Drug Utilization Review Board

Oklahoma Health Care Authority

4545 N. Lincoln Suite 124

Oklahoma City, Oklahoma 73105

OHCA Board Room

April 12, 2005 @ 6:00 p.m.

THE UNIVERSITY OF OKLAHOMA

THE UNIVERSITY OF OKLAHOMA

MEMORANDUM

TO: Drug Utilization Review Board Members

FROM: Ron Graham, D.Ph.

SUBJECT: **Packet Contents for Board Meeting – April 12, 2005**

DATE: April 6, 2005

NOTE: **THE DUR BOARD WILL MEET AT 6:00 P.M.**

Enclosed are the following items related to the April meeting. Material is arranged in order of the Agenda.

Call to Order

Public Comment Forum

Action Item – Approval of DUR Board Meeting Minutes – **See Appendix A.**

Update on DUR/MCAU Program – **See Appendix B.**

Annual Review of Smoking Cessation Products – **See Appendix C.**

30 Day Notice of Intent to Prior Authorize Antidepressants – **See Appendix D.**

Annual Review of Anti-Ucler Products – **See Appendix E.**

Annual Review of Xolair® – **See Appendix F.**

Review and Discuss Selected Narcotic Drug Utilization – **See Appendix G.**

Review and Discuss IBS Products – **See Appendix H.**

Follow Up on Board Member Questions – **See Appendix I.**

FDA and DEA Updates – **See Appendix J.**

Future Business

Adjournment

Drug Utilization Review Board

(DUR Board)

Meeting – April 12, 2005 @ 6:00p.m.

Oklahoma Health Care Authority
4545 N. Lincoln Suite 124
Oklahoma City, Oklahoma 73105
Oklahoma Health Care Authority Board Room

AGENDA

Discussion and Action On the following Items:

Items to be presented by Dr. Whitsett, Chairman:

1. **Call To Order**
   A. Roll Call – Dr. Graham

Items to be presented by Dr. Whitsett, Chairman:

2. **Public Comment Forum**
   A. Acknowledgment of Speakers and Agenda Item

Items to be presented by Dr. Whitsett, Chairman:

3. **Action Item - Approval of DUR Board Meeting Minutes – See Appendix A.**
   A. March 08, 2005 DUR Minutes – Vote

Items to be presented by Dr. Flannigan, Dr. Whitsett, Chairman:

4. **Update on DUR/MCAU Program – See Appendix B.**
   A. Retrospective Drug Utilization Review Report for December 2004 and January 2005
   B. Medication Coverage Activity Audit for March 2005
   C. Help Desk Activity Audit for March 2005
   D. Pharmacotherapy Management Program – Quarterly Report

Items to be presented by Dr. Gorman, Dr. Whitsett, Chairman:

5. **Annual Review of Smoking Cessation Products – See Appendix C.**
   A. Overview of Oklahoma Tobacco Helpline - Linda Wright-Eakers
   B. Current Prior Authorization Criteria
   C. Utilization Review
   D. COP Recommendations

Items to be presented by Dr. Le, Dr. Chonlahan, Dr. Whitsett, Chairman:

6. **30 Day Notice of Intent to Prior Authorize Antidepressants – See Appendix D.**
   A. Available Product Information
   B. COP Recommendations

Items to be presented by Dr. Chonlahan, Dr. Whitsett, Chairman:

7. **Annual Review of Anti-Ulcer Products – See Appendix E.**
   A. Current Prior Authorization Criteria
   B. Utilization Review
   C. COP Recommendations

Items to be presented by Dr. Flannigan, Dr. Whitsett, Chairman:

8. Annual Review of Xolair® – See Appendix F.

A. Current Prior Authorization Criteria
B. Utilization Review
C. COP Recommendations

Items to be presented by Dr. McIlvain, Dr. Whitsett, Chairman:

9. Review and Discuss Selected Narcotic Drug Utilization – See Appendix G.

A. Selected Narcotic Reviews
B. Utilization Review
C. Recommendation Summary
D. New Product Review

Items to be presented by Dr. Browning, Dr. Whitsett, Chairman:

10. Review and Discuss IBS Products – See Appendix H.

A. Disease State
B. Product Review
C. COP Recommendations

Items to be presented by Dr. Gorman, Dr. Flannigan, Dr. Whitsett, Chairman:

11. Follow Up on Board Member Questions – See Appendix I.

A. Diabetes and Hypertension
B. Traditional NSAID Usage
C. NSAID Survey Results

12. FDA and DEA Updates – See Appendix J.

13. Future Business

A. Antihyperlipidemic Review
B. Antifungal Review
C. Estrogen Replacement Products Review
D. Neurontin™ Follow-Up Review
E. Review of Elidel® and Protopic®
F. Renal Product Review
G. New Product Reviews
-Symlin®
-Niravam®

14. Adjournment

APPENDIX A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES of MEETING of MARCH 08, 2005

BOARD MEMBERS:	PRESENT	ABSENT
Brent Bell, D.O., D.Ph.		X
Dorothy Gourley, D.Ph.	X	
Cathy Hollen, D.Ph.	X	
Dan McNeill, Ph.D., PA-C	X	
Cliff Meece, D.Ph.	X	
Dick Robinson, D.Ph., Vice-Chair	X	
James M. Swaim, D.Ph.	X	
Thomas Whitsett, M.D., Chair	X	

COLLEGE of PHARMACY STAFF:	PRESENT	ABSENT
Leslie Browning, D.Ph., PA Coordinator		X
Metha Chonlahan, D.Ph., Clinical Pharmacist	X	
Karen Egesdal, D.Ph., SMAC/ProDUR Coord., OHCA Liaison	X	
Kelly Flannigan, Pharm.D., Operations Manager	X	
Shellie Gorman, Pharm.D., DUR Manager	X	
Ronald Graham, D.Ph., Pharmacy Director	X	
Chris Kim Le, Pharm.D., Clinical Pharmacist	X	
Ann McIlvain, Pharm.D.; Clinical Coordinator	X	
Carol Moore, Pharm.D.; Clinical Pharmacist	X	
Neeraj Patel, Pharm.D.; Clinical Pharmacist	X	
Lester A. Reinke, Ph.D.		X
Visiting Pharmacy Student: Jodi Sparkman	X	

OKLAHOMA HEALTH CARE AUTHORITY STAFF:	PRESENT	ABSENT
Alex Easton, M.B.A.; Pharmacy Operations Manager	X	
Mike Fogarty, C.E.O		X
Lynn Mitchell, M.D., M.P.H, Medical Director		X
Nancy Nesser, D.Ph., J.D.; Pharmacy Director	X	
Howard Pallotta, J.D., Legal		X
Lynn Rambo-Jones, J.D., Legal	X	
Rodney Ramsey; Pharmacy Claims Specialist		X

OTHERS PRESENT:

Mark DeClerk, Lilly	Brian Maves, Pfizer	Jonathan Klock, GSK
Richard Ponder, Johnson & Johnson	Jill Miller, TAP	Evie Knisely, Novartis
Toby Thompson, Pfizer	Charlene Kaiser, Wyeth	Jim Dunlap, Lilly
John Rolls, Ortho-McNeil	Toby Thompson, Pfizer	A. (illegible) M.D.

PRESENT FOR PUBLIC COMMENT:
Evie Knisely, Pharm.D.; Item No. 7

AGENDA ITEM NO. 1: CALL TO ORDER

1A: Roll Call

Dr. Whitsett called the meeting to order. Roll call by Dr. Graham. There was a quorum.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 2: PUBLIC COMMENT FORUM

2A: Acknowledgement of Speakers and Agenda Item

Dr. Whitsett acknowledged speaker for Public Comment.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 3: NEW LEGISLATURE UPDATE & BUDGET ISSUES

Nico Gomez was unavailable, and sent a message via Dr. Nesser that there was no update.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 4: APPROVAL OF DUR BOARD MINUTES

4A: January 11, 2005 DUR Minutes

Dr. Meece moved to approve minutes; second by Dr. Robinson.

ACTION: MOTION CARRIED.

Dr. Gourley moved to approve minutes; second by Dr. McNeill.

4B: February 8, 2005, 2005 DUR Minutes

ACTION: MOTION CARRIED.

AGENDA ITEM NO. 5: UPDATE ON DUR/MCAU PROGRAM

5A: Retrospective Drug Utilization Review Report: November 2004

5B: Medication Coverage Activity Report: February 2005

5C: Help Desk Activity Report: February 2005

Material included in agenda packet; presented by Dr. Flannigan.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 6: VOTE TO PRIOR AUTHORIZE LUNESTA™

Materials included in agenda packet; presented by Dr. McIlvain. Dr. Swaim asked if clients with prior authorizations for Ambien would be required to get a new PA for Lunesta™. Dr. McNeill asked if the prices were comparable for the three products. Dr. McIlvain indicated the Lunesta™ is slightly higher than the other two.

Dr. Meece moved to prior authorize; second by Dr. Robinson.

ACTION: MOTION CARRIED.

AGENDA ITEM NO. 7: VOTE TO PRIOR AUTHORIZE BLADDER CONTROL DRUGS

For Public Comment, Evie Knisley: *(Evie Knisley made no public statement, but was available to answer questions.)*

Dr. Whitsett: *Do we know about Enablex® how it compared in clinical trial with the listed tier-2 drugs?*

Dr. Knisley: *There was one head-to-head study with Detrol® IR so the immediate release Detrol® 4 mg and Enablex® showed numerical superiority, but not statistical superiority, so numerically better, but not statistically better…The advantages are more on the safety side as opposed to the efficacy side.*

Materials included in agenda packet; presented by Dr. Moore. Dr. McNeill asked if a trial of a single dose of a tier-1 product would be acceptable as a trial. Dr. Hollen discussed the option of excluding clients 65 years of age and over. Dr. Whitsett commented that the proposed letter to the nursing home providers seemed appropriate.

Dr. Meece moved to prior authorize; second by Dr. Gourley.

ACTION: MOTION CARRIED.

AGENDA ITEM No. 8: **VOTE TO APPROVE NEW QUANTITY LIMITS**

Materials included in agenda packet; presented by Dr. Egesdal. Dr McNeill asked about the quantity on Lindane® and if it was used to treat the whole family or individual. Dr. Egesdal said 60 ml was for one person. Dr. Egesdal said she had seen claims for up to 480 ml and was concerned about seeing such a large quantity go out. Dr. McNeill felt that 60 ml was a large quantity for a child and wanted to know if 30 ml should be the quantity limit as most of the clients using the product were children. Dr. Swaim said that the product came packaged as 60 ml bottles. Dr. McNeill wondered about the cost of permethrin and felt the possibility of paying for over-the-counter products should be explored for this category.
Dr. McNeill moved to accept; second by Dr. Robinson.
ACTION: MOTION CARRIED.

AGENDA ITEM NO. 9: **ANTIDEPRESSANT PRODUCT BASED PRIOR AUTHORIZATION PROPOSAL**

Materials included in agenda packet; presented by Drs. Le, Chonlahan and Gorman. Dr Whitsett asked about general recommendations regarding how long one should stay on antidepressant therapy. Dr. Le stated the FDA recommends reevaluating in 1 to 2 weeks then again about 4 weeks later with a six month maintenance phase. Changes can then be made according to the client's history. Total time should be six months to a year. Dr. Whitsett feels many clients are reluctant to stop an antidepressant and wonders if there should any educational information sent to our providers. Dr. Le said the recommendation is once a client has returned to their pre-depressed function they are ready to be taken off of the antidepressant. Often the medication is prescribed without a true depression diagnosis. Dr. Whitsett wonders how the clients are doing in terms of duration of therapy. Dr. Whitsett asked about the status of the smoking cessation product. Dr. Le stated that bupropion SR is recommended to be tier-2. Dr. McNeill asked about the Celexa® or Lexapro® liquids and any issues regarding disabilities or inabilities to swallow tablets. Dr. Gorman indicated that the clients who were on the liquids prior to the initiation of the SSRI PBPA were subject to grandfathering. Dr. Gourley pointed out the inability to swallow issue would fall under criteria two for the new Antidepressant category.
ACTION: NONE REQUIRED.

AGENDA ITEM NO. 10: **REVIEW OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) & CARDIOVASCULAR/THROMBOTIC EVENTS**

Materials included in agenda packet; presented by Dr. Gorman. Dr. Whitsett indicated that the clients excluded for pre-existing cardiovascular events is also an important population. Dr. Graham asked about the effects the dosing restrictions may have had on the study population. Dr. Whitsett asked about overall usage since Vioxx® was withdrawn. Dr. Gorman stated that the total usage of Cox-2 Inhibitors have decreased 31 %. Dr. Whitsett asked about how the utilization for traditional NSAIDs may have changed. Dr. Graham discussed the results of the latest mail-out survey. Dr. Whitsett wondered if other states with larger numbers are looking at this issue. Dr. Hollen requested a follow-up on one of the survey responses to see if there was an educational problem.
ACTION: NONE REQUIRED.

AGENDA ITEM NO. 11: **ANNUAL REVIEW OF ANTIHISTAMINES**

Materials included in agenda packet; presented by Dr. Patel.
ACTION: NONE REQUIRED.

AGENDA ITEM NO. 12: **FDA AND DEA UPDATES**

Materials included in agenda packet; presented by Dr. Graham.
ACTION: NONE REQUIRED.

AGENDA ITEM No. 13: **FUTURE BUSINESS**

13A: Prior Authorization Annual Reviews
13B: Antihyperlipidemic Review
13C: Antifungal Review
13D: Estrogen Replacement Products Review
13E: Narcotics Follow-Up Review
13F: Neurontin™ Follow-Up Review
13G: New Product Reviews

Materials included in agenda packet; submitted by Dr. Graham.
ACTION: NONE REQUIRED.

AGENDA ITEM No. 14: **ADJOURNMENT**

The meeting was declared adjourned.

APPENDIX B

Retrospective Drug Utilization Review Report

Claims Reviewed for December 2004

Module	Drug Interaction	Duplication of Therapy	Drug-Disease Precautions	Dosing & Duration
Total # of messages returned by system when no limits were applied	105,388	88,289	846,506	50,168
Limits which were applied	Established, major, females 70-75 yrs old	Antifungals	Contraindicated, females aged 70 & up with heart failure	Antifungals, high dose, females
Total # of messages after limits were applied	116	66	439	40
Total # of clients reviewed after limits were applied	116	65	419	40

LETTERS			
Prescribers		**Pharmacies**	
Sent	**Responded**	**Sent**	**Responded**
107	50	31	17

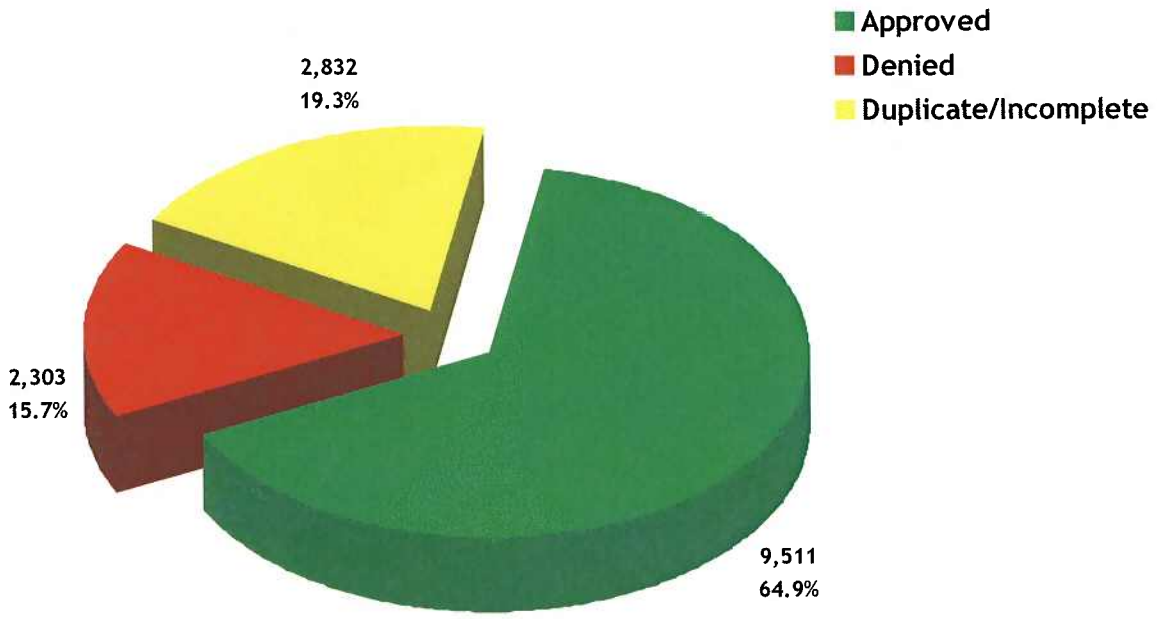
Retrospective Drug Utilization Review Report

Claims Reviewed for January 2005

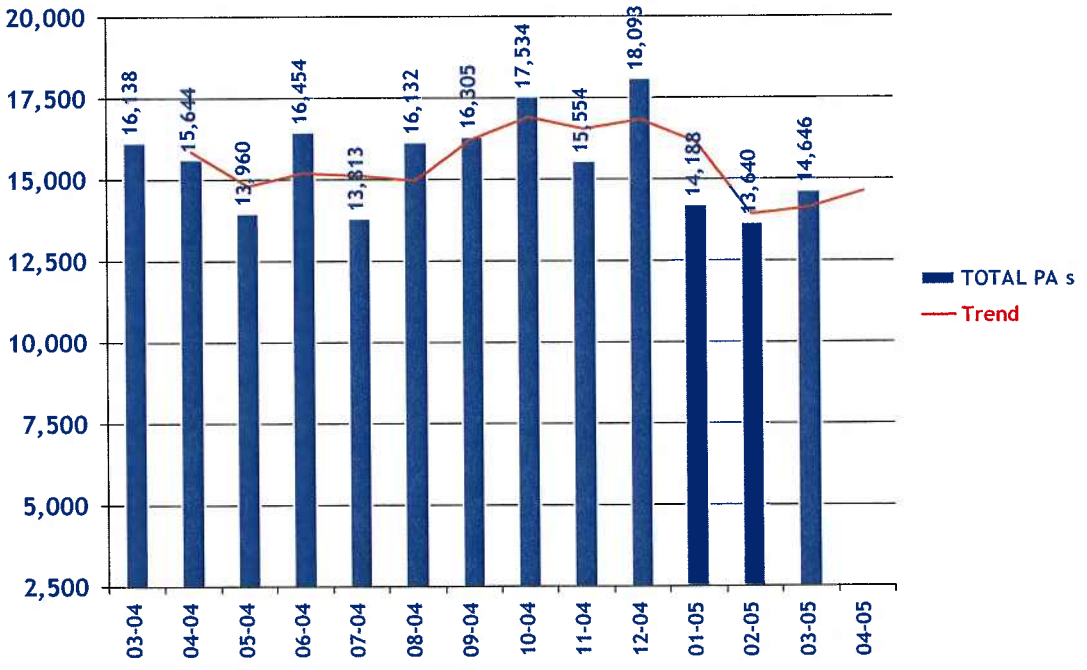
Module	Drug Interaction	Duplication of Therapy	Drug-Disease Precautions	Dosing & Duration
Total # of messages returned by system when no limits were applied	106,566	103,901	850,012	52,148
Limits which were applied	Established, major, females 50-69 yrs old	ACEI's, females 50-69 yrs old	Contraindicated, females aged 50-69 yrs, in nursing home, with heart failure	Thiazolidine-diones, high dose, females
Total # of messages after limits were applied	250	65	110	53
Total # of clients reviewed after limits were applied	250	65	103	53

LETTERS			
Prescribers		**Pharmacies**	
Sent	**Responded**	**Sent**	**Responded**
82	16	15	11

PRIOR AUTHORIZATION ACTIVITY REPORT
March 2005



PRIOR AUTHORIZATION REPORT
March 2004 - March 2005



Activity Audit for

March 01 2005 Through March 31 2005

Date	Antiulcers app.	Antiulcers den.	Anxiolytic/ Hypnotics app.	Anxiolytic/ Hypnotics den.	Antihistamine app.	Antihistamine den.	Growth Hormones app.	Growth Hormones den.	Stimulant app.	Stimulant den.	Nsaids app.	Nsaids den.	ACE Inhibitors app.	ACE Inhibitors den.	HTN Combos app.	HTN Combos den.	Calcium Channel Blockers app.	Calcium Channel Blockers den.	Plavix app.	Plavix den.	ARB app.	ARB den.	Anti-depressants app.	Anti-depressants den.	Daily Total
App.	14		4197		1175		31		1134		129		71		11		129		888		29		168		
Den		14		425		542		4		283		167		78		3		195		127		4		70	
Average Length of Approvals in Days	9		101		98		162		219		317		197		200		325		328		316		129		

Changes to existing PA's	776
Total (Previous Year)	16138

*** Denial Codes**

762 = Lack of clinical information	9.90%
763 = Medication not eligible	2.30%
764 = Existing PA	7.16%
772 = Not qualified for requested Tier	5.78%
773 = Requested override not approved	11.20%

SUPER PA's

Early Refill Attempts	61359
Dosing Change	682
Lost/Broken Rx	137
Stolen	29
Other	93
Wrong D.S. on Previous Rx	99
Quantity vs. Days Supply	352
Brand	250
-- Approved	120
-- Denied	76

Monthly Totals

	Number	Percent of Total
Approved	9440	64.45%
Additional PA's	64	0.44%
Emergency PA's	7	0.05%
Duplicates	660	4.51%
Incompletes	2172	14.83%
Denied *	2303	15.72%
Total	14646	100.00%

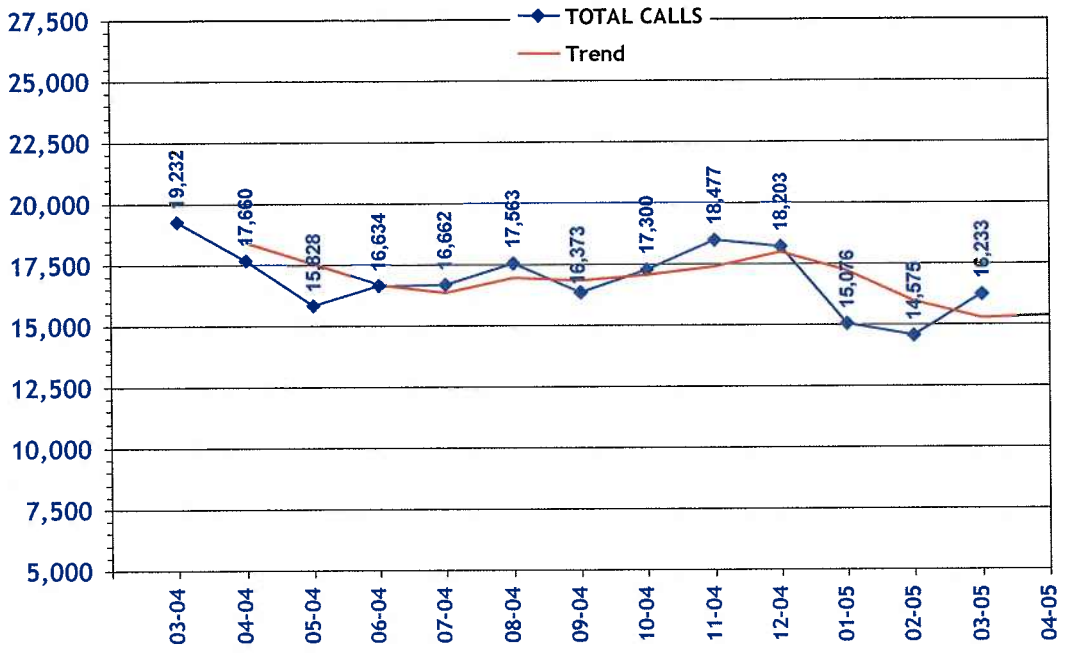
Daily Average of 542.44 for 27 Days

Changes to existing PA's: Backdates, changing units, end dates, etc.

Additional PA's: Done by the help desk (doctor letter responses, PA ran for the wrong person)

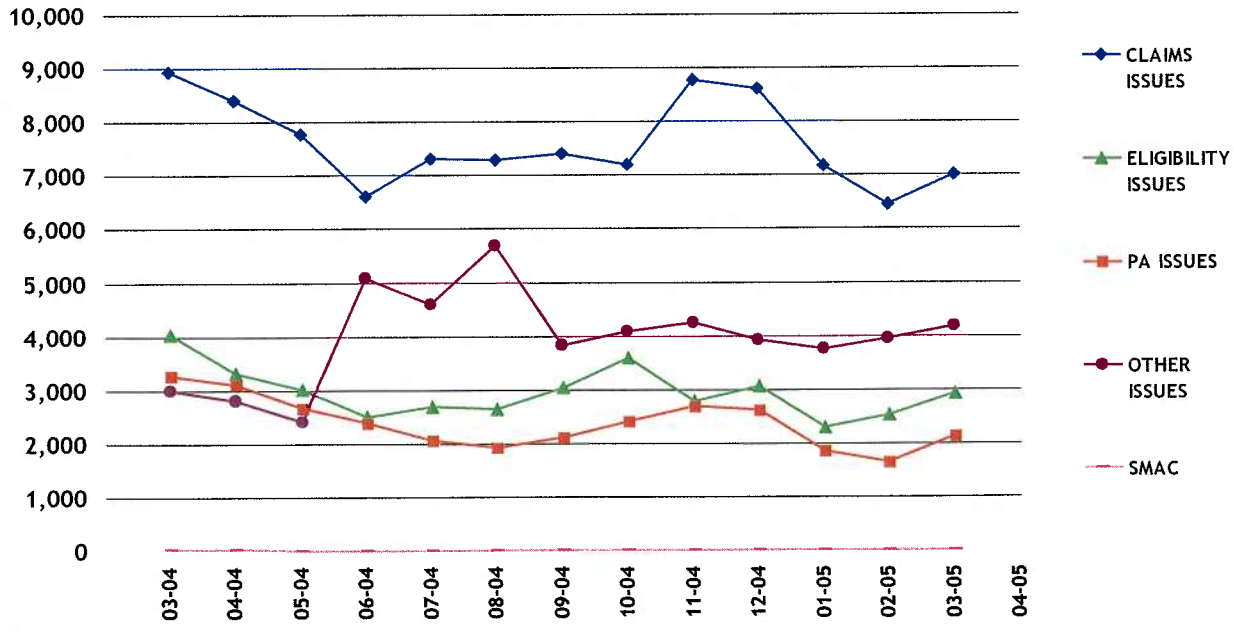
Incompletes: Missing necessary information (NDC, SIG, Diagnosis, etc.)

CALL VOLUME MONTHLY REPORT
March 2004 - March 2005



PHARMACY Management Consultants

CALL VOLUME ISSUES
March 2004 - March 2005



PHARMACY Management Consultants

Pharmacotherapy Management Program
Quarterly Report
July 2004 – March 2005
Oklahoma Medicaid

	CLIENT PROFILES REVIEWED			PRIOR AUTHORIZATIONS				COMMUNICATIONS	
Month	New Clients	Established Clients	Incomplete Information	Total	Approved	Denied	Incomplete	Letters	Calls
July 2004	80	61	26	478	290	18	170	236	32
Aug 2004	102	77	27	681	381	24	276	348	100
Sept 2004	114	46	23	714	401	44	269	234	104
Oct 2004	99	35	20	711	437	55	219	349	73
Nov 2004	87	17	15	571	342	43	186	221	66
Dec 2004	94	49	13	638	382	61	205	348	89
Jan 2005	106	37	15	727	453	60	214	344	83
Feb 2005	73	36	14	507	332	33	142	227	55
March 2005	85	73	15	729	464	43	222	345	86
April 2005	0	0	0	0	0	0	0	0	0
May 2005	0	0	0	0	0	0	0	0	0
June 2005	0	0	0	0	0	0	0	0	0
Totals	840	431	168	5,756	3,482	381	1,903	2,652	688
1st Quarter	296	184	76	1,873	1,072	86	715	818	236
2nd Quarter	280	101	48	1,920	1,161	159	610	918	228
3rd Quarter	264	146	44	1,963	1,249	136	578	916	224
4th Quarter	0	0	0	0	0	0	0	0	0
Totals	840	431	168	5,756	3,482	381	1,903	2,652	688

APPENDIX C

Prior Authorization Annual Review - Fiscal Year 2004
Smoking Cessation Products
Oklahoma Medicaid
March 2005

Definition of Prior Authorization Category for FY '04

- All smoking cessation products are covered, including OTC products.
- All smoking cessation products are covered without prior authorization for the first 90 days (claims should run without a PA).
- After 90 days of use in a 365 day period, further use of smoking cessation products requires prior authorization.
- Criterion for approval of PA after the first 90 days of use: petition must state that the patient is enrolled in a smoking cessation behavior modification program.
- Length of approval: PA can be approved for another 90 days.
- After the patient has had 180 days of treatment in a 365 day period, the patient must wait another 180 days before smoking cessation treatment will be covered again.
- Smoking cessation products do not count against the monthly prescription limit.

Utilization

For the period of July 2003 through June 2004, a total of 732 clients received smoking cessation products through the Medicaid fee-for-service program.

Product (unit)	# of Claims	Total Units	Total Days	Units/ Day	Total Cost	Total Clients	Per Diem
Zyban (ea)	209	12,686	6,783	1.87	$24,129.78	165	$3.56
Spray (ml)	28	1,325	591	2.24	$4,900.24	15	$8.29
Inhalers (cart)	271	27,734	4,571	6.07	$23,073.65	162	$5.05
Patches (ea)	749	16,774	16,846	1.00	$64,307.65	540	$3.82
Gum (ea)	15	2,340	267	8.76	$924.87	12	$3.46
Lozenges (ea)	25	2,532	281	9.01	$1,282.96	9	$4.56
Total	**1,297**	**63,391**	**29,339**	**2.16**	**$118,619.15**	**732***	**$4.04**

*Total unduplicated clients for FY04

Total Cost FY '04	**$118,619.15**
Total Cost FY '03	*$18,142.80*
Total Claims FY '04	**1,297**
Total Claims FY '03	*187*
Total Clients FY '04	**732**
Total Clients FY '03	*129*
Per Diem FY '04	**$4.04**
Per Diem FY '03	*$3.80*

Total petitions submitted in for this category during specified time period: 215

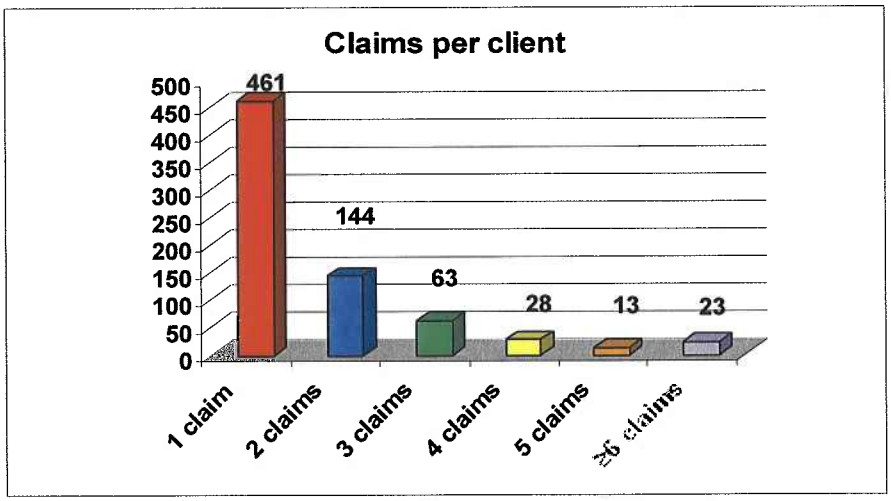
Approved *161*
Denied 34
Incomplete 20

Demographics

Claims were reviewed to determine the age/gender of the clients.

Age	Female	Male	Totals
0 to 9	0	0	0
10 to 19	18	9	27
20 to 34	79	23	102
35 to 49	169	80	249
50 to 64	162	82	244
65 to 79	37	33	100
80 to 94	7	3	10
95 and Over	0	0	0
Totals	**502**	**230**	**732**

Claims were reviewed to determine the number of claims per client.



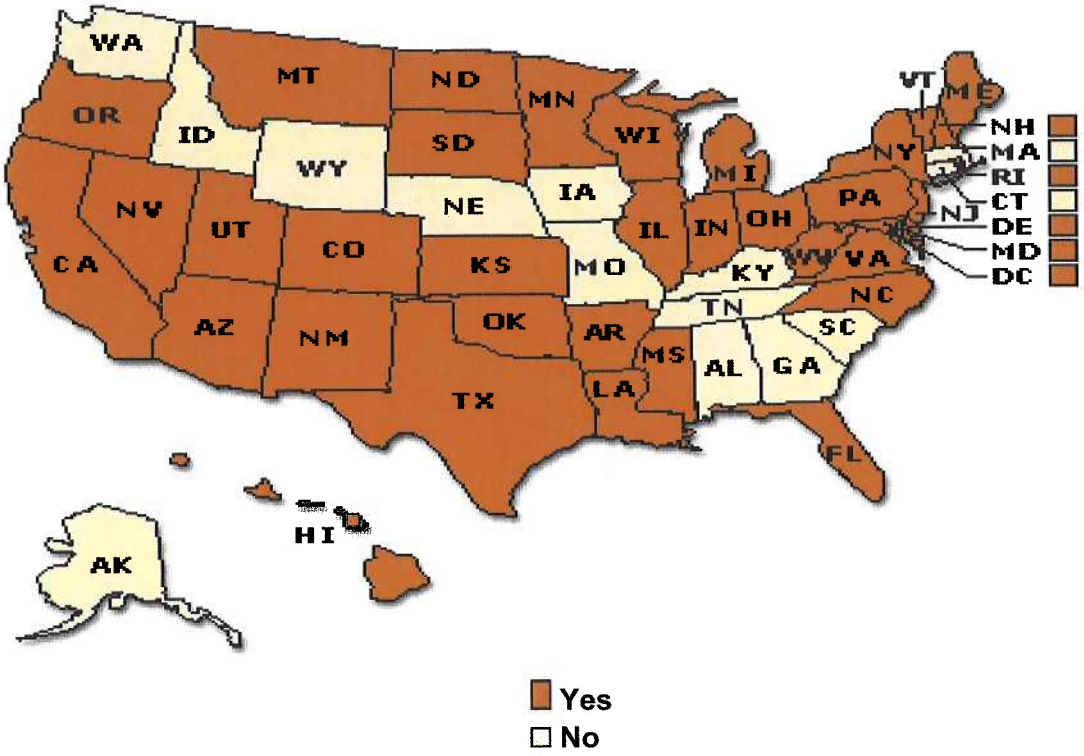
Changes in FY04

Effective February 1, 2004, all smoking cessation products were covered without prior authorization for the first 90 days. After 90 days of use in a 365 day period, further use of smoking cessation products required prior authorization.

Recommendations

The College of Pharmacy recommends no changes at this time.

Coverage Across the Country



Sources: Analysis by the Center for Health and Public Policy Studies, University of California at Berkeley of the State Medicaid Tobacco Dependence Treatment Survey, 2003. Kaiser Family Foundation, statehealthfacts.org

STATE MEDICAID COVERAGE OF TOBACCO DEPENDENCE TREATMENTS - 2003						
NONE	**ZYBAN ONLY**	**MULTIPLE PRODUCTS**	**MULTIPLE PRODUCTS PLUS COUNSELING**	**COUNSELING ONLY**	**PREGNANT WOMEN**	**YOUTH**
AL, AK, CT, GA, ID, IA, KY, MA, MO, NE, SC, TN, WA, WY	AZ, AR, SD	CO, DE, DC, HI, IL, LA, MD, MI, MS, MT, NV, NH, NM, NC, OK, TX, VT, VA	CA, FL, IN, KA, ME, MN, NJ, NY, ND, OH, OR, PA, UT, WV, WI	RI	AZ, AR, CO, IA, KY, MD, MA, MN, MS, NH, RI, UT, VA, WA, WI	CA, KY, MA, MT, NE, NH, VT, VA, WI

Adapted from the Kaiser Family Foundation, statehealthfacts.org.

APPENDIX D

30 Day Notice of Intent to Prior Authorize Antidepressants

Oklahoma Medicaid

March 2005

Review of Dual-Acting Anti-depressants

Indications

All dual acting antidepressants are indicated for MDD. However, some may have other indications or clinical trials demonstrating efficacy in other allied conditions as shown on the following table:

Available Dual Acting Antidepressants and FDA Approved Indications[i]

	MDD	Social Anxiety Disorder	OCD	Generalized Anxiety Disorder	PTSD	Panic Disorder	Smoking Cessation	DPNP*
Venlafaxine	+++	+++	-	+++	+	++	-	-
Duloxetine	+++	-	-	-	-	-	-	+++
Bupropion	+++	-	-	-	-	-	+++	-
Nefazodone	+++	+	-	-	+	+	-	-
Trazodone	+++	-	-	-	-	-	-	-
Mirtazapine	+++	+	-	+	++	+	-	-

+++ FDA approved, ++ Positive placebo-controlled trial(s), + Positive open trial(s) only - No data or mixed findings, *Diabetic peripheral neuropathic pain

Precautions and Common Adverse Effects*

	Contraindications	*Warnings*	*Precautions*
Venlafaxine	MAOI inhibitors; Hypersensitivity	Caution in hypertension; Mania risk in bipolar disorder; Suicidality; Caution seizure disorder	Weight loss; Possible sexual dysfunction; Caution acute narrow-angle glaucoma
Duloxetine	MAOI inhibitors; Hypersensitivity	Increased blood pressure; Mania risk in bipolar disorder; Suicidality; Urinary hesitancy; Caution seizure disorder	Possible sexual dysfunction; Caution hepatic dysfunction and excessive alcohol intake; Caution acute narrow-angle glaucoma
Mirtazapine	MAOI inhibitors; Hypersensitivity	Caution hypotension; Mania risk in bipolar disorder; Suicidality; Caution seizure Disorder	Caution hepatic and renal dysfunction; Agranulocytosis; Solutab contains phenylalanine; Sedation; Weight gain
Bupropion	MAOI inhibitors; Hypersensitivity; Caution of seizure	Caution in hypertension; Suicidality; Mania risk in bipolar disorder	Caution hepatic and renal dysfunction
Nefazodone	MAOI inhibitors; Hypersensitivity	Caution hypotension; Caution of seizures; Arrhythmias; Suicidality	Risk of liver failure; Priapism
Trazodone	MAOI inhibitors; Hypersensitivity	Caution in hypertension or hypotension; Caution of seizures; Syncope; Arrhythmias; Suicidality	Priapism; Sedation

Common Adverse Effects*					
	0 – 5 %	6 – 10 %	11 – 16 %	17 – 23 %	> 24 %
Venlafaxine	blurred vision, hypertension, hypotension, anxiety, parathesia, tremors, pharyngitis, sexual dysfunction	constipation, nervousness, dreams, asthenia, anorexia	dry mouth, sweating, abnormal ejaculation	insomnia, somnolence, dizziness	nausea
Duloxetine	blurred vision, tremors, sexual dysfunction, mild hypertension	dizziness, fatigue, somnolence, diarrhea, anorexia, sweating	constipation, dry mouth, insomnia, asthenia	nausea	
Mirtazapine	confusion, edema, dreams, urinary frequency, aches, tremors, infection	dizziness, asthenia	constipation, weight gain	appetite	dry mouth, somnolence
Bupropion	rash, anxiety, nervousness, somnolence, bad taste, diarrhea, aches, anorexia, parathesia, pharyngitis	constipation, tinnitus, dizziness, tremors, sweating	insomnia, nausea	dry mouth	
Nefazodone	rash, edema, hypotension, tinnitus, concentration, dreams, bad taste, urinary frequency/retention, parathesia, tremors, sexual dysfunction, appetite	blurred vision, confusion, gastric disorder, diarrhea, pharyngitis, infection	constipation, insomnia, asthenia	dizziness, nausea	dry mouth, headache, somnolence
Trazodone	hypertension, syncope, anxiety, concentration, disorientation, bad taste, diarrhea, parathesia, sexual dysfunction, appetite, red eyes, sweating, weight gain	constipation, hypotension, confusion, gastric disorder, insomnia, aches	blurred vision, dry mouth, fatigue, nervousness, nausea	headache	dizziness, drowsiness

*Source: Product Package Inserts ii'iii'iv'v'vi'vii

Recommendations

The college of pharmacy recommends placing the suggested dual-acting anti-depressants on tier-2 pending results of long-term clinical trials assessing the long-term efficacy and safety as compared to the older anti-depressants.

1. Approval of tier-2 after trials of at least two tier-1 anti-depressants with a minimum trial duration of at least 4-6 weeks per tier-1 medication trial. Tier-1 selections from any tier-1 anti-depressant classification.
2. Approval of tier-2 medication if there is a documented adverse effect, drug interaction, or contraindication to two tier-1 classes.
3. Approval of tier-2 medication if there is prior stabilization on the tier-2 medication documented within the last 100 days.
4. Approval of tier-2 medication if there is a unique FDA-approved indication not covered by any tier-1 products.

Antidepressants*	
Tier-1	*Tier-2*
Dual Acting Antidepressants	
Mirtazapine (Remeron®)	Duloxetine (Cymbalta®)
Mirtazapine (Remeron Soltab®)	Venlafaxine (Effexor, Effexor XR®)
Trazodone (Desyrel®)	Bupropion (Wellbutrin XL®)
Bupropion (Wellbutrin, Wellbutrin SR®)	Nefazodone (Serzone®)**
Selective Serotonin Re-Uptake Inhibitors* **	
Fluoxetine (Prozac®)	Fluoxetine (Sarafem®) Fluoxetine Tablets and 40 mg Capsules
Fluvoxamine (Luvox®)	
Paroxetine (Paxil®)	
Paroxetine (Paxil CR®)	
Paroxetine mesylate (Pexeva®)	
Sertraline (Zoloft®)	
Citalopram (Celexa®)	Citalopram (Celexa®) Liquid
Escitalopram (Lexapro®)	Escitalopram (Lexapro®) Liquid
Secondary Amine Tricyclics	
Desipramine (Norpramin®)	
Nortriptyline (Pamelor®)	
Protriptyline (Vivactil®)	
Tertiary Amine Tricyclics	
Amitriptyline (Elavil®)	
Clomipramine (Anafranil®)	
Doxepine (Sinequan®)	
Imipramine (Tofranil-PM®)	
Trimipramine (Surmontil®)	
Tetracyclics	
Amoxapine (Asendin®)	
Maprotiline (Ludiomil®)	
Monoamine Oxidase Inhibitors	
	Phenelzine (Nardil®)
	Tranylcypromine (Parnate®)

* Brand-Name Override required where applicable.
** Bristol-Myer Squibb has discontinued marketing of brand name Serzone® due to possible link to hepatic toxicity.
*** Current SSRI tiers based on Supplemental Rebate participation.

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i Belzer K, Schneier FR. Comorbidity **of Anxiety and Depressive Disorders: Issues in Conceptualization, Assessment, and Treatment.** J Psychiatric Prac. 2004;10:296-306.

ii **Cymbalta** (duloxetine HCL) package insert. Indiana: Eli Lilly and Company. 2005.

iii **Remeron** (mirtazapine) package insert. New Jersey: Organon Inc. 2002.

iv **Trazodone** HCL package insert. Pennsylvania: Teva Pharmaceuticals USA. 2004.

v **Wellbutrin** (Bupropion HCL) package insert. North Carolina: GlaxoSmithKline. 2004.

vi **Nefazodone HCL** package insert. Pennsylvania: Teva Pharmaceuticals USA. 2003.

vii **Effexor** (venlafaxine HCL) package insert. Pennsylvania: Wyeth Pharmaceuticals Inc. 2004.

APPENDIX E

Annual Review of Anti-Ulcer Drugs - Fiscal Year 2004

Oklahoma Medicaid
March 2005

Product Based Prior Authorization

With respect to the anti-ulcer medications there are two tiers of medications in the therapeutic category. A failed trial with a tier-1 anti-ulcer medication within the past 120 consecutive days is required before a tier-2 anti-ulcer medication can be approved.

Criteria required before moving to tier-2 medications include a failure of a maximum 40mg dose of omeprazole and trial of at least one tier-1 product (including omeprazole) or a clinical exception to the use of a tier-1 product.

Clinical exceptions to tier-1 anti-ulcer trials are as follows:

1. H pylori eradication
2. Prophylaxis or treatment of NSAID induced ulcer
3. Erosive esophagitis or maintenance of healed erosive esophagitis
4. GERD complications (e.g. esophageal strictures, dysphagia, Barrett's esophagus)
5. Scleroderma

Anti-Ulcer Medications	
Tier 1	**Tier 2**
esomeprazole magnesium (Nexium®)**	ranitidine (Zantac®) capsules & granules except generic tablets and other forms*
lansoprazole (Prevacid®)** capsules	lansoprazole (Prevacid®) oral disintegrating tablets & granules
generic Rx omeprazole and Prilosec OTC*	Brand Rx (Prilosec®)***
Omeprazole (Zegerid®)**	
pantoprazole sodium (Protonix®)**	
rabeprazole sodium (Aciphex®)**	

All versions of the prescription only product will remain Tier 2 until a SMAC can be applied or a supplemental rebate is established.

* Conversion to tier-1 drug for fiscal year 2004.

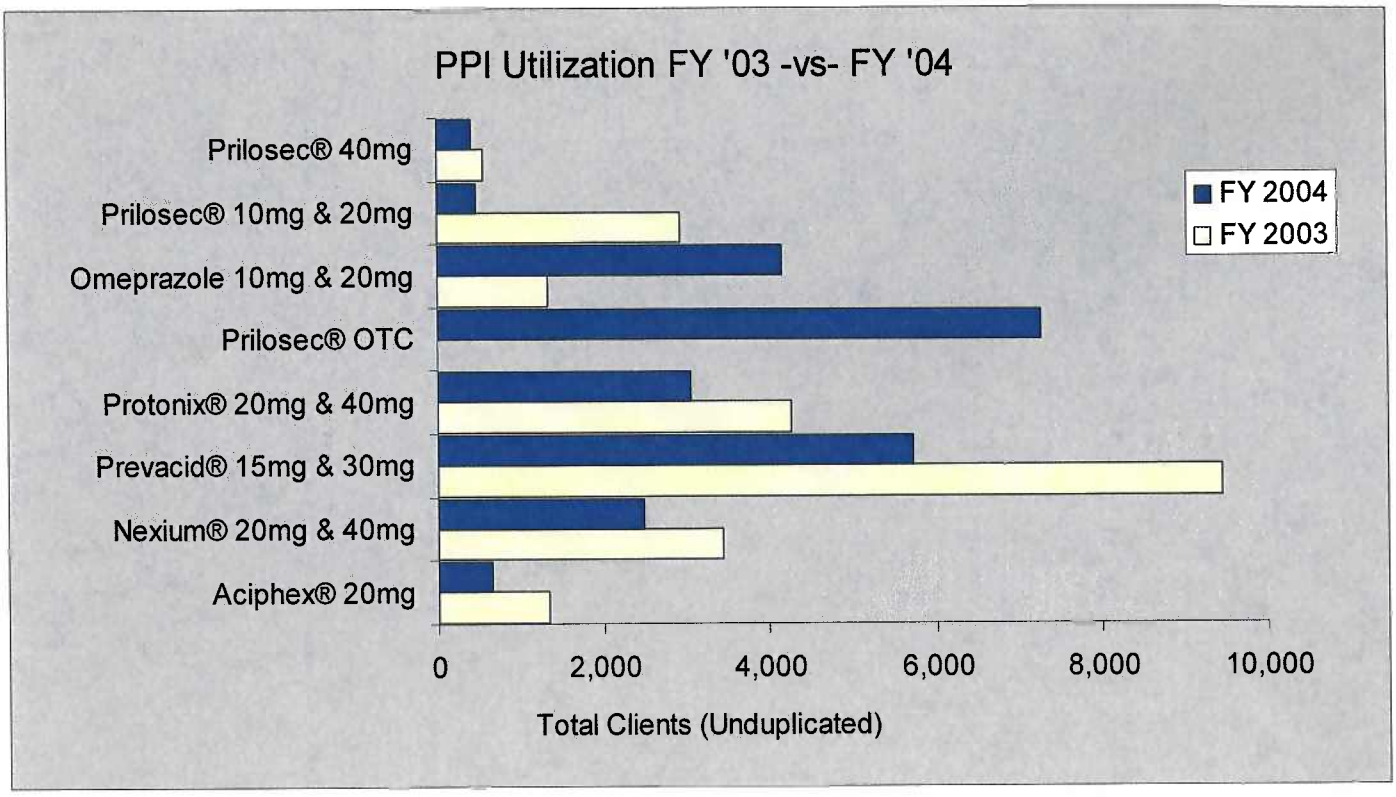
** Conversion to tier-1 drug on 07/01/2004 due to supplemental rebate program.

*** Brand-name prior authorization implemented on 11/01/2004.

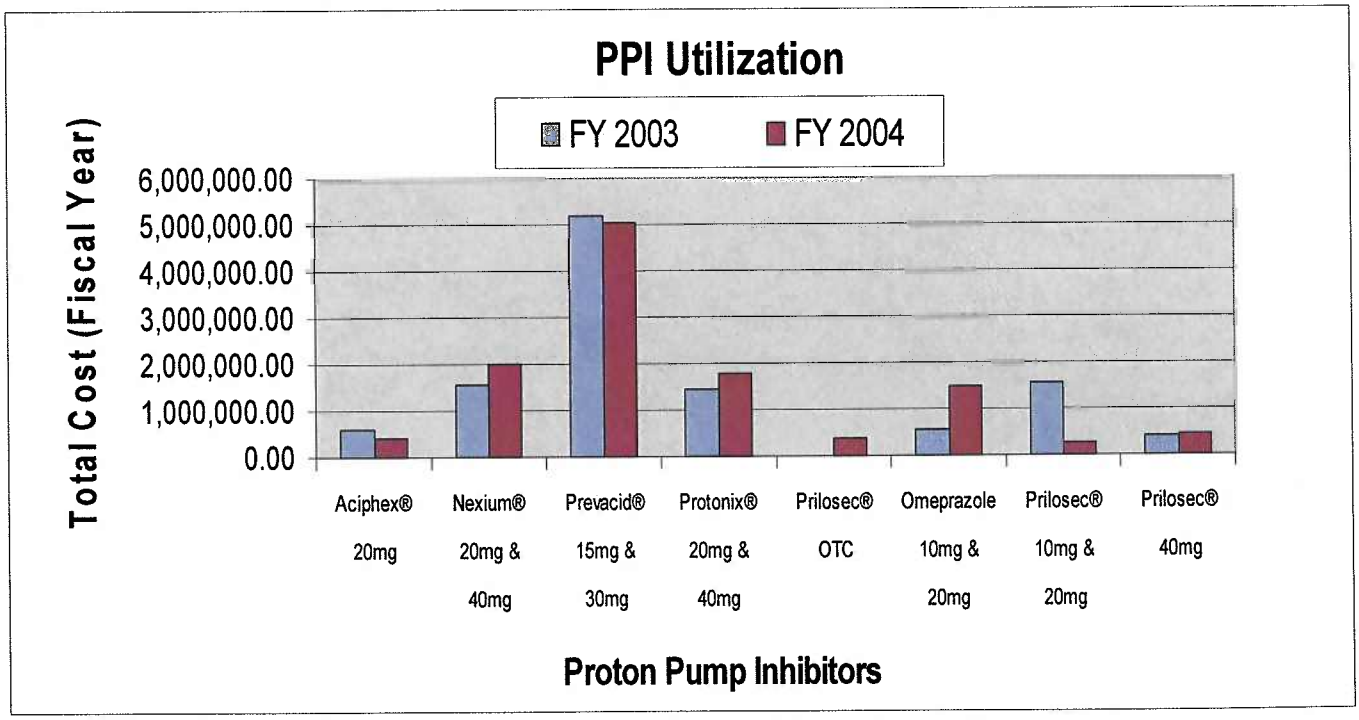
Update on Fiscal Year 2004 Changes

Product moved from tier-2 to tier-1: omeprazole (Prilosec®) OTC & generic 20 mg.

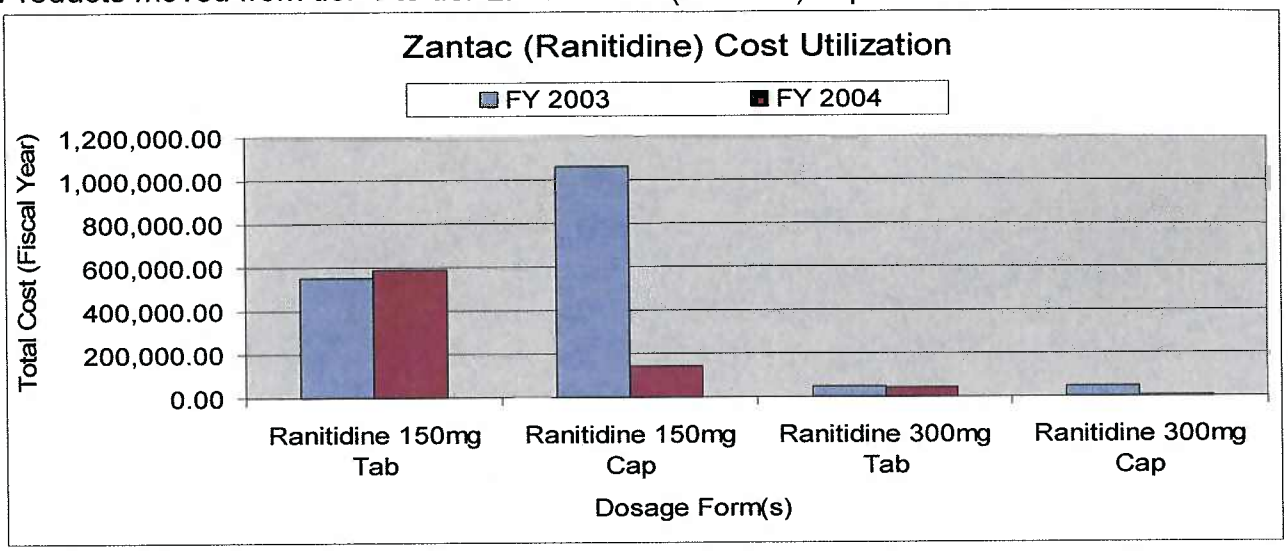
Unduplicated Recipients:



PPI Cost-Utilization:



Products moved from tier-1 to tier-2: ranitidine (Zantac®) capsules & other forms.



Fiscal Year 2005 Changes

Products moved from tier-2 to tier-1 due to supplemental rebate program: esomeprazole magnesium (Nexium®), lansoprazole (Prevacid®), pantoprazole sodium (Protonix®), rabeprazole sodium (Aciphex®), and omeprazole (Zegerid®) packets.

Brand-Name Override was implemented on November 11, 2004. This affects those anti-ulcer medications which are available in generic form.

Utilization

For the period of July 2003 through June 2004, a total of **42,965** clients received H2 antagonists or proton pump inhibitors through the Medicaid fee-for-service program.

Product	# of Claims	Total Units	Total Days	Units/ Day	Total Cost	Total Clients	Per Diem
Tier 1 drugs	130,660	8,763,787	4,205,643	2.08	$3,662,746.95	40,897	$0.88
Tier 2 drugs	61,666	2,627,735	2,310,059	1.14	$10,318,862.56	15,223	$4.47
Total	**192,326**	**11,391,522**	**6,515,702**	**1.75**	**$13,981,609.51**	**42,965***	**$2.15**

*Total reflects unduplicated clients

Total Cost FY 2004	**$13,981,609.51**
Total Cost FY 2003	*$13,980,685.01*
Total Claims FY 2004	**192,326**
Total Claims FY 2003	*178,399*
Total Clients FY 2004	**42,965**
Total Clients FY 2003	*34,881*
Per Diem FY 2004	**$2.15**
Per Diem FY 2003	*$2.44*

Total petitions submitted in for this category during specified time period: 15,764

Approved *4,378*
Denied 7,419
Incomplete 967
Overrides *21*
INCOMPLETES APPROVED 345
DENIEDS APPROVED 2,487

Claims were reviewed to determine the age/gender of the clients.

Age	Female	Male	Totals
0 to 9	1,912	2,075	3,987
10 to 19	2,695	1,832	4,527
20 to 34	3,170	903	4,073
35 to 49	3,894	2,121	6,015
50 to 64	5,150	2,611	7,761
65 to 79	6,542	2,482	9,024
80 to 94	5,751	1,203	6,954
95 and Over	545	79	624
Totals	**29,659**	**13,306**	**42,965**

New product: omeprazole (Zegerid®) packets
Omeprazole (Zegerid®) packets were recently approved as a tier-1 product due to the supplemental rebate program as of 12/01/2004.

New Indication: Approved 11/24/2004 a supplemental new drug application provides for the use of Esomeprazole (Nexium®) delayed-release capsules for the risk reduction of non-steroidal anti-inflammatory drug (NSAID)-associated gastric ulcers.

Recommendations

The college of pharmacy recommends continued monitoring and evaluation of the cost and utilization of this PBPA category.

APPENDIX F

Prior Authorization Annual Review – Fiscal Year '04

Xolair®

Oklahoma Medicaid
April 2005

Definition of Prior Authorization Category for FY '04

This product was approved for sale on June 20, 2003. Prior Authorization of this category was implemented on February 17, 2004. All clients on the medication at that time had to submit a petition for prior authorization to continue treatment.

The criteria are as follows:

1. Client must be between 12-75 years of age.
2. Client must have a diagnosis of severe persistent asthma (as per NAEPP guidelines).
3. Client must have a positive skin test to at least one perennial aeroallergen. Positive perennial allergens must be listed on the petition.
4. Client must have a pretreatment serum IgE level between 30-700 IU/ml.
5. Client weight must be between 30-150kg.
6. Client must have been on high dose ICS (as per NAEPP Guidelines) for at minimum the past 3 months.
7. Medication must be prescribed by either a pulmonary or an allergy/asthma specialist.
8. Client must have been in the ER or hospitalized, due to an asthma exacerbation, twice in the past 6 months with one of the visits occurring within the past 30 days. Date of visits must be listed on petition.

Petitions meeting criteria for coverage will be approved for 12 months of therapy. Renewal petitions after 12 months will be assessed for client compliance. If two or more doses have been missed, the client will not be approved for continuing therapy.

Fiscal Year '04 Changes

No changes to the prior authorization criteria during fiscal year 2004.

Utilization

For the period of July 2003 through June 2004, a total of 19 clients received Xolair® through the Medicaid fee-for-service program.

Product	# of Claims	Total Units	Total Days	Units/ Day	Total Cost	Total Clients	Per Diem
Xolair®	90	308	2,546	0.12	$ 147,027.15	19	$ 57.75
Total	**90**	**308**	**2,546**	**0.12**	**$ 147,027.15**	**19***	**$57.75**

*Total unduplicated clients for FY04

Total petitions submitted in for this category during specified time period: 39

Approved *0*
Denied 26
Incomplete 13

Claims were reviewed to determine the age/gender of the clients.

Age	Female	Male	Totals
0 to 9	3	7	10
10 to 19	5	1	6
20 to 34	2	0	2
35 to 49	1	0	1
50 to 64	0	0	0
65 to 79	0	0	0
80 to 94	0	0	0
95 and Over	0	0	0
Totals	**11**	**8**	**19**

Recommendations

The majority of clients on Xolair® were started on therapy between the time the drug entered the market and when the prior authorization was implemented. The number of clients utilizing Xolair® should decrease for fiscal year 2005 as most of these clients did not meet authorization criteria.

APPENDIX G

Selected Narcotics Drug Utilization Review – 2004

Actiq® (fentanyl)
Duragesic® (fentanyl)
Kadian® (morphine)
Avinza® (morphine)
OxyContin® (oxycodone)
Palladone™ (hydromorphone)

Oklahoma Medicaid
April 2005

Actiq® (oral transmucosal fentanyl citrate lozenge)

- **Indication:** Only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Actiq is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.
- **Pediatric Use:** The appropriate dosing and safety of Actiq in opioid tolerant children with breakthrough cancer pain have not been established below the age of 16 years. Patients and their caregivers must be instructed that Actiq contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep both used and unused dosage units out of the reach of children.
- **Geriatric use:** No difference was noted in the safety profile of the group over 65 as compared to younger patients in Actiq clinical trials. However, greater sensitivity in older individuals cannot be ruled out. Therefore, caution should be exercised in individually titrating Actiq in elderly patients to provide adequate efficacy while minimizing risk.
- **Dosing:** The initial dose should be 200 mcg. From this initial dose, patients should be closely followed and the dosage level changed until the patient reaches a dose that provides adequate analgesia using a single Actiq dosage unit per breakthrough cancer pain episode. Once a successful dose has been found (i.e., an average episode is treated with a single unit), patients should limit consumption to four or fewer units per day. If consumption increases above four units/day, the dose of the long-acting opioid used for persistent cancer pain should be re-evaluated.
- **How supplied:** 200, 400, 600, 800, 1,200, & 1,600 mg lozenges.
- **Current quantity limit:** 120 lozenges per 30 days.
- **Recommendation:** Keep the current quantity limit as it is.

Duragesic® (fentanyl transdermal patch)

- **Indication:** For the management of chronic pain in patients who require continuous opioid analgesia for pain that cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids.
- **Pediatric Use:** Duragesic was not studied in children under 2 years of age. Duragesic should be administered to children only if they are opioid-tolerant and age 2 years or older.
- **Geriatric use:** The clearance of fentanyl may be greatly decreased in the population above the age of 60. Since elderly, cachectic, or debilitated patients may have altered pharmacokinetics due to poor fat stores, muscle wasting, or altered clearance, they should not be started on Duragesic doses higher than 25 µg/h unless they are already taking more than 135 mg of oral morphine a day or an equivalent dose of another opioid.
- **Dosing:** Each Duragesic may be worn continuously for 72 hours. There has been no systematic evaluation of Duragesic as an initial opioid analgesic in the management of chronic pain, since most patients in the clinical trials were converted to Duragesic from other narcotics. Therefore, unless the patient has pre-existing opioid tolerance, the lowest Duragesic dose, 25 µg/h, should be used as the initial dose. The prescribing information contains a chart to estimate the needed Duragesic dose depending on the patient's current opioid dosing. The majority of patients are adequately maintained with Duragesic administered every 72 hours. A small number of patients may not achieve adequate analgesia using this dosing interval and may require systems to be applied every 48 hours rather than every 72 hours. An increase in the Duragesic dose should be evaluated before changing dosing intervals in order to maintain patients on a 72-hour regimen. Dosing intervals less than every 72 hours were not studied in children and adolescents and are not recommended.
- **How supplied:** 25, 50, 75, & 100 mcg/hr patches.
- **Current quantity limit:** 10 patches per 30 days. 100 mcg/hr strength excluded from any limit.
- **Recommendation:** Keep the current quantity limit as it is.

Kadian® (morphine sulfate sustained release capsule)

- **Indication:** For the management of moderate to severe pain where treatment with an opioid analgesic is indicated for more than a few days.
- **Pediatric Use:** The safety of Kadian, both the entire capsule and the pellets sprinkled on applesauce, has not been directly investigated in pediatric patients below the age of 18 years. The range of doses available is not

suitable for the treatment of very young pediatric patients or those who are not old enough to take capsules safely. The applesauce sprinkling method is not an appropriate alternative for these patients.

- **Geriatric use:** Should be administered with caution and in reduced dosages to elderly or debilitated patients.
- **Dosing:** Can be given QD or BID. Capsules should be swallowed whole (not chewed, crushed, or dissolved) or may be opened and the entire contents sprinkled on a small amount of applesauce immediately prior to ingestion. The pellets in the capsules should not be chewed, crushed, or dissolved due to risk of overdose. The prescribing information contains information for estimating the needed Kadian dose depending on the patient's current opioid dosing. Kadian is not recommended for use as an initial opioid analgesic. If breakthrough pain occurs on a 12 hour dosing regimen a supplemental dose of a short-acting analgesic may be given. To avoid accumulation the dosing interval of Kadian should not be reduced below 12 hours.
- **How supplied:** 20, 30, 50, 60, & 100 mg capsules.
- **Current quantity limit:** None.
- **Recommended quantity limit:** 60 capsules per 30 days.

Avinza® (morphine sulfate extended release capsule)

- **Indication:** For the relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time. Avinza is not intended for use as a prn analgesic and is not indicated for postoperative use.
- **Pediatric Use:** Safety and effectiveness of Avinza in pediatric patients below the age of 18 have not been established. The range of dose strengths available may not be appropriate for treatment of very young pediatric patients. Sprinkling on applesauce is not a suitable alternative for these patients.
- **Geriatric use:** Caution should be exercised in the selection of the starting dose of Avinza for an elderly patient, usually starting at the low end of the dosing range. The starting dose should be reduced in debilitated and non-opioid tolerant patients.
- **Dosing:** All doses are intended to be administered once daily. Avinza capsules must be swallowed whole (not chewed, crushed, or dissolved) or Avinza capsules may be opened and the entire bead contents sprinkled on a small amount of applesauce immediately prior to ingestion. The beads must not be chewed, crushed, or dissolved due to risk of acute overdose. The daily dose of Avinza must be limited to a maximum of 1600 mg/day. Avinza doses of over 1600 mg/day contain a quantity of fumaric acid that has not been demonstrated to be safe, and which may result in serious renal toxicity.
- **How supplied:** 30, 60, 90, & 120 mg capsules.
- **Current quantity limit:** None.
- **Recommended quantity limit:** 30 capsules per 30 days.

OxyContin® (oxycodone HCl controlled release tablet)

- **Indication:** For the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. OxyContin is not intended for use as a prn analgesic. OxyContin is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery) for patients not previously taking the drug, or if the pain is mild, or not expected to persist for an extended period of time.
- **Pediatric Use:** Safety and effectiveness of OxyContin have not been established in pediatric patients below the age of 18. It must be remembered that OxyContin tablets cannot be crushed or divided for administration.
- **Geriatric use:** In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. The usual doses and dosing intervals are appropriate for these patients. The starting dose should be reduced to 1/3 to 1/2 of the usual dosage in debilitated, non-tolerant patients.
- **Dosing:** Administered every 12 hours. While symmetric (same dose AM and PM), around-the-clock, q12h dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing, tailored to their pain pattern. It is usually appropriate to treat a patient with only one opioid for around-the-clock therapy. Patients should be titrated to adequate effect (generally mild or no pain with the regular use of no more than two doses of supplemental analgesia per 24 hours). Patients who experience breakthrough pain may require dosage adjustment or rescue medication. It is most appropriate to increase the q12h dose, not the dosing frequency. There is no clinical information on dosing intervals shorter than q12h.
- **How supplied:** 10, 20, 40, & 80 mg tablets.
- **Current quantity limit:** First 60 days of therapy are excluded for dose adjustment. 90 tablets per 30 days thereafter. 80 mg strength excluded from any limit.
- **Recommended quantity limit:** OHCA has not been able to put into place the programming which would allow the first 60 days of therapy to pay without quantity limits, therefore there is no quantity limit currently being applied to this drug. College of pharmacy recommends a quantity limit of 60 tablets per 30 days, excluding the 80 mg strength.

Palladone™ (hydromorphone HCl extended release capsule)

- **FDA approval date 9/24/04**
- **Indication:** For the management of persistent, moderate to severe pain in patients requiring continuous, around-the-clock analgesia with a high potency opioid for an extended period of time, generally weeks to months or longer. Palladone should only be used in patients who are already receiving opioid therapy, have demonstrated opioid tolerance, and who require a minimum total daily dose of opiate medication equivalent to 12 mg of oral hydromorphone. Palladone is not intended to be used as the first opioid product prescribed for a patient, in patients who require opioid analgesia for a short period of time, or patients needing analgesia on an as needed basis (i.e., prn).
- **Pediatric Use:** The safety and effectiveness of Palladone has not been established in patients below the age of 18.
- **Geriatric use:** Age-related increases in exposure in clinical studies were observed between geriatric and younger adult subjects. Greater sensitivity of some older individuals cannot be excluded. Dosages should be adjusted according to the clinical situation.
- **Dosing:** Administered once every 24 hours. Discontinue all other around-the-clock opioid analgesics when Palladone is initiated. Palladone should be titrated to adequate effect (generally mild or less pain with the regular use of no more than two doses of supplemental analgesics per 24 hours). If more than two doses of rescue medication are needed within a 24 hour period for two consecutive days, the dose of Palladone should usually be titrated upward. Should not be taken with any alcohol at all, since alcohol acts as a solvent and can speed up absorption of hydromorphone from the extended release pellets; this can result in overdose and death.
- **How supplied:** 12, 16, 24, & 32 mg capsules.
- **Current quantity limit:** none.
- **Recommended quantity limit:** 30 capsules per 30 days.

Palladone price per capsule:

Strength	AWP	EAC
12 mg	$7.70	$6.78
16 mg	$8.98	$7.90
24 mg	$12.95	$11.40
32 mg	$16.71	$14.71

AWP = average wholesale price; EAC = estimated acquisition cost

Utilization

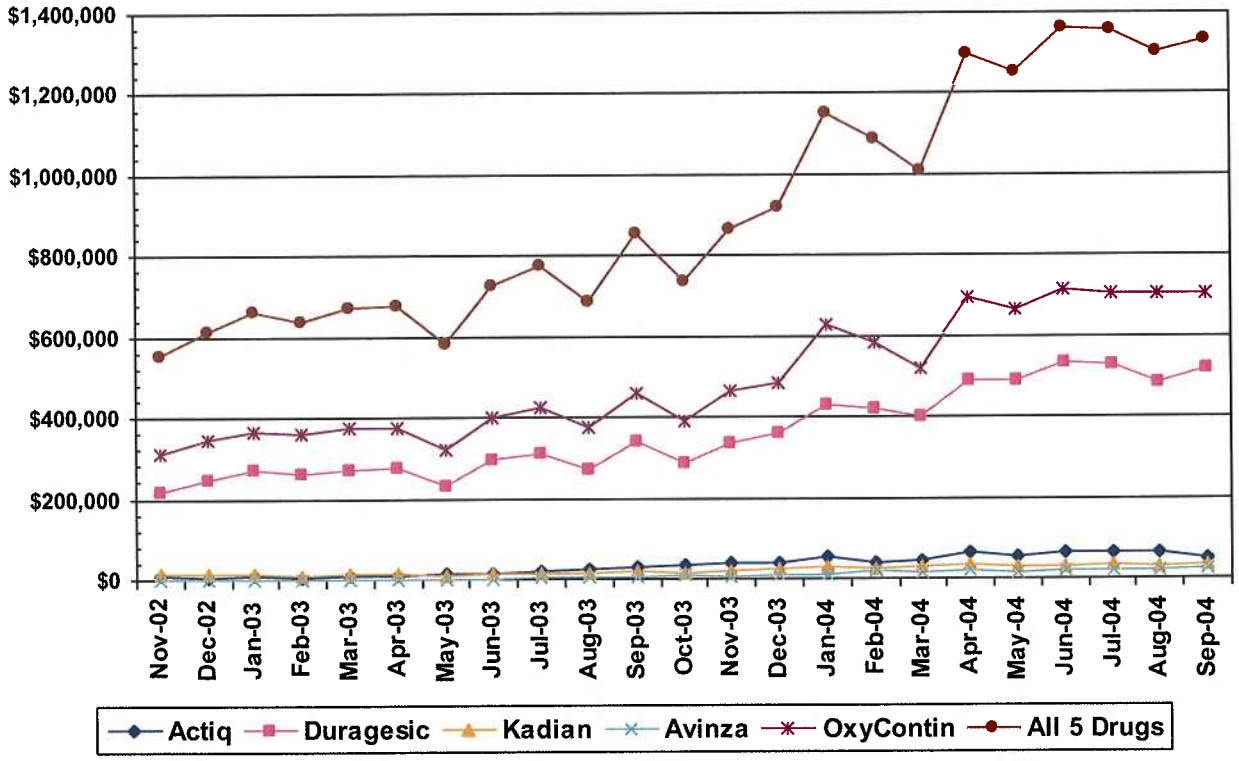
For the period of 11/1/03 through 10/31/04, a total of 7,049 clients received the following selected narcotics through the Medicaid fee-for-service program.

Product		# of Claims	# of Clients	Total Units	Total Days	$/Day	$/Unit	Units / Day	$/Client	Total Cost
Actiq	*2003*	226	81	13,920	4,314	$38.42	$12.01	3.2	$2,345.29	$189,968.12
	2004	597	137	44,101	13,614	$46.50	$13.40	3.2	$4,508.54	$617,669.60
Duragesic	*2003*	12,101	2,839	124,301	329,127	$11.13	$25.52	0.4	$1,161.80	$3,298,344.95
	2004	16,571	3,569	174,311	457,770	$12.47	$29.48	0.4	$1,514.70	$5,405,976.74
Kadian	*2003*	668	188	44,592	20,391	$8.60	$3.58	2.2	$891.62	$167,623.81
	2004	1,221	264	83,538	37,044	$9.81	$3.92	2.3	$1,326.20	$350,117.06
Avinza	*2003*	128	74	5,156	3,659	$6.21	$4.26	1.4	$301.67	$22,323.45
	2004	935	293	37,905	27,485	$7.67	$5.34	1.4	$696.56	$204,092.71
OxyContin	*2003*	15,373	2,843	1,238,220	451,912	$10.33	$3.52	2.7	$1,587.95	$4,514,544.74
	2004	21,871	3,633	1,763,382	643,852	$12.00	$4.00	2.7	$2,040.79	$7,414,200.21
Total	**2003**	**28,496**	**5,462**	**1,426,189**	**809,403**	**$10.83**	**$12.95**	**1.8**	**$1,499.96**	**$8,192,805.07**
	2004	**41,195**	**7,049**	**2,103,237**	**1,179,765**	**$12.53**	**$14.41**	**1.8**	**$1,984.97**	**$13,992,056.32**
% ↑ 2003-2004		**45%**	**29%**	**47%**	**46%**	**16%**	**11%**	**0%**	**32%**	**71%**

2003 = 11/1/02 – 10/31/03
2004 = 11/1/03 – 10/31/04

Palladone – no utilization of this drug during period studied.
See Palladone pricing above.

Cost Trend by Month, 2003 & 2004:



Claims were reviewed to determine the age and gender of the clients:

Age	Female	Male	Totals
0 to 9	12	22	34
10 to 19	37	43	80
20 to 34	354	169	523
35 to 49	1,162	702	1,864
50 to 64	1,287	665	1,952
65 to 79	1,099	355	1,454
80 to 94	902	141	1,043
95 and Over	91	8	99
Totals	**4,944**	**2,105**	**7,049**

Claims were reviewed to determine the number of claims per client:

# of Claims	# of Clients	% of Clients
1 to 5	4,034	57
6 to 10	1,524	22
11 to 15	1,248	18
16 to 20	144	2
21 +	99	1

Diagnostic Information from ICD-9 Coding:
Of the 7,049 patients on these 5 drugs, 1,726 (24.5%) had a cancer diagnosis.

Recommendation Summary:

Drug	Recommended Quantity Limit
Actiq® (fentanyl)	Keep the current quantity limit as it is - 120 lozenges per 30 days.
Duragesic® (fentanyl)	Keep the current quantity limit as it is - 10 patches per 30 days. 100 mcg/hr strength excluded from any limit.
Kadian® (morphine)	60 capsules per 30 days.
Avinza® (morphine)	30 capsules per 30 days.
OxyContin® (oxycodone)	60 tablets per 30 days, excluding the 80 mg strength.
Palladone™ (hydromorphone)	30 capsules per 30 days.

New Product: Combunox® (oxycodone 5 mg / ibuprofen 400 mg)

- **FDA approval date 11/26/04**
- **Clinical Studies:** The FDA approved Combunox based on three single dose clinical trials in a total of 1,405 patients. Two studies involved a total of 949 patients following dental surgery (removal of ipsilateral molars) and a third study involved 456 patients following abdominal/pelvic surgery. In the three studies patients were administered a single dose of the Combunox, ibuprofen alone, oxycodone HCl alone, or placebo for acute, moderate to severe pain. In these single dose studies, Combunox produced greater efficacy than placebo and each of Combunox's individual components as measured by the magnitude of pain relief and the reduction of pain intensity through six hours. No multiple dose efficacy studies have been performed with Combunox.
- **Indication:** For the short term (no more than 7 days) management of acute, moderate to severe pain.
- **Pediatric Use:** Combunox has not been studied in patients under 14 years of age. In clinical studies, 109 patients between the ages of 14 and 17 years were administered a single dose of Combunox, and no apparent differences were noted in the safety of Combunox in patients below and above 17 years of age.
- **Geriatric use:** In clinical studies, 89 patients were 65 years old or over, and no overall differences in safety were observed with these patients. However, since the elderly may be more sensitive to the renal and gastrointestinal effects of NSAIDs and the possible increased risk of respiratory depression with opioids, extra caution should be used when treating the elderly with Combunox.
- **Dosing:** For the management of acute moderate to severe pain, the recommended dose is one tablet. Dosage should not exceed 4 tablets in a 24 hour period and should not exceed 7 days.
- **How supplied:** oxycodone 5 mg / ibuprofen 400 mg tablets.
- **Pricing:** AWP = $1.50 per tablet; EAC = $1.32 per tablet
- **Current quantity limit:** none.
- **Recommended quantity limit:** 28 tablets per 30 days.

Table 2.8.0 - ED mentions for central nervous system agents by drug category: Estimates for the coterminous U.S. by year.
From: http://dawninfo.samhsa.gov/old_dawn/pubs_94_02/pickatable/2002/2.8.0.xls

Drug name	Total 1995	Total 1996	Total 1997	Total 1998	Total 1999	Total 2000	Total 2001	Total 2002	% change 1995-2002
Narcotic analgesics/ combinations	45,254	46,941	54,116	58,946	69,011	82,373	99,317	119,185	163.4
Narcotic analgesics	20,910	22,525	26,298	32,573	41,676	47,833	64,786	81,002	287.4
Narcotic analgesic combinations	24,343	24,416	27,819	26,373	27,335	34,540	34,531	38,183	56.9
anileridine	2	0	0	0	2	...	0	0	-100.0
buprenorphine	2	1	...	0	...	11	10	6	200.0
butorphanol	...	239	...	19	...	...	...	...	
codeine/combinations	8,732	7,594	7,869	6,620	4,974	5,295	3,720	4,961	-43.2
codeine	1,540	1,208	1,033	1,420	894	1,155	930	1,237	
Acetaminophen/codeine	6,838	5,907	6,598	5,049	3,845	3,849	2,641	3,606	-47.3
APAP/butalbital/caffeine/codeine	13	...	...	...	...	9	...	16	
ASA/butalbital/ caffeine/codeine	317	197	...	24	226	217	...	30	-90.5
aspirin-codeine	10	6	5	...	7	...	0	0	-100.0
aspirin/caffeine/ codeine/phenacetin	...	...	2	...	0	0	0	0	
codeine/papaverine	0	0	...	0	1	0	0	0	
codeine/phenacetin	0	1	...	0	0	0	0	0	
codeine combination-NOS	8	...	...	...	0	0	3	...	
dezocine	0	3	0	0	...	0	0	0	
dihydrocodeine/ combinations	...	3	2	...	...	3	...	4	
dihydrocodeine	0	0	...	1	...	...	...	4	
APAP/caffeine/ dihydrocodeine	0	3	0	...	0	0	0	0	
ASA/caffeine/ dihydrocodeine	...	0	...	0	0	1	0	0	
fentanyl/combinations	22	34	203	286	337	576	710	1,506	6,745.5
fentanyl	22	34	203	286	337	576	710	1,506	6,745.5
hydrocodone/ combinations	9,686	11,419	11,570	13,611	15,252	20,098	21,567	25,197	160.1
hydrocodone	1,324	1,574	904	1,907	2,074	2,240	2,214	2,420	82.8
acetaminophen-hydrocodone	8,362	9,845	10,667	11,686	13,043	17,538	19,058	22,227	165.8
aspirin-hydrocodone	0	0	0	2	0	0	...	0	
hydrocodone-ibuprofen	0	0	0	17	...	320	292	550	
hydromorphone	569	609	604	937	1,313	...	...	...	
hydroxy-N-methylmorphinan	2	0	0	0	0	...	1	...	
kaolin-pectin/paregoric	0	0	1	0	0	0	0	0	
levorphanol	...	0	0	1	0	4	0	0	
meperidine/ combinations	1,045	876	864	730	882	1,085	665	722	
meperidine	969	806	731	495	512	706	519	644	
acetaminophen/ meperidine	...	0	0	0	...	...	0	1	
meperidine-promethazine	10	...	...	...	369	...	...	...	

methadone	4,247	4,129	3,832	4,810	5,426	7,819	10,725	11,709	175.7
morphine/combinations	1,283	864	1,300	1,955	2,217	2,483	3,403	2,775	116.3
morphine	1,283	864	1,299	1,954	2,213	2,478	3,403	2,775	116.3
cocaine (Schedule I substance)/ morphine	0	0	...	1	4	4	0	0	
nalbuphine	13	10	14	...	33	...	25	23	
noscapine	0	0	0	0	1	0	...	7	
opium/combinations	...	30	49	24	...	167	96	141	
opium	...	28	49	24	...	167	96	140	
belladonna-opium	0	...	0	0	0	0	0	1	
oxycodone/combinations	3,393	3,190	5,012	5,211	6,429	10,825	18,409	22,397	560.1
oxycodone	...	100	372	1,034	1,804	3,792	11,100	14,996	...
acetaminophen-oxycodone	2,944	2,839	4,353	3,841	4,503	6,637	7,190	7,210	144.9
aspirin-oxycodone	334	251	287	335	121	396	119	191	
oxymorphone	0	0	0	0	0	...	3	2	
papaveretum	0	0	0	1	0	0	0	0	
pentazocine/ combinations	153	196	202	329	262	...	247	17	-88.9
pentazocine	5	0	0	0	3	...	...	1	-80.0
acetaminophen-pentazocine	12	13	...	...	...	...	0	1	-91.7
aspirin- pentazocine	135	184	...	...	...	...	241	15	
phenacetin/ combinations	0	0	...	1	0	1	0	1	
phenacetin	0	0	...	1	0	0	0	1	
aspirin/caffeine/ phenacetin/ pseudoephedrine	0	0	0	0	0	1	0	0	
propoxyphene/ combinations	6,294	5,889	6,502	5,826	5,632	5,485	5,361	4,676	
propoxyphene	1,068	1,065	1,166	1,109	816	593	684	492	-53.9
acetaminophen-propoxyphene	5,224	4,822	5,337	4,714	4,816	4,891	4,675	4,168	
ASA/caffeine/ propoxyphene	...	2	0	...	0	...	...	16	...
sufentanil	...	0	0	4	0	0	1	1	
narcotic analgesics-NOS	9,562	11,855	15,893	18,495	25,946	25,935	32,196	42,211	341.4
narcotic analgesic combinations-NOS	0	0	0	1	3	11	11	2	

Drug Abuse Warning Network (DAWN) is a national public health surveillance system that monitors drug-related emergency department visits and deaths. It is run by the Substance Abuse and Mental Health Services Administration of the U.S. Department of Human Services.

The numbers in the chart above refer to the number of times each drug was mentioned in emergency department visits reported to DAWN.
DAWN has two components:

- one collects data on drug-related visits to a sample of the Nation's emergency departments (EDs);
- the other collects data on drug-related deaths from medical examiner and coroner (ME/C) jurisdictions throughout the country.

Patients are never interviewed. All data are collected through a retrospective review of patient medical records and decedent case files.

Drug mention - This refers to a substance that was recorded ("mentioned") in a DAWN case report. In addition to alcohol-in-combination, up to 4 substances ("mentions") can be reported for each ED episode, and up to 6 substances can be reported for each drug abuse death. Therefore,

the total number of drug mentions exceeds the total number of ED visits or deaths. Even when only one drug is mentioned, it should not be assumed that the substance was the sole and direct cause of the episode or death; allowances should be made for reportable drugs not mentioned or other contributory factors.

Hospital emergency department (ED): Only hospitals that meet eligibility criteria for DAWN are recruited to participate. To be eligible, hospitals must be non-Federal, short-stay, general medical and surgical facilities with EDs that are open 24 hours a day, 7 days a week, and located in the coterminous U.S. Specialty hospitals; hospital units of institutions; long-term care facilities; pediatric hospitals; hospitals operating part-time emergency departments; hospitals in Alaska and Hawaii; and hospitals operated by the Veterans Health Administration and the Indian Health Service are excluded.

APPENDIX H

Review and Discuss Irritable Bowel Syndrome Products - Lotronex® and Zelnorm®

Oklahoma Medicaid
April 2005

Irritable Bowel Syndrome (IBS)
IBS is not a disease, but a functional disorder of the bowel (large intestine) that can cause cramping, bloating, gas, diarrhea and constipation. The disorder can be painful, but does not cause other diseases or damage the bowel.

The symptoms of IBS can be set off by stress, diet, exercise, and hormones. Some foods that may cause symptoms most often are dairy products, chocolate, alcohol, caffeine, carbonated drinks, and fatty foods. Foods that are high in fiber can help relieve symptoms, like apples, peaches, broccoli, carrots, peas, kidney and lima beans, and whole grain bread and cereals. Eating a large meal can also cause symptoms. During the menstrual cycle an increase in symptoms usually occurs.

Physical exam, blood test, X-ray and endoscopy are tests physicians can use to rule out other diseases, but IBS is usually diagnosed based on symptoms. There is no cure for IBS, only symptom relief with diet changes, medicine, stress relief or some combination of the three. Food high in fiber can help reduce IBS symptoms. Eating smaller portions more often through the day or just eating smaller portions at the usual meal time can also be beneficial.

Lotronex®

- Potent and selective antagonist of the serotonin 5-HT3 receptor.
- For women with severe diarrhea-predominant IBS.

Zelnorm®

- Partial agonist of the 5-HT4 receptor.
- Chronic idiopathic constipation in patients less than 65 years of age and short term (12 weeks) treatment of women with IBS whose primary bowel symptom is constipation.

Utilization

For the period of Jan 2004 through Dec 2004:

Product	# of Claims	Total Units	Total Days	Units/ Day	Total Cost	Total Clients	Per Diem
Lotronex 1mg	9	484	316	1.53	$3,046.91	4	$9.64
Zelnorm 2mg	188	10,429	5,436	1.92	$27,105.72	76	$4.99
Zelnorm 6mg	3,408	204,467	105,515	1.94	$522,300.55	1,135	$4.95
Total	**3,605**	**215,380**	**111,267**		**$552,453.18**	**1,201***	

*Unduplicated clients for time period.

Total Cost FY '04 **$552,453.18**
Cost FY03 *$173,166.55*
Total Claims FY '04 **3,605**
Claims FY03 *1,265*
Total Clients FY 04 ***1,201***
Clients FY03 *540*

Claims were reviewed to determine the age/gender of the clients.

FY04 Zelnorm

Age	Female	Male	Totals
0 to 9	6	6	45
10 to 19	83	14	97
20 to 34	155	15	170
35 to 49	267	28	295
50 to 64	238	33	271
65 to 79	195	31	226
80 to 94	109	8	117
95 and Over	9	0	9
Totals	**1,062**	**135**	**1,197**

FY04 Lotronex

Age	Female	Male	Totals
0 to 9	0	0	0
10 to 19	0	0	0
20 to 34	1	0	1
35 to 49	2	0	2
50 to 64	1	0	1
65 to 79	0	0	0
80 to 94	0	0	0
95 and Over	0	0	0
Totals	**4**	**0**	**4**

Cost Comparison

	Average Wholesaler Price (AWP)	Daily Dose*	Monthly Dose (30 day supply)
Zelnorm® 2 mg (6X10)	#60 - $176.19	2 mg BID	#60 - $176.19
Zelnorm® 6 mg 60	#60 - $176.19	6 mg BID	#60 - $176.19
Lotronex® 0.5 mg	#30 - $225.18	0.5mg BID	#60 - $450.36
Lotronex® 1 mg	#30 - $214.45	1 mg BID	#60 - $428.90

Zelnorm® (tegaserod maleate)

Manufacturer Novartis

Classification FDA classification: 5-HT_4 receptor partial agonist
Status: prescription only

Summary Tegaserod is a 5-HT_4 receptor partial agonist indicated for the treatment of IBS with constipation in women and chronic idiopathic constipation in patients under 65 years of age.

Recommendations

- Place a quantity limit on Zelnorm® of 60 units per month.
- Place an age restriction on Zelnorm® of 19 years or greater.
- Place a Prior Authorization on Zelnorm® after 90 days of therapy in a 365 day period.
- Monitor use annually.

Lotronex® (alosetron hydrochloride)

Manufacturer GlaxoSmithKline

Classification FDA classification: Serotonin 5-HT_3 receptor antagonist
Status: prescription only

Summary Alosetron is a serotonin 5-HT_3 receptor antagonist that is only indicated for women who have severe diarrhea-predominant irritable bowel syndrome. It has not been tested in men or patients under the age of 18 and should be used with caution in women over 65 and those with hepatic insufficiency.

To avoid constipation the medication should be started at a dose of 0.5mg BID for 4 weeks and if well tolerated and necessary increased to 1mg BID for 4 weeks. At the end of the 4 weeks, if symptoms are not improved the medication should be discontinued.

If constipation or symptoms of ischemic colitis develop, the medication should be discontinued and the physician contacted.

Recommendations

- Place a quantity limit on Lotronex® of 60 units per month.
- Monitor use annually.

Zelnorm® (tegaserod maleate)

Pharmacological data

Tegaserod is a 5-HT_4 receptor partial agonist that binds with high affinity to these receptors. It has very little binding affinity to 5-HT_3 or dopamine receptors and only moderate affinity to 5-HT_1. By acting as an agonist at neuronal 5-HT_4 receptors, it triggers the release of other neurotransmitters like calcitonin gene-related peptide from sensory neurons. In the gastrointestinal tract, it activates the 5-HT_4 receptors, stimulates the peristaltic reflex and intestinal secretion and at the same time inhibits visceral sensitivity. Enhanced basal motor activity and normalized impaired motility throughout the gastrointestinal tract were seen in vivo studies with tegaserod. During colorectal distension in animals, moderated visceral sensitivity was observed.

Therapeutic indications

- Short-term treatment of women with IBS (irritable bowel syndrome) where constipation is the primary bowel symptom. (Safety and effectiveness in men with IBS has not been established.)
- Chronic idiopathic constipation in patients under 65 years of age. (Effectiveness in patients over 65 years has not been established.)
- Efficacy of treatment beyond 12 weeks for IBS with constipation or chronic idiopathic constipation has not been studied.

Bioavailability/pharmacokinetics

Absorption

- Peak plasma concentrations approximately 1 hour after oral dosing.
- Approximately 10% bioavailability when administered to subjects in a fasting state.
- When administered with food, the bioavailability is reduced 40-60%, C_{max} by 20-40%, plasma concentrations are similarly reduced if tegaserod is taken 30 minutes before a meal or 2.5 hours after a meal. T_{max} is prolonged from 1 to 2 hours if taken after a meal, but decreases to 0.7 hours when taken 30 minutes before a meal.

Distribution

- Approximately 98% bound to plasma proteins, mainly alpha-1-acid glycoprotein.

Metabolism

- The main metabolite of tegaserod 5-methoxyindole-3-carobxylic acid glucuronide is produced by presystemic acid catalyzed hydrolysis in the stomach followed by oxidation and conjugation. This metabolite in vitro has only negligible affinity for 5-HT_4 receptors.
- Direct glucuronidation is the second metabolic pathway that generates three isomeric N-glucuronides.

Elimination

- Plasma clearance is 77±15 L/h and an estimated terminal $T_{1/2}$ of 11 ± 5 hours after intravenous dosing. Almost two-thirds of an oral dose of tegaserod is excreted in the feces unchanged. The remainder is excreted primarily as the main metabolite, 5-methoxyindole-3-carobxylic acid glucuronide, in the urine.

Dosage forms

Oral

- 2-mg & 6-mg tablets (blister packs)
- 6-mg tablets (bottles)

Dosage range

- 2mg BID
- 6mg BID

Known adverse effects/toxicities

- Gastrointestinal System Disorders
  diarrhea, abdominal pain and distention, nausea, vomiting
- Central Peripheral Nervous System
  dizziness, insomnia, headache
- General Disorders and Administration Site Conditions
  fatigue
- Infections and Infestations
  upper respiratory tract infection, sinusitis, fungal infection
- Musculoskeletal and Connective Tissue Disorders
  back pain, myalgia
- Reproductive System and Breast Disorders
  dysmenorrhea
- Respiratory, Thoracic and Mediastinal disorders
  pharyngitis, sinus congestion
- Renal and Urinary Disorders
  urinary tract infection
- Skin and Subcutaneous tissue Disorders
  rash, pruritus

Special precautions

- If new or sudden worsening of abdominal pain, tegaserod should be discontinued.

Contraindications

- Severe renal impairment.
- Moderate/severe hepatic impairment.
- History of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions.

- Hypersensitivity to tegaserod or any of its excipients.

Drug interactions

Drug-drug interaction date with tegaserod in vitro showed no inhibition of the cytochrome P450 isoenzymes CYP2C8, 2C9, 2C19, 2E1 and 3A4. CYP1A2 AND 2D6 could not be excluded. However, in vivo drug-drug interaction studies with CYP2D6 prototype substrate (dextromethorphan) and CYP1A2 (theophylline) showed no relevant interactions. Digoxin, oral contraceptives and warfarin also showed no pharmacokinetic effects.

Patient monitoring guidelines

Tegaserod should be discontinued if:

- new or worse abdominal (stomach) pain occurs
- blood in stools
- diarrhea that results in lightheadedness, dizziness or fainting

Patient information

- Take twice a day on an empty stomach shortly before a meal or as prescribed.
- For IBS, treatment is usually 4-6 weeks. If working may be prescribed for an additional 4-6 weeks.
- For chronic idiopathic constipation regular doctor visits to determine whether to continue therapy.
- If a dose is missed, skip it. Do not double up on a dose. Take at next scheduled time.
- Most common side effects are headache and diarrhea.

Don't start taking tegaserod if:

- You have diarrhea now or often.
- Have bad kidney or liver disease.
- Ever had bowel obstruction (instestinal blockage), symptomatic gallbladder disease or abdominal adhesions causing pain and/or intestinal blockage.
- Allergic to tegaserod or any of its components.
- Not recommended during pregnancy or if breast feeding.

Lotronex® (alosetron hydrochloride)

Pharmacological data

Alosetron is a potent and selective receptor antagonist of the 5-HT^3 receptors. These are ligand-gated cation channels that are distributed extensively in the gastrointestinal tract and other central and peripheral locations on enteric neurons. As these channels are activated, neuronal depolarization occurs which affects visceral pain, colonic transit and gastrointestinal secretions. These processes all relate to irritable bowel syndrome (IBS). Activation of non-selective cation channels is inhibited by 5-HT^3 antagonists like alosetron which causes enteric nervous system regulation.

Therapeutic indications

Only women with severe diarrhea-predominant irritable bowl syndrome (IBS) for whom the benefit of outways the risk who have:

- Chronic IBS symptoms (lasting 6 months or longer)
- Have excluded anatomic or biochemical abnormalities of the gastrointestinal tract
- Not had an adequate response to conventional therapy

Bioavailability/pharmacokinetics

Absorption

- Rapidly absorbed with a mean absolute bioavailability of approximately 50-60%
- Decreases about 25% when taken with food

Distribution

- Volume of distribution is about 65 to 95L
- Plasma protein binding of 82% over a concentration range of 20 to 4,000ng/ml

Metabolism

- 13 metabolites have been detected in urine
- Biological activity of metabolites is unknown

Elimination

- Terminal elimination half-life is about 1.5 hours
- Plasma clearance is about 600mL/min
- Renal clearance is about 94mL/min (6% unchanged)

Dosage forms

Oral

- 0.5-mg Tablet
- 1-mg Tablet

Dosage range

0.5-mg BID to 1-mg BID

Known adverse effects/toxicities

- Constipation
- Abdominal discomfort and pain
- Nausea
- Gastrointestinal discomfort and pain
- Abdominal distention
- Regurgitation and reflux
- Hemorrhoids

Symptoms of toxicitiy are:

- labored breathing
- subdued behavior
- ataxia
- tremors
- convulsions.

Special precautions

Alosetron should not be used by patients who are not able to comply with or understand the Patient-Physician Agreement for Lotronex®. It should only be prescribed by a physician who has enrolled in the prescribing program.

If the patient develops constipation or ischemic colitis symptoms, this medication should be discontinued and the symptoms should be reported to their physician. If the constipation does not resolve after the medication is stopped, they need to contact their physician. Alosetron should not be restarted if advised by the prescribing physician.

Contraindications

Lotronex should not be initiated in patients with constipation and is contraindicated in patients with a history of:

- Chronic/severe constipation or sequelae from constipation
- Intestinal obstruction, stricture, toxic megacolon, gastronintestinal perforation, and/or adhesions
- Ischemic colitis, impaired intestinal circulation, thrombophlebitis, or hypercoagulable state
- Crohn's disease or ulcerative colitis
- Diverticulitis
- Hypersensitivity to any component of the product

Drug interactions

Fluvoxamine

A strong inhibitor of CYP1A2 was shown to increase the mean alosetron plasma concentrations (AUC) about 6 times and lengthened the half-life almost 3 times.

Quinolone antibiotics and cimetidine should also be avoided if possible due to their moderate inhibition on CYP1A2.

Ketoconazole a strong inhibitor of CYP3A4 when administered with alosetron, raised the AUC 29%. Other CYP3A4 inhibitors are clarithyromycin, telithromycin, protease inhibitors, voriconazole, and itraconazole. These have not been tested but should be used with caution.

Patient monitoring guidelines

Patients should be monitored while on Lotronex® for the development of:

Diarrhea
Ischemic colitis
Rectal bleeding
New or worsening abdominal pain

Patient information

- This medication should only be prescribed by a physician that has enrolled in the GlaxoSmithKline Prescribing Program for Lotronex®
- Before taking this medication, the patient must read, sign and understand the Patient-Physician Agreement for Lotronex
- Read the Medication Guide prior to starting Lotronex® and again each time the medication is refilled.
- If constipated, do not start taking Lotronex®
- Discontinue taking Lotronex® and contact your physician if you:
  - Become constipated
  - Develop symptoms of ischemic colitis
    - -new or worsening abdominal pain
    - -bloody diarrhea
    - -blood in stool
- Call your physician again if the constipation continues after discontinuation of Lotronex®.
- Do not start taking Lotronex® again unless the constipation has resolved and the physician recommends it after consultation.
- If after 4 weeks of taking Lotronex® at 1mg BID, and the IBS symptoms are not adequately controlled, discontinue taking the medication and call the physician.

REFERENCES

1. Thompson WG, Creed F, Drossman DA, et al. Functional bowel disese and functional abdominal pain. Gastroenterol Int. 1992;5:75-91.
2. Morris & Dickson, MAD Link, online catalog.
3. Zelnorm® package insert.
4. Lotronex® package insert.

APPENDIX I

Follow-Up to Drug Utilization Review Board Questions

Oklahoma Medicaid
April 2005

Diabetes and Hypertension

Question: *"How are we doing relative to patients who are diabetics and what percentage of these patients are receiving an ACE Inhibitor?"*

Review Period: January 2004 through December 2004

Total Medical/Hospital Claims Reviewed for Diagnoses: 3,478,595
Total Clients Reviewed: 502,907

Total Clients with Hypertension Diagnosis: 43,907
Total Clients with Diabetes Diagnosis: 25,606

Answer: *Of all the clients with a diabetes diagnosis (25,606) a total of 10,566 clients (41.3 %) had a claim during the review period for any ACEI or combination.*

The JNC-VII provides the following information regarding the compelling indication for hypertensive patients with a co morbid condition of diabetes:

> "Combinations of two or more drugs are usually needed to achieve the target goal of <130/80 mmHg. Thiazide diuretics, BBs, ACEIs, ARBs, and CCBs are beneficial in reducing CVD and stroke incidence in patients with diabetes. ACEI- or ARB-based treatments favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce progression to macroalbuminuria."

Total Clients with Diabetes and Hypertension Diagnoses: *15,022*

Total Clients on Reviewed Medications: **12,601**

Medication Class	*Number of Clients*	*% of Total (N=15,022)*
Beta Blockers (BB)	5,444	36.2 %
Calcium Channel Blockers (CCB)	3,702	24.6 %
ACE Inhibitors (ACEI)	7,258	48.3 %
Angiotensin Receptor Blockers (ARB)	1,710	11.4 %
Thiazides (THIAZ)	2,793	18.6 %
HCTZ Based Combinations (HCTZ)	565	3.8 %
CCB / ACEI	353	2.3 %
ACEI / HCTZ	713	4.7 %
BB / HCTZ	128	0.9 %
ARB / HCTZ	830	5.5 %

Clients with two medications:

	BB	CCB	ACEI	ARB	THIAZ	HCTZ	CCB/ACEI	ACEI/HCTZ	BB/HCTZ	ARB/HCTZ
BB	5,444	1,491	2,920	770	1,177	223	140	233	29	312
CCB	1,491	3,702	1,873	533	806	170	81	156	27	251
ACEI	2,920	1,873	7,258	450	1,631	243	75	212	45	212
ARB	770	533	450	1,710	405	62	37	31	18	138
THIAZ	1,177	806	1,631	405	2,793	67	100	112	21	121
HCTZ	223	170	243	62	67	565	22	16	6	41
CCB/ACEI	140	81	75	37	100	22	353	14	4	22
ACEI/HCTZ	233	156	212	31	112	16	14	713	4	25
BB/HCTZ	29	27	18	18	21	6	4	4	128	2
ARB/HCTZ	312	251	212	138	121	41	22	25	2	830

Most frequent combinations:

1. ACEI and BB: 2,920 clients
2. ACEI and CCB: 1,873 clients
3. ACEI and THIAZ: 1,631 clients
4. BB and CCB: 1,491 clients
5. BB and THIAZ: 1,177 clients

For those clients with both diagnoses, 2,421 (16.1%) did not have a claim for a recommended hypertensive medication. However 786 (5.2%) of these clients had a claim for some other class of antihypertensive.

Recommendation: *Include in the next provider newsletter a reminder to physicians that clients with hypertension and diabetes should be prescribed a ACEI, ARB, Thiazide diuretic, BB or CCB based on the JNC-VII guidelines. The American Diabetes Association further supports the use of an ACEI or ARB for diabetic hypertensive patients.*

Summary of Recommendations for Treating Hypertension in Adults With Diabetes

- Blood pressure should be measured at every routine diabetes visit. Patients found to have systolic blood pressure >130 mmHg or diastolic blood pressure >80 mmHg should have blood pressure confirmed on a separate day. Orthostatic measurement of blood pressure should be performed to assess for the presence of autonomic neuropathy.
- Patients with diabetes should be treated to a blood pressure of <130/80 mmHg.
- Patients with a systolic blood pressure of 130–139 mmHg or a diastolic blood pressure of 80–89 mmHg should be given lifestyle/behavioral therapy alone for a maximum of 3 months. If targets are not achieved, pharmacological therapy should be started.
- Patients with a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg should receive drug therapy in addition to lifestyle/behavioral therapy.
- First-line agents include ACE inhibitors, ARBs, ß-blockers, or diuretics. Additional drugs may be chosen from these classes or another drug class.

- In hypertensive patients with microalbuminuria or clinical albuminuria, an ACE inhibitor or an ARB should be strongly considered. If one class is not tolerated, the other should be substituted.
- In patients over age 55 years with hypertension or another cardiovascular risk factor (history of cardiovascular disease, dyslipidemia, microalbuminuria, or smoking), an ACE inhibitor (if not contraindicated) should be considered to reduce the risk of cardiovascular events.
- In patients with a recent myocardial infarction, ß-blockers, in addition, should be considered to reduce mortality.
- In patients with microalbuminuria or overt nephropathy, in whom ACE inhibitors or ARBs are not well tolerated, a non-DCCB should be considered.
- If ACE inhibitors or ARBs are used, monitor renal function and serum potassium levels.
- In elderly hypertensive patients, blood pressure should be lowered gradually to avoid complications.
- Patients not achieving target blood pressure on three drugs, including a diuretic, and patients with severe renal disease should be referred to a specialist experienced in the care of patients with hypertension.

Diabetes and Cardiovacular Disease Review. A Publication of the American Diabetes Association / American College of Cardiology Make the Link! Initiative. Issue 2: Hypertension in Diabetes. Available at: http://www.diabetes.org/uedocuments/ADACardioReview_2.pdf.

Traditional NSAIDs

Question: *What effect did the removal of Vioxx® from the market have on the non-Cox-2 Inhibitor NSAIDs?*

Vioxx® was removed from the market on the last day of the first quarter of fiscal year 2005 (September 30, 2004). There was approximately a 31% decrease in claims for the subsequent quarter.

Number of claims for Cox-2 Inhibitors January 2004 - December 2004.

Brand	3rd Qtr FY '04	4th Qtr FY '04	1st Qtr FY '05	2nd Qtr FY '05
Celebrex®	4,990	5,623	5,830	5,344
Vioxx®	2,665	2,883	2,733	n/a
Bextra®	890	1,180	1,317	1,491

Answer: *There was only an 8% decrease in claims for the traditional NSAID class. There was an 84% increase in meloxicam from the previous quarter which accounted for the rise in cost to the total group.*

Traditional NSAIDs January 2004 - December 2004.

	3rd Qtr FY '04	4th Qtr FY '04	1st Qtr FY '05	2nd Qtr FY '05
Claims	30,804	34,922	38,000	34,828
Cost	$551,331.79	$573,991.62	$762,716.27	$872,317.20

Select NSAIDs July 2004 - December 2004

Drug	1st QTR FY '05		2nd QTR FY '05	
	Claims	*Cost*	*Claims*	*Cost*
Ibuprofen	16,134	$ 131,278.74	14,087	$ 126,478.02
Naproxen	10,916	$ 115,877.48	9,341	$ 100,494.06
Etodolac	2,624	$ 77,346.90	2,307	$ 70,937.35
Nabumetone	2,435	$ 115,169.73	2,329	$ 109,618.46
Diclofenac	1,970	$ 46,283.52	1,822	$ 41,193.42
Ketoprofen	1,252	$ 32,745.80	1,030	$ 29,201.18
Meloxicam	1,642	$ 218,100.68	3,014	$ 372,686.07
Total	36,973	$ 736,803.39	33,930	$ 850,608.56

Overall there appears to be a decrease in total usage of NSAIDs after the removal of Vioxx® from the market. However it is unknown if this trend will continue or if the utilization will return to its previous level.

APPENDIX J

FDA Public Health Advisory on Crestor (rosuvastatin)

Astra-Zeneca Pharmaceuticals today released a revised package insert for Crestor (rosuvastatin) (link to FDA approved labeling). The changes to the label include results from a Phase 4 pharmacokinetic study in Asian-Americans and highlight important information on the safe use of Crestor to reduce the risk for serious muscle toxicity (myopathy/rhabdomyolysis), especially at the highest approved dose of 40 mg. At this time, the FDA is also making statements about the muscle and kidney safety of Crestor based on extensive review of available information.

Background

Crestor, a member of a class of cholesterol-lowering drugs commonly referred to as "statins", was approved in the U.S. in August 2003, based on review of an extensive clinical database involving approximately 12,000 patients. These data supported the safety and efficacy of Crestor for use in lowering serum cholesterol, but also showed that Crestor, like all statins, rarely could cause serious muscle damage (myopathy and rhabdomyolysis). In the approved labeling, the FDA identified in the WARNINGS section of the product label those patients in whom more careful monitoring was warranted when prescribed Crestor. In a section titled: "Myopathy/Rhabdomyolysis", the label states that patients who are of advanced age (> 65 years), have hypothyroidism, and/or renal insufficiency should be considered to have a greater risk for developing myopathy while receiving a statin. Physicians are warned to prescribe Crestor with caution in these patients, particularly at higher doses, as the risk of myopathy increases with higher drug levels.

Based on these concerns, from the time of original approval, the FDA required Astra-Zeneca to make available in the U.S. a 5-mg dose that could be used in patients requiring less aggressive cholesterol-lowering or who were taking concurrent cyclosporine. The maximum recommended dose in the FDA-approved label is limited to 10 mg daily in patients with severe renal impairment or who are also taking gemfibrozil.

Description of current changes to the Crestor label

In a pharmacokinetic study involving a diverse population of Asians residing in the United States, rosuvastatin drug levels were found to be elevated approximately 2-fold compared with a Caucasian control group. As a result of these findings, the "Dosage and Administration" section of the label now states that the 5 mg dose of Crestor should be considered as the start dose for Asian patients and any increase in dose should take into consideration the increased drug exposure in this patient population. Results of this pharmacokinetic study are further discussed under the "Clinical Pharmacology" and "Precautions" section of labeling.

The "Warnings" and "Dosage and Administration" sections of the label have been revised to

more strongly emphasize the risks of myopathy, particularly at the highest approved dose of 40 mg. In order to minimize risks of myopathy and rhabdomyolysis (the most severe form of statin muscle injury), the revised label now explicitly states that the 5 mg dose is available as a start dose for those individuals who do not require aggressive cholesterol reductions or who have predisposing factors for myopathy. This includes patients taking cyclosporine, Asian patients, and patients with severe renal insufficiency. It also emphasizes that the 40 mg dose is not an appropriate start dose and should be reserved only for those patients who have not achieved their cholesterol goals with the 20 mg dose. This information is included in a bolded paragraph under the "Dosage and Administration" section that also reminds prescribers who switch patients from other statins to initiate therapy only with approved doses of Crestor and titrate according to the patient's individualized goal of therapy.

Healthcare professionals are reminded of the following key safety messages from the Crestor label:

- Start doses and maintenance doses of drug should be based on individual cholesterol goals and apparent risks for side-effects
- All patients should be informed that statins can cause muscle injury, which in rare, severe cases, can cause kidney damage and organ failure that are potentially life-threatening
- Patients should be told to promptly report to their healthcare provider signs or symptoms of muscle pain and weakness, malaise, fever, dark urine, nausea or vomiting

Review of Crestor muscle and kidney safety

Concerns have been raised about the possible increased muscle toxicity of Crestor compared to other statins on the market and about possible adverse effects on the kidney. The FDA has conducted an extensive review of Crestor data from pre-marketing and post-marketing clinical trials as well as adverse event reports submitted to the agency.

Muscle

Crestor, like all statins, has been associated with a low incidence of rhabdomyolysis (severe muscle damage). Data available to date from controlled trials, as well as post-marketing safety information, indicate that the risk of serious muscle damage is similar with Crestor compared to other marketed statins. As with all statins, some individuals taking Crestor will experience muscle side effects, most commonly mild aches and very rarely severe muscle damage. Like all drugs in this class, risks of muscle injury can be minimized by adhering to labeled warnings and precautions, carefully following dosing instructions, and instructing patients to be aware of and to report possible side effects to the physician. Finally, like all statins, Crestor should be prescribed at the lowest dose that achieves the goals of therapy (e.g., target LDL-C level).

Kidney

Various forms of kidney failure have been reported in patients taking Crestor, as well as with other statins. Renal failure due to other factors is known to occur at a higher rate in patients who are candidates for statin therapy (e.g., patients with diabetes, hypertension, atherosclerosis, heart failure). No consistent pattern of clinical presentation or of renal injury (i.e., pathology) is evident among the cases of renal failure reported to date that clearly indicate causation by Crestor or other statins.

Mild, transient proteinuria (or protein in the urine, usually from the tubules), with and without microscopic hematuria (minute amounts of blood in the urine), occurred with Crestor, as it has

with other statins, in Crestor's pre-approval trials. The frequency of occurrence of proteinuria appeared dose-related. In clinical trials with doses from 5 to 40 mg daily, this effect was not associated with renal impairment or renal failure (i.e., damage to the kidneys). It is recommended, nevertheless, that a dose reduction and an investigation into other potential causes be considered if a patient on Crestor develops unexplained, persistent proteinuria.

Ongoing controlled clinical trials of Crestor and other statins, epidemiologic studies of the safety and side effects of Crestor, and ongoing pharmacovigilance by FDA will continue to provide information on the balance of risks and benefits of Crestor and other members of this important class of drugs. This information will be made available and, as appropriate, applied to drug labeling in a timely fashion.

The current FDA-approved label can be obtained at:
http://www.fda.gov/cder/foi/label/2005/21366slr005lbl.pdf

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U.S. Food and Drug Administration

FDA News

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Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

U.S. Marshals Seize Lots of GlaxoSmithKline's Paxil CR and Avandamet Tablets Because of Continuing Good Manufacturing Practice Violations

In a response to ongoing concerns about manufacturing quality, the Food and Drug Administration (FDA) and the Department of Justice today initiated seizures of Paxil CR and Avandamet tablets manufactured by GlaxoSmithKline, Inc. (GSK). Manufacturing practices for the two drugs, approved to treat depression and panic disorder (Paxil CR) and Type II Diabetes (Avandamet), failed to meet the standards laid out by FDA that ensure product safety, strength, quality and purity.

"FDA and the Department of Justice will not allow drug manufacturers to ignore our high public health standards for drug manufacturing," said John M. Taylor, FDA Associate Commissioner for Regulatory Affairs. "Once we discover a company is not following the standards, which were created to ensure safety and quality, we expect them to correct the deficiencies in an expedited manner. American consumers deserve the best health care products on the market today, and companies that are not adhering to these standards cannot assure FDA and American consumers of the quality of their products."

FDA is not aware of any harm to consumers by the products subject to this seizure and it does not believe that these products pose a significant health hazard to consumers. Consequently, FDA urges patients who use these two drugs to continue taking their tablets and to talk with their health care provider about possible alternative products for use until the manufacturing problems have been corrected. FDA has determined that neither product is medically necessary and that alternative products are available for consumer use.

The agency is concerned that GSK's violation of manufacturing standards may have resulted in the production of poor quality drug products that could potentially pose risks to consumers. Among the violations noted during FDA's latest inspection was the finding that the Paxil CR tablets could split apart and patients could receive a portion of the tablets that lacks any active ingredient, or alternatively a portion that contains active ingredient and does not have the intended controlled-release effect. Additionally, FDA found that some Avandamet tablets did not have an accurate dose of rosiglitazone, an active ingredient in this product.

The seizures follow warrants issued by the U.S. District Courts for the District of Puerto Rico and the Eastern District of Tennessee. The seizures were executed today by the U.S. Marshals Service at GSK's Cidra, Puerto Rico manufacturing facility, its Knoxville, Tennessee distribution facility, and a Puerto Rico distribution facility. GSK has voluntarily recalled some of the affected lots of Paxil CR and Avandamet; however, it has failed to recall all affected lots of these products. This failure on the part of GSK resulted in today's seizures by federal authorities.

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More Information: Questions and Answers about the Seizure of Paxil CR and Avandamet (March 4, 2005)

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U.S. Food and Drug Administration

FDA Talk Paper

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Media Inquiries: Laura Alvey
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FDA Publishes Final Rule on Chlorofluorocarbons in Metered Dose Inhalers

The Food and Drug Administration (FDA), an agency within the U.S. Department of Health and Human Services (HHS), today announced that albuterol metered-dose inhalers (MDIs) using chlorofluorocarbon (CFC) propellants must no longer be produced, marketed or sold in the United States after December 31, 2008.

In a final rule published today in the *Federal Register*, HHS said sufficient supplies of two approved, environmentally friendly albuterol inhalers will exist by December 31, 2008 to allow the phasing out of similar less environmentally friendly versions.

HHS is encouraged that the manufacturers of three environmentally friendly albuterol inhalers are implementing programs to help assure access to these albuterol MDIs for patients for whom price could be a significant barrier to access to this important medicine. These programs include MDI giveaways, coupons for reducing the price paid and patient-assistance programs based on financial need.

CFC-containing albuterol MDIs, as with other CFC-based MDIs for asthma and chronic obstructive pulmonary disease (which includes emphysema and chronic bronchitis) were previously exempted from a general ban of CFC production and importation under an international agreement established through the Montreal Protocol on Substances that Deplete the Ozone Layer and the U.S. Clean Air Act.

The final rule also forms the basis for the phase-out of the CFC-containing albuterol products through the withdrawal of their "essential use" status as of December 31, 2008. This change in status is based on HHS' determination that:

- At least two non-CFC products with the same active drug are marketed with the same route of administration, for the same indication, and with approximately the same level of convenience of use as the CFC product that contains that active ingredient;
- Supplies and production capacity for the non-CFC product will exist by December 31, 2008 at levels sufficient to meet patient needs;
- Adequate U.S. post marketing use data are available for the non-CFC product; and
- Patients who are required to use the CFC product for medical reasons will be adequately served by the alternative non-CFC product and other available products.

HHS sought and received public comment from a proposed rule in June 2004. This public comment, combined with feedback from a Pulmonary Allergy Drugs Advisory Committee meeting in June 2004, as well as consultation with other Federal agencies, helped the agency develop the final rule.

For additional information, go to: http://www.fda.gov/cder/mdi/default.htm.

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Federal Register (PDF)
Questions and Answers