HEALTH INFORMATION DESIGNS

using medication information cost effectively

May 26, 2005

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

June 6, 2005 at 1:00pm

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

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

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

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

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

1. Administrative items
   Travel vouchers

2. Old Business –

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

3. New Business

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

4. Upcoming meeting agenda — Chairman

5. Adjourn — Chairman

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

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

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

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

Members Absent: Jay Huber, Norman Byers.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

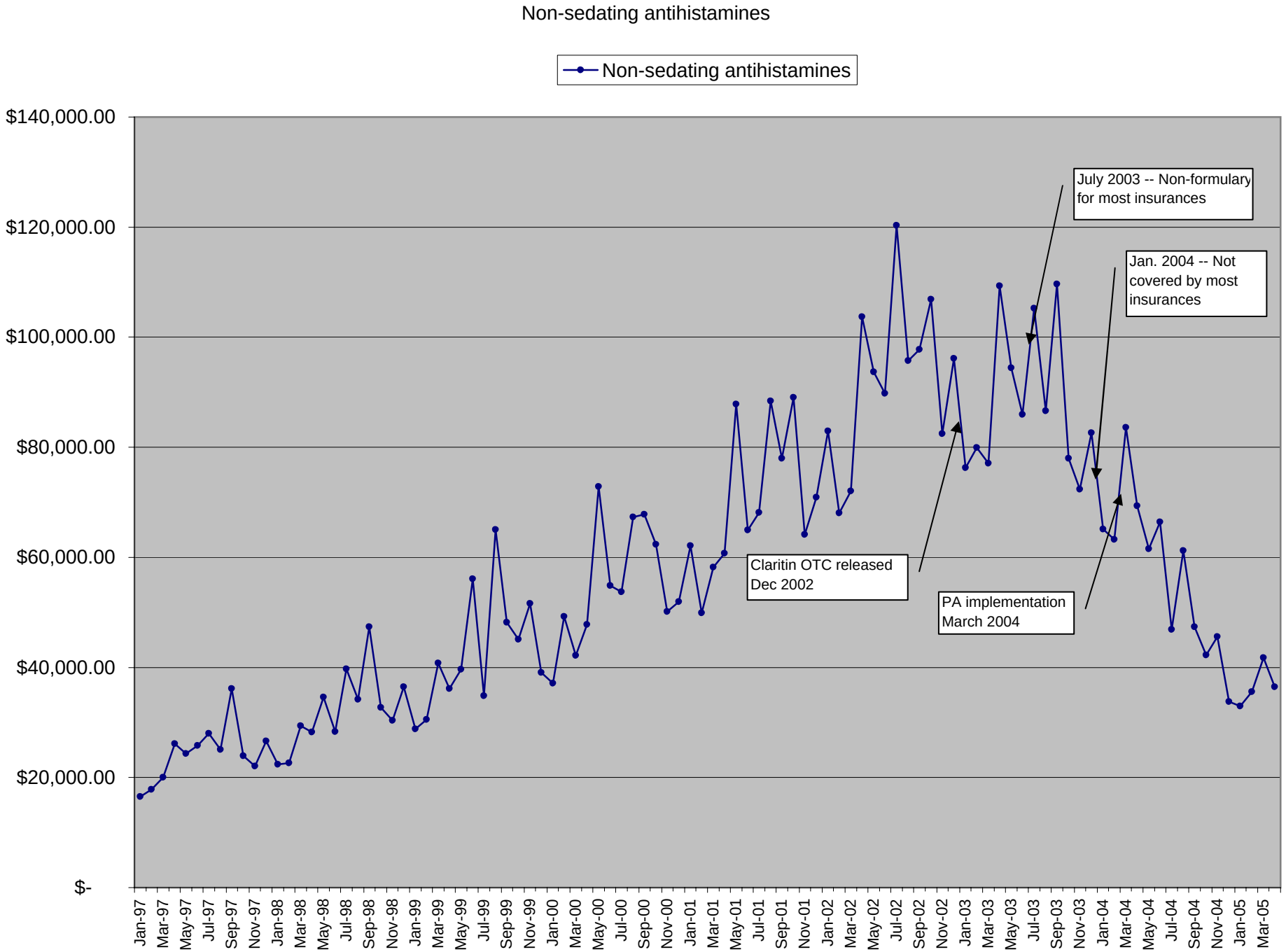
The next meeting was set for June 6, 2005 at 1:00pm at the Heritage Center.

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

Budget Update

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

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


Non-sedating antihistamines
Non-sedating antihistamines
$140,000.00
$120,000.00
$100,000.00
$80,000.00
$60,000.00
$40,000.00
$20,000.00
$-
July 2003 -- Non-formulary for most insurances
Jan. 2004 -- Not covered by most insurances
Claritin OTC released Dec 2002
PA implementation March 2004
Jan-97
Mar-97
May-97
Jul-97
Sep-97
Nov-97
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May-98
Jul-98
Sep-98
Nov-98
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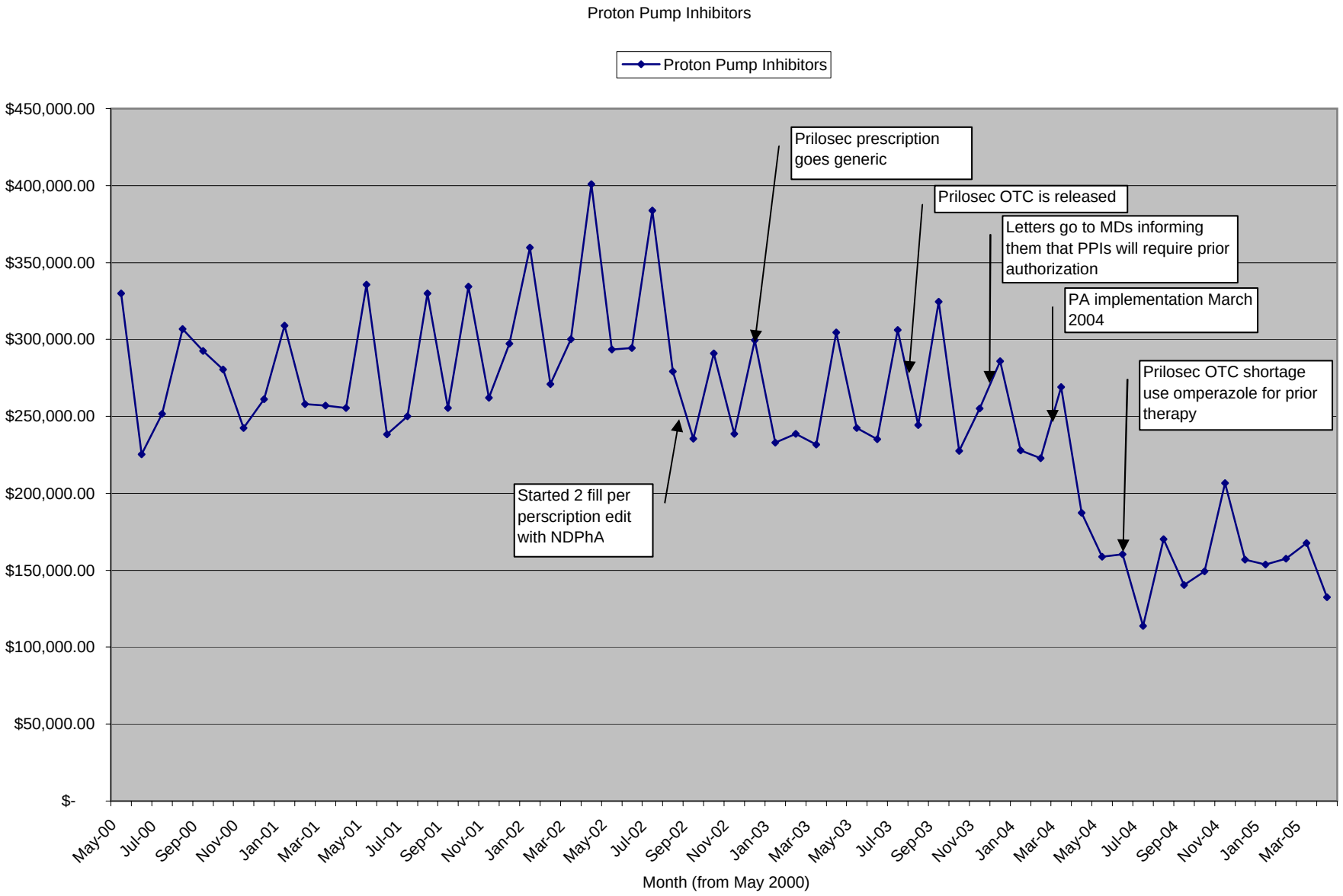
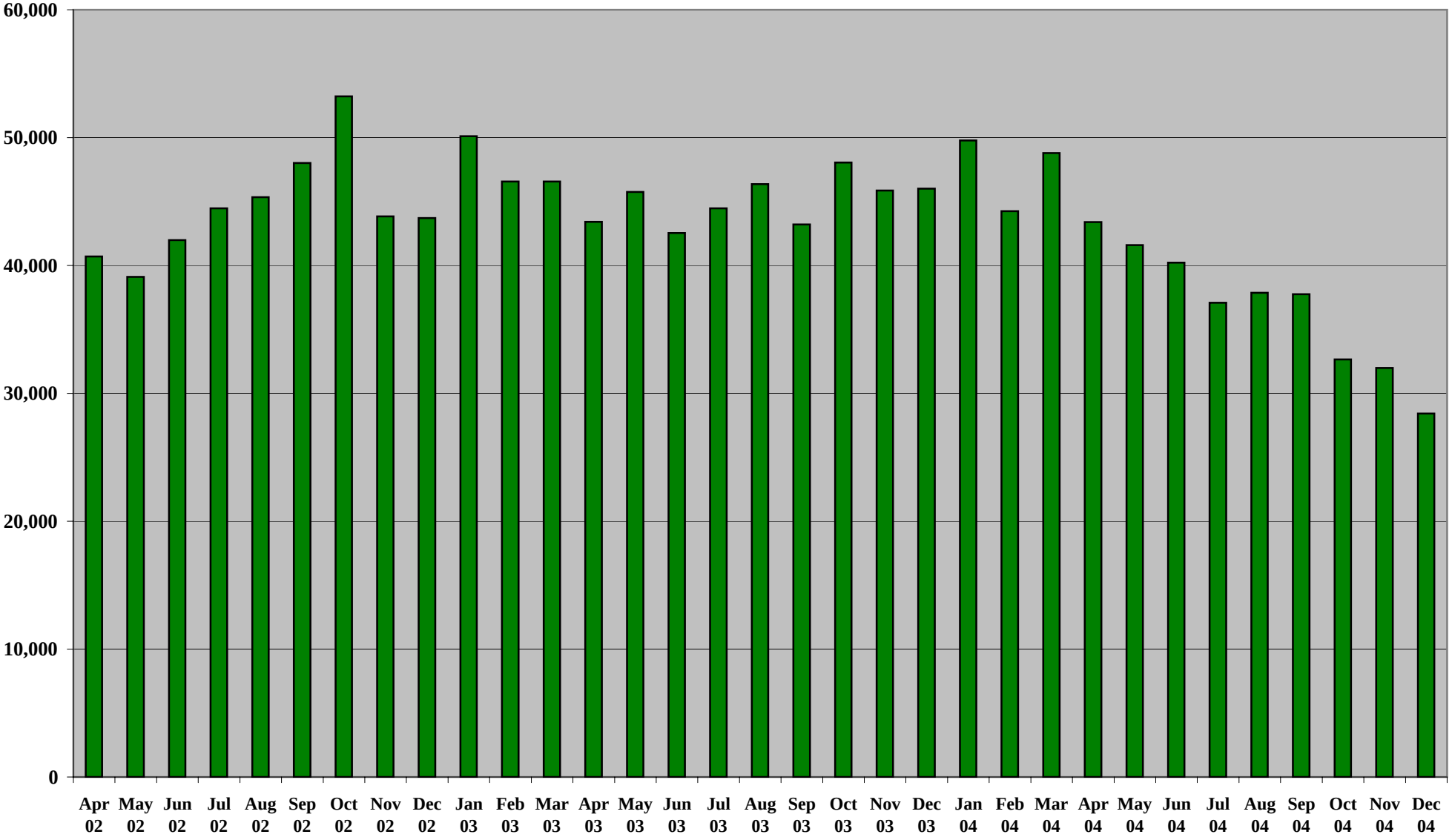

Proton Pump Inhibitors
Proton Pump Inhibitors
$450,000.00
$400,000.00
$350,000.00
$300,000.00
$250,000.00
$200,000.00
$150,000.00
$100,000.00
$50,000.00
$-
Prilosec prescription goes generic
Prilosec OTC is released
Letters go to MDs informing them that PPIs will require prior authorization
PA implementation March 2004
Prilosec OTC shortage use omperazole for prior therapy
Started 2 fill per perscription edit with NDPhA
May-00
Jul-00
Sep-00
Nov-00
Jan-01
Mar-01
May-01
Jul-01
Sep-01
Nov-01
Jan-02
Mar-02
May-02
Jul-02
Sep-02
Nov-02
Jan-03
Mar-03
May-03
Jul-03
Sep-03
Nov-03
Jan-04
Mar-04
May-04
Jul-04
Sep-04
Nov-04
Jan-05
Mar-05
Month (from May 2000)

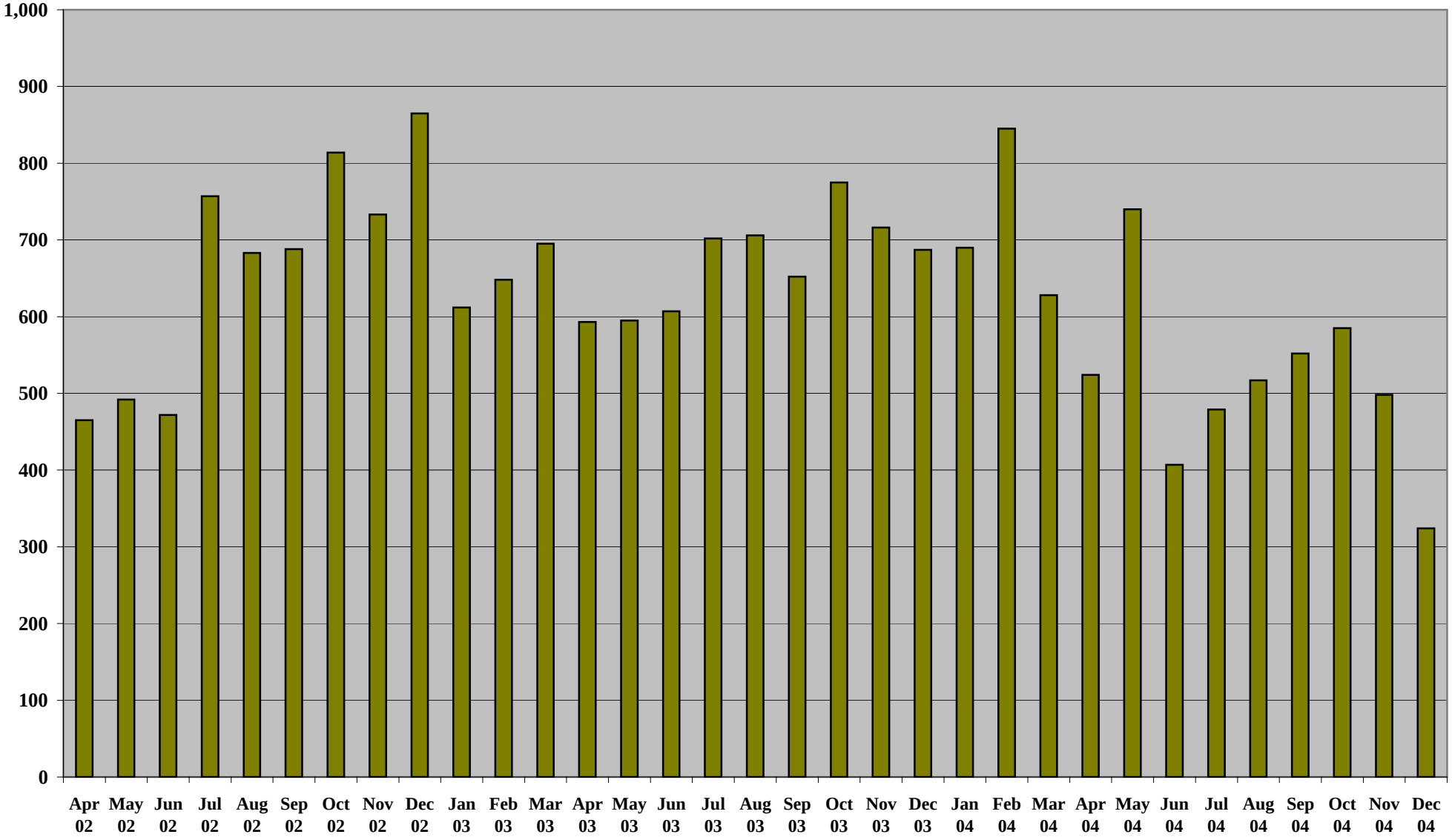
Diagnosis used in determing medical costs
associated with PPI utilization

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

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



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



Health Information Designs, Inc.

North Dakota Medicaid
Recipients Having Diagnosis Of Depression In 2004

5/10/2005

Number Recipients Having Diagnosis of Depression in 2004**	7517

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

Age Breakdown

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

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

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

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

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

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

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

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

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

Part I: TO BE COMPLETED BY PHYSICIAN

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

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

Qualifications for coverage:

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

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

☐ Diagnosis of Urticaria

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

Physician Signature: Date:

Part II: TO BE COMPLETED BY PHARMACY

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

Part III: FOR OFFICIAL USE ONLY

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

Key

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

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

Psych	Cancer or HIV	Already PA'd	Antibiotic or antiviral

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

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

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

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

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

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

HEALTH INFORMATION DESIGNS

using medication information cost effectively

Comparison of Zanaflex Tablets to Capsules

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

Zanaflex tablets are scored so you can give lower doses.

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

Zanaflex capsules do come in 3 strengths

Taken with food does not affect absorption

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

When sprinkled on food absorption is increased over the capsules.

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

ACORDA®
THERAPEUTICS

April 1, 2005

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

Dear Mr. Joyce:

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

Zanaflex® Capsules:

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

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

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

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

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

15 Skyline Drive
Hawthorne, NY 10532
Phone: (914) 347-4300
Fax: (914) 347-4560
Email: acorda@acorda.com
Website: www.acorda.com

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

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

Sincerely,

Mary Lynn Vacchiano

Mary Lynn Vacchiano
National Accounts Manager

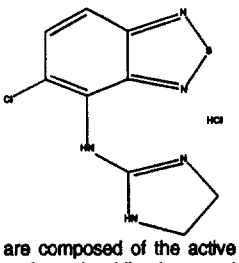
Enclosed:
Package Insert
FDA Approval Letter

Zanaflex®
(tizanidine hydrochloride)

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

DESCRIPTION

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



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

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

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

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

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

PHARMACOKINETICS

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

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

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

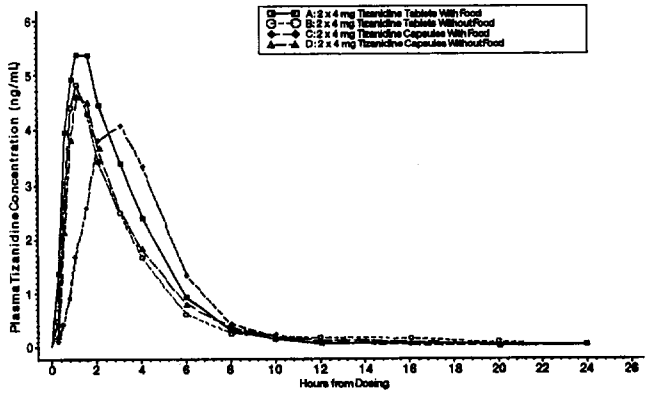
When two 4 mg tablets are administered with food the mean maximal plasma concentration is increased by approximately 30%, and the median time to peak plasma concentration is increased by 25 minutes, to 1 hour and 25 minutes.

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

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

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

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



Zanaflex® Capsules (tizanidine hydrochloride)

SPECIAL POPULATIONS

Age Effects

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

Hepatic Impairment

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

Renal Impairment

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

Gender Effects

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

Race Effects

Pharmacokinetic differences due to race have not been studied.

Drug Interactions

Oral Contraceptives

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

Fluvoxamine

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

CLINICAL STUDIES

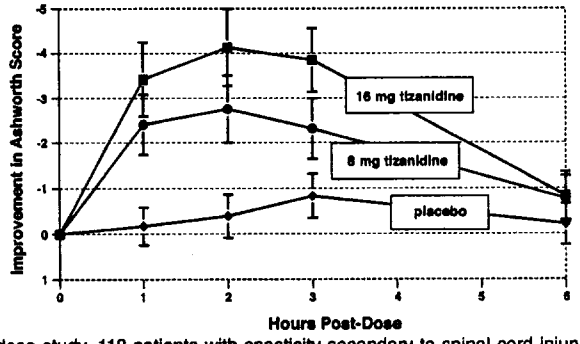
Tizanidine's capacity to reduce increased muscle tone associated with spasticity was demonstrated in two adequate and well controlled studies in patients with multiple sclerosis or spinal cord injury.

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

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

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

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



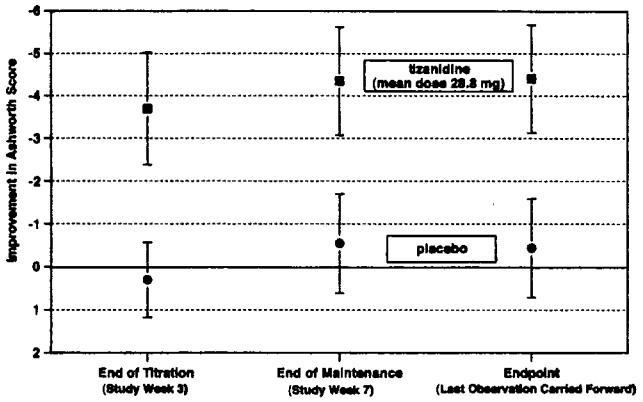
In a multiple dose study, 118 patients with spasticity secondary to spinal cord injury were randomized to either placebo or tizanidine. Steps similar to those taken in the first study were employed to ensure the integrity of blinding.

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

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

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

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



INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

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

WARNINGS

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

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

HYPOTENSION

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

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

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

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

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

RISK OF LIVER INJURY

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

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

SEDATION

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

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

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

HALLUCINOSIS/PSYCHOTIC-LIKE SYMPTOMS

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

PRECAUTIONS

CARDIOVASCULAR

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

OPHTHALMIC

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

USE IN RENALLY IMPAIRED PATIENTS

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

USE IN WOMEN TAKING ORAL CONTRACEPTIVES

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

DISCONTINUING THERAPY

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

INFORMATION FOR PATIENTS

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

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

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

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

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

DRUG INTERACTIONS

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

Acetaminophen

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

Alcohol

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

Fluvoxamine

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

Oral Contraceptives

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

Rofecoxib

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

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

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

EGNANCY

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

LABOR AND DELIVERY

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

NURSING MOTHERS

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

GERIATRIC USE

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

PEDIATRIC USE

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

ADVERSE REACTIONS

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

Zanaflex® Capsules (tizanidine hydrochloride)

COMMON ADVERSE EVENTS LEADING TO DISCONTIUATION

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

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

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

ADVERSE EVENTS REPORTED IN CONTROLLED STUDIES

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

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

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

* (weakness, fatigue, and/or tiredness)

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

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

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

OTHER ADVERSE EVENTS OBSERVED DURING THE EVALUATION OF TIZANIDINE

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DRUG ABUSE AND DEPENDENCE

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

OVERDOSAGE

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

Zanaflex® Capsules (tizanidine hydrochloride)

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

DOSAGE AND ADMINISTRATION

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

HOW SUPPLIED

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

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

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

AcordaZanaflexTab001 Rev. 03-13-05

ACØRDA®
THERAPEUTICS

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-447

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

Dear Dr. Scaife:

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

We acknowledge receipt of your submissions dated the following:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure