HEALTH INFORMATION DESIGNS

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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:

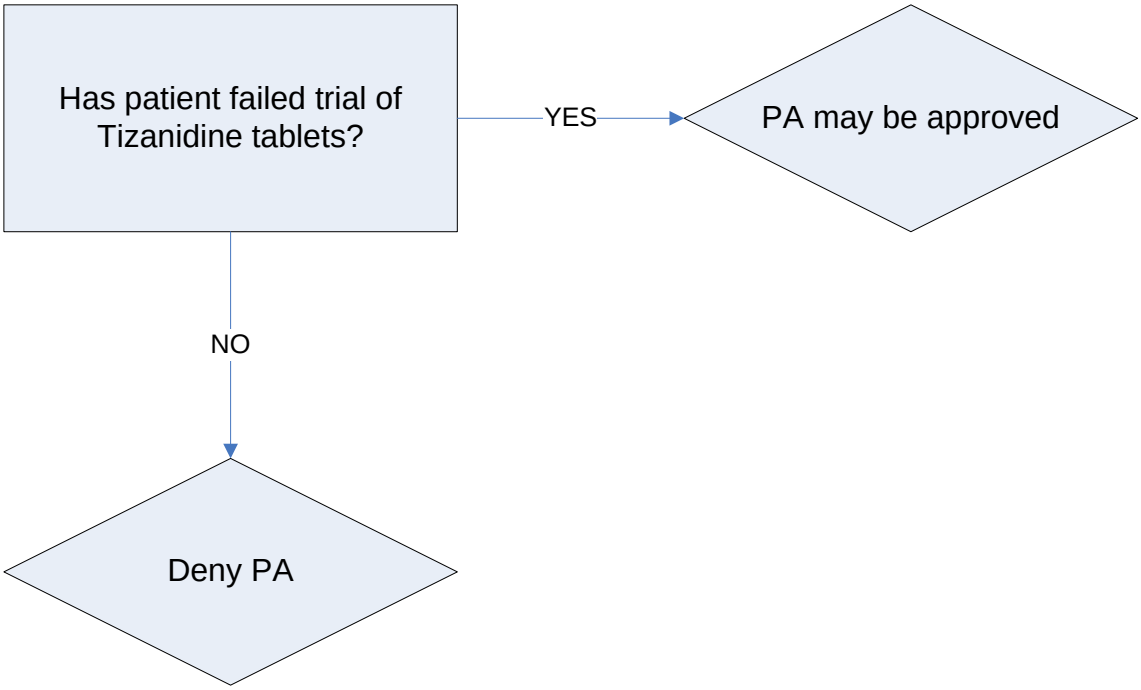
Part II: TO BE COMPLETED BY PHARMACY

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

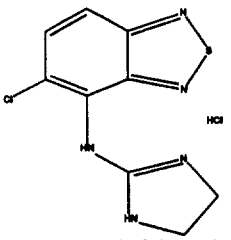


Zanaflex®
(tizanidine hydrochloride)

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.

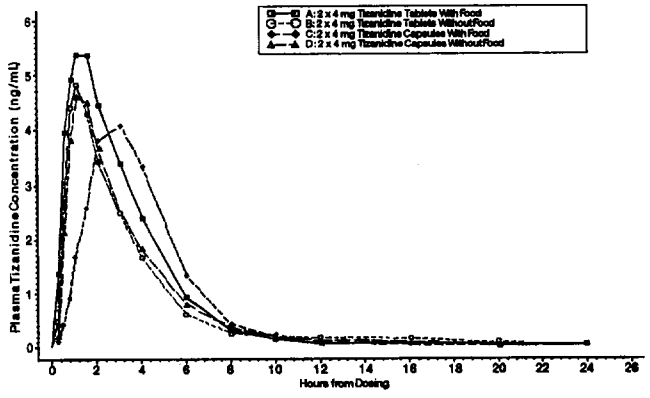
When two 4 mg tablets are administered with food the mean maximal plasma concentration is increased by approximately 30%, and the median time to peak plasma concentration is increased by 25 minutes, to 1 hour and 25 minutes.

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

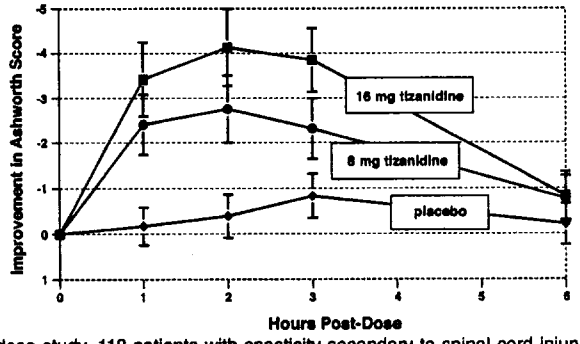
Tizanidine's capacity to reduce increased muscle tone associated with spasticity was demonstrated in two adequate and well controlled studies in patients with multiple sclerosis or spinal cord injury.

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)



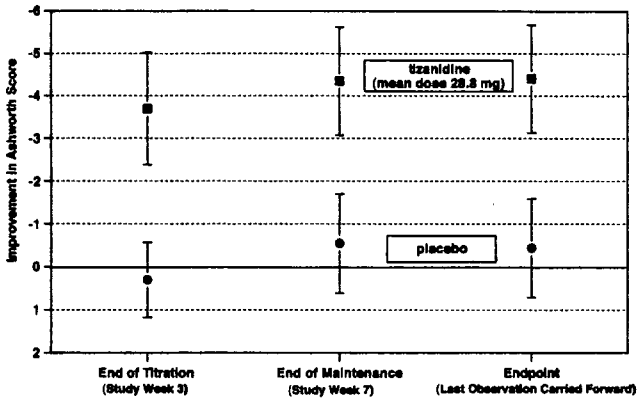
In a multiple dose study, 118 patients with spasticity secondary to spinal cord injury were randomized to either placebo or tizanidine. Steps similar to those taken in the first study were employed to ensure the integrity of blinding.

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

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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)

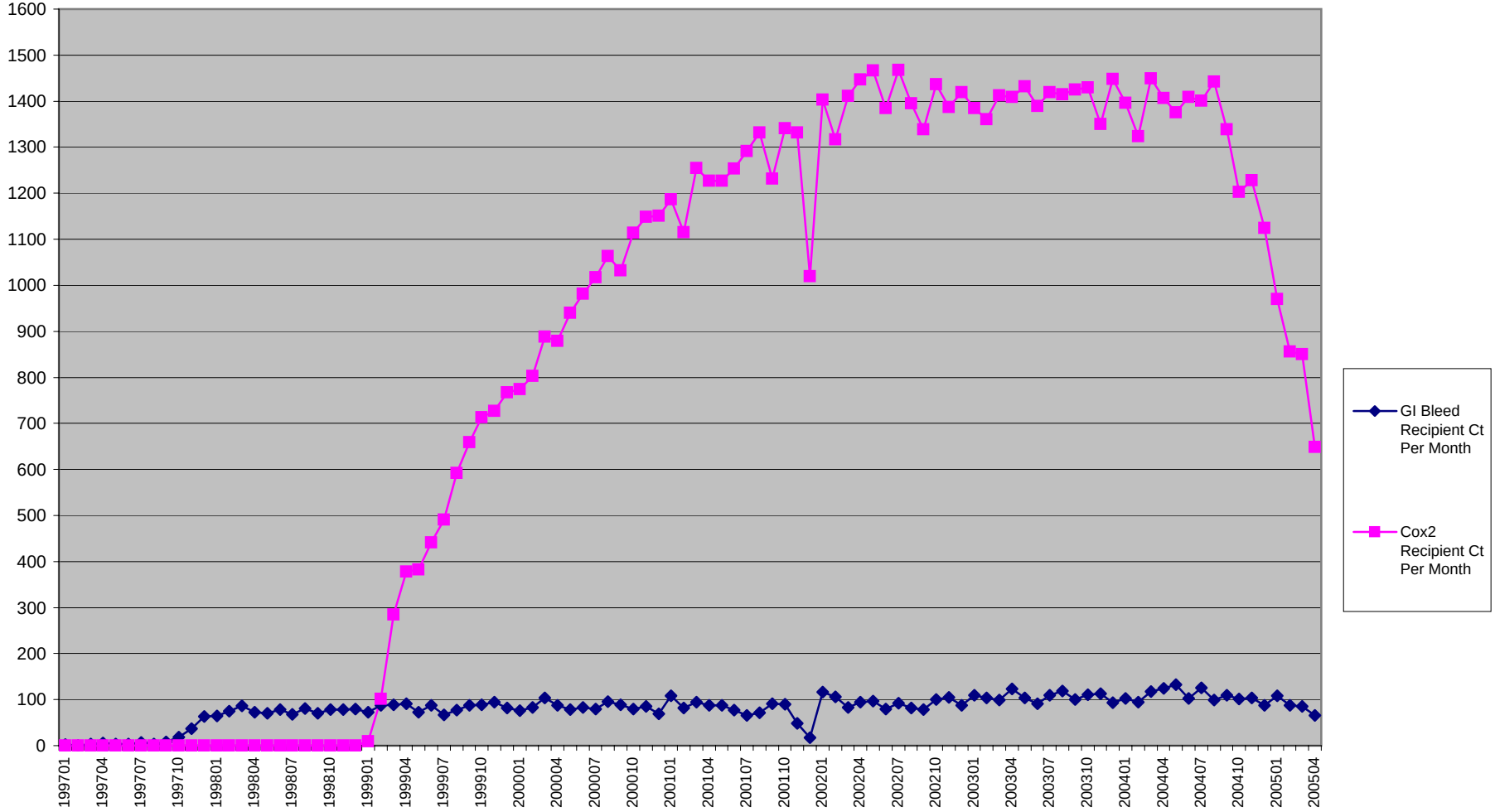
1. All information to be distributed to DUR Board members must be sent to the Administrator of Pharmacy Services for distribution.
   a. Information presented at the DUR Board meeting will be placed on the DHS website at least 8 weeks prior to the scheduled DUR meeting.
   b. Electronic format as an 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.

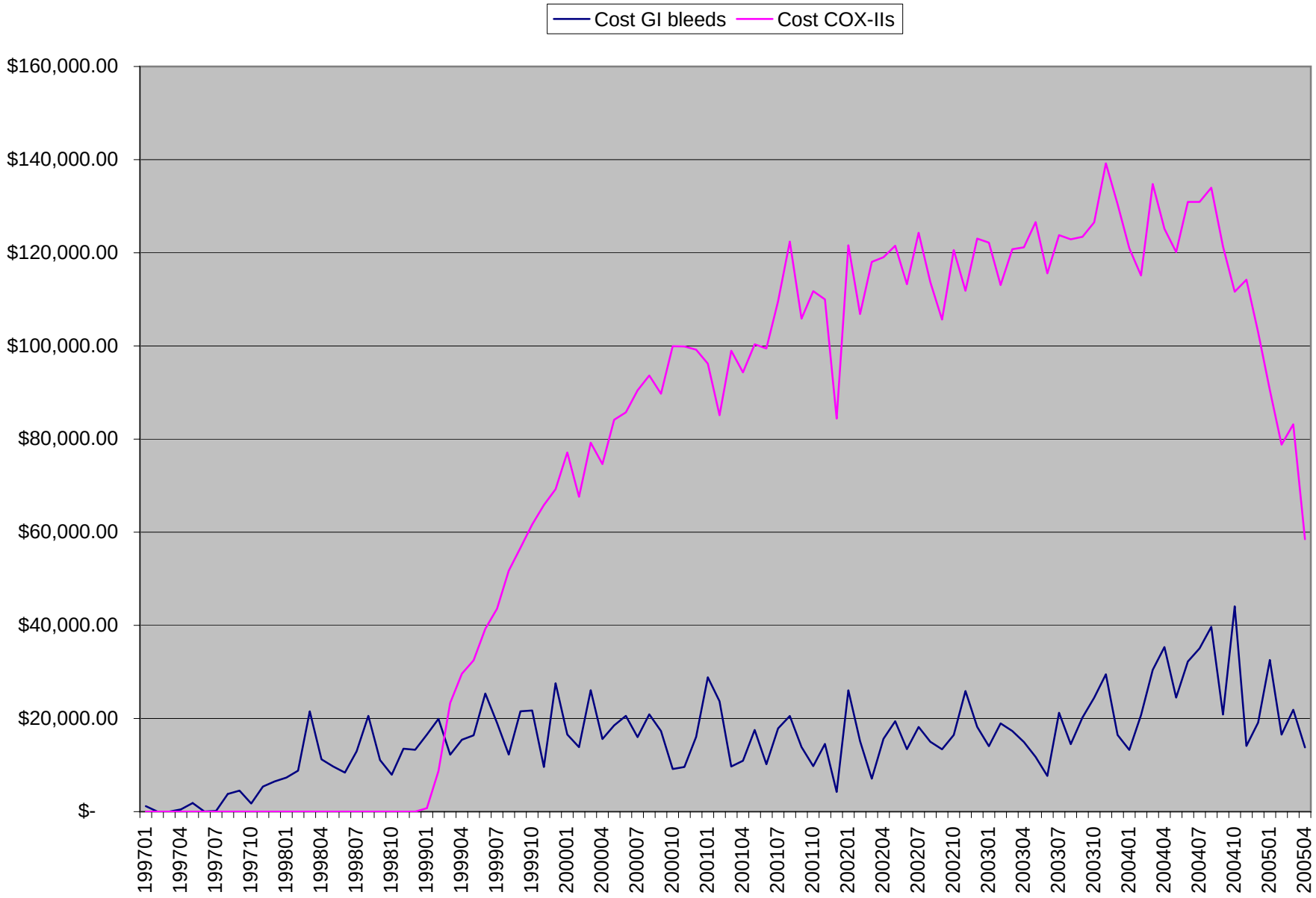
2. Only one person may represent an interested party for presentations made during DUR Board meetings.

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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199707
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200307
200310
200401
200404
200407
200410
200501
200504

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

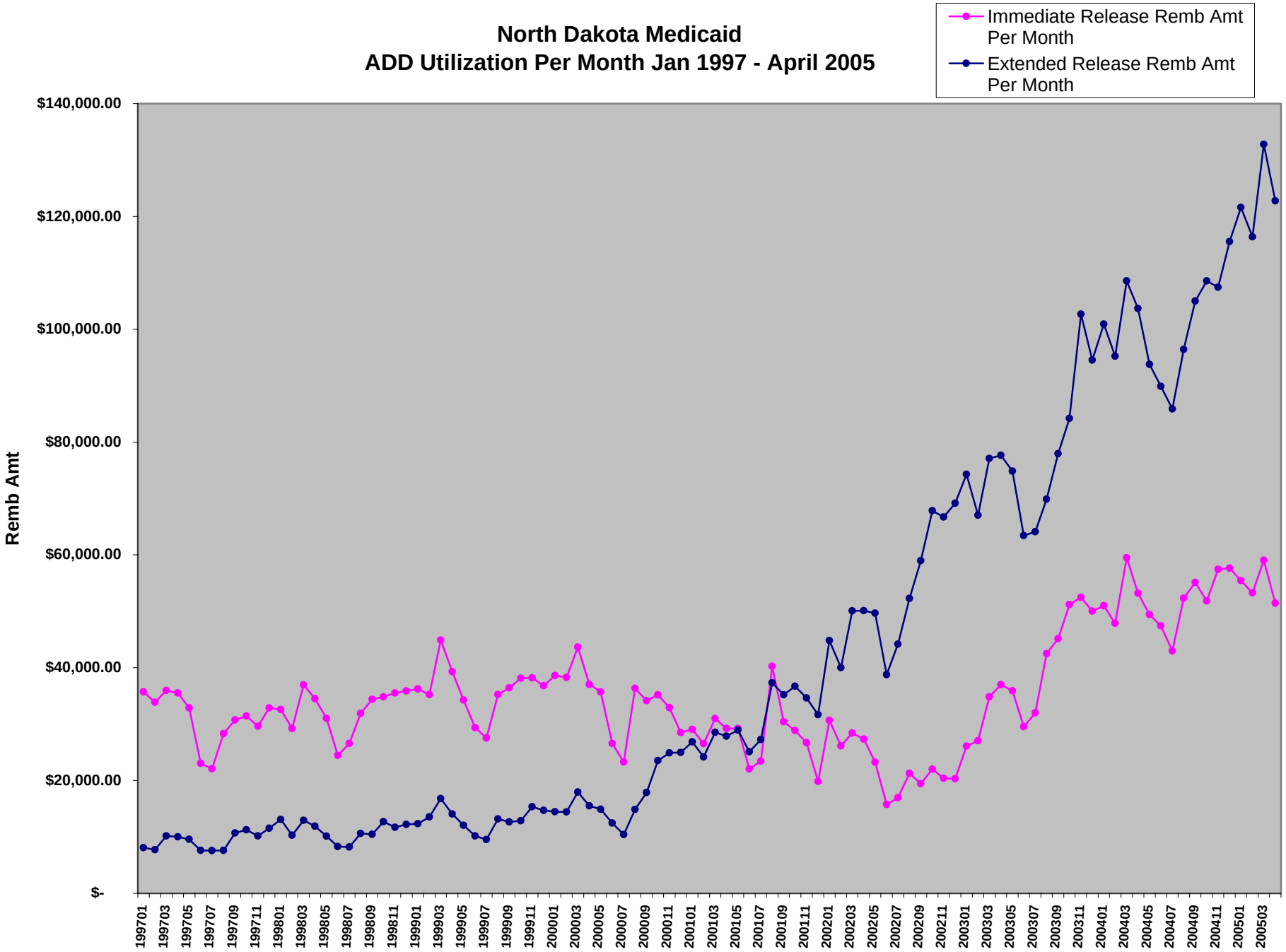
534.20	Gastrojejunal ulcer acute with hemorrhage and perforation w/o obstruction
534.21	Gastrojejunal ulcer acute with hemorrhage and perforation w/ obstruction
534.4	Gastrojejunal ulcer chronic or unspecified with hemorrhage
534.40	Gastrojejunal ulcer chronic or unspecified with hemorrhage w/o obstruction
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
$140,000.00
$120,000.00
$100,000.00
$80,000.00
$60,000.00
$40,000.00
$20,000.00
$-
199701
199703
199705
199707
199709
199711
199801
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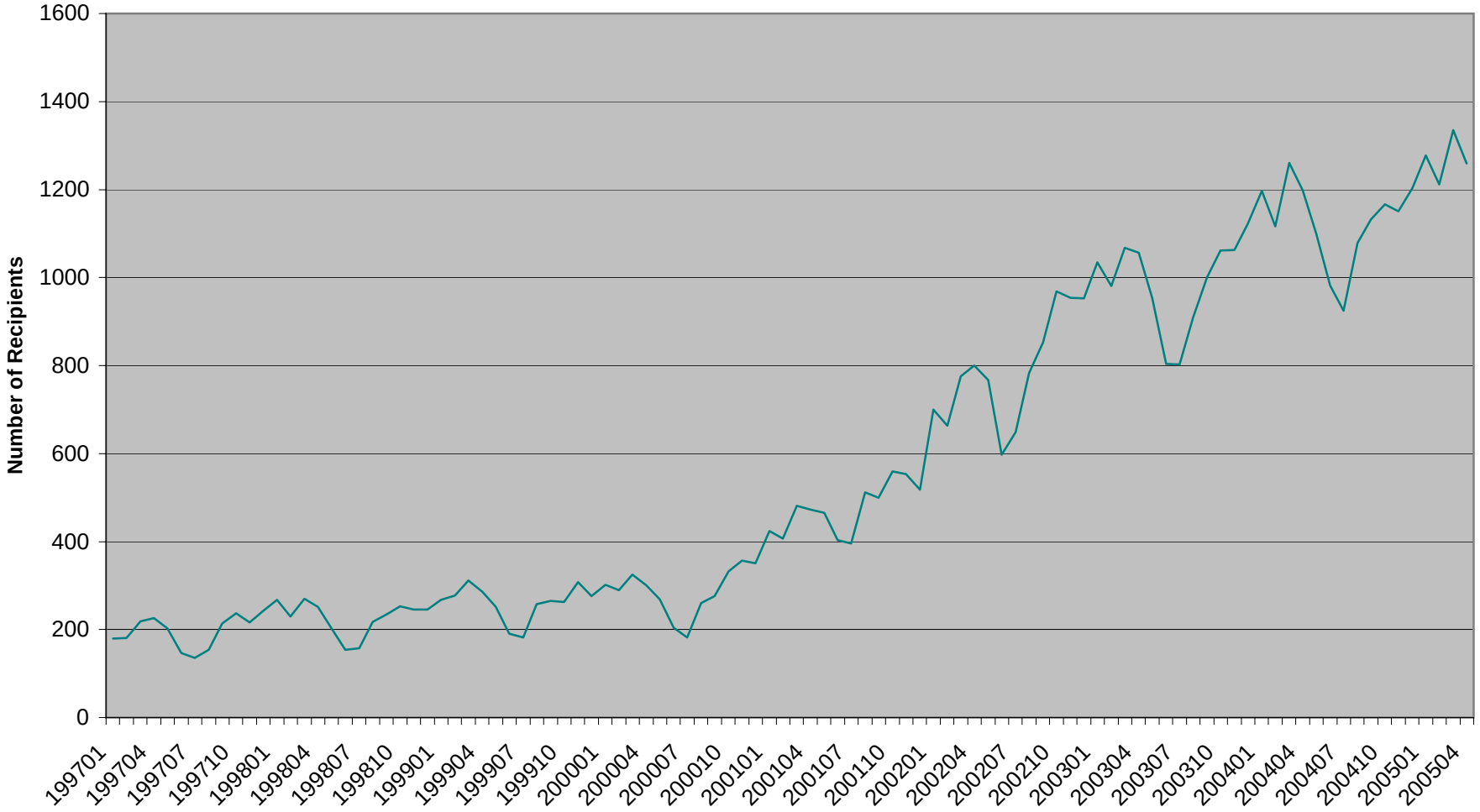
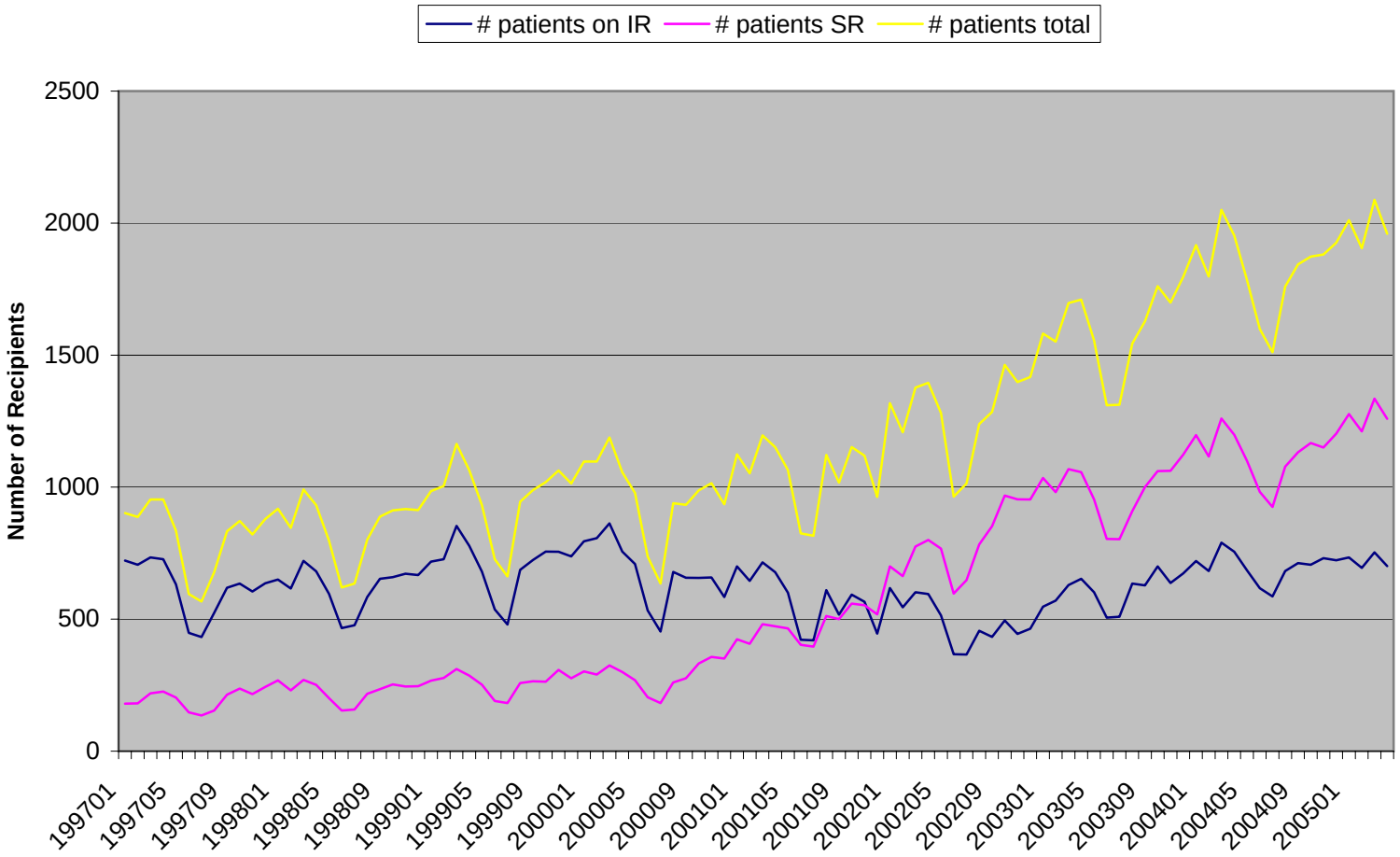
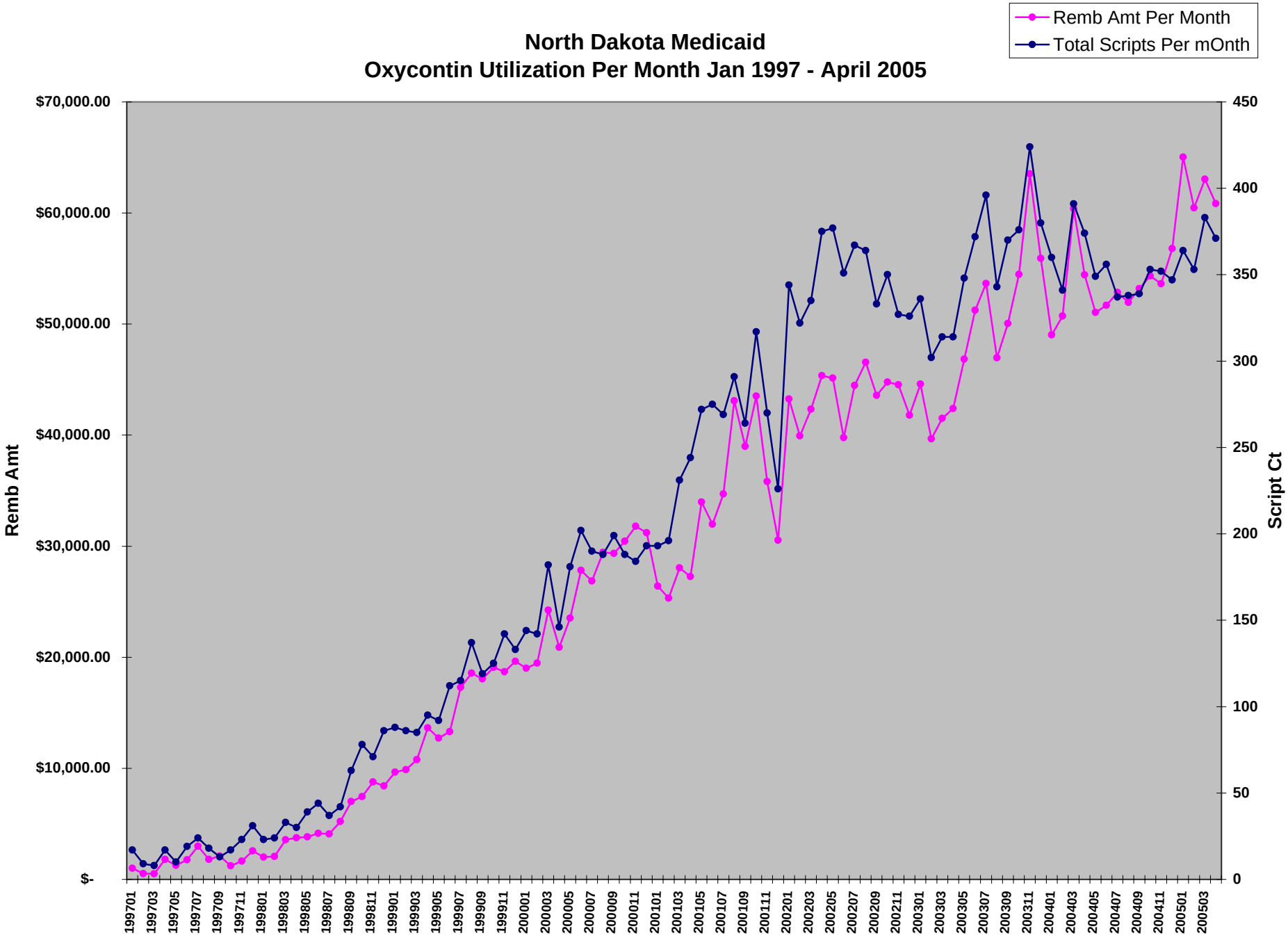
200501
200503

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
$70,000.00
$60,000.00
$50,000.00
$40,000.00
$30,000.00
$20,000.00
$10,000.00
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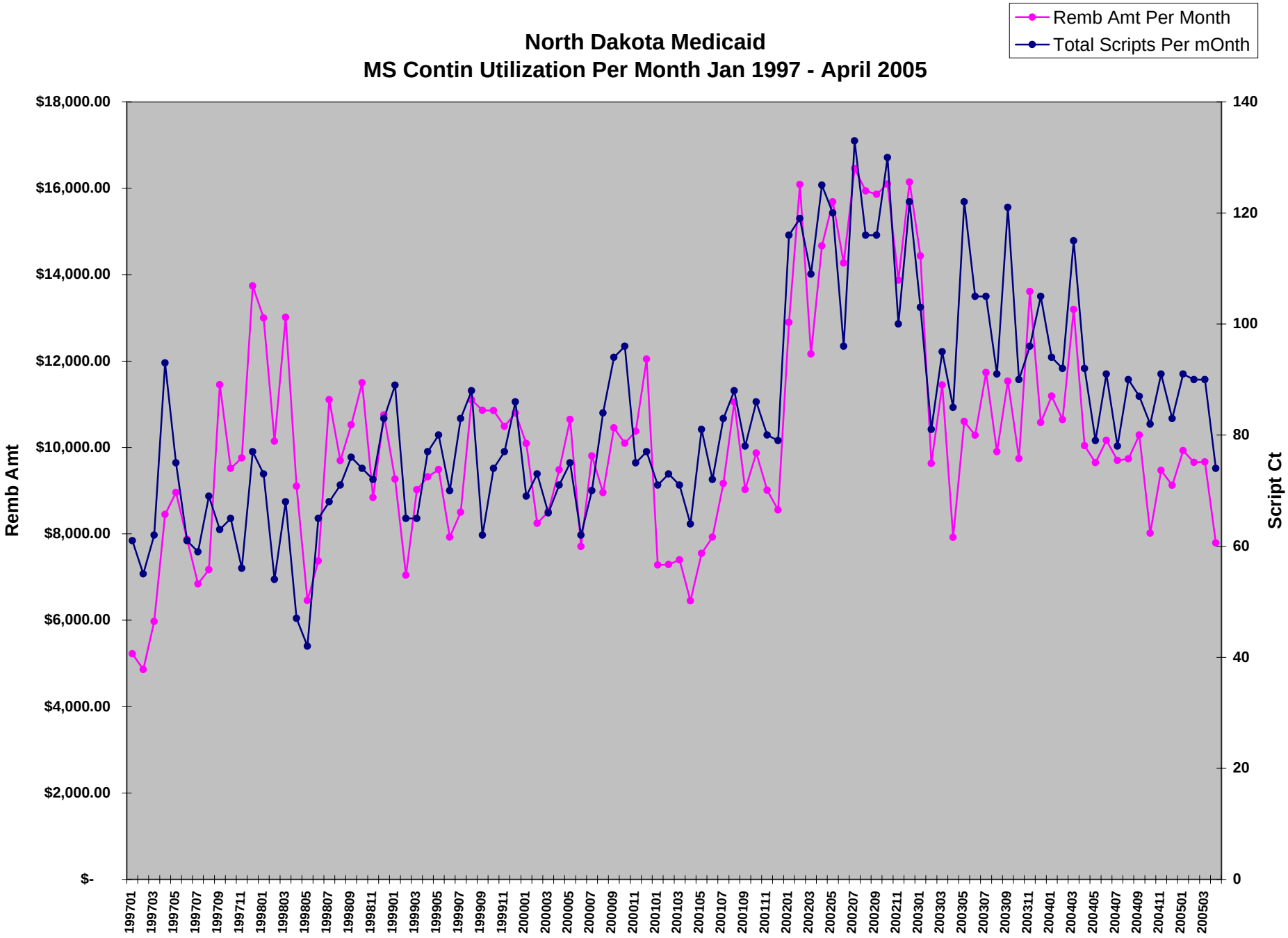
North Dakota Medicaid
MS Contin Utilization Per Month Jan 1997 - April 2005
Remb Amt Per Month
Total Scripts Per mOnth
Remb Amt
Script Ct
$18,000.00
$16,000.00
$14,000.00
$12,000.00
$10,000.00
$8,000.00
$6,000.00
$4,000.00
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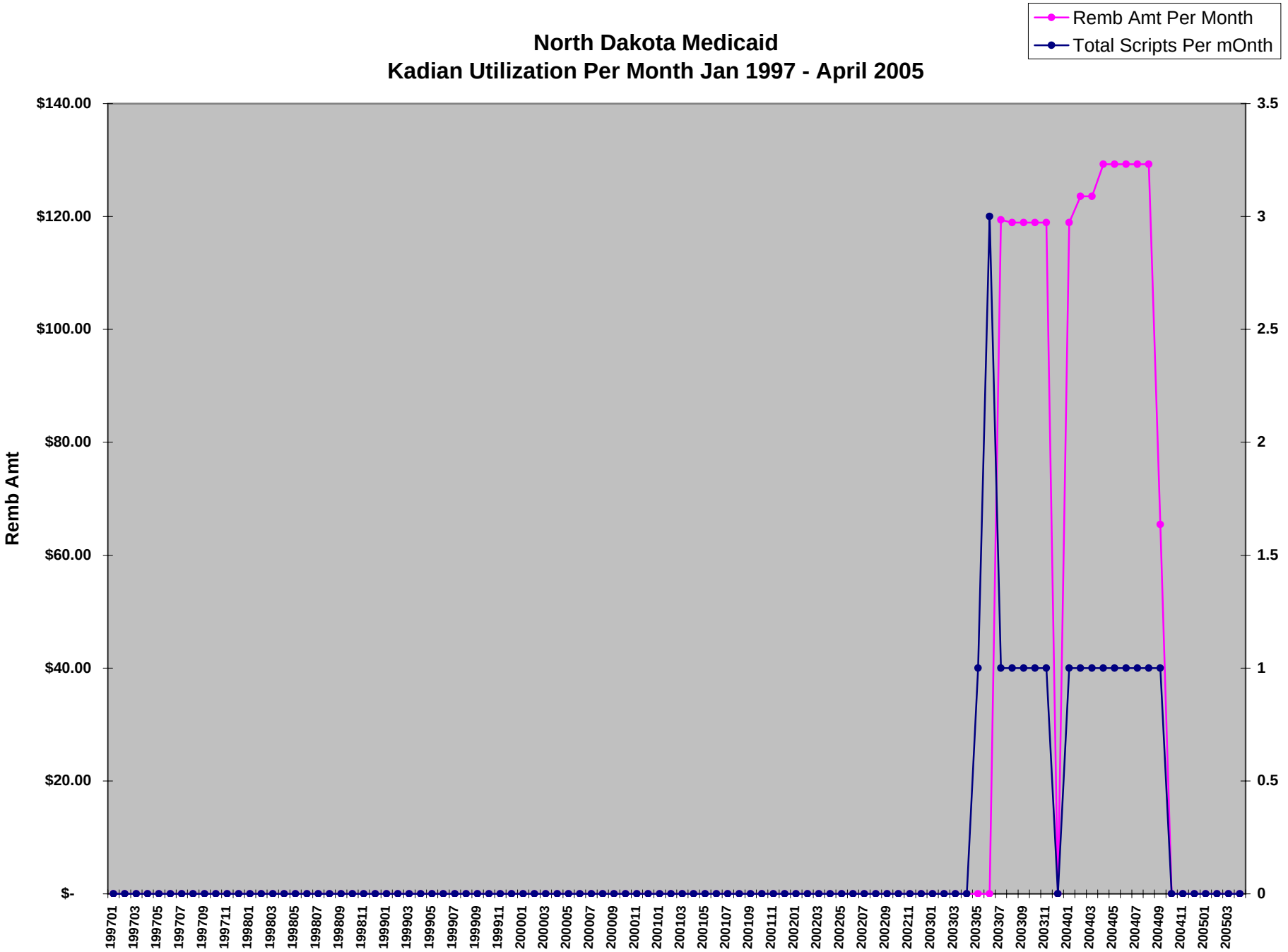
North Dakota Medicaid
Kadian Utilization Per Month Jan 1997 - April 2005
Remb Amt Per Month
Total Scripts Per mOnth
Remb Amt
Script Ct
$140.00
$120.00
$100.00
$80.00
$60.00
$40.00
$20.00
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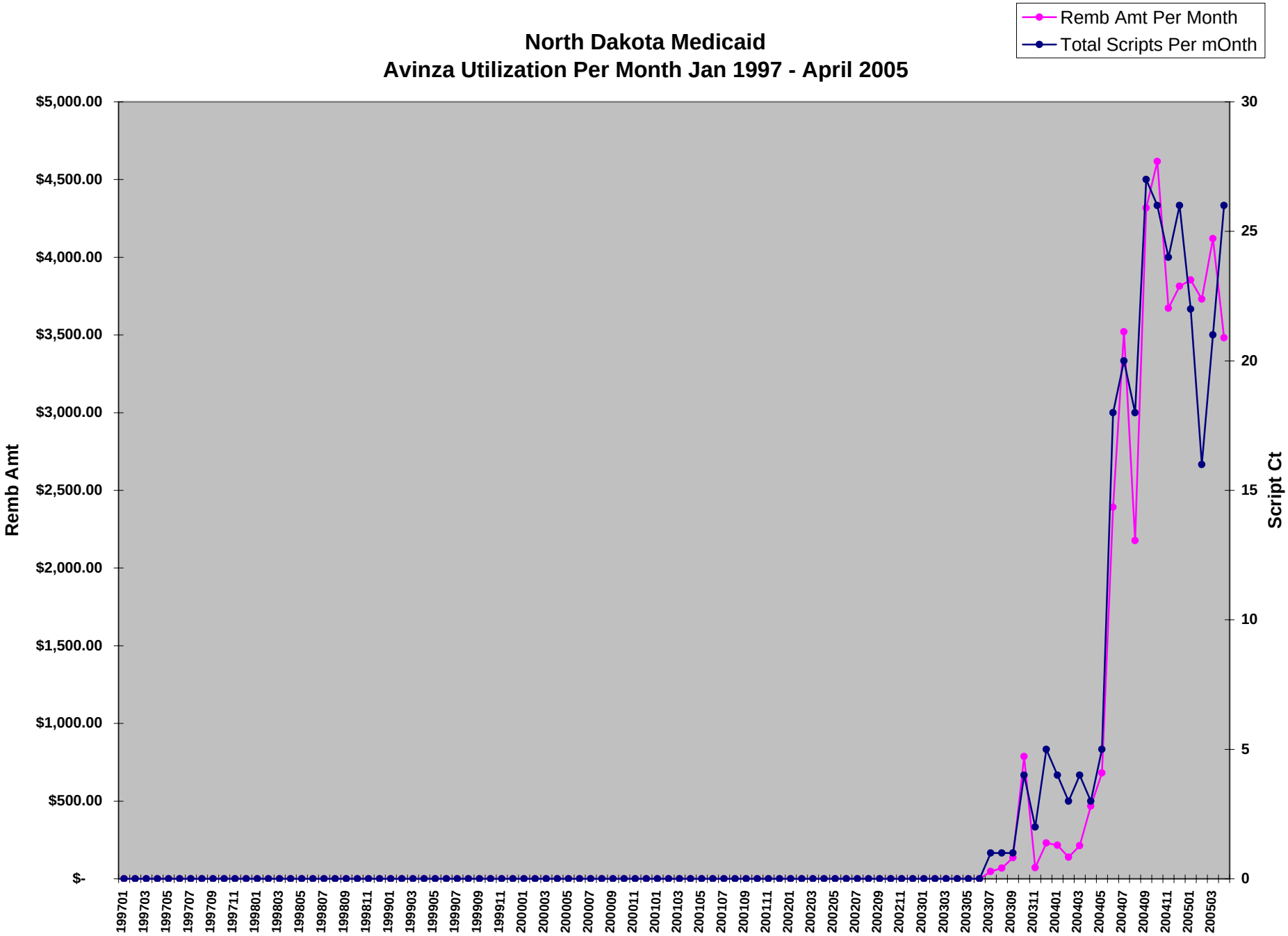
North Dakota Medicaid
Avinza Utilization Per Month Jan 1997 - April 2005
Remb Amt Per Month
Total Scripts Per mOnth
Remb Amt
Script Ct
$5,000.00
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$3,500.00
$3,000.00
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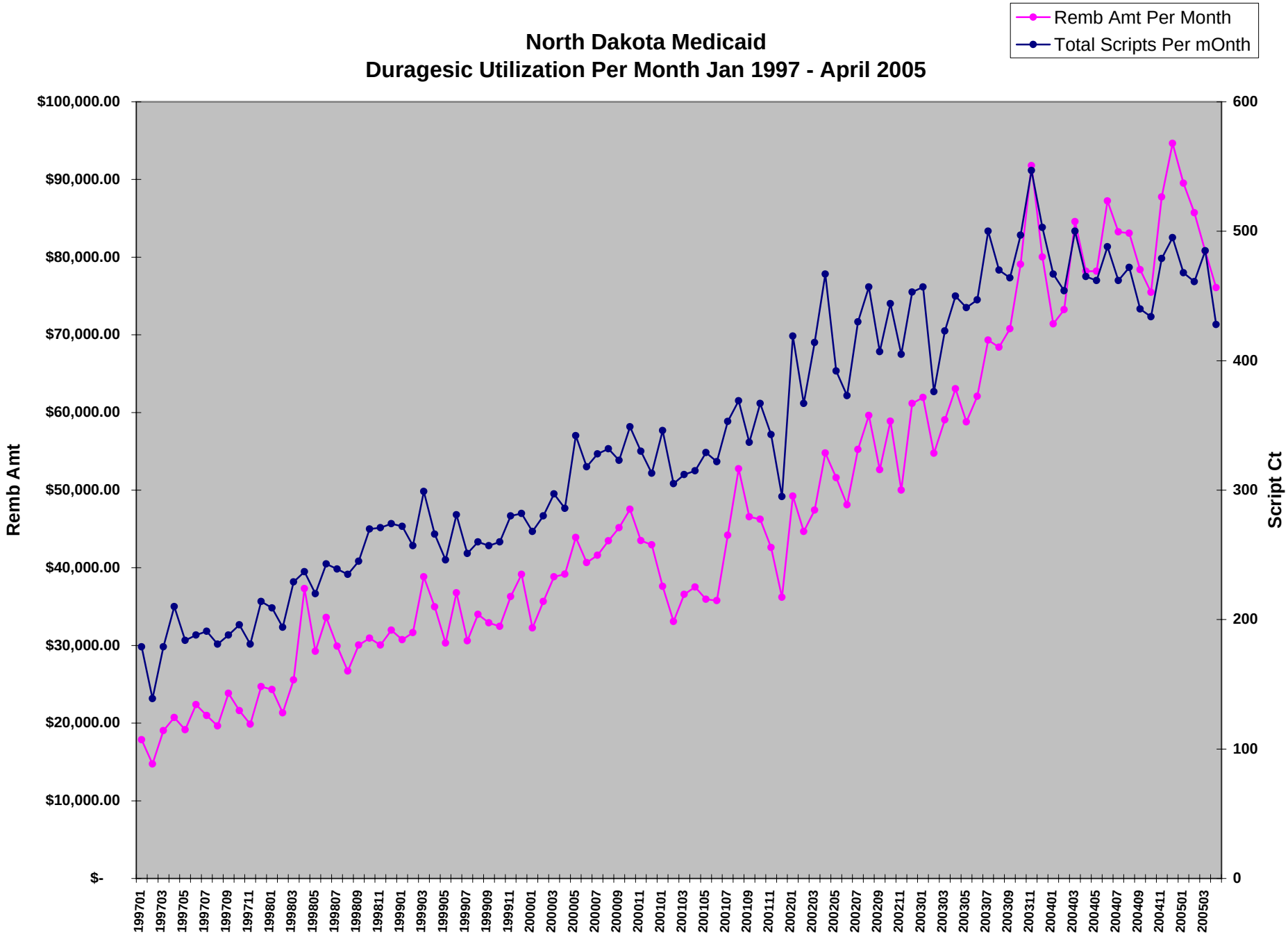
North Dakota Medicaid
Duragesic Utilization Per Month Jan 1997 - April 2005
Remb Amt Per Month
Total Scripts Per mOnth
Remb Amt
Script Ct
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$90,000.00
$80,000.00
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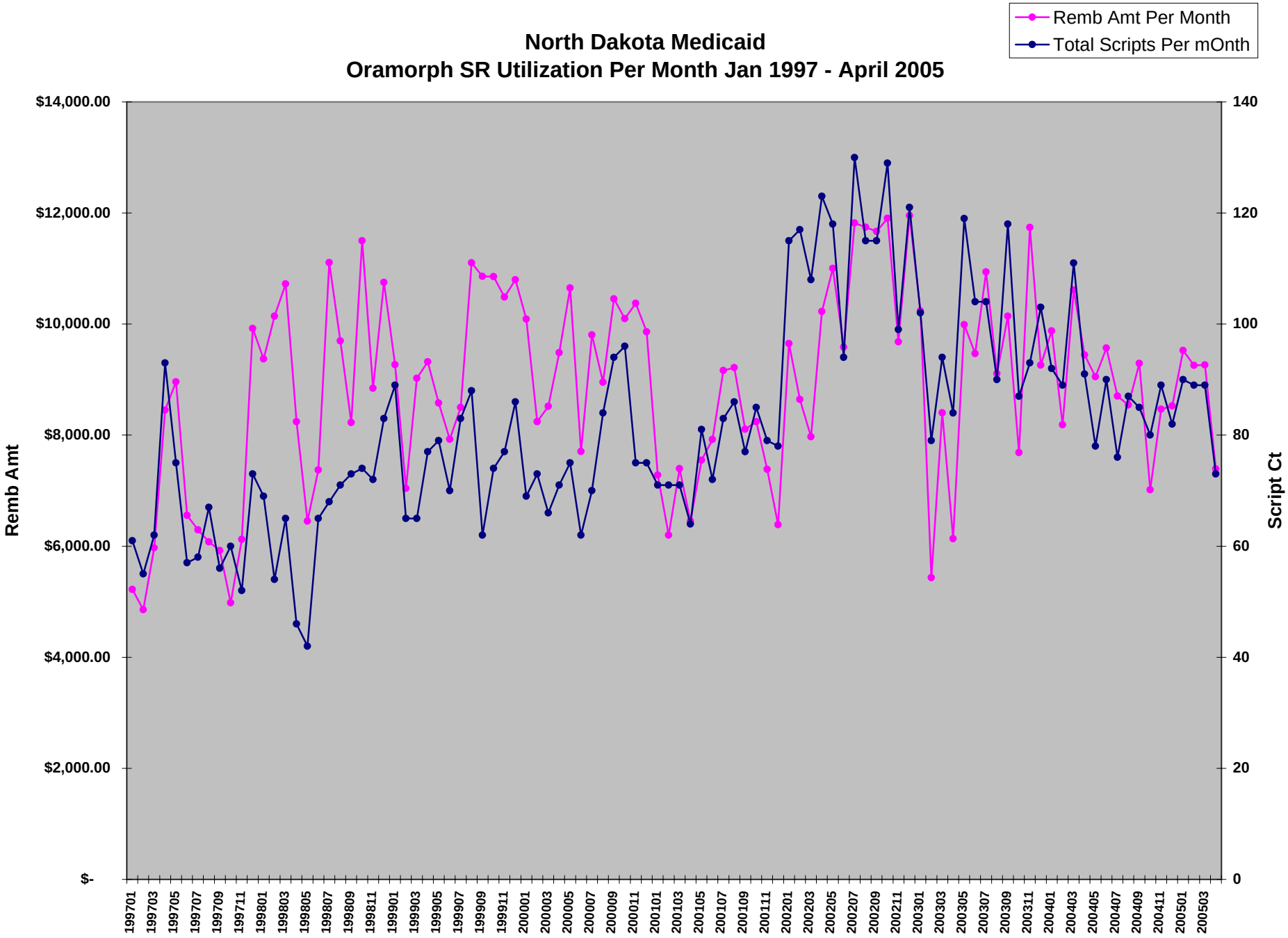
North Dakota Medicaid
Oramorph SR Utilization Per Month Jan 1997 - April 2005
Remb Amt Per Month
Total Scripts Per mOnth
Remb Amt
Script Ct
$14,000.00
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$10,000.00
$8,000.00
$6,000.00
$4,000.00
$2,000.00
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Comparison 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:

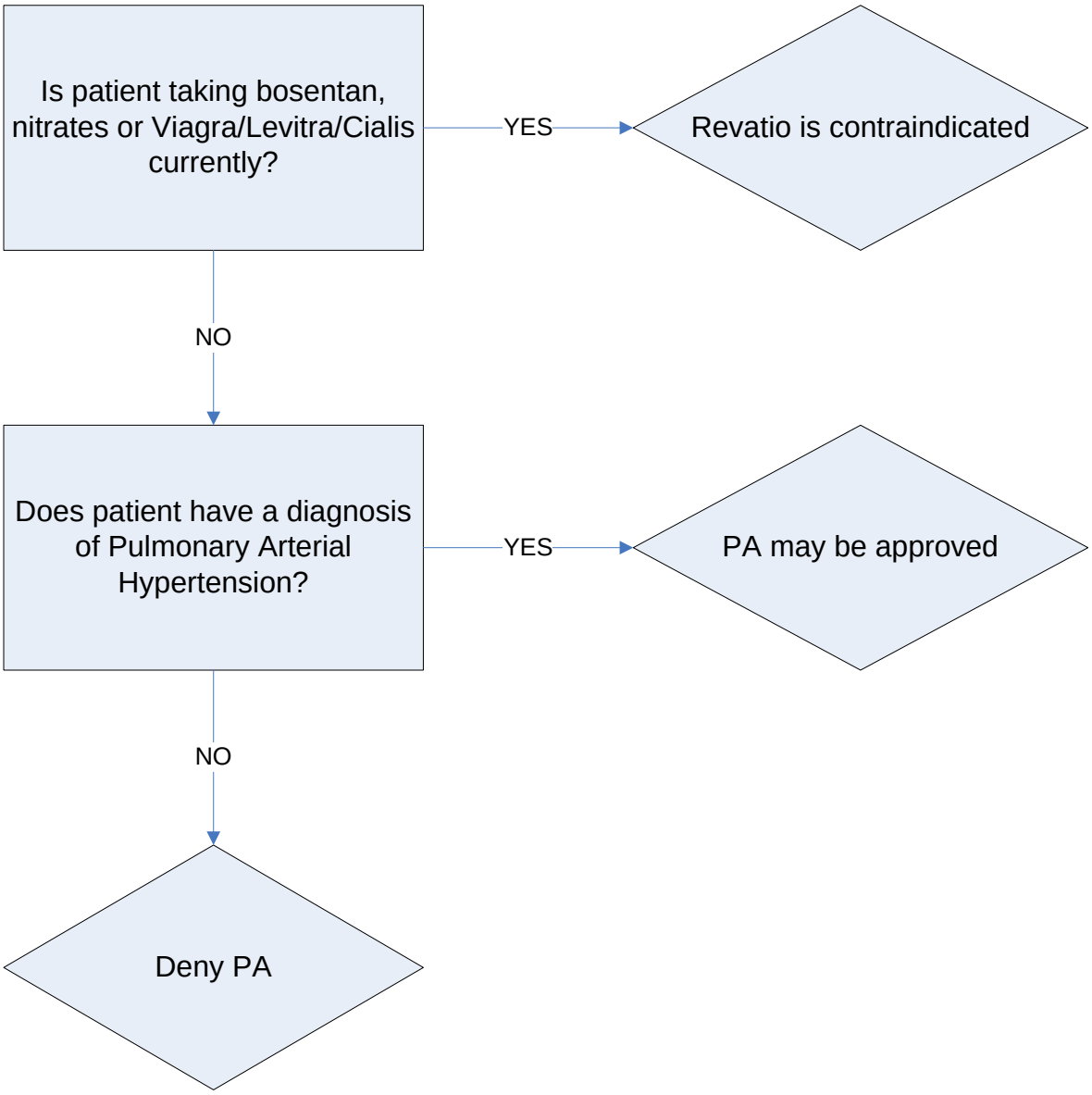
Part II: TO BE COMPLETED BY PHARMACY

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™

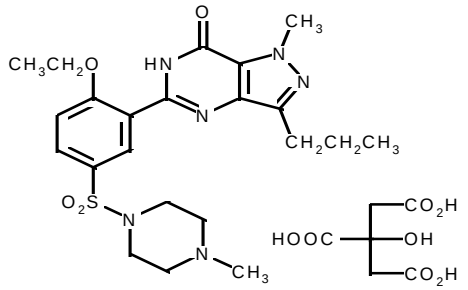
(sildenafil citrate) Tablets, 20 mg

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.

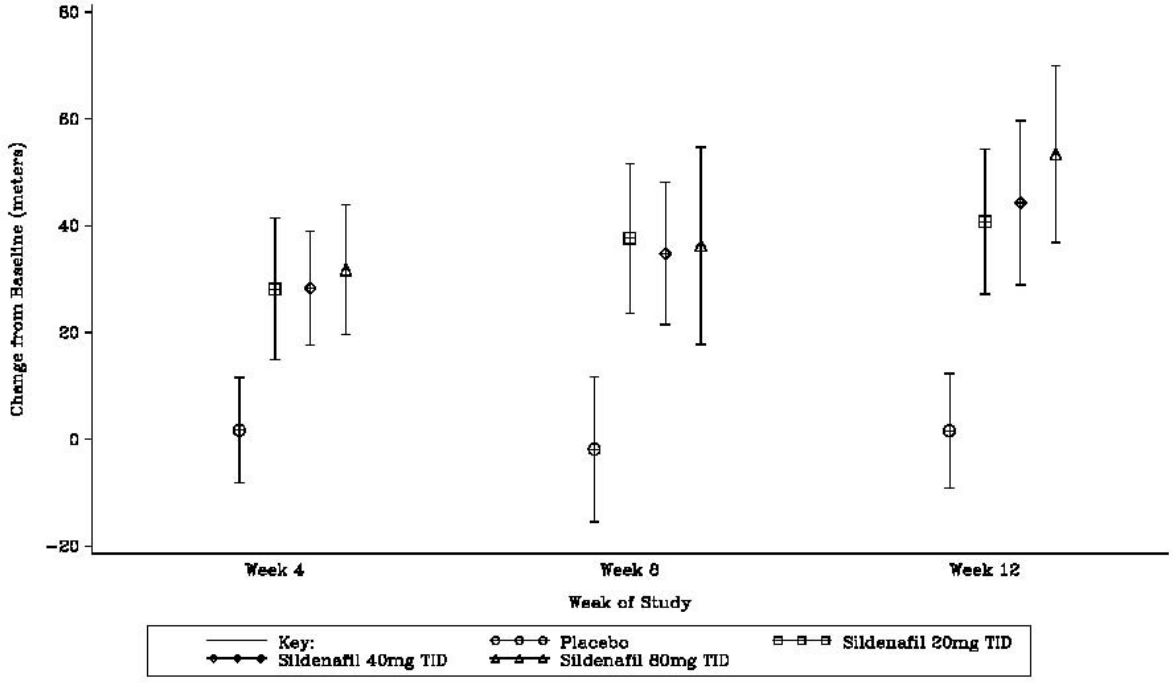
Clinical Studies

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.

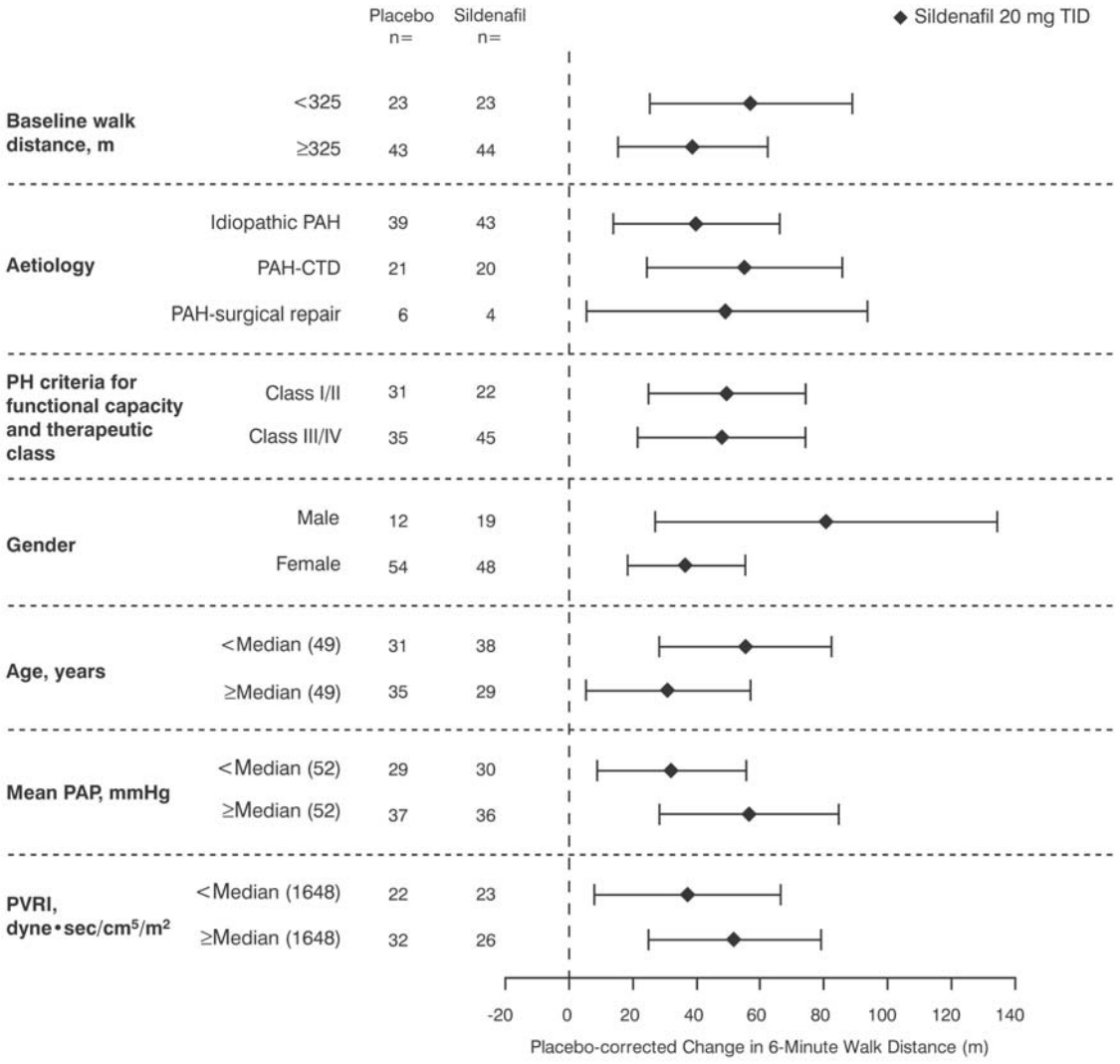
The primary efficacy endpoint was the change from baseline at week 12 in 6-minute walk distance at least 4 hours after the last dose. Placebo-corrected mean increases in walk distance of 45-50 meters were observed with all doses of sildenafil. These increases were highly significantly different from 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.