DUR Board Meeting
March 8, 2010
Pioneer Room
State Capitol

1pm

North Dakota Medicaid
DUR Board Meeting
Agenda
Pioneer Room
State Capitol
March 8, 2010
1pm

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

2. Old business
    - Review and approval of minutes of 12/07/09 meeting — Chairman
    - Budget update — Brendan
    - Yearly PA review — HID
        - Antihistamines
        - PPIs
        - COX-II/NSAIDs
        - Revatio
        - Acto*plus* Met
        - Ophthalmic Anti-infectives

3. New business
    - Intuniv — HID
    - Xolair — HID
    - Suboxone/Subutex — HID
    - Elidel/Protopic — HID
    - Criteria recommendations — Brendan
    - 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
December 7, 2009

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
Members Absent: Todd Twogood, Leann Ness, Kim Krohn
Medicaid Pharmacy Department: Brendan Joyce, Gary Betting
HID Staff Present: Candace Rieth

Chair, J. Hostetter called the meeting to order at 1:10 pm. Chair, J. Hostetter asked for a motion to approve the minutes from the September meeting. G. Pfister moved that the minutes be approved and J. Savageau 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 for the next biennium would be approximately 50 million dollars. The number of recipients eligible for Medicaid benefits has increased to approximately 60 thousand. This may be related to new legislation passed this session allowing continuous eligibility for children.

Hemophilia Second Review
At the September meeting a motion was made to place medications used to treat hemophilia on prior authorization. This is the second review. There was no public comment. Chair, J. Hostetter called for a voice vote on the original motion. Motion passed with no audible dissent.

Sancuso Second Review
At the September meeting a motion was made to place Sancuso on prior authorization. This is the second review. There was no public comment. Chair, J. Hostetter called for a voice vote on the original motion. Motion passed with no audible dissent.

Relistor Second Review
At the September meeting a motion was made to place Relistor on prior authorization. This is the second review. There was no public comment. Chair, J. Hostetter called for a voice vote on the original motion. Motion passed with no audible dissent.

Nuvigil Second Review
At the September meeting a motion was made to place Nuvigil on prior authorization. This is the second review. There was no public comment. A clarification was made to the form and criteria that Nuvigil will need to be prescribed for an approved indication and a patient will need to fail a trial of Provigil before a prior authorization will be approved for Nuvigil. Chair, J. Hostetter called for a voice vote on the original motion. Motion passed with no audible dissent.

Nucynta Second Review
At the September meeting a motion was made to place Nucynta on prior authorization. This is the second review. There was no public comment. Chair, J. Hostetter called for a voice vote on the original motion. Motion passed with no audible dissent.

Yearly PA Review
The Board reviews products annually that have previously been placed on prior authorization. This allows the Board a chance to update the prior authorization forms and criteria. Solodyn, Oracea, Oxycontin, Vusion, and Short-acting beta-agonist forms and criteria were reviewed. No changes were made to the forms or criteria.

Review of Top Drugs and Drug Classes

B. Joyce reviewed the top drugs and drug classes with Board members. When reviewing the top classes by claims cost, the classes that are in the top 5 include antipsychotics, anticonvulsants, antidepressants, cerebral stimulants, and amphetamines. All of these classes are exempt from prior authorization because of legislation. Board members reviewed a list of the top classes by number of claims and the top classes include antidepressants, opiate agonists, anticonvulsants, sedative-hypnotics and antipsychotics. The board has placed Oxycontin (which is an opiate agonist) and Sedative-Hypnotics on prior authorization, but because of legislation the board is unable to place antidepressants, anticonvulsants and antipsychotics on prior authorization. Board members were asked to review these lists prior to the next meeting and give the Department ideas for educational endeavors or candidates for prior authorization.

Stimulant Utilization in children ≤ 5

B. Joyce reviewed stimulant medication utilization in children ≤ 5. The number of recipients in this group grew from zero in 2003 to 85 during the first half of 2009. Board members discussed that more children are in preschool and all day kindergarten. C. McCleary also mentioned that screenings are being performed on a wider scale than in the past.

Criteria Recommendations

The recommended RDUR criteria enclosed in the packet were developed from product information provided by the manufacturers and usually are consistent with new indications, new drugs added, new warnings, etc. These proposed criteria will be added to the current set of criteria, and will be used in future DUR cycles. N. Byers moved to approve the new criteria and J. Savageau 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 March 9, 2010. N. Byers made a motion to adjourn the meeting. C. Huber seconded. The motion passed with no audible dissent. Chair J. Hostetter adjourned the meeting at 2:23 pm.

HEALTH INFORMATION DESIGNS

Prior Authorization Vendor for ND Medicaid

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

***Note:**

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

Part I: TO BE COMPLETED BY PRESCRIBER

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

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

Qualifications for coverage:

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

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

Prescriber Signature: Date:

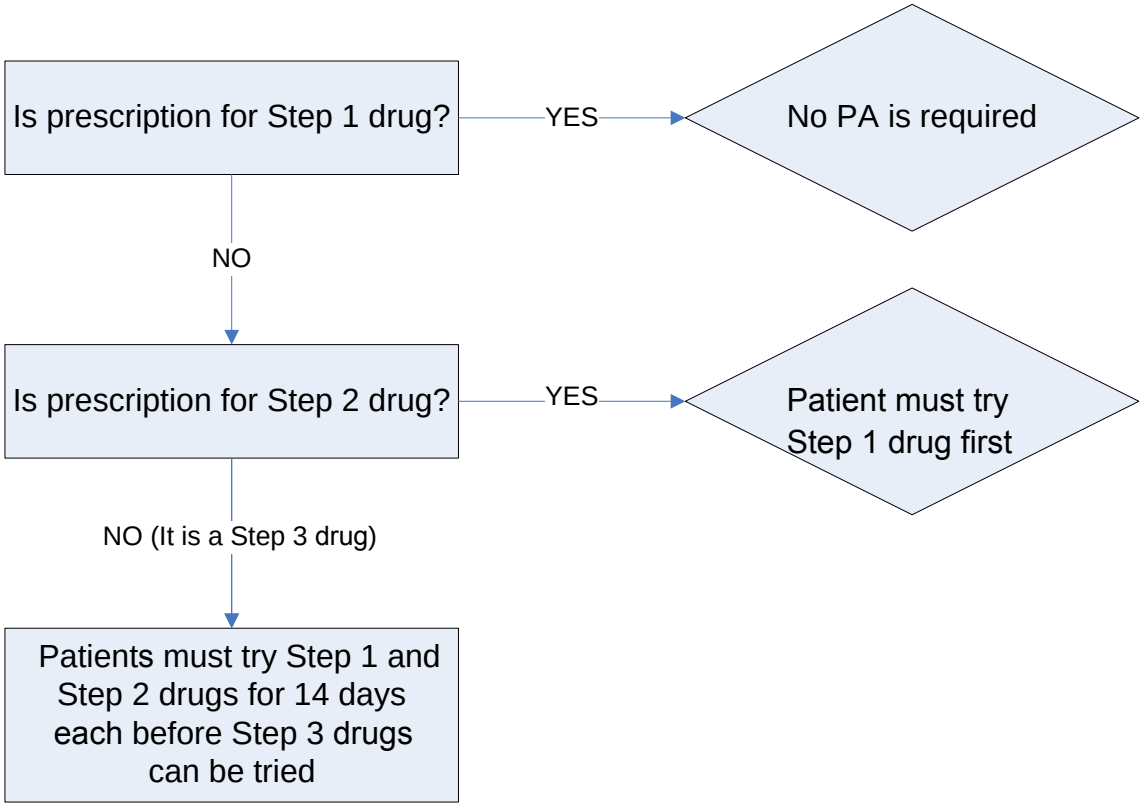
Part II: TO BE COMPLETED BY PHARMACY

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

Part III: FOR OFFICIAL USE ONLY

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

North Dakota Department of Human Services
Antihistamine Authorization Criteria Algorithm



Please Note:

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

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

NORTH DAKOTA MEDICAID
Percentage Market Share Within Sub-Classes
Antihistamine

	FEB 04	SEP 09
All Antihistamine (No Subclass)		
ALLEGRA	25.95	0.00
ALLEGRA-D	0.00	0.00
ALLEGRA-D 12 HOUR	8.65	0.00
ALLEGRA-D 24 HOUR	0.00	0.00
CETIRIZINE HCL	0.00	40.83
CLARINEX	6.51	0.18
CLARINEX-D 24 HOUR	0.00	0.00
CLARITIN	0.84	1.27
CLARITIN-D 12 HOUR	0.37	0.00
CLARITIN-D 24 HOUR	0.09	0.00
FEXOFENADINE HCL	0.00	5.99
LORATADINE	9.58	50.27
LORATADINE D	0.00	0.00
LORATADINE-D	0.00	0.00
XYZAL	0.00	0.36
ZYRTEC	42.42	1.09
ZYRTEC-D	5.58	0.00

HEALTH INFORMATION DESIGNS

Prior Authorization Vendor for ND Medicaid

Proton Pump Inhibitor PA Form

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

ND Medicaid requires that patients receiving proton pump inhibitors must use Prilosec OTC or Omeprazole as first line.

****Note:***

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

Part I: TO BE COMPLETED BY PRESCRIBER

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

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

Qualifications for coverage:

❑ Failed omeprazole therapy	Start Date:	Dose:
	End Date:	Frequency:
□ Pregnancy – Due Date		
□ Inability to take or tolerate oral tablets (must check a box) □ Tube Fed □ Requires soft food or liquid administration □ Other (provide description)		
□ Adverse reaction (attach FDA Medwatch form) to omeprazole.		
□ *I confirm that I have considered a generic or other alternative and that the requested drug is expected to result in the successful medical management of the recipient.*		
Prescriber Signature:		Date:

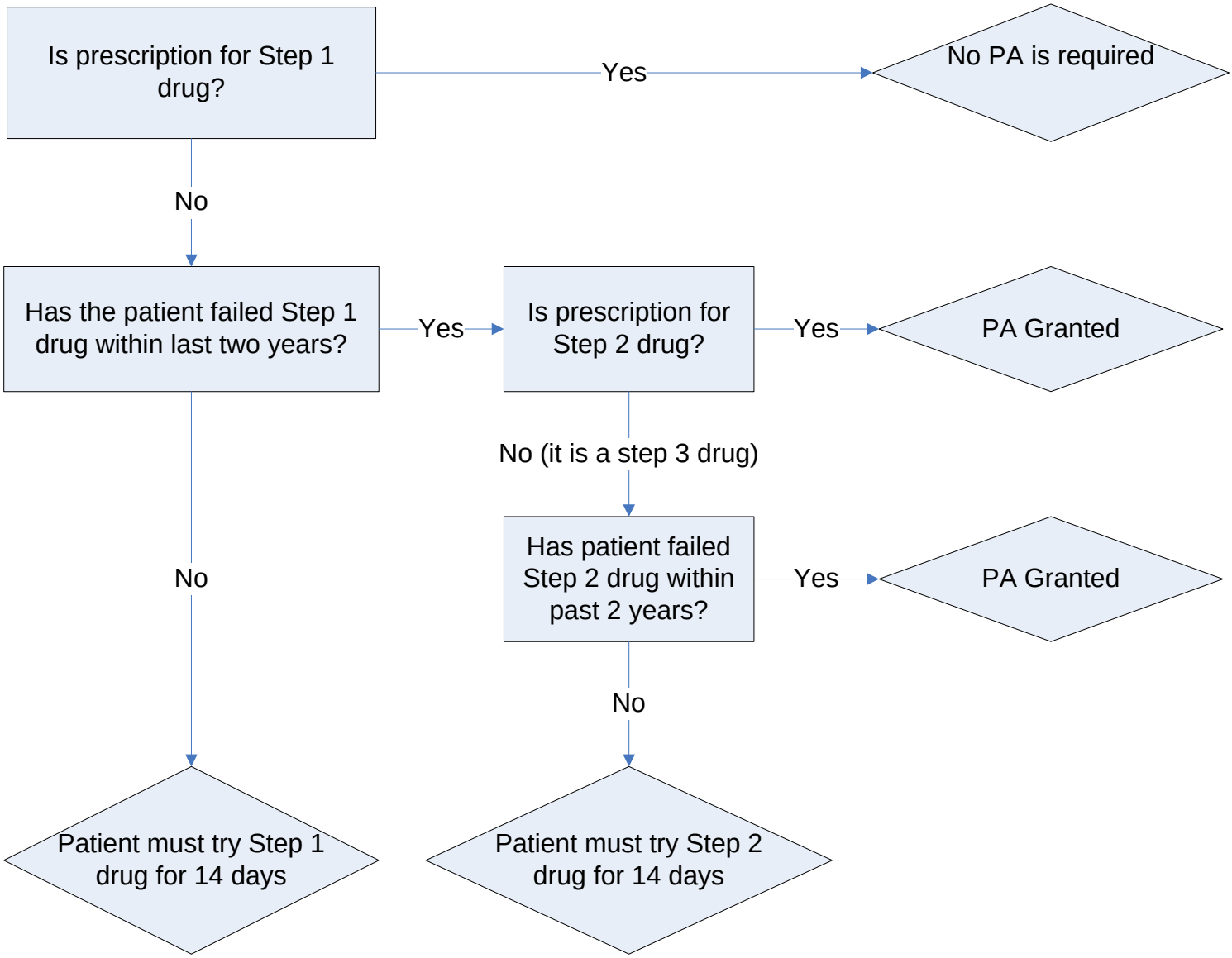
Part II: TO BE COMPLETED BY PHARMACY

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

Part III: FOR OFFICIAL USE ONLY

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

North Dakota Department of Human Services
Proton Pump Inhibitor Authorization Criteria Algorithm



Please Note:

Step 1 drug is defined as Prilosec OTC and omeprazole

Step 2 drug is defined as Protonix, Prevacid (which is 3 times more expensive)

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

NORTH DAKOTA MEDICAID
Percentage Market Share Within Sub-Classes
Proton Pump Inhibitors

	FEB 04	SEP 09
All Proton Pump Inhibitors (No Subclass)		
ACIPHEX	4.93	0.95
KAPIDEX	0.00	0.00
NEXIUM	12.23	3.24
NEXIUM I.V.	0.00	0.00
OMEPRAZOLE	8.29	73.43
PANTOPRAZOLE SODIUM	0.00	6.00
PREVACID	23.88	12.38
PREVACID IV	0.00	0.00
PRILOSEC	2.06	0.00
PRILOSEC OTC	20.88	3.71
PROTONIX	27.73	0.29
PROTONIX IV	0.00	0.00

HEALTH INFORMATION DESIGNS

Prior Authorization Vendor for ND Medicaid

BRAND NAME NSAID/COX-II PA FORM

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

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

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

- **Failed two trials of prescribed NSAID**
- **Recipient is on warfarin or corticosteroid therapy**
- **Recipient has history of gastric or duodenal ulcer or has comorbidities of GI bleed, perforation or obstruction**
- **Recipient has history of endoscopically documented NSAID induced gastritis with GI bleed**

Part I: TO BE COMPLETED BY PRESCRIBER

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

Requested Drug and Dosage:	**Diagnosis for this request:**	
□ Celebrex	□ Warfarin/Corticosteroid therapy	□ GI bleed, perforation or obstruction
□ Other _____	□ Gastric or duodenal ulcer	□ Endoscopically documented NSAID gastritis with GI Bleed

Qualifications for coverage:

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

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

Prescriber Signature	Date

Part II: TO BE COMPLETED BY PHARMACY

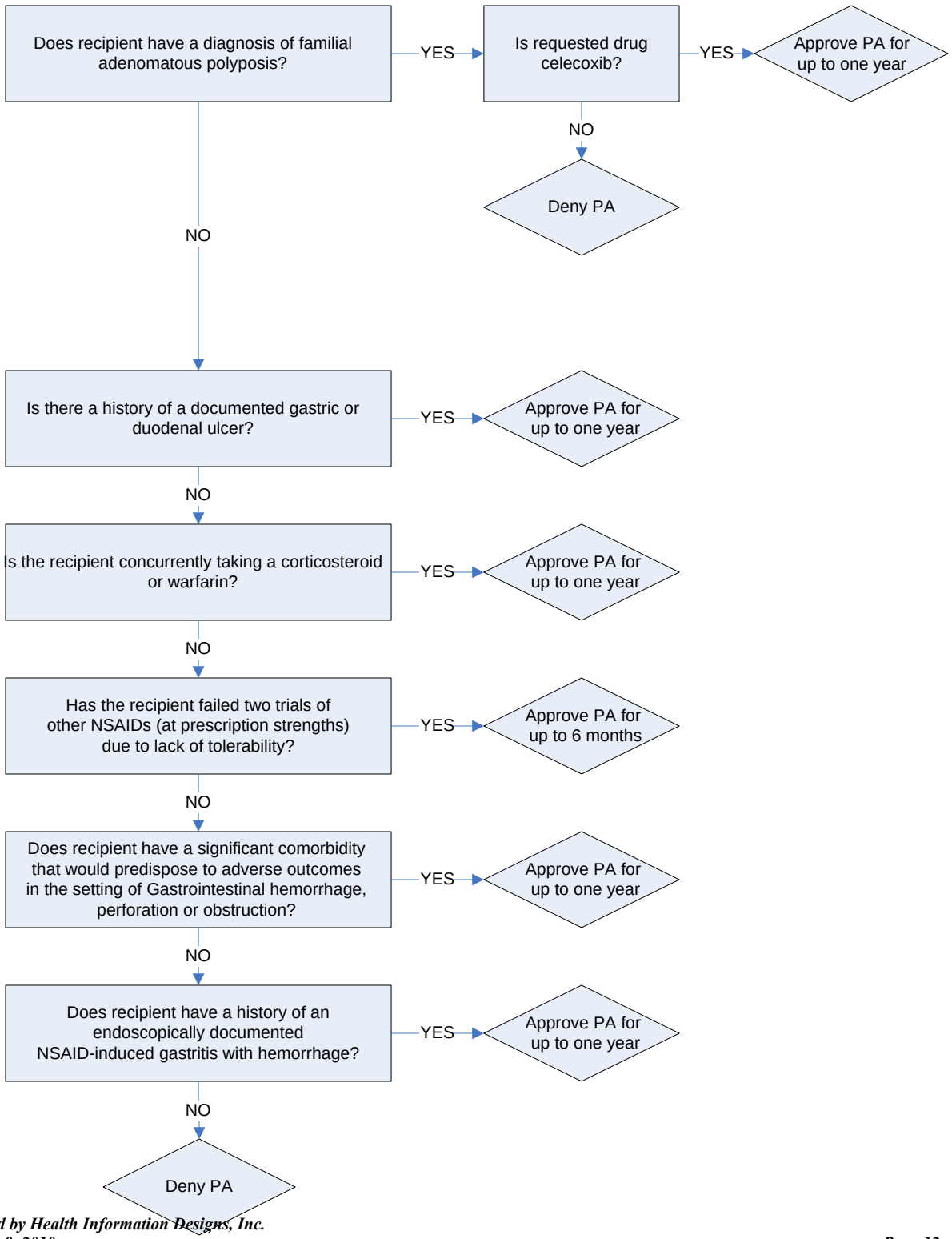
PHARMACY NAME:			ND MEDICAID PROVIDER NUMBER:
TELEPHONE NUMBER	FAX NUMBER	DRUG	NDC #

Part III: FOR OFFICIAL USE ONLY

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

North Dakota Department of Human Services

Name Brand NSAID/COX-II Authorization Algorithm



NORTH DAKOTA MEDICAID
Percentage Market Share Within Sub-Classes
NSAIDS/COXII

	FEB 04	FEB 05	SEP 09
All NSAIDS/COXII (No Subclass)			
ARTHROTEC 50	0.69	0.85	0.00
ARTHROTEC 75	0.47	0.75	0.19
BEXTRA	14.04	15.14	0.00
CELEBREX	30.28	28.78	3.27
CLINORIL	0.00	0.00	0.00
DICLOFENAC POTASSIUM	0.65	1.29	4.71
DICLOFENAC SODIUM	0.78	1.89	4.62
DIFLUNISAL	0.04	0.20	0.00
DOLOBID	0.00	0.00	0.00
EC-NAPROSYN	0.00	0.00	0.00
ETODOLAC	0.60	1.39	2.21
FELDENE	0.00	0.00	0.00
FENOPROFEN CALCIUM	0.00	0.00	0.00
FLECTOR	0.00	0.00	0.10
FLURBIPROFEN	0.09	0.75	0.58
FLURBIPROFEN SODIUM	0.00	0.00	0.00
HYDROCODONE BIT-IBUPROFEN	3.01	3.44	5.58
IBUPROFEN	16.88	23.61	40.87
IBUPROFEN CHILD	0.00	0.00	0.00
IBUPROFEN IB	0.00	0.00	0.00
IBUPROFEN M	0.00	0.00	0.00
IBUPROFEN PMR	0.00	0.00	0.00
INDOCIN	0.00	0.00	0.00
INDOCIN SR	0.00	0.00	0.00
INDOMETHACIN	1.42	1.69	1.83
KETOPROFEN	1.68	1.84	2.40
KETOROLAC TROMETHAMINE	2.07	1.74	3.17
LODINE	0.00	0.00	0.00
LODINE XL	0.00	0.00	0.00
MECLOFENAMATE SODIUM	0.04	0.20	0.29
MECLOMEN	0.00	0.00	0.00
MELOXICAM	0.00	0.00	5.29
MOBIC	0.86	3.24	0.00
MOTRIN	0.39	0.05	0.10
MOTRIN IB	0.00	0.00	0.00
MOTRIN MIGRAINE	0.00	0.00	0.00
NABUMETONE	1.64	3.04	1.83
NAPRELAN	0.00	0.00	0.00
NAPROSYN	0.17	0.10	0.00
NAPROXEN	5.17	6.57	16.35
NAPROXEN SODIUM	0.95	1.00	1.35
OXAPROZIN	0.39	0.50	1.15
PIROXICAM	0.26	0.85	3.85
PONSTEL	0.04	0.10	0.00
RELAFEN	0.04	0.00	0.00
SOLARAZE	0.00	0.00	0.00

SULINDAC	0.56	0.55	0.19
TOLECTIN 200	0.00	0.00	0.00
TOLECTIN 600	0.00	0.00	0.00
TOLECTIN DS	0.00	0.00	0.00
TOLMETIN SODIUM	0.17	0.05	0.00
TORADOL	0.00	0.00	0.00
VICOPROFEN	0.34	0.10	0.00
VIOXX	16.02	0.00	0.00
VOLTAREN	0.26	0.30	0.10
VOLTAREN-XR	0.00	0.00	0.00

Revatio/Adcirca
Prior Authorization Form

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

Prior Authorization Vendor for ND Medicaid

ND Medicaid requires that patients receiving Revatio or Adcirca must have a diagnosis of Pulmonary Arterial Hypertension based on WHO (Group I) Classification for Pulmonary Hypertension.

****Note:***

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

Part I: TO BE COMPLETED BY PRESCRIBER

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

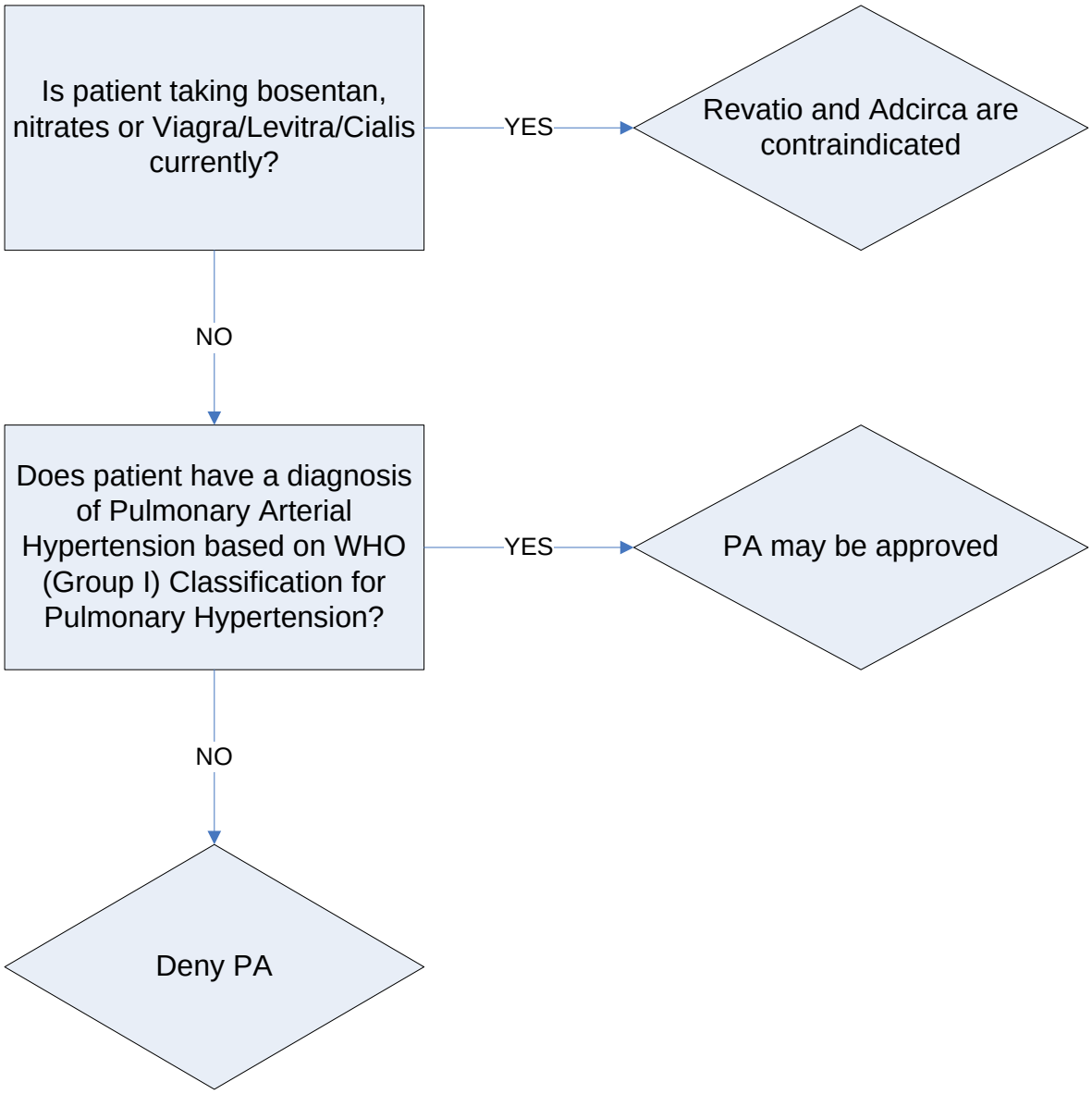
Part II: TO BE COMPLETED BY PHARMACY

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

Part III: FOR OFFICIAL USE ONLY

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

North Dakota Department of Human Services
Revatio/Adcirca Authorization Algorithm



ACTO*plus* met Prior Authorization

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

Prior Authorization Vendor for ND Medicaid

ND Medicaid requires that patients receive Actos and Metformin separately.
Note:

- ***Actos does not require PA***
- ***Metformin does not require PA***
- ***Patients must fail therapy on Actos and Metformin separately before a PA may be granted***

Part I: TO BE COMPLETED BY PRESCRIBER

Recipient Name	Recipient Date of Birth	Recipient Medicaid ID Number	
Prescriber Name			
Prescriber Medicaid Provider Number	Telephone Number	Fax Number	
Address	City	State	Zip Code
Requested Drug and Dosage: □ **ACTO*plus* met**	**Diagnosis for this request:**		
Qualifications for coverage:			
□ Failed both drugs separately	Start Date: End Date:	Dose: Frequency:	
Prescriber Signature		Date	

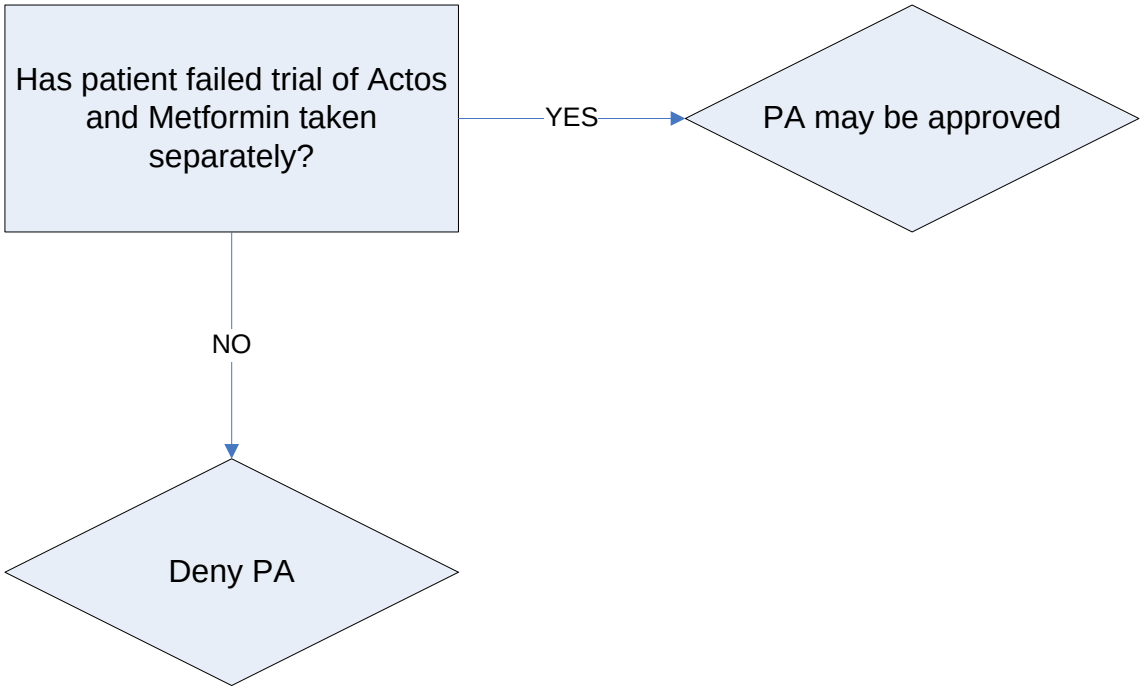
Part II: TO BE COMPLETED BY PHARMACY

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

Part III: FOR OFFICIAL USE ONLY

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

North Dakota Department of Human Services
ACTO*plus met* Authorization Algorithm



OPHTHALMIC ANTI-INFECTIVE PA FORM

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

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

Part I: TO BE COMPLETED BY PRESCRIBER

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

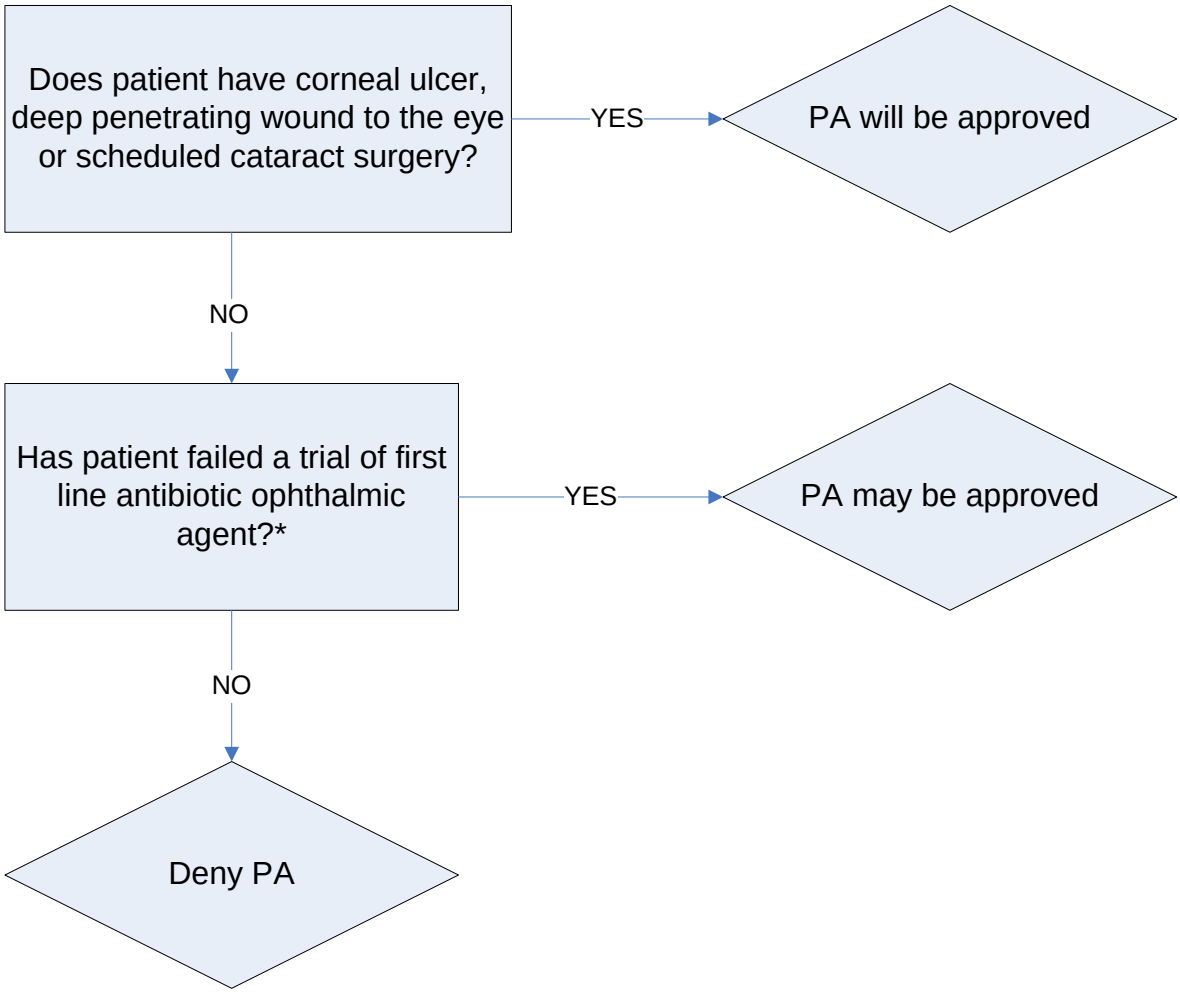
Part II: TO BE COMPLETED BY PHARMACY

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

Part III: FOR OFFICIAL USE ONLY

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

North Dakota Department of Human Services
Ophthalmic Anti-infective Authorization Algorithm



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

NORTH DAKOTA MEDICAID
Percentage Market Share Within Sub-Classes
Ophthalmic Agents

	FEB 04	OCT 06	SEP 09
All Ophthalmic Agents (No Subclass)			
AK-CHLOR	0.00	0.00	0.00
AK-POLY-BAC	0.00	0.00	0.00
AK-SPORE	0.00	0.00	0.00
AK-SULF	0.00	0.00	0.00
AK-TRACIN	0.00	0.00	0.00
AKTOB	0.23	0.69	0.00
ALBA-3	0.00	0.00	0.00
AZASITE	0.00	0.00	0.00
BACITRACIN	1.62	0.34	1.13
BACITRACIN-POLYMYXIN	2.54	0.34	0.00
BACITRACIN/POLYMYXIN	0.00	0.00	0.00
BACITRACIN/POLYMYXIN B	0.00	0.00	0.00
CETAMIDE	0.00	0.00	0.00
CHLORAMPHENICOL	0.00	0.00	0.00
CHLOROMYCETIN	0.00	0.00	0.00
CILOXAN	20.09	1.72	1.51
CIPROFLOXACIN HCL	0.00	4.83	10.57
ERYTHROMYCIN	13.63	7.93	12.08
GARAMYCIN	0.00	0.00	0.00
GENTAK	5.31	6.90	2.26
GENTAMICIN SULFATE	23.79	26.55	32.83
GENTASOL	0.00	0.00	0.00
INFA-3	0.00	0.00	0.00
INFA-CHLOR	0.00	0.00	0.00
INFA-GEN	0.00	0.00	0.00
INFA-SULF	0.00	0.00	0.00
NEOCIDIN	0.00	0.00	0.00
NEOCIN-PG	0.00	0.00	0.00
NEOMYCIN/BACITRACIN/POLYMYXIN	0.00	0.00	0.00
NEOMYCIN/POLYMYXIN/GRAMICIDIN	0.00	0.00	0.00
NEOPOLYGRAM	0.00	0.00	0.00
NEOPTIC	0.00	0.00	0.00
NEOSPORIN	0.00	0.00	0.00
OCUFLOX	3.23	0.00	0.00
OFLOXACIN	0.00	0.69	0.75
P.N.	0.00	0.00	0.00
POLYCIDIN	0.00	0.00	0.00
POLYMYXIN B SUL/TRIMETHOPRIM	0.00	0.00	0.00
POLYTRACIN	0.00	0.00	0.00
QUIXIN	0.46	0.34	0.00
SODIUM SULAMYD	0.00	0.00	0.00
SPECTRO-BACITRACIN	0.00	0.00	0.00
SPECTRO-CHLOR	0.00	0.00	0.00
SPECTRO-GENTA	0.00	0.00	0.00
SPECTRO-POLYTRACIN	0.00	0.00	0.00
SPECTRO-SPORIN	0.00	0.00	0.00

SPECTRO-SULF	0.00	0.00	0.00
SULFACETAMIDE SODIUM	9.01	10.69	9.81
SULFAMIDE	0.00	0.00	0.00
TOBRAMYCIN SULFATE	7.62	6.21	12.08
TOBREX	0.92	1.03	0.00
TOMYCINE	0.00	0.00	0.00
TRI-BIOTIC	0.00	0.00	0.00
TRIBIOTIC	0.00	0.00	0.00
TRIPLE ANTIBIOTIC	0.00	0.00	0.00
VIGAMOX	7.85	30.00	16.23
ZYMAR	3.70	1.72	0.75

North Dakota Department of Human Services
DUR Board Meeting
Intuniv® Review
March 8, 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 ticks, 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. 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 $30 per month for the generic short-acting guanfacine or certain stimulants.

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North Dakota Department of Human Services
DUR Board Meeting
Xolair® Review
March 8, 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			
11/25/08 to 11/24/09			
NDC Code	**Rx Num**	**Total Reimb Amt**	**Label Name**
50242004062	12	$3,834.99	XOLAIR 150 MG VIAL
TOTAL	12	$3,834.99	2 recipients (both adults)

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.

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North Dakota Department of Human Services
DUR Board Meeting
Suboxone® and Subutex® Review
March 8, 2010

I. Overview

Suboxone and Subutex are both schedule III narcotic medications currently approved for the treatment of opioid dependence under the federal Drug Addiction Treatment Act of 2000 (DATA) . Both contain buprenorphine, an opioid agonist-antagonist that produces the same opioid agonist effects as other opioids but produces less psychomimetic effects (e.g., delusions, euphoria, hallucinations, etc.), and less withdrawal symptoms in opioid-dependent patients. Suboxone also contains naloxone, an agent that is included to discourage the diversion and misuse of the buprenorphine component. When taken orally, naloxone has limited bioavailability; when crushed and injected, it will precipitate opioid withdrawal symptoms. Therefore, Suboxone is the preferred agent when being used in an outpatient setting; Subutex should only be administered in a supervised setting, due to the absence of naloxone.

II. Pharmacology

Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is an antagonist at the mu-opioid receptor.

III. Pharmacokinetics

Pharmacokinetic parameters of buprenorphine after the administration of 4mg, 8mg, and 16mg Suboxone doses and 16mg Subutex dose				
Parameter	**Suboxone 4mg**	**Suboxone 8mg**	**Suboxone 16mg**	**Subutex 16mg**
C_{max} ng/mL	1.84 (39)	3.0 (51)	5.95 (38)	5.47 (23)
AUC (hour.ng/mL)	12.52 (35)	20.22 (43)	34.89 (33)	32.63 (25)

IV. Warnings/Precautions

Respiratory Depression – significant respiratory depression has been associated with buprenorphine, particularly by the intravenous route. Patients should be warned of the potential danger of self-administration of benzodiazepines or other depressants while under treatment with Subutex or Suboxone.

CNS Depression – Patients receiving buprenorphine in the presence of other narcotic analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics or other CNS depressants (including alcohol) may exhibit increased CNS depression. When such combined therapy is contemplated, reduction of the dose of one or both agents should be considered.

Dependence – Buprenorphine is a partial agonist at the mu-opiate receptor and chronic administration produces dependence of the opioid type, characterized by withdrawal upon abrupt discontinuation or rapid taper. The withdrawal syndrome is milder than seen with full agonists, and may be delayed in onset.

Hepatitis, hepatic events – Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in the addict population receiving buprenorphine both in clinical trials and in post-marketing adverse event reports. A measurement of liver function tests prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function tests during treatment is also recommended.

Allergic Reactions – Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in the post-marketing experience. The most common signs and symptoms include rashes, hives, and pruritus. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported.

Use in Ambulatory Patients – Suboxone and Subutex may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery

Head Injury and Increased Intracranial Pressure – Suboxone and Subutex, like other opioids, may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions and other circumstances where cerebrospinal pressure may be increased.

Opioid Withdrawal effects – Suboxone is highly likely to produce marked and intense withdrawal symptoms if misused parenterally by individuals dependent on opioid agonists such as heroin, morphine, or methadone. Sublingually, Suboxone may cause opioid withdrawal symptoms in such persons if administered before the agonist effects of the opioid have subsided.

V. Drug Interactions

CYP3A4 Inhibitors – subjects receiving Subutex and Suboxone should be closely monitored and may require dose-reduction if inhibitors of CYP3A4 (e.g., azole antifungal agents, macrolide antibiotics, HIV protease inhibitors) are co-administered.

CYP3A4 Inducers – the interaction of buprenorphine with CYP3A4 inducers has not been investigated; therefore it is recommended that patients receiving Subutex or Suboxone should be closely monitored if inducers of CYP3A4 (e.g., phenobarbital, carbamazepine, phenytoin, rifampin) are co-administered.

Benzodiazepines – based on anecdotal reports, there may be an interaction between buprenorphine and benzodiazepines. There have been a number of reports of coma and death associated with concomitant intravenous misuse of buprenorphine and benzodiazepines by addicts. Patients should be warned of the potential danger.

VI. Adverse Events ≥ 2% in short term studies

Adverse Events (≥5%) by Body System and Treatment Group in a 4-week Study			
Adverse Event	**Suboxone 16mg/day n=107**	**Subutex 16mg/day n=103**	**Placebo n=107**
Asthenia	7 (6.5%)	5 (4.9%)	7 (6.5%)
Chills	8 (7.5%)	8 (7.8%)	8 (7.5%)
Headache	39 (36.4%)	30 (29.1%)	24 (22.4%)
Infection	6 (5.6%)	12 (11.7%)	7 (6.5%)
Pain	24 (22.4%)	19 (18.4%)	20 (18.7%)
Pain Abdomen	12 (11.2%)	12 (11.7%)	7 (6.5%)
Pain Back	4 (3.7%)	8 (7.8%)	12 (11.2%)
Withdrawal Syndrome	27 (25.2%)	19 (18.4%)	40 (37.4%)
Vasodilation	10 (9.3%)	4 (3.9%)	7 (6.5%)
Constipation	13 (12.1%)	8 (7.8%)	3 (2.8%)
Diarrhea	4 (3.7%)	5 (4.9%)	16 (15.0%)
Nausea	16 (15.0%)	14 (13.6%)	12 (11.2%)
Vomiting	8 (7.5%)	8 (7.8%)	5 (4.7%)
Insomnia	15 (14.0%)	22 (21.4%)	17 (15.9%)
Rhinitis	5 (4.7%)	10 (9.7%)	14 (13.1%)
Sweating	15 (14.0%)	13 (12.6%)	11 (10.3%)

VII. Dosage and Administration

Suboxone or Subutex is administered sublingually as a single daily dose in the range of 12 to 16mg/day. When taken sublingually, Suboxone and Subutex have similar clinical effects and are interchangeable. Subutex contains no naloxone and is preferred for use during induction. Following induction, Suboxone, due to the presence of naloxone, is preferred when clinical use includes unsupervised administration. The use of Subutex for unsupervised administration should be limited to those patients who cannot tolerate Suboxone, for example, those patients who have been shown to be hypersensitive to naloxone.

VIII. Conclusion

Sublingual buprenorphine (Suboxone, Subutex), like methadone, is approved for the treatment of opioid detoxification. Injectable buprenorphine is indicated for the treatment of moderate to severe pain, and although not indicated, sublingual buprenorphine has been studied for treatment of both acute and chronic pain. There is very little data on buprenorphine use for cancer pain compared to other opioids. Treatment of cancer pain usually requires high doses of opioids, whereas buprenorphine appears to have an analgesic ceiling at higher doses.

Since buprenorphine has a lower abuse potential and is less dangerous in an overdose, some clinicians prefer to use it for pain management. Because Suboxone and Subutex are considerably more expensive than traditional generically available opioids, these agents might best be reserved for their FDA approved indication.

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North Dakota Department of Human Services
DUR Board Meeting
Elidel® and Protopic® Review
March 8, 2010

I. Overview

Atopic dermatitis (eczema) is an inflammatory skin disease. Patients can exhibit intense itching, scaly or dry skin, lesions with erythema, excoriation, rash, erosions with exudate, skin changes, and an increased susceptibility to skin infections. It is a chronic condition, and patients experience both exacerbations and remissions. Atopic dermatitis is more common in children than adults.

Pimecrolimus (Elidel) and tacrolimus (Protopic) are topical immunomodulators approved for the treatment of atopic dermatitis. These drugs inhibit inflammatory skin reactions and are thought to produce fewer side effects than topical steroids.

II. Indications

Pimecrolimus is indicated as second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adults and children 2 years of age and older, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable.

Tacrolimus, both 0.03% and 0.1% for adults, and only 0.03% for children aged 2 to 15 years, is indicated as second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.

III. Pharmacology

The mechanism of action of pimecrolimus and tacrolimus in atopic dermatitis is not known. It has been demonstrated that these agents inhibit T-lymphocyte activation by first binding to an intracellular protein, FKBP-12 and inhibits the calcium-dependent phosphatase, calcineurin.

IV. Pharmacokinetics

- Pimecrolimus and tacrolimus are highly protein bound
- Pimecrolimus and tacrolimus are metabolized primarily by the CYP3A pathway
- 85% of tacrolimus patients have peak blood concentrations less than 2 ng/mL
- 91% of pimecrolimus patients have peak blood concentrations below 0.4 ng/mL

V. Black Box Warning

Long-term Safety of Topical Calcineurin Inhibitors Has Not Been Established

Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including PROTOPIC Ointment.

Therefore:

- Continuous long-term use of topical calcineurin inhibitors, including PROTOPIC Ointment, in any age group should be avoided, and application limited to areas of involvement with atopic dermatitis.
- PROTOPIC Ointment is not indicated for use in children less than 2 years of age. Only 0.03% PROTOPIC Ointment is indicated for use in children 2-15 years of age.

Long-term Safety of Topical Calcineurin Inhibitors Has Not Been Established

Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including ELIDEL Cream.

Therefore:

- Continuous long-term use of topical calcineurin inhibitors, including ELIDEL Cream, in any age group should be avoided, and application limited to areas of involvement with atopic dermatitis.
- ELIDEL Cream is not indicated for use in children less than 2 years of age.

VI. Precautions

- The use of pimecrolimus or tacrolimus should be avoided on pre-malignant and malignant skin conditions. Some malignant skin conditions, such as cutaneous T-cell lymphoma (CTCL), may present as atopic dermatitis.

- The use of pimecrolimus or tacrolimus in patients with Netherton's Syndrome or other skin diseases, where there is the potential for increased systemic absorption of pimecrolimus or tacrolimus, is not recommended. The safety of these agents has not been established in patients with generalized erythroderma.

- The use of pimecrolimus or tacrolimus may cause local symptoms such as skin burning (burning sensation, stinging, soreness) or pruritus. Localized symptoms are most common during the first few days of therapy and typically improve as the lesions of atopic dermatitis resolve.

- Before commencing treatment with pimecrolimus or tacrolimus, cutaneous bacterial or viral infections at treatment sites should be resolved. Studies have not evaluated the safety and efficacy in the treatment of clinically infected atopic dermatitis.

- While patients with atopic dermatitis are predisposed to superficial skin infections including eczema herpeticum (Kaposi's varicelliform eruption), treatment with pimecrolimus or tacrolimus may be independently associated with an increased

risk of varicella zoster virus infection (chicken pox or shingles), herpes simplex virus infection, or eczema herpeticum.

- Patients who receive pimecrolimus or tacrolimus and who develop lymphadenopathy should have the etiology of their lymphadenopathy investigated. In the absence of a clear etiology for the lymphadenopathy, or in the presence of acute infectious mononucleosis, these agents should be discontinued. Patients should be monitored to ensure that the lymphadenopathy resolves.

- During the course of treatment, patients should minimize or avoid natural or artificial sunlight exposure, even while pimecrolimus or tacrolimus are not on the skin.

- The safety and efficacy of these agents in immunocompromised patients have not been studied.

- Rare post-marketing cases of acute renal failure have been reported in patients treated with tacrolimus. Caution should be exercised in patients predisposed to renal impairment.

VII. Drug Interactions

- Due to low blood levels of pimecrolimus and tacrolimus detected in some patients after topical application, systemic drug interactions are not expected, but cannot be ruled out.

- The concomitant administration of known CYP3A4 inhibitors (e.g., erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers, cimetidine) in patients with widespread erythrodermic disease should be done with caution.

VIII. Adverse Events

Adverse Events ≥ 5% with Pimecrolimus

Pimecrolimus Adverse Reactions ≥5%			
Adverse reaction	**Pediatric patients vehicle controlled (1 year)**		**Adult active comparator (1 year)**
	Pimecrolimus (n=272)	Vehicle (n=75)	Pimecrolimus (n=328)
Headache	25.4%	16%	7%
Folliculitis	2.2%	4%	6.1%
Impetigo	4%	5.3%	2.4%
Skin infection NOS	2.2%	4%	6.4%
Abdominal pain, upper	5.5%	6.7%	0.3%
Diarrhea NOS	7.7%	5.3%	2.1%
Gastroenteritis NOS	7.4%	2.7%	1.8%
Nausea	4%	6.7%	1.8%
Vomiting NOS	6.6%	8%	0.6%
Application site burning	8.5%	6.7%	25.9%
Application site irritation	0.4%	4%	6.4%

Pimecrolimus Adverse Reactions ≥5%			
Adverse reaction	**Pediatric patients vehicle controlled (1 year)**		**Adult active comparator (1 year)**
Application site pruritus	1.8%	0	5.5%
Application site reaction NOS	3.3%	2.7%	14.6%
Bronchitis NOS	10.7%	8%	2.4%
Cough	15.8%	10.7%	2.4%
Influenza	13.2%	4%	9.8%
Nasopharyngitis	26.5%	21.3%	7.6%
Pharyngitis NOS	8.1%	2.7%	0.9%
Rhinitis	4.4%	6.7%	2.1%
Tonsilitis	6.3%	0	0.6%
URI NOS	4.8%	8%	4.3%
Hypersensitivity	5.1%	1.3%	3.4%
Otitis media	2.9%	5.3%	0.6%
Pyrexia	12.5%	5.3%	1.2%
Sore throat	8.1%	5.3%	3.7%
Viral infection	6.6%	1.3%	0

Adverse Events ≥ 5% with Tacrolimus

Open-label studies of tacrolimus 0.1% and 0.03% Adverse event incident rate ≥ 5%			
Adverse reaction	**Adults (n=4,682)**	**Children (n=4,481)**	**Total (n=9,163)**
Headache	13%	9%	11%
Pruritus	25%	19%	22%
Pustular rash	2%	7%	5%
Skin burning	28%	20%	24%
Skin erythema	12%	7%	9%
Skin infection	9%	16%	12%
Asthma	4%	12%	8%
Sinusitis	6%	7%	6%
Otitis media	2%	11%	6%
Accidental injury	6%	8%	7%
Allergic reaction	9%	13%	11%
Fever	2%	14%	8%
Flu-like symptoms	22%	34%	28%
Infection	6%	10%	8%
Lack of drug effect	6%	6%	6%

IX. Dosage and Administration

Elidel – The patient or care giver should apply a thin layer of pimecrolimus cream 1% to the affected skin twice daily. The patient or caregiver should stop using when signs and symptoms (e.g., itch, rash, redness) resolve and should be instructed on what actions to take if symptoms recur. If signs and symptoms persist beyond 6 weeks, patients should be re-examined by their health care provider to confirm the diagnosis of atopic dermatitis. Continuous long-term use of this agent should be avoided, and application should be limited to areas of involvement with atopic dermatitis.

Protopic – Apply a thin layer of tacrolimus ointment to the affected skin twice daily. The minimum amount should be rubbed in gently and completely to control signs and symptoms of atopic dermatitis. Stop using when signs and symptoms of atopic dermatitis resolve. If signs and symptoms (e.g., itch, rash, redness) do not improve within 6 weeks, patients should be re-examined by their healthcare provider to confirm the diagnosis of atopic dermatitis. Continuous long-term use of topical calcineurin inhibitors, including tacrolimus, should be avoided and application should be limited to areas of involvement with atopic dermatitis. The safety of tacrolimus under occlusion, which may promote systemic exposure, has not been evaluated. Therefore, tacrolimus should not be used with occlusive dressings.

X. Treatment Guidelines

Clinical Guideline	Recommendation
Pediatric Health, Atopic Dermatitis: **A Review of Recent Advances in the Field (2008)**	• Treatment is based on disease severity with basic therapy for solely dry skin. • Low to mid potency topical corticosteroids and/or topical calcineurin inhibitors for mild-moderate atopic dermatitis. • Mid-high potency topical corticosteroids and topical calcineurin inhibitors for moderate-severe atopic dermatitis. • Systemic therapy reserved for recalcitrant, severe atopic dermatitis.
Society & British Association of Dermatologists: **Guidelines for the Management of Atopic Eczema (2006)**	• Immunomodulatory agents are an alternative to topical steroids. They should only be considered if the patient is intolerant to or has failed with conventional corticosteroid therapy. • These drugs do not cause skin atrophy; however, they can cause a transient sensation of warmth and burning. • These agents should not usually be considered first-line treatments unless there is a specific reason to avoid or reduce the use of topical corticosteroids.
European Academy of Dermatology and Venereology: **Position Paper on Diagnosis and Treatment of Atopic Dermatitis (2005)**	• Topical corticosteroids are a first-line anti-inflammatory therapy. Application 2-3 times monthly with emollients should suffice in mild disease. • Topical calcineurin inhibitors have demonstrated efficacy against placebo in clinical trials for short-term and long-term use. • The topical calcineurin inhibitors do not induce skin atrophy like corticosteroids, which favors their use on delicate skin areas like the eyelids, perioral skin, genital areas, inguinal fold, and for topical long-term management.

Clinical Guideline	Recommendation
American Academy of Dermatology (AAD), Clinical Guidelines Task Force: **Guidelines of Care for Atopic Dermatitis (2004)**	• Topical corticosteroids are the standard of care to which other treatments are compared. • Calcineurin inhibitors (tacrolimus and pimecrolimus) have demonstrated efficacy in reducing the severity and extent of symptoms in adults and children.

XI. Conclusion

Two topical calcineurin inhibitors, pimecrolimus and tacrolimus, are FDA-approved for the treatment of atopic dermatitis. Guidelines for the treatment of atopic dermatitis state that topical corticosteroids are considered first-line therapy. Topical calcineurin inhibitors are second-line therapy for the short-term and non-continuous chronic treatment of atopic dermatitis in patients who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable. Although a causal relationship has not been established, rare cases of malignancy have been reported in patients treated with topical calcineurin inhibitors. Therefore, the long-term use of these agents should be avoided.

References

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2. Protopic® Prescribing Information, June 2009, Astellas Pharma US, Inc.
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4. FDA Public Health Advisory Elidel (pimecrolimus) cream and Protopic (tacrolimus) ointment. Pharmacist's Letter/Prescriber's Letter 2005;21(4):210407.
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6. Lam J, Friedlander S. Atopic Dermatitis: A review of recent advances in the field. Department of Pediatrics, University of British Columbia, School of Medicine, British Columbia, Vancouver, Canada; Departments of Pediatrics & Medicine (Dermatology), University of California, San Diego School of Medicine, CA. Accessed online at www.medscape.com.

ELIDEL and PROTOPIC UTILIZATION			
11/25/08 - 11/24/09			
Label Name	**Rx Num**	**Total Reimb Amt**	**Avg Cost per Script**
PROTOPIC 0.03% OINTMENT	42	$5,407.41	$128.75
PROTOPIC 0.1% OINTMENT	52	$9,371.11	$180.21
ELIDEL 1% CREAM	318	$34,807.78	$109.46
Total 247 recipients	**412**	**$49,586.30**	
11/25/08 - 11/24/09			
30% of patients received 2 or more tubes			
35 recipients received 2 tubes			
21 recipients received 3 tubes			
7 recipients received 4 tubes			
6 recipients received 5 tubes			
2 recipients received 6 tubes			
2 recipients received 7 tubes			
1 recipient received 10 tubes			
1 recipient received 13 tubes			
Summary by Age			
Age	**Recip Count**	**Age**	**Recip Count**
0	5	24	1
1	19	25	2
2	21	27	1
3	32	28	1
4	10	29	1
5	16	30	2
6	23	31	1
7	10	32	1
8	12	33	2
9	8	34	1
10	9	35	1
11	6	36	1
12	5	37	1
13	6	39	1
14	1	40	2
15	6	41	2
16	5	43	1
17	8	44	3
18	6	45	2
20	1	46	1
21	2	48	1
22	3	49	1
23	3		

NORTH DAKOTA MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS
1ST QUARTER 2010

Criteria Recommendations ***Approved*** ***Rejected***

1. Dronedarone / Heart Failure (Black Box) _____ _____

Alert Message: Multaq (dronedarone) is contraindicated in patients with NYHA Class IV heart failure or NYHA Class II-III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic. In a placebo controlled trial patients in the above categories given dronedarone experienced a greater than two-fold increase in mortality.

Conflict Code: MC – Drug/ (Actual) Disease Warning **(Black Box Warning**)
Drug/Disease:

Util A	Util B	Util C
Dronedarone	Heart Failure	

References:
Facts & Comparisons, 2009 Updates.
Multaq Prescribing Information. July 2009, Sanofi-Aventis U.S.

2. Dronedarone / Potent 3A4 Inhibitors _____ _____

Alert Message: Coadministration of Multaq (dronedarone) with potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, and ritonavir) is contraindicated. Concurrent use of dronedarone with these agents may cause a significant increase in dronedarone plasma concentrations and systemic exposure resulting in an increased risk of QTc prolongation.

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

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

References:
Facts & Comparisons, 2009 Updates.
Multaq Prescribing Information. July 2009, Sanofi-Aventis U.S.

3. Dronedarone / 2nd & 3rd AV Block, Sick Sinus Syndrome, Bradycardia _____ _____

Alert Message: Multaq (dronedarone) is contraindicated in patients with 2nd- or 3rd-degree atrioventricular (AV) block, sick sinus syndrome (except when used in conjunction with a functioning pacemaker), bradycardia < 50bpm, QTc Bazett interval ≥ 500 ms, or PR interval > 280 ms.

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

Util A	Util B	Util C
Dronedarone	2nd Degree AV Block	
	3rd Degree AV Block	
	Sick Sinus Syndrome	
	Bradycardia	

References:
Facts & Comparisons, 2009 Updates.
Multaq Prescribing Information. July 2009, Sanofi-Aventis U.S.

4. Dronedarone / Drugs Causing QT interval Prolongation _____ _____

Alert Message: Multaq (dronedarone) is contraindicated for use with drugs that prolong the QT interval (e.g., certain phenothiazines, tricyclic antidepressants, certain macrolide antibiotics, and Class I and III antiarrhythmics) because of the potential risk of torsade de pointes-type ventricular tachycardia.

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

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

References:
Facts & Comparisons, 2009 Updates.
Multaq Prescribing Information. July 2009, Sanofi-Aventis U.S.

5. Dronedarone / Severe Hepatic Impairment _____ _____

Alert Message: Multaq (dronedarone) is contraindicated in patients with severe hepatic impairment. Dronedarone is extensively metabolized by the liver and use in this population has not been assessed.

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

Util A	Util B	Util C
Dronedarone	Severe Hepatic Impairment	

References:
Facts & Comparisons, 2009 Updates.
Multaq Prescribing Information. July 2009, Sanofi-Aventis U.S.

6. Dronedarone / Pregnancy _____ _____

Alert Message: Multaq (dronedarone) is contraindicated for use in women who are or may become pregnant. If dronedarone is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Dronedarone is pregnancy category X. Women of childbearing age should use effective contraception if using dronedarone.

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

Util A	Util B	Util C (Negating)
Dronedarone	Pregnancy	Delivery
		Miscarriage
		Abortion

Age Range: 12 – 50 years of age

References:
Facts & Comparisons, 2009 Updates.
Multaq Prescribing Information. July 2009, Sanofi-Aventis U.S.

7. Dronedarone / Lactating (Code - V24.1) _____ _____

Alert Message: Multaq (dronedarone) is contraindicated in breast-feeding women. It is not known if dronedarone is excreted in human breast milk but it has been shown to be excreted in rat milk. Due to the potential for serious adverse reactions in nursing infants from dronedarone, a decision should be made whether to discontinue nursing or discontinue the drug.

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

Util A	Util B	Util C
Dronedarone	Lactation ICD-9	

References:
Facts & Comparisons, 2009 Updates.
Multaq Prescribing Information. July 2009, Sanofi-Aventis U.S.

8. Dronedarone / CYP3A4 Inducers _____ _____

Alert Message: Concurrent use of Multaq (dronedarone) and CYP3A4 inducers (e.g. carbamazepine, phenytoin and rifampin) should be avoided. Coadministration of dronedarone with a 3A4 inducer may lead to decreased dronedarone plasma concentrations and loss of pharmacologic effects.

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

Util A	Util B	Util C
Dronedarone	Rifampin	
	Carbamazepine	
	Phenytoin	
	Phenobarbital	

References:
Facts & Comparisons, 2009 Updates.
Multaq Prescribing Information. July 2009, Sanofi-Aventis U.S.

9. Dronedarone / Potassium-depleting Diuretics _____ _____

Alert Message: Caution should be exercised when Multaq (dronedarone) is used with a potassium-depleting diuretic. Hypokalemia or hypomagnesemia may occur with concurrent use of these agents. Potassium levels should be within the normal range prior to administration of dronedarone and maintained in the normal range during administration of dronedarone.

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

Util A	Util B	Util C
Dronedarone	Furosemide	Chlorthalidone
	Bumetanide	Hydrochlorothiazide
	Ethacrynic Acid	Indapamide
	Torsemide	Methyclothiazide
	Metolazone	Chlorthiazide

References:
Facts & Comparisons, 2009 Updates.
Multaq Prescribing Information. July 2009, Sanofi-Aventis U.S.

10. Dronedarone / Digoxin _____ _____

Alert Message: Concurrent use of Multaq (dronedarone) with digoxin may potentiate the electrophysiologic effects of dronedarone (e.g., decreased AV-node conduction) due to inhibition by dronedarone of P-gp mediated transport. In clinical trials concomitant use of these agents resulted in an increased digoxin exposure of 2.5 fold. Consider discontinuation of digoxin prior to initiation of dronedarone or 50% reduction of the digoxin dose and monitor closely.

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

Util A	Util B	Util C
Dronedarone	Digoxin	

References:
Facts & Comparisons, 2009 Updates.
Multaq Prescribing Information. July 2009, Sanofi-Aventis U.S.

11. Dronedarone / Verapamil & Diltiazem _____ _____

Alert Message: Calcium channel blockers (CCBs) with depressant effects on the sinus and AV nodes (e.g. verapamil and diltiazem) can potentiate Multaq's (dronedarone) effects on conduction. All three agents are moderate CYP3A4 inhibitors. Verapamil and diltiazem have been shown to increase dronedarone exposure by 1.4- to 1.7-fold and dronedarone has been shown to increase verapamil and diltiazem exposure by 1.4- to 1.5-fold. Give low doses of the CCB initially and increase only after ECG verification of good tolerability.

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

Util A	Util B	Util C
Dronedarone	Verapamil	
	Diltiazem	

References:
Facts & Comparisons, 2009 Updates.
Multaq Prescribing Information. July 2009, Sanofi-Aventis U.S.
FDA Center for Drug Evaluation and Research, Multaq Medical/Statistical Review(s), Feb 18, 2009. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022425s000_MedR_P1.pdf

12. Dronedarone / Beta Blockers _____ _____

Alert Message: Concurrent use of Multaq (dronedarone) and a beta-blocker may result in bradycardia. Dronedarone may also increase the exposure of certain beta-blockers (e.g. propranolol, metoprolol, timolol and pindolol) due to inhibition by dronedarone of the CYP2D6-mediated beta-blocker metabolism. Give low doses of the beta blocker initially and increase only after ECG verification of good tolerability.

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

Util A	Util B		Util C
Dronedarone	Propranolol	Labetalol	
	Metoprolol	Atenolol	
	Carvedilol	Acebutolol	
	Timolol	Bisoprolol	
	Pindolol	Carteolol	
	Nebivolol	Nadolol	
	Betaxolol	Penbutolol	

*Sotalol not included – contraindicated (see #4).

References:
Facts & Comparisons, 2009 Updates.
Multaq Prescribing Information. July 2009, Sanofi-Aventis U.S.

13. Dronedarone / CYP2D6 Substrates* _____ _____

Alert Message: Caution should be exercised when Multaq (dronedarone) is used in combination with CYP2D6 substrates. Dronedarone, a moderate CYP2D6 inhibitor, may elevate plasma levels of CYP2D6 substrates increasing the risk of adverse reactions. Monitor patients and adjust dose of the 2D6 substrate if necessary.

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

Util A	Util B	Util C
Dronedarone	Fluoxetine	
	Paroxetine	
	Fluvoxamine	
	Venlafaxine	
	Duloxetine	
	Tramadol	

*CYP2D6 substrates that are contraindicated drugs are not included here (see #4).

References:
Facts & Comparisons, 2009 Updates.
Multaq Prescribing Information. July 2009, Sanofi-Aventis U.S.
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14. Dronedarone / Simvastatin, Lovastatin & Atorvastatin _____ _____

Alert Message: Concurrent use of Multaq (dronedarone) with a statin that is a CYP3A4 substrate (i.e. lovastatin, simvastatin and atorvastatin) may result in elevated statin levels and risk of adverse effects (e.g. myopathy). Dronedarone is a moderate inhibitor of CYP3A4 isoenzyme as well as a P-gp transport which may also cause increases in statin levels. Follow the statin label recommendations for concomitant use with CYP3A4 and P-gp inhibitors.

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

Util A	Util B	Util C
Dronedarone	Simvastatin	
	Lovastatin	
	Atorvastatin	

References:
Facts & Comparisons, 2009 Updates.
Multaq Prescribing Information. July 2009, Sanofi-Aventis U.S.

15. Dronedarone / CYP3A4 Substrates w/ Narrow Therapeutic Indexes _____ _____

Alert Message: Concurrent use of Multaq (dronedarone) with drugs that are CYP3A4 substrates and have narrow therapeutic indexes (e.g. tacrolimus, sirolimus) may result in increased plasma concentrations of the CYP3A4 substrate. It is recommended to monitor plasma concentrations of these agents and make any necessary dosage adjustments.

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

Util A	Util B	Util C
Dronedarone	Tacrolimus	
	Sirolimus	

References:
Facts & Comparisons, 2009 Updates.
Multaq Prescribing Information. July 2009, Sanofi-Aventis U.S.