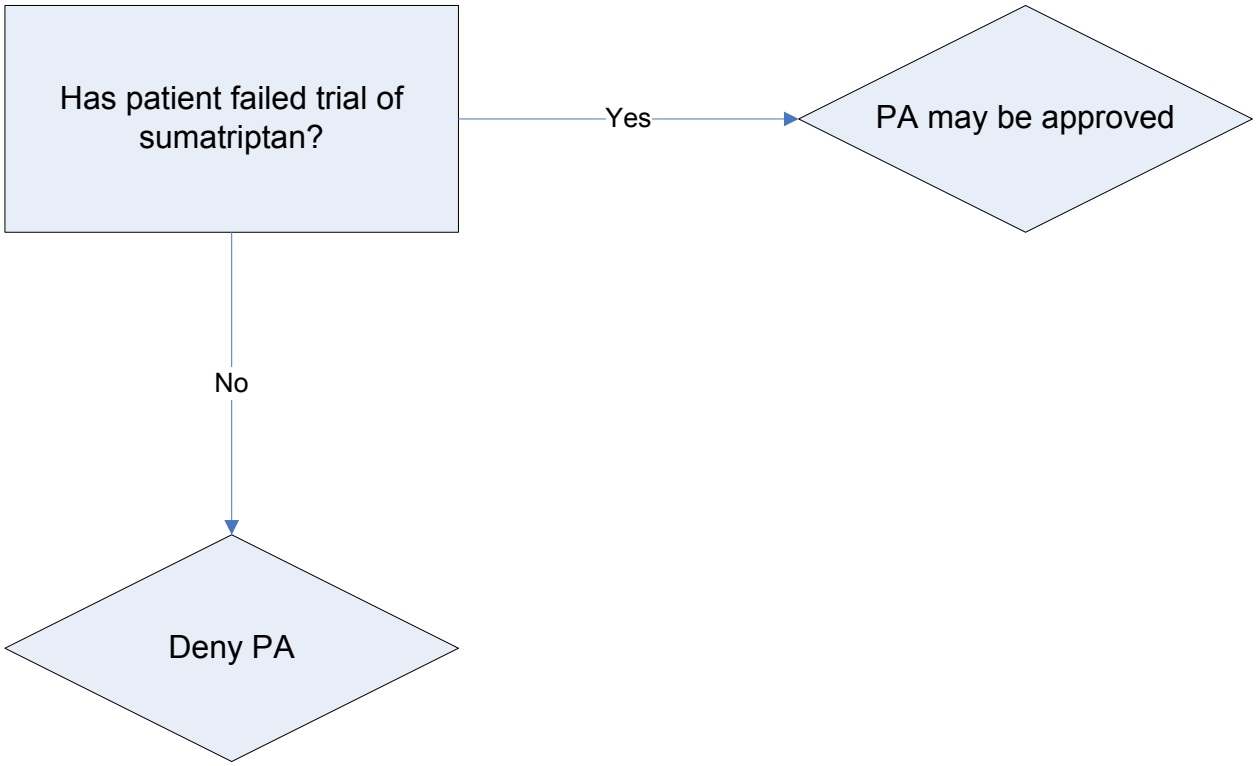
Part II: TO BE COMPLETED BY PHARMACY

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



NORTH DAKOTA MEDICAID
Percentage Market Share Within Sub-Classes
Triptans

	FEB 04	SEP 07	JAN 10
All Triptans(No Subclass)			
AMERGE	2.54	0.00	0.00
AXERT	5.58	0.81	0.00
FROVA	2.54	0.00	0.00
IMITREX	50.25	19.35	4.86
MAXALT	8.12	13.71	5.56
MAXALT MLT	7.11	13.71	4.86
RELPAX	7.11	9.68	9.03
SUMATRIPTAN SUCCINATE	0.00	33.06	68.06
TREXIMET	0.00	1.61	2.08
ZOMIG	13.71	6.45	4.17
ZOMIG ZMT	3.05	1.61	1.39

North Dakota Department of Human Services
DUR Board Meeting
Ampyra® Review
June 14, 2010

I. Overview

Multiple sclerosis (MS) is a chronic, often disabling disease that affects the central nervous system (the brain, optic nerve, and spinal cord). It is thought to be an autoimmune disorder. MS can cause blurred vision, loss of balance, poor coordination, slurred speech, tremors, numbness, extreme fatigue, problems with memory and concentration, paralysis, and blindness.

Most people with MS are diagnosed between the ages of 20 and 50. Approximately 400,000 Americans have MS and every week about 200 people are diagnosed. The progress, severity, and specific symptoms of MS are unpredictable and vary from one person to another.

Ampyra (dalfampridine) was approved by the FDA in January for its ability to improve walking in people with MS. In clinical trials, patients treated with Ampyra had faster walking speeds than those treated with placebo.

II. Pharmacology

Dalfampridine is a broad spectrum potassium channel blocker. In animal studies, dalfampridine has been shown to increase conduction of action potentials in demyelinated axons through inhibition of potassium channels.

III. Pharmacokinetics

Orally administered dalfampridine is rapidly and completely absorbed from the gastrointestinal tract. Single Ampyra tablet 10mg doses administered to healthy volunteers in a fasted state gave peak concentrations ranging from 17.3ng/mL to 21.6ng/mL occurring 3-4 hours post administration (Tmax). In comparison, Cmax with the same 10mg dose of dalfampridine in an oral solution was 42.7ng/mL and occurred approximately 1.3 hours after dosing.

Dalfampridine is largely unbound to plasma proteins (97-99%). The apparent volume of distribution is 2.6L/kg. The elimination half-life of dalfampridine following administration of the extended release tablet formulation is 5.2-6.5 hours. CYP2E1 is the major enzyme responsible for the 3-hydroxylation of dalfampridine.

IV. Warnings/Precautions

- Ampyra is contraindicated in patients with a history of seizures.
- Ampyra is contraindicated in patients with moderate or severe renal impairment.

- Ampyra should not be taken with other forms of 4-aminopyridine (4-AP, fampridine) since the active ingredient is the same.
- Urinary tract infections were reported more frequently.

V. Drug Interactions

No clinically significant drug interaction was identified.

VI. Adverse Events ≥ 2% of Ampyra treated MS patients

Adverse Reaction	Placebo (n=238)	Ampyra 10mg twice daily (n=400)
Urinary tract infection	8%	12%
Insomnia	4%	9%
Dizziness	4%	7%
Headache	4%	7%
Nausea	3%	7%
Asthenia	4%	7%
Back pain	2%	5%
Balance disorder	1%	5%
Multiple sclerosis relapse	3%	4%
Paresthesia	3%	4%
Nasopharyngitis	2%	4%
Constipation	2%	3%
Dyspepsia	1%	2%
Pharyngolaryngeal pain	1%	2%

VII. Dosage and Administration

The maximum recommended dose of Ampyra is one 10mg tablet twice daily, taken with or without food, and should not be exceeded. Doses should be taken approximately 12 hours apart. Patients should not take double or extra doses if a dose is missed.

No additional benefit was demonstrated at doses greater than 10mg twice daily and adverse reactions and discontinuation because of adverse reactions were more frequent at higher doses. Tablets should only be taken whole; do not divide, crush, chew or dissolve.

VIII. Conclusion

Ampyra is the first therapy specifically approved to treat a symptom of MS. The active ingredient in Ampyra is the same as 4-aminopyridine (fampridine) which some pharmacies have been compounding for years. The estimated acquisition cost (EAC) for Ampyra is approximately $1,100 for a month's supply. With the modest efficacy data and uncertain safety profile, further study and clinical practice is needed to determine the place in MS therapy for dalfampridine.

References

1. Ampyra® Prescribing Information, January 2010, Acorda Therapeutics, Inc.
2. National Multiple Sclerosis Society. FAQs about MS. Accessed online at http://nationalmssociety.org.
3. Ampyra(dalfampridine). Pharmacist's Letter/Prescriber's Letter 2010;26(3):260323.

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 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			
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
DUR Board Meeting
Ribapak® Review
June 14, 2010

I. Overview

RibaPak in combination with peginterferon alfa-2a is indicated for the treatment of adults with chronic hepatitis C virus (HCV) infection who have compensated liver disease and have not been previously treated with interferon alpha.

II. Mechanism of Action

Ribavirin is a synthetic nucleoside analogue. The mechanism by which the combination of Ribavirin and an interferon product exerts its effects against the hepatitis C virus has not been fully established.

III. Pharmacokinetics

Following administration of 1200mg/day with food for 12 weeks:
$AUC_{0\text{-}12hr}$ 25,361±7110 ng.hr/mL
C_{max} 2748±818 ng/mL (average time to reach C_{max} was 2 hours

The terminal half-life of ribavirin following administration of a single oral dose is about 120 to 170 hours. The total apparent clearance following administration of a single oral dose is about 26 L/h. There is extensive accumulation of ribavirin after multiple dosing (twice daily) such that C_{max} at steady state was four-fold higher than that of a single dose.

Bioavailability of a single oral dose of ribavirin was increased by co-administration with a high-fat meal. The absorption was slowed (T_{max} was doubled) and the $AUC_{0\text{-}192h}$ and C_{max} increased by 42% and 66%, respectively, when ribavirin was taken with a high-fat meal compared with fasting conditions.

IV. Warnings/Precautions

- **Monotherapy -** ribavirin monotherapy is not effective for the treatment of chronic HCV infection; therefore ribavirin must not be used alone. The safety and efficacy of ribavirin tablets have only been established when used together with peginterferon alfa-2a.
- **Combination therapy -** there are significant adverse events caused by ribavirin/peginterferon alfa-2a therapy including severe depression and suicidal ideation, hemolytic anemia, suppression of bone marrow function, autoimmune and infectious disorders, pulmonary dysfunction, pancreatitis and diabetes. Review the ribavirin monograph and MEDICATION GUIDE for additional safety information prior to initiation of combination therapy.

- **Cardiovascular effects -** fatal and nonfatal MIs have been reported in patients with anemia caused by ribavirin. Assess patients for underlying cardiac disease before initiation of ribavirin therapy.
- **Hepatic decompensation -** ribavirin and peginterferon alfa-2a should be discontinued in patients who develop evidence of hepatic decompensation during treatment.
- **Pregnancy -** ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients.

Black Box Warning

Ribapak (ribavirin) monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication.

The primary clinical toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin.

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, and it may persist in non-plasma compartments for as long as 6 months. Ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of therapy in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month posttreatment follow-up period.

V. Drug Interactions

- **Nucleoside Analogues**-*in vitro* data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. Didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased when didanosine is co-administered with ribavirin, which could cause or worsen clinical toxicities.
- **Drugs Metabolized by Cytochrome P450-**there was no effect on pharmacokinetics of representative drugs metabolized by CYP2C9, CYP2C19, CYP2D6 or CYP3A4.
- **Warfarin-**the anticoagulant action of warfarin may be decreased. Monitor INR during the first 4 weeks of combination therapy and upon discontinuation.

VI. Adverse Reactions Occurring in ≥ 5% of Patients in Chronic Hepatitis C Clinical Trials (Study NV15801)

Body System	CHC Combination Therapy Study NV15801	
	Peginterferon alfa-2a 180mcg + 1000mg or 1200mg Ribavirin 48 week	Interferon alfa-2b + 1000mg or 1200mg Ribavirin 48 week
	%	%
Injection site reaction	23	16
Hypothyroidism	4	5
Fatigue/Asthenia	65	68
Pyrexia	41	55
Rigors	25	37
Pain	10	9
Nausea/vomiting	25	29
Diarrhea	11	10
Abdominal pain	8	9
Dry mouth	4	7
Dyspepsia	6	5
Lymphopenia	14	12
Anemia	11	11
Neutropenia	27	8
Thrombocytopenia	5	<1
Anorexia	24	26
Weight decrease	10	10
Myalgia	40	49
Arthralgia	22	23
Back pain	5	5
Headache	43	49
Dizziness (excluding vertigo)	14	14
Memory impairment	6	5
Irritability/Anxiety/Nervousness	33	38
Insomnia	30	37
Depression	20	28
Concentration impairment	10	13
Mood alteration	5	6
Dyspnea	13	14
Cough	10	7
Dyspnea exertional	4	7
Alopecia	28	33
Pruritus	19	18
Dermatitis	16	13
Dry skin	10	13
Rash	8	5
Sweating increased	6	5
Eczema	5	4
Vision blurred	5	2

VII. Dosage and Administration

The recommended daily dose of RibaPak is 800mg to 1200mg administered orally in two divided doses. The dose should be individualized to the patient depending on baseline disease characteristics (e.g., genotype), response to therapy, and tolerability of the regimen.

Genotype	Peginterferon alfa-2a Dose	RibaPak Dose	Duration
Genotypes 1, 4	180mcg	<75kg = 1000mg ≥75kg = 1200mg	48 weeks 48 weeks
Genotypes 2, 3	180mcg	800mg	24 weeks

VIII. Utilization

Ribavirin Utilization			
02/24/09 - 02/23/10			
Label Name	**Rx Num**	**Total Reimb Amt**	**Cost per Script**
RIBAPAK 600-600 MG DOSEPACK	2	$2,836.72	$1,418.36
RIBASPHERE 200 MG CAPSULE	7	$2,814.56	$402.08
RIBAVIRIN 200 MG CAPSULE	58	$17,138.48	$295.49
Totals	**67**	**$22,789.76**	**24 recipients**

IX. Conclusion

Oral ribavirin is approved for the treatment of chronic hepatitis C; however, monotherapy is not effective and it should not be used alone for this indication. Ribapak has an estimated acquisition cost (EAC) of $25.92 (1,200mg), $21.60 (1,000mg), $17.23 (800mg) and ribavirin has a MAC price of $7.20 (1,200mg), $6.00 (1,000mg), $4.80 (800mg). For patients with genotypes 1 and 4, treatment should be continued for 48 weeks. For patients with genotypes 2 and 3, treatment should be continued for 24 weeks.

References

1. RibaPak® Prescribing Information, August 2005, Par Pharmaceuticals, Inc.
2. Wolters Kluwer Health, Inc, ed. Drug Facts and Comparisons. St Louis, MO. 2009.

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	**(SAMHSA ID)**		
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

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EMLA 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 Emla must meet the following criteria:

- **Patient must be 12 years of age or 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			
Physician Signature		Date	

Part II: TO BE COMPLETED BY PHARMACY

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

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Denied: (Reasons)	

North Dakota Department of Human Services
DUR Board Meeting
Opiate Agonists Review
AHFS Class 280808
June 14, 2010

I. Overview

There are numerous pharmacologic agents available to help manage pain. Opioids, the most potent analgesics, are generally reserved for the treatment of chronic, moderate-to-severe pain that has not responded to non-opioid therapy. Pain management may incorporate both pharmacologic and nonpharmacologic treatments. Successful pain management requires frequent reassessment of patient's pain level and response to therapy.

Opioid receptors are found in inhibitory pain circuits that descend from the midbrain to the spinal cord dorsal horn and also exist in the peripheral nervous system. There are several opioid receptors including mu, delta, kappa, and sigma. Most opioid agonists, like morphine, are selective for the mu receptor. Binding and activation of the mu receptor causes analgesia, euphoria, nausea/vomiting, respiratory depression, sedation, constipation, and over time tolerance and dependence. Opiate agonists have no ceiling to their analgesic effect, but dosing is typically limited by drug-induced adverse effects.

Table 1 lists the agents included in this review.

Table 1. Opiate Agonists Included in this Review

Generic Name	Brand Name	Dosage Form
Alfentanil	Alfenta®	Injection
Codeine	N/A	Tablet, injection
Codeine/APAP	Capital w/Codeine®, Tylenol w/Codeine #3®, Tylenol w/Codeine #4®	Elixir, suspension, tablet
Codeine/ASA	N/A	Tablet
Codeine/APAP/butalbital/caffeine	Fioricet w/codeine®	Capsule
Codeine/ASA/butalbital/caffeine	Fiorinal w/codeine#3®	Capsule
Dihydrocodeine/APAP/caffeine	Panlor DC®, Panlor SS®	Capsule, tablet
Fentanyl	Duragesic®, Actiq®, Fentora®, Sublimaze®, Onsolis®	Buccal tablet, buccal soluble film, extended-release transdermal patch, transmucosal lozenge, injection
Hydrocodone/APAP	Lortab®, Hycet®, Maxidone®, Norco®, Vicodin®, Xodol®, Zamicet®, Zydone®	Capsule, tablet, solution
Hydrocodone/ibuprofen	Ibudone®, Reprexain®, Vicoprofen®	Tablet
Hydromorphone	Dilaudid®	Liquid, tablet, rectal suppository, injection
Levorphanol	Levo-Dromoran®	Tablet, injection

Generic Name	Brand Name	Dosage Form
Meperidine	Demerol®	Solution, tablet, injection
Methadone	Dolophine, Methadose	Oral concentrate, solution, tablet
Morphine	MS Contin®, Oramorph SR®, Avinza®, Kadian®, Roxanol®, Depodur®, Duramorph®, Astramorph®, Infumorph®	Injection, intravenous, epidural, tablet, solution, rectal suppository
Morphine sulfate/naltrexone	Embeda®	Capsule
Opium/belladonna	N/A	Rectal suppository
Oxycodone	Oxy IR®, Dazidox®, Roxicodone®, Oxycontin®	Capsule, oral concentrate, solution, tablet
Oxycodone/APAP	Percocet®, Magnacet®, Primalev®, Tylox®	Capsule, solution, tablet
Oxycodone/ASA	Percodan®	Tablet
Oxycodone/ibuprofen	Combunox®	Tablet
Oxymorphone	Opana®, Numorphan®	Tablet, injection
Propoxyphene HCL	Darvon®	Capsule
Propoxyphene HCL/APAP	N/A	Tablet
Propoxyphene napsylate	Darvon-N®	Tablet
Propoxyphene napsylate/APAP	Darvocet-N 50®, Darvocet-N 100®, Darvocet A500®	Tablet
Remifentanil	Ultiva®	Intravenous
Sufentanil	Sufenta®	Intravenous
Tapentadol	Nucynta®	Tablet
Tramadol	Ultram®, Ultram ER®, Ryzolt®	Tablets, sustained-release tablet
Tramadol/APAP	Ultracet®	Tablet

II. Current Treatment Guidelines

Table 2. Treatment Guidelines for the agents included in this review

Clinical Guideline	Recommendation(s)
Institute for Clinical Systems Improvement (ICSI): **Assessment and Management of Chronic Pain (2009)**	• A thorough medication history is critical to the development of an effective treatment plan. • Define the goals of therapy before prescribing, and tailor medications to meet the individual goals of each patient. • Identify and treat specific source(s) of pain, and base the initial choice of medication on the severity and type of pain. • Patients need to know that whether prescribed or non-prescribed, all drugs have risks and benefits. Watch for and manage side effects. • For opioid therapy: o Use caution before starting a patient on long-term opioid therapy. o Follow the 4 A's (Analgesia,

Clinical Guideline	Recommendation(s)
	Adverse drug reactions, Activity, Adherence) o Use a written opioid agreement for patients anticipated to be on long-term therapy. • Medications are not the sole focus of treatment in managing pain. They should be used when needed to meet overall goals of therapy in conjunction with other treatment modalities: psychosocial and spiritual management, rehab and functional management, non-pharmacologic and complementary medicine, and intervention management. • Use of medication should be directed not just toward pain relief, but for increasing function and restoring quality of life.
Annals of Oncology: **Management of Cancer Pain: ESMO Clinical Recommendations (2008)**	• Step-wise escalation of analgesic therapy should usually follow the 'pain ladder' as described by the WHO: o Step I, Mild Pain: non-opiate analgesics (e.g., APAP, NSAIDs) +/- adjuvant pain meds o Step II, Mild-Moderate Pain: mild opiate (e.g., codeine) +/- non-opiate analgesics +/- adjuvant pain meds o Step III, Moderate-Severe Pain: strong opiate (e.g., morphine) +/- non-opiate analgesics +/- adjuvant pain meds • Patients presenting with severe pain that needs urgent relief should be treated with parenteral opioids, usually administered by IV or SC • Opioid doses should be titrated to effect as rapidly as possible, with around-the-clock dosing and an as-needed 'breakthrough dose' (usually = 10% of total daily dose) to manage transient pain exacerbations. If more than 4 'breakthrough doses' per day are necessary, opioid treatment with a slow-release formulation should be initiated. • Reduction in opioid dose may be achieved

Clinical Guideline	Recommendation(s)
	by using a co-analgesic, such as an antidepressant, neuroleptic psychoactive drug or anticonvulsant. Such combinations may also alleviate refractory side effects such as constipation, nausea, vomiting, and central nervous system toxicity. Other strategies include the continued use of antiemetics, laxatives, major tranquilizers, and psychostimulants; also, switching to another opioid agonist and/or another route may allow titration to adequate analgesia without the same disabling effects. • Neuropathic pain may not be adequately controlled by opioids alone; combination with co-analgesics may improve pain control. Steroids should be considered in case of nerve compression.
American Society of Interventional Pain Physicians: **Opioids in the Management of Chronic Non-Cancer Pain: An Update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines (2008)**	• Comprehensive initial evaluation • Establish diagnosis • Establish medical necessity • Assess risk-benefit ratio • Establish treatment goals • Obtain informed consent and agreement • Initial dose adjustment phase (up to 8-12 weeks)-start low dose and utilize opioids, nonsteroidal anti-inflammatory drugs (NSAIDs) and adjuvants • Stable phase (stable-moderate doses)-assess for four As • Adherence monitoring through random drug screens or pill counts.
Veterans Health Administration, Department of Defense: **VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain (2003)**	• The use of opioid therapy is indicated for moderate to severe pain that has failed to adequately respond to other non-opioid therapeutic interventions. • The ethical imperative to relieve pain should be considered when evaluating therapeutic options.

Clinical Guideline	Recommendation(s)
WHO Three-Step Analgesic Ladder for Cancer Pain Management (1990)	• Mild Pain-prompt oral administration of nonopioid analgesics (e.g. acetaminophen, NSAIDs) +/- adjuvant pain medications • Mild-Moderate Pain-Mild opiate (e.g. codeine) +/- non-opiate analgesic +/- adjuvant pain medications • Moderate-Severe Pain-Strong opiate (e.g. morphine) +/- non-opiate analgesic- (e.g. acetaminophen, NSAIDS) +/- adjuvant pain medications

III. Indications

Table 3. FDA-Approved Indications for the Opiate Agonists

Generic Name	Analgesia	Anesthesia	Cough	Detoxification	Headache
Alfentanil	√	√			
Codeine	√		√[a]		
Codeine/APAP	√				
Codeine/ASA	√				
Codeine/APAP/butalbital/ caffeine					√
Codeine/ASA/butalbital/ caffeine					√
Dihydrocodeine/APAP/ caffeine	√				
Fentanyl injection	√	√			
Fentanyl transdermal/ transmucosal	√				
Hydrocodone			√[a]		
Hydrocodone/APAP	√				
Hydrocodone/ibuprofen	√				
Hydromorphone	√				
Levorphanol	√				
Meperidine	√	√			
Methadone	√			√	
Morphine sulfate	√	√			
Morphine sulfate/naltrexone	√				
Oxycodone	√				
Oxycodone/APAP	√				
Oxycodone/ASA	√				
Oxycodone/ibuprofen	√				
Oxymorphone	√	√			
Propoxyphene HCL	√				
Propoxyphene HCL/APAP	√				
Propoxyphene napsylate	√				
Propoxyphene napsylate/	√				

Generic Name	Analgesia	Anesthesia	Cough	Detoxification	Headache
APAP					
Remifentanil	√	√			
Sufentanil	√	√			
Tapentadol	√				
Tramadol	√				
Tramadol ER	√				
Tramadol/APAP	√				

[a]Currently only available for this indication when part of a multi-ingredient product.

IV. Pharmacokinetics

Table 4. Pharmacokinetic Parameters of the Long-Acting Oral Opiates Included in this Review

Generic Name	Onset	Peak	$t_{1/2}$ (hours)	Metabolism
Alfentanil	Immediate	1.5-2 min	1.5-1.85 hours	Hepatic
Codeine	Oral: 10-30 min Parenteral: 15 min	0.5-1 hour	2.5-3.0	Hepatic CYP2D6 CYP3A4
Dihydrocodeine/APAP/ caffeine		1.6-1.8 hours	3.3-4.5 hours	
Fentanyl	Parenteral: IV-immediate IM-7-8 min Transdermal: 12-24 hours Buccal: 5-15 min	Transdermal: 24-72 hours Buccal: 20-40 min	Parenteral: 3.65 hours Transdermal: 17 hours Buccal: 7 hours	Hepatic CYP3A4
Hydrocodone	1 hour	1.3 hour	3.8-4.5 hours	Hepatic CYP2D6
Hydromorphone	Oral: 30 min Parenteral: 15 min	48-60 min	IR: 2.3 hours ER: 18.6 hours IM/Subcutaneous: 2.6 hours	Hepatic Glucuronidation
Levorphanol	Parenteral: 15-30 min Oral: 10-60 min	Parenteral: 20-90 min Oral: 60 min	11-16 hours	Hepatic
Meperidine	Parenteral: 5-30 min	IM: 25 min	3-6 hours	Hepatic
Methadone	Oral: 30-60 min	2-4 hours	8-59 hours	Hepatic CYP3A4 CYP2D6

Generic Name	Onset	Peak	$t_{1/2}$ (hours)	Metabolism
	Parenteral: 10-20 min			
Morphine	Parenteral: 10-30 min Rectal: 20-60 min	Epidural: 10-15 min Oral: 1 hour Oral: 60 min	1.5-2 hours	Hepatic Glucuronidation
Oxycodone	Oral: 1 hour	1.6 hours	IR: 3.2 hours CR: 4.5 hours	Hepatic CYP2D6
Oxymorphone	Oral: 1 hour Parenteral: 5-10 min	Oral: 1-2 hours	Oral: 7-9 hours Parenteral: 1.3 hours	Hepatic Glucuronic acid conjugation
Propoxyphene	0.25-1 hour	2-2.5 hours	6-12 hours(parent), 30-36 hours (norpropoxyphene)	Hepatic, 25% conversion to norpropoxyphene
Remifentanil	Rapid	3-10 min	10-20 min	Hydrolysis by esterases
Sufentanil	IV: immediate Epidural: 10 min	20 min	2.7 hours	Hepatic + small intestines
Tapentadol		1.25 hours		Conjugation with glucoronic acid: CYP2C9 CYP3A4
Tramadol	IR: 30-60 min	IR: 30-60 min ER: 12 hours	IR: 6.3 hours ER: 7.9 hours	Hepatic CYP2D6 CYP3A4

V. Drug Interactions

Table 5. Significant Drug Interactions with the Opiate Agonists

Opiate Agonists			
Precipitant drug	**Object drug**		**Description**
Acyclovir	Opioid analgesics	↑	Plasma concentrations of meperidine and normeperidine may be increased; use with caution
Amiodarone	Opioid analgesics	↑	Profound bradycardia, sinus arrest, and hypotension have occurred with concomitant administration. Monitor hemodynamic function and administer inotropic, chronotropic, and pressor support as necessary. The bradycardia is usually unresponsive to atropine; large doses of vasopressors have been used.

Opiate Agonists			
Precipitant drug	**Object drug**		**Description**
Anticholinergics	Methadone	↑	Coadministration may result in increased risk of urinary retention and/or severe constipation which may lead to paralytic ileus.
Azole antifungals	Opioid analgesics	↑	Coadministration may lead to increased pharmacological and adverse effects of the narcotic. Use with caution, and monitor for prolonged or recurrent respiratory depression. A lower dose of the narcotic may be necessary.
Barbiturate anesthetics	Opioid analgesics	↑	Barbiturate anesthetics may increase the respiratory and CNS-depressant effects of the narcotics because of additive pharmacologic activity.
Barbiturates	Methadone	↓	Coadministration may reduce methadone actions. Patients receiving chronic methadone treatment may experience withdrawal symptoms. A higher dose of methadone may be required during coadministration of barbiturates.
Benzodiazepines	Opioid analgesics Sufentanil	↑	Coadministration may result in decreased mean arterial pressure and systemic vascular resistance (also see CNS depressant interaction)
Benzodiazepines Diazepam	Opioid analgesics Alfentanil Fentanyl	↑	Diazepam may produce cardiovascular depression when given with high doses of fentanyl and alfentanil. Administration prior to or following high doses of alfentanil decreases blood pressure secondary to vasodilation; recovery may be prolonged.
Beta-blockers Calcium channel blockers	Opioid analgesics Sufentanil	↑	Increased incidence and degree of bradycardia and hypotension during induction of sufentanil in patients on long-term calcium channel or beta-blocker therapy.
Carbamazepine	Opioid analgesics Tramadol	↓	Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, coadministration is not recommended.
Cigarette smoking	Opioid analgesics Propoxyphene	↓	Cigarette smoking may induce liver enzymes responsible for the metabolism of propoxyphene; efficacy is reportedly decreased in smokers. Patients may increase the dosage to obtain adequate pain relief.
Cimetidine	Opioid analgesics	↑	The actions of opioid analgesics may be enhanced, resulting in toxicity. Alfentanil clearance may be reduced; therefore, smaller alfentanil doses may be needed.
CNS depressants (e.g. barbiturates, tranquilizers, inhalation anesthetics, ethanol)	Opioid analgesics	↑	Both the magnitude and duration of CNS and cardiovascular effects may be enhanced. Reduce the dose of one or both agents during concomitant use.
CYP2D6 inhibitors (e.g. fluoxetine, paroxetine, quinidine, amitriptyline)	Opioid analgesics Oxycodone Tramadol	↑	Inhibition of the metabolism of tramadol or oxycodone may occur.
CYP3A4 inducers (e.g., phenytoin, rifampin)	Opioid analgesics Fentanyl Tramadol	↓	May produce increased clearance of fentanyl and tramadol; use with caution.
CYP3A4 inhibitors (e.g., certain protease	Opioid analgesics Fentanyl Tramadol	↑	Coadministration may produce increased fentanyl and tramadol concentrations. Carefully monitor patients receiving fentanyl and potent CYP3A4 inhibitors (e.g., clarithromycin,

Opiate Agonists			
Precipitant drug	**Object drug**		**Description**
inhibitors, erythromycin, ketoconazole)			ketoconazole, ritonavir) for an extended period of time and adjust the dosage as needed.
Droperidol	Opioid analgesics Fentanyl	↑	Pulmonary arterial pressure may be depressed and hypotension may occur.
Erythromycin	Opioid analgesics Alfentanil Fentanyl Methadone	↑	Erythromycin may inhibit the metabolism of the narcotic. Coadministration may result in increased pharmacologic effects of the narcotic. Monitor for prolonged or recurrent respiratory depression and sedation. Consider a lower dose of the narcotic or an alternate narcotic.
Ethanol	Opioid analgesics Alfentanil	↓	Chronic ethanol consumption may produce a pharmacodynamic tolerance to alfentanil. Chronic ethanol consumers may need higher doses of alfentanil.
Hydantoins (e.g. phenytoin)	Opioid analgesics Meperidine Methadone	↓	Hydantoins may decrease the pharmacologic effects of meperidine and methadone, possibly because of increased hepatic metabolism of the narcotic.
Lidocaine	Opioid analgesics Morphine	↑	Respiratory depression and loss of consciousness may occur.
MAOIs	Opioid analgesics	↑	Severe and unpredictable potentiation by MAOIs has been reported with certain opioid analgesics. Opioids are not recommended for use in patients who have received MAOIs within 14 days.
Neostigmine	Opioid analgesics Morphine	↑	Increases the intensity and duration of the analgesic action.
Nitrous oxide	Opioid analgesics Fentanyl Sufentanil	↑	Nitrous oxide may cause cardiovascular depression with high-dose sufentanil and fentanyl.
Nonnucleoside reverse transcriptase inhibitors (NNRTIs) (e.g. nevirapine, efavirenz)	Opioid analgesics Methadone	↓	Concomitant administration may result in reduced methadone action and opiate withdrawal symptoms. Anticipate an increase in the methadone dose when starting an NNRTI and monitor for withdrawal symptoms. Monitor for methadone overdose signs when an NNRTI is discontinued and adjust the methadone dose accordingly.
Nucleoside reverse transcriptase inhibitors (Abacavir, Didanosine, Stavudine, Zidovudine)	Opioid analgesics Methadone	↓	When coadministered with abacavir, methadone clearance increased by 22%. Methadone dose adjustment may be needed in a small number of patients. Coadministration may decrease AUC and C_{max} of didanosine and stavudine; however, coadministration may increase zidovudine concentration. Monitor zidovudine effects closely; a lower dose may be needed
Opioid agonist/antagonist analgesics, opioid partial agonist analgesics	Opioid analgesics	↓	Do not administer opioid agonist/antagonist analgesics (e.g. pentazocine, nalbuphine, butorphanol) or partial agonists (e.g. buprenorphine) to a patient who has received or is receiving a course of therapy with a pure agonist opioid analgesic. In opioid-dependent patients, mixed agonist/antagonist analgesics and partial agonists may precipitate withdrawal symptoms.
Phenothiazines	Opioid analgesics	↑	Although the analgesic effect of narcotics may be potentiated, a higher incidence of toxic effects may occur.
Propofol	Opiate analgesics Oxycodone	↑	Increased risk of bradycardia with concomitant use.
Protease inhibitors	Opioid analgesics	↓↑	Plasma concentrations of propoxyphene and fentanyl may be

Opiate Agonists			
Precipitant drug	**Object drug**		**Description**
(e.g. ritonavir, saquinavir, nelfinavir)	Fentanyl Meperidine Methadone Propoxyphene		increased, possible causing toxicity. The pharmacologic effects of methadone may be decreased. Meperidine levels may decrease and normeperidine levels may increase, possible decreasing efficacy but increasing neurologic toxicity. Concurrent use of propoxyphene or meperidine with a protease inhibitor is contraindicated.
Quinidine	Opioid analgesics Codeine	↓	The analgesic effects of codeine may be decreased. It may be necessary to use an alternative analgesic.
Reserpine	Opioid analgesics Morphine	↓	Inhibits analgesic action.
Rifamycins (e.g. rifampin)	Opioid analgesics Methadone Morphine	↓	Rifampin appears to stimulate methadone metabolism. Coadministration may result in reduced methadone action and opiate withdrawal symptoms. A higher dose of methadone may be required during coadministration of rifampin. The analgesic effects of morphine may be decreased with concurrent administration. May be necessary to administer an alternative analgesic.
Sibutramine	Opioid analgesics Meperidine	↑	Serotonergic effects of these agents may be additive, resulting in serotonin syndrome. Coadministration is not recommended.
SSRIs Nefazodone Venlafaxine	Opioid analgesics Methadone Tapentadol Tramadol	↑	Fluvoxamine may inhibit methadone metabolism and therefore increase toxicity. Use with caution. The serotonergic effects of tapentadol and tramadol, and serotonin reuptake effects of tapentadol, tramadol and serotonin reuptake inhibitors may be additive, increasing the risk for adverse effects (e.g., seizures, serotonin syndrome)
Tricyclic antidepressants Amitriptyline Clomipramine Nortriptyline	Opioid analgesics Morphine Tapentadol	↑	Monitor for increased CNS and respiratory depression when administered with morphine. A serotonin syndrome may occur when tricyclic antidepressants are used with tapentadol.
Urinary acidifiers	Opioid analgesics Methadone	↓	Urinary acidifiers increase the renal clearance of methadone.
Opioid analgesics Propoxyphene	Carbamazepine	↑	Propoxyphene may inhibit the metabolism of carbamazepine, thereby increasing the carbamazepine serum concentrations and toxicity.
Opioid analgesics Methadone	Desipramine	↑	Desipramine blood levels have increased with concurrent methadone therapy.
Opioid analgesics Tramadol	Digoxin	↑	Rare reports of digoxin toxicity have been reported in postmarketing surveillance.
Opioid analgesics Morphine	Diuretics	↓	Reduces efficacy by inducing the release of antidiuretic hormone.
Opioid analgesics Remifentanil	Opioid analgesics Morphine	↓	The analgesic effect of morphine may be decreased with coadministration. It may be necessary to titrate morphine to higher levels than expected.
Opioid analgesics Morphine Propoxyphene Tramadol	Warfarin	↑	The oral anticoagulant effect of warfarin may be increased. Monitor coagulation tests and adjust dose as needed.
Opioid analgesics	Skeletal muscle relaxants	↑	Coadministration may enhance the neuromuscular blocking action and produce an increased degree of respiratory depression.

VI. Adverse Drug Events of the Opiate Agonists

Adverse Event(s)	Alfentanil	Codeine	Fentanyl	Hydromorphone	Levorphanol	Meperidine	Methadone	Morphine	Oxycodone	Oxymorphone	Propoxyphene	Remifentanil	Sufentanil	Tapentadol	Tramadol
Cardiovascular															
Abnormal ECG	-	-	-	-	-	-	√	-	-	-	-	-	-	-	PM
Arrhythmia	14	-	-	-	√	-	√	-	-	-	-	-	0.3-1	-	-
Atrial fibrillation	-	-	-	-	-	-	-	√	-	-	-	<1	-	-	-
Bradycardia	14	√	√	√	√	√	√	√	-	√	-	1-7	3-9	≤1	-
Cardiac arrest	-	√	√	√	√	√	√	√	√	-	-	-	-	-	PM
Chest pain	-	-	<1	-	-	-	-	√	-	-	-	<1	-	-	-
CHF/heart failure	-	-	-	√	-	-	-	-	-	-	-	-	-	-	-
Circulatory depression/ collapse	-	√	√	√	-	√	√	√	√	-	-	-	-	-	-
Deep thrombophlebitis	-	-	√	√	-	-	-	-	√	-	-	-	-	-	-
Extrasystoles	-	-	-	-	√	-	-	-	-	-	-	-	-	-	-
Faintness	-	√	-	√	-	-	√	√	-	-	-	-	-	-	-
Flushing	-	√	√	√	√	√	√	√	-	√	-	1	-	-	-
Hypertension	18	-	√	√	-	-	√	√	-	-	-	1-2	3-9	-	PM
Hypotension	10	√ (ortho static)	√	√	√	√	√	√	√	√	-	4-19	3-9	≤1	<1

Adverse Event(s)	Alfentanil	Codeine	Fentanyl	Hydromorphone	Levorphanol	Meperidine	Methadone	Morphine	Oxycodone	Oxymorphone	Propoxyphene	Remifentanil	Sufentanil	Tapentadol	Tramadol
Palpitation	-	√	√	√	√	√	-	√	√	√	-	-	-	-	PM
Pallor	-	-	-	≥ 1 (ER)	√	-	-	√	-	-	-	-	-	-	-
Phlebitis	-	-	-	-	-	√	√	√ (IV)	-	-	-	-	-	-	-
Syncope	-	√	√	√	√	√	√	√	√	-	-	<1	-	≤1	<1
Tachycardia	12	√	√	√	√	√	√	√	√	√	-	<1	0.3-1	≤1	<1
Vasodilation	-	-	≤4	-	-	-	-	√	√	-	-	-	-	-	1-5
CNS															
Abnormal gait	-	-	1-5	-	-	-	-	√	<1	-	-	-	-	-	<1
Abnormal thinking	-	-	0-2 (trans-mucosal)	-	-	-	-	√	1-5	-	-	-	-	≤1	<1
Agitation	-	√	√	-	-	√	√	√	√	-	-	<1	-	≤1	-
Anxiety	-	-	3-15	√	-	-	-	√	√	-	-	<1	-	1	1-5
Asthenia	-	-	0-38	-	-	-	-	-	6	-	-	-	-	-	6-12
Coma	-	-	-	-	√	-	-	√	<3	-	-	<1	-	-	-
Confusion	-	-	10-13	-	√	-	√	√	<1	√	-	<1	-	1	1-5
Convulsion/ Seizure	-	√	0-2	-	√	√	√	√	-	-	-	-	-	-	<1

Adverse Event(s)	Alfentanil	Codeine	Fentanyl	Hydromorphone	Levorphanol	Meperidine	Methadone	Morphine	Oxycodone	Oxymorphone	Propoxyphene	Remifentanil	Sufentanil	Tapentadol	Tramadol
Depression	-	-	2-10	-	√	-	-	√	<1	√	-	-	-	-	<1
Disorientation	-	√	-	√	√	√	√	√	13	-	-	<1	-	≤1	-
Dizziness	3-9	√	3-17	√	-	-	√	√	-	-	<1	<5	-	24	26-33
Drowsiness	-	-	-	-	√	-	-	√	-	√	-	-	-	-	-
Dysphoria	-	√	-	√	-	√	√	-	-	√	<1	<1	-	-	-
Euphoria	0.3-1	√	3-10	√	-	√	√	√	1-5	√	<1	-	-	≤1	1-5
Fear	-	√	-	√	-	-	-	-	-	-	-	-	-	-	-
Hallucinations	-	-	3-10	√	-	√	-	√	<1	√	<1	<1	-	-	<1
Headache	0.3-1	√	3-20	√	-	√	√	√	7	√	<1	≤18	-	-	18-32
Insomnia	-	√	1-10	√	√	-	√	√	1-5	√	-	-	-	2	-
Lethargy	-	√	-	√	√	√	-	√	-	-	-	-	-	≤1	-
Light-headedness	-	√	-	√	-	-	√	√	-	√	<1	-	-	-	-
Mental clouding	-	√	-	√	-	-	-	√	-	√	-	-	-	-	-
Mood changes	-	√	-	√	-	-	-	√	-	-	-	-	-	-	-
Myoclonic movement	PM	-	1-4	-	-	√	-	-	-	-	-	-	-	-	-

Adverse Event(s)	Alfentanil	Codeine	Fentanyl	Hydromorphone	Levorphanol	Meperidine	Methadone	Morphine	Oxycodone	Oxymorphone	Propoxyphene	Remifentanil	Sufentanil	Tapentadol	Tramadol
Nervousness	-	-	1-10	-	√	-	-	√	1-5	√	-	-	-	≤1	1-5
Postoperative confusion	0.3-1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Shivering	0.3-1	-	√	-	-	-	-	-	-	-	-	1-5	-	-	-
Sleepiness/sedation	1-3	√	3-20	√	-	√	√	√	23	√	<1	-	3-9	≤1	16-25
Somnolence	-	-	-	-	-	-	-	-	-	-	-	-	-	15	-
Stupor	-	-	1-4	-	-	-	-	-	√	-	-	-	-	-	-
Tremor	-	-	1-2	√	-	√	-	√	√	-	-	<1	-	1	<1
Weakness	-	√	-	√	-	√	√	√	-	√	<1	-	-	-	-
Vertigo	-	-	0-4 (trans-mucosal)	-	-	-	-	√	<1	-	-	-	-	-	26-33
GI															
Abdominal pain	-	-	1-10	-	√	-	√	-	1-5	√	<1	-	-	-	-
Anorexia	-	√	-	-	-	-	√	√	1-5	√	-	-	-	-	1-5
Biliary tract spasm	-	√	-	-	√	√	√	√	-	√	-	-	-	-	-
Constipation	-	√	3-20	√	-	√	√	√	23	√	<1	<1	-	8	24-36
Diarrhea	-	-	3-10	√	-	-	-	√	1-5	-	-	<1	-	-	5-10

Adverse Event(s)	Alfentanil	Codeine	Fentanyl	Hydromorphone	Levorphanol	Meperidine	Methadone	Morphine	Oxycodone	Oxymorphone	Propoxyphene	Remifentanil	Sufentanil	Tapentadol	Tramadol
Dry mouth	-	√	1-10	√	√	√	√	√	6	√	-	-	-	4	5-10
Dyspepsia	-	-	3-10	-	√	-	-	√	1-5	√	-	-	-	2	5-13
Nausea	28	√	10-45	√	√	√	√	√	23	-	<1	1.4-4	3-9	30	24-40
Vomiting	18	√	6-31	-	√	√	√	√	12	√	<1	≤22	3-9	18	9-17
GU															
Antidiuretic effect	-	√	-	√	-	√	√	√	<1	√	-	-	-	-	-
Decreased libido/potency	-	√	√	-	-	-	√	√	<1	-	-	-	-	-	-
Spasm of vesical sphincters	-	√	-	-	-	-	-	√	-	-	-	-	-	-	-
Ureteral spasm	-	√	-	-	-	-	-	√	-	√	-	-	-	-	-
Urinary hesitancy	-	√	-	√	-	-	√	√	-	√	-	-	-	≤1	-
Urinary retention	-	√	1-10	√	-	√	√	√	<1	√	-	<1	√	-	1-5
Miscellaneous															
Accidental injury	-	-	0-9	-	-	-	-	√	√	-	-	-	-	-	<1
Anaphylaxis/ anaphylactoid	PM	-	-	-	-	-	√	√	√	-	-	-	PM	-	<1
Application site reactions	-	-	1-10	-	-	-	-	-	-	-	-	1	-	-	-

Adverse Event(s)	Alfentanil	Codeine	Fentanyl	Hydromorphone	Levorphanol	Meperidine	Methadone	Morphine	Oxycodone	Oxymorphone	Propoxyphene	Remifentanil	Sufentanil	Tapentadol	Tramadol
Blurred vision	1-3	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Chest wall rigidity	17	-	√	-	-	-	-	-	-	-	-	-	3-9	-	-
Edema	-	-	√	-	-	-	√	√	√	-	-	-	-	≤1	-
Itching/pruritus	<1	-	1-10	√	√	-	√	√	13	√	-	≤18	25	5	8-11
Injection site pain/reaction	0.3-1	-	-	√	-	√	-	-	-	-	-	<1	√	-	-
Muscle rigidity	-	-	√	√	-	-	-	√	-	-	-	2-11	-	-	-
Rash	-	-	1-8	√	√	-	-	√	1-5	-	-	<1	-	1	1-5
Shock	-	√	-	-	-	√	√	-	√	-	-	-	-	-	-
Skeletal muscle movement	3-9	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sweating	-	-	-	√	√	√	√	√	5	√	-	6	-	-	-
Visual disturbances	-	√	-	√	-	√	-	-	-	-	-	-	-	-	-
Respiratory															
Apnea	1-3	-	3-10	√	√	-	-	√	-	-	-	≤30	0.3-1	-	-

Adverse Event(s)	Alfentanil	Codeine	Fentanyl	Hydromorphone	Levorphanol	Meperidine	Methadone	Morphine	Oxycodone	Oxymorphone	Propoxyphene	Remifentanil	Sufentanil	Tapentadol	Tramadol
Bronchospasm	<1	-	-	-	-	-	-	-	-	-	-	<1	0.3-1	-	-
Dyspnea	-	-	2-22	-	-	-	-	√	-	1-5	-	-	-	≤1	≤1
Hypercarbia	0.3-1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Laryngospasm	0.3-1	-	-	√	-	-	√	√	-	-	-	<1	-	-	-
Pharyngitis	-	-	3-10	-	-	-	-	-	-	√	-	<1	-	-	-
Respiratory arrest	-	√	-	√	-	√	√	√	-	√	-	-	-	-	-
Respiratory depression	3-9 (post op)	√	-	√	-	√	√	√	-	√	-	<1	0.3-1	≤1	-

PM=Postmarketing

VII. Dosing, Administration and Warnings

The FDA-approved dosing guidelines for the Opiate Agonists are summarized in Table 7.

Table 7. Dosage Guidelines for the Opiate Agonists Included in this Review

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Alfentanil	Individualized dosing based on body weight, physical status, underlying pathological conditions, use of other drugs, and type and duration of surgical procedure and anesthesia.	≥ 12 years: Individualized dosing based on body weight, physical status, underlying pathological conditions, use of other drugs, and type and duration of surgical procedure and anesthesia	Injection: 500mcg/ml
Belladonna/Opium	1 or 2 suppositories/day	Safety and efficacy in children have not been established.	Rectal suppositories: 30/16.2mg, 60/16.2mg
Codeine	Oral: 15 to 60mg every 4-6 hours 30mg SC or IM every 4 hours as needed	Oral: 0.5 to 1mg/kg every 4-6 hours ≥3 years: 500mcg/kg or 15mg/m^2 SC or IM every 4 hours as necessary	Tablet: 15mg, 30mg, 60mg Solution, oral: 15mg/5ml Injection: 15mg/ml, 30mg/ml
Codeine/APAP	½ -2 tablets every 4 hours	½-1 mg codeine/kg/dose every 4-6 hours (10-15mg APAP/kg/dose every 4 hours) Liquid: >12 years: 15ml every 4 hours as needed 7-12 years: 10ml 3-4 times daily as needed 3-6 years: 5ml 3-4 times daily as needed	Tablet: 15/300mg, 30/300mg, 30/650mg, 60/300mg Elixir and Suspension: 12/120mg per 5ml
Codeine/ASA	30mg tablets: 1-2 tablets every 4 hours as needed. 60mg tablets: 1 tablet every 4 hours as needed.	Safety and efficacy in children have not been established	Tablet: 30/325mg, 50/325mg
Codeine/butalbital/ APAP/caffeine	1 or 2 capsules every 4 hours	≥12 years: 1 or 2 every 4 hours < 12 yrs: Safety and efficacy in children have not been established	Capsules: 30/50/325/40mg
Dihydrocodeine/ APAP/caffeine	2 every 4 hours	Safety and efficacy in children have not been established	Capsule: 16/356/30mg Tablet: 32/713/60mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Fentanyl	Buccal tablet: Initial dose is 100mcg. Take one additional dose using the same strength for that episode. Patients should take a maximum of two doses for any episode of breakthrough pain. Patients must wait at least 4 hours before treating another episode of breakthrough pain. Lozenge: Initial dose is 200mcg. Titrate as necessary to provide adequate analgesia and minimize adverse reactions. Maximum of 4 units/day. Buccal film: Only prescribers enrolled in the FOCUS program may prescribe fentanyl buccal soluble film. Injection: 50-100mcg IM or slow IV Transdermal: Dose based on previous opioid, potency estimates, opioid tolerance and general condition of the patient. The majority of patients are adequately maintained with fentanyl administered every 72 hours, however, some may require application every 48 hours.	Buccal tablet: The safety and efficacy in pediatric patients below the age of 16 years have not been established. Lozenge: Safety and efficacy in children have not been established. Buccal film: The appropriate dosing and safety of fentanyl in opioid-tolerant children with breakthrough cancer pain have not been established in children younger than 18 years of age. Injection: 2-12 years of age a dose as low as 2-3mcg/kg is recommended. Transdermal: Administer to children only if they are opioid tolerant receiving at least oral morphine 60mg/day and 2 years of age and older with chronic pain.	Buccal tablet: 100mcg, 200mcg, 300mcg 400mcg, 600mcg, 800mcg Lozenge on stick: 200mcg, 400mcg, 600mcg, 800mcg, 1200mcg, 1600mcg Film, buccal: 200mcg per film, 400mcg per film, 800mcg per film, 1200mcg per film Injection: 50mcg/ml Transdermal: 12.5mcg/h, 25mcg/h, 50mcg/h, 75mcg/h, 100mcg/h
Hydrocodone	1-2 tablets/capsules or 15ml every 4-6 hours as needed	≥15 years: 1-2 tablets/capsules or 15ml every 4-6 hours as needed. 2-14 years: 0.27ml/kg every 4-6 hours as needed.	Tablet: 2.5/500mg, 5/300mg, 5/325mg, 5/400mg, 5/500mg, 7.5/300mg, 7.5/325mg, 7.5/400mg, 7.5/500mg, 7.5/650mg, 7.5/750mg, 10/300mg, 10/325mg, 10/400mg, 10/500mg, 10/650mg, 10/660mg Solution: 2.5/167mg/5ml, 3.33/167mg/5ml, 5/333mg/10ml, 7.5/325mg/15ml, 10/325mg/15ml

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Hydrocodone/ ibuprofen	1 tablet every 4-6 hours	≥16 years: 1 tablet every 4-6 hours <16 years: Safety and efficacy in children have not been established.	Tablet: 10/200mg, 5/200mg, 7.5/200mg
Hydromorphone	Tablets: 2-4mg every 4-6 hours as necessary Oral solution: 2.5-10mg (2.5 to 10mL) every 3-6 hours as directed. Injection: 1-2mg SC or IM every 4-6 hours as needed. If given IV, inject slowly over at least 2-3 minutes Rectal: 1 suppository inserted rectally every 6-8 hours or as directed by health care provider	Safety and efficacy in children have not been established.	Tablets: 2mg, 4mg, 8mg Injection: 1mg/ml, 2mg/ml, 4mg/ml Injection, concentrate: 10mg/ml, 250mg (10mg/ml after reconstitution) Oral solution: 1mg/ml Rectal suppository: 3mg
Levorphanol	1 tablet every 6-8 hours (Levo-Dromoran) or 3-6 hours (levorphanol) as needed.	Safety and efficacy in children have not been established.	Tablets: 2mg Injection: 2mg/mL
Meperidine	Oral: 50-150mg every 3-4 hours as necessary Injection: 50-150mg IM or SC every 3-4 hours as necessary Preoperative: 50-100mg IM or SC 30-90 minutes before beginning anesthesia.	Oral: 1.1-75mg/kg (0.5-0.8mg/lb) up to the adult dose, every 3-4 hours as necessary Injection: 1.1 to 1.75mg/kg (0.5 to 0.8mg/lb) IM or SC up to the adult dose every 3-4 hours as necessary. Preoperative: 1.1-2.2mg/kg (0.5 to 1mg/lb) IM or SC up to the adult dose to 90 minutes before beginning anesthesia.	Tablet: 50mg, 100mg Oral liquid: 50mg/5ml Injection (vial, cartridge, ampule, syringe): 10mg/ml, 25mg/ml, 50mg/ml, 75mg/ml, 100mg/ml
Meperidine	Oral: 50-150mg every 3-4 hours as necessary Injection: 50-150mg IM or SC every 3-4 hours as necessary Preoperative: 50-100mg IM or SC 30-90 minutes before beginning anesthesia	Oral: 1.1 -1.75mg/kg (0.5 to 0.8mg/lb) up to the adult dose, every 3-4 hours as necessary Injection: 1.1-1.75mg/kg (0.5 to 0.8mg/lb) IM or SC up to the adult dose every 3-4 hours as necessary Preoperative: 1.1- 2.2mg/kg (0.5 to 1mg/lb) IM or SC up to the adult dose 30 to 90 minutes before beginning anesthesia.	Tablets: 50mg, 100mg Syrup: 50mg/5ml Injection: 10mg/ml, 25mg/ml, 50mg/ml, 75mg/ml, 100mg/ml

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Methadone	Pain: 2.5-10mg every 8-12 hours Detoxification: A single dose of 20-30mg will often be sufficient to suppress withdrawal	Off-label dosing for children: Opiate withdrawal: 0.05-0.2mg/kg every 12-24 hours Pain: 0.7mg/kg day in divided doses every 4-6 hours as needed	Tablets: 5mg, 10mg, 40mg Solution: 5mg/5ml Liquid concentrate 10mg/ml Injection: 10mg/ml
Morphine	IR: 5-30mg every 4 hours as directed. CR/ER: Begin treatment using an IR morphine formulation. CR/ER conversion-administer ½ of the patient's 24-hour requirement as ER morphine on an every 12 hour schedule or administer 1/3 of the patient's daily requirement on an every 8 hour schedule. Injection: 5-20mg SC or IM every 4 hours as needed IV injection: 2-10mg per 70kg of body weight given over 4-5 minutes. Can be given every 4 hours Rectal suppository: 10-20mg every 4 hours	Oral: Safety and efficacy in children have not been established. IM or SC injection: 0.1-0.2mg/kg every 4 hours as needed IV injection: 50-100mcg IV per kg of body weight, not to exceed 10mg/dose Rectal suppository: Safety and efficacy in children have not been established.	IR Tablets: 15mg, 30mg SR Tablets: 15mg, 30mg, 60mg, 100mg, 200mg, Tablets for solution: 10mg, 15mg, 30mg Capsules, extended-release pellets: 10mg, 20mg, 30mg, 45mg, 50mg, 60mg, 75mg, 80mg, 90mg, 100mg, 120mg, 200mg Solution, oral: 10mg/5ml, 20mg/5ml Solution, concentrate: 20mg/ml, 100mg/5ml Injection: 0.5mg/ml, 1mg/ml, 2mg/ml, 4mg/ml, 5mg/ml, 8mg/ml, 10mg/ml, 15mg/ml Injection, extended-release liposomal: 10mg/ml Injection, solution: 25mg/ml, 50mg/ml Suppositories: 5mg, 10mg, 20mg, 30mg
Oxycodone	IR tablets: 10-30mg every 4 hours as needed IR capsules: 5mg every 6 hours as needed Oral solution: 10-30mg every 4 hours as needed Oral concentrate: 5mg every 6 hours as needed	Not recommended for use in children	IR Tablets: 5mg, 10mg, 15mg, 20mg, 30mg CR: 10mg, 15mg, 20mg, 30mg, 40mg, 60mg, 80mg Capsules: 5mg Solution, oral: 5mg/5ml Solution, concentrate: 20mg/ml

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Oxycodone/APAP	5mg/7.5mg/10mg oxycodone strength: 1 tablet, caplet or teaspoonful every 6 hours as needed 2.5mg oxycodone strength: 1-2 tablets every 6 hours as needed	Safety and efficacy in children have not been established	Tablet: 2.5/300mg, 2.5/325mg, 2.5/400mg, 5/300mg, 5/325mg, 5/400mg, 7.5/300mg, 7.5/325mg, 7.5/400mg, 7.5/500mg, 10/300mg, 10/325mg, 10/400mg, 10/500mg, 10/650mg Capsule 5/500mg Solution, oral 5/325mg/5ml
Oxycodone/ASA	1 tablet every 6 hours as needed for pain. Maximum 12 tablets every 24 hours	Safety and efficacy have not been established. Reye syndrome has been associated with aspirin administration to children (including teenagers) with acute febrile illness.	Tablets: 4.5mg oxycodone, 0.38mg oxycodone terephthalate/325mg
Oxycodone/ ibuprofen	1 tablet given orally not to exceed 4 tablets in a 24 hour period	Safety and effectiveness in pediatric patients below the age of 14 have not been established.	Tablets: 5/400mg
Oxymorphone	IR: 10-20mg every 4-6 hours ER: 5mg every 12 hours	Safety and efficacy of oxymorphone in children younger than 18 years of age have not been established.	IR Tablets: 5mg, 10mg ER Tablets: 5mg, 7.5mg, 10mg, 15mg, 20mg, 30mg, 40mg Injection, solution: 1mg/ml
Propoxyphene HCL	65mg every 4 hours as needed	Safety and efficacy in children have not been established.	Capsule: 65mg
Propoxyphene HCL/APAP	65mg (with 650mg acetaminophen) every 4 hours as needed	Safety and efficacy in children have not been established.	Tablet: 65/650mg
Propoxyphene napsylate	100mg every 4 hours as needed	Safety and efficacy in children have not been established.	Tablet: 100mg
Propoxyphene napsylate/APAP	100mg (with 325, 500, or 625mg acetaminophen) every 4 hours as needed	Safety and efficacy in children have not been established.	Tablet: 50/325mg, 100/325mg, 100/500mg, 100/650mg
Remifentanil	Individualize dose given as IV only	≥1 year. Individualize dose	IV: 1mg, 2mg, 5mg
Sufentanil	Individualize dose given as slow IV or IV infusion	2-12 years: 10-25mcg/kg given with 100% oxygen	IV: 50mcg/ml
Tapentadol	50-100mg every 4-6 hours. Daily doses greater than 700mg on the first day of therapy and 600mg on subsequent days have not been studied.	Not recommended for use in children younger than 18 years of age.	Tablets: 50mg, 75mg, 100mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Tramadol	IR tablets: 25mg/day in the morning. After titration, administer 50-100mg every 4-6 hours as needed for pain relief. ER tablets: 100-300mg once daily.	Safety and efficacy in children have not been established.	Tablets: 50mg Tablets, extended release: 100mg, 200mg, 300mg
Tramadol/APAP	2 tablets every 4-6 hours as needed	Safety and efficacy in children have not been established.	Tablets: 37.5mg/325mg

SC=Subcutaneous; IM=Intramuscular; IV=Intravenous

Table 8. Equianalgesic Dosing of Opioid Analgesics

Approximate Equianalgesic Dosing of Opioid Analgesics in Adults			
Opioid	**Oral**	**Parenteral (IM, SC, IV)**	**Rectal**
Codeine	200mg	120-130mg	NA
Fentanyl	NA	0.1mg	NA
Hydrocodone	30mg	NA	NA
Hydromorphone	7.5mg	1.5mg	3mg
Levorphanol	4mg	2mg	NA
Meperidine	300mg	75mg	NA
Methadone	10-20mg	5-10mg	NA
Morphine	60mg single dose, 30mg repeated doses	10mg	-
Oxycodone	20-30mg	NA	NA
Oxymorphone	NA	1mg	10mg

BLACK BOX WARNINGS:

Fentanyl transmucosal:
Oral transmucosal fentanyl is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and tolerant of opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking morphine 60 mg/day or more, transdermal fentanyl 50 mcg/h, or an equianalgesic dose of another opioid for a week or longer. It is contraindicated in the management of acute or postoperative pain. Because life-threatening hypoventilation could occur at any dose in patients not taking long-term opiate therapy, do not use in nonopioid-tolerant patients. Use only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of schedule II opioids to treat cancer pain. Instruct patients and their caregivers that this drug contains medicine in an amount that can be fatal to a child. Keep all units out of the reach of children, and discard opened units properly.

Fentanyl transdermal system:
Fentanyl transdermal systems contain a high concentration of the potent schedule II opioid agonist, fentanyl. Schedule II opioid substances have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in the patches may be a particular target for abuse and diversion.

Fentanyl transdermal system is indicated for management of persistent, moderate to severe chronic pain that requires continuous around-the-clock opioid administration for an extended period of time, and cannot be managed by other means, such as nonsteroidal analgesics, opioid combination products, or immediate-release (IR) opioids.

Use fentanyl transdermal system only in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to fentanyl transdermal system 25 mcg/h. Patients who are considered opioid tolerant are those who have been taking, for a week or longer, morphine 60 mg/day or more, oral oxycodone 30 mg/day or more, oral hydromorphone 8 mg/day or more, or an equianalgesic dose of another opioid.

Because serious or life-threatening hypoventilation could occur, fentanyl transdermal is contraindicated:

- in patients who are not opioid tolerant,
- in the management of acute pain or in patients who require opioid analgesia for a short period of time,
- in the management of postoperative pain, including use after outpatient or day surgeries (eg, tonsillectomies),
- in the management of mild pain, and
- in the management of intermittent pain (eg, use on an as-needed basis).

Because peak fentanyl levels occur between 24 and 72 hours of treatment, serious or life-threatening hypoventilation may occur, even in opioid-tolerant patients, during the initial application period. The concomitant use of fentanyl transdermal system with potent CYP3A4 inhibitors (clarithromycin, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, troleandomycin) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Carefully monitor patients receiving fentanyl transdermal system and potent CYP3A4 inhibitors for an extended period of time and make dosage adjustments if warranted.

Do not administer fentanyl transdermal system to children younger than 2 years of age. Administer to children only if they are opioid tolerant and 2 years of age and older.

Fentanyl transdermal system is only for use in patients who are already tolerant to opioid therapy of comparable potency. Use in nonopioid-tolerant patients may lead to fatal respiratory depression. Overestimating the fentanyl transdermal system dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Because of the 17-hour mean elimination half-life of fentanyl transdermal system, patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours.

Fentanyl transdermal system can be abused in a manner similar to other opioid agonists, legal or illicit. Consider this risk when administering, prescribing, or dispensing fentanyl transdermal system in situations in which there is concern about increased risk of misuse, abuse, or diversion.

Fentanyl transdermal patches are intended for transdermal use (on intact skin) only. Using damaged or cut fentanyl transdermal patches can lead to the rapid release of the contents of the fentanyl transdermal patch and absorption of a potentially fatal dose of fentanyl.

Hydromorphone:
High-potency injection: High-potency injection is a highly concentrated solution of hydromorphone intended for use in opioid-tolerant patients. Do not confuse high potency injection with standard parenteral formulations of injection or other opioids. Overdose and death could result.

Extended-release capsules: Hydromorphone extended-release (ER) capsules are indicated for the management of persistent moderate to severe pain in patients requiring continuous, around-the-clock analgesia with a high-potency opioid for an extended period of time (weeks to months) or longer. Use ER capsules only in patients who are already receiving opioid therapy, have demonstrated opioid tolerance, and require a minimum total daily dose of opiate medication equivalent to oral hydromorphone 12 mg. Patients considered opioid tolerant are those taking, for a week or longer, oral morphine 60 mg/day or more, oral oxycodone 30 mg/day or more, oral hydromorphone 8 mg/day or more, or an equianalgesic dose of another opioid. Administer ER capsules once every 24 hours.

Appropriate patients for treatment with ER capsules include patients who require high doses of potent opioids on an around-the-clock basis to improve pain control, and patients who have difficulty attaining adequate analgesia with IR opioid formulations. ER capsules are contraindicated for use on an as-needed basis.

ER capsules are not intended to be used as the first opioid product prescribed for a patient or in patients who require opioid analgesia for a short period of time.

ER capsules are for opioid-tolerant patients only. Use in nonopioid-tolerant patients may lead to fatal respiratory depression. Overestimating the ER capsule dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Because of the mean apparent 18-hour elimination half-life of ER capsules, patients who receive an overdose will require an extended period of monitoring and treatment that may go beyond 18 hours. Even in the face of improvement, continued medical monitoring is required because of the possibility of extended effects.

Schedule II opioid agonists (eg, fentanyl, hydromorphone, methadone, morphine, oxycodone, oxymorphone) have the highest risk of fatal overdoses because of respiratory depression, as well as the highest potential for abuse. ER capsules can be abused in a manner similar to other opioid agonists, legal or illicit. Consider these risks when administering, prescribing, or dispensing ER capsules in situations in which there is concern about increased risk of misuse, abuse, or diversion.

People at increased risk for opioid abuse include those with a personal or family history of substance abuse (ie, drug or alcohol abuse or addiction) or mental illness (eg, major depression). Assess patients for clinical risks for opioid abuse or addiction prior to prescribing opioids. Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction. Patients at increased risk of opioid abuse may still be appropriately treated with modified-release opioid formulations; however, these patients will require intensive monitoring for signs of misuse, abuse, or addiction.

ER capsules are to be swallowed whole and not broken, chewed, opened, dissolved, or crushed. Taking broken, chewed, dissolved, or crushed ER capsules or capsule contents can lead to the rapid release and absorption of a potentially fatal dose of hydromorphone. Overestimating the ER capsule dose when converting the patient from another opioid medication can result in fatal overdose with the first dose. With the long half-life of ER capsules (18 hours), patients who receive the wrong dose will require an extended period of monitoring and treatment that may go beyond 18 hours. Even in the face of improvement, continued medical monitoring is required because of the possibility of extended effects.

Methadone:
To treat narcotic addiction in detoxification or maintenance programs, methadone should be dispensed only by hospitals, community pharmacies, and maintenance programs approved by the Food and Drug Administration (FDA) and designated state authorities. Approved maintenance programs shall dispense and use methadone in oral form only and according to treatment requirements stipulated in Federal Methadone Regulations. Failure to abide by the requirements in these regulations may result in criminal prosecution, seizure of drug supply, revocation of program approval, and injunction precluding program operation.

Methadone, used as an analgesic, may be dispensed in any licensed pharmacy.

Methadone dispersible tablets are for oral administration only. This preparation contains insoluble excipients and therefore must not be injected. It is recommended that methadone dispersible tablets, if dispensed, be packaged in child-resistant containers and kept out of the reach of children to prevent accidental ingestion.

Cardiac conduction effects: Laboratory studies, in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. These cases appear to be more commonly associated with, but not limited to, higher dose treatment (more than 200 mg/day). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Morphine:
Avinza: Avinza capsules are a modified-release formulation of morphine sulfate indicated for once-daily administration for the relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time. Avinza capsules are to be swallowed whole or the contents of the capsules sprinkled on applesauce. The capsule beads are not to be chewed, crushed, or dissolved because of the risk of rapid release and absorption of a potentially fatal dose of morphine.

Astramorph PF, Duramorph, Infumorph: Because of the risk of severe adverse effects when the epidural or intrathecal route of administration is employed, patients must be observed in a fully equipped and staffed environment for at least 24 hours after the initial dose.

Infumorph: Infumorph is not recommended for single-dose intravenous (IV), intramuscular (IM), or subcutaneous administration because of the very large amount of morphine in the ampul and the associated risk of overdosage.

Oxycodone:
Controlled-release (CR) oxycodone is an opioid agonist and a schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. Consider this when prescribing or dispensing oxycodone CR tablets in situations in which there is concern about an increased risk of misuse, abuse, or diversion.

Oxycodone CR tablets are indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

Oxycodone CR tablets are not intended for use as an as-needed analgesic.

Oxycodone 80 and 160 mg CR tablets are for use in opioid-tolerant patients only. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

Oxycodone CR tablets are to be swallowed whole and are not to be broken, chewed, or crushed. Taking broken, chewed, or crushed oxycodone CR tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone.

Propoxyphene:
Fatalities: Do not prescribe propoxyphene for patients who are suicidal or addiction-prone. Prescribe propoxyphene with caution to patients taking tranquilizers or antidepressant drugs and patients who use alcohol in excess. Tell patients not to exceed the recommended dose and to limit alcohol intake.

Propoxyphene products in excessive doses, either alone or in combination with other CNS depressants (including alcohol), are a major cause of drug-related deaths. Fatalities within the first hour of overdosage are not uncommon. In 1975, a survey was conducted of deaths due to overdosage; in approximately 20% of fatal cases, death occurred within the first hour (5% within 15 minutes). Propoxyphene should not be taken in higher doses than those recommended by the health care provider. Judicious prescribing of propoxyphene is essential for safety. Consider nonnarcotic analgesics for depressed or suicidal patients. Do not prescribe propoxyphene for suicidal or addiction-prone patients. Caution patients about the concomitant use of propoxyphene products and alcohol because of potentially serious CNS-additive effects of these agents. Because of added CNS depressant effects, cautiously prescribe with concomitant sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Advise patients of the additive depressant effects of these combinations. Many propoxyphene-related deaths have occurred in patients with histories of emotional disturbances, suicidal ideation or attempts, or misuse of tranquilizers, alcohol, and other CNS-active drugs. Deaths have occurred as a consequence of the accidental ingestion of excessive quantities of propoxyphene alone or in combination with other drugs. Do not exceed the recommended dosage.

VIII. Conclusion

Opioids are a class of medications that act on common receptors and are natural derivatives of morphine. Opioids are the most potent medications available for treatment of most types of severe pain. Opioids are also associated with many adverse effects, including abuse and addiction. It is estimated that one in five adult Americans experience chronic pain. Chronic non-cancer pain causes personal suffering, reduced productivity, and substantial health care costs.

The efficacy of opiates for non-cancer pain has been demonstrated in short-term trials but is highly variable for the long-term treatment of non-cancer pain.

Guidelines for the management of non-cancer pain recommend opiates for moderate to severe pain. Guidelines for the management of cancer pain recommend mild opiates for mild to moderate pain, and strong opiates for moderate to severe pain. Current guidelines for cancer and non-cancer pain do not give preference to one opiate over another.

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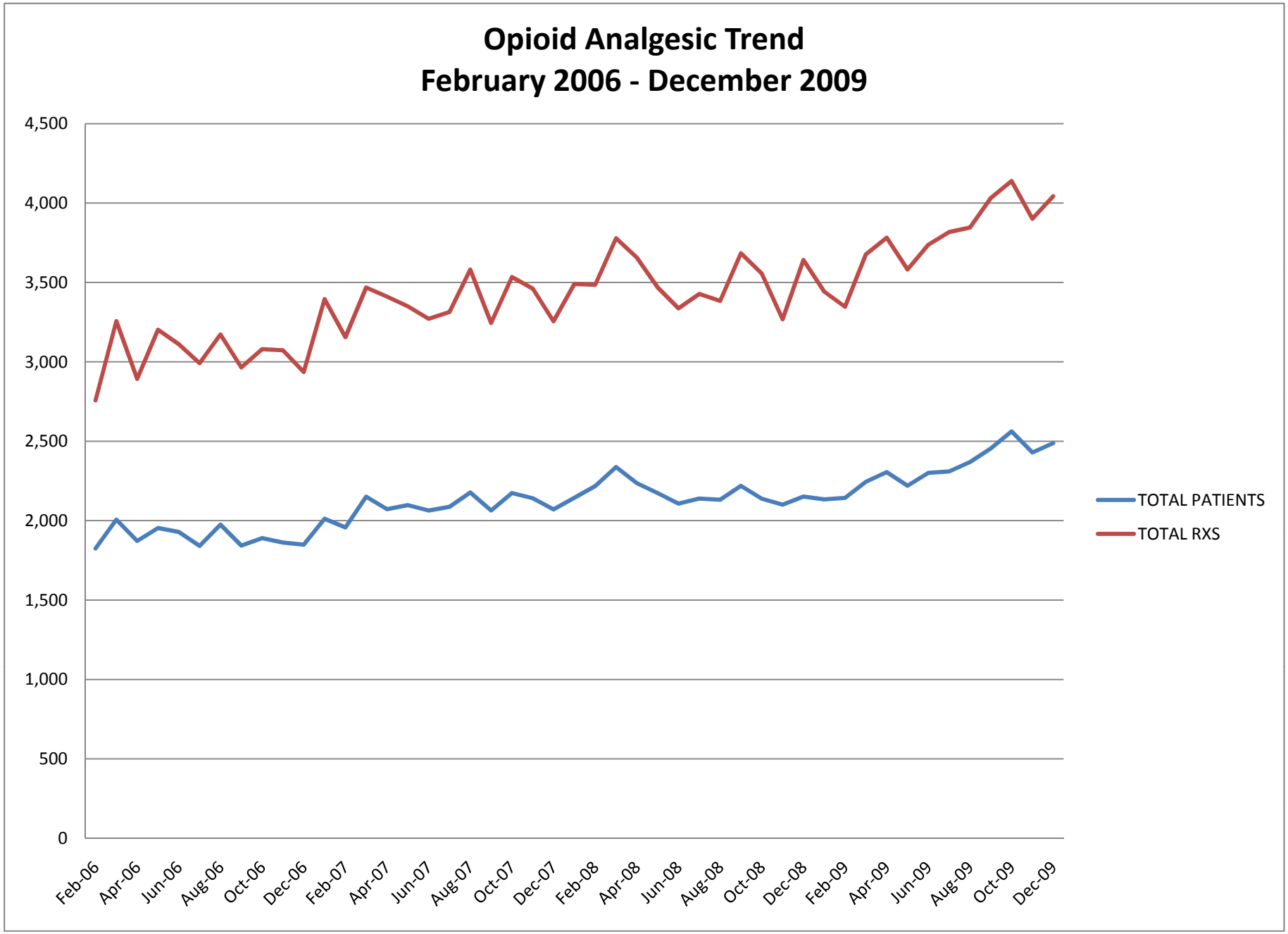
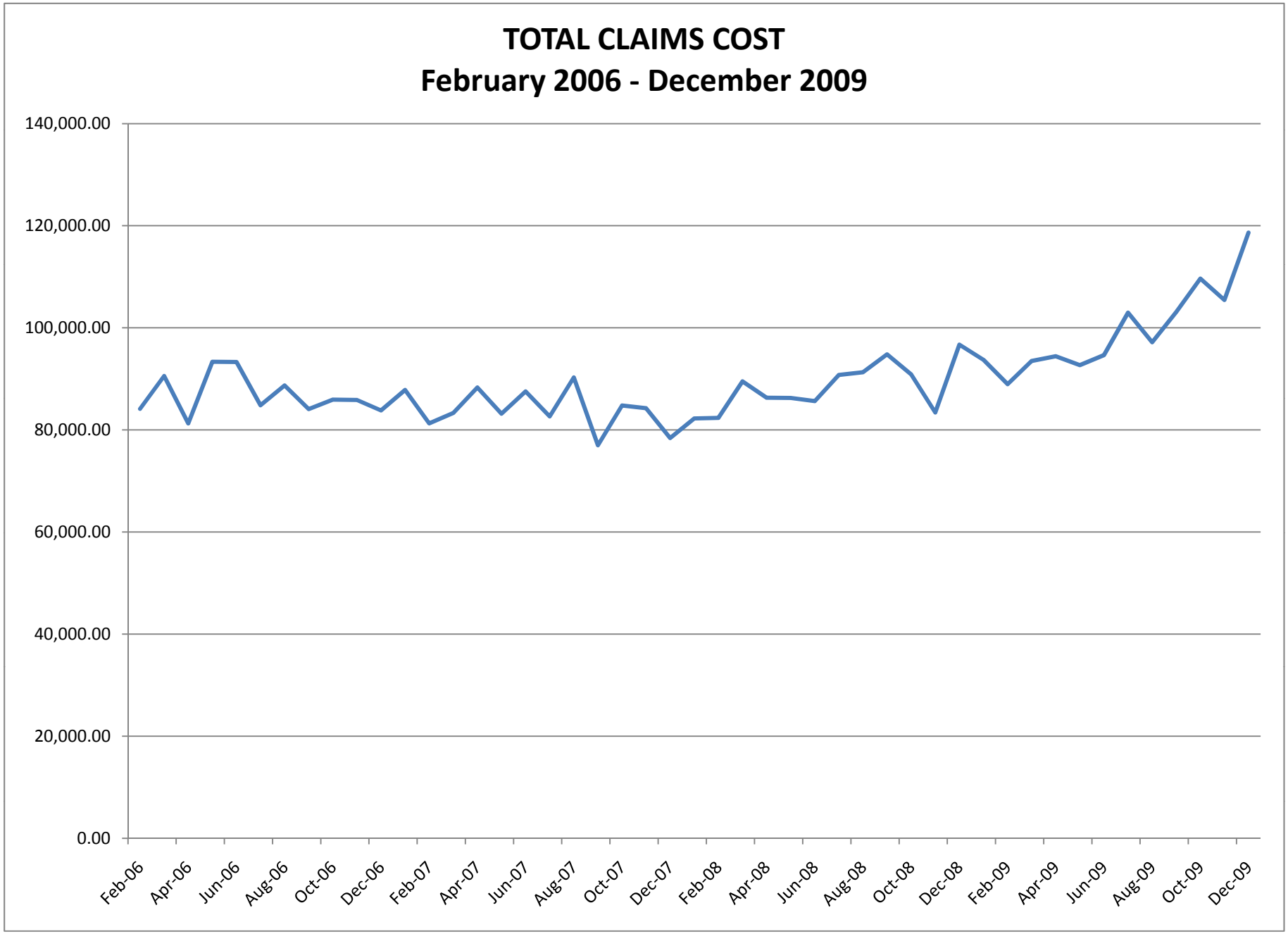
ND Medicaid Narcotic Utilization		
02/24/09 - 02/23/10		
AHFS Class 280808		
Label Name	**Rx Num**	**Total Reimb Amt**
ACETAMINOPHEN-COD #2 TABLET	39	$323.18
ACETAMINOPHEN-COD #3 TABLET	3454	$31,988.33
ACETAMINOPHEN-COD #4 TABLET	22	$467.54
BELLADONNA-OPIUM 16.2-30 SUPP	2	$366.72
BELLADONNA-OPIUM 16.2-60 SUPP	4	$413.68
BUTALBITAL COMP-CODEINE #3 CAP	41	$1,387.65
BUTALBITAL-CAFF-APAP-COD CAP	15	$406.52
CAPITAL WITH CODEINE SUSP	254	$17,388.50
CODEINE SULFATE 15 MG TABLET	1	$29.02
CODEINE SULFATE 30 MG TABLET	32	$629.01
CODEINE SULFATE 60 MG TABLET	1	$13.30
DARVOCET-N 100 TABLET	12	$2,455.40
DILAUDID 2 MG TABLET	12	$116.65
DILAUDID 4 MG TABLET	11	$873.19
DURAGESIC 75 MCG/HR PATCH	3	$484.80
EMBEDA 20-0.8 MG CAPSULE	20	$3,362.09
EMBEDA 30-1.2 MG CAPSULE	17	$4,243.83
EMBEDA 50-2 MG CAPSULE	6	$1,504.91
EMBEDA 60-2.4 MG CAPSULE	4	$2,001.04
ENDOCET 5-325 TABLET	138	$940.81
ENDODAN 4.83-325 MG TABLET	4	$430.01
HYDROCODONE-APAP 2.5-500 TAB	8	$57.17
HYDROCODONE-APAP 5-500 TABLET	6807	$52,425.45
HYDROCODONE-APAP 7.5-500 TAB	1171	$10,903.84
HYDROMORPHONE 2 MG TABLET	449	$4,734.01
HYDROMORPHONE 2 MG/ML VIAL	2	$23.08
HYDROMORPHONE 4 MG TABLET	468	$10,778.07
HYDROMORPHONE HCL 2 MG/ML AMP	1	$6.68
KADIAN 10 MG CAPSULE SR	4	$497.17
MEPERIDINE 100 MG TABLET	1	$28.10
MEPERIDINE 50 MG TABLET	66	$1,341.44
METHADONE 5 MG/5 ML SOLUTION	11	$68.74
METHADONE HCL 10 MG TABLET	565	$11,674.22
METHADONE HCL 5 MG TABLET	158	$1,361.54
METHADONE HCL POWDER	1	$10.24
MORPHINE 10 MG SOLUBLE TABLET	1	$5.95
MORPHINE 10 MG/ML SYRINGE	46	$294.72
MORPHINE 15 MG/ML VIAL	1	$11.23
MORPHINE 2 MG/ML SYRINGE	2	$85.18
MORPHINE 4 MG/ML SYRINGE	2	$12.46
MORPHINE 5 MG/ML VIAL	1	$10.82
MORPHINE SULF 10 MG/5 ML SOLN	44	$873.75
MORPHINE SULF 20 MG/5 ML SOLN	2	$38.43
MORPHINE SULF ER 30 MG TABLET	339	$10,724.84
MORPHINE SULF ER 60 MG TABLET	196	$10,125.76

ND Medicaid Narcotic Utilization		
02/24/09 - 02/23/10		
AHFS Class 280808		
Label Name	**Rx Num**	**Total Reimb Amt**
MORPHINE SULFATE 20 MG/ML SOLN	16	$379.84
MORPHINE SULFATE IR 15 MG TAB	165	$2,035.40
MORPHINE SULFATE IR 30 MG TAB	52	$1,686.77
MORPHINE SULFATE POWDER	2	$6.77
NUCYNTA 100 MG TABLET	10	$2,246.79
NUCYNTA 50 MG TABLET	34	$2,746.73
NUCYNTA 75 MG TABLET	14	$1,170.33
OPANA 10 MG TABLET	15	$6,265.65
OPANA 5 MG TABLET	22	$5,308.65
OPANA ER 10 MG TABLET	22	$4,202.76
OPANA ER 20 MG TABLET	7	$2,124.44
OPANA ER 5 MG TABLET	2	$164.13
OXYCODONE HCL 5 MG CAPSULE	55	$1,303.42
OXYCODONE HCL 5 MG TABLET	1231	$25,274.77
OXYCODONE HCL 5 MG/5 ML SOL	56	$1,287.14
OXYCODONE-APAP 10-650 MG TAB	105	$3,271.69
OXYCODONE-APAP 5-325 MG TAB	3632	$32,907.72
OXYCODONE-APAP 5-500 MG CAP	759	$8,649.53
OXYCODONE-APAP 7.5-500 MG TAB	48	$1,220.39
OXYCODONE-ASA 4.5-0.38-325 TAB	14	$658.38
OXYCONTIN 15 MG TABLET	10	$1,174.43
OXYCONTIN 30 MG TABLET	63	$14,614.86
OXYCONTIN 40 MG TABLET	212	$79,363.60
OXYCONTIN 60 MG TABLET	55	$26,421.28
OXYCONTIN 80 MG TABLET	81	$61,762.32
PANLOR SS TABLET	1	$103.10
PROPOXYPHEN-APAP 100-650 MG TB	2499	$26,457.37
PROPOXYPHENE HCL 65 MG CAP	57	$1,178.75
PROPOXYPHENE-APAP 50-325 MG TB	12	$136.32
ROXICET 5-325 ORAL SOLUTION	31	$646.01
ROXICET 5-325 TABLET	58	$402.66
ROXICET 5-500 CAPLET	13	$2,554.59
ROXICODONE 5 MG TABLET	1	$34.39
RYZOLT ER 100 MG TABLET	1	$110.77
RYZOLT ER 200 MG TABLET	18	$616.40
RYZOLT ER 300 MG TABLET	1	$55.08
TYLOX 5-500 CAPSULE	2	$14.30
ULTRAM ER 100 MG TABLET	28	$2,975.47
ULTRAM ER 200 MG TABLET	63	$11,361.68
ULTRAM ER 300 MG TABLET	54	$13,969.09
7,954 recipients	**23959**	**$532,782.84**

ND Medicaid Narcotic Utilization			
02/24/09 - 02/23/10			
AHFS Class 280808			
Label Name	**Rx Num**	**Total Reimb Amt**	**Cost per Script**
OXYCONTIN 80 MG TABLET	81	$61,762.32	$762.50
EMBEDA 60-2.4 MG CAPSULE	4	$2,001.04	$500.26
OXYCONTIN 60 MG TABLET	55	$26,421.28	$480.39
OPANA 10 MG TABLET	15	$6,265.65	$417.71
OXYCONTIN 40 MG TABLET	212	$79,363.60	$374.36
OPANA ER 20 MG TABLET	7	$2,124.44	$303.49
ULTRAM ER 300 MG TABLET	54	$13,969.09	$258.69
EMBEDA 50-2 MG CAPSULE	6	$1,504.91	$250.82
EMBEDA 30-1.2 MG CAPSULE	17	$4,243.83	$249.64
OPANA 5 MG TABLET	22	$5,308.65	$241.30
OXYCONTIN 30 MG TABLET	63	$14,614.86	$231.98
NUCYNTA 100 MG TABLET	10	$2,246.79	$224.68
DARVOCET-N 100 TABLET	12	$2,455.40	$204.62
ROXICET 5-500 CAPLET	13	$2,554.59	$196.51
OPANA ER 10 MG TABLET	22	$4,202.76	$191.03
BELLADONNA-OPIUM 16.2-30 SUPP	2	$366.72	$183.36
ULTRAM ER 200 MG TABLET	63	$11,361.68	$180.34
EMBEDA 20-0.8 MG CAPSULE	20	$3,362.09	$168.10
DURAGESIC 75 MCG/HR PATCH	3	$484.80	$161.60
KADIAN 10 MG CAPSULE SR	4	$497.17	$124.29
OXYCONTIN 15 MG TABLET	10	$1,174.43	$117.44
RYZOLT ER 100 MG TABLET	1	$110.77	$110.77
ENDODAN 4.83-325 MG TABLET	4	$430.01	$107.50
ULTRAM ER 100 MG TABLET	28	$2,975.47	$106.27
BELLADONNA-OPIUM 16.2-60 SUPP	4	$413.68	$103.42
PANLOR SS TABLET	1	$103.10	$103.10
NUCYNTA 75 MG TABLET	14	$1,170.33	$83.60
OPANA ER 5 MG TABLET	2	$164.13	$82.07
NUCYNTA 50 MG TABLET	34	$2,746.73	$80.79
DILAUDID 4 MG TABLET	11	$873.19	$79.38
CAPITAL WITH CODEINE SUSP	254	$17,388.50	$68.46
RYZOLT ER 300 MG TABLET	1	$55.08	$55.08
MORPHINE SULF ER 60 MG TABLET	196	$10,125.76	$51.66
OXYCODONE-ASA 4.5-0.38-325 TAB	14	$658.38	$47.03
MORPHINE 2 MG/ML SYRINGE	2	$85.18	$42.59
ROXICODONE 5 MG TABLET	1	$34.39	$34.39
RYZOLT ER 200 MG TABLET	18	$616.40	$34.24
BUTALBITAL COMP-CODEINE #3 CAP	41	$1,387.65	$33.85
MORPHINE SULFATE IR 30 MG TAB	52	$1,686.77	$32.44
MORPHINE SULF ER 30 MG TABLET	339	$10,724.84	$31.64
OXYCODONE-APAP 10-650 MG TAB	105	$3,271.69	$31.16
CODEINE SULFATE 15 MG TABLET	1	$29.02	$29.02
MEPERIDINE 100 MG TABLET	1	$28.10	$28.10
BUTALBITAL-CAFF-APAP-COD CAP	15	$406.52	$27.10
OXYCODONE-APAP 7.5-500 MG TAB	48	$1,220.39	$25.42

ND Medicaid Narcotic Utilization			
02/24/09 - 02/23/10			
AHFS Class 280808			
Label Name	**Rx Num**	**Total Reimb Amt**	**Cost per Script**
MORPHINE SULFATE 20 MG/ML SOLN	16	$379.84	$23.74
OXYCODONE HCL 5 MG CAPSULE	55	$1,303.42	$23.70
HYDROMORPHONE 4 MG TABLET	468	$10,778.07	$23.03
OXYCODONE HCL 5 MG/5 ML SOL	56	$1,287.14	$22.98
ACETAMINOPHEN-COD #4 TABLET	22	$467.54	$21.25
ROXICET 5-325 ORAL SOLUTION	31	$646.01	$20.84
PROPOXYPHENE HCL 65 MG CAP	57	$1,178.75	$20.68
METHADONE HCL 10 MG TABLET	565	$11,674.22	$20.66
OXYCODONE HCL 5 MG TABLET	1231	$25,274.77	$20.53
MEPERIDINE 50 MG TABLET	66	$1,341.44	$20.32
MORPHINE SULF 10 MG/5 ML SOLN	44	$873.75	$19.86
CODEINE SULFATE 30 MG TABLET	32	$629.01	$19.66
MORPHINE SULF 20 MG/5 ML SOLN	2	$38.43	$19.22
CODEINE SULFATE 60 MG TABLET	1	$13.30	$13.30
MORPHINE SULFATE IR 15 MG TAB	165	$2,035.40	$12.34
HYDROMORPHONE 2 MG/ML VIAL	2	$23.08	$11.54
OXYCODONE-APAP 5-500 MG CAP	759	$8,649.53	$11.40
PROPOXYPHENE-APAP 50-325 MG TB	12	$136.32	$11.36
MORPHINE 15 MG/ML VIAL	1	$11.23	$11.23
MORPHINE 5 MG/ML VIAL	1	$10.82	$10.82
PROPOXYPHEN-APAP 100-650 MG TB	2499	$26,457.37	$10.59
HYDROMORPHONE 2 MG TABLET	449	$4,734.01	$10.54
METHADONE HCL POWDER	1	$10.24	$10.24
DILAUDID 2 MG TABLET	12	$116.65	$9.72
HYDROCODONE-APAP 7.5-500 TAB	1171	$10,903.84	$9.31
ACETAMINOPHEN-COD #3 TABLET	3454	$31,988.33	$9.26
OXYCODONE-APAP 5-325 MG TAB	3632	$32,907.72	$9.06
METHADONE HCL 5 MG TABLET	158	$1,361.54	$8.62
ACETAMINOPHEN-COD #2 TABLET	39	$323.18	$8.29
HYDROCODONE-APAP 5-500 TABLET	6807	$52,425.45	$7.70
TYLOX 5-500 CAPSULE	2	$14.30	$7.15
HYDROCODONE-APAP 2.5-500 TAB	8	$57.17	$7.15
ROXICET 5-325 TABLET	58	$402.66	$6.94
ENDOCET 5-325 TABLET	138	$940.81	$6.82
HYDROMORPHONE HCL 2 MG/ML AMP	1	$6.68	$6.68
MORPHINE 10 MG/ML SYRINGE	46	$294.72	$6.41
METHADONE 5 MG/5 ML SOLUTION	11	$68.74	$6.25
MORPHINE 4 MG/ML SYRINGE	2	$12.46	$6.23
MORPHINE 10 MG SOLUBLE TABLET	1	$5.95	$5.95
MORPHINE SULFATE POWDER	2	$6.77	$3.39
7,954 recipients	**23959**	**$532,782.84**	


Opioid Analgesic Trend
February 2006 - December 2009
4,500
4,000
3,500
3,000
2,500
2,000
1,500
1,000
500
0
Feb-06
Apr-06
Jun-06
Aug-06
Oct-06
Dec-06
Feb-07
Apr-07
Jun-07
Aug-07
Oct-07
Dec-07
Feb-08
Apr-08
Jun-08
Aug-08
Oct-08
Dec-08
Feb-09
Apr-09
Jun-09
Aug-09
Oct-09
Dec-09
TOTAL PATIENTS
TOTAL RXS


TOTAL CLAIMS COST
February 2006 - December 2009
140,000.00
120,000.00
100,000.00
80,000.00
60,000.00
40,000.00
20,000.00
0.00
Feb-06
Apr-06
Jun-06
Aug-06
Oct-06
Dec-06
Feb-07
Apr-07
Jun-07
Aug-07
Oct-07
Dec-07
Feb-08
Apr-08
Jun-08
Aug-08
Oct-08
Dec-08
Feb-09
Apr-09
Jun-09
Aug-09
Oct-09
Dec-09

SHORT-ACTING AND LONG-ACTING 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 short-acting brand-name narcotic or a long-acting brand-name narcotic must meet the following criteria:

- **Documented failure of a 30-day trial of a generic short-acting brand-name narcotic at a dose equivalent to the brand name narcotic being prescribed.**
- **Documented failure of a 30-day trial of a generic long-acting brand-name narcotic at a dose equivalent to the brand name narcotic being prescribed.**

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 □ KADIAN □ AVINZA □ DURAGESIC 12 □ FENTORA □ COMBUNOX □ ACTIQ □ ONSOLIS

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
DUR Board Meeting
Metozolv® Review
June 14, 2010

I. Overview

Metozolv is a dopamine receptor antagonist indicated for the short-term (4-12 weeks) relief of symptomatic gastroesophageal reflux in patients who fail to respond to conventional therapy. Metozolv is also indicated for the relief of symptoms in adults associated with acute and recurrent diabetic gastroparesis (gastric stasis).

II. Pharmacology

Metoclopramide stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions. While its mode of action is unclear, it appears to sensitize tissues to the action of acetylcholine. Metoclopramide increases the tone and amplitude of gastric contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum and jejunum resulting in accelerated gastric emptying and intestinal transit. It increases the resting tone of the lower esophageal sphincter.

The onset of pharmacological action of metoclopramide is 30 to 60 minutes following an oral dose; pharmacological effects persist for 1-2 hours. In patients with gastroesophageal reflux and low LESP (lower esophageal sphincter pressure) single oral doses of metoclopramide produce dose-related increases in LESP. The increase in LESP from a 5mg dose lasts about 45 minutes and that of a 20mg dose lasts between 2 and 3 hours. Increased rate of stomach emptying has been observed with single oral doses of 10mg.

III. Pharmacokinetics

In a randomized, two-arm, two-way crossover study in 44 healthy adult fasted subjects, Metozolv ODT was bioequivalent to Reglan Tablets.

In a food-effect study with 28 subjects, Metozolv ODT taken immediately after a high-fat meal had a 17% lower peak blood level than when taken after an overnight fast. The time to peak blood levels increased from about 1.75 hours under fasted conditions to 3 hours when taken immediately after a high-fat meal. The extent of metoclopramide absorbed was comparable whether taken with or without food.

Adult Pharmacokinetic Data

Parameter	Value
VD (L/kg)	~3.5
Plasma Protein Binding	~30%
T ½	5-6 hours
Oral Bioavailability	80%±15.5%

IV. Contraindications

- Intestinal obstruction, hemorrhage, or perforation
- Pheochromocytoma
- Known sensitivity or intolerance
- Epilepsy
- Concomitant medication with extrapyramidal reactions

V. Warnings/Precautions

- Tardive dyskinesia
- Acute dystonic reactions, drug-induced parkinsonism, and other extrapyramidal symptoms
- Neuroleptic Malignant Syndrome (NMS)
- Depression
- Hypertension
- Congestive Heart Failure and Ventricular Arrhythmia
- Withdrawal from metoclopramide

Warning: Tardive Dyskinesia
Treatment with metoclopramide can cause tardive dyskinesia, a serious movement disorder that is often irreversible. The risk of developing tardive dyskinesia increases with duration of treatment and total cumulative dose.

Metoclopramide therapy should be discontinued in patients who develop signs or symptoms of tardive dyskinesia. There is no known treatment for tardive dyskinesia. In some patients, symptoms may lessen or resolve after metoclopramide treatment is stopped.

Treatment with metoclopramide for longer than 12 weeks should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing tardive dyskinesia.

VI. Drug Interactions

- Anticholinergic drugs - antagonize effects of metoclopramide
- Narcotic analgesic drugs - may increase sedation
- Monoamine oxidase inhibitors - may cause hypertensive crisis (due to catecholamine release)
- Altered drug absorption - may decrease absorption of drugs from the stomach and increase absorption of drugs from the small bowel
- Insulin - changes in food transit time may require adjustment of insulin dose or timing to avoid hypoglycemia
- Antidepressants, Antipsychotics, and Neuroleptics - concomitant use with metoclopramide is associated with increased risk of tardive dyskinesia and NMS

VII. Adverse Reactions

The most common adverse reactions (>2%) are headache, nausea, vomiting, fatigue, and somnolence.

VIII. Dosage and Administration

Gastroesophageal Reflux Disease: 10-15mg dose up to four times daily at least 30 minutes before eating and at bedtime.

Diabetic Gastroparesis (Diabetic Gastric Stasis): 10mg dose four times daily at least 30 minutes before eating and at bedtime for two to eight weeks.

IX. Conclusion

Metozolv is indicated for the short-term (4-12 weeks) relief of symptomatic gastroesophageal reflux who fail to respond to conventional therapy and for the relief of symptoms in adults associated with acute and recurrent diabetic gastroparesis (gastric stasis). The estimated acquisition cost of Metozolv for a month's supply is approximately 142 dollars compared to 14 dollars for metoclopramide.

References

1. Metozolv® Prescribing Information, September 2009, Salix Pharmaceuticals, Inc.
2. Wolters Kluwer Health, Inc. Drug Facts and Comparisons. St. Louis, MO. 2010.

METOZOLV ODT 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 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 MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS
2ND QUARTER 2010

Recommendations	*Approved*	*Rejected*

1. Liraglutide / Over-utilization _____ _____

Alert Message: The recommended maximum dose of Victoza (liraglutide) is 1.8 mg per day. Exceeding this dose may result in the increased risk of adverse effects (e.g. nausea and vomiting).

Conflict Code: ER - Overutilization
Drug/Disease:
Util A Util B Util C
Liraglutide

Max Dose: 1.8 mg/day

References:
Victoza Prescribing Information, Jan. 2010, Novo Nordisk A/S.

2. Liraglutide / Non-adherence _____ _____

Alert Message: Non-adherence to Victoza (liraglutide) therapy may result in loss of glycemic control and an increased risk of developing adverse diabetic-related complications.

Conflict Code: LR - Nonadherence
Drug/Disease:
Util A Util B Util C
Liraglutide

References:
Victoza Prescribing Information, Jan. 2010, Novo Nordisk A/S.

3. Liraglutide / Black Box Warning – Thyroid Cancer _____ _____

Alert Message: Victoza (liraglutide) causes thyroid C-cell tumors in clinically relevant exposure in rodents. It is unknown whether liraglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans. Counsel patients regarding the risk of medullary thyroid carcinoma and the symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea or persistent hoarseness).

Conflict Code: TA – Therapeutic Appropriateness
Drug/Disease:
Util A Util B Util C
Liraglutide

References:
Victoza Prescribing Information, Jan. 2010, Novo Nordisk A/S.

4. Liraglutide / Medullary Thyroid Carcinoma & Multiple Endocrine Neoplasia Syndrome (Black Box Contraindication) _____ _____

Alert Message: Victoza (liraglutide) is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome. Liraglutide has been shown to cause thyroid C-cell tumors in rats; the human relevance is unknown. It is recommended to counsel patients regarding the risk of medullary thyroid carcinoma and the symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea or persistent hoarseness).

Conflict Code: MC – Drug (Actual) Disease Precaution/Warning
Drug/Disease:

Util A	Util B	Util C
Liraglutide	Medullary Thyroid Carcinoma	
	Multiple Endocrine Neoplasia Syndrome	

References:
Victoza Prescribing Information, Jan. 2010, Novo Nordisk A/S.

5. Liraglutide / Type 1 Diabetes & Ketoacidosis _____ _____

Alert Message: Victoza (liraglutide) should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

Conflict Code: MC – Drug (Actual) Disease Precaution/Warning
Drug/Disease:

Util A	Util B	Util C
Liraglutide	Type 1 Diabetes ICD-9s	
	Ketoacidosis ICD-9	

References:
Victoza Prescribing Information, Jan. 2010, Novo Nordisk A/S.

6. Liraglutide / Insulin Secretagogues _____ _____

Alert Message: The coadministration of Victoza (liraglutide) and an insulin secretagogue may increase the risk of hypoglycemia. Consider lowering the dose of the insulin secretagogue to reduce the risk.

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

Util A	Util B	Util C
Liraglutide	Repaglinide	
	Nateglinide	
	Chlorpropamide	
	Glimepiride	
	Glipizide	
	Glyburide	
	Tolazamide	
	Tolbutamide	

References:
Victoza Prescribing Information, Jan. 2010, Novo Nordisk A/S.

7. Liraglutide / Pancreatitis _____ _____

Alert Message: Victoza (liraglutide) should be used with caution in patients with a history of pancreatitis. In clinical trials, there were more cases of pancreatitis among liraglutide-treated patients than placebo-treated. Counsel patients on symptoms of pancreatitis. If pancreatitis is suspected during liraglutide therapy, liraglutide and any other suspect drugs should be discontinued.

Conflict Code: MC – Drug (Actual) Disease Precaution/Warning
Drug/Disease:

Util A	Util B	Util C
Liraglutide	Pancreatitis	

References:
Victoza Prescribing Information, Jan. 2010, Novo Nordisk A/S.

8. Liraglutide / Pediatric Patients _____ _____

Alert Message: Safety and efficacy of Victoza (liraglutide) have not been established in pediatric patients and the drug is therefore not recommended for use in this population.

Conflict Code: TA – Therapeutic Appropriateness
Drug/Disease:

Util A	Util B	Util C
Liraglutide		

Age Range: 0 – 18 year of age
References:
Victoza Prescribing Information, Jan. 2010, Novo Nordisk A/S.

9. Liraglutide / Renal Impairment _____ _____

Alert Message: Victoza (liraglutide) should be used with caution in patients with renal impairment due to limited data for the drug in this population. Compared to healthy subjects, liraglutide AUC in mild, moderate, and severe renal impairment and ESRD was on average 35%, 19%, 29% and 30% lower, respectively.

Conflict Code: DB – Drug/Disease or Drug Inferred Disease Warning
Drug/Disease:

Util A	Util B	Util C
Liraglutide	Renal Impairment ICD-9s	
	Fosrenol	
	PhosLo	
	Zemplar	
	Renagel	
	Renvela	

References:
Victoza Prescribing Information, Jan. 2010, Novo Nordisk A/S.

10. Liraglutide / Hepatic Impairment _____ _____

Alert Message: Victoza (liraglutide) should be used with caution in patients with hepatic impairment due to limited data for the drug in this population. Compared to healthy subjects, liraglutide AUC in subjects with mild, moderate and severe hepatic impairment was on average 11%, 14% and 42% lower, respectively.

Conflict Code: MC – Drug (Actual) Disease Precaution/Warning
Drug/Disease:

Util A	Util B	Util C
Liraglutide	Hepatic Impairment	

References:
Victoza Prescribing Information, Jan. 2010, Novo Nordisk A/S.

11. Liraglutide / Gastroparesis _____ _____

Alert Message: Victoza (liraglutide) should be used with caution in patients with gastroparesis. Liraglutide slows gastric emptying and may exacerbate the condition.

Conflict Code: MC – Drug (Actual) Disease Precaution/Warning
Drug/Disease:

Util A	Util B	Util C
Liraglutide	Gastroparesis	

References:
Victoza Prescribing Information, Jan. 2010, Novo Nordisk A/S.

12. Liraglutide / Oral Drugs _____ _____

Alert Message: Caution should be exercised when Victoza (liraglutide), a GLP-1 receptor agonist, is coadministered with oral medications. Liraglutide causes delayed gastric emptying and has the potential to impact the rate and extent of absorption of the oral agent.

Conflict Code: TA – Therapeutic Appropriateness
Drug/Disease:

Util A	Util B	Util C
Liraglutide		

References:
Victoza Prescribing Information, Jan. 2010, Novo Nordisk A/S.

13. Saxagliptin / High Dose _____ _____

Alert Message: The recommended dose of Onglyza (saxagliptin) is 2.5 mg or 5.0 mg once daily.

Conflict Code: ER - Overutilization
Drug/Disease:

Util A	Util B	Util C (Negating)
Saxagliptin		Renal Impairment
		Ketoconazole
		Itraconazole
		Clarithromycin
		Telithromycin
		Indinavir
		Ritonavir
		Saquinavir
		Nelfinavir
		Atazanavir
		Nefazodone

Maximum Dose: 5 mg/day

References:
Onglyza Prescribing Information, July 2009, Bristol-Myers Squibb/AstraZeneca.

14. Saxagliptin / Renal Impairment _____ _____

Alert Message: The recommended dose of Onglyza (saxagliptin) is 2.5 mg once daily for patients with moderate or severe renal impairment, or with end-stage renal disease (ESRD) requiring hemodialysis. Assessment of renal function is recommended prior to initiation of saxagliptin therapy and periodically thereafter.

Conflict Code: ER - Overutilization
Drug/Disease:

Util A	Util B	Util C (Include)
Saxagliptin		Renal Impairment

Maximum Dose: 2.5 mg/day

References:
Onglyza Prescribing Information, July 2009, Bristol-Myers Squibb/AstraZeneca.

15. Saxagliptin / Nonadherence _____ _____

Alert Message: Non-adherence to Onglyza (saxagliptin) therapy may result in loss of glycemic control and an increased risk of developing adverse diabetic-related complications.

Conflict Code: LR - Nonadherence
Drug/Disease:

Util A	Util B	Util C
Saxagliptin		

References:
Onglyza Prescribing Information, July 2009, Bristol-Myers Squibb/AstraZeneca.

16. Saxagliptin / Strong 3A4/5 Inhibitors _____ _____

Alert Message: The dose of Onglyza (saxagliptin) should be limited to 2.5 mg daily when coadministered with strong CYP3A4/5 inhibitors (e.g., ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, ritonavir, saquinavir, and telithromycin). Concurrent use of saxagliptin with a strong 3A4/5 inhibitor may result in significantly elevated saxagliptin levels and risk of adverse events.

Conflict Code: ER - Overutilization
Drug/Disease:

Util A	Util B	Util C (Include)
Saxagliptin		Ketoconazole
		Itraconazole
		Clarithromycin
		Telithromycin
		Indinavir
		Ritonavir
		Saquinavir
		Nelfinavir
		Atazanavir
		Nefazodone

Maximum Dose: 2.5 mg/day

References:
Onglyza Prescribing Information, July 2009, Bristol-Myers Squibb/AstraZeneca.

17. Saxagliptin / Sulfonylureas _____ _____

Alert Message: The concurrent use of Onglyza (saxagliptin) 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 Interaction
Drug/Disease:

Util A	Util B	Util C
Saxagliptin	Chlorpropamide	
	Tolbutamide	
	Tolazamide	
	Glyburide	
	Glipizide	
	Glimepiride	

References:
Onglyza Prescribing Information, July 2009, Bristol-Myers Squibb/AstraZeneca.

18. Saxagliptin / Sitagliptin _____ _____

Alert Message: Therapeutic duplication of dipeptidyl peptidase-4 inhibitor therapy may be occurring.

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

Util A	Util B	Util C
Saxagliptin	Sitagliptin	

References:
Onglyza Prescribing Information, July 2009, Bristol-Myers Squibb/AstraZeneca.
Januvia Prescribing Information, July 2008, Merck & Co., Inc.

19. Asenapine / Overutilization _____ _____

Alert Message: The recommended starting and target dose of Saphris (asenapine) for the treatment of schizophrenia is 5 mg sublingually twice daily. In controlled trials, there was no indication of added benefit with a higher dose, but there was a clear increase in certain adverse reactions. The safety of doses above 10 mg twice daily has not been evaluated in clinical trials.

Conflict Code: ER – Overutilization
Drugs/Disease:

Util A	Util B	Util C (Include)
Asenapine		Schizophrenia

Max Dose: 10 mg/day

Reference:
Saphris Prescribing Information, August 2009, Schering-Plough.

20. Asenapine / Overutilization _____ _____

Alert Message: The recommended starting dose of Saphris (asenapine) for the treatment of bipolar disorder is 10 mg sublingually twice daily. The dose can be decreased to 5 mg twice daily if there are adverse effects. The safety of doses above 10 mg twice daily has not been evaluated in clinical trials.

Conflict Code: ER – Overutilization
Drugs/Disease:

Util A	Util B	Util C (Include)
Asenapine		Bipolar Disorder

Max Dose: 20 mg/day

Reference:
Saphris Prescribing Information, August 2009, Schering-Plough.

21. Asenapine / Nonadherence _____ _____

Alert Message: Nonadherence to the prescribed therapy with Saphris (asenapine) may lead to decreased patient outcomes and additional medical cost.

Conflict Code: LR - Nonadherence
Drugs/Disease:

Util A	Util B	Util C
Asenapine		

Reference:
Saphris Prescribing Information, August 2009, Schering-Plough.
Theida P, Beard S, Richter A, et.al., An Economic Review of Compliance with Medication Therapy in the Treatment of Schizophrenia, Psychiatric Services, 2003;54:508-516.
Weiden PJ, Olfson M, Cost of Relapse in Schizophrenia, Schizophrenia Bulletin, 1995; 21(3):419-29.
Perkins DO, Predictors of Noncompliance in Patients with Schizophrenia, J Clin Psychiatry, 2002; 63:1121-1128.

22. Asenapine / Seizures _____ _____

Alert Message: Saphris (asenapine) should be used with caution in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Conflict Code: DB – Drug/Disease or Drug Inferred Disease Precaution
Drugs/Disease:

Util A	Util B	Util C
Asenapine	Seizures	
	Convulsions	
	Epilepsy	
	Alzheimer's	
	Anticonvulsants	

Reference:
Saphris Prescribing Information, August 2009, Schering-Plough.

23. Asenapine / Orthostatic Hypotension _____ _____

Alert Message: Saphris (asenapine) can produce hypotension and syncope due to its alpha-1 adrenergic antagonist activity. Asenapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions that predispose a patient to hypotension (e.g., dehydration, hypovolemia, and antihypertensive medications) and the elderly.

Conflict Code: DB – Drug/Disease or Drug Inferred Disease Precaution
Drugs/Disease:

Util A	Util B		Util C
Asenapine	Heart Failure	CCBs	
	Myocardial Infarction	ARBs	
	Conduction Abnormalities	Diuretics	
	Dehydration	Antiadrenergic Antihypertensives	
	Hypovolemia	Beta Blockers	
	ACE Inhibitors	Direct Renin Inhibitors	
	Selective Aldosterone Receptor Antagonist		

References:
Saphris Prescribing Information, August 2009, Schering-Plough.

24. Asenapine / Hyperprolactinemia _____ _____

Alert Message: Saphris (asenapine) like other dopamine-2 antagonists can elevate prolactin levels initially and during chronic administration. Prolactin elevating agents may cause galactorrhea, amenorrhea, gynecomastia, impotence, and decreased bone density.

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

Util A	Util B	Util C
Asenapine	Hyperprolactinemia	
	Galactorrhea	
	Amenorrhea	
	Gynecomastia	
	Impotence	
	Osteoporosis	

References:
Saphris Prescribing Information, August 2009, Schering-Plough.

25. Asenapine / Fluvoxamine _____ _____

Alert Message: Caution should be exercised when co-administering Saphris (asenapine), a CYP1A2 substrate, with the potent CYP1A2 inhibitor fluvoxamine. Concurrent therapy with the agents may result in elevated asenapine plasma concentrations and risk of adverse effects.

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

Util A	Util B	Util C
Asenapine	Fluvoxamine	

References:
Saphris Prescribing Information, August 2009, Schering-Plough.

26. Asenapine / Paroxetine _____ _____

Alert Message: Caution should be exercised when co-administering Saphris (asenapine), a weak CYP2D6 inhibitor, with paroxetine (a CYP2D6 substrate and potent inhibitor). Coadministration of paroxetine 20 mg with asenapine 5mg twice daily has been shown to result in an almost 2-fold increase in paroxetine exposure. Asenapine may also enhance the inhibitory effects of paroxetine on its own metabolism.

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

Util A	Util B	Util C
Asenapine	Paroxetine	

References:
Saphris Prescribing Information, August 2009, Schering-Plough.

27. Asenapine / Other Drugs that are both 2D6 Substrates & Inhibitors _____ _____

Alert Message: Caution should be exercised when co-administering Saphris (asenapine), a weak CYP2D6 inhibitor, with drugs that are both substrates and inhibitors of CYP2D6 (e.g., fluoxetine and duloxetine). Concurrent therapy with asenapine may cause increases in the levels of the 2D6 substrate/inhibitor. Asenapine may also enhance the inhibitory effects of the other drugs on its own metabolism.

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

Util A	Util B	Util C
Asenapine	Fluoxetine	
	Duloxetine	

References:
Saphris Prescribing Information, August 2009, Schering-Plough.
Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine, Division of Clinical Pharmacology.

28. Asenapine / QT Prolongation (ICD-9s) _____ _____

Alert Message: Saphris (asenapine) has been shown to cause a 2 to 5 msec increase in the QTc interval. Asenapine use should be avoided in patients with congenital long QT syndrome, a history of cardiac arrhythmias, bradycardia, hypokalemia or hypomagnesemia, and in patients receiving any drug that prolongs the QTc interval (e.g., Class IA & III antiarrhythmics, antipsychotics, macrolides and fluoroquinolones).

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

Util A	Util B	Util C
Asenapine	QT Prolongation	
	Cardiac Arrhythmias	
	Bradycardia	
	Hypokalemia	
	Hypomagnesemia	

References:
Saphris Prescribing Information, August 2009, Schering-Plough.

29. Asenapine / Hepatic Impairment _____ _____

Alert Message: Saphris (asenapine) is not recommended in patients with severe hepatic impairment. In a study of subjects with hepatic impairment who were treated with a single 5 mg dose of asenapine the patients with severe hepatic impairment (Child-Pugh C) experienced a 7-fold increase in asenapine concentrations as compared to subjects with normal hepatic function. Study results indicated no dosage adjustment for patients with mild to moderate hepatic impairment.

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

Util A	Util B	Util C
Asenapine	Severe Hepatic Impairment	

References:
Saphris Prescribing Information, August 2009, Schering-Plough.

30. Asenapine / QT Prolongation Drugs _____ _____

Alert Message: Saphris (asenapine) has been shown to cause a 2 to 5 msec increase in the QTc interval. Asenapine use should be avoided in patients with congenital long QT syndrome, a history of cardiac arrhythmias, bradycardia, hypokalemia or hypomagnesemia, and in patients receiving any drug that prolongs the QTc interval (e.g., Class IA & III antiarrhythmics, antipsychotics, macrolides and fluoroquinolones).

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

Util A	Util B			
Asenapine	Foscarnet	Perphenazine	Pentamidine	Paliperidone
	Fosphenytoin	Fluphenazine	Pimozide	Ziprasidone
	Alfuzosin	Granisetron	Quetiapine	Amitriptyline
	Amantadine	Haloperidol	Quinidine	Amoxapine
	Amiodarone	Ibutilide	Ranolazine	Clomipramine
	Arsenic Trioxide	Indapamide	Risperidone	Desipramine
	Atazanavir	Isradipine	Salmeterol	Doxepin
	Azithromycin	Itraconazole	Sertraline	Imipramine
	Chloral Hydrate	Ketoconazole	Solifenacin	Nortriptyline
	Chlorpromazine	Lapatinib	Sotalol	Protriptyline
	Clozapine	Levofloxacin	Tacrolimus	Trimipramine
	Disopyramide	Lithium	Tamoxifen	Propafenone
	Dofetilide	Methadone	Telithromycin	Procainamide
	Dolasetron	Moexipril/HCTZ	Thioridazine	Gemifloxacin
	Droperidol	Moxifloxacin	Tizanidine	Fluoxetine
	Erythromycin	Nicardipine	Tolterodine	Dronedarone
	Felbamate	Nilotinib	Vardenafil	Mexiletine
	Flecainide	Octreotide	Venlafaxine	Clarithromycin
	Fluconazole	Ondansetron	Voriconazole	Erythromycin
	Gemifloxacin	Norfloxacin	Ciprofloxacin	Iloperidone

References:
Saphris Prescribing Information, August 2009, Schering-Plough.

31. Iloperidone / Over-utilization _____ _____

Alert Message: The maximum recommended dose of Fanapt (iloperidone) is 12 mg twice daily (24 mg/day). Doses above 24 mg/day have not been systematically evaluated in clinical trials. Iloperidone must be titrated slowly from a low starting dose (1 mg twice daily) to avoid orthostatic hypotension.

Conflict Code: ER – Over Utilization
Drug/Disease

Util A	Util B	Util C (Negating – Potent 2D6 & 3A4 Inhibitors)			
Iloperidone		Bupropion	Indinavir	Itraconazole	Telithromycin
		Fluoxetine	Nelfinavir	Ketoconazole	Clarithromycin
		Paroxetine	Ritonavir	Nefazodone	
		Quinidine	Saquinavir		

Max Dose: 24 mg/day

References:
Fanapt Prescribing Information, May 2009, Vanda Pharmaceuticals Inc.
Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). http://medicine.iupui.edu/clinpharm/ddis/table.asp. Accessed June 09, 2009.

32. Iloperidone / Nonadherence _____ _____

Alert Message: Nonadherence to the prescribed antipsychotic therapy with Fanapt (iloperidone) may lead to decreased patient outcomes and additional medical cost.

Conflict Code: LR – Nonadherence
Drug/Disease

Util A	Util B	Util C
Iloperidone		

References:
Fanapt Prescribing Information, May 2009, Vanda Pharmaceuticals Inc.

33. Iloperidone / Potent 2D6 and/or 3A4 Inhibitors _____ _____

Alert Message: The dose of Fanapt (iloperidone) should be reduced by one-half when administered concomitantly with a strong CYP2D6 and/or CYP3A4 inhibitor. Iloperidone is metabolized by both CYP2D6 and CYP3A4 enzymes and concurrent therapy with these agents may cause increased iloperidone blood levels leading to adverse effects (e.g., QT prolongation, hypotension and tachycardia). If the inhibitor agent is withdrawn from combination therapy the iloperidone dose should be increased.

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

Util A	Util B	Util C (Inclusive)			
Iloperidone		Bupropion	Indinavir	Itraconazole	Telithromycin
		Fluoxetine	Nelfinavir	Ketoconazole	
		Paroxetine	Ritonavir	Nefazodone	
		Quinidine	Clarithromycin	Saquinavir	

Max Dose: 12 mg/day

References:
Fanapt Prescribing Information, May 2009, Vanda Pharmaceuticals Inc.
Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). http://medicine.iupui.edu/clinpharm/ddis/table.asp.

34. Iloperidone / QT Prolongation or Problems Associated w/ Prolongation _____ _____

Alert Message: Fanapt (iloperidone) prolongs the QT interval and may be associated with arrhythmias and sudden death. Avoid the use of iloperidone in patients who have congenital prolongation of the QT interval, a recent acute myocardial infarction, cardiac arrhythmia, hypokalemia and/or uncompensated heart failure.

Conflict Code: MC – Drug (Actual) Disease Precaution
Drug/Disease

Util A	Util B	Util C
Iloperidone	Prolongation of QT Interval	
	Myocardial Infarction	
	Uncompensated Heart Failure	
	Hypokalemia	
	Arrhythmias	

References:
Fanapt Prescribing Information, May 2009, Vanda Pharmaceuticals Inc.

35. Iloperidone / QT Prolongation Drugs _____ _____

Alert Message: Fanapt (iloperidone) prolongs the QT interval and may be associated with arrhythmias and sudden death. Avoid the use of iloperidone in combination with drugs that are known to prolong the QTc or inhibit iloperidone metabolism.

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

Util A	Util B				Util C
Iloperidone	Foscarnet	Perphenazine	Pentamidine	Paliperidone	
	Fosphenytoin	Fluphenazine	Pimozide	Ziprasidone	
	Alfuzosin	Granisetron	Quetiapine	Amitriptyline	
	Amantadine	Haloperidol	Quinidine	Amoxapine	
	Amiodarone	Ibutilide	Ranolazine	Clomipramine	
	Arsenic Trioxide	Indapamide	Risperidone	Desipramine	
	Atazanavir	Isradipine	Salmeterol	Doxepin	
	Azithromycin	Itraconazole	Sertraline	Imipramine	
	Chloral Hydrate	Ketoconazole	Solifenacin	Nortriptyline	
	Chlorpromazine	Lapatinib	Sotalol	Protriptyline	
	Clozapine	Levofloxacin	Tacrolimus	Trimipramine	
	Disopyramide	Lithium	Tamoxifen	Propafenone	
	Dofetilide	Methadone	Telithromycin	Procainamide	
	Dolasetron	Moexipril/HCTZ	Thioridazine	Gemifloxacin	
	Droperidol	Moxifloxacin	Tizanidine	Fluoxetine	
	Erythromycin	Nicardipine	Tolterodine	Dronedarone	
	Felbamate	Nilotinib	Vardenafil	Mexiletine	
	Flecainide	Octreotide	Venlafaxine	Clarithromycin	
	Fluconazole	Ondansetron	Voriconazole	Erythromycin	
	Gemifloxacin	Norfloxacin	Ciprofloxacin	Asenapine	

References:
Fanapt Prescribing Information, May 2009, Vanda Pharmaceuticals Inc.
ArizonaCERT: Drugs That Prolong the QT Interval and/or Induce Torsades de Pointes
Available at: http://www.azcert.org/consumers/interaction-advisory.cfm

36. Iloperidone / Hepatic Impairment _____ _____

Alert Message: Fanapt (iloperidone) is not recommended for use in patients with hepatic impairment. No study has been conducted in patients with mild or moderate liver impairment.

Conflict Code: MC – Drug (Actual) Disease Precaution

Drug/Disease

Util A	Util B	Util C
Iloperidone	Hepatic Impairment	

References:

Fanapt Prescribing Information, May 2009, Vanda Pharmaceuticals Inc.

37. Iloperidone / Alpha1-Adrenergic Receptor Blockers _____ _____

Alert Message: Due to its alpha-1adrenergic receptor antagonist properties, Fanapt (iloperidone) has the potential to enhance the effect of certain antihypertensive agents that have the same mechanism of action and may result in problematic hypotension.

Conflict Code: DD – Drug/Drug Interaction

Drug/Disease

Util A	Util B	Util C
Iloperidone	Silodosin	
	Prazosin	
	Terazosin	
	Doxazosin	
	Tamsulosin	
	Alfuzosin	

References:

Fanapt Prescribing Information, May 2009, Vanda Pharmaceuticals Inc.