HEALTH INFORMATION DESIGNS

using medication information cost effectively

February 9, 2005

The next North Dakota Drug Utilization Review (DUR) Board Meeting will be held:

February 14, 2005 at 1:00pm

Kelly Inn Colony Room A
1800 North 12th Street
Bismarck, ND

If you are unable to attend, please contact Brendan Joyce at (701) 328-4023 (sojoyb@state.nd.us).

Please remember to silence all pagers and cell phones prior to the start of the meeting.

1550 Pumphrey Ave • Auburn, AL 36832 • Phone: (334)502-3262 • Fax: (334) 502-6589
Auburn, Alabama • Jackson, Mississippi • Little Rock, Arkansas • Salisbury, Maryland

North Dakota Medicaid
DUR Board Meeting
Agenda

February 14, 2005

1. Administrative items – travel expenses, signature forms

2. Old Business
   - Review and approval of minutes of 12/13/04 meeting
   - Budget update
   - Introduction of new Prior Authorization Vendor
   - Clarification of all approved prior authorization programs per vendor
   - PhRMA presentation / response to Oregon Rx presentation

3. New Business
   - Identifying upcoming medications to review for prior authorization

4. Upcoming meeting agenda

5. Adjourn

Drug Utilization Review (DUR) Board Meeting
Minutes
December 13, 2004

Members Present: Brendan Joyce, Norm Byers, Bob Treitline, Al Samuelson, Gary Betting, Greg Pfister, Leann Ness, John Savageau, Pat Churchill, Greg Pfister, Carrie Sorrenson, Scott Setzepfandt, Cheryl Huber,

Members absent: Jay Huber

John Savageau (the chair) called the meeting to order at 1:02 pm. The chair asked for a motion to approve the meeting minutes from the 9/27/04 and 11/1/04 meetings. Pat Churchill so moved and Cheryl Huber seconded the motion for the 9/27/04 minutes. Bob Treitline moved to approve the minutes from the 11/1/04 meeting and Greg Pfister seconded this motion. The chair called for two separate voice votes on the two motions, and both passed with no audible dissenters.

The chair asked for an update on the budget. Brendan Joyce reported that for the current fiscal year (through October 2004), the Department is a few hundred thousand dollars to the good, but for the current biennium, the Department is still over budget at the moment and is projecting expenditures to exceed appropriation for pharmacy services by $3.6 million. Norman Byers asked what is in the Department's budget proposal. Brendan Joyce had no specifics, but reported that the Governor's budget appears to fund the Department to continue to provide services with no cutbacks. The proposed budget includes the savings derived from continued expansion of the prior authorization program.

The chair moved to the next item (ACE Inhibitors). Brendan Joyce presented an algorithm that was derived based on the motion from the previous meeting. He explained that the same grandfathering would be used for these medications, but stabilization on samples would not qualify the patient for exemption from the prior authorization. Much discussion was held regarding the definition of a failure for the medications. Norman Byers suggested that a failure should be side effects or 60 days at an adequate dose without desired response. The chair asked for audience input, and none was volunteered. The chair asked for a motion to approve the algorithm. Greg Pfister moved to accept it and Norm Byers seconded the motion. The chair then asked for a motion to define failure as any side effect or inadequate blood pressure control after 60 days at an adequate dose. Bob Treitline so moved and Norm Byers seconded the motion. The chair asked for a voice vote for the first motion and all approved (no audible dissenters). The chair asked for a voice vote for the second motion and all approved (no audible dissenters). Brendan Joyce then asked the Board to consider a motion to recommend that the Department perform prior authorization on ACE Inhibitors as outlined with the algorithm. Norm Byers so moved and Pat Churchill seconded the motion. The chair asked for a voice vote and it was approved with no audible dissenters.

The chair moved to the next item (ARBs). Brendan Joyce restated the motion as written in the previous meeting's minutes. The chair asked, and no audience members asked to present

on the ARBs. Scott Setzepfandt asked if other states had required failure of one class of drugs before they could start another and if any state required it with ACEs and ARBs. Brendan Joyce responded that he was unsure if any state did this with these two classes of medications, but it has definitely been done time and again with other classes of medications (e.g. H2RAs and PPIs). Norman Byers moved to approve the motion from the previous meeting. Pat Churchill seconded the motion. The chair asked for a voice vote and all approved (no audible dissenters).

The chair moved to the next agenda item (PPIs). Brendan Joyce presented the algorithm for the proposed step therapy for PPI prior authorization. Bob Treitline moved to accept the algorithm. Greg Pfister seconded the motion. Pedro Mendoza presented comments regarding this class of medication. After discussion, the chair called for a voice vote on the motion and it passed with no audible dissenters.

The chair called for a break while John Santa with the Oregon Rx project prepared for his presentation. When the meeting reconvened, John Santa presented his information. Brendan Joyce then presented information regarding the CNS project that is in operation in ND. Copies of these presentations are available upon request.

The chair chose to delay the final agenda item until the next meeting. The next meeting was scheduled for February 14, 2005 at 1:00 pm. One agenda item will be a 30-minute PhRMA presentation regarding the Oregon Rx project. Scott Setzepfandt shared an article with the DUR Board members. Cheryl Huber moved to adjourn the meeting and Carrie Sorrenson seconded the motion. The chair adjourned the meeting at 3:22 pm.

HEALTH INFORMATION DESIGNS

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Welcome

Health Information Designs. Inc., (HID) is the most experienced and qualified provider of drug utilization review and pharmacy benefit management services in the country. We specialize in helping our clients promote clinically appropriate and cost effective prescribing, dispensing and utilization of prescription dugs.

For 29 years, HID has worked to improve the quality and cost effectiveness of health care through clinically rational use of prescription medication. Our clients include public and private health care plans throughout the U.S. with a combined total of over 11 million covered lives.

Who We Are

Health Information Designs, Inc. was founded in 1976 and is incorporated as a C Corporation in the State of Delaware. HID's initial mission was to market drug utilization review (DUR) services nationally and since its founding it has provided DUR services for clients in approximately two-thirds of the various U.S. states. HID was sold to Value Health, Inc. in 1987 and in turn was sold to Health Data, Inc. in 1997. HID's headquarters were in Fairfax, Virginia, until they were moved to Auburn, Alabama, in January of 2000.

Who We Serve

HID has one or more clients in the following starred areas.

1550 Pumphrey Ave • Auburn, AL 36832 • Phone: (334)502-3262 • Fax: (334) 502-6589
Auburn, Alabama • Jackson, Mississippi • Little Rock, Arkansas • Salisbury, Maryland

M E M O R A N D U M

DATE: (date?)

TO: Physicians Who Prescribe to Medicaid Patients

FROM: Brendan K. Joyce, PharmD, Administrator Pharmacy Services

SUBJECT: Prior Authorization of Specified Drug Benefits for Medicaid Patients

The 2003 Legislative Assembly passed House Bill 1430, creating a Drug Utilization Review (DUR) Board to advise the Department of Human Services in developing a **Prior Authorization (PA)** process to help assure that beneficiaries receive appropriate medications in the most cost-effective manner, thus conserving state expenditures for drugs whenever possible. The pharmaceutical benefits segment of the Medicaid budget has been increasing dramatically for several years. For the current biennium, the Department expended $ 59.4 million dollars (retail drug costs) for covered beneficiaries.

The DUR Board, consisting of six physicians, six pharmacists, and two non-voting members of the Department and one from the Pharmaceutical Research and Manufacturers of America, has reviewed and supports the Department's plan to implement the PA process for **Dispense as Written prescriptions (DAW)** This notice provides important details on how physicians and patients will continue to access Medicaid pharmaceutical benefits under the PA process for this class of drugs.

You are receiving this notice because Department records indicate that you have prescribed drugs in this manner to Medicaid beneficiaries during the past 90 days. A listing of your patients who received [filled prescriptions for] these drugs during that time period is included, indicating the specific brand name drug they received. Also included is the Prior Authorization (PA) form you may utilize to direct [determine] the continuation of the drug regimen prescribed for these patients.

DIRECTIONS FOR PHYSICIANS

As noted on the PA form, the Department has determined that it is most cost effective to prescribe generic drugs whenever possible. **As the prescribing physician, the next time you prescribe a "dispense as written" prescription, you must request a PA. The criteria must be met before the PA can be approved. Please make additional copies of the PA Form as needed. If you do not respond, PA will be required (the Department will deny the claim at the pharmacy) the first time the patient receives this prescription under a new prescription number.** You will then be contacted and asked to change the prescription to a generic or to request prior authorization for the product specified on the original prescription. If you cannot be reached immediately to facilitate a PA request, the pharmacy is authorized to dispense one emergency five-day supply of the prescribed drug.

For additional information regarding the implementation of the Medicaid Prior Authorization program, please contact Brendan Joyce, PharmD, DHS Director of Pharmaceutical Services, at (701) 328-4023.

North Dakota Medicaid
Dispense as Written Request Form for Prior Authorization

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

- **The generic product was not effective**
- **There was an adverse reaction with the generic product**

Part I: TO BE COMPLETED BY PHYSICIAN

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

REQUESTED DRUG:	**Requested Dosage:** (must be completed) **Diagnosis for this request:**

Qualifications for coverage:

☐ Failed generic equivalent Start Date:
End Date:
Dose: Frequency:

☐ Adverse Reaction to generic equivalent (attach FDA Medwatch form) or Contraindicated: (provide description below)

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

Physician Signature: Date:

Part II: TO BE COMPLETED BY PHARMACY

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

Part III: FOR OFFICIAL USE ONLY

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

PLEASE FAX COMPLETED FORM TO: (866) 254-0761

M E M O R A N D U M

DATE: (date?)

TO: Physicians Who Prescribe to Medicaid Patients

FROM: Brendan K. Joyce, PharmD, Administrator Pharmacy Services

SUBJECT: Prior Authorization of Specified Drug Benefits for Medicaid Patients

The 2003 Legislative Assembly passed House Bill 1430, creating a Drug Utilization Review (DUR) Board to advise the Department of Human Services in developing a **Prior Authorization (PA)** process to help assure that beneficiaries receive appropriate medications in the most cost-effective manner, thus conserving state expenditures for drugs whenever possible. The pharmaceutical benefits segment of the Medicaid budget has been increasing dramatically for several years. For the current biennium, the Department expended $59.4 million (retail drug costs) for covered beneficiaries.

The DUR Board, consisting of six physicians, six pharmacists, and two non-voting members of the Department and one from the Pharmaceutical Research and Manufacturers of America, has reviewed and supports the Department's plan to implement the PA process for **Cox-II and brand name NSAIDS**. This notice provides important details on how physicians and patients will continue to access Medicaid pharmaceutical benefits under the PA process for this class of drugs.

You are receiving this notice because Department records indicate that you have prescribed drugs in this class to Medicaid beneficiaries during the past 90 days. A listing of your patients who received [filled prescriptions for] these drugs during that time period is included, indicating the specific Cox II or brand name NSAID they received. Also included is the Prior Authorization (PA) form you may utilize to direct [determine] the continuation of the drug regimen prescribed for these patients.

DIRECTIONS FOR PHYSICIANS

As noted on the PA form, the Department has determined that the most cost-effective anti-inflammatory treatment is generic NSAIDS. **As the prescribing physician, the next time you prescribe a Cox II or brand name NSAID for your patient, you must request a PA. The criteria must be met in order for the PA to be approved**. **Please make additional copies of the PA Form as needed. If you do not respond, the next time the patient seeks a renewal for this prescription, the Department will deny the claim at the pharmacy.** You will then be contacted and asked to change the prescription to a generic NSAID or to request prior authorization for the product specified on the original prescription. If you cannot be reached immediately to facilitate a PA request, the pharmacy is authorized to dispense one emergency five-day supply of the prescribed drug.

For additional information regarding the implementation of the Medicaid Prior Authorization program, please contact Brendan Joyce, PharmD, DHS Director of Pharmaceutical Services, at (701) 328-4023.

North Dakota Medicaid
Brand Name NSAID and Cox II Request Form for Prior Authorization

ND Medicaid requires that patients 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 > 65 years old
Recipient has history of gastric or duodenal ulcer, or has comorbidity of GI bleed, perforation or obstruction
Recipient has a history of endoscopically documented NSAID induced gastritis with GI bleed.
Recipient is on warfarin or corticosteroid therapy

Part I: TO BE COMPLETED BY PHYSICIAN

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

REQUESTED DRUG:	**Requested Dosage:**	**Diagnosis for this request:**
☐ CELEBREX ☐ BEXTRA ☐ MOBIC		☐ Warfarin/Corticosteriod therapy ☐ Gastric or duodenal ulcer ☐ GI Bleed, perofration or obstruction ☐ Endoscopically documented NSAID gastritis with GI Bleed

Qualifications for coverage:

☐ Failed NSAID therapy	Start Date:	Dose:
	End Date:	Frequency:
☐ Failed NSAID therapy	Start Date:	Dose:
	End Date:	Frequency:

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

Physician Signature:		Date:

Part II: TO BE COMPLETED BY PHARMACY

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

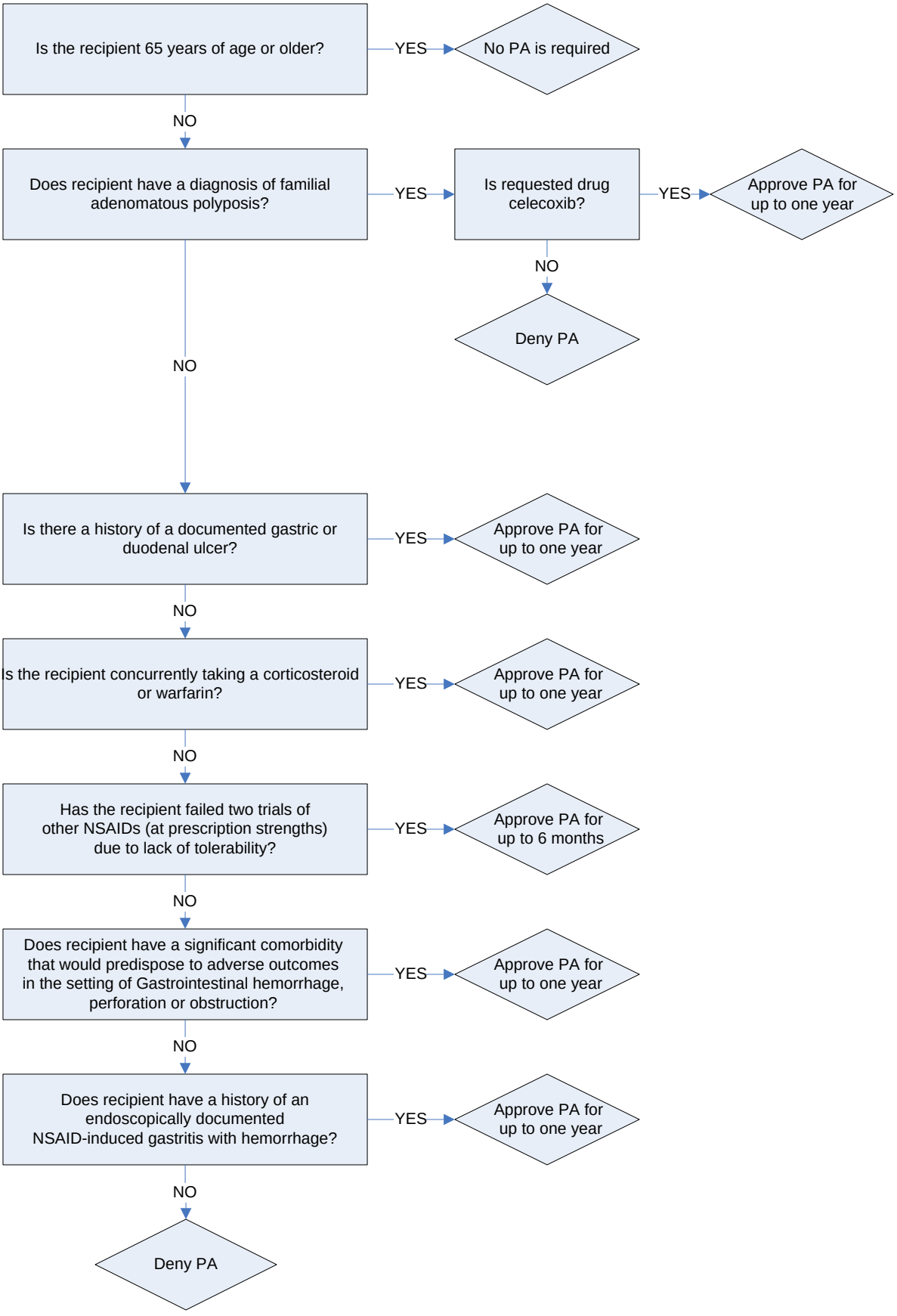
Part III: FOR OFFICIAL USE ONLY

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

PLEASE FAX COMPLETED FORM TO: (866) 254-0761

North Dakota Department of Human Services

Cox-2 Inhibitor Authorization Criteria Algorithm



M E M O R A N D U M

DATE: (date?)

TO: Physicians Who Prescribe to Medicaid Patients

FROM: Brendan K. Joyce, PharmD, Administrator Pharmacy Services

RE: Prior Authorization of Specified Drug Benefits for Medicaid Patients

The 2003 Legislative Assembly passed House Bill 1430, creating a Drug Utilization Review (DUR) Board to advise the Department of Human Services in developing a **Prior Authorization (PA)** process to help assure that beneficiaries receive appropriate medications in the most cost-effective manner, thus conserving state expenditures for drugs whenever possible. The pharmaceutical benefits segment of the Medicaid budget has been increasing dramatically for several years. For the current biennium, the Department expended $59.4 million (retail drug costs) for covered beneficiaries.

The DUR Board, consisting of six physicians, six pharmacists, and two non-voting members of the Department and one from the Pharmaceutical Research and Manufacturers of America, has reviewed and supports the Department's plan to implement the PA process for **ACE Inhibitors**. This notice provides important details on how physicians and patients will continue to access Medicaid pharmaceutical benefits under the PA process for this class of drugs.

You are receiving this notice because Department records indicate that you have prescribed drugs in this class to Medicaid beneficiaries during the past 90 days. A listing of your patients who received [filled prescriptions for] these drugs during that time period is included, indicating the specific ACE Inhibitor they received. Also included is the Prior Authorization (PA) form you may utilize to direct [determine] the continuation of the drug regimen prescribed for these patients.

DIRECTIONS FOR PHYSICIANS

As noted on the PA form, the Department has determined that the most cost-effective treatment with ACE Inhibitors is to prescribe generic products. **As the prescribing physician, the next time you prescribe a brand name ACE Inhibitor for your patient, you must request a PA. The criteria must be met before the PA can be approved. Please make additional copies of the PA Form as needed. If you do not respond, the next time the patient seeks a renewal for this prescription, the Department will deny the claim at the pharmacy.** You will then be contacted and asked to change the prescription to a generic ACE Inhibitor or to request prior authorization for the product specified on the original prescription. If you cannot be reached immediately to facilitate a PA request, the pharmacy is authorized to dispense one emergency five-day supply of the prescribed drug.

For additional information regarding the implementation of the Medicaid Prior Authorization program, please contact Brendan Joyce, PharmD, DHS Director of Pharmaceutical Services, at (701) 328-4023.

North Dakota Medicaid
ACE Inhibitor Request Form for Prior Authorization

ND Medicaid requires that patients receiving an ACE Inhibitor, must use at least two generics as first line.

****Note:***

- **Captopril, Lisinopril, Moexipril, Benazepril, Fosinopril do not require a PA**
- **If the patient has not failed two generics but has subsequently had a successful trial of a brand drug the PA will be approved.**
- **Altace will only be aproved for a recipient who is > 55 years old with previous CV disease or diabetes plus one other risk factor for CV disease.**

Part I: TO BE COMPLETED BY PHYSICIAN

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

REQUESTED DRUG:	**Requested Dosage:** (must be completed)	**Diagnosis for this request:**
		Other CV Risk Factors:

Qualifications for coverage:

☐ Failed generic drug	Start Date:	Dose:
	End Date:	Frequency:
☐ Failed generic drug	Start Date:	Dose:
	End Date:	Frequency:

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

Physician Signature: Date:

Part II: TO BE COMPLETED BY PHARMACY

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

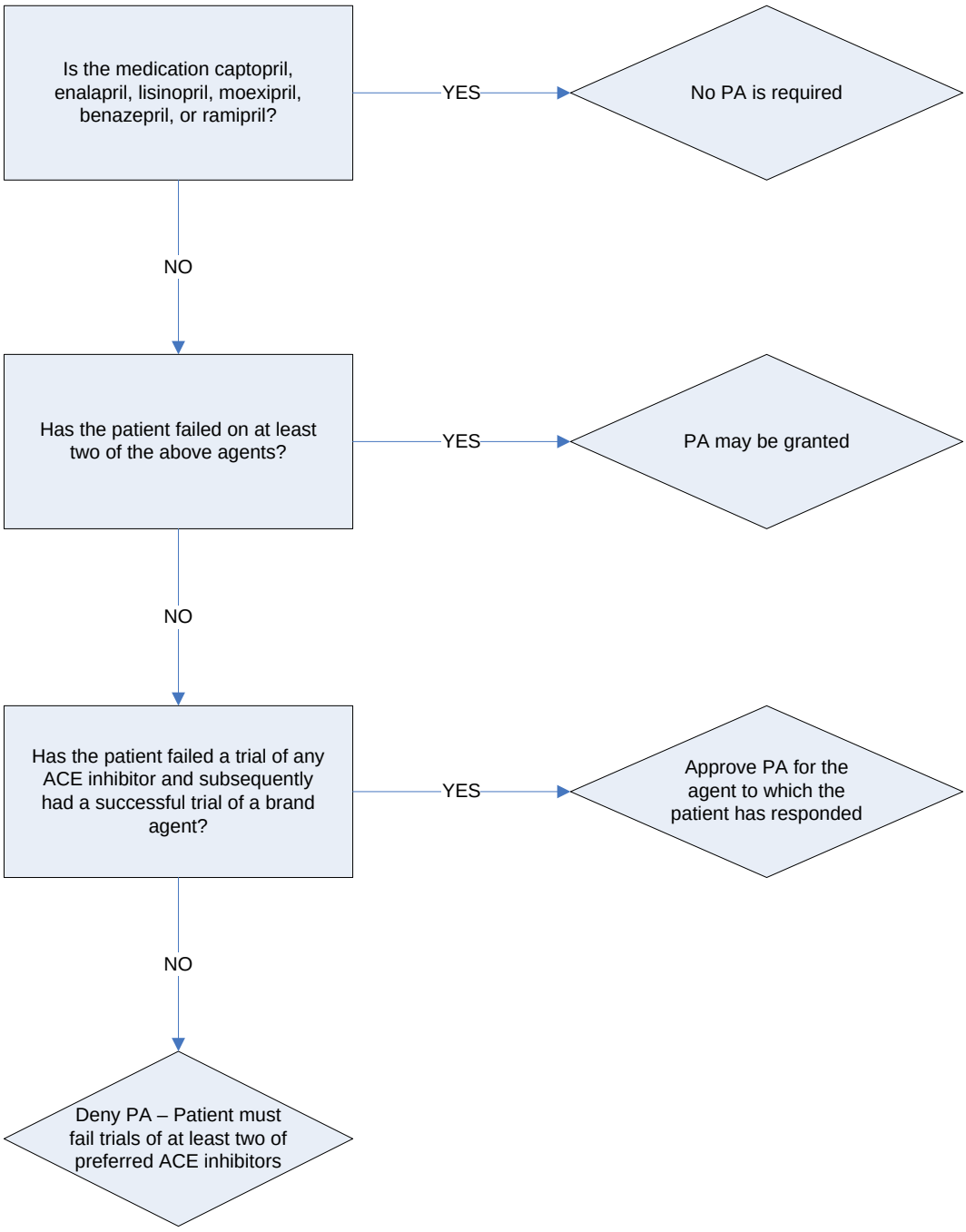
Part III: FOR OFFICIAL USE ONLY

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

PLEASE FAX COMPLETED FORM TO: (866) 254-0761

North Dakota Department of Human Services

Ace Inhibitor Authorization Criteria Algorithm



PLEASE NOTE: ramilpril (Altace) is considerably more expensive than other preferred ACE inhibitors. DHS recommends that the use of ramipril be reserved for patients 55 years of age or older with previous cardiovascular (CV) disease or diabetes plus one other risk factor for CV disease.

M E M O R A N D U M

DATE: (date?)

TO: Physicians Who Prescribe to Medicaid Patients

FROM: Brendan K. Joyce, PharmD, Administrator Pharmacy Services

SUBJECT: Prior Authorization of Specified Drug Benefits for Medicaid Patients

Last year, the 2003 Legislative Assembly passed House Bill 1430, creating a Drug Utilization Review (DUR) Board to advise the Department of Human Services in developing a **Prior Authorization (PA)** process to help assure that beneficiaries receive appropriate medications in the most cost-effective manner, thus conserving state expenditures for drugs whenever possible. The pharmaceutical benefits segment of the Medicaid budget has been increasing dramatically for several years. For the current biennium, the Department expended $59.4 million (retail drug costs) for covered beneficiaries.

The DUR Board, consisting of six physicians, six pharmacists, and two non-voting members of the Department and one from the Pharmaceutical Research and Manufacturers of America, has reviewed and supports the Department's plan to implement the PA process for **Angiotensin II Receptor Antagonists (ARBs).** This notice provides important details on how physicians and patients will continue to access Medicaid pharmaceutical benefits under the PA process for this class of drugs.

You are receiving this notice because Department records indicate that you have prescribed drugs in this class to Medicaid beneficiaries during the past 90 days. A listing of your patients who received [filled prescriptions for] these drugs during that time period is included, indicating the specific ARB they received. Also included is the Prior Authorization (PA) form you may utilize to direct [determine] the continuation of the drug regimen prescribed for these patients.

DIRECTIONS FOR PHYSICIANS

As noted on the PA form, the Department has determined that the most cost-effective treatment with ARBs is to initially prescribe a generic ACE Inhibitor. **As the prescribing physician, the next time you prescribe an ARB for your patient, you must request a PA. The criteria must be met before the PA can be approved. Please make additional copies of the PA Form as needed. If you do not respond, the next time the patient seeks a renewal for this prescription, the Department will deny the claim at the pharmacy.** You will then be contacted and asked to change the prescription to a generic ACE inhibitor or request prior authorization for the product specified on the original prescription. If you cannot be reached immediately to facilitate a PA request, the pharmacy is authorized to dispense one emergency five-day supply of the prescribed drug.

For additional information regarding the implementation of the Medicaid Prior Authorization program, please contact Brendan Joyce, PharmD, DHS Director of Pharmaceutical Services, at (701) 328-4023.

North Dakota Medicaid
ARB * Request Form for Prior Authorization

ND Medicaid requires that patients receiving an ARB, must use and fail one ACE Inhibitor.

- Angiotensin II receptor antagonists:
- Atacand, Atacand/HCT, Avapro, Avalide, Benicar, Benicar/HCT, Cozaar, Diovan, Diovan/HCT
- Hyzaar, Micardis, Micardis/HCT, Teveten, Teveten/HCT

Part I: TO BE COMPLETED BY PHYSICIAN

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

REQUESTED DRUG:	**Requested Dosage:** (must be completed)
	Diagnosis for this request:

Qualifications for coverage:

☐ Failed ACE Inhibitor	Start Date:	Dose:
	End Date:	Frequency:

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

Physician Signature: Date:

Part II: TO BE COMPLETED BY PHARMACY

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

Part III: FOR OFFICIAL USE ONLY

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

PLEASE FAX COMPLETED FORM TO: (866) 254-0761

Health Information Designs, Inc.
(334) 502-3262

NORTH DAKOTA MEDICAID

02/09/2005

Program Summary

3 Month Assessment

Period Covered:	04/01/04 - 06/30/04
Rx Claims Cost:	$ 15,065,523.01
Number Rx:	303,571
Total Recipients:	30,813
Avg. Recipients Per Month:	22,391
Avg Paid Per Member Over Period:	$488.93
Avg. Paid Per Member Per Month:	$224.28
Avg Paid Per Rx	$49.63

3 Month Assessment

Period Covered:	07/01/04 - 09/30/04
Rx Claims Cost:	$ 15,178,605.71
Number Rx:	291,206
Total Recipients:	29,912
Avg. Recipients Per Month:	21,750
Avg Paid Per Member Over Period:	$507.44
Avg. Paid Per Member Per Month:	$232.62
Avg Paid Per Rx	$52.12

6 Month Assessment

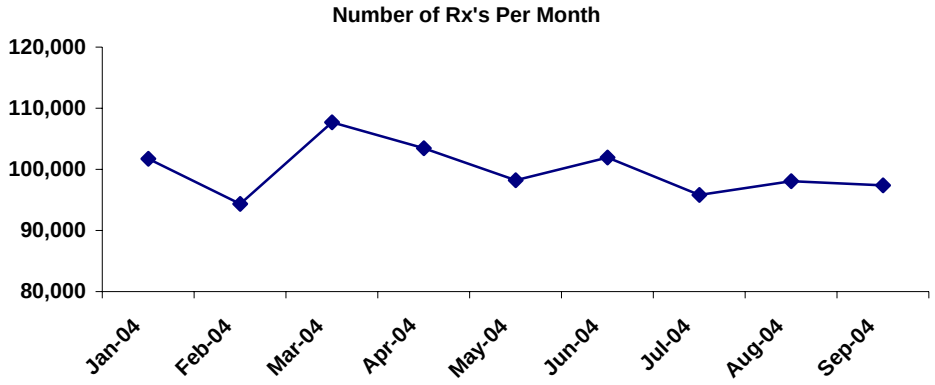
Period Covered:	04/01/04 - 09/30/04
Rx Claims Cost:	$ 30,244,128.72
Number Rx:	594,777
Total Recipients:	37,639
Avg. Recipients Per Month:	22,070
Avg Paid Per Member Over Period:	$803.53
Avg. Paid Per Member Per Month:	$228.39
Avg Paid Per Rx	$50.85

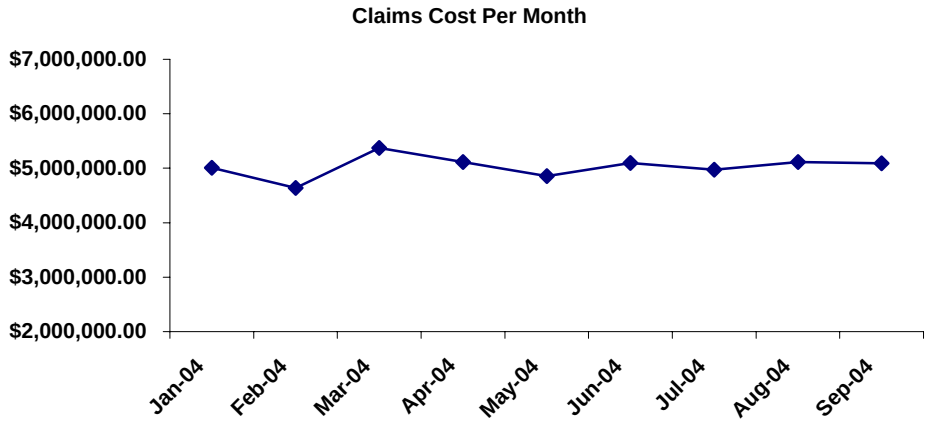
Health Information
Designs, Inc.
(334) 502-3262

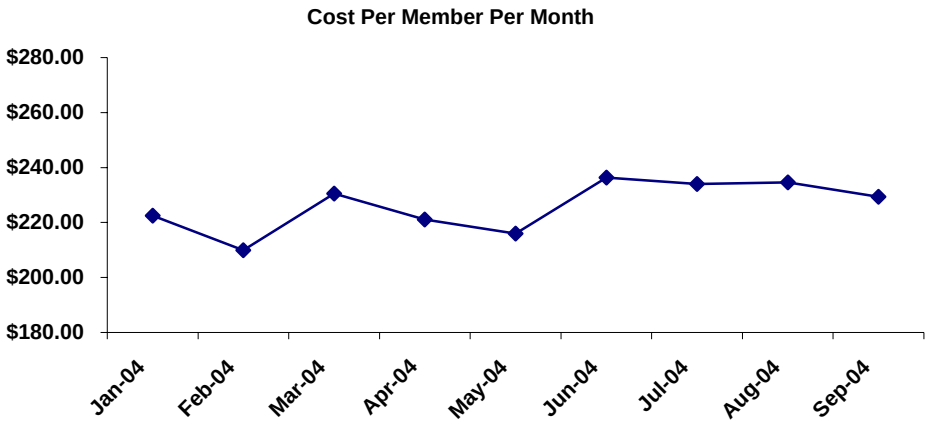
NORTH DAKOTA MEDICAID
Cost Management Analysis

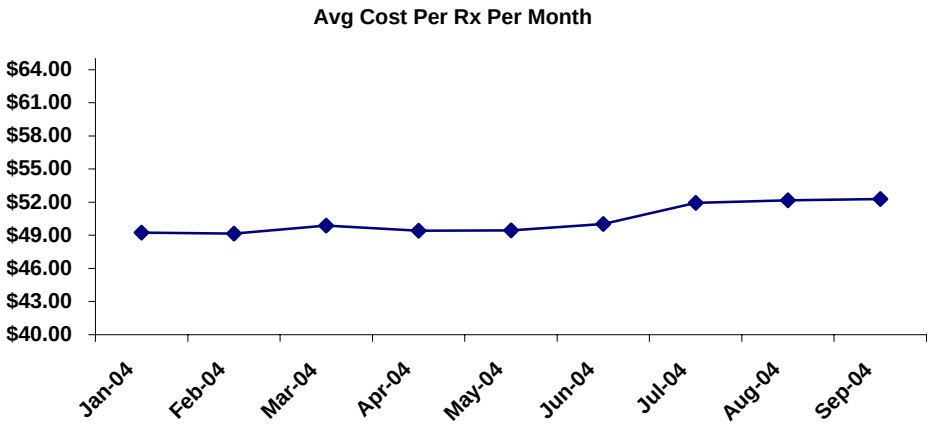
02/09/2005

Period Covered	Recipients	# Rx's	Rx Claims Cost	Cost per Member Per Month	Cost/Claim
Jan-04	22,516	101,705	$ 5,009,250.74	$ 222.48	$ 49.25
Feb-04	22,101	94,371	$ 4,638,277.75	$ 209.87	$ 49.15
Mar-04	23,301	107,694	$ 5,372,335.23	$ 230.56	$ 49.89
Apr-04	23,121	103,438	$ 5,112,708.56	$ 221.13	$ 49.43
May-04	22,478	98,222	$ 4,855,222.64	$ 216.00	$ 49.43
Jun-04	21,573	101,911	$ 5,097,591.81	$ 236.29	$ 50.02
Jul-04	21,258	95,796	$ 4,974,887.17	$ 234.02	$ 51.93
Aug-04	21,793	98,043	$ 5,113,405.31	$ 234.64	$ 52.15
Sep-04	22,199	97,367	$ 5,090,313.23	$ 229.30	$ 52.28






Cost Per Member Per Month
$280.00
$260.00
$240.00
$220.00
$200.00
$180.00
Jan-04
Feb-04
Mar-04
Apr-04
May-04
Jun-04
Jul-04
Aug-04
Sep-04

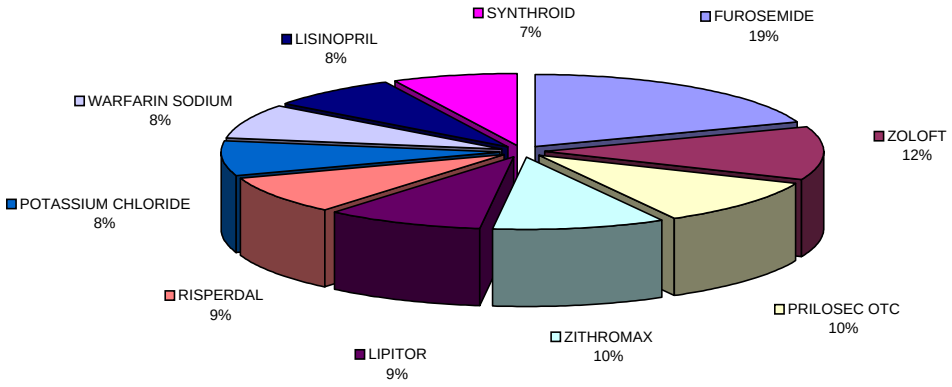

Avg Cost Per Rx Per Month
$64.00
$61.00
$58.00
$55.00
$52.00
$49.00
$46.00
$43.00
$40.00
Jan-04
Feb-04
Mar-04
Apr-04
May-04
Jun-04
Jul-04
Aug-04
Sep-04

TOP 25 DRUGS BASED ON NUMBER OF CLAIMS FROM 07/01/2004 - 09/30/2004

Drug	AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
FUROSEMIDE	DIURETICS	8,650	$ 69,654.74	$ 8.05	2.97%
ZOLOFT	ANTIDEPRESSANTS	5,326	$ 400,389.71	$ 75.18	1.83%
PRILOSEC OTC	PROTON-PUMP INHIBITORS	4,596	$ 104,608.73	$ 22.76	1.58%
ZITHROMAX	MACROLIDES	4,524	$ 208,067.43	$ 45.99	1.55%
LIPITOR	HMG-COA REDUCTASE INHIBITORS	3,958	$ 287,069.98	$ 72.53	1.36%
RISPERDAL	ANTIPSYCHOTIC AGENTS	3,828	$ 574,088.88	$ 149.97	1.31%
POTASSIUM CHLORIDE	REPLACEMENT PREPARATIONS	3,517	$ 57,763.22	$ 16.42	1.21%
WARFARIN SODIUM	ANTICOAGULANTS	3,397	$ 44,681.07	$ 13.15	1.17%
LISINOPRIL	ANGIOTENSIN-CONVERTING ENZYME INHIBITORS	3,394	$ 41,219.28	$ 12.14	1.17%
SYNTHROID	THYROID AGENTS	3,171	$ 47,480.66	$ 14.97	1.09%
HYDROCODONE W/ACETAMINOPHEN	OPIATE AGONISTS	3,018	$ 36,671.62	$ 12.15	1.04%
TRAZODONE HCL	ANTIDEPRESSANTS	2,757	$ 24,532.12	$ 8.90	0.95%
LORAZEPAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	2,748	$ 33,820.18	$ 12.31	0.94%
ALBUTEROL	SYMPATHOMIMETIC (ADRENERGIC) AGENTS	2,687	$ 40,989.22	$ 15.25	0.92%
NEURONTIN	MISCELLANEOUS ANTICONVULSANTS	2,644	$ 329,759.80	$ 124.72	0.91%
SEROQUEL	ANTIPSYCHOTIC AGENTS	2,643	$ 524,781.44	$ 198.56	0.91%
ZYPREXA	ANTIPSYCHOTIC AGENTS	2,525	$ 764,087.16	$ 302.61	0.87%
NORVASC	DIHYDROPYRIDINES	2,470	$ 118,848.28	$ 48.12	0.85%
FLUOXETINE HCL	ANTIDEPRESSANTS	2,405	$ 34,348.22	$ 14.28	0.83%
ATENOLOL	BETA-ADRENERGIC BLOCKING AGENTS	2,399	$ 18,391.88	$ 7.67	0.82%
METOPROLOL TARTRATE	BETA-ADRENERGIC BLOCKING AGENTS	2,355	$ 20,155.27	$ 8.56	0.81%
LEVOTHYROXINE SODIUM	THYROID AGENTS	2,239	$ 27,169.36	$ 12.13	0.77%
HYDROCHLOROTHIAZIDE	DIURETICS	2,202	$ 14,699.64	$ 6.68	0.76%
LEXAPRO	ANTIDEPRESSANTS	2,197	$ 128,377.92	$ 58.43	0.75%
EFFEXOR XR	ANTIDEPRESSANTS	2,183	$ 207,341.75	$ 94.98	0.75%
TOTAL TOP 25		81,833	$ 4,158,997.56	$ 50.82	28.10%

Total Rx Claims From 07/01/2004 - 09/30/2004	291,206

Top 10 Drugs
Based on Number of Claims

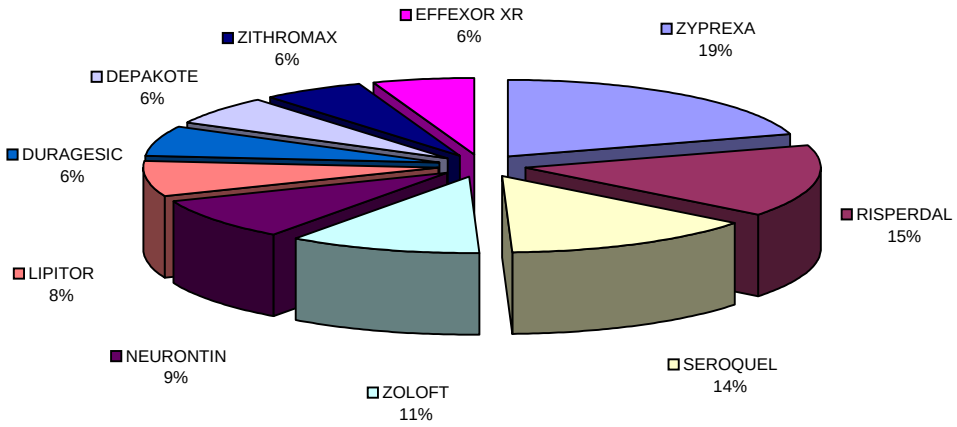


TOP 25 DRUGS BASED ON TOTAL CLAIMS COST FROM 07/01/2004 - 09/30/2004

Drug	AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
ZYPREXA	ANTIPSYCHOTIC AGENTS	2,525	$ 764,087.16	$ 302.61	0.87%
RISPERDAL	ANTIPSYCHOTIC AGENTS	3,828	$ 574,088.88	$ 149.97	1.31%
SEROQUEL	ANTIPSYCHOTIC AGENTS	2,643	$ 524,781.44	$ 198.56	0.91%
ZOLOFT	ANTIDEPRESSANTS	5,326	$ 400,389.71	$ 75.18	1.83%
NEURONTIN	MISCELLANEOUS ANTICONVULSANTS	2,644	$ 329,759.80	$ 124.72	0.91%
LIPITOR	HMG-COA REDUCTASE INHIBITORS	3,958	$ 287,069.98	$ 72.53	1.36%
DURAGESIC	OPIATE AGONISTS	1,343	$ 240,810.62	$ 179.31	0.46%
DEPAKOTE	MISCELLANEOUS ANTICONVULSANTS	1,859	$ 231,086.08	$ 124.31	0.64%
ZITHROMAX	MACROLIDES	4,524	$ 208,067.43	$ 45.99	1.55%
EFFEXOR XR	ANTIDEPRESSANTS	2,183	$ 207,341.75	$ 94.98	0.75%
CELEBREX	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS	2,148	$ 196,085.28	$ 91.29	0.74%
ADVAIR DISKUS	SYMPATHOMIMETIC (ADRENERGIC) AGENTS	1,439	$ 191,861.74	$ 133.33	0.49%
TOPAMAX	MISCELLANEOUS ANTICONVULSANTS	969	$ 178,273.00	$ 183.98	0.33%
LAMICTAL	MISCELLANEOUS ANTICONVULSANTS	770	$ 177,823.57	$ 230.94	0.26%
GEODON	ANTIPSYCHOTIC AGENTS	827	$ 165,629.05	$ 200.28	0.28%
PLAVIX	MISCELLANEOUS THERAPEUTIC AGENTS	1,438	$ 163,690.69	$ 113.83	0.49%
ARICEPT	PARASYMPATHOMIMETIC (CHOLINERGIC AGENTS)	1,305	$ 163,614.13	$ 125.37	0.45%
ABILIFY	ANTIPSYCHOTIC AGENTS	581	$ 152,792.52	$ 262.98	0.20%
SINGULAIR	MISCELLANEOUS THERAPEUTIC AGENTS	1,807	$ 145,736.28	$ 80.65	0.62%
OXYCONTIN	OPIATE AGONISTS	979	$ 144,910.16	$ 148.02	0.34%
TRILEPTAL	MISCELLANEOUS ANTICONVULSANTS	912	$ 128,981.51	$ 141.43	0.31%
LEXAPRO	ANTIDEPRESSANTS	2,197	$ 128,377.92	$ 58.43	0.75%
CONCERTA	ANOREXIGENICS;RESPIR.,CEREBRAL STIMULANT	1,556	$ 126,823.18	$ 81.51	0.53%
CLOZARIL	ANTIPSYCHOTIC AGENTS	637	$ 123,706.32	$ 194.20	0.22%
KEPPRA	MISCELLANEOUS ANTICONVULSANTS	592	$ 120,543.52	$ 203.62	0.20%
TOTAL TOP 25		48,990	$ 6,076,331.72	$ 124.03	16.82%

Total Rx Claims From 07/01/2004 - 09/30/2004	291,206

Top 10 Drugs
Based on Total Claims Cost



NORTH DAKOTA MEDICAID
RETROSPECTIVE DUR
CRITERIA RECOMMENDATIONS
FIRST QUARTER 2005

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

1. Memantine / Overutilization _____ _____

Alert Message: Namenda (memantine) may be over-utilized. The recommended maximum dose is 20 mg/day.
Conflict Code: HD – High Dose
Severity: Major
Drugs:

Util A	Util B	Util C
Memantine		

Max Dose: 20mg/day
References:
Namenda Product Information, Oct. 2003, Forest Laboratories.

2. Memantine / Underutilization _____

_____

Alert Message: After reviewing your patient's refill frequency of Namenda (memantine) we are concerned that they may be non-adherent to the prescribed dosing regimen which may lead to sub-therapeutic effects.
Conflict Code: LR - Underutilization Precaution
Severity: Major
Drugs:

Util A	Util B	Util C
Memantine		

References:
Namenda Product Information, Oct. 2003, Forest Laboratories

3. Memantine / Renal Failure _____ _____

Alert Message: Namenda (memantine) is predominantly renally eliminated and dose reduction may be necessary in patients with moderate renal impairment. Memantine use has not been evaluated in patients with severe renal impairment and is therefore is not recommended.
Conflict Code: ER – Overutilization
Severity: Moderate
Drugs:

Util A	Util B	Util C
Memantine 10mg	Renal Impairment	

References:
Namenda Product Information, Oct. 2003, Forest Laboratories.

Criteria Recommendations *Approved* *Rejected*

4. Memantine / Urine Alkalinizers _____ _____

Alert Message: Namenda (memantine) should be used with caution under conditions that can alkalinize the urine (e.g., carbonic anhydrase inhibitors, sodium bicarbonate, diet, renal tubular acidosis or severe infections of urinary tract). Memantine is predominantly renally eliminated and alkalinization of urinary pH may lead to an accumulation of the drug with a possible increase in adverse effects.
Conflict Code: DB – Drug/Drug Marker and/or Diagnosis
Severity: Moderate
Drugs:

Util A	Util B	Util C
Memantine	Acetazolamide	
	Dichlorphenamide	
	Methazolamide	
	Renal Tubular Acidosis	
	Urinary Tract Infection	

References:
Namenda Product Information, Oct. 2003, Forest Laboratories.
Micromedex Healthcare Series, Drugdex Drug Evaluations, 2004.

5. Memantine / Drugs eliminated by Renal Cationic System _____ _____

Alert Message: Coadministration of Namenda (memantine) and drugs that are eliminated via the renal cationic system should be done with caution. Memantine is predominantly renally eliminated and concurrent use with drugs that use the same elimination route may potentially result in altered plasma levels of both agents.
Conflict Code: DD – Drug-Drug Interaction
Severity: Moderate
Drugs:

Util A	Util B	Util C
Memantine	Hydrochlorothiazide	
	Triamterene	
	Cimetidine	
	Ranitidine	
	Quinidine	

References:
Namenda Product Information, Oct. 2003, Forest Laboratories.

6. Memantine / NMDA Receptor Antagonists _____ _____

Alert Message: The concurrent use of Namenda (memantine) with other N-methyl D-aspartate (NMDA) antagonists has not been evaluated and therefore should be approached with caution.
Conflict Code: DD – Drug/Drug Interaction
Drugs:

Util A	Util B	Util C
Memantine	Amantadine	
	Dextromethorphan	
	Ketamine	

References:
Namenda Product Information, Oct. 2003, Forest Laboratories.

Criteria Recommendations *Approved* *Rejected*

7. Duloxetine / Hepatic Insufficiency _____ _____

Alert Message: It is recommended that Cymbalta (duloxetine) not be administered to patients with any hepatic insufficiency. These patients experience decreased duloxetine metabolism and elimination. After a single 20 mg dose of duloxetine cirrhotic patients with moderate liver impairment had a mean plasma clearance about 15% that of age-and gender-matched healthy subjects, a 5-fold increase in AUC, and a half-life approximately three times longer.
Conflict Code: MC – Drug (Actual) Disease Precaution
Severity: Major
Drugs:

Util A	Util B	Util C
Duloxetine	Hepatic Insufficiency	

References:
Cymbalta Product Information, 2004, Eli Lilly and Company.

8. Duloxetine / End Stage Renal Disease _____ _____

Alert Message: Cymbalta (duloxetine) is not recommended in patients with end stage renal disease. A single 60 mg dose of duloxetine resulted in Cmax and AUC values approximately 100% greater in patients with end stage renal disease receiving intermittent hemodialysis than in patients with normal renal function.
Conflict Code: DB - Drug-Drug Marker and/or Diagnosis
Drugs:

Util A	Util B	Util C
Duloxetine	End Stage Renal Disease	
	Sevelamer	
	Paricalcitol	
	Calcitriol	

References:
Cymbalta Product Information, 2004, Eli Lilly and Company.

9. Duloxetine / MAO Inhibitors _____ _____

Alert Message: The concurrent use of Cymbalta (duloxetine) and monoamine oxidase inhibitors is contraindicated due to the risk for developing serotonin syndrome, which may include hyperthermia, tremor, myoclonus, and irritability. It is recommended that duloxetine not be used within 14 days of discontinuing treatment with an MAOI, and at least 5 days should be allowed after discontinuing duloxetine before starting an MAOI.
Conflict Code: DD – Drug/Drug Interaction
Severity: Major
Drugs:

Util A	Util B	Util C
Duloxetine	Phenelzine	
	Isocarboxazid	
	Tranylcypromine	

References:
Cymbalta Product Information, 2004, Eli Lilly and Company.

Criteria Recommendations *Approved* *Rejected*

10. Duloxetine / Thioridiazine _____ _____

Alert Message: Cymbalta (duloxetine) and thioridiazine should not be co-administered. Duloxetine is a moderate inhibitor of CYP 2D6 and concurrent use with thioridiazine, a CYP 2D6 substrate, may increase the risk of serious ventricular arrhythmias and sudden death associated with elevated plasma levels of thioridiazine.
Conflict Code: DD – Drug/Drug Interaction
Severity: Major

Util A	Util B	Util C
Duloxetine	Thiordiazine	

References:
Cymbalta Product Information, 2004, Eli Lilly and Company.

11. Duloxetine / Narrow-Angle Glaucoma _____ _____

Alert Message: Cymbalta (duloxetine) should be used with caution in patients with controlled narrow-angle glaucoma and is contraindicated in patients with uncontrolled narrow-angle glaucoma. In clinical trials, duloxetine has been shown to increase the risk of mydriasis.
Conflict Code: MC – Drug (Actual) Disease Precaution
Severity: Moderate
Drugs:

Util A	Util B	Util C
Duloxetine	Narrow Angle Glaucoma	

References:
Cymbalta Product Information, 2004, Eli Lilly and Company.

12. Duloxetine / Fluoxetine _____ _____

Alert Message: Cymbalta (duloxetine) should be used with caution in patients receiving Luvox (fluvoxamine), a potent CYP 1A2 inhibitor. Elimination of duloxetine is mainly through hepatic metabolism involving P450 isozymes, CYP2D6 and CYP1A2. Concurrent use of these agents resulted in an approximate 6 fold increase in the AUC and a 2.5 fold increase in the Cmax of duloxetine.
Conflict Code: DD – Drug/Drug Interaction
Severity: Moderate
Drugs:

Util A	Util B	Util C
Duloxetine	Fluvoxamine	

References:
Cymbalta Product Information, 2004, Eli Lilly and Company.

13. Duloxetine / Potent 2D6 Inhibitors _____ _____

Alert Message: Cymbalta (duloxetine) should be used with caution in patients receiving potent CYP 2D6 inhibitors, (paroxetine, fluoxetine and quinidine). The concurrent use of these agents may result in elevated concentrations of duloxetine.
Conflict Code: DD – Drug/Drug Interactions
Severity: Moderate
Drugs:

Util A	Util B	Util C
Duloxetine	Paroxetine	
	Fluoxetine	
	Quinidine	

References:
Cymbalta Product Information, 2004, Eli Lilly and Company.

Criteria Recommendations	*Approved*	*Rejected*

14. Duloxetine / Certain Tricyclic Antidepressants. _____ _____

Alert Message: Cymbalta (duloxetine) should be used with caution in patients receiving certain tricyclic antidepressants (despiramine, amitriptyline, nortriptyline and imipramine). Duloxetine is a moderate inhibitor of CYP2D6 and concurrent use with these agents may result in elevated TCA plasma concentrations. TCA plasma levels may need to be monitored and TCA dose reduction may be necessary.
Conflict Code: DD – Drug/Drug Interaction
Severity: Moderate
Drugs:

Util A	Util B	Util C
Duloxetine	Nortriptyliine	
	Imipramine	
	Amitriptyline	
	Desipramine	

References:
Cymbalta Product Information, 2004, Eli Lilly and Company.

15. Duloxetine / CYP2D6 Metabolized Drugs _____ _____

Alert Message: Cymbalta (duloxetine) should be used with caution in patients receiving drugs that are extensively metabolized by CYP2D6 isozyme and which have a narrow therapeutic index (Type 1C antiarrhythmics and phenothiazines). Duloxetine is a moderate inhibitor of CYP2D6 and concurrent use with these agents may result in elevated plasma concentrations of the CYP2D6 substrate.
Conflict Code: DD – Drug/Drug Interaction
Severity: Moderate
Drugs:

Util A	Util B	Util C
Duloxetine	Propafenone	
	Flecainide	
	Chlorpromazine	
	Fluphenazine	
	Mesoridazine	
	Perphenazine	
	Prochlorperazine	
	Trifluroperazine	

*Excluded thioridiazine – has individual criteria

References:
Cymbalta Product Information, 2004, Eli Lilly and Company.

16. Duloxetine / High Dose _____ _____

Alert Message: Cymbalta (duloxetine) may be over-utilized. The recommended dosing range is 40 mg to 60 mg a day. There is no evidence that doses greater than 60 mg/day confer any additional benefit.
Conflict Code: HD – High Dose
Drugs:

Util A	Util B	Util C
Duloxetine		

Max Dose: 60mg/day
References:
Cymbalta Product Information, 2004, Eli Lilly and Company.

Criteria Recommendations	*Approved*	*Rejected*

17. Duloxetine / Underuse _____ _____

Alert Message: After reviewing your patient's refill frequency for Cymbalta (duloxetine) we are concerned that they may be non-adherent to the prescribed dosing regimen which may lead to sub-therapeutic effects.
Conflict Code: LR – Underuse Precaution
Severity: Major
Drugs:

Util A	Util B	Util C
Duloxetine		

*Receive 65 day supply or less in 90 days.
References:
Cymbalta Product Information, 2004, Eli Lilly and Company.

18. Estazolam/ Azole Antifungals _____ _____

Alert Message: Estazolam use is contraindicated with the potent CYP3A4 enzymes inhibitors, ketoconazole or itraconazole, due to their inhibition of estazolam metabolism. Concomitant use of these agents may result in estazolam toxicity.
Conflict Codes: DD – Drug/Drug Interaction
Severity: Major
Drugs:

Util A	Util B	Util C
Estazolam	Ketoconazole	
	Itraconazole	

References:
Micromedex Healthcare Series, Drugdex Drug Evaluations, 2004.
Prosom Product Information, Jan. 2004, Abbott Laboratories.

19. Estazolam/ Certain 3A4 inhibitors (Moderate) _____ _____

Alert Message: Estazolam, a CYP 3A4 substrate, should be prescribed with caution in patients receiving drugs that exhibit significant inhibition of 3A4 metabolism (e.g., nefazodone, fluvoxamine, cimetidine, diltiazem, isoniazid and some macrolide antibiotics). Concomitant therapy may result in elevated estazolam concentrations. Consideration should be given to appropriate dosage reduction of estazolam.
Conflict Codes: DD – Drug/Drug Interaction
Severity: Moderate
Drugs:

Util A	Util B	Util C
Estazolam	Nefazodone	Erythromycin
	Fluvoxamine	Clarithromycin
	Cimetidine	
	Diltiazem	
	Isoniazid	

References:
Micromedex Healthcare Series, Drugdex Drug Evaluations, 2004.
Prosom Product Information, Jan. 2004, Abbott Laboratories.

20. Estazolam/ CYP3A4 Inducers _____ _____

Alert Message: Estazolam, a CYP 3A4 substrate, should be used with caution in patients receiving potent CYP3A4 enzymes inducers (e.g., carbamazepine, phenytoin, rifampin and barbiturates). While no in-vivo drug-drug interaction studies have been conducted between estazolam and inducers of CYP3A it would be expected that concomitant use would decrease estazolam concentrations. Monitor for signs of benzodiazepine clinical effectiveness.
Conflict Codes: DD – Drug/Drug Interaction
Severity: Moderate
Drugs:

Util A	Util B		Util C
Estazolam	Carbamazepine	Phenobarbital	
	Phenytoin	Butalbital	
	Rifampin	Butabarbital	
	Mephobarbital	Secobarbital	
	Pentobarbital		

References:
Micromedex Healthcare Series, Drugdex Drug Evaluations, 2004.
Prosom Product Information, Jan. 2004, Abbott Laboratories.

21. Celecoxib / Overutilization _____ _____

Alert Message: A recent clinical trial involving the use of Celebrex (celecoxib) to prevent colon polyps was halted due to an increased risk of cardiovascular (CV) events. Patients taking 400 mg of celecoxib twice a day had a 3.4 times greater risk of CV events compared to placebo and 2.5 times greater for 200 mg twice a day. The FDA is advising that all physicians prescribing celecoxib consider the evolving information in evaluating the risks and benefits for the individual patient. Dosage reduction or alternative therapy may be necessary.
Conflict Code: ER - Overutilization
Drugs

Util A	Util B	Util C
Celecoxib		

Max Dose: > 400mg
References:
FDA Statement on Halting of a Clinical Trial of the Cox-2 Inhibitor Celebrex, Dec. 17, 2004.

22. Valdecoxib / Therapeutic Appropriateness _____ _____

Alert Message: Serious skin reactions have been reported in patients receiving Bextra (valdecoxib). These skin reactions are most likely to occur in the first 2 weeks of treatment, but can occur any time during therapy. In a few cases, these reactions have resulted in death. Valdecoxib should be discontinued at the first appearance of a skin rash, mucosal lesions, or any sign of hypersensitivity. Valdecoxib contains sulfa, and patients with a history of allergic reactions to sulfa may be at a greater risk of skin reactions.
Conflict Code: TA – Therapeutic Appropriateness
Severity: Major – **Boxed Warning**
Drugs:

Util A	Util B	Util C
Valdecoxib		

References:
Bextra Product Information, Nov. 2004, Pfizer Inc.
Medwatch: FDA Safety Information and Adverse Event Reporting Program, 2004.

Criteria Recommendations	*Approved*	*Rejected*

23. Valdecoxib / Therapeutic Appropriateness _____ _____

Alert Message: Bextra (valdecoxib) is contraindicated for treatment of postoperative pain immediately following coronary artery bypass graft surgery (CABG). Patients treated with valdecoxib for pain following CABG have a higher risk for cardiovascular/thromboembolic events, deep surgical infections or sternal wound complications.
Conflict Code: TA - Therapeutic Appropriateness
Severity: Major
Drugs:

Util A	Util B	Util C
Valdecoxib		

References:
Bextra Product Information, Nov. 2004, Pfizer Inc.
Medwatch: FDA Safety Information and Adverse Event Reporting Program, 2004.

HEALTH INFORMATION DESIGNS

using medication information cost effectively

March 22, 2005

The next North Dakota Drug Utilization Review (DUR) Board Meeting will be held:

April 11, 2005 at 1:00pm

Heritage Center
612 East Blvd
Bismarck, ND

If you are unable to attend, please contact Brendan Joyce at (701) 328-4023 (sojoyb@state.nd.us).

Please remember to silence all pagers and cell phones prior to the start of the meeting.

1550 Pumphrey Ave • Auburn, AL 36832 • Phone: (334)502-3262 • Fax: (334) 502-6589
Auburn, Alabama • Jackson, Mississippi • Little Rock, Arkansas • Salisbury, Maryland

North Dakota Medicaid
DUR Board Meeting
Agenda
Heritage Center
April 11, 2005 1:00P.M.

1.	Administrative items -Travel vouchers	
2.	Old Business	
	- Review and approval of minutes of 02/14/05 meeting	Chairman
	- Budget update	Brendan Joyce
	- Cost Savings reports for PPIs and Antihistamines	HID
3.	New Business	
	- Review of Antidepressants	HID
	- Review of Calcium Channel Blockers	HID
	- Review of Beta Blockers	HID
	- Review of compounding fees for pharmacies	Brendan Joyce
4.	Upcoming meeting agenda	Chairman
5.	Adjourn	Chairman

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

Drug Utilization Review (DUR) Board Meeting
Minutes
February 14, 2005

Members Present: Al Samuelson, Gary Betting, Greg Pfister, John Savageau, Pat Churchill, Carrie Sorenson, Scott Setzepfandt, Cheryl Huber, Brendan Joyce, Bob Treitline, Leann Ness.

Members Absent: Jay Huber, Norman Byers.

Chair John Savageau called the meeting to order at 1:05 p.m., then asked for a motion to approve the minutes from the Dec. 13, 2004, meeting. Bob Treitline moved that the minutes be approved, and Pat Churchill seconded the motion. Carrie Sorenson asked that the minutes reflect the correct spelling of her name, "Sorenson." The chair called for a voice vote to approve the minutes, which passed with no audible dissenters.

The chair asked for an update on the budget. Brendan Joyce said that the Spend Down Table had not been updated for December, so the information is the same as at the last meeting. Mr. Joyce also informed the Board that the state Legislature is currently debating the April 2007 budget. Al Samuelson asked Mr. Joyce to explain to the Board any current legislation that might affect the DUR Board. Mr. Joyce said that HB1470 has passed the House and will be debated in the Senate at a later date. This bill would restructure the appointment process for Board members, requiring four physicians and four pharmacists to be appointed by their respective associations. A new consumer member would be appointed by the Governor. There would be no change in the method of appointing the two remaining physicians and pharmacists. Mr. Joyce explained that this bill would also allow an exemption from prior authorization for all mental health drugs, including antipsychotics, antidepressants and anticonvulsants. The bill would also exempt HIV drugs as well as drugs used in the treatment of cancer. If a generic is available, brand-name drugs would still require a prior authorization.

Mr. Samuelson asked if this bill would affect the relationship between the Board and the Department of Human Services. Mr. Joyce said that the DUR Board is federally mandated to act in an advisory capacity to the department.

The chair introduced Steve Espy, R.Ph., from Health Information Designs, Inc. (HID), the pharmacy services contractor for the RDUR and prior authorization programs. Mr. Espy explained HID's history and services, and described clients the company serves. He said that HID started the RDUR contract in June of 2004 and began the PA contract on Feb. 1, 2005. Mr. Espy gave the prior authorization help desk phone number as (866) 773-0695 and the fax number as (866) 254-0761. He said that HID had developed a web site for the DUR Board that includes copies of current PA request forms, algorithms, meeting announcements and other pertinent information. The web address is www.hidndmedicaid.com.

Mr. Samuelson asked about the new contractor and how HID was chosen for the contract. Mr. Joyce explained that the Board was notified of the RFP for the contract at a previous meeting, and that the Legislature provided appropriations for the contract when legislation passed for the

prior authorization process. He said that HID was the lowest bidder, and references gave excellent reviews of the work HID had performed for them.

Mr. Espy reviewed the provider letters, request forms and algorithms for the next classes of drugs to be implemented into the prior authorization system. He explained that the prior authorization of DAW drugs will be implemented March 8, 2005, the Cox II and brand-name NSAIDS on April 5 and the ACE inhibitors on May 3. He added that an implementation date for ARBs had not yet been established. Mr. Joyce asked that the criteria on the form that relates to the drug Altace be corrected.

The chair then asked Mr. Espy to review and explain the reports included in the DUR Board packet. Mr. Espy first explained the Cost Summary report, which identifies costs for two specific quarters. Included are the total cost of Medicaid prescriptions, the number of unduplicated recipients that received pharmacy services, the costs per member per month and the cost per prescription. Mr. Espy then explained the Cost Management report that graphs the associated costs, showing the pattern of claims costs. Mr. Espy noted that this was a useful tool for the Board to utilize when considering costs associated with the pharmacy program. He then reviewed the Top 25 Drugs based on number of claims from July 1 thru Sept. 30, 2004, and the Top 25 Drugs based on cost of claims for the same period.

The chair also asked Mr. Espy to review criteria provided in the DUR packets. Mr. Espy explained that the HID criteria manager introduces new criteria on a quarterly basis, based on the introduction of new drugs, new indications, new warnings or adverse effects. The additional criteria are to be added to existing criteria provided by HID when the company initiated RDUR services in 2004.

Mr. Joyce reviewed the RDUR process, reminding Board members of how the criteria are used in the letter intervention and explaining that the criteria do not affect the prior authorization process. Mr. Joyce recommended that the Board adopt the criteria. Bob Treitline asked if this would affect the POS criteria, and Mr. Joyce responded that POS criteria would not be affected. Mr. Treitline moved to adopt the criteria, and Greg Pfister seconded the motion.

Scott Setzepfandt said the criteria looked routine, and then suggested the Board table the vote and allow industry representatives to review the criteria for appropriateness and spelling. Mr. Joyce responded that the Board should not be burdened down with another agenda item, saying he would be glad to respond to any questions or concerns expressed by industry representatives. The chair asked for a voice vote, and the motion carried with no dissenting votes.

Mr. Samuelson asked if any movement existed to adopt a preferred drug list. Mr. Joyce said that a bill allowing for a PDL was defeated in the state Legislature.

The chair called for a break while Richard Dolinar, M.D., prepared for his presentation. When the meeting reconvened, Dr. Dolinar gave a presentation on evidence-based medicine, including handouts and slides. Questions and discussion followed.

The chair asked Mr. Espy to present recommendations for new classes of drugs to be reviewed for prior authorization. Mr. Espy said that he had reviewed other state programs as well as the availability of drug classes in the North Dakota Medicaid program. He said that both the calcium channel blocker and the beta blocker classes included a sufficient number of generic drugs for first-line therapy for hypertension, and recommended that the Board review these classes for prior authorization.

Mr. Espy then referred to one of the reports provided earlier, noting that three brand-name antidepressants were included in the Top 25 Drugs. He noted that Zoloft was the second-most prescribed drug in the Medicaid program, and suggested that brand-name antidepressants should not be considered for first-line therapy in the treatment of depression because of the availability of generic Prozac, Paxil and Celexa. Mr. Espy then suggested that the Board consider action to ensure that generics be used first. He said action could consist of:

- Explaining the availability of generics to providers through Academic Detailing
- Utilizing the letter intervention process
- Requiring prior authorization on brand-name antidepressants

Mr. Samuelson asked about Neurontin, and mentioned its position among the Top 25 Drugs. Mr. Espy explained that the implementation of the DAW PA on March 8 should affect Neurontin utilization. Mr. Treitline then asked about the utilization of time-released doses in long-term-care facilities, which had been discussed at a previous meeting.

Mr. Samuelson noted that the current prior authorization program did not appear to be saving money, judging from the information in the program summary report. Mr. Joyce explained that there were no cost increases between the two reported quarters, which was very unusual in Medicaid. Mr. Samuelson then asked that HID provide some cost-saving reports to the DUR Board at its next meeting. Mr. Treitline asked that the Board consider calcium channel blockers for prior authorization at a future board meeting.

The next meeting was scheduled for April 11, 2005, and will be held in the legislative building. Mr. Joyce said he would provide information on Part D of the Medicare Prescription Benefit and its effects on North Dakota Medicaid at the meeting.

Mr. Samuelson moved to adjourn the meeting, and Ms. Sorenson seconded the motion. The chair adjourned the meeting a 3:14 p.m.

Health Information
Designs, Inc.
(334) 502-3262

NORTH DAKOTA MEDICAID
Trend Summary Analysis
COX-II INHIBITORS

Period Covered	Recipients	% Change	# Rx's	% Change	Rx Claims Cost	% Change
Jun-04	1,409		1,582		$130,844.38	
Jul-04	1,401	-0.57%	1,525	-3.60%	$131,010.97	0.13%
Aug-04	1,441	2.86%	1,559	2.23%	$134,025.11	2.30%
Sep-04	1,337	-7.22%	1,418	-9.04%	$121,348.28	-9.46%
Oct-04	1,200	-10.25%	1,288	-9.17%	$111,463.99	-8.15%
Nov-04	1,215	1.25%	1,321	2.56%	$113,720.85	2.02%
Dec-04	1,105	-9.05%	1,196	-9.46%	$101,495.49	-10.75%

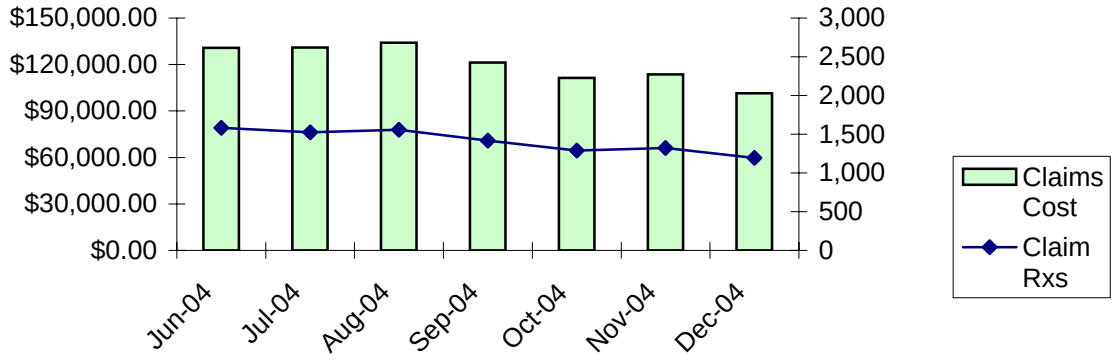
NORTH DAKOTA MEDICAID
Trend Summary Analysis
PPI'S

Period Covered	Recipients	% Change	# Rx's	% Change	Rx Claims Cost	% Change
Jun-04	2,138		2,478		$112,324.02	
Jul-04	2,093	-2.10%	2,336	-5.73%	$107,718.13	-4.10%
Aug-04	2,136	2.05%	2,396	2.57%	$120,762.55	12.11%
Sep-04	2,183	2.20%	2,381	-0.63%	$133,087.08	10.21%
Oct-04	2,183	0.00%	2,369	-0.50%	$141,596.61	6.39%
Nov-04	2,246	2.89%	2,486	4.94%	$154,435.40	9.07%
Dec-04	2,299	2.36%	2,554	2.74%	$147,993.06	-4.17%

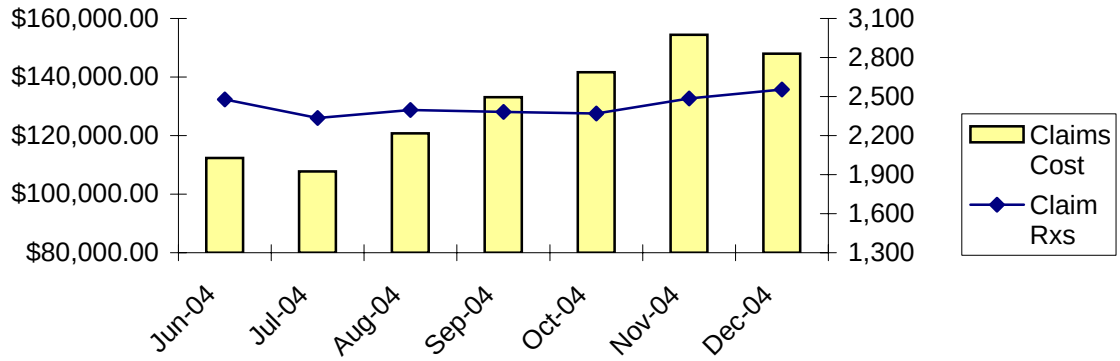
NORTH DAKOTA MEDICAID
Trend Summary Analysis
ANTIHISTAMINES

Period Covered	Recipients	% Change	# Rx's	% Change	Rx Claims Cost	% Change
Jun-04	1,212		1,363		$49,284.37	
Jul-04	1,050	-13.37%	1,129	-17.17%	$41,026.58	-16.76%
Aug-04	1,093	4.10%	1,164	3.10%	$40,571.05	-1.11%
Sep-04	1,145	4.76%	1,219	4.73%	$41,359.55	1.94%
Oct-04	1,013	-11.53%	1,063	-12.80%	$34,850.52	-15.74%
Nov-04	953	-5.92%	1,028	-3.29%	$33,430.56	-4.07%
Dec-04	902	-5.35%	985	-4.18%	$30,541.33	-8.64%

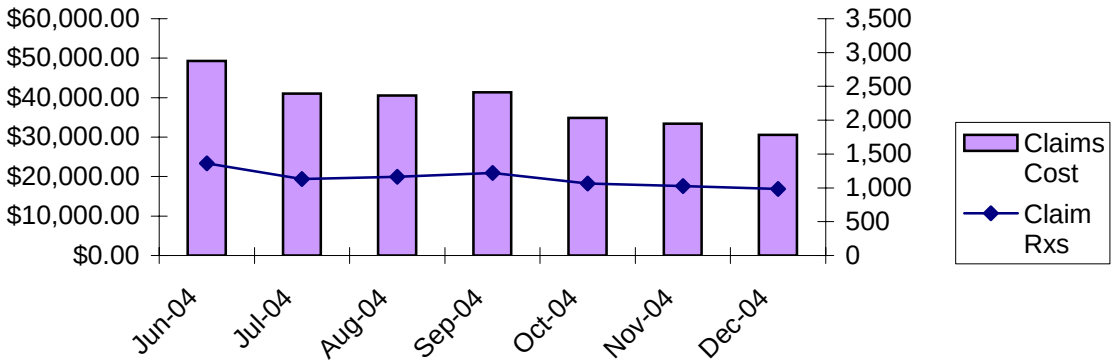
COX II INHIBITORS



PPI'S



ANTIHISTAMINES



ANTIDEPRESSANTS

DRUG	DEPRESSION	OCD	PANIC DISORDER	BULIMIA NERVOSA	PDD	PTSD	OTHER USES
CITALOPRAM	X	UR	UL	UL	UL	UR	Social phobia
ESCITALOPRA	X						
FLUOXETINE	X	X	X	X	X	UL	Bipolar Disorder
FLUVOXAMINE	UL	X		UL			
PAROXETINE	X	X	X*	UR	UL	X	Scoical anxiety
SERTRALINE	X	X	X	UR	X	X	Social phobia
DULOXETINE	X						Diabetic Neuorpathy
VENLAFAXINE	X						Social anxiety
BUPROPION	X						
MIRTAZAPINE	X						
ESCITALOPRAM	X						
							generic available

UL = Unlabled use UR= Use reported

H2S STUDY		
Paid Claims January 1997		
NDC Name	# of Scripts	Amt Paid
LUVOX	70	$ 6,489.01
PAXIL	514	$ 26,352.00
PROZAC	589	$ 46,626.90
ZOLOFT	937	$ 53,761.98
Totals	**2,110**	**$ 133,229.89**
Paid Claims January 1998		
NDC Name	# of Scripts	Amt Paid
LUVOX	69	$ 7,601.38
PAXIL	583	$ 33,628.46
PROZAC	569	$ 48,457.59
ZOLOFT	1,019	$ 60,793.89
Totals	**2,240**	**$ 150,481.32**
Paid Claims January 1999		
NDC Name	# of Scripts	Amt Paid
CELEXA	53	$ 2,502.64
LUVOX	87	$ 9,078.80
PAXIL	663	$ 39,405.93
PROZAC	553	$ 48,644.36
ZOLOFT	1,103	$ 68,295.74
Totals	**2,459**	**$ 167,927.47**
Paid Claims January 2000		
NDC Name	# of Scripts	Amt Paid
CELEXA	229	$ 12,470.22
LUVOX	83	$ 9,883.52
PAXIL	790	$ 49,715.23
PROZAC	553	$ 49,880.05
ZOLOFT	1,164	$ 74,276.34
Totals	**2,819**	**$ 196,225.36**

Paid Claims January 2001		
NDC Name	# of Scripts	Amt Paid
CELEXA	448	$ 27,811.44
FLUVOXAMINE MALEATE	12	$ 1,440.47
LUVOX	107	$ 15,654.39
PAXIL	975	$ 66,004.48
PROZAC	675	$ 65,116.69
ZOLOFT	1,560	$ 102,159.94
Totals	**3,784**	**$ 278,765.11**
Paid Claims January 2002		
NDC Name	# of Scripts	Amt Paid
CELEXA	777	$ 50,110.27
FLUOXETINE HCL	668	$ 57,192.10
FLUVOXAMINE MALEATE	112	$ 13,612.11
LUVOX	17	$ 3,402.22
PAXIL	1,091	$ 80,538.20
PROZAC	112	$ 12,601.52
PROZAC WEEKLY	69	$ 5,318.52
ZOLOFT	1,827	$ 125,753.56
Totals	**4,688**	**$ 349,827.68**
Paid Claims January 2003		
NDC Name	# of Scripts	Amt Paid
CELEXA	487	$ 28,847.88
FLUOXETINE HCL	453	$ 6,767.35
FLUVOXAMINE MALEATE	46	$ 5,058.07
LEXAPRO	169	$ 9,312.33
LUVOX	1	$ 39.40
PAXIL	610	$ 41,892.66
PAXIL CR	100	$ 7,106.25
PROZAC	9	$ 1,288.98
PROZAC WEEKLY	51	$ 4,360.63
ZOLOFT	1,110	$ 70,943.06
Totals	**3,040**	**$ 175,653.91**

Paid Claims January 2004		
NDC Name	# of Scripts	Amt Paid
CELEXA	539	$ 35,027.77
FLUOXETINE HCL	679	$ 10,027.18
FLUVOXAMINE MALEATE	66	$ 5,053.22
LEXAPRO	585	$ 33,832.11
PAROXETINE HCL	594	$ 35,999.43
PAXIL	46	$ 2,960.42
PAXIL CR	253	$ 20,249.43
PROZAC	18	$ 2,435.57
PROZAC WEEKLY	43	$ 3,889.33
ZOLOFT	1,603	$ 113,301.55
Totals	**4,426**	**$ 262,776.01**
Paid Claims January 2005		
NDC Name	# of Scripts	Amt Paid
CELEXA	75	$ 3,659.40
CITALOPRAM	407	$ 15,353.43
FLUOXETINE HCL	744	$ 10,565.99
FLUVOXAMINE MALEATE	61	$ 4,610.68
LEXAPRO	703	$ 42,557.54
PAROXETINE HCL	536	$ 30,494.78
PAXIL	9	$ 789.92
PAXIL CR	235	$ 20,003.51
PROZAC	17	$ 3,156.73
PROZAC WEEKLY	34	$ 3,411.16
ZOLOFT	1,653	$ 125,260.37
Totals	**4,474**	**$ 259,863.51**

CALCIUM CHANNEL BLOCKERS

DRUG	HTN	ANGINA	OTHER USES
AMLODIPINE	X	X	
DILITIAZEM SR	X		
DILITIAZEM ER	X	X	
FELODIPINE	X		
ISRADIPINE	X		
NICARDIPINE*	X	X	
NIFEDIPINE	X	X	
NISOLDIPINE	X		
VERAPAMIL IR	X	X	ARRHYTHMIAS
VERAPAMIL SR	X		
VERAPAMIL CR	X	X	

* SR form not available generically

generic available

Calcium Channel Blockers
1/1/04-12/31/04

NAME OF DRUG	$	# of Rxs
Calan SR	2229	39
Cover HS	2682	59
AdalatCC	1398	24
Norvasc	473988	10006
Procardia	1081	19
Nifedipine	88997	2353
Verapamil	46988	2443
Plendil	20004	464
Sular	3217	90
Tiazac	4843	84
Diltiazem	143063	4484
Cardizem	6345	157
Verelan PM	22606	412

BETABLOCKERS

DRUG	HTN	ARRHYTMIAS	ANGINA	OTHR USES
ACEBUTOLOL	X	X		
ATENOLOL	X		X	ACUTE MI
BETAXOLOL	X			
BISOPROLOL FUMARATE	X			
CARTEOLOL	X			
CARVEDIOL	X			CHF
LABETALOL	X			
METOPROLOL SUCCINATE	X		X	CHF
METOPROLOL TARTRATE	X		X	
NADOLOL	X		X	
PENBUTOLOL	X			
PINDOLOL	X			
PROPRANOLOL IR	X	X	X	POST MI
PROPRANOLOL ER	X		X	POST MI
TIMOLOL	X			POST MI

Beta Blockers
1/1/04-12/31/04

NAME OF DRUG	$	#of Rxs
Coreg	164815	2038
Inderal LA	64574	1801
Metoprolol	86452	8732
Bisoprolol	3899	157
Toprol XL	157084	6164
Tenormin	1859	29
Propranolol	21724	2561
Atenolol	76690	9599
Acebutolol	2142	99

HEALTH INFORMATION DESIGNS

using medication information cost effectively

May 26, 2005

The next North Dakota Drug Utilization Review (DUR) Board Meeting will be held:

June 6, 2005 at 1:00pm

Pioneer Room*
State Capitol
Ground Level
Judical Wing
Bismarck, ND

If you are unable to attend, please contact Brendan Joyce at (701) 328-4023 (sojoyb@state.nd.us).

Please remember to silence all pagers and cell phones prior to the start of the meeting.

1550 Pumphrey Ave • Auburn, AL 36832 • Phone: (334)502-3262 • Fax: (334) 502-6589
Auburn, Alabama • Jackson, Mississippi • Little Rock, Arkansas • Salisbury, Maryland

North Dakota Medicaid DUR Board
Meeting Agenda Pioneer Room
June 6, 2005 1:00 P.M.

1. Administrative items
   Travel vouchers

2. Old Business –

Review and approval of minutes of 04/11/05 meeting	Chairman
Budget update	Brendan Joyce
Review of the utilization of PPIs and Antihistamines	HID
Review of the effect of the PPI PA on total medical expenses	HID
Review of Antidepressant utilization	HID
Review of updated Antihistamine form	HID

3. New Business

Upcoming DUR Board Changes	Brendan Joyce
Emergency Item: ED drugs and Sex offenders	Brendan Joyce
Review of the Medicare Modernization Act on North Dakota Medicaid pharmacy expenditures	HID
Review of Zanaflex capsules	HID

4. Upcoming meeting agenda — Chairman

5. Adjourn — Chairman

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

Drug Utilization Review (DUR) Meeting Minutes
April 11, 2005

Members Present: Al Samuelson, Gary Betting, Greg Pfister, John Savageau, Pat Churchill, Carrie Sorenson, Scott Setzepfandt, Cheryl Huber, Bob Treitline, Leann Ness, Brendan Joyce.

HID Staff Present: Brenda Winslett, Rob Dibenedetto, John Williams, Steve Espy.

Members Absent: Jay Huber, Norman Byers.

Chair John Savageau called the meeting to order at 1:05pm, then asked for a motion to approve the minutes from the February 14, 2005 meeting Pat Churchill moved the minutes be approved and Cheryl Huber seconded the motion. The chair called for a voice vote to approve the minutes, which passed with no audile dissenters.

Budget Update: Brendan Joyce indicated that the biennium budget will end below expectation and the net budget will only provide a 4% increase in the budget. Historically the pharmacy expenditures have risen 12% to 13% per year.

John Savageau asked Brendan to explain the impact of the Medicare Modernization Act (MMA) on the pharmacy budget. Brendan gave a description of the potential effect to include change in average age of recipient, most common drugs paid for, number of claims per month, etc. Brendan explained that he has asked HID to prepare impact reports on the potential changes, John Savageau asked Steve Espy to make this an agenda item for the next meeting.

Cost Savings: Steve Espy presented cost savings report on the impact of the PA process for the PPI and antihistamine classes. The report covered the time period from June 2004 through December 2004.

The PPI report indicated a significant decrease in PPI utilization in June 2004 and a steady increase each month thereafter. Steve explained that the unavailability of Prilosec OTC and the inclusion of Omperazole as the drug to be used before a brand PPI could be approved attributed to an increase in cost in the last few months of 2004. Steve mentioned that the December 2004 cost of $147,993 was significantly less than the $269,000 in March 2004, which was the month prior to implementation of the PA for PPIs.

Steve then discussed the cost savings of antihistamines. The graphs indicate a steady decrease in utilization of the antihistamines from $49,284 in June 2004 to $30,541 in December 2004.

Bob Treitline requested a report that would indicate changes in numbers of GI bleeds or MD office visits, or changes to other GI drugs. John Savageau asked Steve Espy to include this report as an agenda item for the next meeting. Al Samuelson asked that HID include a longer time frame on those reports and also to include other factors that could have a bearing on utilization. John Savageau asked Steve to include this report as an agenda item for the next meeting.

Steve Espy asked the Board to consider this information and review to be incompliance with the State mandate to review drugs that require a PA on an annual basis. Bob Treitline moved that the current forms be updated to include relative costs, also asked the last line on the antihistamine form, " Patients must try and fail generic loratadine prior to receiving a leukotriene modifer or intranasal steroid to treat allergic rhinitis" be removed. Cheryl Huber seconded the motion. The chair called for a voice vote to approve the motion. The motion passed with no audile dissenters. John Savageau asked the new modified forms be included in the package for the next DUR meeting.

The Board verbally confirmed that the information and review did comply with the State mandate.

Drug Reviews: Steve Espy began by explaining that the information presented is not a clinical review. Following the previous methods of reviewing drug classes, the information indicates the availability of generic products to treat the same indications.

Antidepressants: Steve provided the Board with a list of antidepressant drugs, indicating generic or brand, and the primary indications for which each drug is approved. This was followed by the utilization of each drug over the last several years. Steve told the board that the purpose of this report was to make providers aware of the availability of generics to treat similar diagnoses. He suggested to the board that this information could be used to educate providers with the intent to increase generic utilization. Discussion followed concerning this class of drugs including information about recent legislative action. After the discussion the board directed Steve to report the utilization of antidepressants for those recipients with a diagnosis of depression. The report will be presented as an agenda item at the next DUR Board meeting and is to include the specialty of the prescriber, dosage forms, duration of treatment, and age groups of recipients broken down by decades.

*Calcium Channel Blockers***:** Steve Espy provided the Board with a list of the Calcium Channel Blockers, indicating generic or brand status, and the primary indications of each drug.
Also, he provided the board with the utilization of these drugs for the calendar year 2004. The discussion that followed concerned the change in utilization after the implementation of the MMA. Many members of the board felt it was prudent to await the outcome of this implementation before the board considers any action on this drug type. Steve suggested that the board would feel similarly about the next class of drugs, Beta Blockers. The board agreed to wait on both classes.

Brendan Joyce suggested to the board that HID provide the board with utilization breakdown by drug class, (excluding recipients that will be affected by the MMA) to assist the Board in determining where to concentrate its future efforts. Jophn Savageau asked Steve Espy to include this report as an agenda item for the next meeting

Compounding: Brendan Joyce gave a brief description of the amount of compounding in North Dakota pharmacies, as well as the reimbursement policy for prescriptions that are compounded.

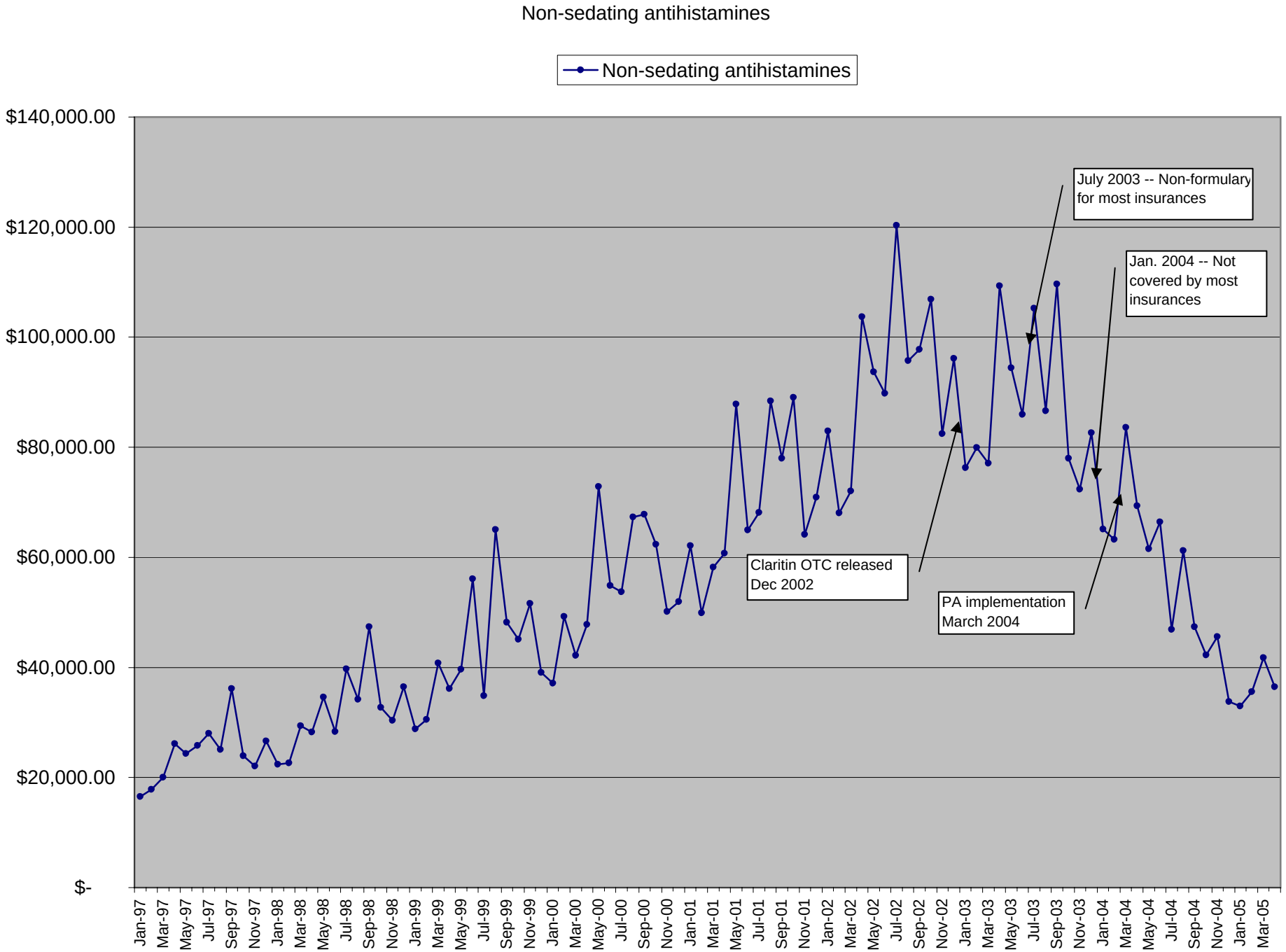
The next meeting was set for June 6, 2005 at 1:00pm at the Heritage Center.

Cheryl Huber moved for adjournment. Greg Pfister seconded the motion. The motion carried on a voice vote.

Budget Update

Projected appropriations for biennium 2003-2005 was $95,210,239.00
Projected expenditures for biennium 2003-2005 is $ 95,681,069.00

The legislatures appropriated $105,000,000.00 for biennium 2005-2007
This represents a 9.7% increase
The average growth in the pharmacy program is 13+%
The projection does take in effect the decrease in federal matching funds
It is expected that Part D will have no effect to minimal effect on the budget for the first 18 months.


Non-sedating antihistamines
Non-sedating antihistamines
$140,000.00
$120,000.00
$100,000.00
$80,000.00
$60,000.00
$40,000.00
$20,000.00
$-
July 2003 -- Non-formulary for most insurances
Jan. 2004 -- Not covered by most insurances
Claritin OTC released Dec 2002
PA implementation March 2004
Jan-97
Mar-97
May-97
Jul-97
Sep-97
Nov-97
Jan-98
Mar-98
May-98
Jul-98
Sep-98
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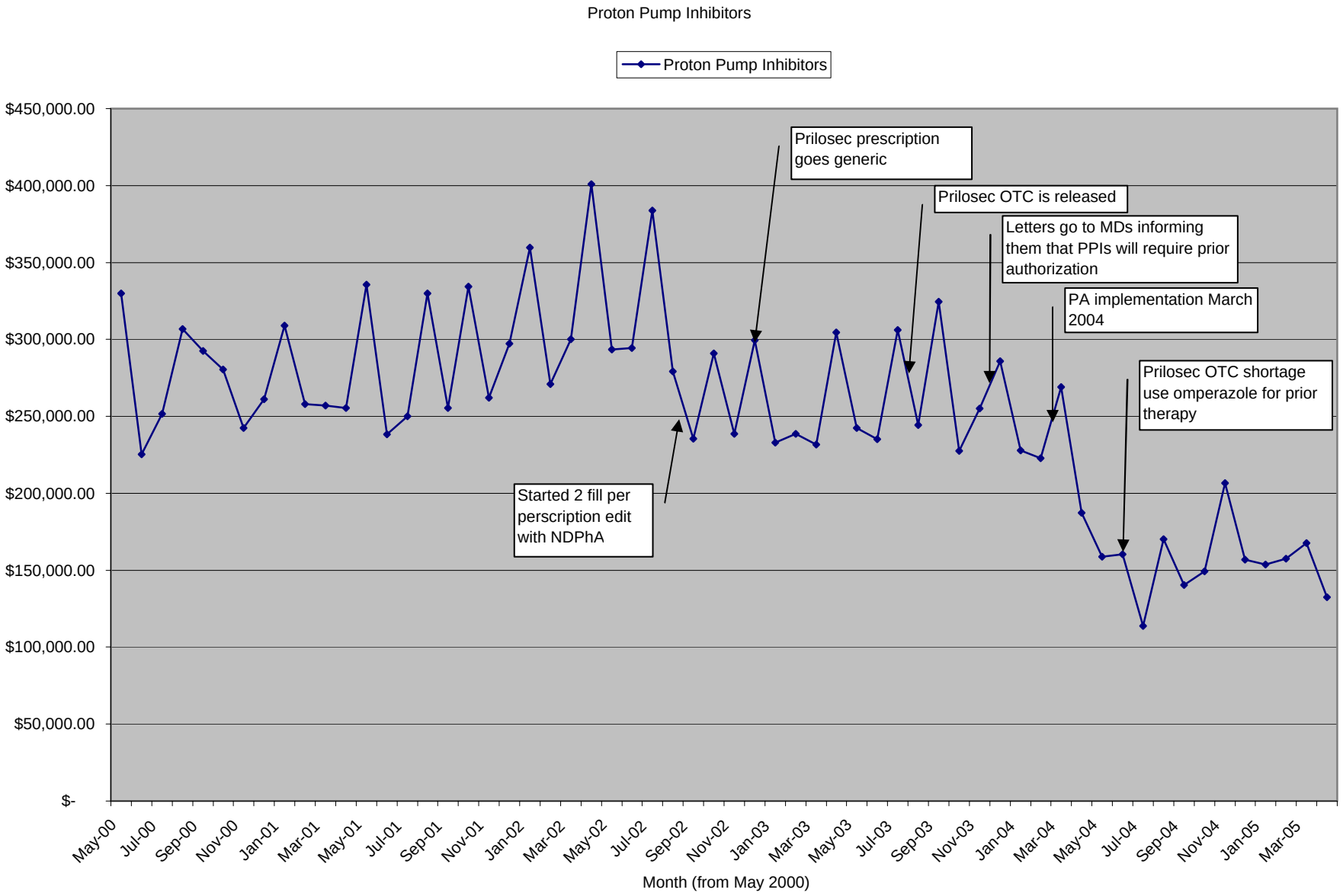
Proton Pump Inhibitors
Proton Pump Inhibitors
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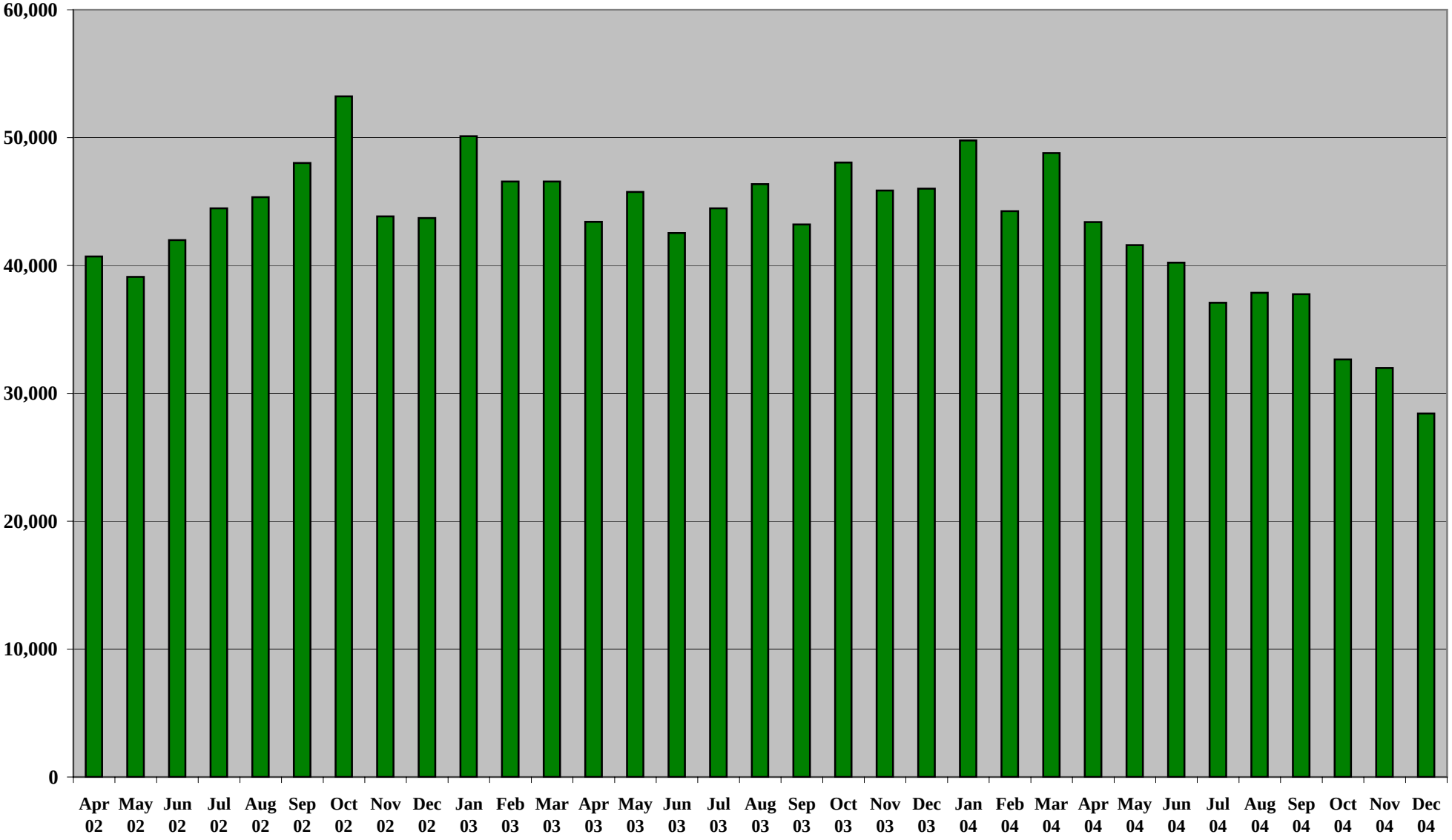
$350,000.00
$300,000.00
$250,000.00
$200,000.00
$150,000.00
$100,000.00
$50,000.00
$-
Prilosec prescription goes generic
Prilosec OTC is released
Letters go to MDs informing them that PPIs will require prior authorization
PA implementation March 2004
Prilosec OTC shortage use omperazole for prior therapy
Started 2 fill per perscription edit with NDPhA
May-00
Jul-00
Sep-00
Nov-00
Jan-01
Mar-01
May-01
Jul-01
Sep-01
Nov-01
Jan-02
Mar-02
May-02
Jul-02
Sep-02
Nov-02
Jan-03
Mar-03
May-03
Jul-03
Sep-03
Nov-03
Jan-04
Mar-04
May-04
Jul-04
Sep-04
Nov-04
Jan-05
Mar-05
Month (from May 2000)

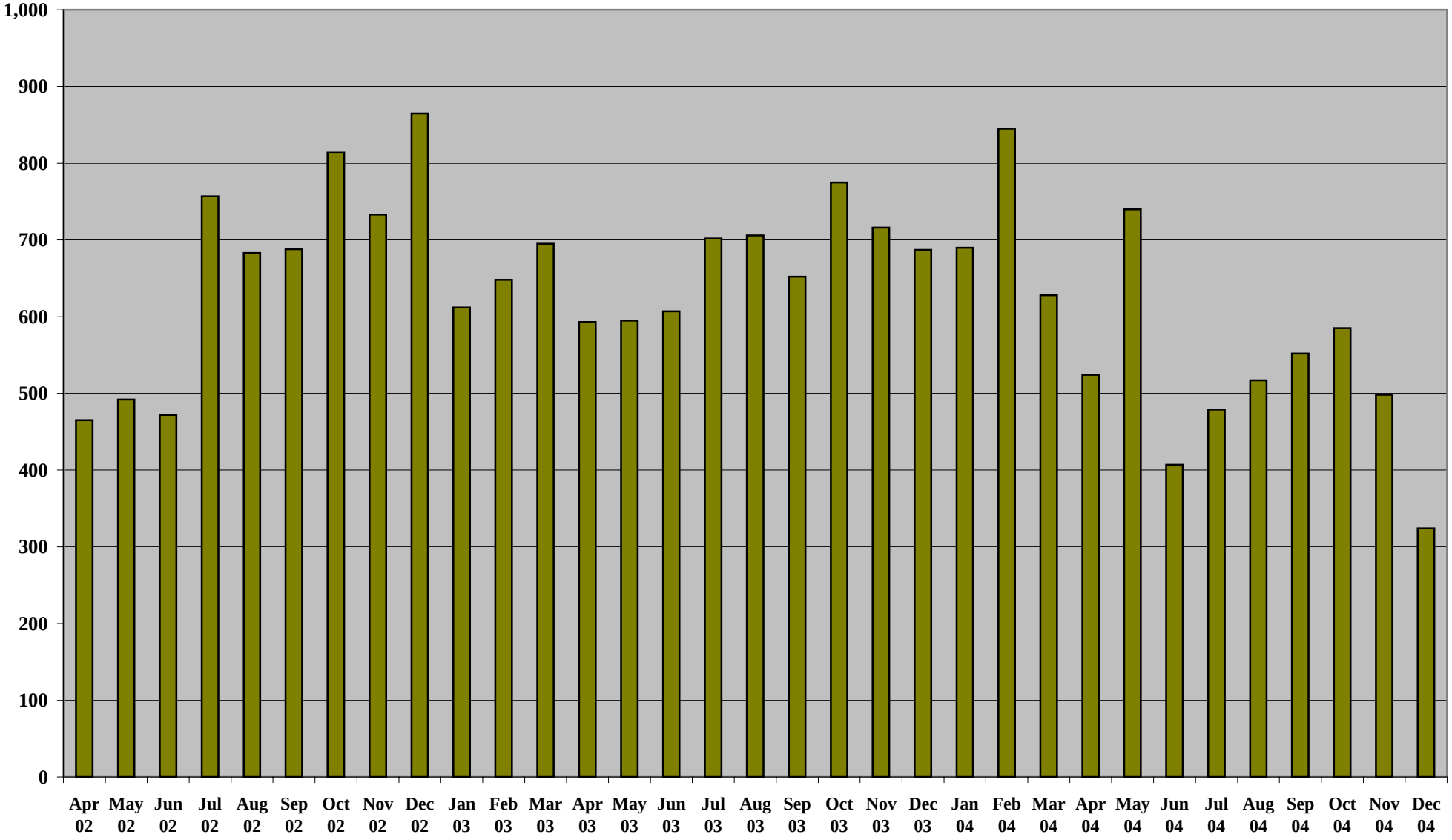
Diagnosis used in determing medical costs
associated with PPI utilization

531	gastric ulcer
532	duodenal ulcer
533	peptic ulcer site uns
534	gastrojejuinal ulcer
535	gastritis and duodenitis
5301	esophagitis
5302	ulcer of esophagus
5303	stricture/stenosis esophagus
5304	perf of esophagus
5305	dyskinesia esophagus
5306	diverticulum esophagus acquired
5307	gastroesophageal laceration hemorr
5789	uns hemorr of GI tract
53010	esophagitis NOS
53011	esophagitis reflux
53019	esophagitis nec
53081	esophageal reflux
53082	esophageal hemorr
53089	esophageal errosion
53100	gastric ulcer acute w/hemorr
53101	gastric ulcer acute w/hemorr
53110	gastric ulcer acute w/perf
53111	gastric ulcer acute w/perf
53120	gastric ulcer hemorr and perf
53121	gastric ulcer hemorr and perf
53130	gastric ulcer acute
53131	gastric ulcer acute
53140	gastric ulcer chronic hemorr
53141	gastric ulcer chronic hemorr
53150	chronic stomach ulcer w/perf
53151	chronic stomach ulcer w/perf obs
53160	gastric ulcer chronic hemorr and perf
53161	gastric ulcer chronic hemorr and perf
53170	gastric ulcer w/o hemorr or perf
53171	gastric ulcer w/o hemorr or perf
53190	stomach ulcer uns
53191	stomach ulcer uns w/obs
53200	duodenal ulcer acute w/hemorr
53201	duodenal ulcer acute w/hemorr

NORTH DAKOTA MEDICAID
Total Medical Claims Per Month for All Recipients of at Least One Prescription for a P.P.I. Before Implementation of the P.A. March 2004



NORTH DAKOTA MEDICAID
Medical Claims Per Month for GI Diagnoses for All Recipients of at Least One Prescription for a P.P.I. Before Implementation of the P.A. March 2004



Health Information Designs, Inc.

North Dakota Medicaid
Recipients Having Diagnosis Of Depression In 2004

5/10/2005

Number Recipients Having Diagnosis of Depression in 2004**	7517

** Recipient in Dual Elgibile Files from 10/04 - 02/05 were excluded

Age Breakdown

Age Range	Number Recipients
0-9	471
10-19	1691
20-29	1532
30-39	1368
40-49	1077
50-59	663
60-69	317
70-79	175
80-89	131
90-99	86
100-up	6

North Dakota Medicaid
Recipients Having Diagnosis Of Depression
In 2004
Antidepressant Drug Treatment

Drug Name	Number Unique Recipients Receiving Treatment
AMITRIPTYLINE HCL 10 MG TAB	105
AMITRIPTYLINE HCL 100 MG TAB	16
AMITRIPTYLINE HCL 150 MG TAB	5
AMITRIPTYLINE HCL 25 MG TAB	140
AMITRIPTYLINE HCL 50 MG TAB	58
AMITRIPTYLINE HCL 75 MG TAB	16
AMOXAPINE 50 MG TABLET	1
ANAFRANIL 50 MG CAPSULE	1
ANAFRANIL 75 MG CAPSULE	1
BUDEPRION SR 100 MG TABLET	6
BUDEPRION SR 150 MG TABLET	89
BUPROBAN 150 MG TABLET	2
BUPROPION HCL 100 MG TABLET	18
BUPROPION HCL 75 MG TABLET	27
BUPROPION HCL ER 100 MG TAB	4
BUPROPION HCL SR 100 MG TAB	64
BUPROPION HCL SR 150 MG TABLET	1
BUPROPION SR 150 MG TABLET	111
CELEXA 10 MG TABLET	21
CELEXA 10 MG/5 ML SOLUTION	4
CELEXA 20 MG TABLET	135
CELEXA 40 MG TABLET	96
CITALOPRAM HBR 10 MG TABLET	4
CITALOPRAM HBR 20 MG TABLET	26
CITALOPRAM HBR 40 MG TABLET	33
CLOMIPRAMINE 25 MG CAPSULE	2
CLOMIPRAMINE 50 MG CAPSULE	9
CLOMIPRAMINE 75 MG CAPSULE	2
CYMBALTA 20 MG CAPSULE	3
CYMBALTA 30 MG CAPSULE	20
CYMBALTA 60 MG CAPSULE	26
DESIPRAMINE 10 MG TABLET	5
DESIPRAMINE 100 MG TABLET	3
DESIPRAMINE 25 MG TABLET	8
DESIPRAMINE 50 MG TABLET	9
DESYREL 150 MG TABLET	3
DOXEPIN 10 MG CAPSULE	12
DOXEPIN 100 MG CAPSULE	7
DOXEPIN 150 MG CAPSULE	2
DOXEPIN 25 MG CAPSULE	14
DOXEPIN 50 MG CAPSULE	8
DOXEPIN 75 MG CAPSULE	4
EFFEXOR 100 MG TABLET	2
EFFEXOR 25 MG TABLET	2
EFFEXOR 37.5 MG TABLET	12
EFFEXOR 50 MG TABLET	1

Drug Name	Number Unique Recipients Receiving Treatment
EFFEXOR 75 MG TABLET	21
EFFEXOR XR 150 MG CAPSULE SA	252
EFFEXOR XR 37.5 MG CAP SA	116
EFFEXOR XR 75 MG CAPSULE SA	283
FLUOXETINE 10 MG CAPSULE	151
FLUOXETINE 20 MG CAPSULE	442
FLUOXETINE 20 MG/5 ML SOLN	9
FLUOXETINE 20 MG/5 ML SOLUTION	1
FLUOXETINE HCL 10 MG CAPSULE	22
FLUOXETINE HCL 10 MG TABLET	53
FLUOXETINE HCL 20 MG CAPSULE	135
FLUOXETINE HCL 20 MG TABLET	50
FLUOXETINE HCL 40 MG CAPSULE	1
FLUVOXAMINE MAL 100 MG TAB	17
FLUVOXAMINE MALEATE 50 MG TB	13
IMIPRAMINE HCL 10 MG TABLET	8
IMIPRAMINE HCL 25 MG TABLET	34
IMIPRAMINE HCL 50 MG TABLET	22
LEXAPRO 10 MG TABLET	366
LEXAPRO 20 MG TABLET	247
LEXAPRO 5 MG TABLET	2
LEXAPRO 5 MG/5 ML SOLUTION	1
MIRTAZAPINE 15 MG TABLET	132
MIRTAZAPINE 30 MG TABLET	85
MIRTAZAPINE 45 MG TABLET	41
NARDIL 15 MG TABLET	1
NEFAZODONE HCL 100 MG TABLET	4
NEFAZODONE HCL 150 MG TABLET	4
NEFAZODONE HCL 200 MG TABLET	7
NEFAZODONE HCL 250 MG TABLET	3
NEFAZODONE HCL 50 MG TABLET	1
NORTRIPTYLINE HCL 10 MG CAP	15
NORTRIPTYLINE HCL 25 MG CAP	42
NORTRIPTYLINE HCL 50 MG CAP	17
NORTRIPTYLINE HCL 75 MG CAP	6
PAMELOR 10 MG/5 ML SOLUTION	1
PARNATE 10 MG TABLET	1
PAROXETINE HCL 10 MG TABLET	37
PAROXETINE HCL 20 MG TABLET	109
PAROXETINE HCL 30 MG TABLET	47
PAROXETINE HCL 40 MG TABLET	89
PAXIL 10 MG TABLET	4
PAXIL 20 MG TABLET	3
PAXIL 30 MG TABLET	2
PAXIL 40 MG TABLET	3
PAXIL CR 12.5 MG TABLET	85
PAXIL CR 25 MG TABLET	154
PAXIL CR 37.5 MG TABLET	46
PROZAC 10 MG PULVULE	3
PROZAC 20 MG PULVULE	16
PROZAC 20 MG/5 ML SOLUTION	1

Drug Name	Number Unique Recipients Receiving Treatment
PROZAC 40 MG PULVULE	1
PROZAC WEEKLY 90 MG CAPSULE	23
REMERON 15 MG SOLTAB	11
REMERON 15 MG TABLET	4
REMERON 30 MG SOLTAB	8
REMERON 30 MG TABLET	3
REMERON 45 MG SOLTAB	2
REMERON 45 MG TABLET	3
SARAFEM 20 MG PULVULE	1
SERZONE 100 MG TABLET	1
SERZONE 150 MG TABLET	1
SERZONE 200 MG TABLET	1
SERZONE 250 MG TABLET	2
TOFRANIL 25 MG TABLET	1
TOFRANIL 50 MG TABLET	1
TRAZODONE 100 MG TABLET	196
TRAZODONE 150 MG TABLET	78
TRAZODONE 300 MG TABLET	1
TRAZODONE 50 MG TABLET	419
WELLBUTRIN 100 MG TABLET	1
WELLBUTRIN 75 MG TABLET	2
WELLBUTRIN SR 100 MG TABLET	47
WELLBUTRIN SR 150 MG TABLET	181
WELLBUTRIN SR 200 MG TABLET	41
WELLBUTRIN XL 150 MG TABLET	280
WELLBUTRIN XL 300 MG TABLET	323
ZOLOFT 100 MG TABLET	611
ZOLOFT 20 MG/ML ORAL CONC	9
ZOLOFT 25 MG TABLET	61
ZOLOFT 50 MG TABLET	371
ZYBAN 150 MG TABLET SA	8

ANTI-HISTAMINE PRIOR AUTHORIZATION
ND DEPARTMENT OF HUMAN SERVICES
MEDICAL SERVICES DIVISION

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

ND Medicaid requires that patients receiving anti-histamines must use **Loratadine*** as first line.

- **Loratadine OTC may be prescribed WITHOUT prior authorization. Loratadine OTC is covered by Medicaid when prescribed by a physician.**
- **Prior authorization is NOT required for patients < 13 years of age.**
- **Patients must use loratadine OTC for a minimum of 14 days for the trial to be considered a failure. Patient preference does not constitute failure.**
- Net cost to Medicaid: loratadine <<< Zyrtec < Clarinex < Allegra

Part I: TO BE COMPLETED BY PHYSICIAN

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

REQUESTED DRUG: Allegra Clarinex Zyrtec	**Requested Dosage:** (must be completed) **Diagnosis for this request:**

Qualifications for coverage:

❑ Failed loratadine	Start Date:	Dose:
	End Date:	Frequency:

Adverse Reaction (attach FDA Medwatch form) to loratadine or contraindicated: (provide description below)

Diagnosis of Urticaria

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

Physician Signature: Date:

Part II: TO BE COMPLETED BY PHARMACY

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

Part III: FOR OFFICIAL USE ONLY

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

Key

Class	Psych	Cancer or HIV	Already PA'd	Antibiotic or antiviral	
% of Spend (total)	42.89%	0.56%	3.82%	9.50%	56.77%
% of Spend (top 320)	47.63%	0.62%	4.25%	10.55%	63.05%

Totals above are based on Top 320 drugs which account for 90.04% of spend
(eliminates 1391 drugs which account for 9.96% of spend)

Psych	Cancer or HIV	Already PA'd	Antibiotic or antiviral

Drug Name	Total Rxs	Total Remb Amt	Non Dual Total Rxs	Non Dual Tot Remb Amt	Percentage Decrease	Percent of Spend	Running Percent of Spend
SEROQUEL	997	$199,238.78	456	$91,764.41	53.9%	3.99%	3.99%
ZYPREXA	803	$256,080.83	212	$72,759.41	71.6%	3.16%	7.16%
RISPERDAL	1225	$189,639.76	395	$62,589.60	67.0%	2.72%	9.88%
ZITHROMAX	1772	$75,107.01	1457	$60,019.53	20.1%	2.61%	12.49%
CONCERTA	603	$51,554.43	595	$50,746.24	1.6%	2.21%	14.70%
ZOLOFT	1764	$136,784.50	628	$47,515.28	65.3%	2.07%	16.76%
ABILIFY	234	$65,261.98	176	$46,077.96	29.4%	2.00%	18.77%
SYNAGIS	37	$45,804.33	37	$45,804.33	0.0%	1.99%	20.76%
ADDERALL XR	449	$41,432.90	443	$40,720.74	1.7%	1.77%	22.53%
TOPAMAX	314	$62,535.80	200	$38,649.25	38.2%	1.68%	24.21%
STRATTERA	369	$37,575.65	355	$36,138.47	3.8%	1.57%	25.78%
LAMICTAL	296	$68,127.17	167	$34,655.09	49.1%	1.51%	27.29%
SINGULAIR	616	$49,577.34	434	$34,291.58	30.8%	1.49%	28.78%
WELLBUTRIN XL	471	$42,697.80	375	$33,621.65	21.3%	1.46%	30.24%
ADVAIR DISKUS	533	$72,633.86	257	$33,272.72	54.2%	1.45%	31.69%
GEODON	297	$61,396.29	163	$31,662.18	48.4%	1.38%	33.07%
EFFEXOR XR	675	$66,298.54	322	$31,047.96	53.2%	1.35%	34.42%
TRILEPTAL	328	$48,146.23	227	$30,557.97	36.5%	1.33%	35.75%
OXYCONTIN	354	$61,183.71	150	$28,526.33	53.4%	1.24%	36.99%
DEPAKOTE	591	$77,415.51	232	$28,367.96	63.4%	1.23%	38.22%
LIPITOR	1355	$98,791.87	330	$24,166.39	75.5%	1.05%	39.27%
AMOX TR-POTASSIU	443	$24,195.27	401	$21,818.77	9.8%	0.95%	40.22%
GABAPENTIN	702	$66,571.55	208	$21,774.77	67.3%	0.95%	41.17%
DURAGESIC	454	$87,378.37	90	$20,477.61	76.6%	0.89%	42.06%
LEXAPRO	744	$45,799.71	337	$20,431.16	55.4%	0.89%	42.95%
OMEPRAZOLE	622	$53,224.75	237	$19,991.30	62.4%	0.87%	43.82%
AMBIEN	500	$36,164.11	274	$19,291.82	46.7%	0.84%	44.66%
PULMICORT	180	$29,811.54	114	$18,063.21	39.4%	0.79%	45.44%
KEPPRA	211	$40,852.57	104	$17,034.12	58.3%	0.74%	46.18%
RITALIN LA	190	$14,201.62	182	$13,690.03	3.6%	0.60%	46.78%
PAXIL CR	256	$22,115.73	152	$13,335.48	39.7%	0.58%	47.36%
IMITREX	97	$15,429.24	84	$13,274.45	14.0%	0.58%	47.94%
DEPAKOTE ER	193	$24,930.85	101	$13,266.25	46.8%	0.58%	48.51%
PEGASYS	10	$13,602.78	9	$12,843.22	5.6%	0.56%	49.07%
ENBREL	19	$18,875.36	14	$12,370.85	34.5%	0.54%	49.61%
ACCU-CHEK	166	$12,220.44	163	$12,112.52	0.9%	0.53%	50.14%
OMNICEF	188	$12,430.62	180	$11,898.92	4.3%	0.52%	50.65%
CELEBREX	626	$57,356.37	138	$11,694.54	79.6%	0.51%	51.16%
PAROXETINE HCL	582	$33,438.09	194	$10,935.16	67.3%	0.48%	51.64%
HUMALOG	264	$24,934.16	108	$10,840.03	56.5%	0.47%	52.11%
LEVAQUIN	377	$28,941.46	136	$10,624.58	63.3%	0.46%	52.57%
BEXTRA	385	$32,815.15	125	$10,478.02	68.1%	0.46%	53.03%
NEURONTIN	154	$24,952.94	62	$10,453.13	58.1%	0.45%	53.48%

CLOZARIL	212	$41,308.99	55	$9,935.56	75.9%	0.43%	53.91%
CEFZIL	138	$10,474.42	130	$9,841.76	6.0%	0.43%	54.34%
LANTUS	396	$30,005.65	140	$9,828.06	67.2%	0.43%	54.77%
ALBUTEROL	904	$12,691.43	660	$9,302.76	26.7%	0.40%	55.17%
ORTHO EVRA	246	$9,187.16	240	$8,957.69	2.5%	0.39%	55.56%
PREVACID	194	$25,001.66	77	$8,950.29	64.2%	0.39%	55.95%
ZYRTEC	223	$11,562.21	175	$8,843.15	23.5%	0.38%	56.34%
ZYPREXA ZYDIS	65	$27,079.26	25	$8,808.08	67.5%	0.38%	56.72%
METADATE CD	109	$8,802.86	109	$8,802.86	0.0%	0.38%	57.10%
COPAXONE	12	$13,867.98	7	$8,787.35	36.6%	0.38%	57.49%
ELIDEL	126	$10,137.62	104	$8,720.68	14.0%	0.38%	57.87%
ACTOS	237	$31,753.81	63	$8,301.37	73.9%	0.36%	58.23%
PLAVIX	487	$55,742.74	79	$8,267.23	85.2%	0.36%	58.59%
BUPROPION HCL	191	$11,490.28	123	$7,664.25	33.3%	0.33%	58.92%
PRILOSEC OTC	1400	$32,438.29	327	$7,659.56	76.4%	0.33%	59.25%
AMOXICILLIN	916	$8,963.62	754	$7,461.81	16.8%	0.32%	59.58%
ZOCOR	317	$32,376.59	75	$7,361.75	77.3%	0.32%	59.90%
HYDROCODONE W/A	966	$11,316.06	652	$7,351.39	35.0%	0.32%	60.22%
ZOFRAN	35	$15,655.07	24	$7,257.06	53.6%	0.32%	60.53%
CLOZAPINE	327	$23,055.38	116	$7,184.61	68.8%	0.31%	60.85%
FLOVENT	165	$13,312.99	93	$7,091.93	46.7%	0.31%	61.15%
FLONASE	221	$13,972.60	114	$7,089.47	49.3%	0.31%	61.46%
TAMIFLU	124	$7,668.68	116	$7,005.74	8.6%	0.30%	61.77%
XOPENEX	124	$10,302.04	89	$6,986.91	32.2%	0.30%	62.07%
CYMBALTA	127	$12,854.75	68	$6,786.32	47.2%	0.30%	62.37%
PROVIGIL	85	$12,265.13	46	$6,702.73	45.4%	0.29%	62.66%
DEPAKOTE SPRINKL	122	$12,130.66	68	$6,668.12	45.0%	0.29%	62.95%
FLUOXETINE HCL	796	$11,361.41	470	$6,493.78	42.8%	0.28%	63.23%
AVANDIA	176	$19,229.27	56	$6,464.73	66.4%	0.28%	63.51%
MIRTAZAPINE	687	$22,566.67	196	$6,426.15	71.5%	0.28%	63.79%
COPEGUS	6	$6,253.00	6	$6,253.00	0.0%	0.27%	64.06%
AMPHETAMINE SALT	121	$6,588.19	116	$6,170.19	6.3%	0.27%	64.33%
REBIF	6	$7,563.43	5	$6,135.93	18.9%	0.27%	64.60%
ONE TOUCH ULTRA	80	$6,152.64	78	$6,125.02	0.4%	0.27%	64.86%
NORVASC	854	$41,794.83	136	$5,986.46	85.7%	0.26%	65.12%
SKELAXIN	81	$9,063.62	58	$5,868.30	35.3%	0.26%	65.38%
DDAVP	49	$7,884.32	40	$5,625.18	28.7%	0.24%	65.62%
TRACLEER	2	$5,543.08	2	$5,543.08	0.0%	0.24%	65.87%
PROMETHAZINE W/C	557	$6,388.40	485	$5,527.61	13.5%	0.24%	66.11%
CEPHALEXIN	573	$7,835.07	381	$5,492.76	29.9%	0.24%	66.34%
ALBUTEROL SULFAT	550	$10,471.10	303	$5,404.14	48.4%	0.24%	66.58%
DETROL LA	397	$34,281.59	60	$5,286.87	84.6%	0.23%	66.81%
LOVENOX	22	$10,581.61	12	$5,219.20	50.7%	0.23%	67.04%
RISPERDAL CONSTA	10	$5,396.67	9	$5,135.98	4.8%	0.22%	67.26%
PULMOZYME	5	$5,010.11	5	$5,010.11	0.0%	0.22%	67.48%
COMBIVENT	219	$14,645.27	70	$4,740.34	67.6%	0.21%	67.68%
BACLOFEN	281	$12,953.14	105	$4,738.41	63.4%	0.21%	67.89%
CITALOPRAM HBR	465	$15,249.62	144	$4,667.66	69.4%	0.20%	68.09%
ULTRACET	197	$11,775.22	95	$4,665.91	60.4%	0.20%	68.30%
PROTONIX	139	$14,015.97	45	$4,654.55	66.8%	0.20%	68.50%
PROGRAF	14	$6,012.29	10	$4,570.22	24.0%	0.20%	68.70%
NEXIUM	83	$10,613.71	35	$4,564.20	57.0%	0.20%	68.90%
DITROPAN XL	227	$21,870.44	52	$4,542.99	79.2%	0.20%	69.09%
CIPRODEX	72	$5,166.25	62	$4,494.96	13.0%	0.20%	69.29%
VALTREX	69	$6,278.89	52	$4,482.29	28.6%	0.19%	69.48%
METFORMIN HCL	646	$11,504.34	241	$4,433.37	61.5%	0.19%	69.68%
BUDEPRION SR	108	$7,653.59	61	$4,296.15	43.9%	0.19%	69.86%
DUONEB	146	$17,661.02	40	$4,283.91	75.7%	0.19%	70.05%

BETASERON	9	$12,642.50	3	$4,276.65	66.2%	0.19%	70.24%
TEGRETOL XR	180	$9,757.37	77	$4,176.00	57.2%	0.18%	70.42%
TRAZODONE HCL	940	$8,965.81	421	$4,163.06	53.6%	0.18%	70.60%
CELLCEPT	15	$7,554.82	9	$4,160.84	44.9%	0.18%	70.78%
CRESTOR	185	$13,281.57	58	$4,088.42	69.2%	0.18%	70.96%
FREESTYLE TEST ST	53	$4,060.42	53	$4,060.42	0.0%	0.18%	71.13%
CLONIDINE HCL	496	$4,779.92	410	$3,904.55	18.3%	0.17%	71.30%
MORPHINE SULFATE	181	$9,650.67	43	$3,848.51	60.1%	0.17%	71.47%
COMBIVIR	11	$7,058.55	6	$3,816.36	45.9%	0.17%	71.64%
MINOCYCLINE HCL	109	$4,711.82	86	$3,759.89	20.2%	0.16%	71.80%
LEVOTHYROXINE SO	1170	$14,039.16	330	$3,747.95	73.3%	0.16%	71.96%
OXYCODONE HCL	155	$7,943.82	72	$3,731.03	53.0%	0.16%	72.13%
FOSAMAX	455	$30,508.01	64	$3,702.71	87.9%	0.16%	72.29%
AVONEX	14	$14,788.52	3	$3,659.94	75.3%	0.16%	72.45%
PROPOXYPHENE NA	566	$7,634.98	295	$3,657.16	52.1%	0.16%	72.61%
NASACORT AQ	129	$8,489.22	58	$3,626.00	57.3%	0.16%	72.76%
DEXTROAMPHETAM	104	$3,943.09	94	$3,611.15	8.4%	0.16%	72.92%
PREMARIN	265	$9,302.03	104	$3,582.36	61.5%	0.16%	73.08%
TOPROL XL	531	$14,979.88	132	$3,477.44	76.8%	0.15%	73.23%
CLONAZEPAM	598	$7,524.55	281	$3,459.82	54.0%	0.15%	73.38%
METHYLPHENIDATE	118	$3,577.38	104	$3,287.39	8.1%	0.14%	73.52%
TRAMADOL HCL	368	$7,116.58	178	$3,242.60	54.4%	0.14%	73.66%
INDERAL LA	149	$7,981.44	63	$3,220.19	59.7%	0.14%	73.80%
GLYCOLAX	233	$7,769.45	109	$3,202.97	58.8%	0.14%	73.94%
KALETRA	7	$4,446.25	5	$3,176.75	28.6%	0.14%	74.08%
LORAZEPAM	890	$11,241.05	269	$3,171.80	71.8%	0.14%	74.22%
BENZACLIN	51	$3,170.85	51	$3,170.85	0.0%	0.14%	74.36%
ZETIA	139	$9,567.76	44	$3,157.21	67.0%	0.14%	74.49%
ALLEGRA	91	$5,887.42	50	$3,152.28	46.5%	0.14%	74.63%
HUMALOG MIX 75/25	94	$10,714.62	21	$3,102.93	71.0%	0.13%	74.76%
SYNTHROID	826	$12,429.72	222	$3,099.64	75.1%	0.13%	74.90%
TRICOR	138	$10,410.66	40	$3,092.83	70.3%	0.13%	75.03%
ARICEPT	468	$59,705.98	29	$3,089.13	94.8%	0.13%	75.17%
AMOXICILLIN TRIHYD	195	$3,061.28	195	$3,061.28	0.0%	0.13%	75.30%
CYCLOBENZAPRINE	378	$4,369.97	277	$3,040.67	30.4%	0.13%	75.43%
ACETAMINOPHEN W	462	$4,642.22	334	$3,031.50	34.7%	0.13%	75.57%
LISINOPRIL	1137	$13,991.12	261	$3,020.94	78.4%	0.13%	75.70%
VFEND	2	$2,987.17	2	$2,987.17	0.0%	0.13%	75.83%
ALTACE	243	$11,603.67	69	$2,968.05	74.4%	0.13%	75.96%
DIFFERIN	40	$3,293.71	34	$2,949.92	10.4%	0.13%	76.08%
AMOXIL	313	$2,990.06	307	$2,925.56	2.2%	0.13%	76.21%
OXYCODONE W/ACE	392	$4,587.93	250	$2,925.25	36.2%	0.13%	76.34%
ORTHO TRI-CYCLEN	81	$3,041.40	78	$2,920.26	4.0%	0.13%	76.47%
FUROSEMIDE	2765	$22,168.84	392	$2,836.65	87.2%	0.12%	76.59%
SYMBYAX	19	$5,403.13	10	$2,823.95	47.7%	0.12%	76.71%
ZOMIG	21	$2,904.28	20	$2,804.75	3.4%	0.12%	76.83%
METHYLIN	144	$3,280.17	120	$2,797.93	14.7%	0.12%	76.96%
FLUCONAZOLE	251	$3,816.97	179	$2,792.05	26.9%	0.12%	77.08%
RELPAX	30	$3,439.96	25	$2,763.91	19.7%	0.12%	77.20%
HUMULIN N	200	$8,857.81	56	$2,761.93	68.8%	0.12%	77.32%
IBUPROFEN	487	$3,794.30	361	$2,737.68	27.8%	0.12%	77.44%
NITROFURANTOIN M	154	$5,486.83	78	$2,736.54	50.1%	0.12%	77.56%
ZANTAC	73	$5,250.32	60	$2,732.49	48.0%	0.12%	77.67%
NASONEX	78	$4,920.90	41	$2,698.98	45.2%	0.12%	77.79%
XELODA	4	$2,684.63	4	$2,684.63	0.0%	0.12%	77.91%
HYDROCODONE/ACI	285	$4,893.56	194	$2,673.44	45.4%	0.12%	78.02%
HUMULIN 70/30	278	$12,824.22	48	$2,651.86	79.3%	0.12%	78.14%
HYDROXYZINE HCL	192	$6,500.08	91	$2,610.22	59.8%	0.11%	78.25%

HUMIRA	7	$7,069.42	2	$2,597.24	63.3%	0.11%	78.37%
CARBATROL	45	$3,555.21	32	$2,584.33	27.3%	0.11%	78.48%
NOVOLOG	39	$4,379.44	23	$2,550.39	41.8%	0.11%	78.59%
PEPTAMEN JUNIOR	2	$2,546.65	2	$2,546.65	0.0%	0.11%	78.70%
PROMETHAZINE HCl	265	$4,030.35	183	$2,537.17	37.0%	0.11%	78.81%
MOBIC	61	$5,611.19	25	$2,492.48	55.6%	0.11%	78.92%
SULFAMETHOXAZOL	406	$4,027.99	233	$2,491.42	38.1%	0.11%	79.03%
BIAXIN XL	37	$2,673.90	35	$2,485.42	7.0%	0.11%	79.14%
KINERET	5	$6,157.39	2	$2,465.84	60.0%	0.11%	79.24%
AVONEX ADMINISTR	4	$2,457.96	4	$2,457.96	0.0%	0.11%	79.35%
SEREVENT DISKUS	80	$7,062.03	26	$2,444.47	65.4%	0.11%	79.46%
LORATADINE	405	$5,871.72	159	$2,387.20	59.3%	0.10%	79.56%
ZYVOX	7	$7,268.28	3	$2,380.18	67.3%	0.10%	79.66%
COREG	181	$15,244.14	29	$2,378.75	84.4%	0.10%	79.77%
FELBATOL	28	$5,551.71	17	$2,377.74	57.2%	0.10%	79.87%
RHINOCORT AQUA	59	$4,021.86	35	$2,367.76	41.1%	0.10%	79.97%
WELLBUTRIN SR	30	$4,003.95	16	$2,356.61	41.1%	0.10%	80.08%
TRINESSA	96	$2,583.97	88	$2,351.50	9.0%	0.10%	80.18%
BIAXIN	38	$2,691.93	33	$2,348.30	12.8%	0.10%	80.28%
LAMISIL	23	$4,502.25	12	$2,325.09	48.4%	0.10%	80.38%
AVANDAMET	36	$4,702.59	16	$2,295.35	51.2%	0.10%	80.48%
VALPROIC ACID	95	$4,646.56	45	$2,280.03	50.9%	0.10%	80.58%
AUGMENTIN XR	38	$2,928.18	31	$2,269.00	22.5%	0.10%	80.68%
DIOVAN	196	$9,814.25	47	$2,264.75	76.9%	0.10%	80.78%
ALDARA	19	$2,606.24	17	$2,259.14	13.3%	0.10%	80.88%
LITHIUM CARBONAT	193	$3,929.34	109	$2,250.94	42.7%	0.10%	80.97%
IMIPRAMINE HCL	147	$3,172.28	102	$2,213.33	30.2%	0.10%	81.07%
NOVOLOG MIX 70/30	31	$3,924.11	14	$2,212.04	43.6%	0.10%	81.17%
GENOTROPIN	3	$2,198.55	3	$2,198.55	0.0%	0.10%	81.26%
BACTROBAN	80	$3,698.83	49	$2,190.39	40.8%	0.10%	81.36%
CIPROFLOXACIN HC	288	$5,628.73	121	$2,185.03	61.2%	0.10%	81.45%
DILANTIN	278	$7,154.44	76	$2,149.81	70.0%	0.09%	81.55%
CARNITOR	34	$2,753.09	28	$2,119.47	23.0%	0.09%	81.64%
CARBAMAZEPINE	248	$5,856.76	89	$2,116.41	63.9%	0.09%	81.73%
DEPO-PROVERA	43	$2,338.26	38	$2,107.23	9.9%	0.09%	81.82%
HYDROCODONE BIT	88	$2,683.81	70	$2,081.49	22.4%	0.09%	81.91%
FLOLAN	1	$2,079.34	1	$2,079.34	0.0%	0.09%	82.00%
TIZANIDINE HCL	91	$4,235.63	43	$2,052.85	51.5%	0.09%	82.09%
AMITRIPTYLINE HCL	522	$4,092.57	272	$2,043.65	50.1%	0.09%	82.18%
VALCYTE	3	$3,796.19	2	$2,010.02	47.1%	0.09%	82.27%
KETEK PAK	42	$2,507.54	33	$2,008.46	19.9%	0.09%	82.36%
MARINOL	8	$3,784.94	3	$1,982.45	47.6%	0.09%	82.44%
BUSPIRONE HCL	242	$6,170.27	79	$1,972.86	68.0%	0.09%	82.53%
NYSTATIN	202	$3,808.12	127	$1,959.15	48.6%	0.09%	82.61%
ACIPHEX	35	$4,600.05	13	$1,942.04	57.8%	0.08%	82.70%
ALPRAZOLAM	482	$3,984.92	227	$1,938.60	51.4%	0.08%	82.78%
DANTRIUM	24	$3,818.50	11	$1,937.20	49.3%	0.08%	82.87%
ZONEGRAN	36	$6,379.02	16	$1,904.20	70.1%	0.08%	82.95%
TRI-SPRINTEC	74	$2,013.64	69	$1,896.80	5.8%	0.08%	83.03%
POTASSIUM CHLORI	1067	$17,102.22	144	$1,895.71	88.9%	0.08%	83.11%
WARFARIN SODIUM	883	$11,885.81	141	$1,895.45	84.1%	0.08%	83.20%
DIASTAT	15	$2,112.88	14	$1,891.09	10.5%	0.08%	83.28%
ARIMIDEX	28	$6,518.95	8	$1,869.92	71.3%	0.08%	83.36%
PROTOPIC	15	$1,934.63	14	$1,869.44	3.4%	0.08%	83.44%
DESMOPRESSIN AC	21	$2,510.28	17	$1,842.84	26.6%	0.08%	83.52%
YASMIN 28	54	$1,949.44	51	$1,837.08	5.8%	0.08%	83.60%
TEGRETOL	75	$5,465.08	24	$1,832.77	66.5%	0.08%	83.68%
GUANFACINE HCL	96	$1,891.85	92	$1,816.53	4.0%	0.08%	83.76%

EFFEXOR	66	$5,731.44	21	$1,814.84	68.3%	0.08%	83.84%
IPRATROPIUM BROM	172	$8,538.73	39	$1,813.52	78.8%	0.08%	83.92%
TRIAMCINOLONE AC	316	$3,207.87	179	$1,803.88	43.8%	0.08%	84.00%
ACCUNEB	37	$2,105.95	33	$1,779.30	15.5%	0.08%	84.07%
FORTEO	11	$6,197.69	3	$1,774.35	71.4%	0.08%	84.15%
ZELNORM	24	$3,084.87	12	$1,772.48	42.5%	0.08%	84.23%
FLUVOXAMINE MALE	65	$4,934.41	22	$1,763.81	64.3%	0.08%	84.30%
SUSTIVA	7	$3,071.87	4	$1,756.64	42.8%	0.08%	84.38%
PRAVACHOL	90	$8,416.13	19	$1,754.28	79.2%	0.08%	84.46%
MAXAIR AUTOHALER	26	$1,993.65	24	$1,746.32	12.4%	0.08%	84.53%
SONATA	36	$3,702.79	15	$1,744.46	52.9%	0.08%	84.61%
AZMACORT	55	$4,444.74	21	$1,744.22	60.8%	0.08%	84.68%
COZAAR	224	$11,292.88	44	$1,742.09	84.6%	0.08%	84.76%
INSULIN SYRINGE	183	$3,889.95	82	$1,735.74	55.4%	0.08%	84.84%
MUPIROCIN	104	$4,449.38	44	$1,720.32	61.3%	0.07%	84.91%
AUGMENTIN ES-600	21	$1,715.14	21	$1,715.14	0.0%	0.07%	84.99%
MAXALT	11	$1,698.03	11	$1,698.03	0.0%	0.07%	85.06%
VIGAMOX	54	$2,477.67	38	$1,688.03	31.9%	0.07%	85.13%
RANITIDINE HCL	521	$6,653.16	133	$1,674.40	74.8%	0.07%	85.21%
PREDNISONE	698	$4,517.38	281	$1,667.77	63.1%	0.07%	85.28%
PROZAC WEEKLY	29	$2,794.19	16	$1,664.37	40.4%	0.07%	85.35%
GLIPIZIDE ER	279	$6,887.34	70	$1,662.26	75.9%	0.07%	85.42%
NORTREL	82	$2,037.85	66	$1,652.82	18.9%	0.07%	85.49%
SUBOXONE	7	$1,640.14	7	$1,640.14	0.0%	0.07%	85.57%
CLINDAMYCIN HCL	121	$2,306.55	87	$1,638.10	29.0%	0.07%	85.64%
PROZAC	16	$3,537.34	6	$1,625.04	54.1%	0.07%	85.71%
VIAGRA	43	$2,439.89	29	$1,613.92	33.9%	0.07%	85.78%
SEASONALE	17	$1,725.81	16	$1,595.61	7.5%	0.07%	85.85%
PHENYTOIN SODIUM	171	$5,248.20	50	$1,587.62	69.7%	0.07%	85.92%
RIMANTADINE HCL	236	$5,812.71	70	$1,584.06	72.7%	0.07%	85.99%
CIPRO HC	29	$2,216.90	21	$1,560.66	29.6%	0.07%	86.05%
ATROVENT	64	$3,864.33	28	$1,552.22	59.8%	0.07%	86.12%
THALOMID	2	$3,872.52	1	$1,551.13	59.9%	0.07%	86.19%
ULTRASE MT 20	3	$2,339.84	2	$1,550.92	33.7%	0.07%	86.26%
CARISOPRODOL	102	$2,117.08	75	$1,488.86	29.7%	0.06%	86.32%
TAZORAC	18	$1,568.67	17	$1,486.72	5.2%	0.06%	86.39%
EMEND	8	$2,069.03	6	$1,486.45	28.2%	0.06%	86.45%
PENICILLIN V POTAS	154	$1,701.72	132	$1,482.97	12.9%	0.06%	86.51%
NUVARING	41	$1,507.08	40	$1,465.15	2.8%	0.06%	86.58%
CLOTRIMAZOLE/BET	138	$4,519.98	51	$1,457.98	67.7%	0.06%	86.64%
TOBI	3	$4,458.10	2	$1,455.18	67.4%	0.06%	86.70%
PATANOL	47	$3,121.64	23	$1,452.75	53.5%	0.06%	86.77%
CLINDAMYCIN PHOS	63	$1,875.29	52	$1,439.71	23.2%	0.06%	86.83%
FLOXIN	37	$1,929.70	27	$1,437.53	25.5%	0.06%	86.89%
NIASPAN	37	$2,683.22	20	$1,433.76	46.6%	0.06%	86.96%
TEQUIN	57	$4,163.54	22	$1,404.14	66.3%	0.06%	87.02%
PEG-INTRON	1	$1,396.74	1	$1,396.74	0.0%	0.06%	87.08%
METFORMIN HCL ER	97	$3,063.53	43	$1,392.37	54.6%	0.06%	87.14%
PEDIASURE	7	$1,391.90	7	$1,391.90	0.0%	0.06%	87.20%
GABITRIL	30	$2,822.69	18	$1,391.46	50.7%	0.06%	87.26%
CEFTIN	32	$1,389.37	32	$1,389.37	0.0%	0.06%	87.32%
SPIRONOLACTONE	352	$6,851.53	71	$1,381.40	79.8%	0.06%	87.38%
AVINZA	22	$3,853.32	10	$1,378.37	64.2%	0.06%	87.44%
DOXYCYCLINE HYCL	239	$1,977.68	168	$1,375.52	30.4%	0.06%	87.50%
LOTREL	112	$7,945.02	22	$1,368.04	82.8%	0.06%	87.56%
ACTIQ	6	$1,841.51	2	$1,354.55	26.4%	0.06%	87.62%
BROMETANE DX	124	$1,454.78	117	$1,350.55	7.2%	0.06%	87.68%
AMARYL	217	$6,659.81	39	$1,349.20	79.7%	0.06%	87.74%

ZOVIRAX	32	$2,160.83	21	$1,336.99	38.1%	0.06%	87.79%
ONE TOUCH TEST S	17	$1,331.68	17	$1,331.68	0.0%	0.06%	87.85%
CEFUROXIME	45	$2,324.56	25	$1,316.37	43.4%	0.06%	87.91%
PEDIASURE WITH FI	6	$1,311.00	6	$1,311.00	0.0%	0.06%	87.97%
MIRAPEX	69	$6,827.72	14	$1,306.57	80.9%	0.06%	88.02%
MEGESTROL ACETA	49	$5,357.27	10	$1,303.58	75.7%	0.06%	88.08%
TRIMOX 250	147	$1,301.87	147	$1,301.87	0.0%	0.06%	88.14%
ATENOLOL	791	$6,057.37	184	$1,292.52	78.7%	0.06%	88.19%
CARDEC DM	51	$1,308.86	49	$1,276.88	2.4%	0.06%	88.25%
CARBAXEFED DM RI	42	$1,270.72	42	$1,270.72	0.0%	0.06%	88.30%
KYTRIL	2	$1,269.06	2	$1,269.06	0.0%	0.06%	88.36%
TRUVADA	2	$1,259.99	2	$1,259.99	0.0%	0.05%	88.41%
SPIRIVA	72	$7,365.40	12	$1,248.06	83.1%	0.05%	88.47%
GLYBURIDE-METFOI	70	$3,239.72	28	$1,228.30	62.1%	0.05%	88.52%
PRENATAL PLUS	217	$1,711.65	152	$1,213.42	29.1%	0.05%	88.57%
OXYCODONE HCL-A	14	$1,370.60	13	$1,197.00	12.7%	0.05%	88.63%
PREMPRO	72	$2,746.21	33	$1,196.91	56.4%	0.05%	88.68%
HYDROCHLOROTHIA	768	$5,182.81	199	$1,190.47	77.0%	0.05%	88.73%
METROGEL-VAGINA	29	$1,567.34	22	$1,173.55	25.1%	0.05%	88.78%
GAMMAGARD S/D	1	$1,172.50	1	$1,172.50	0.0%	0.05%	88.83%
AMANTADINE HCL	221	$2,329.28	112	$1,152.11	50.5%	0.05%	88.88%
AGGRENOX	40	$4,744.21	10	$1,151.42	75.7%	0.05%	88.93%
PREVPAC	7	$1,803.08	4	$1,144.20	36.5%	0.05%	88.98%
FLUMADINE	73	$1,170.04	71	$1,142.50	2.4%	0.05%	89.03%
CRYSELLE	58	$1,478.50	46	$1,137.67	23.1%	0.05%	89.08%
HUMULIN R	119	$3,778.17	34	$1,132.71	70.0%	0.05%	89.13%
FAMOTIDINE	446	$6,135.99	89	$1,130.33	81.6%	0.05%	89.18%
NICOTINE TRANSDE	40	$1,605.46	29	$1,130.09	29.6%	0.05%	89.23%
LESSINA	47	$1,243.42	42	$1,121.82	9.8%	0.05%	89.28%
NIFEDIPINE ER	108	$4,495.57	23	$1,121.25	75.1%	0.05%	89.33%
NAMENDA	172	$19,324.98	11	$1,115.28	94.2%	0.05%	89.37%
RAPAMUNE	2	$1,110.96	2	$1,110.96	0.0%	0.05%	89.42%
OXYCODONE/APAP	17	$1,192.00	14	$1,101.70	7.6%	0.05%	89.47%
AVELOX	32	$2,507.53	13	$1,100.34	56.1%	0.05%	89.52%
MAXALT MLT	18	$1,781.75	12	$1,099.92	38.3%	0.05%	89.57%
ENDOCET	65	$1,477.52	38	$1,095.31	25.9%	0.05%	89.61%
DILTIAZEM HCL	224	$7,154.37	39	$1,095.16	84.7%	0.05%	89.66%
GLYBURIDE	251	$3,804.69	72	$1,094.79	71.2%	0.05%	89.71%
BENZONATATE	103	$1,678.90	68	$1,091.88	35.0%	0.05%	89.76%
ALAVERT	117	$2,320.28	56	$1,084.82	53.2%	0.05%	89.80%
APRI	64	$1,359.98	52	$1,082.79	20.4%	0.05%	89.85%
ATACAND	113	$5,386.79	23	$1,082.77	79.9%	0.05%	89.90%
HYDROCODONE-ACI	109	$1,512.78	79	$1,079.77	28.6%	0.05%	89.94%
NEOMYCIN/POLYMY	71	$1,651.77	52	$1,075.26	34.9%	0.05%	89.99%
ERYTHROMYCIN-BE	14	$1,189.69	13	$1,068.89	10.2%	0.05%	90.04%
LACTULOSE	191	$4,070.81	47	$1,068.88	73.7%	0.05%	90.08%
NALTREXONE HYDR	25	$2,166.95	12	$1,067.04	50.8%	0.05%	90.13%
BENZTROPINE MESY	293	$3,228.48	97	$1,062.08	67.1%	0.05%	90.18%
PREDNISOLONE	95	$1,098.51	93	$1,053.56	4.1%	0.05%	90.22%
ENALAPRIL MALEAT	528	$6,513.30	101	$1,038.97	84.0%	0.05%	90.27%
KETEK	19	$1,347.80	14	$1,038.66	22.9%	0.05%	90.31%
FOCALIN	28	$1,083.03	27	$1,037.10	4.2%	0.05%	90.36%
NIZATIDINE	75	$4,168.38	17	$1,031.18	75.3%	0.04%	90.40%
REMERON	23	$1,992.80	12	$1,029.94	48.3%	0.04%	90.45%
PANCREASE MT 16	4	$1,854.41	2	$1,025.69	44.7%	0.04%	90.49%
EVISTA	111	$8,168.57	18	$1,015.02	87.6%	0.04%	90.54%
VERELAN PM	36	$2,142.48	17	$1,011.01	52.8%	0.04%	90.58%
ASCENSIA ELITE	16	$1,085.63	15	$1,006.15	7.3%	0.04%	90.62%

HEALTH INFORMATION DESIGNS

using medication information cost effectively

Comparison of Zanaflex Tablets to Capsules

Zanaflex tablets are only available in 2 strengths but are available generically

Zanaflex tablets are scored so you can give lower doses.

Taken with food will decrease absorption so it be important not to interchange the exact doses or there could be increase in adverse events.

Zanaflex capsules do come in 3 strengths

Taken with food does not affect absorption

Can be sprinkled on food for severe spastic patients who have difficult time taking oral medications

When sprinkled on food absorption is increased over the capsules.

1550 Pumphrey Ave • Auburn, AL 36832 • Phone: (334)502-3262 • Fax: (334) 502-6589
Auburn, Alabama • Jackson, Mississippi • Little Rock, Arkansas • Salisbury, Maryland

ACORDA®
THERAPEUTICS

April 1, 2005

Brendan Joyce
600 East Boulevard Avenue
Department 325
Bismarck, ND 58505

Dear Mr. Joyce:

Acorda Therapeutics, Inc. is pleased to announce the launch of new **Zanaflex® Capsules** (tizanidine hydrochloride), a short-acting drug for the management of spasticity. We respectfully request your consideration of **Zanaflex® Capsules** for inclusion on each of your health plan drug formularies. **Zanaflex® Capsules** are a new formulation of **Zanaflex®** (tizanidine hydrochloride). **Zanaflex® Capsules** offer new dosing options and an improved pharmacokinetic profile while retaining the efficacy and safety of **Zanaflex®** tablets.

Zanaflex® Capsules:

Product Name	NDC#	Package Size	WAC
Zanaflex® Capsules 2mg	10144-602-15	150	$180.00
Zanaflex® Capsules 4mg	10144-604-15	150	$214.50
Zanaflex® Capsules 6mg	10144-606-15	150	$358.50

The following attributes make Zanaflex® Capsules an important addition to your formulary:

- **Zanaflex® Capsules** are available in a 2mg, 4mg and a new 6mg strength.
- The availability of the 6mg strength offers improved dosing flexibility and convenience.
- **Zanaflex® Capsules** can be sprinkled on food for patients who have difficulty swallowing.
- **Zanaflex® Capsules** have a different product profile from tizanidine or **Zanaflex®** tablets. **Zanaflex® Capsules** are not therapeutically equivalent to **Zanaflex®** tablets or tizanidine tablets, and are therefore not interchangeable.
- When taking tizanidine tablets or **Zanaflex®** tablets under fed conditions, plasma levels increase. When taking **Zanaflex® Capsules** with food, plasma levels are more stable and decrease slightly. **Zanaflex® Capsules** support administration with meals which may improve compliance.
- **Zanaflex® Capsules** are a new patented dosage form of tizanidine.
- **Zanaflex® Capsules** are not A-B rated.

Switching between **Zanaflex® Capsules** and **Zanaflex®** tablets or tizanidine tablets may result in increased adverse events. Please see enclosed full prescribing information.

Because of the short duration of effect, treatment with **Zanaflex® Capsules** should be reserved for those daily activities and times when relief of spasticity is most important. The most frequent adverse events reported by patients taking **Zanaflex® Capsules** are dry mouth, sedation, asthenia and dizziness, and are most often considered mild to moderate.

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Hawthorne, NY 10532
Phone: (914) 347-4300
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Email: acorda@acorda.com
Website: www.acorda.com

If you have any questions or if you would like to receive additional product information, please contact me at **(214) 906-4004**.

Acorda Therapeutics, Inc. is a privately-held biotechnology company with its headquarters in Hawthorne, New York. The company develops therapies for people with disorders of the nervous system. Acorda is working in all phases of drug development and commercialization. Thank you for your consideration.

Sincerely,

Mary Lynn Vacchiano

Mary Lynn Vacchiano
National Accounts Manager

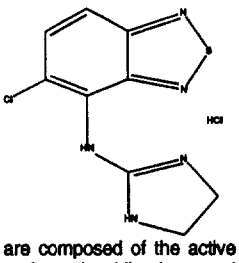
Enclosed:
Package Insert
FDA Approval Letter

Zanaflex®
(tizanidine hydrochloride)

Tablets 2 and 4 mg
Capsules 2, 4 and 6 mg

DESCRIPTION

ZANAFLEX (tizanidine hydrochloride) is a centrally acting α_2-adrenergic agonist. Tizanidine HCl (tizanidine) is a white to off-white, fine crystalline powder, odorless or with a faint characteristic odor. Tizanidine is slightly soluble in water and methanol; solubility in water decreases as the pH increases. Its chemical name is 5-chloro-4-(2-imidazolin- 2-ylamino)-2,1,3-benzothiodiazole hydrochloride. Tizanidine's molecular formula is $C_9H_8ClN_5S$-HCl, its molecular weight is 290.2 and its structural formula is: ▸



Zanaflex is supplied as 2 and 4 mg tablets and 2, 4, and 6 mg capsules for oral administration. Zanaflex tablets are composed of the active ingredient, tizanidine hydrochloride (2.288 mg equivalent to 2 mg tizanidine base and 4.576 mg equivalent to 4 mg tizanidine base), and the inactive ingredients, silicon dioxide colloidal, stearic acid, microcrystalline cellulose and anhydrous lactose.

Zanaflex capsules are composed of the active ingredient, tizanidine hydrochloride (2.29 mg equivalent to 2 mg tizanidine base, 4.58 mg equivalent to 4 mg tizanidine base, and 6.87 mg equivalent to 6 mg tizanidine base), and the inactive ingredients, hydroxypropyl methyl cellulose, silicon dioxide, sugar spheres, titanium dioxide, gelatin, and colorants.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Tizanidine is an agonist at α_2-adrenergic receptor sites and presumably reduces spasticity by increasing presynaptic inhibition of motor neurons. In animal models, tizanidine has no direct effect on skeletal muscle fibers or the neuromuscular junction, and no major effect on monosynaptic spinal reflexes. The effects of tizanidine are greatest on polysynaptic pathways. The overall effect of these actions is thought to reduce facilitation of spinal motor neurons.

The imidazoline chemical structure of tizanidine is related to that of the anti-hypertensive drug clonidine and other α_2-adrenergic agonists. Pharmacological studies in animals show similarities between the two compounds, but tizanidine was found to have one-tenth to one-fiftieth (1/50) of the potency of clonidine in lowering blood pressure.

PHARMACOKINETICS

Zanaflex tablets and capsules are bioequivalent to each other under fasted conditions, but not under fed conditions.

A single dose of either two 4 mg tablets or two 4 mg capsules was administered under fed and fasting conditions in an open label, four period, randomized crossover study in 96 human volunteers, of whom 81 were eligible for the statistical analysis.

Following oral administration of either the tablet or capsule (in the fasted state), tizanidine has peak plasma concentrations occurring 1.0 hour after dosing with a half-life of approximately 2 hours.

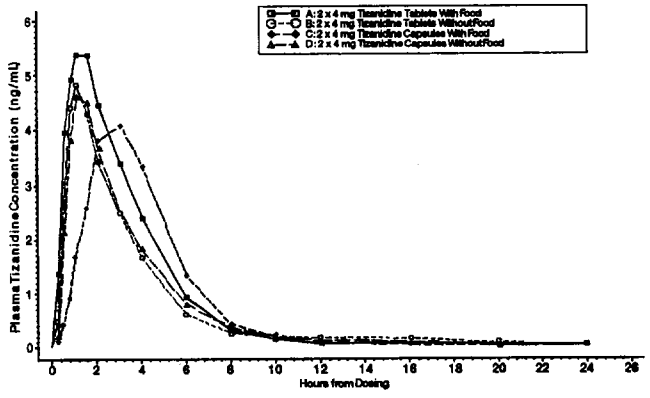
When two 4 mg tablets are administered with food the mean maximal plasma concentration is increased by approximately 30%, and the median time to peak plasma concentration is increased by 25 minutes, to 1 hour and 25 minutes.

In contrast, when two 4 mg capsules are administered with food the mean maximal plasma concentration is decreased by 20%, the median time to peak plasma ncentration is increased by 2 hours to 3 hours. Consequently, the mean Cmax for the sule when administered with food is approximately 2/3's the Cmax for the tablet n administered with food.

d also increases the extent of absorption for both the tablets and capsules. The ease with the tablet (~30%) is significantly greater than with the capsule (~10%). sequently when each is administered with food, the amount absorbed from the sule is about 80% of the amount absorbed from the tablet (See Figures 1 and 2).

ninistration of the capsule contents sprinkled on applesauce is not bioequivalent to ninistration of an intact capsule under fasting conditions. Administration of the capsule contents on applesauce results in a 15% - 20% increase in Cmax and AUC of tizanidine compared to administration of an intact capsule while fasting, and a 15 minute decrease in the median lag time and time to peak concentration.

Figure 1: Mean Tizanidine Concentration vs. Time Profiles For Zanaflex Tablets and Capsules (2 x 4 mg) Under Fasted and Fed Conditions



Zanaflex® Capsules (tizanidine hydrochloride)

SPECIAL POPULATIONS

Age Effects

No specific pharmacokinetic study was conducted to investigate age effects. Cross study comparison of pharmacokinetic data following single dose administration of 6 mg tizanidine showed that younger subjects cleared the drug four times faster than the elderly subjects. Tizanidine has not been evaluated in children (see PRECAUTIONS).

Hepatic Impairment

Pharmacokinetic differences due to hepatic impairment have not been studied. However, due to reliance on first pass metabolism, tizanidine should be used with caution in patients with significant hepatic impairment (see WARNINGS).

Renal Impairment

Tizanidine clearance is reduced by more than 50% in elderly patients with renal insufficiency (creatinine clearance < 25 mL/min) compared to healthy elderly subjects; this would be expected to lead to a longer duration of clinical effect. Tizanidine should be used with caution in renally impaired patients (see PRECAUTIONS).

Gender Effects

No specific pharmacokinetic study was conducted to investigate gender effects. Retrospective analysis of pharmacokinetic data, however, following single and multiple dose administration of 4 mg tizanidine showed that gender had no effect on the pharmacokinetics of tizanidine.

Race Effects

Pharmacokinetic differences due to race have not been studied.

Drug Interactions

Oral Contraceptives

No specific pharmacokinetic study was conducted to investigate interaction between oral contraceptives and tizanidine. Retrospective analysis of population pharmacokinetic data following single and multiple dose administration of 4 mg tizanidine, however, showed that women concurrently taking oral contraceptives had 50% lower clearance of tizanidine compared to women not on oral contraceptives (see PRECAUTIONS).

Fluvoxamine

Significant alterations of pharmacokinetic parameters including AUC, t1/2, and Cmax have been observed with concomitant administration (see CONTRAINDICATIONS).

CLINICAL STUDIES

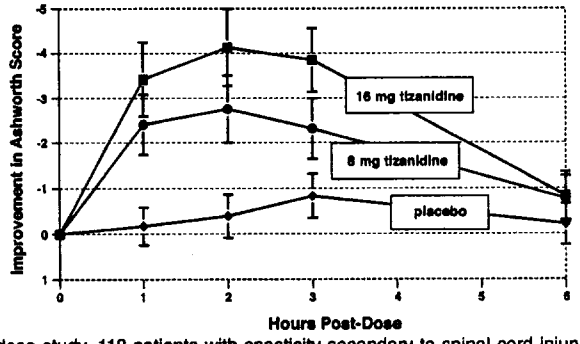
Tizanidine's capacity to reduce increased muscle tone associated with spasticity was demonstrated in two adequate and well controlled studies in patients with multiple sclerosis or spinal cord injury.

In one study, patients with multiple sclerosis were randomized to receive single oral doses of drug or placebo. Patients and assessors were blind to treatment assignment and efforts were made to reduce the likelihood that assessors would become aware indirectly of treatment assignment (e.g., they did not provide direct care to patients and were prohibited from asking questions about side effects). In all, 140 patients received either placebo, 8 mg or 16 mg of tizanidine.

Response was assessed by physical examination; muscle tone was rated on a 5 point scale (Ashworth score), with a score of 0 used to describe normal muscle tone. A score of 1 indicated a slight spastic catch while a score of 2 indicated more marked muscle resistance. A score of 3 was used to describe considerable increase in tone, making passive movement difficult. A muscle immobilized by spasticity was given a score of 4. Spasm counts were also collected.

Assessments were made at 1, 2, 3 and 6 hours after treatment. A statistically significant reduction of the Ashworth score for Zanaflex compared to placebo was detected at 1, 2 and 3 hours after treatment. Figure 2 below shows a comparison of the mean change in muscle tone from baseline as measured by the Ashworth scale. The greatest reduction in muscle tone was 1 to 2 hours after treatment. By 6 hours after treatment, muscle tone in the 8 and 16 mg tizanidine groups was indistinguishable from muscle tone in placebo treated patients. Within a given patient, improvement in muscle tone was correlated with plasma concentration. Plasma concentrations were variable from patient to patient at a given dose. Although 16 mg produced a larger effect, adverse events including hypotension were more common and more severe than in the 8 mg group. There were no differences in the number of spasms occurring in each group.

Figure 2: Single Dose Study—Mean Change in Muscle Tone from Baseline as Measured by the Ashworth Scale ± 95% Confidence Interval (A Negative Ashworth Score Signifies an Improvement in Muscle Tone from Baseline)



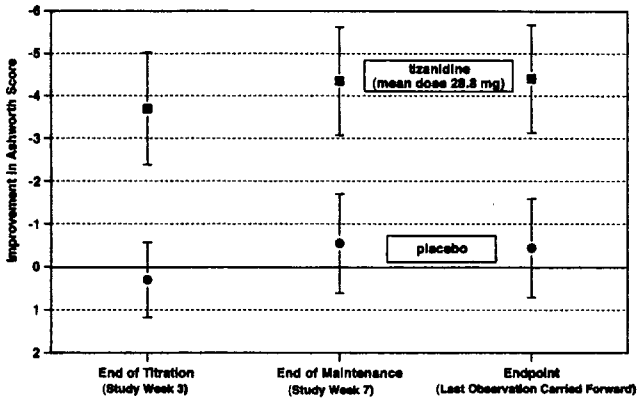
In a multiple dose study, 118 patients with spasticity secondary to spinal cord injury were randomized to either placebo or tizanidine. Steps similar to those taken in the first study were employed to ensure the integrity of blinding.

Patients were titrated over 3 weeks up to a maximum tolerated dose or 36 mg daily given in three unequal doses (e.g., 10 mg given in the morning and afternoon and

16 mg given at night). Patients were then maintained on their maximally tolerated dose for 4 additional weeks (i.e., maintenance phase). Throughout the maintenance phase, muscle tone was assessed on the Ashworth scale within a period of 2.5 hours following either the morning or afternoon dose. The number of daytime spasms was recorded daily by patients.

At endpoint (the protocol-specified time of outcome assessment), there was a statistically significant reduction in muscle tone and frequency of spasms in the tizanidine treated group compared to placebo. The reduction in muscle tone was not associated with a reduction in muscle strength (a desirable outcome) but also did not lead to any consistent advantage of tizanidine treated patients on measures of activities of daily living. Figure 3 below shows a comparison of the mean change in muscle tone from baseline as measured by the Ashworth scale.

Figure 3: Multiple Dose Study—Mean Change in Muscle Tone 0.5–2.5 Hours After Dosing as Measured by the Ashworth Scale ± 95% Confidence Interval (A Negative Ashworth Score Signifies an Improvement in Muscle Tone from Baseline)



INDICATIONS AND USAGE

Tizanidine is a short-acting drug for the management of spasticity. Because of the short duration of effect, treatment with tizanidine should be reserved for those daily activities and times when relief of spasticity is most important (see DOSING AND ADMINISTRATION).

CONTRAINDICATIONS

Zanaflex is contraindicated in patients with known hypersensitivity to Zanaflex or its ingredients.

Concomitant use of Zanaflex with fluvoxamine, a potent inhibitor of Cytochrome P450 1A2, is contraindicated. Significant alterations of pharmacokinetic parameters of tizanidine including AUC, t1/2, Cmax, increased oral bioavailability and decreased plasma clearance have been observed with concomitant fluvoxamine administration (see CLINICAL PHARMACOLOGY, WARNINGS, ADVERSE REACTIONS).

WARNINGS

LIMITED DATA BASE FOR CHRONIC USE OF SINGLE DOSES ABOVE 8 MG AND MULTIPLE DOSES ABOVE 24 MG PER DAY

Clinical experience with long-term use of tizanidine at doses of 8 to 16 mg single doses or total daily doses of 24 to 36 mg (see Dosage and Administration) is limited. In safety studies, approximately 75 patients have been exposed to individual doses of 12 mg or more for at least one year or more and approximately 80 patients have been exposed to total daily doses of 30 to 36 mg/day for at least one year or more. There is essentially no long-term experience with single, daytime doses of 16 mg. Because long-term clinical study experience at high doses is limited, only those adverse events with a relatively high incidence are likely to have been identified (see WARNINGS, PRECAUTIONS AND ADVERSE REACTIONS).

HYPOTENSION

Tizanidine is an α_2-adrenergic agonist (like clonidine) and can produce hypotension. In a single dose study where blood pressure was monitored closely after dosing, two-thirds of patients treated with 8 mg of tizanidine had a 20% reduction in either the diastolic or systolic BP. The reduction was seen within 1 hour after dosing, peaked 2 to 3 hours after dosing and was associated, at times, with bradycardia, orthostatic hypotension, lightheadedness/dizziness and rarely syncope. The hypotensive effect is dose related and has been measured following single doses of ≥2 mg.

Clinically significant hypotension (decreases in both systolic and diastolic pressure) has been reported with concomitant administration of fluvoxamine following single doses of 4 mg (see DRUG INTERACTIONS, CONTRAINDICATIONS, ADVERSE REACTIONS).

The chance of significant hypotension may possibly be minimized by titration of the dose and by focusing attention on signs and symptoms of hypotension prior to dose advancement. In addition, patients moving from a supine to fixed upright position may be at increased risk for hypotension and orthostatic effects.

Caution is advised when tizanidine is to be used in patients receiving concurrent antihypertensive therapy and should not be used with other α_2-adrenergic agonists.

Caution is recommended when considering concomitant use of tizanidine with other inhibitors of CYP1A2, such as, antiarrhythmics (amiodarone, mexiletine, propafenone), cimetidine, fluoroquinolones (ciprofloxacin, norfloxacin), rofecoxib, oral contraceptives, and ticlopidine.

RISK OF LIVER INJURY

Tizanidine occasionally causes liver injury, most often hepatocellular in type. In controlled clinical studies, approximately 5% of patients treated with tizanidine had elevations of liver function tests (ALT/SGPT, AST/SGOT) to greater than 3 times the upper limit of normal (or 2 times if baseline levels were elevated) compared to 0.4% in the control patients. Most cases resolved rapidly upon drug withdrawal with no reported residual problems. In occasional symptomatic cases, nausea, vomiting, anorexia and jaundice have been reported. In postmarketing experience, three deaths associated with liver failure have been reported in patients treated with tizanidine. In one case, a 49-year-old male developed jaundice and liver enlargement following 2 months of tizanidine treatment, primarily at 6 mg t.i.d. A liver biopsy showed multilobular necrosis without eosinophilic infiltration. Treatment was discontinued and the patient died in hepatic coma 10 days later. There was no evidence of hepatitis B and C in this patient and other therapy included only oxazepam and ranitidine. There was thus no explanation, other than a reaction to tizanidine, to explain the liver injury. In the two other cases, patients were taking other drugs with known potential for liver toxicity. One patient, treated with tizanidine at a dose of 4 mg/day, was also on carbamazepine when he developed cholestatic jaundice after 2 months of treatment; this patient died with pneumonia about 20 days later. Another patient, treated with tizanidine for 11 days, was also treated with dantrolene for about 2 weeks prior to developing fatal fulminant hepatic failure.

Monitoring of aminotransferase levels is recommended during the first 6 months of treatment (e.g., baseline, 1, 3 and 6 months) and periodically thereafter, based on clinical status. Because of the potential toxic hepatic effect of tizanidine, the drug should be used only with extreme caution in patients with impaired hepatic function.

SEDATION

In the multiple dose, controlled clinical studies, 48% of patients receiving any dose of tizanidine reported sedation as an adverse event. In 10% of these cases, the sedation was rated as severe compared to < 1% in the placebo treated patients. Sedation may interfere with everyday activity.

The effect appears to be dose related. In a single dose study, 92% of the patients receiving 16 mg, when asked, reported that they were drowsy during the 6 hour study. This compares to 76% of the patients on 8 mg and 35% of the patients on placebo. Patients began noting this effect 30 minutes following dosing. The effect peaked 1.5 hours following dosing. Of the patients who received a single dose of 16 mg, 51% continued to report drowsiness 6 hours following dosing compared to 13% in the patients receiving placebo or 8 mg of tizanidine.

In the multiple dose studies, the prevalence of patients with sedation peaked following the first week of titration and then remained stable for the duration of the maintenance phase of the study.

HALLUCINOSIS/PSYCHOTIC-LIKE SYMPTOMS

Tizanidine use has been associated with hallucinations. Formed, visual hallucinations or delusions have been reported in 5 of 170 patients (3%) in two North American controlled clinical studies. These 5 cases occurred within the first 6 weeks. Most of the patients were aware that the events were unreal. One patient developed psychoses in association with the hallucinations. One patient among these 5 continued to have problems for at least 2 weeks following discontinuation of tizanidine.

PRECAUTIONS

CARDIOVASCULAR

Prolongation of the QT interval and bradycardia were noted in chronic toxicity studies in dogs at doses equal to the maximum human dose on a mg/m2 basis. ECG evaluation was not performed in the controlled clinical studies. Reduction in pulse rate has been noted in association with decreases in blood pressure in the single dose controlled study (see WARNINGS).

OPHTHALMIC

Dose-related retinal degeneration and corneal opacities have been found in animal studies at doses equivalent to approximately the maximum recommended dose on a mg/m² basis. There have been no reports of corneal opacities or retinal degeneration in the clinical studies.

USE IN RENALLY IMPAIRED PATIENTS

Tizanidine should be used with caution in patients with renal insufficiency (creatinine clearance < 25 mL/min), as clearance is reduced by more than 50%. In these patients, during titration, the individual doses should be reduced. If higher doses are required, individual doses rather than dosing frequency should be increased. These patients should be monitored closely for the onset or increase in severity of the common adverse events (dry mouth, somnolence, asthenia and dizziness) as indicators of potential overdose.

USE IN WOMEN TAKING ORAL CONTRACEPTIVES

Tizanidine should be used with caution in women taking oral contraceptives, as clearance of tizanidine is reduced by approximately 50% in such patients. In these patients, during titration, the individual doses should be reduced.

DISCONTINUING THERAPY

If therapy needs to be discontinued, especially in patients who have been receiving high doses for long periods, the dose should be decreased slowly to minimize the risk of withdrawal and rebound hypertension, tachycardia, and hypertonia.

INFORMATION FOR PATIENTS

Patients should be advised of the limited clinical experience with tizanidine both in regard to duration of use and the higher doses required to reduce muscle tone (see WARNINGS).

Because of the possibility of tizanidine lowering blood pressure, patients should be warned about the risk of clinically significant orthostatic hypotension (see WARNINGS).

Because of the possibility of sedation, patients should be warned about performing activities requiring alertness, such as driving a vehicle or operating machinery (see Warnings). Patients should also be instructed that the sedation may be additive when tizanidine is taken in conjunction with drugs (baclofen, benzodiazepines) or substances (e.g., alcohol) that act as CNS depressants.

Patients should be advised of the change in the absorption profile of Zanaflex if taken

with food and the potential changes in efficacy and adverse effect profiles that may result (see PHARMACOKINETICS).
Patients should be advised not to stop tizanidine suddenly as rebound hypertension and tachycardia may occur (see PRECAUTIONS: Discontinuing Therapy).
Tizanidine should be used with caution where spasticity is utilized to sustain posture and balance in locomotion or whenever spasticity is utilized to obtain increased function.

DRUG INTERACTIONS

Invitro studies of cytochrome P450 isoenzymes using human liver microsomes indicate that neither tizanidine nor the major metabolites are likely to affect the metabolism of other drugs metabolized by cytochrome P450 isoenzymes.

Acetaminophen

Tizanidine delayed the Tmax of acetaminophen by 16 minutes. Acetaminophen did not affect the pharmokinetics of tizanidine.

Alcohol

Alcohol increased the AUC of tizanidine by approximately 20%, while also increasing its Cmax by approximately 15%. This was associated with an increase in side effects of tizanidine. The CNS depressant effects of tizanidine and alcohol are additive.

Fluvoxamine

Clinically significant hypotension (decreases in both systolic and diastolic pressure) has been reported with concomitant administration of fluvoxamine following single doses of 4 mg (see DRUG INTERACTIONS, CONTRAINDICATIONS).

Oral Contraceptives

No specific pharmokinetic study was conducted to investigate interaction between oral contraceptives and tizanidine, but retrospective analysis of population pharmokinetic data following single and multiple dose administration of 4 mg tizanidine showed that women concurrently taking oral contraceptives had 50% lower clearance of tizanidine than women not on oral contraceptives.

Rofecoxib

Rofecoxib may potentiate the adverse effects of tizanidine. Eight case reports of a potential rofecoxib-tizanidine drug interaction have been identified in postmarketing safety reports. Most of the adverse events reported involved the nervous system (e.g., hallucinations, psychosis, somnolence, hypotonia, etc.) and the cardiovascular system (e.g., hypotension, tachycardia, bradycardia). In all cases, adverse events resolved following discontinuation of tizanidine, rofecoxib, or both. Rechallenges with both drugs were not performed. The possible mechanism and the potential for a drug interaction between tizanidine and rofecoxib remain unclear.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

No evidence for carcinogenicity was seen in two dietary studies in rodents. Tizanidine was administered to mice for 78 weeks at doses up to 16 mg/kg, which is equivalent to 2 times the maximum recommended human dose on a mg/m2 basis. Tizanidine was also administered to rats for 104 weeks at doses up to 9 mg/kg, which is equivalent to 2.5 times the maximum recommended human dose on a mg/m² basis. There was no statistically significant increase in tumors in either species.
Tizanidine was not mutagenic or clastogenic in the following *in vitro* assays: the bacterial Ames test and the mammalian gene mutation test and chromosomal aberration test in Chinese hamster cells. It was also negative in the following *in vivo* assays: the bone marrow micronucleus test in mice, the bone marrow micronucleus and cytogenicity test in Chinese hamsters, the dominant lethal mutagenicity test in mice, and the unscheduled DNA synthesis (UDS) test in mice.
Tizanidine did not affect fertility in male rats at doses of 10 mg/kg, approximately 2.7 times the maximum recommended human dose on a mg/m² basis, and in females at ses of 3 mg/kg, approximately equal to the maximum recommended human dose a mg/m² basis; fertility was reduced in males receiving 30 mg/kg (8 times the aximum recommended human dose on a mg/m² basis) and in females receiving 10 g/kg (2.7 times the maximum recommended human dose on a mg/m² basis). At se doses, maternal behavioral effects and clinical signs were observed including rked sedation, weight loss, and ataxia.

EGNANCY

egnancy Category C

production studies performed in rats at a dose of 3 mg/kg, equal to the maximum recommended human dose on a mg/m² basis, and in rabbits at 30 mg/kg, 16 times the maximum recommended human dose on a mg/m² basis, did not show evidence of teratogenicity. Tizanidine at doses that are equal to and up to 8 times the maximum recommended human dose on a mg/m² basis increased gestation duration in rats. Prenatal and postnatal pup loss was increased and developmental retardation occurred. Post-implantation loss was increased in rabbits at doses of 1 mg/kg or greater, equal to or greater than 0.5 times the maximum recommended human dose on a mg/m² basis. Tizanidine has not been studied in pregnant women. Tizanidine should be given to pregnant women only if clearly needed.

LABOR AND DELIVERY

The effect of tizanidine on labor and delivery in humans is unknown.

NURSING MOTHERS

It is not known whether tizanidine is excreted in human milk, although as a lipid soluble drug, it might be expected to pass into breast milk.

GERIATRIC USE

Tizanidine should be used with caution in elderly patients because clearance is decreased four-fold.

PEDIATRIC USE

There are no adequate and well-controlled studies to document the safety and efficacy of tizanidine in children.

ADVERSE REACTIONS

In multiple dose, placebo-controlled clinical studies, 264 patients were treated with tizanidine and 261 with placebo. Adverse events, including severe adverse events, were more frequently reported with tizanidine than with placebo.

Zanaflex® Capsules (tizanidine hydrochloride)

COMMON ADVERSE EVENTS LEADING TO DISCONTIUATION

Forty-five of 264 (17%) patients receiving tizanidine and 13 of 261 (5%) patients receiving placebo in three multiple dose, placebo-controlled clinical studies, discontinued treatment for adverse events. When patients withdrew from the study, they frequently had more than one reason for discontinuing. The adverse events most frequently leading to withdrawal of tizanidine treated patients in the controlled clinical studies were asthenia (weakness, fatigue and/or tiredness) (3%), somnolence (3%), dry mouth (3%), increased spasm or tone (2%), and dizziness (2%).

MOST FREQUENT ADVERSE CLINICAL EVENTS SEEN IN ASSOCIATION WITH THE USE OF TIZANIDINE

In multiple dose, placebo-controlled clinical studies involving 264 patients with spasticity, the most frequent adverse effects were dry mouth, somnolence/sedation, asthenia (weakness, fatigue and/or tiredness) and dizziness. Three-quarters of the patients rated the events as mild to moderate and one-quarter of the patients rated the events as being severe. These events appeared to be dose related.

ADVERSE EVENTS REPORTED IN CONTROLLED STUDIES

The events cited reflect experience gained under closely monitored conditions of clinical studies in a highly selected patient population. In actual clinical practice or in other clinical studies, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Table 1 lists treatment emergent signs and symptoms that were reported in greater than 2% of patients in three multiple dose, placebo-controlled studies who received tizanidine where the frequency in the tizanidine group was at least as common as in the placebo group. These events are not necessarily related to tizanidine treatment. For comparison purposes, the corresponding frequency of the event (per 100 patients) among placebo treated patients is also provided.

Table 1: Multiple Dose, Placebo-Controlled Studies—Frequent (> 2%) Adverse Events Reported for Which Zanaflex Tablets Incidence is Greater than Placebo

Event	Placebo N = 261 %	Zanaflex Tablet N = 264 %
Dry mouth	10	49
Somnolence	10	48
Asthenia*	18	41
Dizziness	4	16
UTI	7	10
Infection	5	6
Constipation	1	4
Liver function tests abnormal	<1	3
Vomiting	0	3
Speech disorder	0	3
Amblyopia (blurred vision)	<1	3
Urinary frequency	2	3
Flu syndrome	2	3
SGPT/ALT increased	<1	3
Dyskinesia	0	3
Nervousness	<1	3
Pharyngitis	1	3
Rhinitis	2	3

* (weakness, fatigue, and/or tiredness)

In the single dose, placebo-controlled study involving 142 patients with spasticity, the patients were specifically asked if they had experienced any of the four most common adverse events: dry mouth, somnolence (drowsiness), asthenia (weakness, fatigue and/or tiredness) and dizziness. In addition, hypotension and bradycardia were observed. The occurrence of these adverse effects are summarized in Table 2. Other events were, in general, reported at a rate of 2% or less.

Table 2: Single Dose, Placebo-Controlled Study—Common Adverse Events Reported

Event	Placebo N = 48 %	Zanaflex Tablet 8mg N = 45 %	Zanaflex Tablet 16 mg N = 49 %
Somnolence	31	78	92
Dry mouth	35	76	88
Asthenia*	40	67	78
Dizziness	4	22	45
Hypotension	0	16	33
Bradycardia	0	2	10

OTHER ADVERSE EVENTS OBSERVED DURING THE EVALUATION OF TIZANIDINE

Tizanidine was administered to 1385 patients in additional clinical studies where adverse event information was available. The conditions and duration of exposure varied greatly, and included (in overlapping categories) double-blind and open-label studies, uncontrolled and controlled studies, inpatient and outpatient studies, and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.
In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. The frequencies presented, therefore, represent the proportion of the 1385 patients exposed to tizanidine who experienced an event of the type cited on at least one occasion while receiving tizanidine. All reported events are included except those already listed in Table 1. If the COSTART

term for an event was so general as to be uninformative, it was replaced by a more informative term. It is important to emphasize that, although the events reported occurred during treatment with tizanidine, they were not necessarily caused by it.
Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled studies appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients.

BODY AS A WHOLE
Frequent: Fever
Infrequent: Allergic reaction, moniliasis, malaise, abscess, neck pain, sepsis, cellulites, death, overdose
Rare: Carcinoma, congenital anomaly, suicide attempt

CARDIOVASCULAR SYSTEM
Infrequent: Vasodilatation, postural hypotension, syncope, migraine, arrhythmia
Rare: Angina pectoris, coronary artery disorder, heart failure, myocardial infarct, phlebitis, pulmonary embolus, ventricular extrasystoles, ventricular tachycardia

DIGESTIVE SYSTEM
Frequent: Abdomen pain, diarrhea, dyspepsia
Infrequent: Dysphagia, cholelithiasis, fecal impaction, flatulence, gastrointestinal hemorrhage, hepatitis, melena,
Rare: Gastroenteritis, hematemesis, hepatoma, intestinal obstruction, liver damage

HEMIC AND LYMPHATIC SYSTEM
Infrequent: Ecchymosis, hypercholesteremia, anemia, hyperlipemia, leukopenia, leukocytosis, sepsis
Rare: Petechia, purpura, thrombocythemia, thrombocytopenia

METABOLIC AND NUTRITIONAL SYSTEM
Infrequent: Edema, hypothyroidism, weight loss
Rare: Adrenal cortex insufficiency, hyperglycemia, hypokalemia, hyponatremia, hypoproteinemia, respiratory acidosis

MUSCULOSKELETAL SYSTEM
Frequent: Myasthenia, back pain
Infrequent: Pathological fracture, arthralgia, arthritis, bursitis

NERVOUS SYSTEM
Frequent: Depression, anxiety, paresthesia
Infrequent: Tremor, emotional lability, convulsion, paralysis, thinking abnormal, vertigo, abnormal dreams, agitation, depersonalization, euphoria, migraine, stupor, dysautonomia, neuralgia
Rare: Dementia, hemiplegia, neuropathy

RESPIRATORY SYSTEM
Infrequent: Sinusitis, pneumonia, bronchitis
Rare: Asthma

SKIN AND APPENDAGES
Frequent: Rash, sweating, skin ulcer
Infrequent: Pruritus, dry skin, acne, alopecia, urticaria
Rare: Exfoliative dermatitis, herpes simplex, herpes zoster, skin carcinoma

SPECIAL SENSES
Infrequent: Ear pain, tinnitus, deafness, glaucoma, conjunctivitis, eye pain, optic neuritis, otitis media, retinal hemorrhage, visual field defect
Rare: Iritis, keratitis, optic atrophy

UROGENITAL SYSTEM
Infrequent: Urinary urgency, cystitis, menorrhagia, pyelonephritis, urinary retention, kidney calculus, uterine fibroids enlarged, vaginal moniliasis, vaginitis
Rare: Albuminuria, glycosuria, hematuria, metrorrhagia

Post-marketing experience has reported bradycardia, dizziness, significant hypotension, and somnolence with concomitant administration of fluvoxamine (see CONTRAINDICATIONS, PRECAUTIONS, WARNINGS, DRUG INTERACTIONS).

DRUG ABUSE AND DEPENDENCE

Abuse potential was not evaluated in human studies. Rats were able to distinguish tizanidine from saline in a standard discrimination paradigm, after training, but failed to generalize the effects of morphine, cocaine, diazepam, or phenobarbital to tizanidine. Monkeys were shown to self-administer tizanidine in a dose-dependent manner, and abrupt cessation of tizanidine produced transient signs of withdrawal at doses > 35 times the maximum recommended human dose on a mg/m2 basis. These transient withdrawal signs (increased locomotion, body twitching, and aversive behavior toward the observer) were not reversed by naloxone administration.
Tizanidine is closely related to clonidine, which is often abused in combination with narcotics and is known to cause symptoms of rebound upon abrupt withdrawal. Three cases of rebound symptoms on sudden withdrawal of tizanidine have been reported. The case reports suggest that these patients were also misusing narcotics. Withdrawal symptoms included hypertension, tachycardia, hypertonia, tremor, and anxiety. As with clonidine, withdrawal is expected to be more likely in cases where high doses are used, especially for prolonged periods.

OVERDOSAGE

A search of a safety surveillance database revealed a total of eighteen cases of tizanidine overdose. Of the fourteen intentional overdoses, five have resulted in fatality, and in at least three of these cases, other CNS depressants were involved. One fatality was secondary to pneumonia and sepsis, which were sequelae of the ingestion. The majority of cases involve depressed consciousness (somnolence, stupor, or coma), depressed cardiovascular function (bradycardia, hypotension), and depressed respiratory function (respiratory depression or failure).
Should overdose occur, basic steps to ensure the adequacy of an airway and the

Zanaflex® Capsules (tizanidine hydrochloride)

monitoring of cardiovascular and respiratory systems should be undertaken. In general, symptoms resolve within one to three days following discontinuation of tizanidine and administration of appropriate therapy. Due to the similar mechanism of action, symptoms and management of tizanidine overdose are similar to those following clonidine overdose. For the most recent information concerning the management of overdose, contact a poison control center.

DOSAGE AND ADMINISTRATION

A single dose of 8 mg of tizanidine reduces muscle tone in patients with spasticity for a period of several hours. The effect peaks at approximately 1 to 2 hours and dissipates between 3 to 6 hours. Effects are dose-related.
Although single doses of less than 8 mg have not been demonstrated to be effective in controlled clinical studies, the dose-related nature of tizanidine's common adverse events make it prudent to begin treatment with single oral doses of 4 mg. Increase the dose gradually (2 to 4 mg steps) to optimum effect (satisfactory reduction of muscle tone at a tolerated dose).
The dose can be repeated at 6 to 8 hour intervals, as needed, to a maximum of three doses in 24 hours. The total daily dose should not exceed 36 mg.
Experience with single doses exceeding 8 mg and daily doses exceeding 24 mg is limited. There is essentially no experience with repeated, single, daytime doses greater than 12 mg or total daily doses greater than 36 mg (see WARNINGS).
Food has complex effects on tizanidine pharmacokinetics, which differ with the different formulations. These pharmacokinetic differences may result in clinically significant differences when [1] switching administration of the tablet between the fed or fasted state, [2] switching administration of the capsule between the fed or fasted state, [3] switching between the tablet and capsule in the fed state, or [4] switching between the intact capsule and sprinkling the contents of the capsule on applesauce. These changes may result in increased adverse events or delayed/more rapid onset of activity, depending upon the nature of the switch. For this reason, the prescriber should be thoroughly familiar with the changes in kinetics associated with these different conditions (see PHARMACOKINETICS).

HOW SUPPLIED

2 MG Tablets
Zanaflex® (tizanidine hydrochloride) is available as 2 mg white tablets, with a bisecting score on one side and debossed with "A592" on the other.
They are supplied in: Bottles of 150 (NDC 10144- 592-15).
4 MG Tablets
Zanaflex® (tizanidine hydrochloride) is available as 4 mg white tablets, with a quadrisecting score on one side and debossed with "A594" on the other.
They are supplied in: Bottles of 150 (NDC 10144-594-15).
2 MG Capsules
ZANAFLEX® (tizanidine hydrochloride) is available as a 2 mg two-piece hard gelatin capsule consisting of a standard blue opaque body with a standard blue opaque cap. The capsules are printed with 2 mg in white.
They are supplied in: Bottles of 150 (NDC 10144-602-15).
4 MG Capsules
Zanaflex® (tizanidine hydrochloride) is available as a 4 mg two-piece hard gelatin capsule consisting of a white opaque body with a light blue opaque cap. The capsules are printed with 4 mg in white.
They are supplied in: Bottles of 150 (NDC 10144-604-15).
6 MG Capsules
Zanaflex® (tizanidine hydrochloride) is available as a 6 mg two-piece hard gelatin capsule consisting of a light blue opaque body with a light blue opaque cap. The capsules are printed with 6 mg in white.
They are supplied in: Bottles of 150 (NDC 10144-606-15).
Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Dispense in containers with child resistant closure.

℞ Only
Manufactured by:
Elan Pharma International, Ltd.
Athlone, Ireland

Marketed by:
Acorda Therapeutics, Inc.
Hawthorne, NY 10532

AcordaZanaflexTab001 Rev. 03-13-05

ACØRDA®
THERAPEUTICS

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-447

Elan Pharmaceuticals
Attention: Michael Scaife, PhD
7475 Lusk Boulevard
San Diego, CA 92121

Dear Dr. Scaife:

Please refer to your new drug application (NDA) dated October 31, 2001, received November 1, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tizanidine 2 mg, 4 mg, and 6 mg capsules.

We acknowledge receipt of your submissions dated the following:

January 29, 2002
February 14, 2002
February 19, 2002
March 13, 2002
March 22, 2002
April 24, 2002
May 9, 2002
June 17, 2002
June 28, 2002
August 12, 2002
August 20, 2002
August 23, 2002
August 28, 2002 (2)
August 29, 2002 (2)

This new drug application provides for the use of tizanidine capsules for acute treatment of spasticity.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

You have agreed to the following dissolution method and specifications for all three capsule strengths:

Procedure:	As per (USP 23) <711> Sinker required
Apparatus type:	USP Type II Apparatus (Rotating Paddles)
Medium:	0.01N HCl (De-aerated)
Volume (mL):	500 mL
Temperature:	37 ± 0.5 °C
Speed of rotation (r.p.m.):	50 r.p.m.
Sample time (hours):	0.25 hours (15 minutes)
Acceptance Specification:	Q = 80% at 15 minutes

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). These revisions are terms of the NDA approval. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-447." Approval of this submission by FDA is not required before the labeling is used.

If you choose to use a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit any proprietary name to the Agency for our review prior to its implementation.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (21 CFR 314.55). Based on the information submitted, we are deferring submission of pediatric studies for patients under 16 years old until December 31, 2005.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Lana Chen, R.Ph., Regulatory Management Officer, at (301) 594-5529.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

HEALTH INFORMATION DESIGNS

using medication information cost effectively

July 30, 2005

The next North Dakota Drug Utilization Review (DUR) Board Meeting will be held:

August 8, 2005 at 1:00 P.M.

Kelly Inn Colony Room A
1800 North 12th Street
Bismarck, ND

The teleconference number will be 1 (866) 725-5850, password 3345023262.

If you are unable to attend, please contact Brendan Joyce at (701) 328-4023 (sojoyb@state.nd.us).

Please remember to silence all pagers and cell phones prior to the start of the meeting.

1550 Pumphrey Ave • Auburn, AL 36832 • Phone: (334)502-3262 • Fax: (334) 502-6589
Auburn, Alabama • Jackson, Mississippi • Little Rock, Arkansas • Salisbury, Maryland

North Dakota Medicaid
DUR Board Meeting Agenda
August 8, 2005 1:00 P.M.
Kelly Inn, Bismarck, ND

1.	Administrative items	
	• Travel vouchers	Brendan Joyce
2.	Old Business	
	• Review and approval of minutes of 06/06/05 meeting	Chairman
	• Budget update	Brendan Joyce
	• 2nd review of Zanaflex® capsule for PA implementation	HID
3.	New Business	
	• Review of DUR Board Procedures	HID
	• Review impact of COX II inhibitors on program	HID
	• Review daily consumption of ADHD agents	HID
	• Review utilization of sustained release narcotics	HID
	• Summary of state actions on sustained release narcotics	HID
	• Summary of state actions on statins	HID
	• Review Revatio® for prior authorization	HID
4.	Upcoming meeting agenda	Chairman
5.	Adjourn	Chairman

Please remember: turn all cell phones and pagers to "silent" mode during the meeting.

DRUG UTILIZATION REVIEW (DUR) MEETING MINUTES
JUNE 6, 2005

Members Present
Al Samuelson, Gary Betting, John Savageau, Pat Churchill, Carrie Sorenson, Scott Setzepfandt, Cheryl Huber, Bob Treitline, Leann Ness, Brendan Joyce

Members Absent
Jay Huber, Norman Byers

HID Staff Present
Steve Espy

Chair John Savageau called the meeting to order at 1:04pm. He then asked for a motion to approve the minutes from the April 11, 2005 meeting. Pat Churchill moved the minutes be approved. Carrie Sorenson seconded the motion. The chair called for a voice vote to approve the minutes, which passed with no audible dissent.

Budget Update
Brendan Joyce reported that the 2003-2005 biennium expenditures was projected at $95,210,239, and the expected expenditures were projected at $95, 681,069. He further stated that the legislature has appropriated $105,000,000 for the Medicaid agency for the 2005-2007 biennium—a 9.7% increase. Expenditures are projected at $119,600,000. This projection takes into effect the decrease in federal matching funds. It is expected that Part D will result in no effect to minimal effect on the budget for the first 18 months of the program. After discussion, Al Samuelson asked that the budget figures be included in future DUR Packs.

Review of Antihistamines and PPI Utilization
Steve Espy provided board members with graphs depicting utilization of antihistamines and PPIs by date. These graphs indicated a decrease in utilization of these classes after the March 2004 PA implementation.

Review of Effect of PPI PA on Total Medical Expenses
Steve Espy provided the board with a list of GI diagnoses that were used in the review. The first graph indicated the total number of medical claims for recipients who had received at least one PPI drug per month. The next graph indicated the number of medical claims that included one of the GI diagnoses listed. This analysis revealed that total medical claims, as well as the medical claims for GI diagnoses, had not increased, but had actually decreased, since the implementation of PA for the PPI drug class. John Savageau requested that HID provide a similar report concerning COX II inhibitors. The report should indicate whether the addition of COX II inhibitors would decrease the number of GI diagnoses.

Review of Depression
Steve Espy provided the board with the number of recipients who had a diagnosis of depression in 2004. This number was broken down by age in 10 year increments. Recipients who were considered dual eligible from 10/04-12/04 were not included. The next report indicated antidepressant drugs and the number of unique recipients taking each drug during 2004. Steve Espy explained that, per the board's earlier request, he had also provided a list of recipients, drug prescribed, and length of therapy. He made this list available on his computer for board members to review at the end of the meeting.

Brendan discussed legislative bill 1470 prohibiting the limitation of any mental health drug. He pointed out that 325 drugs account for 90 percent of drug expenditures, and that 47 percent were antipsychotic drugs. He went on to say that 63 percent of the drugs are exempt from prior authorization. Brendan challenged the board to find ways to influence prescribers to prescribe drugs that do not require a PA, or are generic. After discussion, John Savageau recommended the Medicaid agency send educational letters explaining the cost effectiveness of prescribing generics to providers who are prescribing brand name mental health drugs when generics are available—particularly Paxil CR. Al Samuelson suggested using newsletters to educate the providers, as well. He also recommended that providers be informed of the number of dollars their prescribing is costing the state, and the resulting savings if they switched to generics.

There was also much discussion of the overuse of once daily ADD agents. John Savageau asked that HID provide the board with information regarding the incidence of multiple dosing, or daily consumption of the ADD agents.

Antihistamine Form
A revised antihistamine form was provided in response to the board's previous request that it indicate relevant cost of the antihistamine. Scott Setzepfandt requested that the revision date be included on the form.

DUR Board Changes
Brendan Joyce reviewed the changes to the Board as required by the legislative bill 1470. The changes include:

- The ND Medical Association shall appoint 4 doctors to the board
- The ND Pharmacy Association shall appoint 4 pharmacists to the board
- The Medicaid agency shall appoint 2 members at large
- The Governor shall appoint one consumer member

These changes are effective July 1, 2005.

Brendan thanked each member present for their continued attendance, and noted that the department will be exploring ways to increase attendance. Available options include scheduling future meetings on a different day of the week, at a different time of day, or changing the number of meetings per year.

Emergency Item
Brendan asked the board to approve the department obtaining a list of registered sex offenders and denying coverage to those listed for any of the three erectile dysfunction drugs. John Savageau moved, and Cheryl Huber seconded the motion, to approve the exclusion of sex offenders from coverage of erectile dysfunction drugs. The motion was approved with no audible dissent.

Medicare Modernization Act
Steve provided the board with a list of the top 100 drugs, based on expenditures for the month of Jan 2005. This list included the total number of prescriptions and expenditures, the number of non-dual eligible recipients, expenditures, and percentage difference. The purpose of this report was to demonstrate to the board the change in utilization of these drugs after the implementation of the MMA. Brendan Joyce explained that the number of drug classes that the board may want to PA was decreased dramatically due to the change in utilization. He noted that sustained release opioids and statins were two classes the board might want to consider. After discussion, the board requested that HID provide the utilization of Oxycontin and Pallidone, as well as what other states may be doing with this class of drugs. The board also requested a summary of other states' initiatives for the class of statins drugs

Review of Zanaflex Capsules
Steve Espy presented a summary of the difference between the Zanaflex tablets and Zanaflex capsules. He then recommended that the board suspend their procedures and vote to prior authorize the Zanaflex capsules. After much discussion, Bob Treitline moved and Pat Churchill seconded the motion to prior authorize Zanaflex capsules. The motion was approved by voice vote of the board. John Savageau asked Steve Espy to include a review of the procedures as an agenda item for the next meeting. Cheryl Huber moved that the board rescind the PA for Zanaflex until the procedures could be reviewed. Al Samuelson seconded the motion. The motion failed by voice vote.

Public Comment
Questions were raised regarding whether the review of statins would be a clinical review, and whether pharmaceutical companies should be prepared to provide information. The answer provided was that this was going to be a review of what other states are doing with statins. Another question raised regarded clarification of the Oxycontin report. The answer provided was that this report will not be a clinical review but a review of utilization and what other states are doing with the drug.

The next meeting will be August 8, 2005. The agenda will include:

- Review of incidence of GI bleed with the addition of COX II inhibitors
- Review of daily consumption of ADD drugs
- Review of utilization of Oxycontin and Pallidone, as well as summary of what other states are doing with these drugs.
- Review of the procedures of the DUR Board

- Review of Zanaflex
- Summary of what other states are doing with statins

Cheryl Huber moved to adjourn, and Bob Treitline seconded the motion. The motion carried by voice vote.

Budget info:

SFY 2004 = $45,974,797
SFY 2005 (through June) = $43,965,147
Projected final SFY 2005 = $46,451,263
(1.036% increase)

Upcoming biennium, is difficult to predict as clawback is essentially an unknown. However, we anticipate the shortfall will be significant as appropriated growth was roughly 5% per year and NHE projections are roughly 11% per year.

Zanaflex Capsule PRIOR AUTHORIZATION
ND DEPARTMENT OF HUMAN SERVICES
MEDICAL SERVICES DIVISION

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

ND Medicaid requires that patients receiving Zanaflex capsules must use Tizanidine tablets first line.
****Note:***

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

Part I: TO BE COMPLETED BY PHYSICIAN

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

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

Qualifications for coverage:

❑Failed generic drug	Start Date: End Date:	Dose: Frequency:

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

Physician Signature: Date:

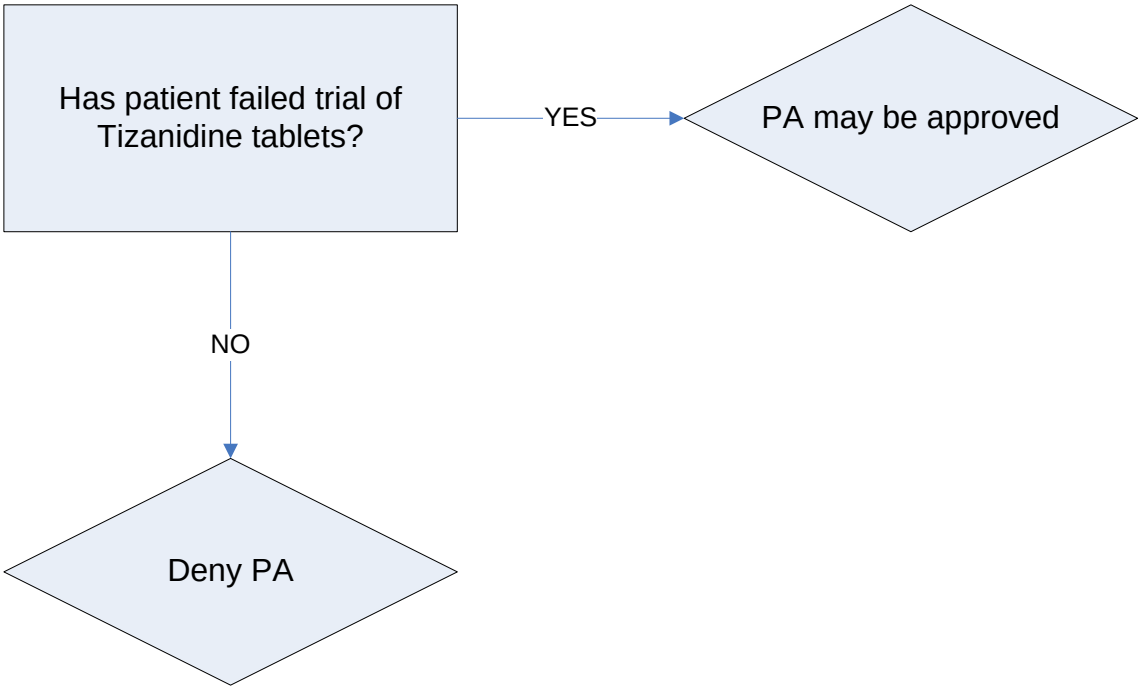
Part II: TO BE COMPLETED BY PHARMACY

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

Part III: FOR OFFICIAL USE ONLY

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

North Dakota Department of Human Services
Zanaflex Authorization Algorithm

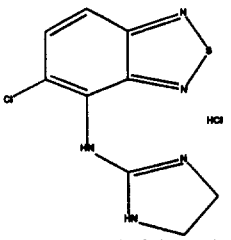


Zanaflex®
(tizanidine hydrochloride)

Tablets 2 and 4 mg
Capsules 2, 4 and 6 mg

DESCRIPTION

ZANAFLEX (tizanidine hydrochloride) is a centrally acting α_2-adrenergic agonist. Tizanidine HCl (tizanidine) is a white to off-white, fine crystalline powder, odorless or with a faint characteristic odor. Tizanidine is slightly soluble in water and methanol; solubility in water decreases as the pH increases. Its chemical name is 5-chloro-4-(2-imidazolin- 2-ylamino)-2,1,3-benzothiodiazole hydrochloride. Tizanidine's molecular formula is $C_9H_8ClN_5S$-HCl, its molecular weight is 290.2 and its structural formula is: ▸



Zanaflex is supplied as 2 and 4 mg tablets and 2, 4, and 6 mg capsules for oral administration. Zanaflex tablets are composed of the active ingredient, tizanidine hydrochloride (2.288 mg equivalent to 2 mg tizanidine base and 4.576 mg equivalent to 4 mg tizanidine base), and the inactive ingredients, silicon dioxide colloidal, stearic acid, microcrystalline cellulose and anhydrous lactose.

Zanaflex capsules are composed of the active ingredient, tizanidine hydrochloride (2.29 mg equivalent to 2 mg tizanidine base, 4.58 mg equivalent to 4 mg tizanidine base, and 6.87 mg equivalent to 6 mg tizanidine base), and the inactive ingredients, hydroxypropyl methyl cellulose, silicon dioxide, sugar spheres, titanium dioxide, gelatin, and colorants.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Tizanidine is an agonist at α_2-adrenergic receptor sites and presumably reduces spasticity by increasing presynaptic inhibition of motor neurons. In animal models, tizanidine has no direct effect on skeletal muscle fibers or the neuromuscular junction, and no major effect on monosynaptic spinal reflexes. The effects of tizanidine are greatest on polysynaptic pathways. The overall effect of these actions is thought to reduce facilitation of spinal motor neurons.

The imidazoline chemical structure of tizanidine is related to that of the anti-hypertensive drug clonidine and other α_2-adrenergic agonists. Pharmacological studies in animals show similarities between the two compounds, but tizanidine was found to have one-tenth to one-fiftieth (1/50) of the potency of clonidine in lowering blood pressure.

PHARMACOKINETICS

Zanaflex tablets and capsules are bioequivalent to each other under fasted conditions, but not under fed conditions.

A single dose of either two 4 mg tablets or two 4 mg capsules was administered under fed and fasting conditions in an open label, four period, randomized crossover study in 96 human volunteers, of whom 81 were eligible for the statistical analysis.

Following oral administration of either the tablet or capsule (in the fasted state), tizanidine has peak plasma concentrations occurring 1.0 hour after dosing with a half-life of approximately 2 hours.

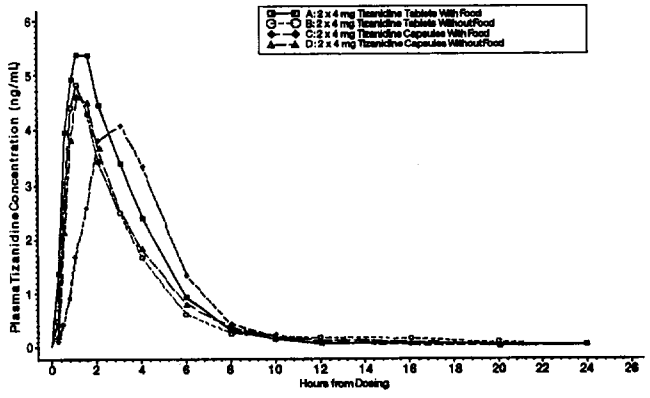
When two 4 mg tablets are administered with food the mean maximal plasma concentration is increased by approximately 30%, and the median time to peak plasma concentration is increased by 25 minutes, to 1 hour and 25 minutes.

In contrast, when two 4 mg capsules are administered with food the mean maximal plasma concentration is decreased by 20%, the median time to peak plasma ncentration is increased by 2 hours to 3 hours. Consequently, the mean Cmax for the sule when administered with food is approximately 2/3's the Cmax for the tablet n administered with food.

d also increases the extent of absorption for both the tablets and capsules. The ease with the tablet (~30%) is significantly greater than with the capsule (~10%). sequently when each is administered with food, the amount absorbed from the sule is about 80% of the amount absorbed from the tablet (See Figures 1 and 2).

ninistration of the capsule contents sprinkled on applesauce is not bioequivalent to ninistration of an intact capsule under fasting conditions. Administration of the capsule contents on applesauce results in a 15% - 20% increase in Cmax and AUC of tizanidine compared to administration of an intact capsule while fasting, and a 15 minute decrease in the median lag time and time to peak concentration.

Figure 1: Mean Tizanidine Concentration vs. Time Profiles For Zanaflex Tablets and Capsules (2 x 4 mg) Under Fasted and Fed Conditions



Zanaflex® Capsules (tizanidine hydrochloride)

SPECIAL POPULATIONS

Age Effects

No specific pharmacokinetic study was conducted to investigate age effects. Cross study comparison of pharmacokinetic data following single dose administration of 6 mg tizanidine showed that younger subjects cleared the drug four times faster than the elderly subjects. Tizanidine has not been evaluated in children (see PRECAUTIONS).

Hepatic Impairment

Pharmacokinetic differences due to hepatic impairment have not been studied. However, due to reliance on first pass metabolism, tizanidine should be used with caution in patients with significant hepatic impairment (see WARNINGS).

Renal Impairment

Tizanidine clearance is reduced by more than 50% in elderly patients with renal insufficiency (creatinine clearance < 25 mL/min) compared to healthy elderly subjects; this would be expected to lead to a longer duration of clinical effect. Tizanidine should be used with caution in renally impaired patients (see PRECAUTIONS).

Gender Effects

No specific pharmacokinetic study was conducted to investigate gender effects. Retrospective analysis of pharmacokinetic data, however, following single and multiple dose administration of 4 mg tizanidine showed that gender had no effect on the pharmacokinetics of tizanidine.

Race Effects

Pharmacokinetic differences due to race have not been studied.

Drug Interactions

Oral Contraceptives

No specific pharmacokinetic study was conducted to investigate interaction between oral contraceptives and tizanidine. Retrospective analysis of population pharmacokinetic data following single and multiple dose administration of 4 mg tizanidine, however, showed that women concurrently taking oral contraceptives had 50% lower clearance of tizanidine compared to women not on oral contraceptives (see PRECAUTIONS).

Fluvoxamine

Significant alterations of pharmacokinetic parameters including AUC, t1/2, and Cmax have been observed with concomitant administration (see CONTRAINDICATIONS).

CLINICAL STUDIES

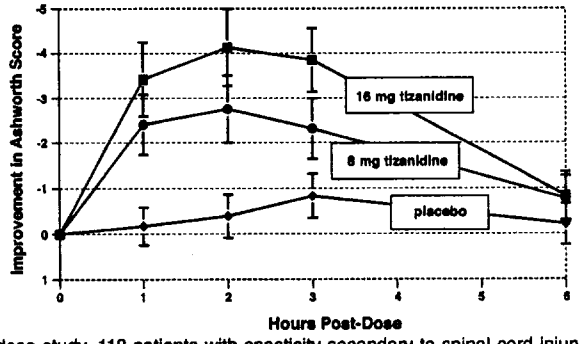
Tizanidine's capacity to reduce increased muscle tone associated with spasticity was demonstrated in two adequate and well controlled studies in patients with multiple sclerosis or spinal cord injury.

In one study, patients with multiple sclerosis were randomized to receive single oral doses of drug or placebo. Patients and assessors were blind to treatment assignment and efforts were made to reduce the likelihood that assessors would become aware indirectly of treatment assignment (e.g., they did not provide direct care to patients and were prohibited from asking questions about side effects). In all, 140 patients received either placebo, 8 mg or 16 mg of tizanidine.

Response was assessed by physical examination; muscle tone was rated on a 5 point scale (Ashworth score), with a score of 0 used to describe normal muscle tone. A score of 1 indicated a slight spastic catch while a score of 2 indicated more marked muscle resistance. A score of 3 was used to describe considerable increase in tone, making passive movement difficult. A muscle immobilized by spasticity was given a score of 4. Spasm counts were also collected.

Assessments were made at 1, 2, 3 and 6 hours after treatment. A statistically significant reduction of the Ashworth score for Zanaflex compared to placebo was detected at 1, 2 and 3 hours after treatment. Figure 2 below shows a comparison of the mean change in muscle tone from baseline as measured by the Ashworth scale. The greatest reduction in muscle tone was 1 to 2 hours after treatment. By 6 hours after treatment, muscle tone in the 8 and 16 mg tizanidine groups was indistinguishable from muscle tone in placebo treated patients. Within a given patient, improvement in muscle tone was correlated with plasma concentration. Plasma concentrations were variable from patient to patient at a given dose. Although 16 mg produced a larger effect, adverse events including hypotension were more common and more severe than in the 8 mg group. There were no differences in the number of spasms occurring in each group.

Figure 2: Single Dose Study—Mean Change in Muscle Tone from Baseline as Measured by the Ashworth Scale ± 95% Confidence Interval (A Negative Ashworth Score Signifies an Improvement in Muscle Tone from Baseline)



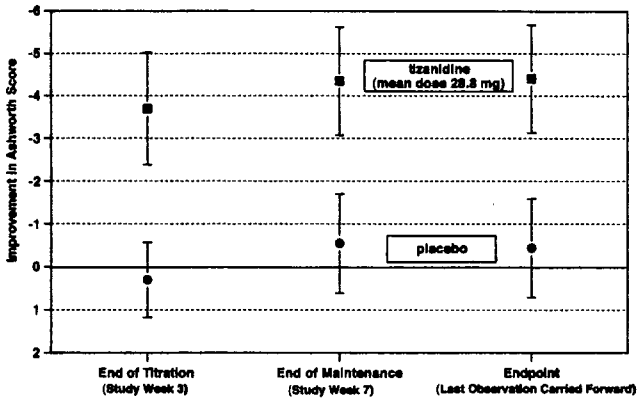
In a multiple dose study, 118 patients with spasticity secondary to spinal cord injury were randomized to either placebo or tizanidine. Steps similar to those taken in the first study were employed to ensure the integrity of blinding.

Patients were titrated over 3 weeks up to a maximum tolerated dose or 36 mg daily given in three unequal doses (e.g., 10 mg given in the morning and afternoon and

16 mg given at night). Patients were then maintained on their maximally tolerated dose for 4 additional weeks (i.e., maintenance phase). Throughout the maintenance phase, muscle tone was assessed on the Ashworth scale within a period of 2.5 hours following either the morning or afternoon dose. The number of daytime spasms was recorded daily by patients.

At endpoint (the protocol-specified time of outcome assessment), there was a statistically significant reduction in muscle tone and frequency of spasms in the tizanidine treated group compared to placebo. The reduction in muscle tone was not associated with a reduction in muscle strength (a desirable outcome) but also did not lead to any consistent advantage of tizanidine treated patients on measures of activities of daily living. Figure 3 below shows a comparison of the mean change in muscle tone from baseline as measured by the Ashworth scale.

Figure 3: Multiple Dose Study—Mean Change in Muscle Tone 0.5–2.5 Hours After Dosing as Measured by the Ashworth Scale ± 95% Confidence Interval (A Negative Ashworth Score Signifies an Improvement in Muscle Tone from Baseline)



INDICATIONS AND USAGE

Tizanidine is a short-acting drug for the management of spasticity. Because of the short duration of effect, treatment with tizanidine should be reserved for those daily activities and times when relief of spasticity is most important (see DOSING AND ADMINISTRATION).

CONTRAINDICATIONS

Zanaflex is contraindicated in patients with known hypersensitivity to Zanaflex or its ingredients.

Concomitant use of Zanaflex with fluvoxamine, a potent inhibitor of Cytochrome P450 1A2, is contraindicated. Significant alterations of pharmacokinetic parameters of tizanidine including AUC, t1/2, Cmax, increased oral bioavailability and decreased plasma clearance have been observed with concomitant fluvoxamine administration (see CLINICAL PHARMACOLOGY, WARNINGS, ADVERSE REACTIONS).

WARNINGS

LIMITED DATA BASE FOR CHRONIC USE OF SINGLE DOSES ABOVE 8 MG AND MULTIPLE DOSES ABOVE 24 MG PER DAY

Clinical experience with long-term use of tizanidine at doses of 8 to 16 mg single doses or total daily doses of 24 to 36 mg (see Dosage and Administration) is limited. In safety studies, approximately 75 patients have been exposed to individual doses of 12 mg or more for at least one year or more and approximately 80 patients have been exposed to total daily doses of 30 to 36 mg/day for at least one year or more. There is essentially no long-term experience with single, daytime doses of 16 mg. Because long-term clinical study experience at high doses is limited, only those adverse events with a relatively high incidence are likely to have been identified (see WARNINGS, PRECAUTIONS AND ADVERSE REACTIONS).

HYPOTENSION

Tizanidine is an α_2-adrenergic agonist (like clonidine) and can produce hypotension. In a single dose study where blood pressure was monitored closely after dosing, two-thirds of patients treated with 8 mg of tizanidine had a 20% reduction in either the diastolic or systolic BP. The reduction was seen within 1 hour after dosing, peaked 2 to 3 hours after dosing and was associated, at times, with bradycardia, orthostatic hypotension, lightheadedness/dizziness and rarely syncope. The hypotensive effect is dose related and has been measured following single doses of ≥2 mg.

Clinically significant hypotension (decreases in both systolic and diastolic pressure) has been reported with concomitant administration of fluvoxamine following single doses of 4 mg (see DRUG INTERACTIONS, CONTRAINDICATIONS, ADVERSE REACTIONS).

The chance of significant hypotension may possibly be minimized by titration of the dose and by focusing attention on signs and symptoms of hypotension prior to dose advancement. In addition, patients moving from a supine to fixed upright position may be at increased risk for hypotension and orthostatic effects.

Caution is advised when tizanidine is to be used in patients receiving concurrent antihypertensive therapy and should not be used with other α_2-adrenergic agonists.

Caution is recommended when considering concomitant use of tizanidine with other inhibitors of CYP1A2, such as, antiarrhythmics (amiodarone, mexiletine, propafenone), cimetidine, fluoroquinolones (ciprofloxacin, norfloxacin), rofecoxib, oral contraceptives, and ticlopidine.

RISK OF LIVER INJURY

Tizanidine occasionally causes liver injury, most often hepatocellular in type. In controlled clinical studies, approximately 5% of patients treated with tizanidine had elevations of liver function tests (ALT/SGPT, AST/SGOT) to greater than 3 times the upper limit of normal (or 2 times if baseline levels were elevated) compared to 0.4% in the control patients. Most cases resolved rapidly upon drug withdrawal with no reported residual problems. In occasional symptomatic cases, nausea, vomiting, anorexia and jaundice have been reported. In postmarketing experience, three deaths associated with liver failure have been reported in patients treated with tizanidine. In one case, a 49-year-old male developed jaundice and liver enlargement following 2 months of tizanidine treatment, primarily at 6 mg t.i.d. A liver biopsy showed multilobular necrosis without eosinophilic infiltration. Treatment was discontinued and the patient died in hepatic coma 10 days later. There was no evidence of hepatitis B and C in this patient and other therapy included only oxazepam and ranitidine. There was thus no explanation, other than a reaction to tizanidine, to explain the liver injury. In the two other cases, patients were taking other drugs with known potential for liver toxicity. One patient, treated with tizanidine at a dose of 4 mg/day, was also on carbamazepine when he developed cholestatic jaundice after 2 months of treatment; this patient died with pneumonia about 20 days later. Another patient, treated with tizanidine for 11 days, was also treated with dantrolene for about 2 weeks prior to developing fatal fulminant hepatic failure.

Monitoring of aminotransferase levels is recommended during the first 6 months of treatment (e.g., baseline, 1, 3 and 6 months) and periodically thereafter, based on clinical status. Because of the potential toxic hepatic effect of tizanidine, the drug should be used only with extreme caution in patients with impaired hepatic function.

SEDATION

In the multiple dose, controlled clinical studies, 48% of patients receiving any dose of tizanidine reported sedation as an adverse event. In 10% of these cases, the sedation was rated as severe compared to < 1% in the placebo treated patients. Sedation may interfere with everyday activity.

The effect appears to be dose related. In a single dose study, 92% of the patients receiving 16 mg, when asked, reported that they were drowsy during the 6 hour study. This compares to 76% of the patients on 8 mg and 35% of the patients on placebo. Patients began noting this effect 30 minutes following dosing. The effect peaked 1.5 hours following dosing. Of the patients who received a single dose of 16 mg, 51% continued to report drowsiness 6 hours following dosing compared to 13% in the patients receiving placebo or 8 mg of tizanidine.

In the multiple dose studies, the prevalence of patients with sedation peaked following the first week of titration and then remained stable for the duration of the maintenance phase of the study.

HALLUCINOSIS/PSYCHOTIC-LIKE SYMPTOMS

Tizanidine use has been associated with hallucinations. Formed, visual hallucinations or delusions have been reported in 5 of 170 patients (3%) in two North American controlled clinical studies. These 5 cases occurred within the first 6 weeks. Most of the patients were aware that the events were unreal. One patient developed psychoses in association with the hallucinations. One patient among these 5 continued to have problems for at least 2 weeks following discontinuation of tizanidine.

PRECAUTIONS

CARDIOVASCULAR

Prolongation of the QT interval and bradycardia were noted in chronic toxicity studies in dogs at doses equal to the maximum human dose on a mg/m2 basis. ECG evaluation was not performed in the controlled clinical studies. Reduction in pulse rate has been noted in association with decreases in blood pressure in the single dose controlled study (see WARNINGS).

OPHTHALMIC

Dose-related retinal degeneration and corneal opacities have been found in animal studies at doses equivalent to approximately the maximum recommended dose on a mg/m² basis. There have been no reports of corneal opacities or retinal degeneration in the clinical studies.

USE IN RENALLY IMPAIRED PATIENTS

Tizanidine should be used with caution in patients with renal insufficiency (creatinine clearance < 25 mL/min), as clearance is reduced by more than 50%. In these patients, during titration, the individual doses should be reduced. If higher doses are required, individual doses rather than dosing frequency should be increased. These patients should be monitored closely for the onset or increase in severity of the common adverse events (dry mouth, somnolence, asthenia and dizziness) as indicators of potential overdose.

USE IN WOMEN TAKING ORAL CONTRACEPTIVES

Tizanidine should be used with caution in women taking oral contraceptives, as clearance of tizanidine is reduced by approximately 50% in such patients. In these patients, during titration, the individual doses should be reduced.

DISCONTINUING THERAPY

If therapy needs to be discontinued, especially in patients who have been receiving high doses for long periods, the dose should be decreased slowly to minimize the risk of withdrawal and rebound hypertension, tachycardia, and hypertonia.

INFORMATION FOR PATIENTS

Patients should be advised of the limited clinical experience with tizanidine both in regard to duration of use and the higher doses required to reduce muscle tone (see WARNINGS).

Because of the possibility of tizanidine lowering blood pressure, patients should be warned about the risk of clinically significant orthostatic hypotension (see WARNINGS).

Because of the possibility of sedation, patients should be warned about performing activities requiring alertness, such as driving a vehicle or operating machinery (see Warnings). Patients should also be instructed that the sedation may be additive when tizanidine is taken in conjunction with drugs (baclofen, benzodiazepines) or substances (e.g., alcohol) that act as CNS depressants.

Patients should be advised of the change in the absorption profile of Zanaflex if taken

with food and the potential changes in efficacy and adverse effect profiles that may result (see PHARMACOKINETICS).
Patients should be advised not to stop tizanidine suddenly as rebound hypertension and tachycardia may occur (see PRECAUTIONS: Discontinuing Therapy).
Tizanidine should be used with caution where spasticity is utilized to sustain posture and balance in locomotion or whenever spasticity is utilized to obtain increased function.

DRUG INTERACTIONS

Invitro studies of cytochrome P450 isoenzymes using human liver microsomes indicate that neither tizanidine nor the major metabolites are likely to affect the metabolism of other drugs metabolized by cytochrome P450 isoenzymes.

Acetaminophen

Tizanidine delayed the Tmax of acetaminophen by 16 minutes. Acetaminophen did not affect the pharmokinetics of tizanidine.

Alcohol

Alcohol increased the AUC of tizanidine by approximately 20%, while also increasing its Cmax by approximately 15%. This was associated with an increase in side effects of tizanidine. The CNS depressant effects of tizanidine and alcohol are additive.

Fluvoxamine

Clinically significant hypotension (decreases in both systolic and diastolic pressure) has been reported with concomitant administration of fluvoxamine following single doses of 4 mg (see DRUG INTERACTIONS, CONTRAINDICATIONS).

Oral Contraceptives

No specific pharmokinetic study was conducted to investigate interaction between oral contraceptives and tizanidine, but retrospective analysis of population pharmokinetic data following single and multiple dose administration of 4 mg tizanidine showed that women concurrently taking oral contraceptives had 50% lower clearance of tizanidine than women not on oral contraceptives.

Rofecoxib

Rofecoxib may potentiate the adverse effects of tizanidine. Eight case reports of a potential rofecoxib-tizanidine drug interaction have been identified in postmarketing safety reports. Most of the adverse events reported involved the nervous system (e.g., hallucinations, psychosis, somnolence, hypotonia, etc.) and the cardiovascular system (e.g., hypotension, tachycardia, bradycardia). In all cases, adverse events resolved following discontinuation of tizanidine, rofecoxib, or both. Rechallenges with both drugs were not performed. The possible mechanism and the potential for a drug interaction between tizanidine and rofecoxib remain unclear.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

No evidence for carcinogenicity was seen in two dietary studies in rodents. Tizanidine was administered to mice for 78 weeks at doses up to 16 mg/kg, which is equivalent to 2 times the maximum recommended human dose on a mg/m2 basis. Tizanidine was also administered to rats for 104 weeks at doses up to 9 mg/kg, which is equivalent to 2.5 times the maximum recommended human dose on a mg/m² basis. There was no statistically significant increase in tumors in either species.
Tizanidine was not mutagenic or clastogenic in the following *in vitro* assays: the bacterial Ames test and the mammalian gene mutation test and chromosomal aberration test in Chinese hamster cells. It was also negative in the following *in vivo* assays: the bone marrow micronucleus test in mice, the bone marrow micronucleus and cytogenicity test in Chinese hamsters, the dominant lethal mutagenicity test in mice, and the unscheduled DNA synthesis (UDS) test in mice.
Tizanidine did not affect fertility in male rats at doses of 10 mg/kg, approximately 2.7 times the maximum recommended human dose on a mg/m² basis, and in females at ›ses of 3 mg/kg, approximately equal to the maximum recommended human dose a mg/m² basis; fertility was reduced in males receiving 30 mg/kg (8 times the ıximum recommended human dose on a mg/m² basis) and in females receiving 10 g/kg (2.7 times the maximum recommended human dose on a mg/m² basis). At ›se doses, maternal behavioral effects and clinical signs were observed including ırked sedation, weight loss, and ataxia.

EGNANCY

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›production studies performed in rats at a dose of 3 mg/kg, equal to the maximum recommended human dose on a mg/m² basis, and in rabbits at 30 mg/kg, 16 times the maximum recommended human dose on a mg/m² basis, did not show evidence of teratogenicity. Tizanidine at doses that are equal to and up to 8 times the maximum recommended human dose on a mg/m² basis increased gestation duration in rats. Prenatal and postnatal pup loss was increased and developmental retardation occurred. Post-implantation loss was increased in rabbits at doses of 1 mg/kg or greater, equal to or greater than 0.5 times the maximum recommended human dose on a mg/m² basis. Tizanidine has not been studied in pregnant women. Tizanidine should be given to pregnant women only if clearly needed.

LABOR AND DELIVERY

The effect of tizanidine on labor and delivery in humans is unknown.

NURSING MOTHERS

It is not known whether tizanidine is excreted in human milk, although as a lipid soluble drug, it might be expected to pass into breast milk.

GERIATRIC USE

Tizanidine should be used with caution in elderly patients because clearance is decreased four-fold.

PEDIATRIC USE

There are no adequate and well-controlled studies to document the safety and efficacy of tizanidine in children.

ADVERSE REACTIONS

In multiple dose, placebo-controlled clinical studies, 264 patients were treated with tizanidine and 261 with placebo. Adverse events, including severe adverse events, were more frequently reported with tizanidine than with placebo.

Zanaflex® Capsules (tizanidine hydrochloride)

COMMON ADVERSE EVENTS LEADING TO DISCONTIUATION

Forty-five of 264 (17%) patients receiving tizanidine and 13 of 261 (5%) patients receiving placebo in three multiple dose, placebo-controlled clinical studies, discontinued treatment for adverse events. When patients withdrew from the study, they frequently had more than one reason for discontinuing. The adverse events most frequently leading to withdrawal of tizanidine treated patients in the controlled clinical studies were asthenia (weakness, fatigue and/or tiredness) (3%), somnolence (3%), dry mouth (3%), increased spasm or tone (2%), and dizziness (2%).

MOST FREQUENT ADVERSE CLINICAL EVENTS SEEN IN ASSOCIATION WITH THE USE OF TIZANIDINE

In multiple dose, placebo-controlled clinical studies involving 264 patients with spasticity, the most frequent adverse effects were dry mouth, somnolence/sedation, asthenia (weakness, fatigue and/or tiredness) and dizziness. Three-quarters of the patients rated the events as mild to moderate and one-quarter of the patients rated the events as being severe. These events appeared to be dose related.

ADVERSE EVENTS REPORTED IN CONTROLLED STUDIES

The events cited reflect experience gained under closely monitored conditions of clinical studies in a highly selected patient population. In actual clinical practice or in other clinical studies, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Table 1 lists treatment emergent signs and symptoms that were reported in greater than 2% of patients in three multiple dose, placebo-controlled studies who received tizanidine where the frequency in the tizanidine group was at least as common as in the placebo group. These events are not necessarily related to tizanidine treatment. For comparison purposes, the corresponding frequency of the event (per 100 patients) among placebo treated patients is also provided.

Table 1: Multiple Dose, Placebo-Controlled Studies—Frequent (> 2%) Adverse Events Reported for Which Zanaflex Tablets Incidence is Greater than Placebo

Event	Placebo N = 261 %	Zanaflex Tablet N = 264 %
Dry mouth	10	49
Somnolence	10	48
Asthenia*	18	41
Dizziness	4	16
UTI	7	10
Infection	5	6
Constipation	1	4
Liver function tests abnormal	<1	3
Vomiting	0	3
Speech disorder	0	3
Amblyopia (blurred vision)	<1	3
Urinary frequency	2	3
Flu syndrome	2	3
SGPT/ALT increased	<1	3
Dyskinesia	0	3
Nervousness	<1	3
Pharyngitis	1	3
Rhinitis	2	3

* (weakness, fatigue, and/or tiredness)

In the single dose, placebo-controlled study involving 142 patients with spasticity, the patients were specifically asked if they had experienced any of the four most common adverse events: dry mouth, somnolence (drowsiness), asthenia (weakness, fatigue and/or tiredness) and dizziness. In addition, hypotension and bradycardia were observed. The occurrence of these adverse effects are summarized in Table 2. Other events were, in general, reported at a rate of 2% or less.

Table 2: Single Dose, Placebo-Controlled Study—Common Adverse Events Reported

Event	Placebo N = 48 %	Zanaflex Tablet 8mg N = 45 %	Zanaflex Tablet 16 mg N = 49 %
Somnolence	31	78	92
Dry mouth	35	76	88
Asthenia*	40	67	78
Dizziness	4	22	45
Hypotension	0	16	33
Bradycardia	0	2	10

OTHER ADVERSE EVENTS OBSERVED DURING THE EVALUATION OF TIZANIDINE

Tizanidine was administered to 1385 patients in additional clinical studies where adverse event information was available. The conditions and duration of exposure varied greatly, and included (in overlapping categories) double-blind and open-label studies, uncontrolled and controlled studies, inpatient and outpatient studies, and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.
In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. The frequencies presented, therefore, represent the proportion of the 1385 patients exposed to tizanidine who experienced an event of the type cited on at least one occasion while receiving tizanidine. All reported events are included except those already listed in Table 1. If the COSTART

term for an event was so general as to be uninformative, it was replaced by a more informative term. It is important to emphasize that, although the events reported occurred during treatment with tizanidine, they were not necessarily caused by it.
Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled studies appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients.

BODY AS A WHOLE
Frequent: Fever
Infrequent: Allergic reaction, moniliasis, malaise, abscess, neck pain, sepsis, cellulites, death, overdose
Rare: Carcinoma, congenital anomaly, suicide attempt

CARDIOVASCULAR SYSTEM
Infrequent: Vasodilatation, postural hypotension, syncope, migraine, arrhythmia
Rare: Angina pectoris, coronary artery disorder, heart failure, myocardial infarct, phlebitis, pulmonary embolus, ventricular extrasystoles, ventricular tachycardia

DIGESTIVE SYSTEM
Frequent: Abdomen pain, diarrhea, dyspepsia
Infrequent: Dysphagia, cholelithiasis, fecal impaction, flatulence, gastrointestinal hemorrhage, hepatitis, melena,
Rare: Gastroenteritis, hematemesis, hepatoma, intestinal obstruction, liver damage

HEMIC AND LYMPHATIC SYSTEM
Infrequent: Ecchymosis, hypercholesteremia, anemia, hyperlipemia, leukopenia, leukocytosis, sepsis
Rare: Petechia, purpura, thrombocythemia, thrombocytopenia

METABOLIC AND NUTRITIONAL SYSTEM
Infrequent: Edema, hypothyroidism, weight loss
Rare: Adrenal cortex insufficiency, hyperglycemia, hypokalemia, hyponatremia, hypoproteinemia, respiratory acidosis

MUSCULOSKELETAL SYSTEM
Frequent: Myasthenia, back pain
Infrequent: Pathological fracture, arthralgia, arthritis, bursitis

NERVOUS SYSTEM
Frequent: Depression, anxiety, paresthesia
Infrequent: Tremor, emotional lability, convulsion, paralysis, thinking abnormal, vertigo, abnormal dreams, agitation, depersonalization, euphoria, migraine, stupor, dysautonomia, neuralgia
Rare: Dementia, hemiplegia, neuropathy

RESPIRATORY SYSTEM
Infrequent: Sinusitis, pneumonia, bronchitis
Rare: Asthma

SKIN AND APPENDAGES
Frequent: Rash, sweating, skin ulcer
Infrequent: Pruritus, dry skin, acne, alopecia, urticaria
Rare: Exfoliative dermatitis, herpes simplex, herpes zoster, skin carcinoma

SPECIAL SENSES
Infrequent: Ear pain, tinnitus, deafness, glaucoma, conjunctivitis, eye pain, optic neuritis, otitis media, retinal hemorrhage, visual field defect
Rare: Iritis, keratitis, optic atrophy

UROGENITAL SYSTEM
Infrequent: Urinary urgency, cystitis, menorrhagia, pyelonephritis, urinary retention, kidney calculus, uterine fibroids enlarged, vaginal moniliasis, vaginitis
Rare: Albuminuria, glycosuria, hematuria, metrorrhagia

Post-marketing experience has reported bradycardia, dizziness, significant hypotension, and somnolence with concomitant administration of fluvoxamine (see CONTRAINDICATIONS, PRECAUTIONS, WARNINGS, DRUG INTERACTIONS).

DRUG ABUSE AND DEPENDENCE

Abuse potential was not evaluated in human studies. Rats were able to distinguish tizanidine from saline in a standard discrimination paradigm, after training, but failed to generalize the effects of morphine, cocaine, diazepam, or phenobarbital to tizanidine. Monkeys were shown to self-administer tizanidine in a dose-dependent manner, and abrupt cessation of tizanidine produced transient signs of withdrawal at doses > 35 times the maximum recommended human dose on a mg/m2 basis. These transient withdrawal signs (increased locomotion, body twitching, and aversive behavior toward the observer) were not reversed by naloxone administration.
Tizanidine is closely related to clonidine, which is often abused in combination with narcotics and is known to cause symptoms of rebound upon abrupt withdrawal. Three cases of rebound symptoms on sudden withdrawal of tizanidine have been reported. The case reports suggest that these patients were also misusing narcotics. Withdrawal symptoms included hypertension, tachycardia, hypertonia, tremor, and anxiety. As with clonidine, withdrawal is expected to be more likely in cases where high doses are used, especially for prolonged periods.

OVERDOSAGE

A search of a safety surveillance database revealed a total of eighteen cases of tizanidine overdose. Of the fourteen intentional overdoses, five have resulted in fatality, and in at least three of these cases, other CNS depressants were involved. One fatality was secondary to pneumonia and sepsis, which were sequelae of the ingestion. The majority of cases involve depressed consciousness (somnolence, stupor, or coma), depressed cardiovascular function (bradycardia, hypotension), and depressed respiratory function (respiratory depression or failure).
Should overdose occur, basic steps to ensure the adequacy of an airway and the

Zanaflex® Capsules (tizanidine hydrochloride)

monitoring of cardiovascular and respiratory systems should be undertaken. In general, symptoms resolve within one to three days following discontinuation of tizanidine and administration of appropriate therapy. Due to the similar mechanism of action, symptoms and management of tizanidine overdose are similar to those following clonidine overdose. For the most recent information concerning the management of overdose, contact a poison control center.

DOSAGE AND ADMINISTRATION

A single dose of 8 mg of tizanidine reduces muscle tone in patients with spasticity for a period of several hours. The effect peaks at approximately 1 to 2 hours and dissipates between 3 to 6 hours. Effects are dose-related.
Although single doses of less than 8 mg have not been demonstrated to be effective in controlled clinical studies, the dose-related nature of tizanidine's common adverse events make it prudent to begin treatment with single oral doses of 4 mg. Increase the dose gradually (2 to 4 mg steps) to optimum effect (satisfactory reduction of muscle tone at a tolerated dose).
The dose can be repeated at 6 to 8 hour intervals, as needed, to a maximum of three doses in 24 hours. The total daily dose should not exceed 36 mg.
Experience with single doses exceeding 8 mg and daily doses exceeding 24 mg is limited. There is essentially no experience with repeated, single, daytime doses greater than 12 mg or total daily doses greater than 36 mg (see WARNINGS).
Food has complex effects on tizanidine pharmacokinetics, which differ with the different formulations. These pharmacokinetic differences may result in clinically significant differences when [1] switching administration of the tablet between the fed or fasted state, [2] switching administration of the capsule between the fed or fasted state, [3] switching between the tablet and capsule in the fed state, or [4] switching between the intact capsule and sprinkling the contents of the capsule on applesauce. These changes may result in increased adverse events or delayed/more rapid onset of activity, depending upon the nature of the switch. For this reason, the prescriber should be thoroughly familiar with the changes in kinetics associated with these different conditions (see PHARMACOKINETICS).

HOW SUPPLIED

2 MG Tablets
Zanaflex® (tizanidine hydrochloride) is available as 2 mg white tablets, with a bisecting score on one side and debossed with "A592" on the other.
They are supplied in: Bottles of 150 (NDC 10144- 592-15).
4 MG Tablets
Zanaflex® (tizanidine hydrochloride) is available as 4 mg white tablets, with a quadrisecting score on one side and debossed with "A594" on the other.
They are supplied in: Bottles of 150 (NDC 10144-594-15).
2 MG Capsules
ZANAFLEX® (tizanidine hydrochloride) is available as a 2 mg two-piece hard gelatin capsule consisting of a standard blue opaque body with a standard blue opaque cap. The capsules are printed with 2 mg in white.
They are supplied in: Bottles of 150 (NDC 10144-602-15).
4 MG Capsules
Zanaflex® (tizanidine hydrochloride) is available as a 4 mg two-piece hard gelatin capsule consisting of a white opaque body with a light blue opaque cap. The capsules are printed with 4 mg in white.
They are supplied in: Bottles of 150 (NDC 10144-604-15).
6 MG Capsules
Zanaflex® (tizanidine hydrochloride) is available as a 6 mg two-piece hard gelatin capsule consisting of a light blue opaque body with a light blue opaque cap. The capsules are printed with 6 mg in white.
They are supplied in: Bottles of 150 (NDC 10144-606-15).
Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Dispense in containers with child resistant closure.

℞ Only
Manufactured by:
Elan Pharma International, Ltd.
Athlone, Ireland

Marketed by:
Acorda Therapeutics, Inc.
Hawthorne, NY 10532

AcordaZanaflexTab001 Rev. 03-13-05

ACØRDA®
THERAPEUTICS

The State of Maryland
Department of Health and Mental Hygiene
Maryland Pharmacy Program
Division of Pharmacy Services
Drug Utilization Review (DUR) Board
Policies and Procedures

Administration

Administrative coordination of the DUR Board functions is performed by the retrospective DUR vendor or other party as designated by the Department of Health and Mental Hygiene, Division of Pharmacy Services.

Function

The activities of the DUR Board include:

1. Advise the Pharmacy Program of the Department of Health and Mental Hygiene in the area of DUR as defined by the Omnibus Budget Reconciliation Act of 1990, section 1927 g(3).

2. Review prospective and retrospective DUR criteria, prior authorization criteria and quantity or dosage form limitations developed by the Division of Pharmacy Services or by one of the contracted vendors

3. Evaluate the use of criteria and interventions, including assessing the operational effect of the criteria and interventions, in order to identify areas of prescribing and dispensing of specific drugs that may result in adverse patient outcomes.

4. Evaluate patient drug utilization that may represent potential fraud and abuse.

5. Identifies educational needs and develops educational plans to improve prescribing or dispensing practices, and evaluate the effect of these educational interventions.

6. Review and approve the annual DUR report describing the nature and scope of the DUR program, summarizing education/intervention strategies used, and estimating the cost savings generated.

Composition

The DUR Board is composed of nine persons: four physicians and five pharmacists who are licensed and actively practicing and have recognized knowledge and expertise in one or more of the following areas:

1. The clinically appropriate prescribing of covered outpatient drugs.
2. The clinically appropriate dispensing and monitoring of covered outpatient drugs.
3. Drug use review, evaluation, and intervention.
4. Medical quality assurance.

Board Appointments and Terms

1. The DUR Board is appointed by the Secretary of the Department of Health and Mental Hygiene.

2. The retrospective DUR vendor makes recommendations regarding the nominees for the DUR Board to the Division of Pharmacy Services, who makes recommendations to the Secretary.

3. DUR Board terms are for three years and are staggered, so that new Board members are appointed each year.

4. DUR Board members may not serve more than two consecutive terms.

5. DUR Board members may be replaced at the discretion of the Secretary due to absences or conflicts of interest or other matters that would not serve the best interests of the Maryland Medicaid population.

V. Meetings

Meetings are held at least quarterly at a time and place to be specified by the retrospective DUR vendor in collaboration with the Division of Pharmacy Services.

VI. Board Chairperson

1. The DUR Board elects, from among its members, a Chairperson

2. The Chairperson presides over the meetings of the DUR Board.

3. The term of the Chairperson is two years.

4. At the completion of the Chair's term, a new Chairperson will be elected by the DUR Board.

VII. Prospective DUR Criteria Review

Throughout the year the DUR Board will be asked to review selected prospective DUR criteria. Currently prospective criteria are maintained by First Health Services Corporation (FHSC) and are based on First DataBank (FDB) criteria. Some modifications to FDB criteria are possible and can be made based on DUR Board review. Current prospective DUR criteria elements in use include those noted on the following table.

Maryland Prospective DUR Criteria Elements

Maryland DUR Board Criteria Element	Maryland DUR Board Criteria Element Definition (Parallels OBRA 1990 Requirements)	Comparable FHSC Problem Type – SX (First Data Bank Module)	FHSC Definition of Problem Type
Therapeutic duplication	The prescribing and dispensing of two or more drugs from the same therapeutic class such that the combined daily dose puts the patient at risk of an adverse medical event.	Therapeutic duplication	Alert occurs when a drug that is to be dispensed is in the same therapeutic class as another drug filled within the previous eight weeks.
Drug-disease contraindication	The potential for an undesirable alteration of the therapeutic effect of a given prescription because of the presence of a disease condition. Drug-pregnancy contraindications are included in this element. All drugs without an FDA pregnancy rating or with an FDA pregnancy rating of C, D, or X are flagged with a drug-disease contraindication. Pregnancy is identified by diagnosis, if known, or the use of prenatal vitamins in a female 12 to 50 years of age. Drug-age contraindications are also included in this element.	Drug-known disease precaution	Alert occurs when the current prescription is contraindicated for a known disease that is document in patient's profile. Pregnancy and lactation warnings are included in this module.
		Drug-geriatric precaution	Alert occurs when drug therapy may not be appropriate for a patient in the geriatric age group.
		Drug-pediatric precaution	Alert occurs when drug therapy may not be appropriate for a patient in the pediatric age group.
Adverse drug-drug interaction	The potential for an adverse medical effect as a result of the patient using two or more drugs together.	Drug-drug interactions	Alert occurs when a drug that is to be dispensed may interact with a previously filled drug from any participating pharmacy.
Incorrect drug dosage	A dosage that lies outside the daily dosage range specified by predetermined standards as necessary to achieve therapeutic benefit. Drug dosage criteria may be age-specific or indication-specific.	Minimum-Maximum dose precaution	Alert occurs when daily dose of the drug is below the minimum or exceeds the maximum levels. The module provides a check against criteria for pediatric, adult and geriatric patient groups.

Prospective DUR Criteria Alerts

1. At each quarterly meeting the DUR Board will review a summary of prospective DUR criteria alerts from the previous quarter, based on alerts generated from pharmacy claims data for fee-for-service Medicaid recipients. The DUR Board will evaluate specific criteria and give their recommendation if criteria should continue to be alerted to the dispensing pharmacist based on the severity of the alert.

2. The DUR Board will make recommendations for prospective DUR alerts which should result in claims denial and require authorization based on the severity of the alert.

Retrospective DUR

1. Each year the retrospective DUR vendor and the Division of Pharmacy Services presents ideas for retrospective analyses to the DUR Board for their input and prioritization.

2. Currently the goal is to perform quarterly retrospective analyses.

3. The retrospective DUR vendor develops a draft plan including, therapeutic exception to be evaluated, criteria for patient selection and educational or administrative interventions. The plan will be presents it to the DUR Board for input and approval.

4. After the evaluation is performed, the retrospective DUR vendor presents results and recommendations for additional action to the DUR Board in the form of a written report for input and approval.

Prior Authorization Criteria, Quantity and Dosage form Limitations

1. The DUR Board will review and evaluate any prior authorization criteria, dosage form limitations or quantity limitations that the Division of Pharmacy Services is planning to implement with regard to fee-for-service Medicaid recipients.

2. The Board will review these criteria based on their clinical expertise and advise the Division of Pharmacy Services if criteria are appropriate for implementation. The Division of Pharmacy Services will have final approval of all prior authorization criteria, quantity or dosage form limitation implemented.

Confidentiality

1. All DUR Board members will sign a confidentiality agreement with the Division of Pharmacy Services and the retrospective DUR vendor.

2. All patient or provider information will be blinded on all materials reviewed at DUR Board meetings.

3. No patient or provide information will be included in any DUR reports.

Public Communication

1. DUR Board meetings are by invitation only. One representative from the pharmaceutical industry will be selected for regular attendance and will act as the liaison for the industry.

2. Requests from the public for information regarding the DUR Board or DUR Board meetings will be directed to the Division of Pharmacy Services for review.

ALABAMA MEDICAID AGENCY
Drug Utilization Review Board

TOPIC: DUR Board Memberships/Appointments

DATE: December 2001 DUR Policy #2

According to the Alabama Administrative Code, 560-X-16.-23, the DUR Board will consist of four practicing physicians, four practicing pharmacists, two representatives from the state's pharmacy schools, two representatives from the state's medical schools, and two representatives from the Alabama Medicaid Agency.

Members of the DUR Board are recommended to the Agency by the Medical Association of the State of Alabama (MASA) and the Alabama Pharmacy Association (APA) Nominations are considered and appointments are made by the Medicaid Commissioner. Members serve two-year terms and may be nominated by their respective associations for no more than two consecutive terms Nominations should be for physicians and pharmacists who are actively participating as providers and have clearly demonstrated clinical expertise. Members serving as representatives from Alabama's Schools of Pharmacy and School of Medicine serve two-year terms for no more than two consecutive terms.

Services performed by the DUR Board will be reimbursed through individual professional service contracts between members and the Alabama Medicaid Agency. Payment will consist of an hourly rate for time spent traveling to/from meetings, reviewing meeting materials and actual meeting time.

Board meetings are held at a minimum of once per quarter and more frequently as called by the Chairperson or Medicaid. Unless otherwise noted, meetings will be held at the Alabama Medicaid Agency, 501 Dexter Avenue, Montgomery, Alabama. Members are required to attend, at a minimum, fifty percent of meetings per year. Failure to do so without explanation of extenuating circumstances will result in the termination of the member's appointment. In such cases, nominations for replacement of the vacant position will be sought from the respective association. Individuals appointed to the DUR Board to replace previous members will serve the remaining time left in the original appointment.

Concur:_____
DUR Board Chairperson

ALABAMA MEDICAID AGENCY
Drug Utilization Review Board

TOPIC: Operating Procedures

DATE: December 2001 DUR Policy #3

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1. The DUR Board will be chaired by a physician or pharmacist and consist of a minimum of eight voting members The Committee will consist of a minimum of four physicians licensed in the State of Alabama and four clinical pharmacists licensed in the State of Alabama.
2. Members shall be licensed in the State of Alabama and actively participating as providers.
3. The Board may include one voting representative from each of the Alabama's Schools of Pharmacy and Medicine.
4. The DUR Board shall include one Medicaid staff physician and one Medicaid staff pharmacist who will maintain voting rights.
5. The chairperson and vice-chairperson shall be elected by members of the Board and shall have voting privileges. The offices of chairperson and vice-chairperson shall be occupied on a rotating basis by a pharmacist and physician, i.e., a pharmacist shall serve as vice-chairperson while a physician is chairperson, and vice-versa. The vice-chairperson will serve as chairperson after serving his/her one-year term as vice-chairperson.
6. It is the responsibility of the chairperson to conduct DUR Board meetings. In the chairperson's absence, this responsibility will be assumed by the vice-chairperson. No policy decisions independent of the DUR Board and Medicaid's approval shall be made by the chairperson or vice-chairperson.
7. Ex Officio members will consist of Alabama Medicaid representatives and two contract representatives. (Pharmacy Administrative Services Contract, currently with HID).
8. Members will serve two-year terms and may be re-appointed to the DUR Board. To assure continuity within the committee, a rotation system will be utilized. Medicaid reserves the right to extend re-appointment invitations. Nominations for board positions will be submitted by the Alabama Pharmacy Association and the Medical Association of the State of Alabama. Appointments are made by the Medicaid Commissioner.
9. Voting members will serve as professional consultants and advisors to the Alabama Medicaid Agency. Compensation for services rendered shall be on the basis of time at the rate of forty dollars ($40.00) per hour. Total compensation shall not exceed ten thousand ($10,000.00) per year. DUR Board members will sign a statement of Integrity.

10. Meetings will be held at a minimum of once a quarter and more frequently as called by the chairperson. Unless otherwise notified, meetings will be held in Montgomery in the Medicaid Boardroom.
11. Meetings will be held when a quorum, consisting of at least half of the members, is present. If a quorum is not present, the committee may hold discussions on agenda items, but may not vote.
12. Members are required to attend at least fifty percent of the meetings each year to maintain active status on the Board
13. An agenda and any necessary supplementary materials will be prepared and supplied to committee members and agency staff at least two weeks prior to meetings to allow sufficient review time.
14. Minutes of all committee meetings shall be prepared by the secretary and maintained in the permanent records of the Alabama Medicaid Agency, Program Management Division.

Concur:_____
DUR Board Chairperson

Concur: John Searcy ms
John Searcy, M.D., Medical Director

Concur: Kathy Hall
Kathy Hall, Deputy Commissioner

Concur: Louise F Jones bnc
Louise F. Jones, Program Management

ALABAMA MEDICAID AGENCY
DRUG UTILIZATION BOARD

TOPIC: Statement of Integrity

DATE: December 2001

Each member of the DUR Board as a part of the contract process should sign the Statement of Integrity.

Statement of Integrity

In service to the Drug Utilization Review Board of Alabama Medicaid and the Alabama Medicaid Agency, I hereby agree as follows:

A. As certain confidential information may be disclosed to me, I agree to hold confidential any information not appropriate for disclosure to the public domain.

B. I further agree to hold resource documents in a safe and secure manner so as to prevent inadvertent or inappropriate disclosure to a third party with no legal and legitimate need to know.

C. I agree that I will at all times comply with applicable federal, state and local laws and regulations pertaining to my service as a member of the Drug Utilization Review Board of the Alabama Medicaid Agency.

D. I agree to actively participate in Board discussions and attend regularly scheduled meetings with few exceptions. I understand I will be asked to resign from the committee if I am absent from more than fifty percent of the meetings during a one year period.

Signature:_____ Date:_____

New Jersey Drug Utilization Review Board
By-Laws

Article 1

Preamble

These bylaws are prepared in accordance with Public Law (P.L.) 1998, Chapter 41. These bylaws are intended to meet the needs of the New Jersey Drug Utilization Review Board, further referred to as the DURB.

The DURB is intended to participate in the drug utilization review (DUR) process for New Jersey State-funded programs including: the Medicaid program, pursuant to P.L. 1968, c. 413, the Pharmaceutical Assistance to the Aged and Disabled Program, pursuant to P.L. 1975, c. 194 (C.30: 4D-20 et seq.), the Aids Drug Distribution Program (ADDP) and the Division of Family Development (DFD) General Assistance (GA) Program.

The DURB shall serve as an Advisory Board for the Commissioner, New Jersey Department of Human Services (DHS) and the Commissioner, New Jersey Department of Health and Senior Services (DHSS).

Article 2

Name

The name of the Board shall be the New Jersey Drug Utilization Review Board.

Article 3

Purpose

A. The DURB with the approval of the Department of Human Services (DHS) and Department of Health and Senior Services (DHSS) shall be responsible for recommending clinical standards and point-of-sale (POS) editing processes for the aforementioned State-funded fee-for-service (FFS) pharmacy benefit programs.

B. Clinical standards shall be based on well-accepted medical standards of the local practices of prescribers, in order to monitor for:

1. therapeutic appropriateness;

2. overutilization or underutilization;

3. therapeutic duplication;

4. drug-disease contraindications;

5. drug-drug interactions;

6. incorrect drug dosage; and

7. clinical drug abuse or misuse.

C. The DURB shall consider drug utilization data in evaluating the affect of proposed DUR criteria prior to the recommendation of DUR standards to the Commissioners of Human Services and Health and Senior Services.

D. The DURB shall consider relevant information provided by interested parties including pharmaceutical manufacturers, beneficiaries, pharmacists and the Medical Exception Process (MEP) contractor, the First Health Services Corporation (FH) prior to recommending DUR standards. Information to consider may be provided by face-to-face discussions or information compiled by the DURB.

E. The DURB shall be responsible for performing retrospective reviews of drug utilization review (DUR) data from the State's pharmacy benefit programs. The DURB shall formulate a retrospective program, which shall include educational materials, for the purpose of educating prescribers and pharmacists regarding appropriate drug utilization. This function or parts thereof may be delegated by the DURB to the MEP contractor, the First Health Services Corporation.

F. The DURB has several responsibilities related to the MEP. Specifically, the DURB shall recommend clinical edits for approval of the Commissioners of Human Services and Health and Senior Services. Also, the DURB evaluates the MEP reports provided to the DURB by the MEP contractor. The DURB is also responsible for evaluating specific exceptions to the MEP and provide policy recommendations as to the disposition of MEP standards, in accordance with the policies of both Departments.

Article 4

Membership

A. The public members of the DURB shall be appointed by the Governor upon the advice and consent of the Senate.

B. The DURB shall be composed of 15 members. Two members shall be nonvoting ex-officio members, one appointed by the Commissioner of Human Services and the other by the Commissioner of Health and Senior Services. The other members shall be public members appointed in accordance with P.L. 1998, c.41.

C. The public members shall be appointed for two-year terms and shall serve until a successor is appointed and qualified, and are eligible for reappointment; except that of the public members first appointed, eight shall be appointed for a term of two years and five for a term of one year.

Article 5

Officers

A. The public members shall appoint a chairperson and a secretary.

B. The chairperson and secretary shall be appointed for terms of one year and may serve consecutive terms.

Article 6

Job Descriptions

A. Chairman

- Assist the ex-officios in developing meeting agendas for the NJDURB;
- Assist the ex-officios in prioritizing agenda topics for discussion by the NJDURB during scheduled sessions and subcommittee meetings;
- Serve as the principle contact for members regarding their attendance at scheduled Board meetings and any subcommittee meetings determined appropriate by the Board;
- Recommend members for subcommittee participation based on member expertise for topics scheduled to be discussed;
- Assist the ex-officios with coordinating outside consultation regarding pending Board matters;
- Monitor membership requirements for the Board, including term expirations;
- Coordinate membership recruitment for recommendation to the Governor's Office for appointment and Senate confirmation;
- Facilitate meeting participation to ensure completion of meeting agendas in accordance with Roberts Rules of Order;

B. Secretary

- Record and/or review/approve draft NJDURB minutes for presentation to the Board;
- Maintain an accurate attendance record for incorporation into the NJDURB minutes;
- Develop/maintain an up-to-date list of outside consultants to facilitate NJDURB decision-making;
- Assist the ex-officios in coordinating the NJDURB meeting schedule and that of subcommittees determined appropriate by the Board;
- Prepare draft correspondence at the direction of the NJDURB.
- Coordinate requests for presentation by outside attendees of Board meetings.
- Notify NJDURB members of changes in the assigned meeting schedule due to emergencies or inclement weather.

Article 7

Meetings

A. The DURB shall meet at least quarterly or as called upon by the chairperson or the ex-officio members.

B. Meetings shall conform to all provisions of the "Open Public Meeting Act," P.L. 1975, c. 231 (C.10:4-6 et seq).

1. The public shall have access to meetings, all phases of deliberation, policy formulation and decision-making processes of the DURB, except where information may violate confidentiality rules, as specified in E below.

2. Notification of all meetings shall be made at least 48 hours prior to a meeting in at least two newspapers and prominently posted in at least one public place where similar announcements are placed. Notification shall be made to the Secretary of State. The notification shall include the time, date, location and to the extent known, the agenda of any regular, special or rescheduled meeting, which notice shall accurately state whether formal action may or may not be taken. A meeting may take place if an emergency situation exists thus circumventing the 48 hour notification rule as long as:

i. Three-quarters of the members are present; and

ii. The meeting and the delay in public notification may result in substantial harm to the public interest; and

iii. The meeting is limited to only the matters which created such urgency; and

iv. Notification of the meeting to the public is made immediately following the meeting with an explanation for the need for such a meeting.

C. An annual notification shall be made at least 48 hours prior to a meeting in at least two newspapers and prominently posted in at least one public place where similar announcements are placed and notification to the Secretary of State. The notification shall include the time, date and location of the meetings. The annual notice is made in addition to the notification, which must be made at least 48 hours prior to each meeting.

D. The press and public shall have access to all meetings of the DURB.

E. The identification of beneficiaries, prescribers and provider pharmacies may be identifiable to the Board. However, all such information, which can be used to identify beneficiaries, prescribers or provider pharmacies shall not be made public in any manner to the news media or public. Further, the DURB or its members shall not release any information without the written approval of the Commissioners of Human Services and Health and Senior Services or their representatives on the DURB.

F. The DURB shall have access to information regarding utilization of prescription drugs by beneficiaries, prescribers and pharmacists. The DURB may release non-identifying information only for the purposes of legitimate research.

G. Minutes of meetings shall be of public record and shall show the time and place of the meetings, the members present, the subjects considered, the actions taken, the vote of each member and any other related information discussed at the meeting which does not violate confidentiality rules of the DURB.

Article 8

Quorum & Voting

A. No official meeting shall take place without a quorum, which shall be composed of no less than a majority of the currently appointed membership of the Board. For example, with nine (9) members appointed, five (5) members would constitute a quorum.

B. No motion to take any action shall be valid except upon the affirmative vote of a majority of the authorized membership of the

ND Medicaid DUR Board
Procedures
(Developed 7/28/03)
(Modified 7/28/03)

1. All information to be distributed to DUR Board members must be sent to the Administrator of Pharmacy Services for distribution.
   a. All information received 14 days prior to the subsequent meeting will be forwarded to DUR Board members.
   b. Electronic format as an attachment to an e-mail is the preferred format.
   c. Electronic format as a CD-ROM or diskette is considered the second best option.
   d. If the format must be paper, 15 copies must be supplied to the Administrator of Pharmacy Services.
   e. The Department of Human Services will forward e-mail attachments to DUR Board members upon receipt of the e-mail.
   f. The Department of Human Services will mail all information received via hardcopy, CD-ROM, or diskette weekly on Thursday afternoons as well as one last mailing 14 days prior to the scheduled DUR Board meeting.
   g. The majority of communication from the Department of Human Services will be via e-mail and e-mail attachments.

2. Only one person may represent an interested party for presentations made during DUR Board meetings.

3. Presentations made by interested parties are limited to five (5) minutes (does not include Q&A or discussion generated by DUR Board members).

4. Process for DUR Board recommendations.
   a. The first meeting in which a discussion is held on specific medication(s), the DUR Board will draft a proposal for any action on the medication(s) after reviewing information supplied by the Department of Human Services and interested parties.
   b. This draft will be distributed to DUR Board members and those that have notified the Department of Human Services that they wish to receive such information.
   c. Comments on the proposal will be accepted in the same process as the general information (send to Department of Human Services at least 14 days prior to the next meeting).
   d. The subsequent meeting will involve a review of the comments received and will allow public comments per DUR Board guidelines mentioned above.
   e. The DUR Board will then develop and vote on a finalized proposal.

Proposed

North Dakota DUR Board Procedures

ND Medicaid DUR Board
Procedures
(Developed 7/28/03)
(Modified 7/29/05)

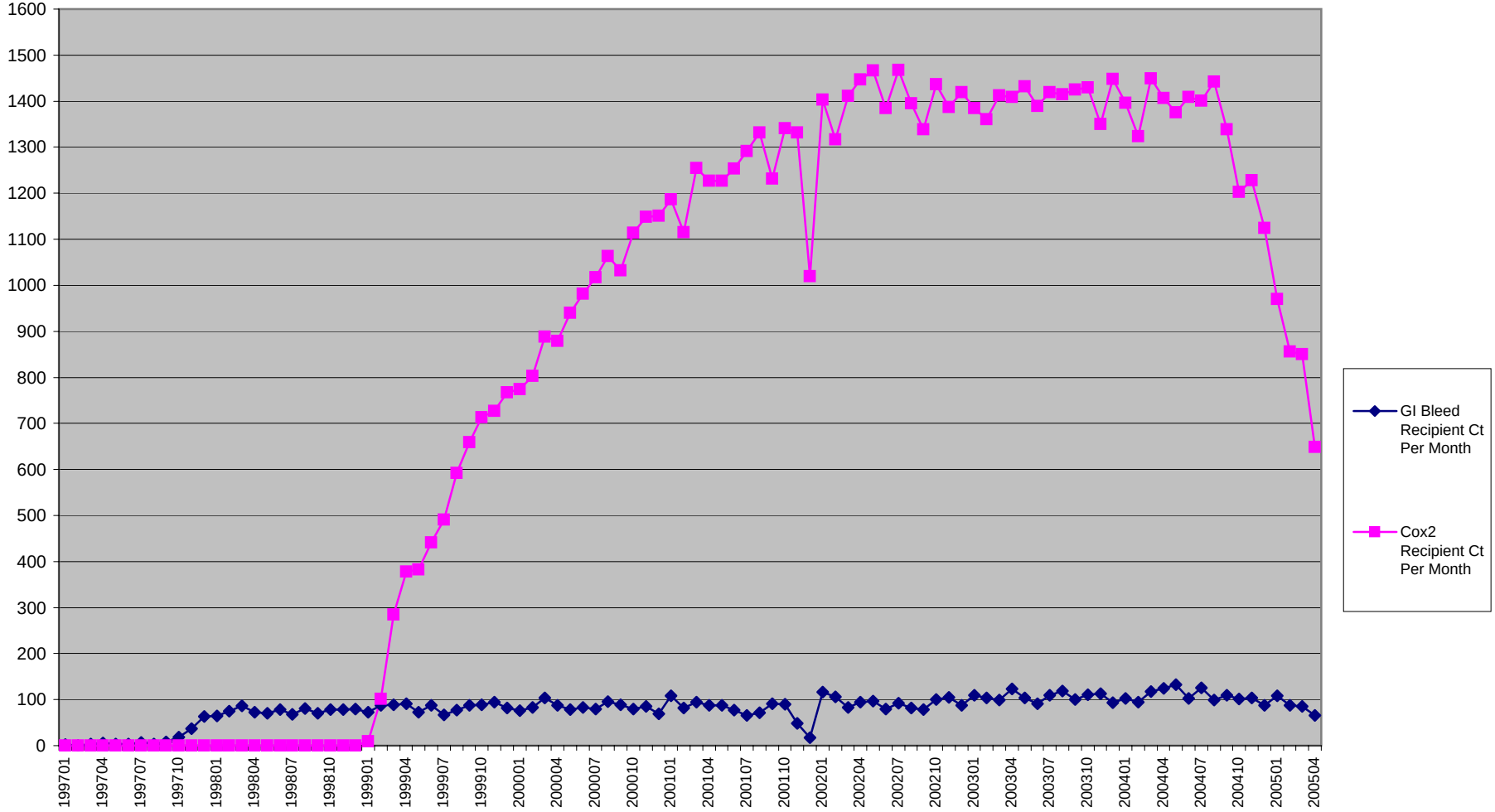
1. All information to be distributed to DUR Board members must be sent to the Administrator of Pharmacy Services for distribution.
   a. Information presented at the DUR Board meeting will be placed on the DHS website at least 8 weeks prior to the scheduled DUR meeting.
   b. Electronic format as an attachment to an e-mail is the next preferred format.
   c. If the format must be paper, 15 copies must be supplied to the Administrator of Pharmacy Services. The Department of Human Services will mail this information to DUR Board members weekly on Thursday afternoons as well as one last mailing 14 days prior to the scheduled DUR Board meeting.
   d. The Department of Human Services will forward the website link to DUR Board members, and interested parties, upon notice of posted DUR information on the website.
   e. The majority of communication from the Department of Human Services will be via DHS website, e-mail and e-mail attachments.

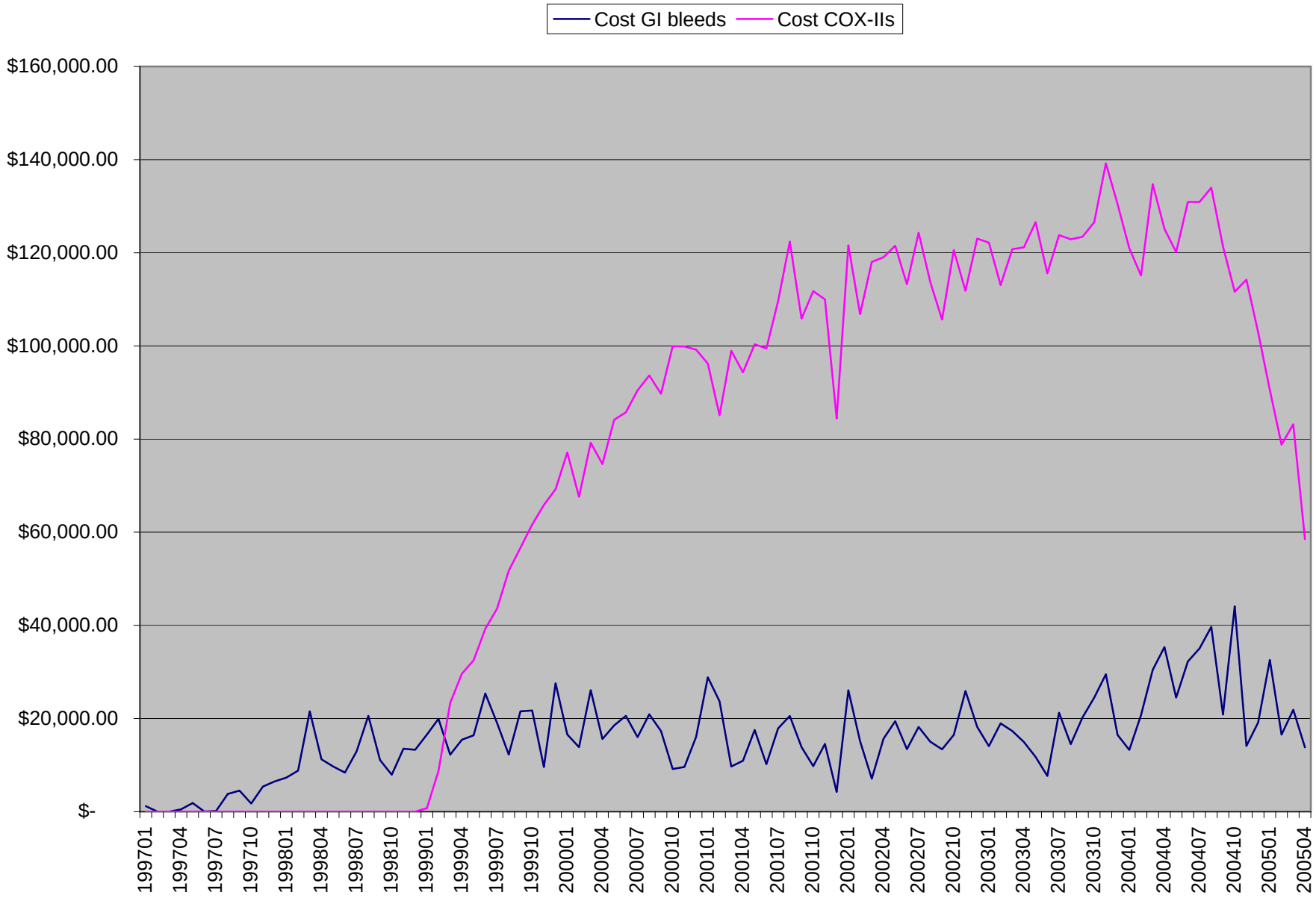
2. Only one person may represent an interested party for presentations made during DUR Board meetings.

3. Presentations made by interested parties are limited to five (5) minutes. This does not include Q&A or discussion generated by DUR Board members.

4. Process for DUR Board recommendations:
   a. Posting of information on DHS website will give DUR Board members and the public 8 weeks to draft a proposal for any action on the medication(s) after reviewing information supplied by the Department of Human Services and interested parties.
   b. This draft will be distributed to DUR Board members and those that have notified the Department of Human Services that they wish to receive such information.
   c. Comments on the proposal will be accepted. Send to DHS at least 14 days prior to the scheduled meeting.
   d. At the scheduled meeting, the DUR Board will review the comments received and will allow public comments per DUR Board guidelines mentioned above.
   e. The DUR Board will then develop and vote on a finalized proposal

North Dakota Medicaid
01/01/1997 - 04/30/2005




Cost GI bleeds
Cost COX-IIs
$160,000.00
$140,000.00
$120,000.00
$100,000.00
$80,000.00
$60,000.00
$40,000.00
$20,000.00
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GI Bleed

Gastrointestinal bleeding refers to any bleeding that originates in the gastrointestinal tract, from the mouth to the large bowel. The degree of bleeding can range from nearly undetectable to acute, massive, life-threatening bleeding. Bleeding may originate from any site along the gastrointestinal tract, but is often divided into:

Upper GI bleeding (considered any source located between the mouth and outflow tract of the stomach)
Lower GI bleeding (considered any source located from the outflow tract of the stomach to the anus, small and large bowel included)

ICD-9's	Description
530.21	Ulcer of esophaguse with bleeding
530.82	Esophageal Hemorrhage
531.0	Gastric ulcer with hemorrhage
531.00	Gastric ulcer with hemorrhage w/o obstruction
531.01	Gastric ulcer with hemorrhage w/ obstruction
531.2	Gastric ulcer with hemorrhage & perforation
531.20	Gastric ulcer with hemorrhage & perforation w/o obstruction
531.21	Gastric ulcer with hemorrhage & perforation w/ obstruction
531.4	Gastric ulcer - chronic or unspecified with hemorrhage
531.40	Gastric ulcer - chronic or unspecified with hemorrhage w/o obstruction
531.41	Gastric ulcer - chronic or unspecified with hemorrhage w/ obstruction
531.6	Gastric ulcer - chronic or unspecified with hemorrhage and perforation
531.60	Gastric ulcer - chronic or unspecified with hemorrhage and perforation w/o obstruction
531.61	Gastric ulcer - chronic or unspecified with hemorrhage and perforation w/ obstruction
532.0	Duodenal ulcer acute with hemorrhage
532.00	Duodenal ulcer acute with hemorrhage w/o obstruction
532.01	Duodenal ulcer acute with hemorrhage w/ obstruction
532.2	Duodenal ulcer acute with hemorrhage and perforation
532.20	Duodenal ulcer acute with hemorrhage and perforation w/o obstruction
532.21	Duodenal ulcer acute with hemorrhage and perforation w/ obstruction
532.4	Duodenal ulcer chronic or unspecificed with hemorrhage
532.40	Duodenal ulcer chronic or unspecificed with hemorrhage w/o obstruction
532.41	Duodenal ulcer chronic or unspecificed with hemorrhage w/ obstruction
532.6	Duodenal ulcer chronic or unspecified with hemorrhage and perforation
532.60	Duodenal ulcer chronic or unspecified with hemorrhage and perforation w/o obstruction
532.61	Duodenal ulcer chronic or unspecified with hemorrhage and perforation w/ obstruction
533.0	Peptic ulcer acute with hemorrhage
533.00	Peptic ulcer acute with hemorrhage w/o obstruction
533.01	Peptic ulcer acute with hemorrhage w/ obstruction
533.2	Peptic ulcer acute with hemorrhage and perforation
533.20	Peptic ulcer acute with hemorrhage and perforation w/o perforation
533.21	Peptic ulcer acute with hemorrhage and perforation w/ perforation
533.4	Peptic ulcer chronic or unspecified with hemorrhage
533.40	Peptic ulcer chronic or unspecified with hemorrhage w/o obstruction
533.41	Peptic ulcer chronic or unspecified with hemorrhage w/ obstruction
533.6	Peptic ulcer chronic or unspecified with hemorrhage and perforation
533.60	Peptic ulcer chronic or unspecified with hemorrhage and perforation w/o obstruction
533.61	Peptic ulcer chronic or unspecified with hemorrhage and perforation w/ obstruction
534.0	Gastrojejunal ulcer acute with hemorrhage
534.00	Gastrojejunal ulcer acute with hemorrhage w/o obstruction
534.01	Gastrojejunal ulcer acute with hemorrhage w/ obstruction
534.2	Gastrojejunal ulcer acute with hemorrhage and perforation

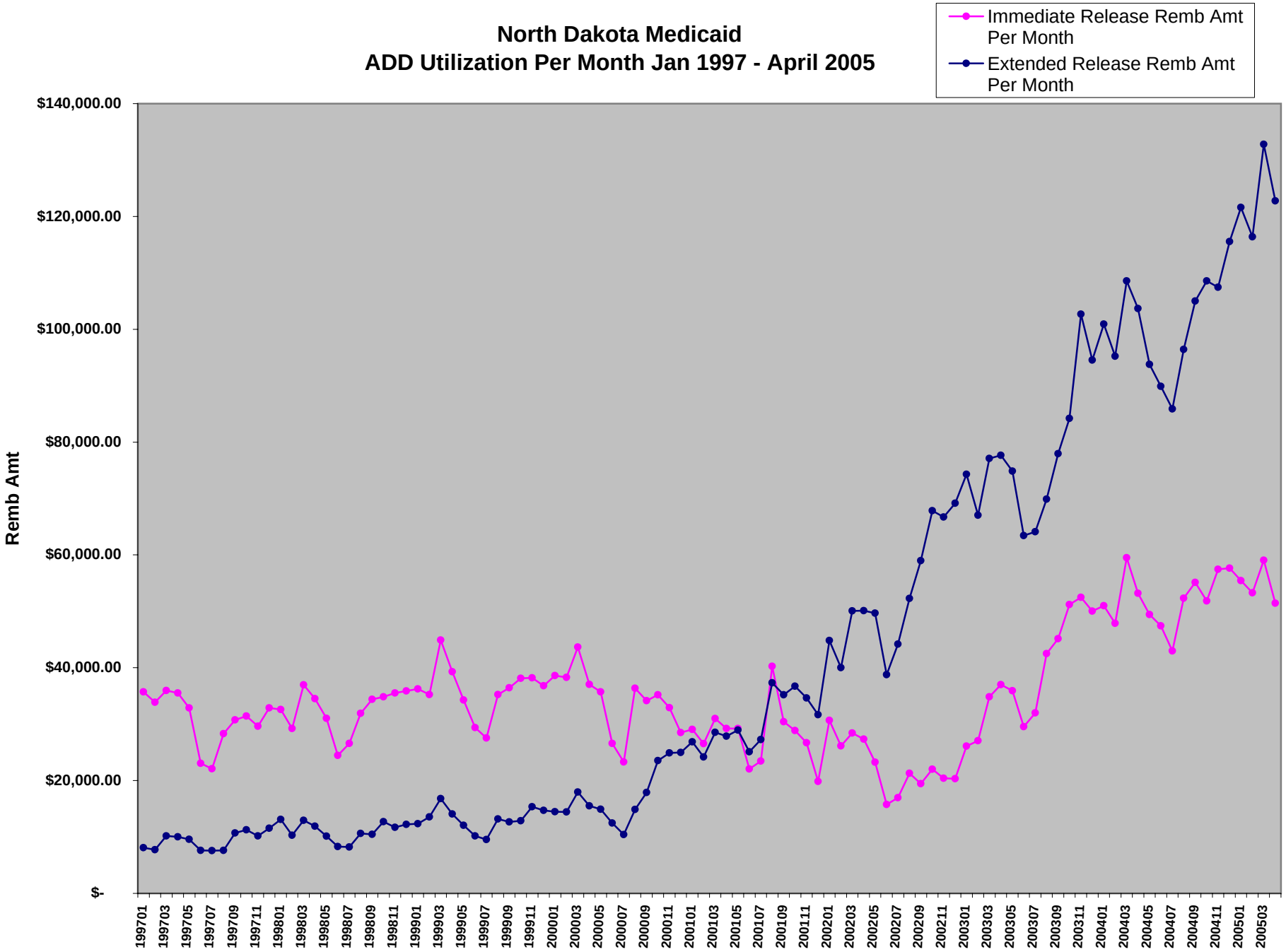
534.20	Gastrojejunal ulcer acute with hemorrhage and perforation w/o obstruction
534.21	Gastrojejunal ulcer acute with hemorrhage and perforation w/ obstruction
534.4	Gastrojejunal ulcer chronic or unspecified with hemorrhage
534.40	Gastrojejunal ulcer chronic or unspecified with hemorrhage w/o obstruction
534.41	Gastrojejunal ulcer chronic or unspecified with hemorrhage w/ obstruction
534.6	Gastrojejunal ulcer chronic or unspecified with hemorrhage or perforation
534.60	Gastrojejunal ulcer chronic or unspecified with hemorrhage or perforation w/o pbstruction
534.61	Gastrojejunal ulcer chronic or unspecified with hemorrhage or perforation w/ obstruction
537.83	Angiodysplasia of stomach and duodenum with hemorrhage
537.84	Dieulafoy lesion (hemorrhage) of stomach and duodenum
562.02	Diverticulosis of small intestine with hemorrhage
562.03	Diverticulitis of samll intestine with hemorrhage
562.12	Diverticulosis of colon with hemorrhage
562.13	Deverticulitis of colon with hemorrhage
569.3	Hemorrhage of rectum and anus
569.85	Anfiodysplasia of intestine with hemorrhage
569.86	Dieulafoy lesion (hemorrhage) of intestine
578	Gastrointestinal hemorrhage
578.0	Hematemesis (Vomiting of blood)
578.1	Blood in stool
578.9	Hemorrhage of gastrointestinal tract, unspecified
456.0	Esophageal varices with bleeding
456.20	Esophageal varices in disease classified elsewhere with bleeding

North Dakota Medicaid
04/01/04 - 03/31/05
ADD Extended Release Drugs
Avg Daily Consumption

Drug Name	Total Qty Dispensed	Avg Daily Consumption	Avg Tablet Cost
ADDERALL XR 10 MG CAPSULE SA	27,298	1.059918189	$ 2.67595
ADDERALL XR 15 MG CAPSULE SA	17,404	1.1099836	$ 2.67393
ADDERALL XR 20 MG CAPSULE SA	56,629	1.279631942	$ 2.53064
ADDERALL XR 25 MG CAPSULE SA	11,671	1.080676899	$ 2.76938
ADDERALL XR 30 MG CAPSULE SA	43,012	1.090622108	$ 2.55055
ADDERALL XR 5 MG CAPSULE SA	6,314	1.110900474	$ 2.43360
CONCERTA 18 MG TABLET SA	34,190	1.014941775	$ 2.48587
CONCERTA 27 MG TABLET SA	24,867	0.998292588	$ 2.63128
CONCERTA 36 MG TABLET SA	85,276	1.143695824	$ 2.59917
CONCERTA 54 MG TABLET SA	64,471	1.013799534	$ 2.93330
METADATE CD 10 MG CAPSULE	4,293	1.09352518	$ 1.67899
METADATE CD 20 MG CAPSULE	53,636	1.738432465	$ 1.66499
METADATE CD 30 MG CAPSULE	1,620	1.08	$ 1.40022
RITALIN LA 10 MG CAPSULE	3,007	1.223259633	$ 2.24545
RITALIN LA 20 MG CAPSULE	22,642	1.059900091	$ 2.23945
RITALIN LA 30 MG CAPSULE	19,292	1.130686009	$ 2.38016
RITALIN LA 40 MG CAPSULE	17,435	1.141197786	$ 2.16836
STRATTERA 10 MG CAPSULE	10,420	1.495654994	$ 2.65900
STRATTERA 18 MG CAPSULE	9,636	1.095463812	$ 2.56451
STRATTERA 25 MG CAPSULE	34,131	1.180128301	$ 2.85173
STRATTERA 40 MG CAPSULE	79,078	1.388303223	$ 2.77020
STRATTERA 60 MG CAPSULE	26,263	1.0258877	$ 2.74663

NDC USAGE Sustained Release ADD drugs 01/01/99 to 05/24/05 for Program All
Qty Dispensed Between 60 and 90

Rx Num	Total Price	Label Name
127	$13,531.86	RITALIN LA 20 MG CAPSULE
111	$13,487.21	RITALIN LA 30 MG CAPSULE
111	$11,536.18	RITALIN LA 40 MG CAPSULE
13	$2,022.43	RITALIN LA 10 MG CAPSULE
252	$31,487.12	CONCERTA 18 MG TABLET SA
965	$133,389.44	CONCERTA 36 MG TABLET SA
65	$8,238.52	CONCERTA 54 MG TABLET SA
3	$472.80	CONCERTA 27 MG TABLET SA
14	$1,594.72	METADATE CD 10 MG CAPSULE
1103	$111,312.05	METADATE CD 20 MG CAPSULE
1431	$105,914.53	METADATE CD 20 MG CAPSULE
23	$771.10	METADATE CD 20 MG CAPSULE
8	$561.28	METADATE CD 30 MG CAPSULE
36	$4,579.37	ADDERALL XR 5 MG CAPSULE SA
179	$27,642.01	ADDERALL XR 10 MG CAPSULE SA
86	$14,296.16	ADDERALL XR 15 MG CAPSULE SA
1137	$157,628.83	ADDERALL XR 20 MG CAPSULE SA
57	$9,912.79	ADDERALL XR 25 MG CAPSULE SA
230	$33,970.50	ADDERALL XR 30 MG CAPSULE SA
5951	$682,348.90	


North Dakota Medicaid
ADD Utilization Per Month Jan 1997 - April 2005
Immediate Release Remb Amt Per Month
Extended Release Remb Amt Per Month
Remb Amt
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$40,000.00
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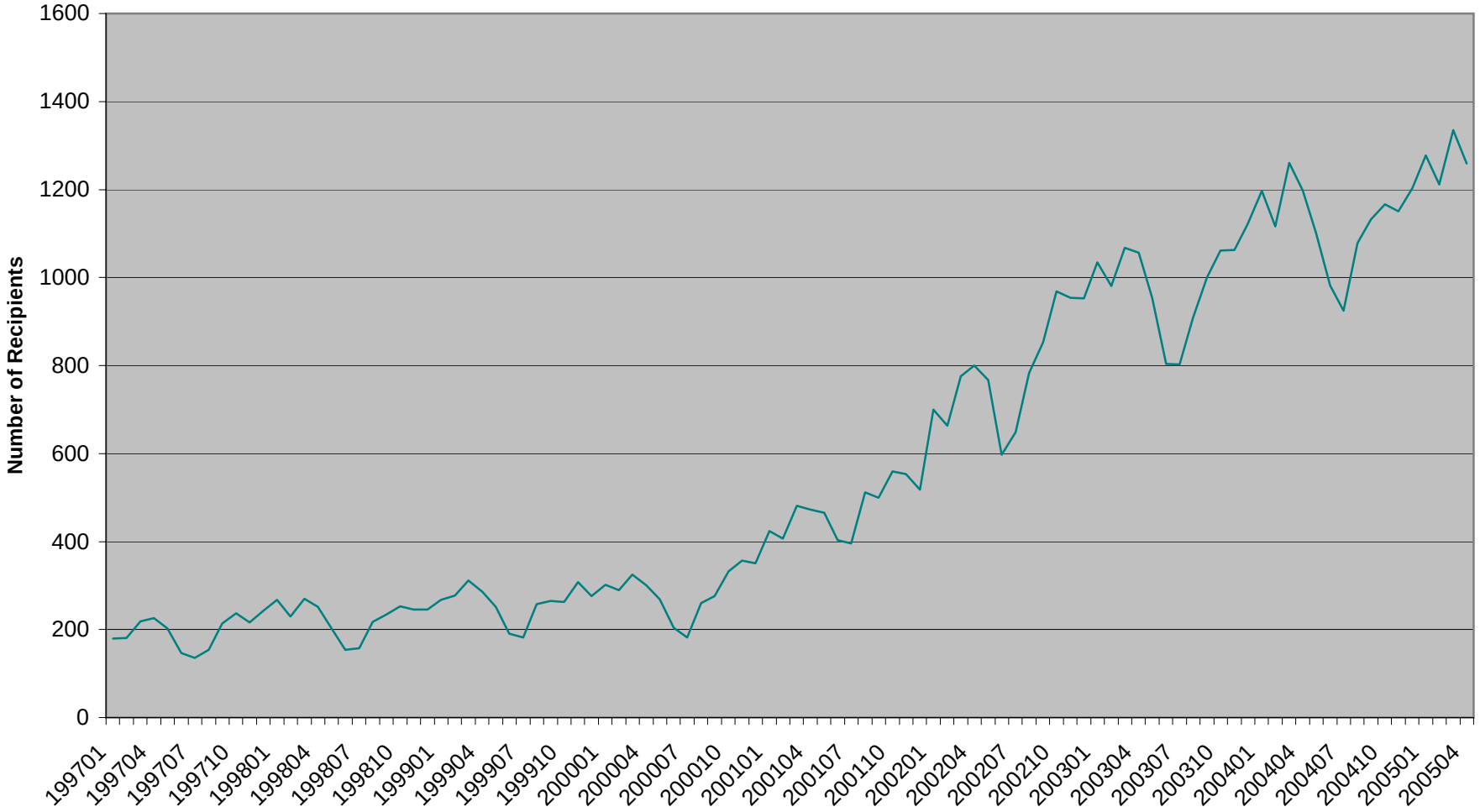
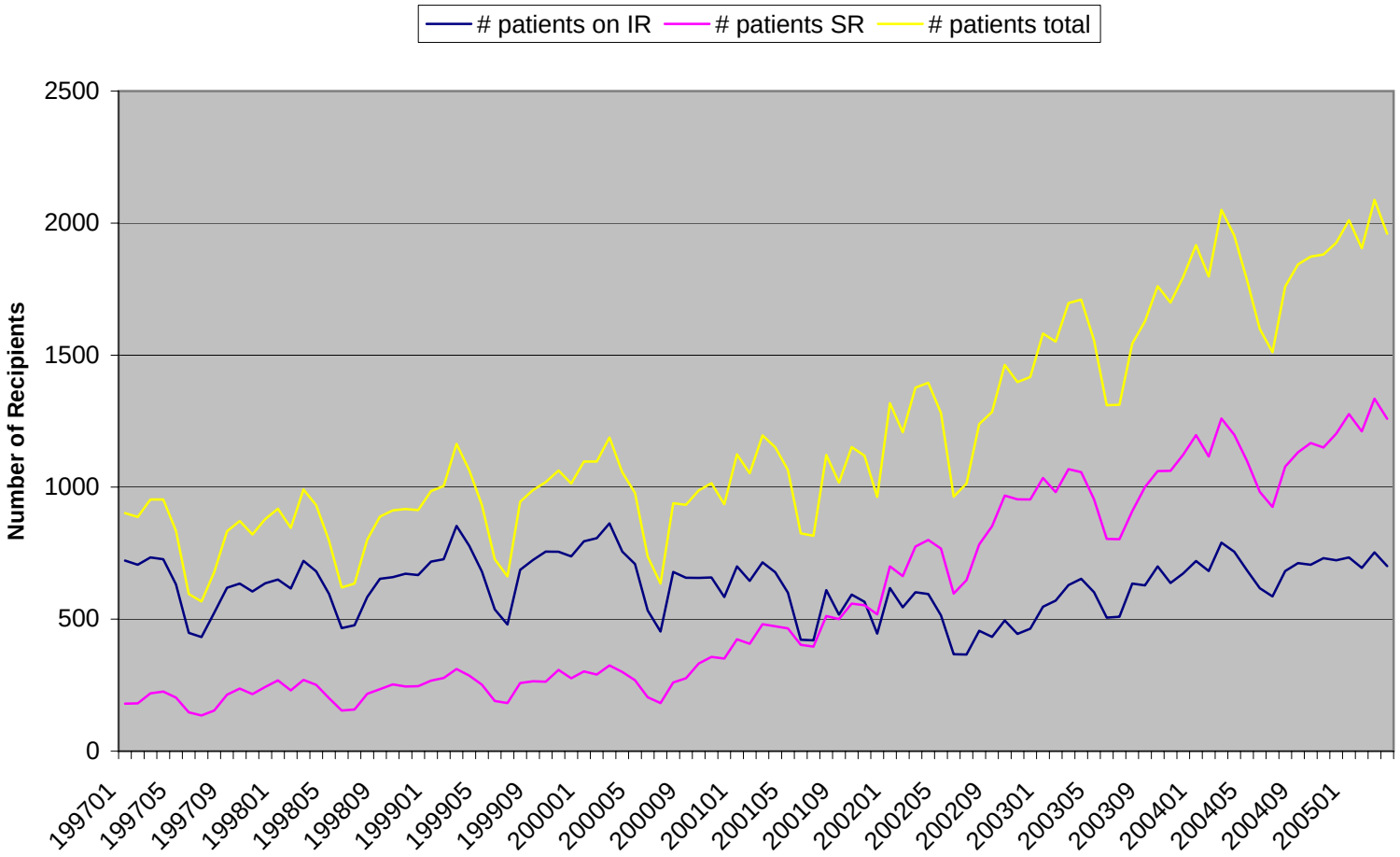
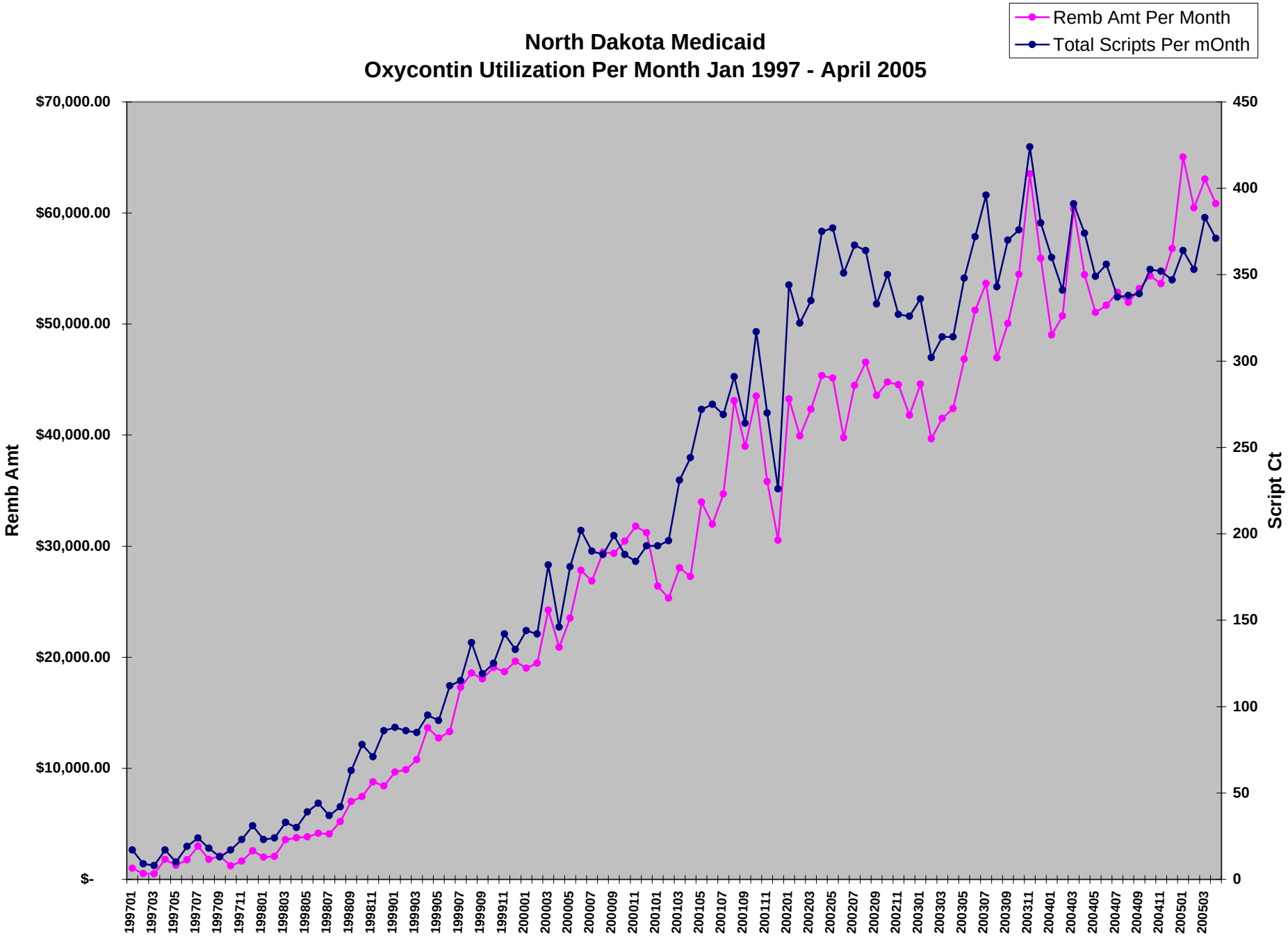
North Dakota Medicaid
Number of Recipients receiving SR ADD Medications
Per Month Jan 1997-April 2005



North Dakota Medicaid
IR/SR Utilization Jan 1997-April 2005




North Dakota Medicaid
Oxycontin Utilization Per Month Jan 1997 - April 2005
Remb Amt Per Month
Total Scripts Per mOnth
Remb Amt
Script Ct
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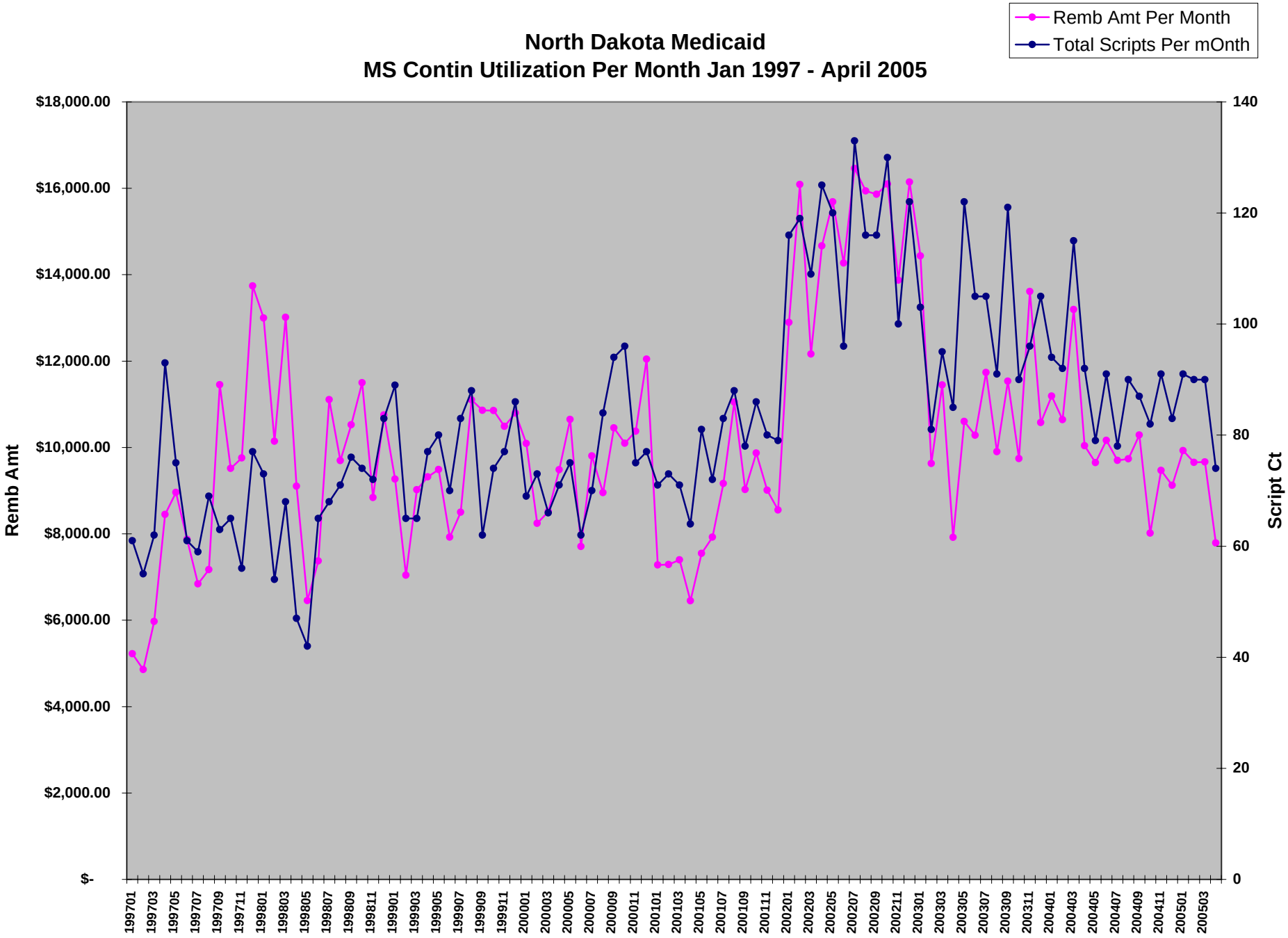
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MS Contin Utilization Per Month Jan 1997 - April 2005
Remb Amt Per Month
Total Scripts Per mOnth
Remb Amt
Script Ct
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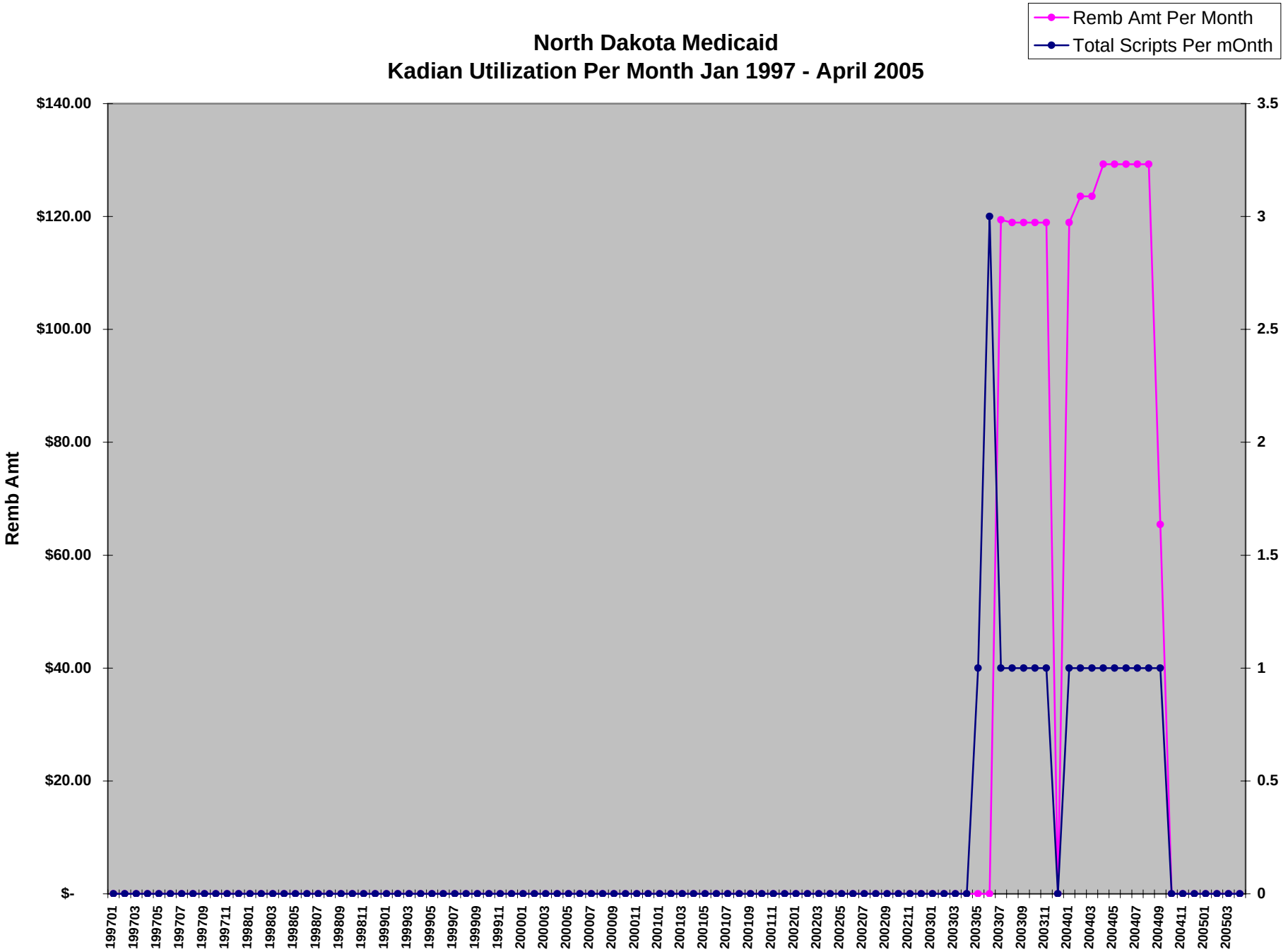
North Dakota Medicaid
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Remb Amt Per Month
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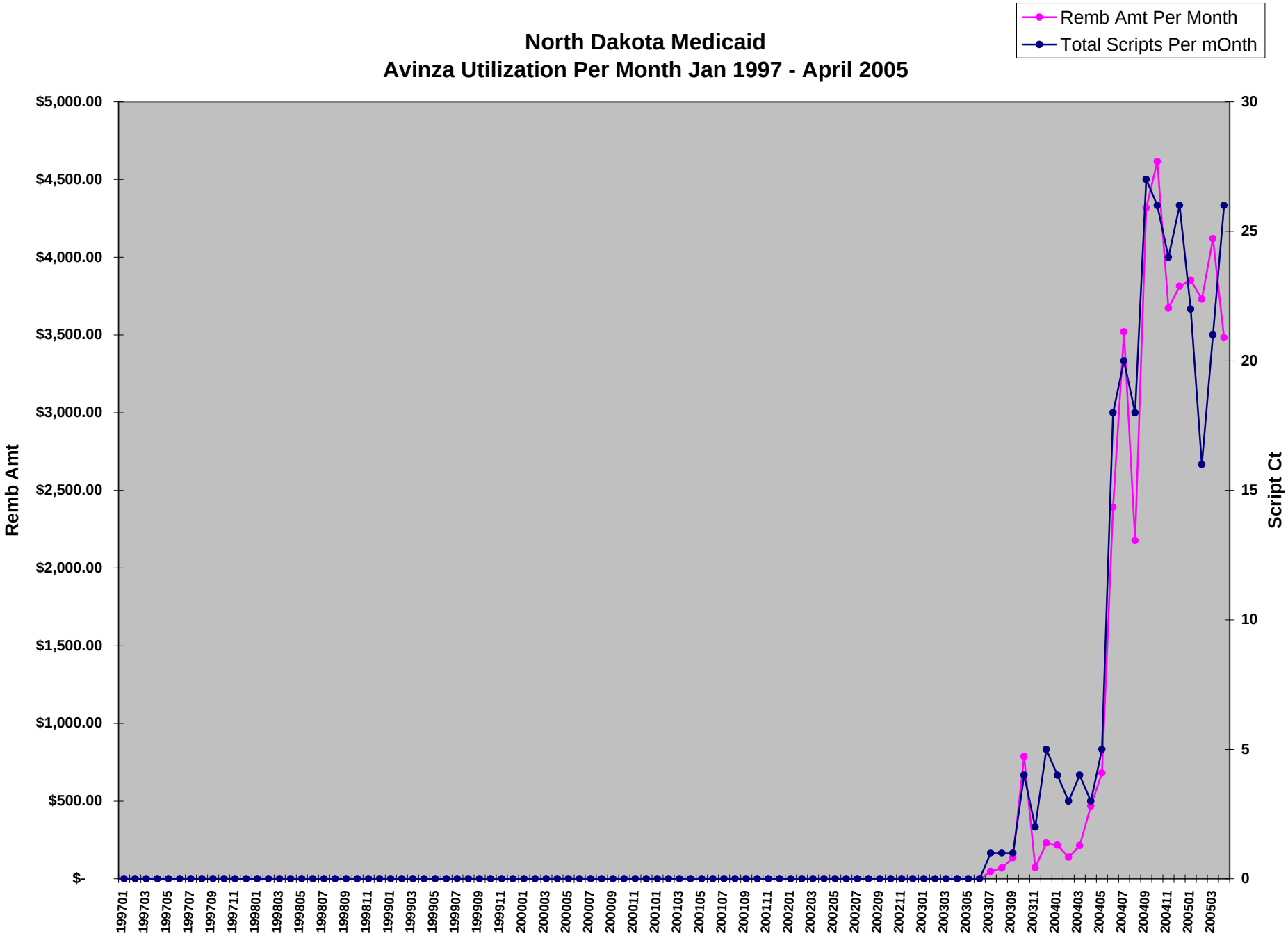
North Dakota Medicaid
Avinza Utilization Per Month Jan 1997 - April 2005
Remb Amt Per Month
Total Scripts Per mOnth
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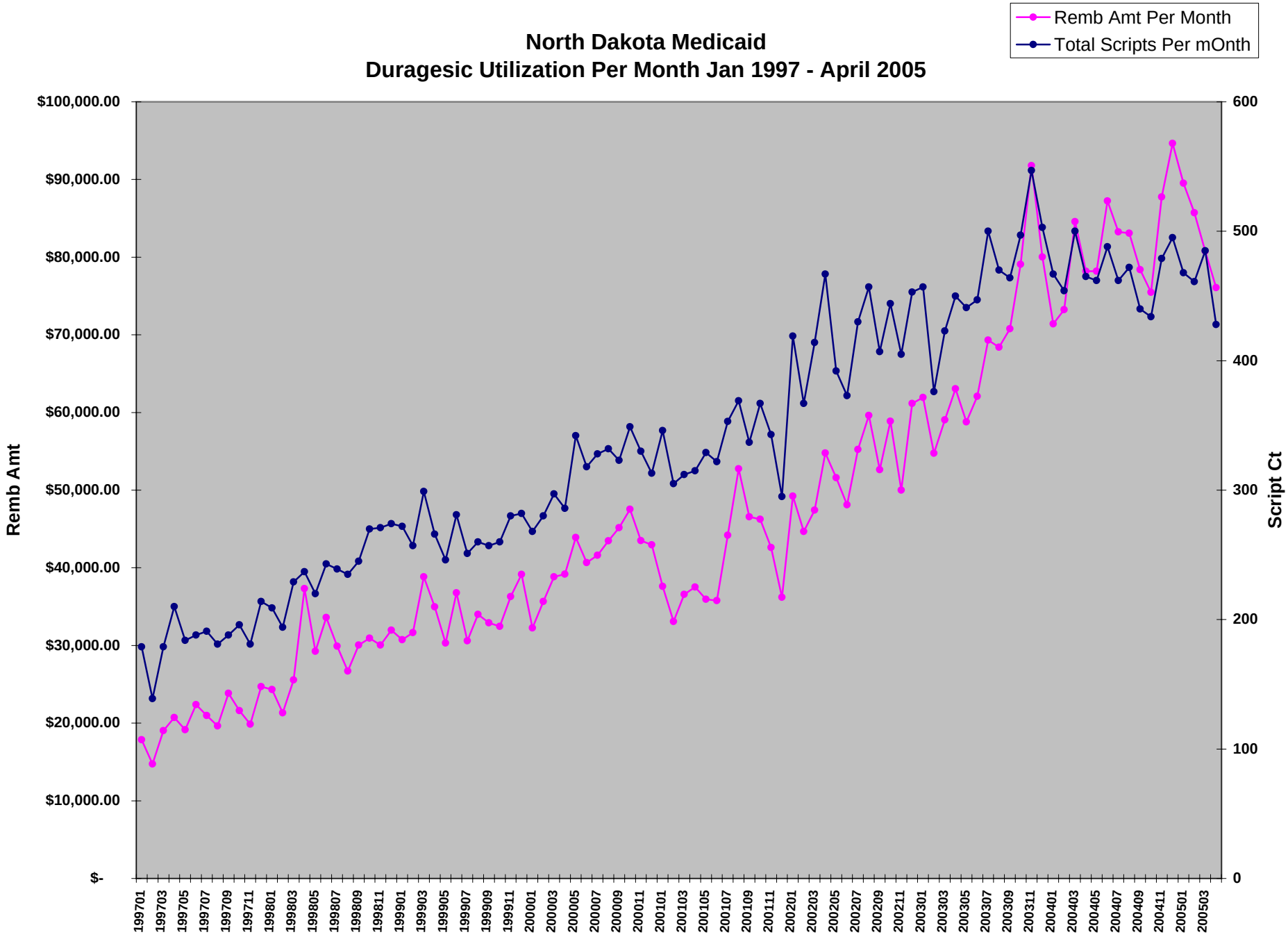
North Dakota Medicaid
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Remb Amt Per Month
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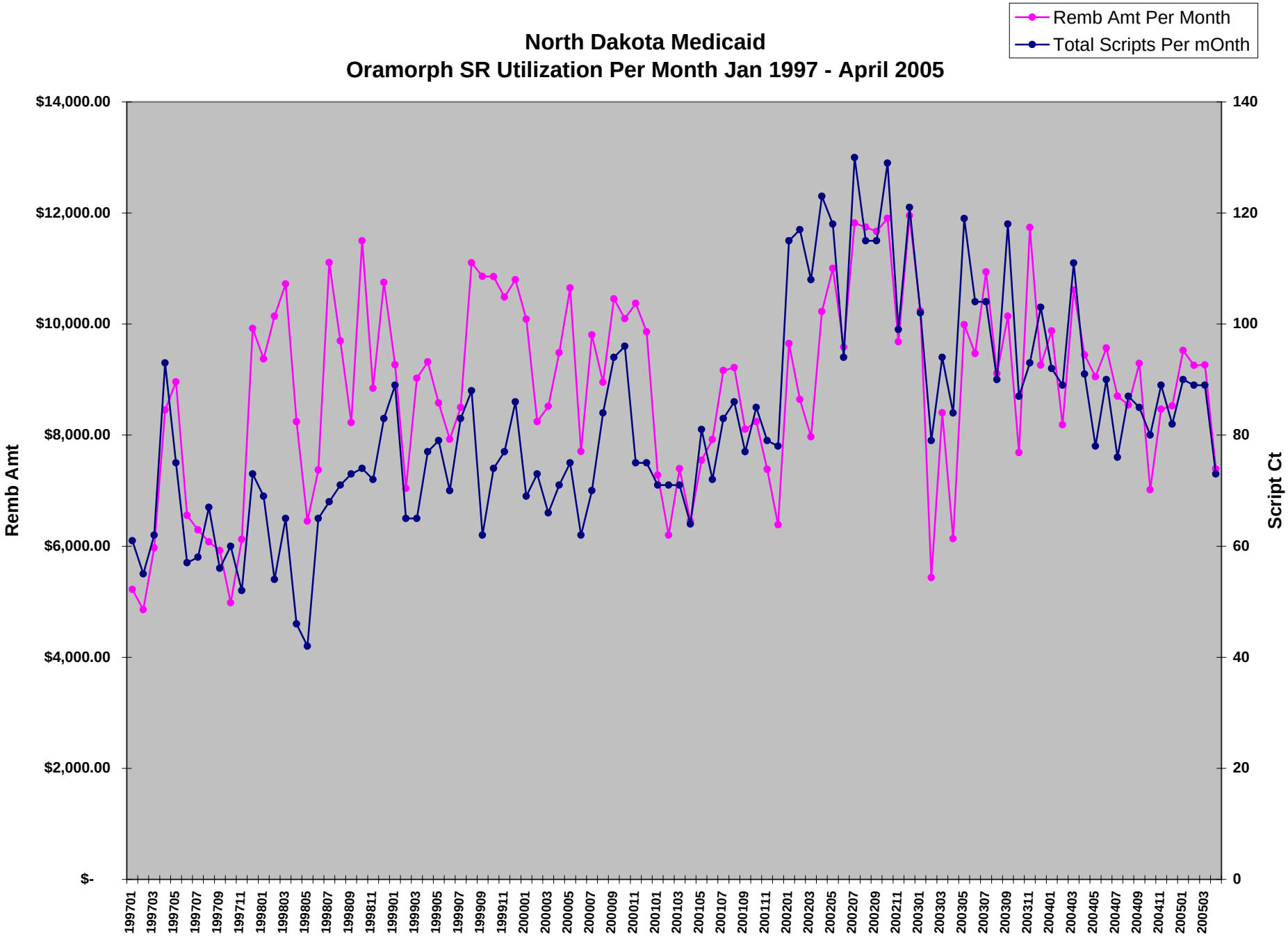
North Dakota Medicaid
Oramorph SR Utilization Per Month Jan 1997 - April 2005
Remb Amt Per Month
Total Scripts Per mOnth
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Comparison of Opioid Analgesics For Non-Cancer Pain[1]

The Oregon Health Resources Commission studied comparative efficacy of different long-acting opioid medications in reducing pain and improving functional outcomes in adult patients being treated for chronic Non-Cancer Pain.

Amended Summary of Results

A. There is no comparative evidence that supports a difference between long-acting opioids in reducing pain and improving functional outcomes.

B. There is no evidence that any long-acting opioid has been shown to be superior in comparing long-acting opioids to other types of drugs.

C. There is no evidence supporting a difference in the incidence and nature of adverse effects, including addiction and abuse between the long-acting opioids.

D. There is no evidence to show that long-acting opioids have fewer adverse effects than short-acting opioids.

Disclaimer: Even though evidence does not demonstrate a difference between long-acting opioids or between long-acting opioids when compared to other drugs, limitations of studies currently available for review preclude a confident conclusion that no differences exist. It is possible that better controlled studies may yet demonstrate such differences.

[1] Oregon Health Resources Commission: OPIOID Update Report-Revision #3, May 2005, http://www.oregonrx.org

SUMMARY OF OXYCONTIN

	Oxycontin
STATE	PA
Alabama	YES (generic also)
Arkansas	NO
South Carolina	YES
Mississippi	YES
Kentucky	YES
Nebraska	NO
Montana	YES
Minnesota	NO
Nevada	YES
Maryland	NO
Rhode Island	NO
Colorado	NO
Wyoming	YES

SUMMARY OF STATINS

STATE	PDL	PA
Alabama	YES	NPF
Arkansas	YES	NPF
South Carolina	YES	NPF
Mississippi	YES	NPF
Kentucky	YES	NPF
Nebraska	NO	NO
Montana	YES	NPF
Minnesota	YES	NPF
Nevada	YES	NPF
Maryland	YES	NPF
Rhode Island	NO	NO
Colorado	NO	NO
Wyoming	YES	NPF

Revatio PRIOR AUTHORIZATION
ND DEPARTMENT OF HUMAN SERVICES
MEDICAL SERVICES DIVISION

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

ND Medicaid requires that patients receiving Revatio 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 PHYSICIAN

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

REQUESTED DRUG:	**Requested Dosage:** (must be completed) **Diagnosis for this request:**

Qualifications for coverage:

❑Indication for the treatment of Pulmonary Arterial Hypertension (WHO Group I Classification)

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

Physician Signature: Date:

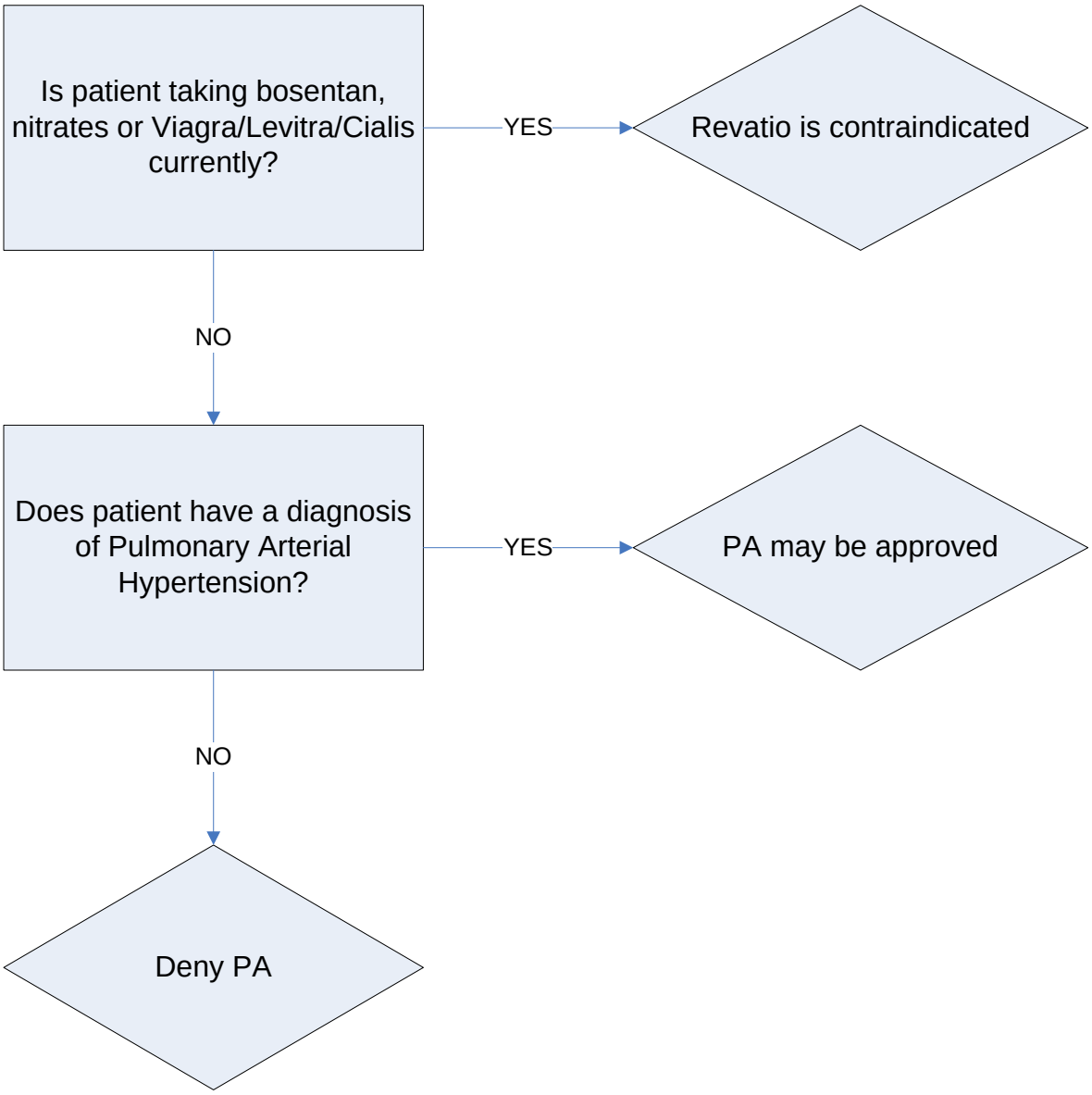
Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:		ND MEDICAID PROVIDER NUMBER:
Phone:		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
Revatio Authorization Algorithm



REVATIO™

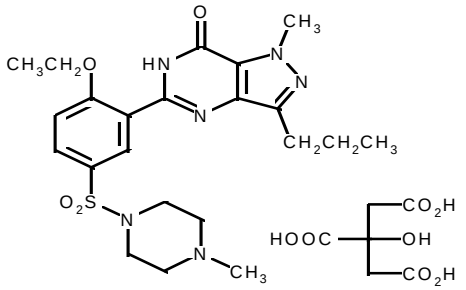
(sildenafil citrate) Tablets, 20 mg

Rx Only

DESCRIPTION

REVATIO™, an oral therapy for pulmonary arterial hypertension, is the citrate salt of sildenafil, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type-5 (PDE5).

Sildenafil citrate is designated chemically as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo [4,3-*d*] pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate and has the following structural formula:



Sildenafil citrate is a white to off-white crystalline powder with a solubility of 3.5 mg/mL in water and a molecular weight of 666.7. REVATIO (sildenafil citrate) is formulated as white, film-coated round tablets equivalent to 20 mg of sildenafil for oral administration. In addition to the active ingredient, sildenafil citrate, each tablet contains the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, lactose monohydrate, and triacetin.

CLINICAL PHARMACOLOGY

Mechanism of Action

Sildenafil is an inhibitor of cGMP specific phosphodiesterase type-5 (PDE5) in the smooth muscle of the pulmonary vasculature, where PDE5 is responsible for degradation of cGMP. Sildenafil, therefore, increases cGMP within pulmonary vascular smooth muscle cells resulting in relaxation. In patients with pulmonary hypertension, this can lead to vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilatation in the systemic circulation.

Studies *in vitro* have shown that sildenafil is selective for PDE5. Its effect is more potent on PDE5 than on other known phosphodiesterases (10-fold for PDE6, >80-fold for PDE1, >700-fold for PDE2, PDE3, PDE4, PDE7, PDE8, PDE9, PDE10, and PDE11). The approximately 4,000-fold selectivity for PDE5 versus PDE3 is important because PDE3 is involved in control of cardiac contractility. Sildenafil is only about 10-fold as potent for PDE5 compared to PDE6,

an enzyme found in the retina and involved in the phototransduction pathway of the retina. This lower selectivity is thought to be the basis for abnormalities related to color vision observed with higher doses or plasma levels (see **Pharmacodynamics**).

In addition to pulmonary vascular smooth muscle and the corpus cavernosum, PDE5 is also found in other tissues including vascular and visceral smooth muscle and in platelets. The inhibition of PDE5 in these tissues by sildenafil may be the basis for the enhanced platelet anti-aggregatory activity of nitric oxide observed *in vitro*, and the mild peripheral arterial-venous dilatation *in vivo*.

Pharmacokinetics and Metabolism

Absorption and Distribution: REVATIO is rapidly absorbed after oral administration, with absolute bioavailability of about 40%. Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. When REVATIO is taken with a high-fat meal, the rate of absorption is reduced, with a mean delay in T_{max} of 60 minutes and a mean reduction in C_{max} of 29%. The mean steady state volume of distribution (Vss) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.

Metabolism and Excretion: Sildenafil is cleared predominantly by the CYP3A4 (major route) and cytochrome P450 2C9 (CYP2C9, minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-desmethylation of sildenafil, and is, itself, further metabolized. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an *in vitro* potency for PDE5 approximately 50% of the parent drug. In healthy volunteers, plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil, so that the metabolite accounts for about 20% of sildenafil's pharmacologic effects. In patients with pulmonary arterial hypertension, however, the ratio of the metabolite to sildenafil is higher. Both sildenafil and the active metabolite have terminal half-lives of about 4 hours. The concomitant use of potent cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir ketoconazole, itraconazole) as well as the nonspecific CYP inhibitor, cimetidine, is associated with increased plasma levels of sildenafil (see **DOSAGE AND ADMINISTRATION and PRECAUTIONS/Drug Interactions)**.

After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the feces (approximately 80% of the administered oral dose) and to a lesser extent in the urine (approximately 13% of the administered oral dose).

Pharmacokinetics in Special Populations

Geriatrics: Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, with free plasma concentrations approximately 40% greater than those seen in healthy younger volunteers (18-45 years).

Renal Insufficiency: In volunteers with mild (CLcr =50-80 mL/min) and moderate (CLcr =30-49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of sildenafil (50 mg) was not altered. In volunteers with severe (CLcr <30 mL/min) renal impairment, sildenafil clearance was reduced, resulting in approximately doubling of AUC and C_{max} compared to age-matched volunteers with no renal impairment.

Hepatic Insufficiency: In volunteers with hepatic cirrhosis (Child-Pugh class A and B), sildenafil clearance was reduced, resulting in increases in AUC (84%) and C_{max} (47%) compared to age-matched volunteers with no hepatic impairment. Patients with severe hepatic impairment (Child-Pugh class C) have not been studied.

Population pharmacokinetics
Age, gender, race, and renal and hepatic function were included as factors assessed in the population pharmacokinetic model to evaluate sildenafil pharmacokinetics in pulmonary arterial hypertension patients. The data set available for the population pharmacokinetic evaluation contained a wide range of demographic data and laboratory parameters associated with hepatic and renal function. None of these factors had a statistically significant impact on sildenafil pharmacokinetics in patients with pulmonary hypertension.

In patients with pulmonary hypertension, the average steady-state concentrations were 20-50% higher when compared to those of healthy volunteers. There was also a doubling of C_{min} levels compared to healthy volunteers. Both findings suggest a lower clearance and/or a higher oral bioavailability of sildenafil in patients with pulmonary hypertension compared to healthy volunteers.

Pharmacodynamics
Effects of REVATIO on Blood Pressure: Single oral doses of sildenafil (100 mg) administered to healthy volunteers produced decreases in supine blood pressure (mean maximum decrease in systolic/diastolic blood pressure of 8.4/5.5 mmHg). The decrease in blood pressure was most notable approximately 1-2 hours after dosing, and was not different from placebo at 8 hours. Similar effects on blood pressure were noted with 25 mg, 50 mg and 100 mg doses of sildenafil, therefore the effects are not related to dose or plasma levels within this dosage range. Larger effects were recorded among patients receiving concomitant nitrates (see **CONTRAINDICATIONS**).

Single oral doses of sildenafil up to 100 mg in healthy volunteers produced no clinically relevant effects on ECG. After chronic dosing of 80 mg t.i.d. to patients with pulmonary arterial hypertension, no clinically relevant effects on ECG were reported.

After chronic dosing of 80 mg t.i.d. sildenafil to healthy patients, the largest mean change from baseline in supine systolic and supine diastolic blood pressures was a decrease of 9.0 mmHg and 8.4 mmHg, respectively.

After chronic dosing of 80 mg t.i.d. sildenafil to patients with systemic hypertension, the mean change from baseline in systolic and diastolic blood pressures was a decrease of 9.4 mmHg and 9.1 mmHg, respectively.

After chronic dosing of 80 mg t.i.d. sildenafil to patients with pulmonary arterial hypertension, lesser reductions than above in systolic and diastolic blood pressures were observed (a decrease in both of 2 mmHg).

Effects of REVATIO on Vision: At single oral doses of 100 mg and 200 mg, transient dose-related impairment of color discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. An

evaluation of visual function at doses up to 200 mg revealed no effects of REVATIO on visual acuity, intraocular pressure, or pupillometry.

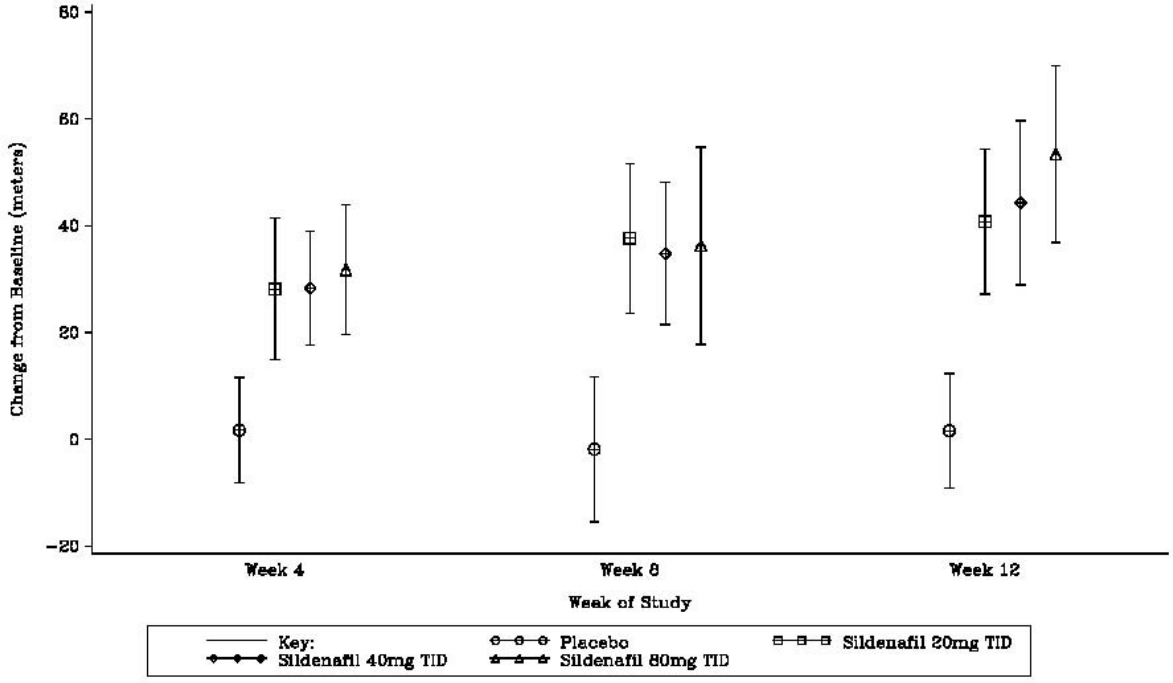
Clinical Studies

A randomized, double-blind, placebo-controlled study was conducted in 277 patients with pulmonary arterial hypertension (PAH, defined as a mean pulmonary artery pressure of ≥25 mmHg at rest with a pulmonary capillary wedge pressure <15 mmHg). Patients were predominantly functional classes II-III. Allowed background therapy included a combination of anticoagulation, digoxin, calcium channel blockers, diuretics or oxygen. The use of prostacyclin analogues, endothelin receptor antagonists, and arginine supplementation were not permitted. Subjects who had failed to respond to bosentan were also excluded. Patients with left ventricular ejection fraction <45% or left ventricular shortening fraction <0.2 also were not studied.

Patients were randomized to receive placebo (n=70) or REVATIO 20 mg (n=69), 40 mg (n=67) or 80 mg (n=71) t.i.d. for a period of 12 weeks. They had either primary pulmonary hypertension (63%), PAH associated with connective tissue disease (30%), or PAH following surgical repair of left-to-right congenital heart lesions (7%). The study population consisted of 25% men and 75% women with a mean age of 49 years (range: 18-81 years) and baseline 6-minute walk test distance between 100 and 450 meters.

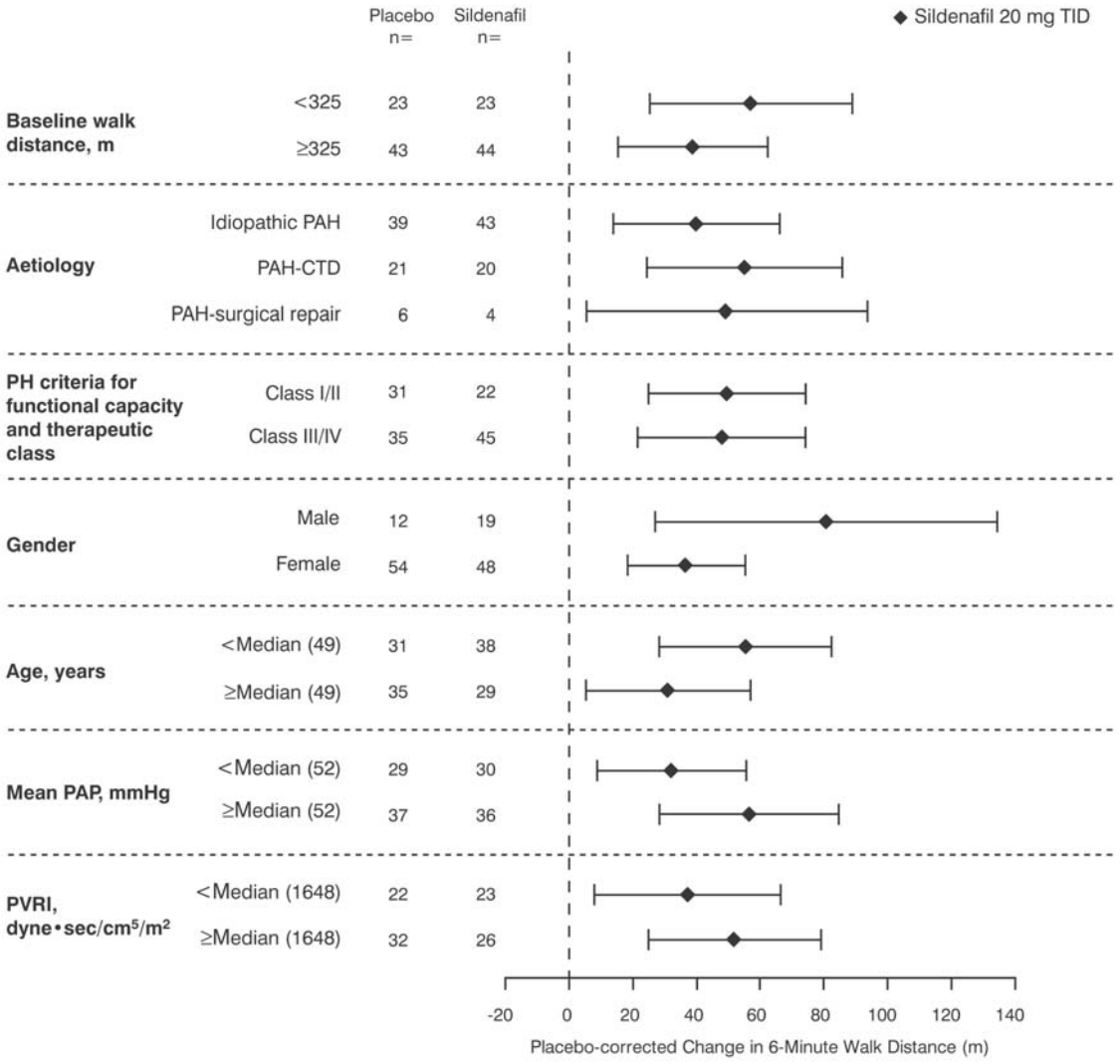
The primary efficacy endpoint was the change from baseline at week 12 in 6-minute walk distance at least 4 hours after the last dose. Placebo-corrected mean increases in walk distance of 45-50 meters were observed with all doses of sildenafil. These increases were highly significantly different from placebo, but the dose groups were not different from each other (Figure 1). The improvement in walk distance was apparent after 4 weeks of treatment and was maintained at week 8 and week 12.

Figure 1: Change from Baseline in 6-Minute Walk Distance (meters): Mean (95% Confidence Interval)



Pre-defined subpopulations in the pivotal study were also evaluated for efficacy, including patient differences in baseline walk distance, disease etiology, functional class, gender, age, and secondary hemodynamic parameters (Figure 2).

Figure 2: Placebo Corrected Change From Baseline in 6-Minute Walk Distance (meters) by study subpopulation: Mean (95% Confidence Interval)



Key: PAH = pulmonary arterial hypertension; CTD = connective tissue disease; PH, pulmonary hypertension; PAP = pulmonary arterial pressure; PVRI = pulmonary vascular resistance index; TID = three times daily.

Patients on all REVATIO doses achieved a statistically significant reduction in mean pulmonary arterial pressure (mPAP) compared to those on placebo. Doses of 20 mg, 40 mg, and 80 mg t.i.d. produced a placebo-corrected decrease in mPAP of -2.7 mmHg, -3.0 mmHg, and -5.1 mmHg, respectively. There was no evidence of a difference in effect between sildenafil 20 mg t.i.d. and the higher doses tested. Data from other hemodynamic parameters can be found in Table 1. The relationship between these effects and improvements in 6-minute walk distance is unknown.

Table 1. Changes from Baseline to Week 12 in Hemodynamic Parameters at Sildenafil 20 mg t.i.d. Dose

PARAMETER [mean (95% CI)]	Placebo (N=65)*	Sildenafil 20 mg t.i.d. (N=65)*
PVR (dyn·s/cm^5)	49 (-54, 153)	-122 (-217, -27)
SVR (dyn·s/cm^5)	-78 (-197, 41)	-167 (-307, -26)
RAP (mmHg)	0.3 (-0.9, 1.5)	-0.8 (-1.9, 0.3)
CO (L/min)	-0.1 (-0.4, 0.2)	0.4 (0.1, 0.7)
HR (beats/min)	-1.3 (-4.1, 1.4)	-3.7 (-5.9, -1.4)

∗The number of patients per treatment group varied slightly for each parameter due to missing assessments.

259 of the 277 treated patients entered a long-term, uncontrolled extension study. At the end of 1 year, 94% of these patients were still alive. Additionally, walk distance and functional class status appeared to be stable in patients taking sildenafil. Without a control group, these data must be interpreted cautiously.

INDICATIONS AND USAGE

REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability.

The efficacy of REVATIO has not been evaluated in patients currently on bosentan therapy.

CONTRAINDICATIONS

Consistent with its known effects on the nitric oxide/cGMP pathway (see **CLINICAL PHARMACOLOGY**), sildenafil was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using organic nitrates, either regularly and/or intermittently, in any form is therefore contraindicated.

REVATIO is contraindicated in patients with a known hypersensitivity to any component of the tablet.

WARNINGS

The concomitant administration of the protease inhibitor ritonavir (a highly potent CYP3A4 inhibitor) substantially increases serum concentrations of sildenafil, therefore co-administration with REVATIO is not recommended (see **Drug Interactions** and **DOSAGE AND ADMINISTRATION**).

REVATIO has vasodilator properties, resulting in mild and transient decreases in blood pressure (see **PRECAUTIONS**). Prior to prescribing REVATIO, physicians should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilatory effects, for example patients with resting hypotension (BP <90/50), or with fluid depletion, severe left ventricular outflow obstruction, or autonomic dysfunction.

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of REVATIO to patients with veno-occlusive disease, administration of REVATIO to such patients

is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, the possibility of associated PVOD should be considered.

There is no controlled clinical data on the safety or efficacy of REVATIO in the following groups; if prescribed, this should be done with caution:

- Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;
- Patients with coronary artery disease causing unstable angina;
- Patients with hypertension (BP >170/110);
- Patients with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).
- Patients currently on bosentan therapy.

PRECAUTIONS

General

Before prescribing REVATIO, it is important to note the following:

- Caution is advised when phosphodiesterase type 5 (PDE5) inhibitors are co-administered with alpha-blockers. PDE5 inhibitors, including sildenafil, and alpha-adrenergic blocking agents are both vasodilators with blood pressure lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly, leading to symptomatic hypotension. In the sildenafil interaction studies with alpha-blockers (see **Drug Interactions**), cases of symptomatic hypotension consisting of dizziness and lightheadedness were reported. No cases of syncope or fainting were reported during these interaction studies. Consideration should be given to the fact that safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and concomitant use of anti-hypertensive drugs.

- REVATIO should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease) or in patients who have conditions, which may predispose them to priapism (such as sickle cell anemia, multiple myeloma or leukemia).

- In humans, sildenafil has no effect on bleeding time when taken alone or with aspirin. *In vitro* studies with human platelets indicate that sildenafil potentiates the anti-aggregatory effect of sodium nitroprusside (a nitric oxide donor). The combination of heparin and sildenafil had an additive effect on bleeding time in the anesthetized rabbit, but this interaction has not been studied in humans.

- The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%). The incidence of epistaxis was also higher in sildenafil-treated patients with concomitant oral vitamin K antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist).

- The safety of REVATIO is unknown in patients with bleeding disorders and patients with active peptic ulceration.

Information for Patients
Physicians should discuss with patients the contraindication of REVATIO with regular and/or intermittent use of organic nitrates.

Drug Interactions
In PAH patients, the concomitant use of vitamin K antagonists and sildenafil resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo.

Effects of Other Drugs on REVATIO
***In vitro* studies:** Sildenafil metabolism is principally mediated by the CYP3A4 (major route) and CYP2C9 (minor route) cytochrome P450 isoforms. Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance and inducers of these isoenzymes may increase sildenafil clearance.

***In vivo* studies:** Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance and/or an increase of oral bioavailability when co-administered with CYP3A4 substrates and the combination of CYP3A4 substrates and beta-blockers. These were the only factors with a statistically significant impact on sildenafil pharmacokinetics.

Population data from patients in clinical trials indicated a reduction in sildenafil clearance when it was co-administered with CYP3A4 inhibitors. Sildenafil exposure without concomitant medication is shown to be 5-fold higher at a dose of 80 mg t.i.d. compared to its exposure at a dose of 20 mg t.i.d. This concentration range covers the same increased sildenafil exposure observed in specifically-designed drug interaction studies with CYP3A4 inhibitors (except for potent inhibitors such as ketoconazole, itraconazole, and ritonavir). Cimetidine (800 mg), a nonspecific CYP inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with sildenafil (50 mg) to healthy volunteers. When a single 100 mg dose of sildenafil was co-administered with erythromycin, a CYP3A4 inhibitor, at steady state (500 mg twice daily [b.i.d.] for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC). In a study performed in healthy volunteers, co-administration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, at steady state (1200 mg t.i.d.) with sildenafil (100 mg single dose) resulted in a 140% increase in sildenafil C_{max} and a 210% increase in sildenafil AUC. Stronger CYP3A4 inhibitors will have still greater effects on plasma levels of sildenafil (see **DOSAGE AND ADMINISTRATION**).

In another study in healthy volunteers, co-administration with the HIV protease inhibitor ritonavir, a potent CYP3A4 inhibitor, at steady state (500 mg b.i.d.) with sildenafil (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil C_{max} and a 1000% (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200 ng/mL, compared to approximately 5 ng/mL when sildenafil was dosed alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**). Although the interaction between other protease inhibitors and REVATIO has not been studied, their concomitant use is expected to increase sildenafil levels.

In a study of healthy male volunteers, co-administration of sildenafil at steady state (80 mg t.i.d.) with the endothelin receptor antagonist bosentan (a moderate inducer of CYP3A4, CYP2C9 and possibly of cytochrome P450 2C19) at steady state (125 mg b.i.d.) resulted in a 63% decrease of sildenafil AUC and a 55% decrease in sildenafil C_{max}. The combination of both drugs did not

lead to clinically significant changes in blood pressure (supine or standing). Concomitant administration of potent CYP3A4 inducers is expected to cause greater decreases in plasma levels of sildenafil.

In drug-drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope (see **PRECAUTIONS: General**).

Concomitant administration of oral contraceptives (ethinyl estradiol 30 μg and levonorgestrel 150 μg) did not affect the pharmacokinetics of sildenafil.

Concomitant administration of a single 100 mg dose of sildenafil with 10 mg of atorvastatin did not alter the pharmacokinetics of either sildenafil or atorvastatin.

Single doses of antacid (magnesium hydroxide/aluminum hydroxide) did not affect the bioavailability of sildenafil.

Effects of REVATIO on Other Drugs
***In vitro* studies:** Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC50 >150 μM).

***In vivo* studies:** When sildenafil 100 mg oral was co-administered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

No significant interactions were shown with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolized by CYP2C9.

Sildenafil (50 mg) did not potentiate the increase in bleeding time caused by aspirin (150 mg).

Sildenafil (50 mg) did not potentiate the hypotensive effect of alcohol in healthy volunteers with mean maximum blood alcohol levels of 0.08%.

Sildenafil at steady state (80 mg t.i.d.) resulted in a 50% increase in AUC and a 42% increase in C_{max} of bosentan (125 mg b.i.d.).

In a study of healthy volunteers, sildenafil (100 mg) did not affect the steady-state pharmacokinetics of the HIV protease inhibitors saquinavir and ritonavir, both of which are CYP3A4 substrates.

Sildenafil had no impact on the plasma levels of oral contraceptives (ethinyl estradiol 30 μg and levonorgestrel 150 μg).

Carcinogenesis, Mutagenesis, Impairment of Fertility
Sildenafil was not carcinogenic when administered to rats for up to 24 months at 60 mg/kg/day, a dose resulting in total systemic exposure (AUC) to unbound sildenafil and its major metabolite 33 and 37 times, for male and female rats respectively, the human exposure at the Recommended Human Dose (RHD) of 20 mg t.i.d. Sildenafil was not carcinogenic when administered to male and female mice for up to 21 and 18 months, respectively, at doses up to a maximally tolerated level of 10 mg/kg/day, a dose equivalent to the RHD on a mg/m^2 basis.

Sildenafil was negative in *in vitro* bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and *in vitro* human lymphocytes and *in vivo* mouse micronucleus assays to detect clastogenicity.

There was no impairment of fertility in male or female rats given up to 60 mg sildenafil/kg/day, a dose producing a total systemic exposure (AUC) to unbound sildenafil and its major metabolite of 19 and 38 times for males and females, respectively, the human exposure at the RHD of 20 mg t.i.d.

Pregnancy
Pregnancy Category B. No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in pregnant rats or rabbits, dosed with 200 mg sildenafil/kg/day during organogenesis, a level that is, on a mg/m^2 basis, 32- and 68-times, respectively, the RHD of 20 mg t.i.d. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m^2 basis). There are no adequate and well-controlled studies of sildenafil in pregnant women.

Nursing Mothers
It is not known if sildenafil citrate and/or metabolites are excreted in human breast milk. Since many drugs are excreted in human milk, caution should be used when REVATIO is administered to nursing women.

Pediatric Use
Safety and Effectiveness of sildenafil in pediatric pulmonary hypertension patients has not been established.

Geriatric Use
Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, but studies did not include sufficient numbers of subjects to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger pulmonary arterial hypertension patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Safety data were obtained from the pivotal study and an open-label extension study in 277 treated patients with pulmonary arterial hypertension. Doses up to 80 mg t.i.d. were studied.

The overall frequency of discontinuation in REVATIO-treated patients at the recommended dose of 20 mg t.i.d. was low (3%) and the same as placebo (3%).

In the pivotal placebo-controlled trial in pulmonary arterial hypertension, the adverse drug reactions that were reported by at least 3% of REVATIO patients treated at the recommended dosage (20 mg t.i.d.) and were more frequent in REVATIO patients than placebo patients, are shown in Table 2. Adverse events were generally transient and mild to moderate in nature.

Table 2. Sildenafil Adverse Events in ≥3% of Patients and More Frequent than Placebo

ADVERSE EVENT %	Placebo (n=70)	Sildenafil 20 mg t.i.d. (n=69)	Placebo Subtracted
Epistaxis	1	9	8
Headache	39	46	7
Dyspepsia	7	13	6
Flushing	4	10	6
Insomnia	1	7	6
Erythema	1	6	5
Dyspnea exacerbated	3	7	4
Rhinitis nos	0	4	4
Diarrhea nos	6	9	3
Myalgia	4	7	3
Pyrexia	3	6	3
Gastritis nos	0	3	3
Sinusitis	0	3	3
Paresthesia	0	3	3

At doses higher than the recommended 20 mg t.i.d. there was a greater incidence of some adverse events including flushing, diarrhea, myalgia and visual disturbances. Visual disturbances were identified as mild and transient, and were predominately color-tinge to vision, but also increased sensitivity to light or blurred vision.

In the pivotal study, the incidence of retinal hemorrhage at the recommended sildenafil 20 mg t.i.d. dose was 1.4% versus 0% placebo and for all sildenafil doses studied was 1.9% versus 0% placebo. The incidence of eye hemorrhage at both the recommended dose and at all doses studied was 1.4% for sildenafil versus 1.4% for placebo. The patients experiencing these events had risk factors for hemorrhage including concurrent anticoagulant therapy.

In post-marketing experience with sildenafil citrate at doses indicated for male erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil citrate, to sexual activity, to the patient's underlying cardiovascular disease, or to a combination of these or other factors.

OVERDOSAGE

In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but rates were increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and it is not eliminated in the urine.

DOSAGE AND ADMINISTRATION

The recommended dose of REVATIO is 20 mg three times a day (t.i.d.). REVATIO tablets should be taken approximately 4-6 hours apart, with or without food. In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg t.i.d. is not recommended. Dosages lower than 20 mg t.i.d. were not tested. Whether dosages lower than 20 mg t.i.d. are effective is not known.

In general, dose selection for elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see **CLINICAL PHARMACOLOGY**)

No dose adjustments are required for renal impaired patients (including severe renal impairment, creatinine clearance <30 mL/min), or for hepatic impaired patients (Child Pugh class A and B).

No dose adjustments are required for the co-administration of REVATIO with erythromycin or saquinavir.

Co-administration of REVATIO with CYP3A4 inducers (including bosentan; and more potent inducers such as barbiturates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, rifabutin) may alter plasma levels of either or both medications. Dosage adjustments may be necessary (see **PRECAUTIONS: Drug Interactions**).

Co-administration of potent CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir) with REVATIO substantially increases serum concentrations of sildenafil and is therefore not recommended (see **WARNINGS** and **PRECAUTIONS: Drug Interactions**).

Sildenafil was shown to potentiate the hypotensive effects of nitrates and its administration in patients who use nitric oxide donors, or nitrates in any form, is therefore contraindicated.

HOW SUPPLIED

REVATIO (sildenafil citrate) is supplied as white, film-coated, round tablets containing sildenafil citrate equivalent to the nominally indicated amount of sildenafil as follows:

REVATIO Tablets			
Package Configuration	Tablet Strength (mg)	NDC	Engraving on Tablet
Bottle of 90	20 mg	0069-4190-68	RVT20

Recommended Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Pfizer Labs
Division of Pfizer Inc, NY, NY 10017

LAB-0313-3 June 2005

In 2003, the 3rd World Symposium on Pulmonary Hypertension was convened in Venice to modify classification based on the new understanding of disease mechanisms. The revised system developed by this group provides the current frame work for understanding pulmonary hypertension.

The system includes several improvements over the former 1998 Evian Classification system. The terms "primary" and "secondary" were discontinued because they had limited diagnostic value. In addition, new classifications were added, including primary veno-occlusive disease (PVOD). Risk factor descriptions were updated, and the classification of congenital systemic-to pulmonary shunts was revised. A new classification of genetic factors in PH was recommended, but not implemented because available data were judged to be inadequate.

The Venice 2003 Revised Classification system can be summarized as follows:

- WHO Group I - Pulmonary arterial hypertension (PAH)
- WHO Group II - Pulmonary hypertension with left heart disease
- WHO Group III - Pulmonary hypertension associated with lung diseases and/or hypoxemia
- WHO Group IV - Pulmonary hypertension due to chronic thrombotic and/or embolic disease
- WHO Group V - Miscellaneous

These terms are currently in use, but they are not yet as commonly used as the old terms of PPH and SPH[1]

[1] Executive Summary from the World Symposium on Primary Pulmonary Hypertension 1998, Evian France 6 - 10 September 1998 (Modified Venice 2003).

RETROSPECTIVE DUR
CRITERIA RECOMMENATIONS

Criteria Recommendations	*Approved*	*Rejected*

1. Atypical Antipsychotics/ / FDA Approved Indications _____ _____

Alert Message: The atypical antipsychotics are not approved for the treatment of behavioral disorders in elderly patients with dementia. The FDA has determined that patients with dementia treated with atypical antipsychotics are at an increased risk of death compared to placebo. In analysis of seventeen placebo-controlled studies of four drugs in this class, the rate of death for those elderly patients with dementia was about 1.6 to 1.7 times that of placebo.
Conflict Code: TA Therapeutic Appropriateness (Box Warning)
Drug/Disease:

Util A	Util B	Util C (Negating)
Clozapine		Schizophrenia
Risperidone		Bipolar
Olanzapine		
Quetiapine		
Ziprasidone		
Aripiprazole		

Age Range: 65 year of age or older
References:
MedWatch: FDA Safety Information and Adverse Event Reporting Program, 2005.
Micromedex Healthcare Series, Drugdex Drug Evaluations, 2005.
Physicians' Desk Reference, Micromedex Healthcare Series, 2005.

2. Promethazine / Patients less than 2 years of age _____ _____

Alert Message: Promethazine is contraindicated for use in pediatric patients less than two years of age because of the potential for fatal respiratory depression. Respiratory depression and apnea, sometimes associated with death, are strongly associated with promethazine products and are not directly related to individualized weight-based dosing, which might otherwise permit safe administration.
Conflict Code: TA – Therapeutic Appropriateness (Boxed Warning)
Drug/ Disease:

Util A	Util B	Util C
Promethazine		

Age Range: <2 years of age
References:
Phenergan Prescribing Information, Dec. 2004, Wyeth Pharmaceuticals Inc.
Medwatch: FDA Safety Information and Adverse Event Reporting Program, 2005.

3. Promethazine / Pediatric Patients 2 years and older _____ _____

Alert message: Caution should be exercised when administering promethazine to pediatric patients 2 years of age and older. It is recommended that the lowest effective dose of promethazine be used in pediatric patients 2 years of age and older and concomitant administration of other drugs with respiratory depressant effects be avoided.
Conflict Code: TA – Therapeutic Appropriateness (Boxed Warning)
Drug/ Disease:

Util A	Util B	Util C
Promethazine		

Age Range: 2 – 18 years
References:
Phenergan Prescribing Information, Dec. 2004, Wyeth Pharmaceuticals Inc.

4. Tizanidine / Fluvoxamine _____ _____

Alert Message: Concurrent use of tizanidine with fluvoxamine, a potent CYP1A2 inhibitors, is contraindicated. Significant alterations of pharmacokinetic parameters of tizanidine including AUC, t1/2, Cmax, increased oral bioavailability and decreased plasma clearance have been observed with concomitant fluvoxamine administration. Coadministration of these agents has resulted in profound hypotension, bradycardia and excessive drowsiness.
Conflict Code: DD – Drug/Drug Interaction
Drug/Disease:

Util A	Util B	Util C
Tizanidine	Fluvoxamine	

References:
Zanaflex Prescribing Information, April 2005, Athena Neurosciences.
Micromedex Healthcare Series, Drugdex Drug Evaluations, 2005.

5. Tizanidine / CYP1A2 Inhibitors _____ _____

Alert Message: Caution is recommended when considering concomitant use of tizanidine with other inhibitors of CYP1A2, such as antiarrhythmics (amiodarone, mexiletine, propafenone), cimetidine, fluoroquinolones (ciprofloxacin, norfloxacin) and ticlopidine. The concurrent use of these agents may increase the risk of profound hypotension, somnolence and dizziness.
Conflict Code: DD - Drug/Drug Interaction
Drug/Disease:

Util A	Util B		Util C
Tizanidine	Amiodarone	Ciprofloxacin	
	Mexiletine	Norfloxacin	
	Propafenone	Ticlopidine	
	Cimetidine		

References:
Granfors MT, Backman JT, Neuvonen M, et.al. Ciprofloxacin greatly increases concentrations and hypotensive effect of tizanidine by inhibiting its cytochrome P450 1A2-mediated presystemic metabolism. Clin Pharmacol Ther. 2004 Dec;76(6):598-606.
Zanaflex Prescribing Information, April 2005, Athena Neurosciences.

6. SNRI's / Therapeutic Duplication _____ _____

Therapeutic duplication of serotonin norepinephrine reuptake inhibitors may be occurring. Concomitant use of these drugs may cause additive adverse effects.
Conflict Code: TD - Therapeutic Duplication
Drug/Disease:

Util A	Util B	Util C
Duloxetine		
Venlafaxine		

References:
Facts & Comparisons, 2005 Updates.
Micromedex Healthcare Series, Drugdex Drug Evaluations, 2005.

Criteria Recommendations	*Approved*	*Rejected*

7. Overactive Bladder Medications / Therapeutic Duplication _____ _____

Therapeutic duplication of medications to treat overactive bladder may be occurring. Concomitant use of these drugs may cause additive adverse effects.
Conflict Code: TD – Therapeutic Duplication
Drug/Disease:

Util A	Util B	Util C
Darifenacin		
Solifenacin		
Oxybutynin		
Flavoxate		
Tolterodine		
Tropsium		

References:
Facts & Comparisons, 2005 Updates.
Micromedex Healthcare Series, Drugdex Drug Evaluations, 2005.

8. Darifenacin / High Dose _____ _____

Alert Message: Enablex (darifenacin) may be over-utilized. The recommended maximum dose is 15 mg per day.
Conflict Code: HD – High Dose
Drug/Disease:

Util A	Util B	Util C
Darifenacin		

Maximum Dose: 15mg/day
References:
Facts & Comparisons, 2005 Updates.
Micromedex Healthcare Series, Drugdex Drug Evaluations, 2005.
Enablex Prescribing Information, Dec. 2004, Novartis Pharmaceuticals, Inc.

9. Darifenacin / Potent 3A4 Inhibitors _____ _____

Alert Message: The daily dose of Enablex (darifenacin), a CYP 3A4 substrate, should not exceed 7.5 mg when coadministered with a potent CYP3A4 inhibitor (e.g., ketoconazole itraconazole, ritonavir, nelfinavir, clarithromycin, and nefazodone). Exceeding the recommended dose during concurrent therapy may increase the risk of adverse effects of darifenacin.
Conflict Code: DD – Drug/Drug Interaction
Drug/Disease:

Util A	Util B	Util C	
Darifenacin		Ketoconazole	Erythromycin
		Itraconazole	Troleandomycin
		Ritonavir	Indinavir
		Nelfinavir	
		Clarithromycin	
		Nefazodone	

Max Dose: 7.5mg
References:
Micromedex Healthcare Series, Drugdex Drug Evaluations, 2005.
Facts & Comparisons, 2005.

Criteria Recommendations *Approved* *Rejected*

10. Darifenacin / / Hepatic Impairment _____ _____

Alert Message: The daily dose of Enablex (darifenacin) should not exceed 7.5 mg once daily for patients with moderate hepatic impairment. Darifenacin is not recommended for use in patients with severe hepatic impairment.
Conflict Code: ER - Overutilization
Drug/Disease:

Util A	Util B	Util C
Darifenacin		Hepatic Impairment

Max Dose: 7.5 mg
References:
Micromedex Healthcare Series, Drugdex Drug Evaluations, 2005.
Facts & Comparisons, 2005.

11. Darifenacin / CYP2D6 Substrates _____ _____

Alert Message: Caution should be exercised when Enablex (darifenacin), a moderate 2D6 inhibitor, is used concomitantly with medications that are predominantly metabolized by CYP2D6 and which have a narrow therapeutic window (e.g. flecainide and thioridazine). Concurrent use with darifenacin may result in elevated plasma concentrations of the substrates and increase risk of adverse effects.
Conflict Code: DD – Drug/Drug Interaction
Drug/Disease:

Util A	Util B	Util C
Darifenacin	Flecainide Thioridazine	

References:
Facts & Comparisons, 2005 Updates.
Enablex Prescribing Information, Dec. 2004, Novartis Pharmaceuticals, Inc.

12. Darifenacin / Digoxin _____ _____

Alert Message: Caution should be exercised when Enablex (darifenacin) is used concomitantly with digoxin. Concurrent use of darifenacin (30mg daily) with digoxin (0.25mg) at steady state resulted in a 16% increase in digoxin exposure. Routine monitoring of digoxin should continue.
Conflict Code: DD – Drug/Drug Interaction
Drug/Disease:

Util A	Util B	Util C
Darifenacin	Digoxin	

References:
Facts & Comparisons, 2004 Updates.
Enablex Prescribing Information, Dec. 2004, Novartis Pharmaceuticals, Inc.

13. Darifenacin / Narrow Angle Glaucoma _____ _____

Alert Message: Enablex (darifenacin), an anticholinergic agent, should be used with caution in patients being treated for narrow-angle glaucoma and only when the potential benefits outweigh the risks. Darifenacin is contraindicated in patients with uncontrolled narrow-angle glaucoma.
Conflict Code: MC – Drug Actual Disease Precaution
Drug/Disease:

Util A	Util B	Util C
Darifenacin	Narrow-angle Glaucoma	

References:
Facts & Comparisons, 2005 Updates.
Enablex Prescribing Information, Dec. 2004, Novartis Pharmaceuticals, Inc.

14. Darifenacin / Urinary Retention _____ _____

Alert Message: Enablex (darifenacin), an anticholinergic agent, is contraindicated in patients with urinary retention or gastric retention and in patients who are at risk for these conditions.
Conflict Code: MC – Drug Actual Disease Precaution
Drug/Disease:

Util A	Util B	Util C
Darifenacin	Urinary Retention	
	Gastric Retention	

References:
Facts & Comparisons, 2005 Updates.
Enablex Prescribing Information, Dec. 2004, Novartis Pharmaceuticals, Inc.

15. Darifenacin / GI Obstruction-Decreased GI Motility _____ _____

Alert Message: Enablex (darifenacin), an anticholingeric agent, should be administered with caution to patients with GI obstructive disorders because of the risk of gastric retention. Darifenacin, like other anticholinergic drugs, may decrease GI motility and should be used with caution in patients with severe constipation, ulcerative colitis, and myasthenia gravis.
Conflict Code: DB – Drug/Drug marker and/or Diagnosis
Drug/Disease:

Util A	Util B	Util C
Darifenacin	Ulcerative Colitis	
	Myasthenia Gravis	
	Intestinal Obstruction	
	Slow Transit Constipation	

References:
Facts & Comparisons, 2005 Updates.
Enablex Prescribing Information, Dec. 2004, Novartis Pharmaceuticals, Inc.

16. Anticholinergic Agents / Therapeutic Duplication _____ _____

Alert Message: The concomitant use of anticholinergic agents may increase the frequency and/or severity of dry mouth, constipation, blurred vision and other anticholinergic adverse effects.
Conflict Code: TD – Therapeutic Duplication
Drug/Disease:

Util A	Util B	Util C
Belladonna	Benzotropine	
Atropine	Biperiden	
Scopolamine	Procyclidine	
Homatropine	Trihexyphenidyl	
Tropicamide	Flavoxate	
Hyoscyamine	Oxybutynin	
Glycopyrrolate	Tolterodine	
Mepenzolate	Tropsium	
Propantheline	Solifenacin	
Dicyclomine	Orphenadrine	
Clidinium	Darifenacin	

References:
Facts & Comparisons, 2005 Updates.

Criteria Recommendations	*Approved*	*Rejected*

17. Solifenacin / High Dose _____ _____

Alert Message: Vesicare (solifenacin) may be over-utilized. The recommended maximum dose is 10 mg per day. Higher doses have resulted in a higher incidence of adverse reactions.
Conflict Code: HD – High Dose
Drug/Disease:

Util A	Util B	Util C
Solifenacin		

Maximum Dose: 10mg/day
References:
Facts & Comparisons, 2005 Updates.
Micromedex Healthcare Series, Drugdex Drug Evaluations, 2005.

18. Solifenacin / / Hepatic Impairment _____ _____

Alert Message: The daily dose of Vesicare (solifenacin) should not exceed 5.0 mg for patients with moderate hepatic impairment. Solifenacin is not recommended for use in patients with severe hepatic impairment.
Conflict Code: ER - Overutilization
Drug/Disease:

Util A	Util B	Util C
Solifenacin		Hepatic Impairment

Max Dose: 5.0 mg
References:
Facts & Comparisons, 2005.

19. Solifenacin / / Renal Impairment _____ _____

Alert Message: The daily dose of Vesicare (solifenacin) should not exceed 5.0 mg for patients with severe renal impairment (Ccr less than 30 mL/min). Significant increases in the AUC and elimination half-life have been noted with single oral doses of solifenacin 10 mg and have been correlated to the degree of renal impairment.
Conflict Code: ER - Overutilization
Drug/Disease:

Util A	Util B	Util C
Solifenacin		Chronic Renal Failure

Max Dose: 5.0 mg
References:
Facts & Comparisons, 2005.

20. Solifenacin / Potent 3A4 Inhibitors _____ _____

Alert Message: The daily dose of Vesicare (solifenacin), a CYP 3A4 substrate, should not exceed 5.0 mg when coadministered with a potent CYP3A4 inhibitor (e.g., ketoconazole itraconazole, ritonavir, nelfinavir, clarithromycin, and nefazodone). Exceeding the recommended dose during concurrent therapy may increase the risk of adverse effects.
Conflict Code: DD – Drug/Drug Interaction
Drug/Disease:

Util A	Util B	Util C	
Darifenacin		Ketoconazole	Erythromycin
		Itraconazole	Troleandomycin
		Ritonavir	Indinavir
		Nelfinavir	
		Clarithromycin	
		Nefazodone	

Max Dose: 5.0mg
References:
Facts & Comparisons, 2005.
Vesicare Prescribing Information, Nov. 2004 GlaxoSmithKline.

Criteria Recommendations *Approved* *Rejected*

21. Solifenacin / Narrow Angle Glaucoma _____ _____

Alert Message: Vesicare (solifenacin), an anticholingeric agent, should be used with caution in patients being treated for narrow-angle glaucoma and only when the potential benefits outweigh the risks. Solifenacin is contraindicated in patients with uncontrolled narrow-angle glaucoma.
Conflict Code: MC – Drug Actual Disease Precaution
Drug/Disease:

Util A	Util B	Util C
Solifenacin	Narrow-angle Glaucoma	

References:
Facts & Comparisons, 2005 Updates.

22. Solifenacin / Urinary Retention & Gastric Retention _____ _____

Alert Message: Vesicare (solifenacin), an anticholingeric agent, is contraindicated in patients with urinary retention or gastric retention and in patients who are at risk for these conditions.
Conflict Code: MC – Drug Actual Disease Precaution
Drug/Disease:

Util A	Util B	Util C
Solifenacin	Urinary Retention	
	Gastric Retention	

References:
Facts & Comparisons, 2005 Updates.

23. Solifenacin / GI Obstruction-Decreased GI Motility _____ _____

Alert Message: Vesicare (solifenacin), an anticholinergic agent, should be administered with caution to patients with GI obstructive disorders because of the risk of gastric retention. Solifenacin, like other anticholinergic drugs, may decrease GI motility and should be used with caution in patients with constipation, ulcerative colitis, and myasthenia gravis.
Conflict Code: DB – Drug/Drug marker and/or Diagnosis
Drug/Disease:

Util A	Util B	Util C
Solifenacin	Ulcerative Colitis	
	Myasthenia Gravis	
	Intestinal Obstruction	
	Slow Transit Constipation	

References:
Facts & Comparisons, 2005 Updates.

24. Solifenacin / QT Prolongation & QT Prolongation Drugs _____ _____

Alert Message: Vesicare (solifenacin) should be administered with caution to patients with a history of QT prolongation or who are on medications known to prolong the QT interval. A significant period effect on QTc has been observed following the administration of solifenacin (10 or 30 mg) in healthy female volunteers. The QT prolonging effect was greater with the 30 mg dose as compared with the 10 mg dose and did not appear to be as great as that of the positive control moxifloxacin at its therapeutic dose.
Conflict Code: DB – Drug/Drug marker and/or Diagnosis
Drug/Disease:

Util A	Util B			Util C
Solifenacin	QT Prolongation ICD-9s			
	Quinidine	Thioridazine	Moxifloxacin	Chlorpromazine
	Procainamide	Mesoridazine	Mefloquine	Levofloxacin
	Disopyramide	Droperidol	Tacrolimus	
	Amiodarone	Pimozide	Gatifloxacin	
	Bretylium	Sotalol	Pentamidine	
	Dofetilide	Sparofloxacin	Ziprasidone	

References:
Facts & Comparisons, 2005 Updates.
Vesicare Prescribing Information, Nov. 2004, GlaxoSmithKline.

Criteria Recommendations	*Approved*	*Rejected*

25. Tolterodine IR & XL/High Dose _____ _____

Alert Message: Detrol/Detrol LA (tolterodine) may be over-utilized. The manufacturer's recommended dose is 4 mg daily.
Conflict Code: HD – High Dose
Drug/Disease:

Util A	Util B	Util C
Tolterodine		

Max Dose: 4mg
References:
Facts & Comparisons, 2005 Updates.
Detrol LA Prescribing Information, April 2004, Pfizer, Inc.

26. Tolterodine IR/Hepatic Impairment _____ _____

Alert Message: The daily dose of Detrol or Detrol LA (tolterodine) should not exceed 2 mg for patients with significantly reduced hepatic or renal function.
Conflict Code: HD – High Dose
Drug/Disease:

Util A	Util B	Util C (Inclusive)
Tolterodine		Hepatic Impairment
		Renal Impairment
		Lanthanum
		Sevelamer
		Doxercalciferol
		Paricalcitol
		Calcitriol

Max Dose: 2mg
References:
Facts & Comparisons, 2005 Updates.
Detrol LA Prescribing Information, April 2004, Pfizer, Inc.

27. Tolterodine//Potent 3A4 Inhibitors _____ _____

Alert Message: The daily dose of Detrol/ Detrol LA (tolterodine), a CYP 3A4 substrate, should not exceed 2.0 mg when coadministered with a potent CYP3A4 inhibitor (e.g., ketoconazole itraconazole, erythromycin, clarithromycin, cyclosporine and vinblastine). Exceeding the recommended dose during concurrent therapy may increase the risk of adverse effects of tolterodine.
Conflict Code: HD - High Dose (drug/drug Interaction)
Drug/Disease:

Util A	Util B	Util C (Inclusive)	
Tolterodine		Ketoconazole	Erythromycin
		Itraconazole	Cyclosporine
		Ritonavir	Troleandomycin
		Nelfinavir	Indinavir
		Clarithromycin	Vinblastine
		Nefazodone	Cyclosporine

Max Dose: 2mg
References:
Facts & Comparisons, 2005 Updates.
Detrol LA Prescribing Information, April 2004, Pfizer, Inc.
Detrol Prescribing Information, July 2003, Pfizer, Inc.

Criteria Recommendations *Approved* *Rejected*

28. Oxybutynin/High Dose (Adults) _____ _____
Alert Message: Ditropan (oxybutynin immediate-release) may be over-utilized. The manufacturer's recommended maximum dose is 5 mg 4 times per day.
Conflict Code: HD – High Dose
Drug/Disease:

Util A	Util B	Util C
Oxybutynin IR		

Age Range: 18 years and older
Max Dose: 20mg/day
References:
Facts & Comparisons, 2005 Updates.

29. Oxybutynin/High Dose-Pediatric _____ _____
Alert Message: Ditropan (oxybutynin immediate-release) may be over-utilized. The manufacturer's recommended maximum dose is 5 mg 3 times per day.
Conflict Code: HD – High Dose
Drug/Disease:

Util A	Util B	Util C
Oxybutynin IR		

Age Range: 5 – 18 years
Max Dose: 15 mg/day
References:
Facts & Comparisons, 2005 Updates.
Ditropan Prescribing Information, Sept. 2003, Ortho-McNeil Pharmaceuticals, Inc.

30. Oxybutynin Extended Release/High Dose _____ _____
Alert Message: Ditropan XL (oxybutynin extended-release) may be over-utilized. The manufacturer's recommended maximum dose is 30 mg per day.
Conflict Code: HD – High Dose
Drug/Disease:

Util A	Util B	Util C
Oxybutynin XL		

Max Dose: 30mg/day
References:
Facts & Comparisons, 2005 Updates.

31. Oxybutynin / Hepatic & Renal Impairment _____ _____
Alert Message: Ditropan/Ditropan XL/ (oxybutynin) should be used with caution in patients with renal or hepatic impairment.
Conflict Code: DB – Drug-Drug Marker and/or Diagnosis
Drug/Disease:

Util A	Util B	Util C
Oxybutynin	Renal Impairment	
	Hepatic Impairment	

References:
Facts & Comparisons, 2005 Updates.

32. Oxybutynin Transdermal / High Dose _____ _____
Alert Message: Oxytrol (oxybutynin transdermal) may be over-utilized. The manufacturer's recommended dose is one 3.9 mg/day system applied twice weekly (every 3 to 4 days).
Conflict Code: HD – High Dose
Drug/Disease:

Util A	Util B	Util C
Oxybutynin Transdermal		

Max Dose: 3.9 mg/day
References:
Facts & Comparisons, 2005 Updates.

Criteria Recommendations	*Approved*	*Rejected*

33. Oxybutynin/Contraindications _____ _____

Alert Message: Ditropan/Ditropan XL/Oxytrol (oxybutynin), an anticholinergic agent, is contraindicated in patients with urinary retention, gastric retention and other severe conditions of decreased gastrointestinal motility, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.
Conflict Code: MC - Drug (Actual) Disease Contraindication/Precaution
Drug/Disease:

Util A	Util B	Util C
Oxybutynin	Urinary Retention	
	Gastric Retention	
	Paralytic Ileus	

References:
Ditropan Prescribing Information, March 2003, OrthoMcNeil Pharmaceuticals Inc.
Micromedex Healthcare Series, Drugdex Drug Evaluations, 2005.

34. Oxybutynin / Disease State Precautions _____ _____

Alert Message: Ditropan/Ditropan XL (oxybutynin), an anticholinergic agent, should be used with caution in patients with hyperthyroidism, cardiac arrhythmia, congestive heart failure, coronary heart disease, hiatal hernia, hypertension, autonomic neuropathy, ulcerative colitis and prostatic hypertrophy. Oxybutynin may aggravate the symptoms of these conditions.
Conflict Code: MC - Drug (Actual) Disease Precaution
Drug/Disease:

Util A	Util B	Util C
Oxybutynin	Hyperthyroidism	
	Cardiac Arrhythmia	
	Congestive Heart Failure	
	Coronary Heart Disease	
	Hiatal Hernia	
	Hypertension	
	Ulcerative Colitis	
	Prostatic Hypertrophy	

References:
Ditropan Prescribing Information, Mar. 2003, OrthoMcNeil Pharmaceuticals Inc.
Micromedex Healthcare Series, Drugdex Drug Evaluations, 2005.

35. Oxybutynin / GI Obstruction-Decreased GI Motility _____ _____

Alert Message: Ditropan/Ditropan XL/Oxytrol (oxybutynin), an anticholinergic agent, should be administered with caution to patients with GI obstructive disorders because of the risk of gastric retention. Oxybutynin, like other anticholinergic drugs, may decrease GI motility and should be used with caution in patients with severe constipation, ulcerative colitis, and myasthenia gravis.
Conflict Code: MC - Drug (Actual) Disease Precaution
Drug/Disease:

Util A	Util B	Util C
Oxybutynin	Ulcerative Colitis	
	Myasthenia Gravis	
	Intestinal Obstruction	
	Slow Transit Constipation	

References:
Facts & Comparisons, 2005 Updates.

Criteria Recommendations	*Approved*	*Rejected*

36. Oxybutynin/GERD _____ _____

Alert Message: Ditropan/Ditropan XL/Oxytrol (oxybutynin) should be used with caution in patients who have gastrointestinal reflux or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis.
Conflict Code: DB – Drug/Drug marker and/or Diagnosis
Drug/Disease:

Util A	Util B	Util C
Oxybutynin	GERD	
	Bisphosponates	
	Potassium	
	NSAIDS	
	Iron	
	Quinidine	
	Doxycycline	
	Clindamycin	
	Tetracycline	
	Trimethoprim	

References:
Facts & Comparisons, 2005 Updates.
Ditropan Prescribing Information, March 2004, OrthoMcNeil Pharmaceuticals, Inc.
Oxytrol Prescribing Information, Feb. 2003, Watson Pharma, Inc.

37. Flavoxate/High Dose _____ _____

Alert Message: Flavoxate may be overutilized. The manufacturer's recommended maximum dose is 800 mg (200 mg 4 times a day).
Conflict Code: HD – High Dose
Drug/Disease:

Util A	Util B	Util C
Flavoxate		

Max Dose: 800mg/day
References:
Facts & Comparisons, 2005 Updates.
Micromedex Healthcare Series, Drugdex Drug Evaluations, 2005.

38. Flavoxate/Contraindications _____ _____

Alert Message: Flavoxate, an anticholinergic agent, is contraindicated in patients who have pyloric or duodenal obstruction, obstructive intestinal lesions or ileus, achalasia, GI hemorrhage, or obstructive uropathies of the lower urinary tract.
Conflict Code: MC – Drug (Actual Disease) Contraindication/Precaution
Drug/Disease:

Util A	Util B	Util C
Flavoxate	Pyloric Obstruction	
	Duodenal Obstruction	
	Obstructive Intestinal Lesions or Ileus	
	Achalasia	
	GI Hemorrhage	
	Urinary obstruction	

References:
Facts & Comparisons, 2005 Updates.

Criteria Recommendations *Approved* *Rejected*

39. Flavoxate/Glaucoma _____ _____

Alert Message: Flavoxate should be used with caution in patients who have glaucoma. Flavoxate is an anticholinergic agent and use in these patients may aggravate the condition.
Conflict Code: DB – Drug/Drug Marker and/or Diagnosis
Drug/Disease:

Util A	Util B	Util C
Flavoxate	Glaucoma	
	Brimonidine	
	Apraclonidine	
	Dipivefrin	
	Levobunolol	
	Betaxolol	
	Metipranolol	
	Carteolol	
	Timolol	
	Pilocarpine	

References:
Micromedex Healthcare Series, Drugdex Drug Evaluations, 2005.
Facts & Comparisons, 2005 Updates.

40. Trospium / High Dose _____ _____

Alert Message: Sanctura (trospium) may be over-utilized. The manufacturer's recommended daily dose is 20 mg twice daily.
Conflict Code: HD – High Dose
Drug/Disease:

Util A	Util B	Util C
Trospium		

Max Dose: 40mg/day
References:
Sanctura Prescribing Information, July 2004, Odyssey Pharmaceuticals, Inc.
Facts & Comparisons, 2005 Updates.

41. Trospium / / Renal Impairment _____ _____

Alert Message: The daily dose of Sanctura (trospium) should not exceed 20 mg once daily at bedtime for patients with severe renal impairment (Ccr less than 30 mL/min). A 4.5-fold and 2-fold increase in mean AUC and Cmax, respectively, and the appearance of an additional elimination phase with a long half-life (33hr) was detected in patients with severe renal sufficiency.
Conflict Code: ER - Overutilization
Drug/Disease:

Util A	Util B	Util C
Trospium		Chronic Renal Failure

Max Dose: 20 mg/day
References:
Facts & Comparisons, 2005.
Sanctura Prescribing Information, July 2004, Odyssey Pharmaceuticals, Inc.

42. Trospium / Urinary & Gastric Retention _____ _____

Alert Message: Sanctura (trospium), an anticholinergic agent, is contraindicated in patients with urinary retention or gastric retention and patients at risk for these conditions.
Conflict Code: MC – Drug Actual Disease Precaution
Drug/Disease:

Util A	Util B	Util C
Trospium	Urinary Retention	
	Gastric Retention	

References:
Facts & Comparisons, 2005 Updates.
Sanctura Prescribing Information, July 2004, Odyssey Pharmaceuticals, Inc.

43. Trospium / Narrow Angle Glaucoma _____ _____

Alert Message: Sanctura (trospium), an anticholinergic agent, should be used with caution in patients being treated for narrow-angle glaucoma and only when the potential benefits outweigh the risks. Trospium is contraindicated in patients with uncontrolled narrow-angle glaucoma.
Conflict Code: MC – Drug Actual Disease Precaution
Drug/Disease:

Util A	Util B	Util C
Trospium	Narrow-angle Glaucoma	

References:
Facts & Comparisons, 2005 Updates.
Sanctura Prescribing Information, July 2004, Odyssey Pharmaceuticals, Inc.

44. Trospium / GI Obstruction-Decreased GI Motility _____ _____

Alert Message: Sanctura (trospium) should be administered with caution to patients with GI obstructive disorders because of the risk of gastric retention. Trospium, like other anticholinergic drugs, may decrease GI motility and should be used with caution in patients with ulcerative colitis, intestinal atony and myasthenia gravis.
Conflict Code: MC – Drug Actual Disease Precaution
Drug/Disease:

Util A	Util B	Util C
Tropsium	Ulcerative Colitis	
	Myasthenia Gravis	
	Intestinal Atony	

References:
Facts & Comparisons, 2005 Updates.

45. Trospium/Drugs Eliminated by ATS _____ _____

Alert Message: Sanctura (trospium) is eliminated via active tubular secretion and has the potential for pharmacokinetic interactions with other drugs that are eliminated by the same route (e.g., digoxin, procainamide, morphine, vancomycin, metformin, and tenofovir). Coadministration of trospium with drugs that are eliminated by active tubular secretion may increase the serum concentration of trospium and/or the coadministered drug because of competition for this elimination pathway. Careful patient monitoring is recommended.
Conflict Code: DD – Drug/Drug Interaction
Drug/Disease:

Util A	Util B		Util C
Trospium	Digoxin	Vancomycin	
	Procainamide	Metformin	
	Morphine	Tenofovir	

References:
Facts & Comparisons, 2005.
Sanctura Prescribing Information, July 2004, Odyssey Pharmaceuticals, Inc.

Criteria Recommendations	*Approved*	*Rejected*

46. Telithromycin / Pimozide _____ _____

Alert Message: The concurrent use of Ketek (telithromycin) and pimozide is contraindicated due to increased risk of cardiotoxicity (e.g., QT prolongation, torsades de pointes, cardiac arrest). Although no formal drug interaction studies have been conducted, telithromycin may inhibit pimozide CYP 3A4-mediated metabolism causing elevated plasma levels. Both agents are known to cause QTc prolongation.
Conflict Code: DD – Drug/Drug Interaction
Drug/Disease:

Util A	Util B	Util C
Telithromycin	Pimozide	

References:
Ketek Prescribing Information, Oct. 2004, Aventis Pharmaceuticals, Inc.
Physicians' Desk Reference, Micromedex Healthcare Series, 2005.

September 1st, 2005

The next North Dakota Drug Utilization Review (DUR) Board Meeting will be held:

November 7th, 2005 at 1:00pm

Pioneer Room
State Capital
612 East Blvd
Bismarck, ND

Please remember to silence all pagers and cell phones prior to the start of the meeting.

North Dakota Medicaid
DUR Board Meeting
Agenda
Pioneer Room
November 7th, 2005
1pm

1.	Administrative items -Travel vouchers	
2.	Old Business	
	- Review and approval of minutes of 08/08/05 meeting	Chairman
	- Budget update	Brendan Joyce
	- Review Policy and Procedures	HID
	- Review Guidelines ADD/ADHD	HID
	- 2nd Review for Revatio	HID
3.	New Business	
	- Review of Statins	HID
	- Review Sustained Release Opioid Agents	HID
	- Review of Actoplus Met	HID
	- Review of Fosamax Plus D	HID
	- Review of Actonel with Calcium	HID
	- Criteria Recommendations	HID
	- Meeting Dates 2006	HID
4.	Upcoming meeting agenda	Chairman
5.	Adjourn	Chairman

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

Drug Utilization Review (DUR) Meeting Minutes
August 8th, 2005

Members Present: Albert Samuelson, Greg Pfister, John Savageau, Patricia Churchill, Carrie Sorenson, Cheryl Huber, Leann Ness, Norma Byers, Scott Setzepfandt, Gary Betting

Medicaid Pharmacy Department: Brendan Joyce

HID Staff Present: Candace Rieth, Steve Espy

Members Absent: Jay Huber, Bob Treitline

Chair John Savageau called the meeting to order at 1:05pm and asked for a motion to approve the minutes from the June 6, 2005 meeting. Norman Byers moved that the minutes be approved and Albert Samuelson seconded the motion. The chair called for a voice vote to approve the minutes, which passed with no audible dissent.

Budget Update:
Brendan Joyce reported the expenditures for FY 2004 were 45,974,797. There was 2.8% increase between FY 2004 and the projected FY 2005 budget. He further explained that the Department had to maintain only a 2.5% growth to stay within the upcoming biennium budget. Previous growth projections were 11%.

Review of Zanaflex:
This is the 2nd review of Zanaflex capsules for PA implementation. Brendan Joyce distributed a handout from the manufacturer. Steve Espy explained that he spoke with a representative from Acorda and offered the opportunity for the representative to present to the Board. Instead, a handout about Zanaflex capsules was sent to Brendan. Brendan noted the difference in price between Zanaflex capsules and Tizanidine tablets was $1.61./capsule and .55 /tablet. John Savageau explained the criteria for Prior Authorization for Zanaflex capsules. Scott Setzepfandt suggested that dysphagia be included as a criteria. John Savageau moved to accept the prior authorization form and algorithm as presented. Carrie Sorenson seconded the motion. The motion was approved by voice vote with no audible dissent.

Review of Board Policy and Procedures:
John Saveageau, at the previous meeting, asked for a review of the Board Policy and Procedures. John explained to the Board the need to accelerate the decisions the Board makes. HID gave examples in the DUR pak of several states Board Policy and Procedures for the Board to review. John Saveageau explained the difference between the current and the proposed Board Procedures. After much discussion, Albert Samuelson moved to accept the new procedures. Patricia Churchill seconded the motion. The motion carried by voice vote with one dissenting vote.

Public Comment:
There was public comment from Joel Gilbertson, an attorney speaking on behalf of PhRMA. Mr. Gilbertson raised concerns about the period of time the Board has to discuss recommendations as well as the language of the proposed Policy and Procedures. Brendan explained that even though the Board voted to accept the new procedures that until the Department agreed, the Board would operate under the old procedures. This topic will be brought up again at the next Board meeting for finalization. Brendan also stated that the Department will be requiring that in the future, the DUR pack will be posted on the internet 8 weeks in advance. Brendan also stated that all future meetings will be held quarterly. Representative Bill Devlin suggested that the Board stay with the current Policy and Procedures and let the legislature make the changes to the Policy and Procedures down the road.

Review of Impact of Cox II inhibitors on GI Bleed:
Steve Espy reviewed the graphs enclosed in the DUR pack. The graphs indicated that the increased utilization of Cox II inhibitors did not alter the incidence of GI bleed.

Review of Average Daily Consumption of ADHD Agents:
Steve Espy reviewed the table provided that reported all but one sustained release ADHD agent was being prescribed more than once daily. Steve also reviewed the graphs that depicted the utilization of immediate release and sustained release products. There was discussion concerning the increase in utilization of these agents and Cheryl Huber shared points of interest from several pediatric psychiatrists:

- ADHD is not just a school time disease
- Multiple dosing of sustained release products is necessary to prevent abrupt changes throughout the day
- Multiple dosing is necessary when patients are in after school programs and also for homework at night
- Many of the patients using multiple doses of a sustained release product also have co-morbidities
- Education should be directed at family practice rather than psychiatrists

The Board instructed HID to obtain guidelines and standards of care for use of the ADHD agents. There was public comment that followed. Dr. Byers asked if there was a way to know which prescriptions were being written by family practice doctors and which were written by specialists.

Utilization of SROA agents:
Steve Espy reviewed the graphs of several specific sustained release narcotics, indicating the dramatic increase in utilization of Oxycontin and Duragesic. There was much discussion on the appropriate use of these drugs and if there are ways to control utilization. Brendan Joyce asked the Board to recommend to the Department that he do a survey of the providers to find out diagnoses, directions and whether or not the doctor is using a contract on the patients taking these medications. John Savageau asked HID to produce a report that indicated the number of single prescriptions for the SROA agents.

Summary of state actions of Oxycontin:
Steve Espy reviewed the list of states provided and their actions on Oxycontin. Ten out of thirteen states require a prior authorization for Oxycontin.

Summary of State actions on statins:
Steve Espy reviewed the list of states provided and their action on the drug class statins. The majority of the states require a prior authorization on statins. The Board instructed HID to bring back, as an agenda item, utilization data, cost analysis and proposed criteria for potential prior authorization of the statin drug class.

Review of Revatio:
Brendan Joyce reviewed the enclosed information provided for Revatio, including the PA form and criteria. He mentioned the necessity of the prior authorization in relation to the federal mandate concerning sexual offenders. Norman Byers moved to consider the recommendation to place Revatio on PA. Greg Pfister seconded the motion; the motion was approved by voice vote with no audible dissent. Brendan Joyce reminded the Board that this would be brought back for a second consideration at the next Board meeting.

Review of Recommended Criteria:
Brendan Joyce advised the Board that the enclosed recommended RDUR criteria are developed from product information provided be the manufactures and usually are consistent with new indications, new drugs added, new warnings, etc. These criteria will be added to the current set of critieria and will be used in future RDUR cycles. Patricia Churchill moved to approve the new criteria and Carrie Sorenson seconded the motion. The motion was approved by voice vote with no audible dissent

Steve Espy suggested the next meeting date of 11/7/05 and also recommended to set the four quarterly meetings for 2006; 1/9, 4/10, 7/10 and 10/9. These dates can be approved at the next meeting. Acting Chair Cheryl Huber adjourned the meeting at 3:35.

Budget Info:

With the start of the new biennium, the Department is working on evaluating previous utilization in the program and the projected impact of Part D. This is obviously complex, so no projections on expenditures are available as of September 1, 2005. We assume that projections will be available in time for the DUR Board meeting in November.

ND Medicaid DUR Board
Procedures
(Developed 7/28/03)
(Modified 7/28/03)

1. All information to be distributed to DUR Board members must be sent to the Administrator of Pharmacy Services for distribution.
   a. All information received 14 days prior to the subsequent meeting will be forwarded to DUR Board members.
   b. Electronic format as an attachment to an e-mail is the preferred format.
   c. Electronic format as a CD-ROM or diskette is considered the second best option.
   d. If the format must be paper, 15 copies must be supplied to the Administrator of Pharmacy Services.
   e. The Department of Human Services will forward e-mail attachments to DUR Board members upon receipt of the e-mail.
   f. The Department of Human Services will mail all information received via hardcopy, CD-ROM, or diskette weekly on Thursday afternoons as well as one last mailing 14 days prior to the scheduled DUR Board meeting.
   g. The majority of communication from the Department of Human Services will be via e-mail and e-mail attachments.

2. Only one person may represent an interested party for presentations made during DUR Board meetings.

3. Presentations made by interested parties are limited to five (5) minutes (does not include Q&A or discussion generated by DUR Board members).

4. Process for DUR Board recommendations.
   a. The first meeting in which a discussion is held on specific medication(s), the DUR Board will draft a proposal for any action on the medication(s) after reviewing information supplied by the Department of Human Services and interested parties.
   b. This draft will be distributed to DUR Board members and those that have notified the Department of Human Services that they wish to receive such information.
   c. Comments on the proposal will be accepted in the same process as the general information (send to Department of Human Services at least 14 days prior to the next meeting).
   d. The subsequent meeting will involve a review of the comments received and will allow public comments per DUR Board guidelines mentioned above.
   e. The DUR Board will then develop and vote on a finalized proposal.

ND Medicaid DUR Board
Procedures
(Developed 7/28/03)
(Modified 7/29/05)

1. All information to be distributed to DUR Board members must be sent to the Administrator of Pharmacy Services for distribution.
   a. Information presented at the DUR Board meeting will be placed on the DHS website at least 8 weeks prior to the scheduled DUR meeting.
   b. Electronic format as an attachment to an e-mail is the next preferred format.
   c. If the format must be paper, 15 copies must be supplied to the Administrator of Pharmacy Services. The Department of Human Services will mail this information to DUR Board members weekly on Thursday afternoons as well as one last mailing 14 days prior to the scheduled DUR Board meeting.
   d. The Department of Human Services will forward the website link to DUR Board members, and interested parties, upon notice of posted DUR information on the website.
   e. The majority of communication from the Department of Human Services will be via DHS website, e-mail and e-mail attachments.

2. Only one person may represent an interested party for presentations made during DUR Board meetings.

3. Presentations made by interested parties are limited to five (5) minutes. This does not include Q&A or discussion generated by DUR Board members.

4. Process for DUR Board recommendations:
   a. Posting of information on DHS website will give DUR Board members and the public 8 weeks to draft a proposal for any action on the medication(s) after reviewing information supplied by the Department of Human Services and interested parties.
   b. This draft will be distributed to DUR Board members and those that have notified the Department of Human Services that they wish to receive such information.
   c. Comments on the proposal will be accepted. Send to DHS at least 14 days prior to the scheduled meeting.
   d. At the scheduled meeting, the DUR Board will review the comments received and will allow public comments per DUR Board guidelines mentioned above.
   e. The DUR Board will then develop and vote on a finalized proposal

Specialty Codes for ADD Medications filled
January 1, 2005 to June 28th, 2005

Drug Name	Rx Num	Total Price
Adderall XR	2525	$240,148.11
Concerta, Metadate CD, Ritalin LA	5100	$433,906.35
TOTAL	7625	$674,054.46

Summary by Specialty

Specialty	Claims Count	Qty Dispensed	Total Dollars
01-General Practice	1642	51995	$138,461.82
13-Neurology	1	30	$80.51
16-OB/GYN	1	30	$74.95
19-Dentist	1	30	$97.77
20-Orthopedic Surgery	5	150	$25.00
26-Psychiatry	3519	124747	$321,908.82
30-Radiology	1	16	$27.22
37-Pediatrics	1487	50059	$128,654.16
41-Internal Medicine	248	7312	$21,218.57
42-Oncology	1	30	$97.77
70-Clinic	148	4486	$12,518.83
82-Emergency Medical Service	3	120	$234.13
93-Nurse Practitioner	568	18754	$50,654.91
		Grand Total	$674,054.46

In 2003, the 3rd World Symposium on Pulmonary Hypertension was convened in Venice to modify classification based on the new understanding of disease mechanisms. The revised system developed by this group provides the current frame work for understanding pulmonary hypertension.

The system includes several improvements over the former 1998 Evian Classification system. The terms "primary" and "secondary" were discontinued because they had limited diagnostic value. In addition, new classifications were added, including primary veno-occlusive disease (PVOD). Risk factor descriptions were updated, and the classification of congenital systemic-to pulmonary shunts was revised. A new classification of genetic factors in PH was recommended, but not implemented because available data were judged to be inadequate.

The Venice 2003 Revised Classification system can be summarized as follows:

- WHO Group I - Pulmonary arterial hypertension (PAH)
- WHO Group II - Pulmonary hypertension with left heart disease
- WHO Group III - Pulmonary hypertension associated with lung diseases and/or hypoxemia
- WHO Group IV - Pulmonary hypertension due to chronic thrombotic and/or embolic disease
- WHO Group V - Miscellaneous

These terms are currently in use, but they are not yet as commonly used as the old terms of PPH and SPH[1]

[1] Executive Summary from the World Symposium on Primary Pulmonary Hypertension 1998, Evian France 6 - 10 September 1998 (Modified Venice 2003).

Revatio PRIOR AUTHORIZATION
ND DEPARTMENT OF HUMAN SERVICES
MEDICAL SERVICES DIVISION

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

ND Medicaid requires that patients receiving Revatio 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 PHYSICIAN

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

REQUESTED DRUG:	**Requested Dosage:** (must be completed) **Diagnosis for this request:**

Qualifications for coverage:

- ❑ Indication for the treatment of Pulmonary Arterial Hypertension (WHO Group I Classification)

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

Physician Signature: Date:

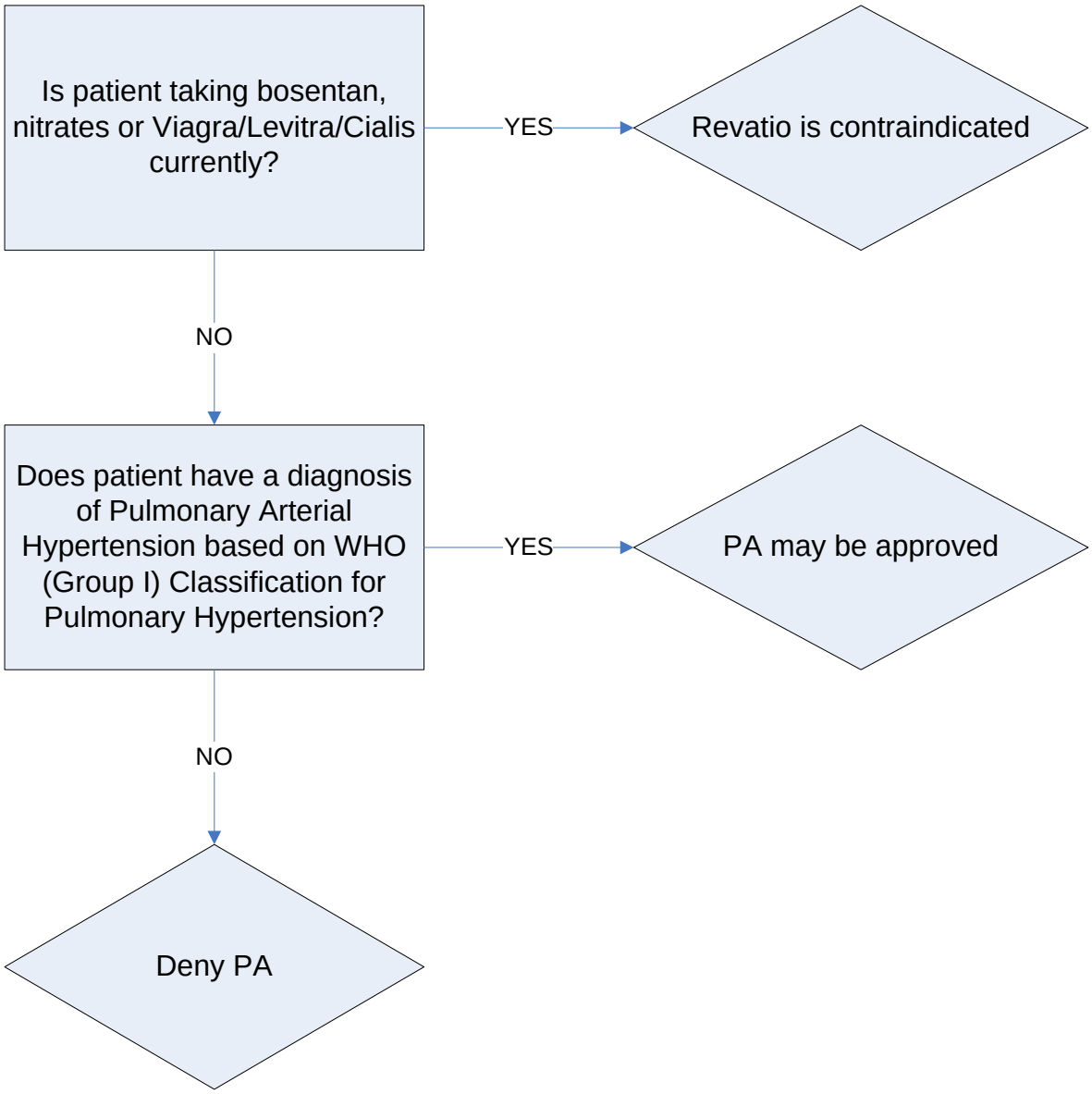
Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:		ND MEDICAID PROVIDER NUMBER:
Phone:		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
Revatio Authorization Algorithm



Statin Overview[i]

Trade Name	Generic Name	Release
Lipitor	Atorvastatin	ER
Lescol, Lescol XL	Fluvastatin	ER/IR
Altocor ER, Mevacor	Lovastatin	ER/IR
Pravachol	Pravastatin	ER
Crestor	Rosuvastatin	ER
Zocor	Simvastatin	ER

Equivalent doses of statins:

Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
--	40mg	20mg	20mg	--	10mg
10mg	80mg	40 or 80mg	40mg	--	20mg
20mg	--	80mg	80mg	5 or 10mg	40mg
40mg	--	--	--	--	80mg
80mg	--	--	--	20mg	--
--	--	--	--	40mg	--

What these drugs have in common

- All statins lower cholesterol and lower LDL. All but Crestor have been shown to improve heart disease
- All statins may cause serious harm in muscles or liver
- No differences exist among statins by age, sex, or diabetes. Little data exists about use in African-Americans, Hispanics, or other ethnic groups

How statins compare in their ability to reduce LDL-c

- For patients who require LDL-c reductions of up to 40% to meet their goal, any of the statins are effective
- In patients requiring an LDL-c reduction of 40% or greater to meet the National Cholesterol Education Program goals, atorvastatin 20mg or more, lovastatin 80mg, rosuvastatin 10mg or more, and simvastatin 20mg or more daily are likely to meet the goal

Key Differences

- Atorvastatin, pravastatin, and simvastatin lower risk of stroke
- Pravastatin has the least drug interactions
- Atorvastatin, lovastatin, and simvastatin have the most drug interactions. This concerns people who have HIV or had a transplant; then fluvastatin or pravastatin are better due to fewer drug interactions.
- Lovastatin currently available in generic form, pravastatin and simvastatin will be available generically by spring 2006.

How do statins work

- Statins block the enzyme HMG-CoA reductase that is the rate-limiting step in the manufacture of cholesterol
- Reduce LDL-cholesterol, total cholesterol and triglycerides and slightly increase high-density lipoprotein (HDL-c)
- May have anti-inflammatory effects
- Equally effective at lowering C-reactive protein levels

Usual starting doses/max doses

- Rosuvastain 10mg, atorvastatin 10mg and 20mg of the other statins
- Taking a statin at bedtime or with the evening meal improves its ability to lower LDL
- Maximum daily dose for rosuvastatin is 40mg
- All other statins, maximum FDA-approved daily dose is 80mg
- For lovastatin and pravastatin, the maximum dose usually is prescribed as 40mg twice a day

[i] Drug Class Review on HMG-CoA Reductase Inhibitors (statins) 2005 by Oregon Health & Science University

Health Information Designs, Inc.

North Dakota Medicaid
Statin Utilization
Excluding Dual Eligibles
11/01/2004 - 06/27/2005

9/2/2005

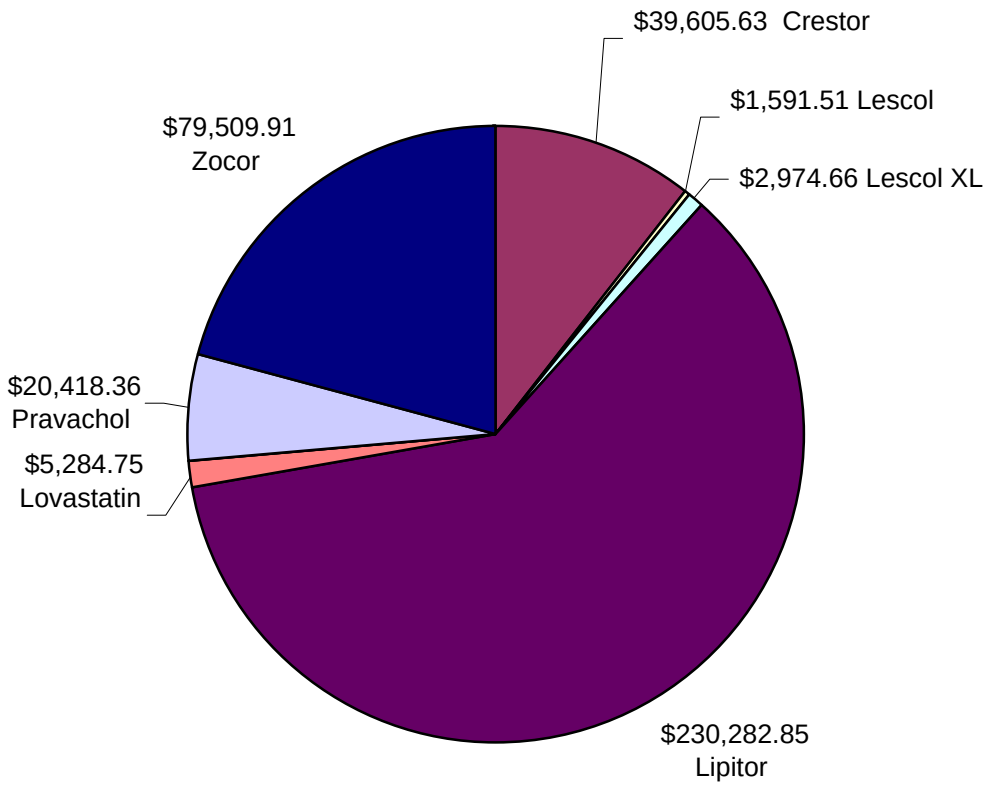
By Cost

	200411	200412	200501	200502	200503	200504	200505	200506
ALTOCOR	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
CRESTOR	$ 3,939.57	$ 4,812.00	$ 4,192.50	$ 3,268.88	$ 5,780.43	$ 4,741.23	$ 6,386.32	$ 6,484.70
LESCOL	$ 172.05	$ 117.53	$ 121.86	$ -	$ 243.93	$ 123.51	$ 443.97	$ 368.66
LESCOL XL	$ 327.91	$ 365.93	$ 295.28	$ 233.80	$ 404.35	$ 354.80	$ 486.17	$ 506.42
LIPITOR	$ 22,607.53	$ 24,396.92	$ 24,591.11	$ 23,588.51	$ 37,667.29	$ 30,661.15	$ 33,571.66	$ 33,198.68
LOVASTATIN	$ 458.83	$ 686.02	$ 527.67	$ 750.22	$ 791.97	$ 636.02	$ 791.41	$ 642.61
MEVACOR	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
PRAVACHOL	$ 1,688.75	$ 2,095.43	$ 2,084.33	$ 1,982.25	$ 3,203.14	$ 3,467.08	$ 2,510.48	$ 3,386.90
ZOCOR	$ 7,718.42	$ 7,067.18	$ 7,606.65	$ 7,469.73	$ 11,399.56	$ 10,039.13	$ 14,527.94	$ 13,681.30
Total	$ 36,913.06	$ 39,541.01	$ 39,419.40	$ 37,293.39	$ 59,490.67	$ 50,022.92	$ 58,717.95	$ 58,269.27

By Number of Prescriptions

	200411	200412	200501	200502	200503	200504	200505	200506
ALTOCOR	0	0	0	0	0	0	0	0
CRESTOR	61	72	62	53	80	65	87	88
LESCOL	4	2	4	0	4	2	7	6
LESCOL XL	6	7	5	4	6	5	7	7
LIPITOR	299	335	342	311	494	412	435	446
LOVASTATIN	13	18	13	19	20	17	21	15
MEVACOR	0	0	0	0	0	0	0	0
PRAVACHOL	17	21	23	21	30	33	29	32
ZOCOR	79	75	78	78	114	98	136	127
Total	479	530	527	486	748	632	722	721

Statin Utilization (Non-Dual) Cost 11/01/04 - 06/27/05



STATIN PRIOR AUTHORIZATION
ND DEPARTMENT OF HUMAN SERVICES
MEDICAL SERVICES DIVISION

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 statin must first fail a trial of a generic statin.
****Note: These preferred medications do not require a PriorAuthorization-lovastatin, pravastatin, or simvastatin***

Part I: TO BE COMPLETED BY PHYSICIAN

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

REQUESTED DRUG:

Requested Dosage: (must be completed)

Diagnosis for this request:

Other CV Risk Factors:

Qualifications for coverage:

- ❑ Failed generic drug — Start Date: / End Date: / Dose: / Frequency:

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

Physician Signature: Date:

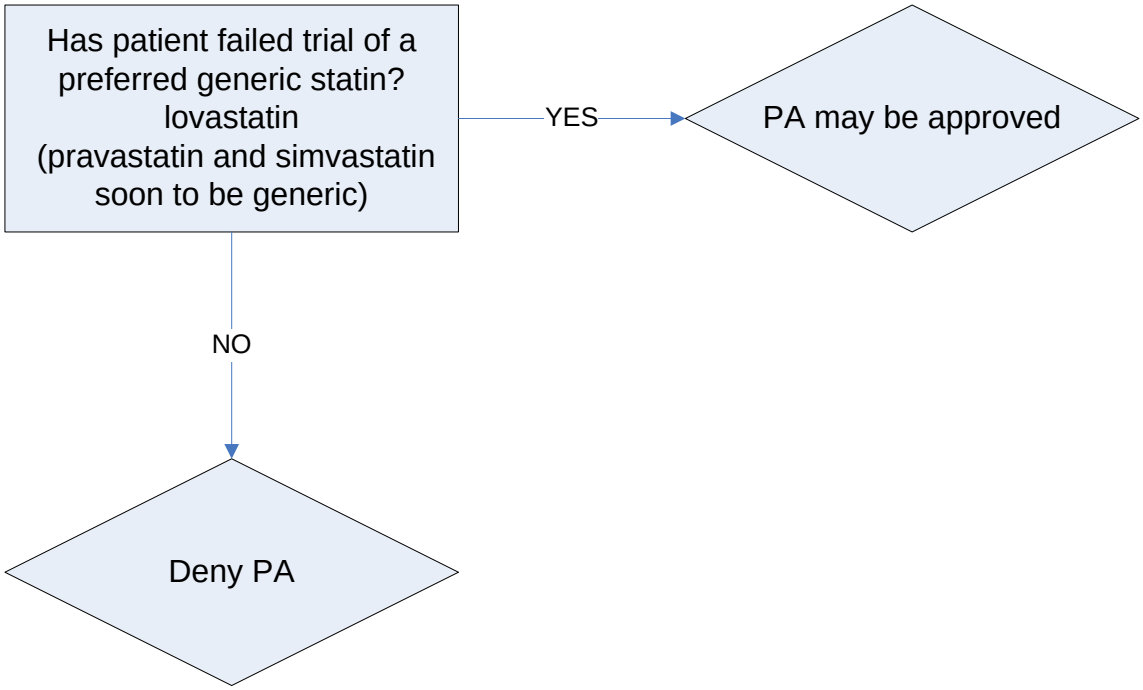
Part II: TO BE COMPLETED BY PHARMACY

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

Part III: FOR OFFICIAL USE ONLY

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

North Dakota Department of Human Services
Statin Authorization Algorithm



HEALTH INFORMATION DESIGNS

Review PRN use of Sustained Release Opioid Analgesics (SROA)

- List of medications used for review: Oxycontin, MS Contin, Kadian, Avinza, Duragesic, Oramorph
- Criteria used: patients receiving only one prescription for SROA in the time period from November 1st, 2004 - June 27th, 2005
- Number of scripts per medication:
- Avinza-10
- Duragesic-49
- Fentanyl-46
- Morphine-21
- Oxycontin-64
- Approximately 190 prescriptions for prn SROA's were written during this time frame. Of these 190 prescriptions, approximately 120 providers were responsible for the prn SROA prescriptions.

NORTH DAKOTA DEPARTMENT OF HUMAN SERVICES

Medical Services

John Hoeven, Governor
Carol K. Olson, Executive Director

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

[TODAY]

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

DEAR [tadrs1]:

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

You are receiving this notice because Department records indicate that you have prescribed Sustained Release Opioid Analgesics on a prn (as needed) basis. These medications are intended for the management of moderate-to-severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. These medications **are not** intended for use as a prn (as needed) analgesic.

In presenting this information to you, we recognize that the management of each patient's drug therapy depends upon an assessment of the patient's entire clinical situation about which we are not fully aware. Enclosed is a survey to fill out based on your individual treatment plan with each patient(s) listed. Please return the survey to the Department in the enclosed envelope.

Thank you for your professional consideration.

Sincerely,

Brendan K. Joyce, PharmD
Administrator, Pharmacy Services

PRESCRIBER RESPONSE

All information used to generate the enclosed letter, including Prescriber identification, was obtained from Pharmacy Claims Data. If there appears to be an error in the information provided, please note the discrepancy. Thank you for your cooperation.

1. This patient is under my care:
_____ Yes
_____ No

2. This patient has a diagnosis of:
_____

3. The directions for use on patient's prescription:
_____

4. Do you currently have a narcotic contract with this patient:
_____ Yes
_____ No

5. Please check here if you wish to receive reference information on the identified problem___. (Please provide a fax number if available_____-_____-_____.)
Comments: _____
_____
_____

[adrs1] Case# [case_no]
Letter Type [letter_type]
[alert_msg]
[criteria]

Administered by Health Information Designs, Inc.
1550 Pumphrey Ave.
Auburn, AL 36832-9956
(800)225-6998 x 3020 Fax (800)881-5573

ACTO*plus* met PRIOR AUTHORIZATION
ND DEPARTMENT OF HUMAN SERVICES
MEDICAL SERVICES DIVISION

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

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

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

Part I: TO BE COMPLETED BY PHYSICIAN

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

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

Qualifications for coverage:

❑ Failed both drugs separately	Start Date:	Dose:
	End Date:	Frequency:

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

Physician Signature: Date:

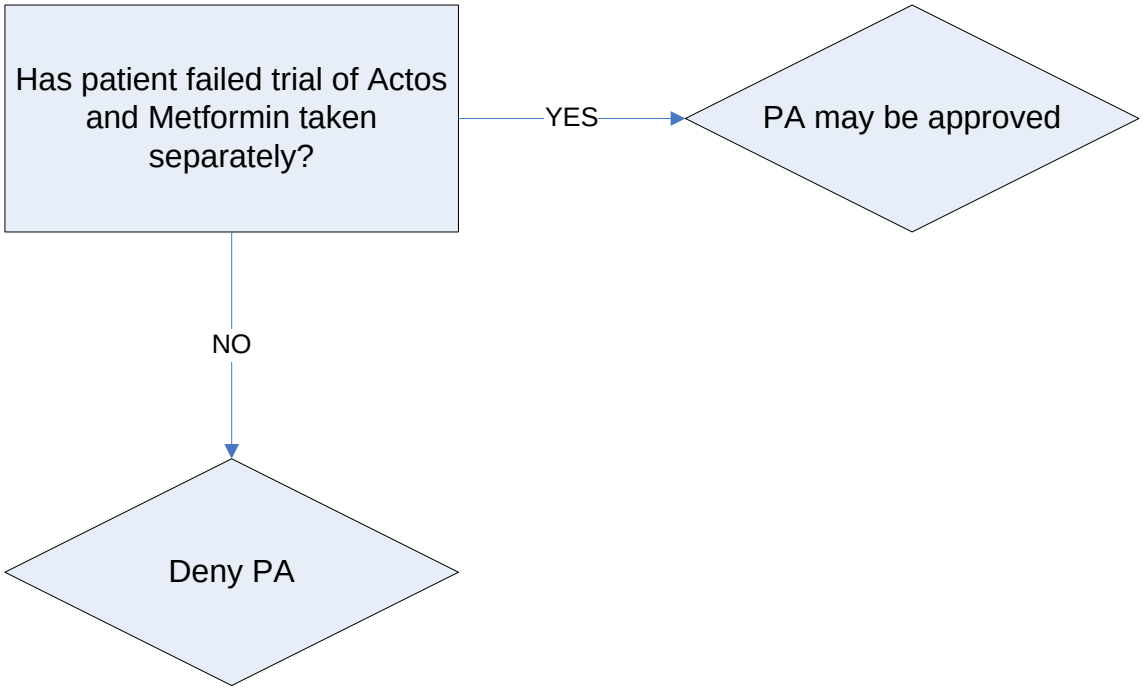
Part II: TO BE COMPLETED BY PHARMACY

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

Part III: FOR OFFICIAL USE ONLY

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

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



Post Part D Utilization Data of Actonel and Fosamax

Fosamax	**64 scripts per month**
Actonel	**13 scripts per month**

Average Cost

Fosamax	**$ 68.30/script**
Actonel	**$ 71.84/script**

Fosamax plus D PRIOR AUTHORIZATION
ND DEPARTMENT OF HUMAN SERVICES
MEDICAL SERVICES DIVISION

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

ND Medicaid requires that patients receive Fosamax without D.
****Note:***

- ***Fosamax does not require a PA***

Part I: TO BE COMPLETED BY PHYSICIAN

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

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

Qualifications for coverage:

❑ Failed Fosamax without D	Start Date: End Date:	Dose: Frequency:

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

Physician Signature: Date:

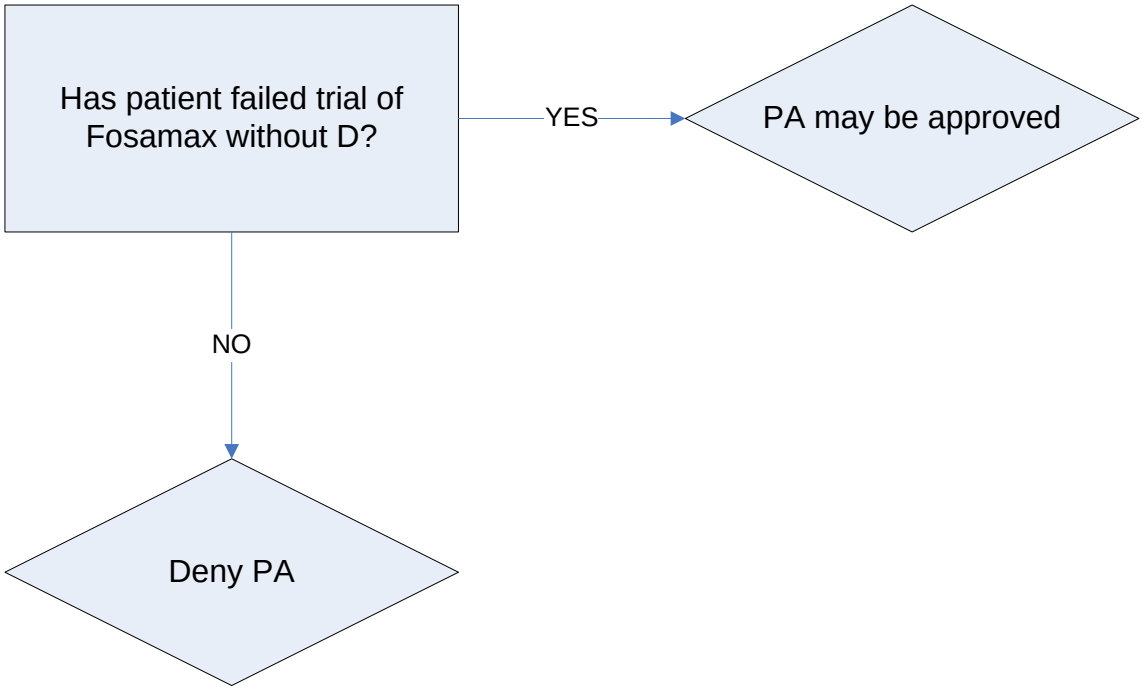
Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:		ND MEDICAID PROVIDER NUMBER:
Phone:		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
Fosamax plus D Authorization Algorithm



Actonel with Calcium PRIOR AUTHORIZATION
ND DEPARTMENT OF HUMAN SERVICES
MEDICAL SERVICES DIVISION

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

ND Medicaid requires that patients receive Actonel without Calcium.
***Note:**

- ***Actonel does not require a PA***

Part I: TO BE COMPLETED BY PHYSICIAN

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

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

Qualifications for coverage:

- ❑ Failed Actonel without Calcium — Start Date: / End Date: — Dose: / Frequency:

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

Physician Signature: Date:

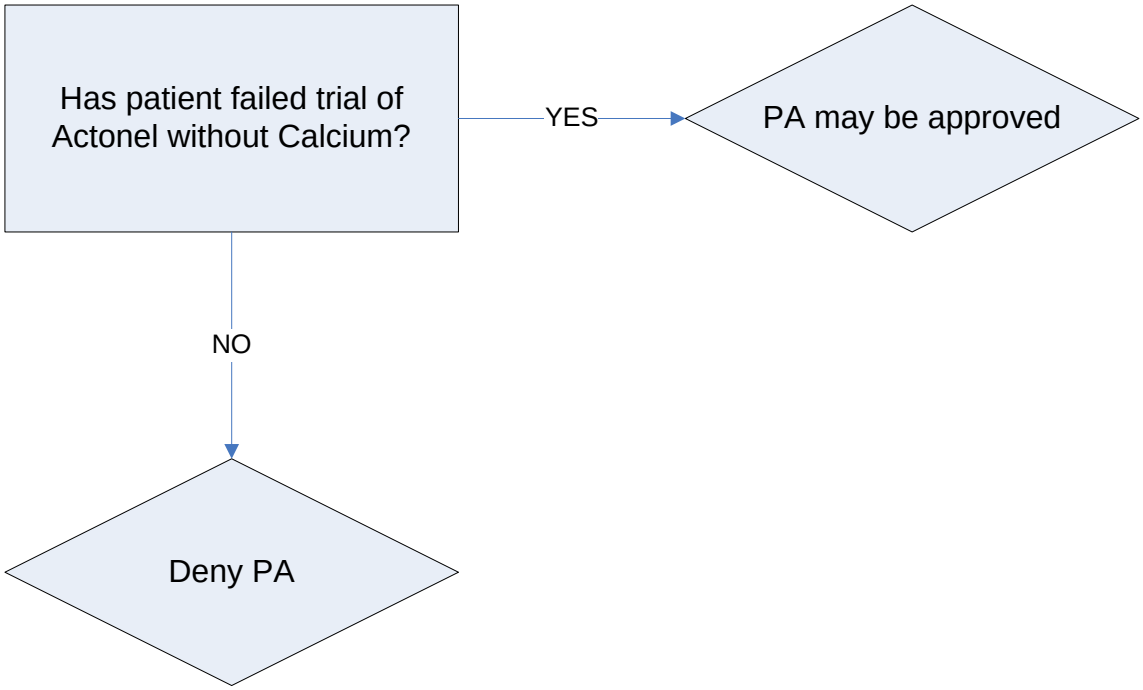
Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:	ND MEDICAID PROVIDER NUMBER:
Phone:	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
Actonel with Calcium Authorization Algorithm



NORTH DAKOTA MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
SEPTEMBER 2005

Recommendation ***Approved*** ***Rejected***

1. Oxcarbazepine / / Therapeutic Appropriateness _____ _____

Alert Message: Serious dermatological reactions, including Stevens-Johnson Syndrome and toxic epidermal necrolysis, have been reported in both children and adults in association with Trileptal (oxcarbazepine) use. The median onset for reported cases was 19 days. Such serious skin reactions may be life-threatening, and some patients required hospitalization with very rare reports of fatal outcome. Recurrence of serious skin reactions following re-challenge with oxcarbazepine has also been reported.
Conflict Code: TA – Therapeutic Appropriateness – Warning
Drugs/Disease

Util A	Util B	Util C
Oxcarbazepine		

References:
Trileptal Prescribing Information, March 2005, Novartis Pharmaceuticals Corporation.
MedWatch: The FDA Safety Information and Adverse Event Reporting Program, 2005.

2. Oxcarbazepine / / Therapeutic Appropriateness _____ _____

Alert Message: Multi-organ hypersensitivity reactions have occurred in close temporal association (median time to detection 13 days: range 4-60) to the initiation of Trileptal (oxcarbazepine) therapy in adult and pediatric patients. Although there have been a limited number of reports, many of these cases resulted in hospitalization and some were considered life threatening. Signs and symptoms of this disorder were diverse. If reaction is suspected discontinue oxcarbazepine and start alternative treatment.
Conflict Code: TA – Therapeutic Appropriateness – Precaution
Drugs/Disease

Util A	Util B	Util C
Oxcarbazepine		

References:
Trileptal Prescribing Information, March 2005, Novartis Pharmaceuticals Corporation.
MedWatch: The FDA Safety Information and Adverse Event Reporting Program, 2005.

3. Fentanyl Transdermal/Potent CYP 450 3A4 inhibitors _____ _____

Alert message: Concurrent use of fentanyl products with potent CYP 3A4 inhibitors (e.g., ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazodone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse effects and may cause potentially fatal respiratory depression. Patients receiving fentanyl and potent CYP 3A4 inhibitors should be monitored for an extended period of time and dosage adjustments made if warranted.
Conflict Code: DD – Drug/Drug Interactions
Severity: Major
Drugs/Disease:

Util A	Util B		Util C
Fentanyl	Ritonavir	Clarithromycin	
	Ketoconazole	Nelfinavir	
	Itraconazole	Nefazodone	
	Troleandomycin	Erythromycin	

References:
MedWatch: The FDA Safety Information and Adverse Event Reporting Program, 2005.
Actiq Prescribing Information, Sept. 2004, Cephalon, Inc.
Duragesic Prescribing Information, Feb. 2005, Janssen Pharmaceutica Products, L.P.

Recommendation	*Approved*	*Rejected*

4**. Isotretinoin / Tetracyclines** _____ _____

Alert Message: The concurrent use of isotretinoin and tetracyclines should be avoided. An increased incidence of pseudotumor cerebri has been reported in patients receiving these agents in combination. Early signs of pseudotumor cerebri include papilledema, severe headache, nausea, vomiting and visual disturbances. If symptoms are present discontinue drug immediately and consult a neurologist.
Conflict Code: DD – Drug-Drug Interaction
Drugs:

Util A	Util B	Util C
Isotretinoin	Tetracycline	
	Minocycline	
	Doxycycline	

References:
Accutane Product Information, Aug. 2005, Roche Laboratories, Inc.
Micromedex Healthcare Series, Drugdex Drug Evaluations, 2005.
Facts & Comparisons, 2005 Updates.

5. Salmeterol / High Dose _____ _____

Alert Message: Salmeterol doses greater than 100 mcg per day (given in two equally divided doses) have been associated with significant increases in heart rate, reductions in diastolic pressure, and prolongation of QTc interval which may potentially produce life-threatening arrhythmias.
Conflict Code: ER - Overutilization
Drugs:

Util A	Util B	Util C
Salmeterol		

References:
Micromedex Healthcare Series, Drugdex Drug Evaluations, 2005.
Facts & Comparisons, 2005 Updates.
Serevent Product Information, Sept. 2004, GlaxoSmithKline.
Advair Product Information, Sept. 2004, GlaxoSmithKline.

6. Formoterol / High Dose _____ _____

Alert Message: Foradil (formoterol fumarate) may be over-utilized. The manufacturer's recommended maximum daily dose is 12 mcg (one capsule) twice daily. The use of higher doses has not shown greater efficacy and may be a sign of worsening respiratory disease.
Conflict Code: ER - Overutilization
Drugs:

Util A	Util B	Util C
Formoterol		

Max Dose: 24mcg/day
References:
Micromedex Healthcare Series, Drugdex Drug Evaluations, 2005.
Facts & Comparisons, 2005 Updates.
Foradil Product Information, June 2003, Schering Corporation.

Proposed ND DUR Board Meeting Dates
2006

February 6th

May 1st

August 7th

November 6th