THE UNIVERSITY OF OKLAHOMA

MEMORANDUM

TO: Drug Utilization Review Board Members

FROM: Ron Graham, D.Ph.

SUBJECT: **Packet Contents for Board Meeting – November 9, 2004**

DATE: November 4, 2004

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

Enclosed are the following items related to the November 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.**

(30) Day Notice to Vote on Recommended Prior Authorization Changes for ADHD Medications – **See Appendix C.**

Annual Review of PBPA Category – NSAIDS - **See Appendix D.**

(30) Day Notice of Intent to Prior Authorize - Zegerid® (New Product) - **See Appendix E.**

Review and Discuss Zyvox® Utilization – **See Appendix F.**

Review and Discuss Bladder Control Product Utilization – **See Appendix G.**

(30) Day Notice of Intent to Prior Authorize - Xopenex® **- See Appendix H.**

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

Future Business

Adjournment

Drug Utilization Review Board

(DUR Board)

Meeting – November 9, 2004 @ 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. October 12, 2004 DUR Minutes - Vote

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

4. **Update on DUR/MCAU Program - See Appendix B.**
   A. Retrospective DUR Report for August 2004
   B. Medication Coverage Activity Audit for October 2004
   C. Help Desk Activity Audit for October 2004

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

5. **(30) Day Notice to Vote on Recommended Prior Authorization Changes for ADHD Medications - See Appendix C.**
   A. New COP Recommendations

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

6. **Annual Review of PBPA Category – NSAIDS – See Appendix D.**
   A. Utilization Review
   B. COP Recommendations

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

7. **(30) Day Notice of Intent to Prior Authorize - Zegerid® (New Product) – See Appendix E.**
   A. Drug Monograph
   B. COP Recommendations

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

8. **Review and Discuss Zyvox® Utilization – See Appendix F.**
   A. Utilization Review
   B. COP Recommendations

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

9. **Review and Discuss Bladder Control Product Utilization – See Appendix G.**
   A. Utilization Review
   B. COP Recommendations

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

10. **(30) Thirty Day Notice of Intent to Prior Authorize - Xopenex® - See Appendix H.**
   A. Proposed PA Criteria after 90 days of therapy per 360 day period
   B. Economic Impact

11. **FDA and DEA Updates – See Appendix I.**

12. **Future Business**
   A. PBPA Annual Reviews
   B. Neurontin™ Follow-Up Review
   C. MS Copolymers Review
   D. SMAC Update
   E. Supplemental Rebate Update
   F. New Product Reviews

13. **Adjournment**

APPENDIX A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES of MEETING of OCTOBER 12, 2004

BOARD MEMBERS:	PRESENT	ABSENT
Rick G. Crenshaw, D.O.		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	
(VACANT)		
(VACANT)		

COLLEGE of PHARMACY STAFF:	PRESENT	ABSENT
Leslie Browning, D.Ph./Clinical Pharmacist		X
Karen Egesdal, D.Ph./Clinical Pharmacist/OHCA Liaison	X	
Kelly Flannigan, Pharm.D../Clinical Pharmacist	X	
Shellie Gorman, Pharm.D./Clinical Pharmacist	X	
Ronald Graham, D.Ph., Manager, Operations/DUR	X	
Chris Kim Le, Pharm.D.; Clinical Pharmacist		X
Ann McIlvain, Pharm.D.; Clinical Pharmacist	X	
Carol Moore, Pharm.D.; Clinical Pharmacist		X
Neeraj Patel, Pharm.D.; Clinical Pharmacist	X	
Lester A. Reinke, Ph.D.	X	
Visiting Pharmacy Student: n/a		

OKLAHOMA HEALTH CARE AUTHORITY STAFF:	PRESENT	ABSENT
Kristall Bright; Pharmacy Financial Analyst		X
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:

Lana Stewart, Merck	Mike Avey, Sepracor	Robb Hast, Cephalon
Cindy Flesher, Bristol Myers Squibb	Tammie Capps, Purdue	Rhonda Clark, Purdue
Rebecca Waldrop, Sanofi	Holly Jacques, Merck	Angela Menchaca, Amgen
Ron Schnare, Abbott	Terry McCuran, Bristol Myers Squibb	

PRESENT FOR PUBLIC COMMENT:
Tammie Capps, Purdue; Agenda Item No. 8

AGENDA ITEM NO. 1: **CALL TO ORDER**

1A: Roll Call

Dr. Whitsett called the meeting to order. Roll call by Dr. Graham established the presence of a quorum.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 2: **PUBLIC COMMENT FORUM**

2A: Acknowledgement of Speakers and Agenda Item

Dr. Whitsett acknowledged Public Comment speaker as noted above.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 3: **APPROVAL OF DUR BOARD MINUTES**

3A: September 14, 2004 DUR Minutes

Dr. Meece moved to approve minutes as submitted; motion seconded by Dr. Swaim.

ACTION: MOTION CARRIED

AGENDA ITEM NO. 4: **UPDATE ON DUR/MCAU PROGRAM**

4A: Therapy Management Quarterly Update

From July through September 2004 (1st Quarter SFY05), 556 client profiles have been reviewed. Approval/denial/incomplete totals were noted in report submitted to the Board. Materials included in agenda packet; presented by Dr. Flannigan.

4B: Retrospective DUR Report: July 2004

Contraindicated nursing home females over 65 years were selected for retrospective review for July 2004. Pharmacy and physician response was 24% and 36% respectively. Materials included in agenda packet; presented by Dr. Flannigan. Additional information on certain drug-disease alerts reported will be followed up on in the future.

4C: Medication Coverage Activity Report: September 2004

The September 2004 activity audit noted total number of petitions submitted was 16,305 including super-PA's and special circumstance PA's. Approval/denial/duplicate percentages were indicated on the reports included in the agenda packet for this meeting. Monthly and 1st Quarter SFY05 reports included in agenda packet; presented by Dr. Flannigan.

4D: Help Desk Activity Report: September 2004

Total calls for September 2004 numbered 16,373 (84.1% pharmacies, 8.5% clients, 2.1% physicians, 5.3% other). Monthly and 1st Quarter SFY05 reports included in agenda packet; presented by Dr. Flannigan.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 5: **EPOCRATES RX® DRUG REFERENCE GUIDE DEMONSTRATION**

Alex Easton, OHCA Pharmacy Operations Manager, presented the ePocrates® demonstration.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 6: **REVIEW & DISCUSS ANTI-DEMENTIA DRUG UTILIZATION**

Materials included in agenda packet; presented by Dr. Gorman. Dr. Whitsett suggested the COP look at the degree or stage of dementia of these nursing home patients with the possibility of improving their condition or is it being used in end-stage severe dementia.

ACTION: NONE REQUIRED.

AGENDA ITEM No. 7: **REVIEW & DISCUSS GUIDELINES FOR TREATING NAUSEA & VOMITING IN PREGNANCY (NVP)**

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

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 8: REVIEW & DISCUSS NARCOTIC ANALGESIC DRUG UTILIZATION

For Public Comment, Tammie Capps: *We don't really have any comments. We were just going to comment on the presentation, but I did want to make you aware of maybe some news that you all were not aware of. That in this last legislative session, we worked with the Bureau of Narcotics to expand their prescription monitoring program, that's going to expand it to II's, III's, IV's and V's. And what that does is in the past, it's supposed to be for physicians to get into the system to see if there's any type of aberrant behavior by patients and the way that the law was written is even doctors couldn't get into the system to be able to check if there is aberrant behavior, so the Bill has gone through. It's been signed off by the Governor. They intend to implement it at the end of this year, so they're going to use that . . . what's called the optimum system. It may be interesting in terms of utilization review once this program comes into being, to track utilization and how it impacts your all's utilization. One of the things that the Bureau has said that their major problem is methamphetamine, and of course that's not something that you would be able to track. And they said that really in terms of aberrant behavior, they do have problems with Schedule II's, but not compared to Schedule III's, IV's and V's and that's because they're not scrutinized. So I just kind of wanted to give you that and just as a partnership program with industry, I know you all shy a little bit away from the drug companies in terms of marketing, but it may be interesting. I'm very excited about this new program for the physicians and pharmacists, Rx on-line. And if you're going to do a blitz program just know that we have thousands of representatives in the field, that if you have an approved piece, we would not be able to create a piece, but if you have a piece that you would want that distributed to physicians, I think that many of us would be willing to partner with you all and get the word out quickly because there's nothing but good news for all of us on that, in that information. So just let us know if we can help in any way. Thank you and that was it.*

Materials included in agenda packet; presented by Dr.McIlvain.

Tammie Capps: *I'm sorry, just one . . . I wasn't going to bring it up until somebody else brought it up, but also a very interesting finding in the Bureau of Narcotics is they've got forty legitimate methadone deaths from real prescriptions for real patients. It's because what they're . . . they're doing a study with the University here. Tim you may be somehow connected with it. It's John Duncan down at the Bureau, and it may be something that you might be interested in seeking out because what . . . what they think is happening is that lots of insurance companies are racheting down on some of the brand products and going to the generics. And what's happened is, they're using methadone and doctors don't feel very comfortable with using methadone. It's a very difficult drug to dose. And they've had forty deaths I think for this year alone.*

Dr. Whitsett: *They . . . who's they?*

Tammie Capps: *The Bureau of Narcotics . . . in Oklahoma alone.*

Dr. Graham: *How many oxycontin deaths have we had . . . do you know?*

Tammie Capps: *You know, I don't know that. It would be, you know we didn't . . . we were talking about the PMP . . . a good question. When I talked with the Bureau in terms of . . . because we do lots of partnership programs with them, just like the PMP . . . is that they said that to say that there isn't an oxycontin problem would be wrong, but to say that it's the major culprit here in the State, and he attributes it to the PMP that physicians actually are a little bit scared to use it.*

Dr. Whitsett: *And I don't know the people who are using methadone, whether this was frequently of either people who have terminal diseases and then they . . . terminal diseases die.*

Dr. Graham: *That's what a lot of them use.*

Dr. Whitsett: *And so, I'm not sure . . .*

Tammie Capps: *And I don't know the details, but I just thought since you brought up the methadone . . . it's . . . seen in two or three other states as well, so maybe . . . forty's a lot.*

Dr. Gourley: *. . . suicide, intended overdoses.*

Dr. Whitsett: *Well at some point we may want someone from the Oklahoma Bureau of Narcotics to . . .*

Dr. Graham: *We had John Duncan here at one time a couple of years ago.*

Dr. Whitsett: *Yeah, so it may be time to let him revisit us.*

Dr. Graham: *I'll call him and see if he's interested.*

Dr. Whitsett: *See if he has something he feels he needs to share with us that we could communicate to other people.*

Dr. McNeill: *You know, $15 million in 2003 for this class of drugs alone . . . have you explored or thought about some ways to trim this down a little bit? I mean is this . . . I can't imagine that this is responsible prescribing.*

Dr. Graham: *We brought quantity limits and also some other recommendations to the Board at one time on some of the narcotics, at least the higher priced ones.*

Dr. McNeill: *Well you know, $2.2 million in Lortab alone . . . you know, that's . . . that's a lot of Lortab. So I think we ought to look at this again. One could argue, well if you make it harder for me to get Lortab, then I'll just go to Vicodan, or I'll just go to oxycontin if it's not appropriately being prescribed or sought.*

Dr. Graham: *We did a, I think, didn't you do a retro DUR on the hydrocodones and the . . .*
Dr. McIlvain: *Yeah, a couple of months ago we did a retro DUR on the duplication of narcotics, just all the narcotics. There was a lot of it, a lot of . . .*
Dr. Meece: *Anagelsics are what's eating us up right now.*
Dr. McNeill: *Well I have a hard time getting upset. I mean getting excited about $50,000 for methadone when Lortab's you know, over $2 million, that's all.*
Dr. Hollen: *Are there any prospective DUR in place as far as quantity or use?*
Dr. Graham: *We looked at the acetaminophen part. There's some states that can do that, and we're not able to do that right now.*
Dr. Hollen: *OK, so we're just not capable of doing . . . OK.*
Dr. Graham: *. . . got the acetaminophen at a cap, a quantity cap, then they can't use the other because you're maxed out that day.*
Dr. Meece: *That's hard to sell. I mean people don't understand what that APAP's doing to them.*
Dr. Graham: *That's right. And see, it's really, it's really . . . you'll blow your liver or kidneys out faster with that than . . . so, it's really a more serious issue.*
Dr. Gourley: *So all we're really to look at right now is duplication.*
Dr. Gorman: *We have the ingredient and the therapy, it's in both modules, pro DUR (inaudible) . . . duplication and therapeutic duplication, mostly just a warning . . .*
Dr. Gourley: *So we wouldn't be able to see because we don't prior authorize it, we wouldn't be able to see the usage specifically for certain write downs, we'd just do male/female and . . .*
Dr. Graham: *Yeah, it's you know, hydrocodone especially is used for so many different things . . . dental issues, whatever, you know.*
Dr. Whitsett: *It would be interesting maybe to break out the duration of usage . . . a lot of short term usage for dental procedures or etcetera . . . and similar and then those that are using it month in, month out, year in, year out.*
Dr. McIlvain: *Well on page 46, that last little . . . there. It kind of addresses that, the number of claims per client; 80% of the clients got between one and five claims during the year 2003, so it looks like the bulk of it is short term.*
Dr. Whitsett: *OK, so that's comforting.*
Dr. Meece: *So duragesic would probably go over $6 million this year, right? For the first half, it's 2.8.*
Dr. Graham: *Pretty close, yeah.*
Dr. Whitsett: *It would be interesting to see the deaths . . . earlier . . .several that are . . . medicolegal issues right now. Duragesic, otherwise.*
Dr. Graham: *I'm just wondering if John Duncan has access to that information. I'll find out.*
ACTION: NONE REQUIRED.

AGENDA ITEM NO. 9: **REVIEW & DISCUSS RHEUMATOID ARTHRITIS DRUG (DMARDs) UTILIZATION**

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

AGENDA ITEM NO. 10: **FDA & DEA UPDATES**

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

AGENDA ITEM No. 11: **FUTURE BUSINESS**

11A: PBPA Annual Reviews
11B: Neurontin™ Follow-Up Review
11C: MS Copolymers Review
11D: Supplemental Rebate Update
11E: SMAC Update
11F: Bladder Control Medications
11G: New Product Reviews

Materials included in agenda packet; submitted by Dr. Graham.

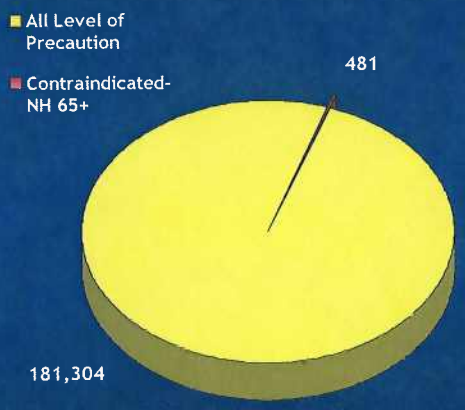
ACTION: NONE REQUIRED.

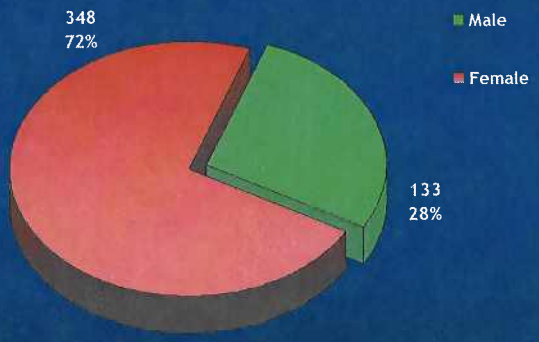
AGENDA ITEM No. 12: **ADJOURNMENT**

The meeting was declared adjourned.

APPENDIX B

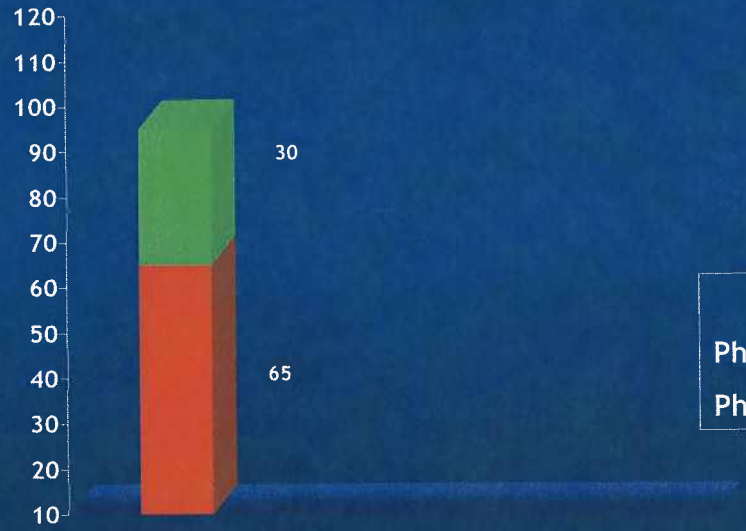
Oklahoma Medicaid RetroDUR Activity Report
August 2004 Drug-Disease Level - Contraindicated
Nursing Home Males over 65 years of age





Oklahoma Medicaid RetroDUR Activity Report
Follow-Up
August 2004 Drug-Disease Level - Contraindicated
Nursing Home Males over 65 years of age

Total Clients Reviewed = 95



Total Responses			
Pharmacy	=	0/30	0%
Physician	=	0/30	0%

Activity Audit for

October 01 2004 Through October 31 2004

Date	Antiulcers		Anxiolytic/ Hypnotics		Antihistamine		Growth Hormones		Stimulant		Smoking Cess.		Nsaids		ACE Inhibitors		HTN Combos		Calcium Channel Blockers		Plavix		ARB		Anti-depressants		Daily Total
	app.	den.	app.	den.	app.	den.	app.	den.	app.	den.	app.	den.	app.	den.	app.	den.	app.	den.	app.	den.	app.	den.	app.	den.	app.	den.	
1	8	9	244	39	38	29	0	0	107	27	0	0	18	30	3	2	0	0	5	13	26	11	0	0	0	1	610
2	4	4	82	11	9	8	0	0	23	16	0	0	2	12	0	0	0	0	3	4	7	5	0	0	0	0	190
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	6	12	172	25	44	35	3	0	70	30	0	0	15	29	3	4	1	0	3	7	23	7	0	0	1	0	490
5	9	19	211	47	57	44	0	1	95	37	1	0	29	48	2	11	1	1	4	16	30	10	0	0	1	0	674
6	6	11	210	36	62	36	0	0	123	53	0	0	18	48	7	6	0	1	1	19	34	14	0	0	0	2	687
7	8	12	154	33	43	30	0	0	63	28	0	0	10	29	1	6	1	0	3	8	19	9	0	0	1	0	458
8	3	4	102	17	33	15	0	0	67	12	0	0	15	21	3	3	0	0	1	8	15	8	0	0	0	0	327
9	0	3	59	23	17	8	0	0	31	11	0	0	5	10	1	1	0	1	1	3	10	5	0	0	0	0	189
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12	5	15	179	39	47	43	0	0	66	28	0	0	13	41	3	7	0	1	6	20	24	8	0	0	7	14	566
13	6	17	197	49	48	37	8	2	86	30	0	0	10	43	0	3	0	1	2	12	40	9	0	0	4	14	618
14	4	13	154	24	40	16	0	0	66	32	0	0	17	30	1	2	0	0	5	10	14	4	0	0	3	8	443
15	9	16	164	33	33	25	0	0	78	34	0	0	19	24	3	7	0	0	8	12	24	14	0	0	12	16	531
16	6	14	45	18	13	15	0	0	21	8	0	0	9	5	0	2	0	0	4	2	5	4	0	0	2	2	175
17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18	5	12	158	32	25	11	2	0	59	22	0	0	5	20	2	5	1	0	5	6	20	15	0	0	3	18	426
19	9	18	147	33	61	27	0	0	91	38	0	0	15	37	2	4	1	0	9	15	25	15	0	0	15	15	577
20	11	17	186	33	39	32	0	0	93	29	0	0	13	34	3	2	0	0	10	14	23	8	0	0	11	17	575
21	10	21	169	39	44	28	0	0	80	39	1	0	16	41	2	12	0	1	5	23	18	25	0	0	10	19	603
22	10	9	121	31	41	15	0	0	62	19	0	0	9	15	4	2	0	1	3	8	19	17	0	0	10	18	414
23	1	4	32	16	10	25	0	0	16	14	0	0	5	11	0	1	0	0	1	4	6	5	0	0	1	8	160
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25	2	5	91	17	31	18	5	0	58	18	0	0	6	17	0	3	0	1	4	6	15	15	0	0	9	11	332
26	6	27	162	33	41	31	1	0	77	28	0	0	13	34	1	3	0	1	10	15	32	9	0	0	23	21	568
27	13	13	136	35	56	29	0	0	125	34	0	0	15	37	2	6	0	0	8	11	10	12	0	0	31	30	603
28	2	23	141	28	55	36	6	0	56	23	0	0	16	40	0	7	0	0	4	6	20	9	0	0	28	20	520
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31	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Activity Audit for

October 01 2004 Through October 31 2004

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.	Smoking Cess. app.	Smoking Cess. 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.	165		3720		958		28		1785		2		329		49		7		114		517		1		200		
Den.		338		772		651		3		672		0		723		112		9		278		266		0		265	
Average Length of Approvals in Days	93		100		102		172		276		76		338		321		271		330		268		365		282		

Smoking Cessation	0 PA's for Zyban	2 Total PA's Approved
	2 PA's for Nicotine Patch	2 Unique RID's

Changes to existing PA's	1093
Total (Previous Year)	9615

Monthly Totals

	Number	Percent of Total
Approved	9305	53.07%
Additional PA's	10	0.06%
SUPER PA's	1276	7.28%
Emergency PA's	6	0.03%
Duplicates	946	5.40%
Incompletes	1361	7.76%
Denied *	4630	26.41%
Total	17534	100.00%

Daily Average of 674.38 for 26 Days

*** Denial Codes**

762 = Lack of clinical information	43.11%
763 = Medication not eligible	2.48%
764 = Existing PA	26.57%
772 = Not qualified for requested Tier	18.51%

SUPER PA's

Early Refill Attempts	59851
Dosing Change	559
lost/stolen/broke	176
Other	106
wrong DS	87
Quantity vs. Days Supply	348

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.)

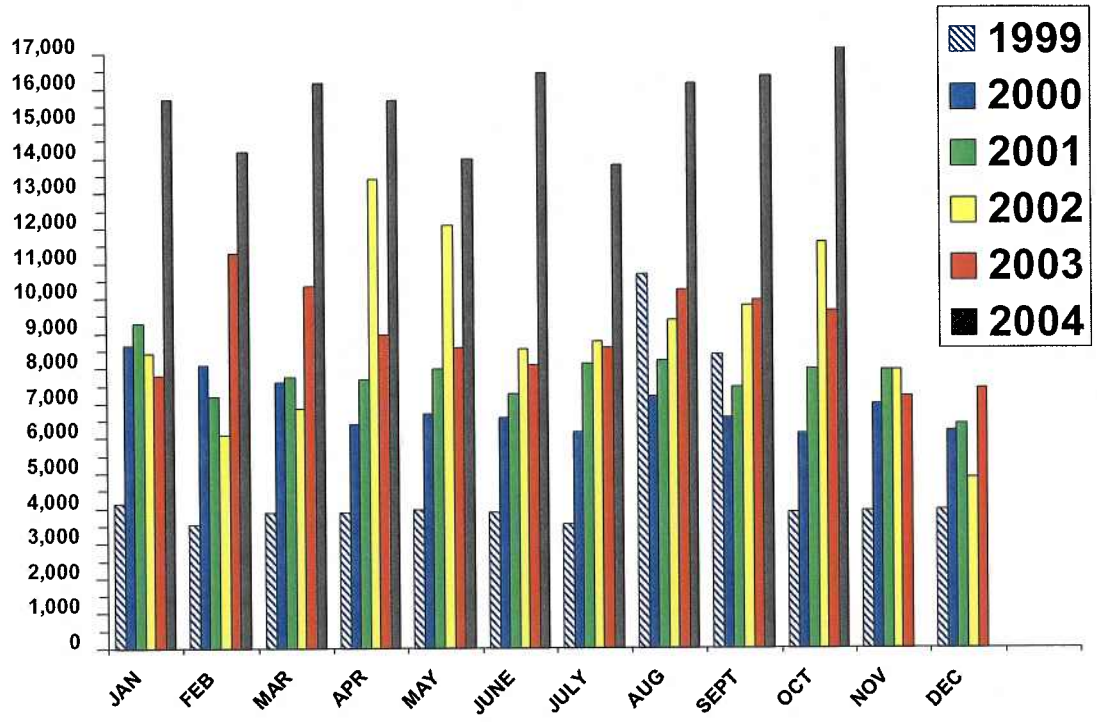
PRIOR AUTHORIZATION ACTIVITY AUDIT

Monthly Totals

MONTH	1999 Total *(approved/ duplicates/ denied)*	2000 Total *(approved/ duplicates/ denied)*	2001 Total *(approved/ duplicates/ denied)*	2002 Total *(approved/ duplicates/ denied)*	2003 Total *(approved/ duplicates/ denied)*	2004 Total *(approved/ duplicates/ denied)*
January	4,124	8,669	9,296	8,427	7,797	15,688
February	3,542	8,077	7,194	6,095	11,272	14,188
March	3,856	7,588	7,748	6,833	10,358	16,138
April	3,867	6,390	7,676	13,381	8,953	15,644
May	3,959	6,711	7,980	12,082	8,589	13,960
June	3,884	6,565	7,249	8,550	8,084	16,454
July	3,523	6,181	8,133	8,775	8,565	13,813
August	10,676	7,183	8,195	9,353	10,213	16,132
September	8,387	6,585	7,438	9,793	9,918	16,305
October	3,863	6,140	7,956	11,584	9,615	17,534
November	3,919	6,961	7,949	7,921	7,201	
December	3,953	6,206	6,385	4,867	7,391	
Calendar Year Total	**57,553**	**83,256**	**93,199**	**107,661**	**107,956**	**155,856**

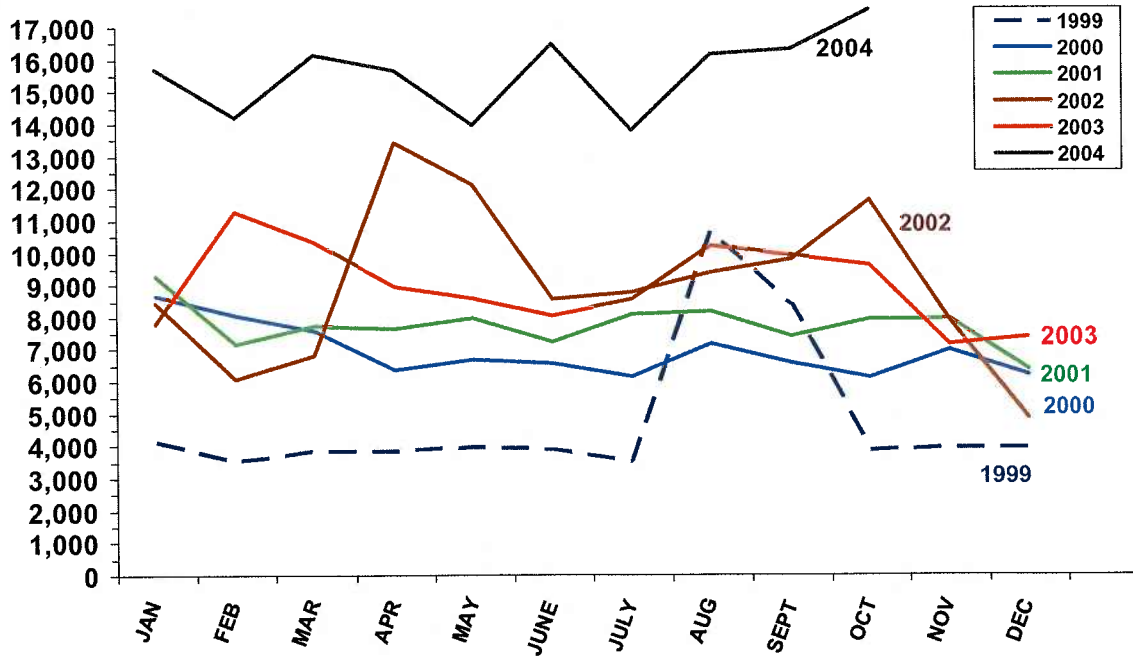
Monthly PA Activity

Calendar Years 2000-2004

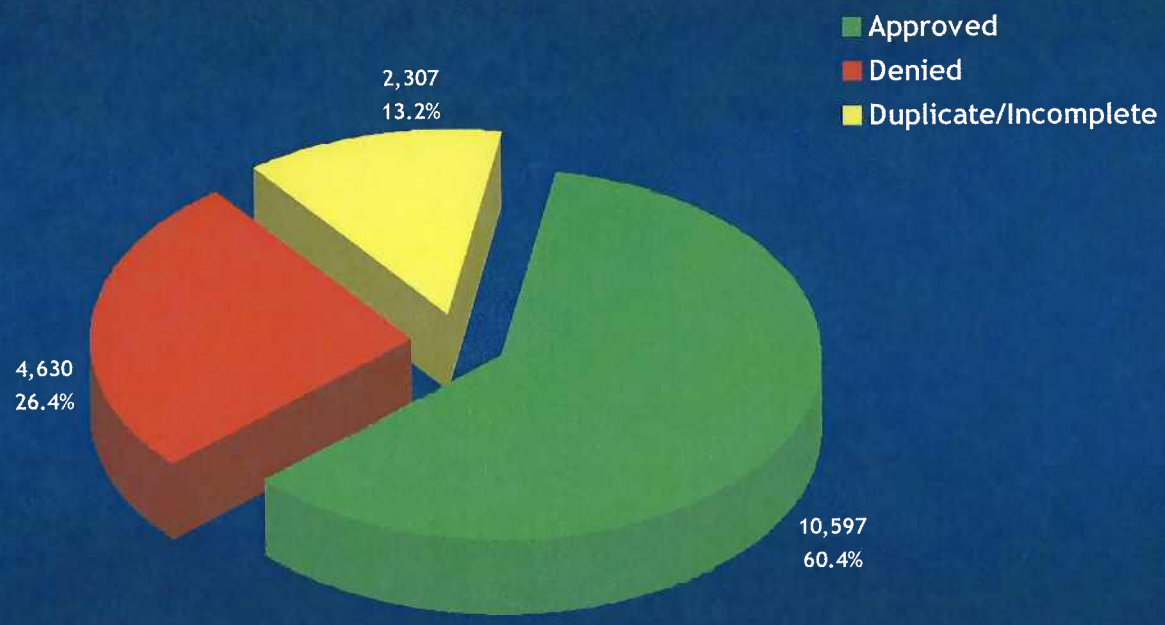


Monthly PA Activity

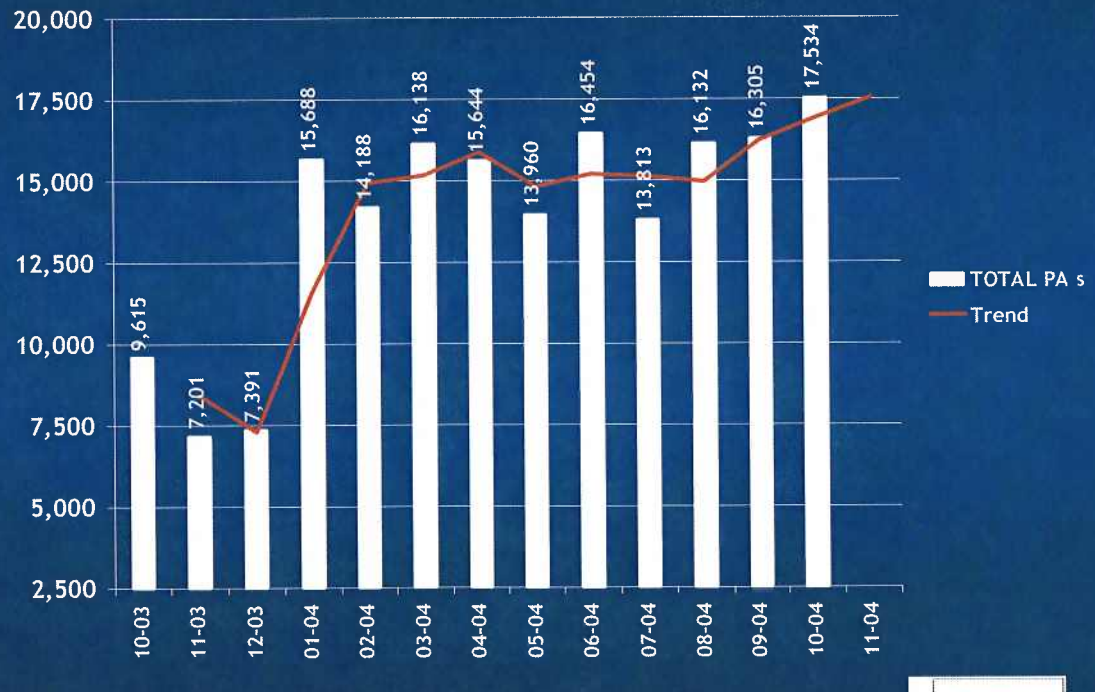
Calendar Years 2000-2004



PRIOR AUTHORIZATION ACTIVITY REPORT
October 2004



PRIOR AUTHORIZATION REPORT
October 2003 - October 2004



CALL VOLUME -OCTOBER 2004

OCTOBER '04	CALLER					ISSUE					TYPE OF CALL					RESOLUTION							
																	Resolved						
	Call Volume	Physician	Pharmacies	Clients	Other	Eligibility	Claims	PA Issue	SMAC	Other	Regular	Callback	Proactive	ProDUR	Other	Helpdesk Resolved	Transferred Pharmacist	Transferred Supervisor	OHCA	Reversals/ Adjustments	EDS	Customer Service	Provider Contracts
1	959	16	859	59	25	253	367	122	0	217	902	7	1	33	11	939	7	2	0	1	1	9	0
2	165	0	162	3	0	53	70	14	0	28	163	0	0	2	0	157	0	0	0	2	0	6	0
3	44	0	43	1	0	15	19	2	0	8	44	0	0	0	0	44	0	0	0	0	0	0	0
4	771	14	659	84	14	193	268	123	0	187	751	3	0	12	5	750	4	0	0	1	0	16	0
5	785	18	656	84	27	207	254	119	0	205	752	6	0	16	11	761	6	0	0	2	0	15	1
6	692	14	578	71	29	166	220	123	0	183	652	11	1	25	3	678	5	1	0	1	0	7	0
7	732	18	634	61	19	184	266	89	0	193	703	9	3	11	6	723	1	1	0	0	0	7	0
8	773	7	678	73	15	156	386	74	0	156	757	6	0	6	4	768	1	1	0	0	0	3	0
9	175	0	170	4	1	33	88	15	0	39	172	3	0	0	0	175	0	0	0	0	0	0	0
10	47	0	47	0	0	14	16	3	0	14	47	0	0	0	0	47	0	0	0	0	0	0	0
11	860	19	726	88	27	216	298	139	0	207	813	17	1	26	3	831	7	1	1	0	2	18	0
12	770	8	657	74	31	116	343	117	0	192	735	13	2	15	3	753	8	0	0	1	0	8	0
13	676	12	580	64	20	142	211	109	0	214	640	17	3	15	1	659	3	0	0	0	0	14	0
14	917	20	817	57	23	206	400	109	0	202	891	6	5	10	5	900	9	0	0	1	0	7	0
15	774	10	659	87	18	196	286	100	0	192	745	2	0	18	9	757	4	3	0	0	0	10	0
16	174	0	159	15	0	38	92	18	0	26	163	0	0	10	1	172	0	0	0	0	0	2	0
17	59	0	54	5	0	12	32	5	0	10	57	0	0	2	0	57	0	1	0	1	0	0	0
18	776	11	688	63	14	197	309	109	0	158	749	7	1	17	2	765	5	0	0	0	0	6	0
19	778	23	648	78	29	104	385	122	0	167	748	8	3	10	9	767	3	1	0	0	0	7	0
20	791	26	663	80	22	104	383	118	0	186	763	15	1	9	3	776	6	0	0	0	1	8	0
21	751	10	660	44	37	138	337	80	0	196	711	10	8	15	7	722	9	1	0	1	0	16	2
22	680	19	570	72	19	153	249	116	0	162	662	4	0	9	5	660	6	2	0	1	1	10	0
23	151	0	142	5	4	16	88	13	0	34	136	1	0	12	2	149	1	0	0	0	0	1	0
24	55	0	48	2	1	8	29	2	0	16	53	0	0	1	1	54	0	1	0	0	0	0	0
25	743	21	631	72	19	103	353	112	0	172	723	2	2	13	3	720	8	1	0	1	1	10	2
26	794	26	658	95	15	114	367	117	0	195	768	6	0	15	5	770	4	0	0	1	0	19	0
27	677	16	566	73	22	156	235	110	0	176	651	6	2	10	8	653	3	2	0	0	1	0	0
28	822	8	723	76	15	118	458	91	0	154	807	5	0	4	6	809	4	1	0	0	0	8	0
29	703	25	600	60	18	149	267	128	0	164	675	7	2	10	9	668	14	2	1	0	1	10	7
30	166	0	160	3	3	22	98	13	0	22	156	1	0	7	2	163	1	1	1	0	0	0	0
31	40	0	36	2	2	5	25	2	0	8	39	0	0	0	1	39	0	1	0	0	0	0	0
Total	**17,300**	**341**	**14,931**	**1,555**	**469**	**3,587**	**7,199**	**2,414**	**0**	**4,083**	**16,628**	**172**	**35**	**333**	**125**	**16,886**	**119**	**23**	**3**	**14**	**8**	**217**	**12**
Percentage	**100.00%**	**1.97%**	**86.31%**	**8.99%**	**2.71%**	**20.73%**	**41.61%**	**13.95%**	**0.00%**	**23.60%**	**96.12%**	**0.99%**	**0.20%**	**1.92%**	**0.72%**	**97.61%**	**0.69%**	**0.13%**	**0.02%**	**0.08%**	**0.05%**	**1.25%**	**0.07%**

NOTE: 10-8-04: Server for entire campus was down from 1:00 pm-4:20 pm; no computer access during this period.

CALL VOLUME

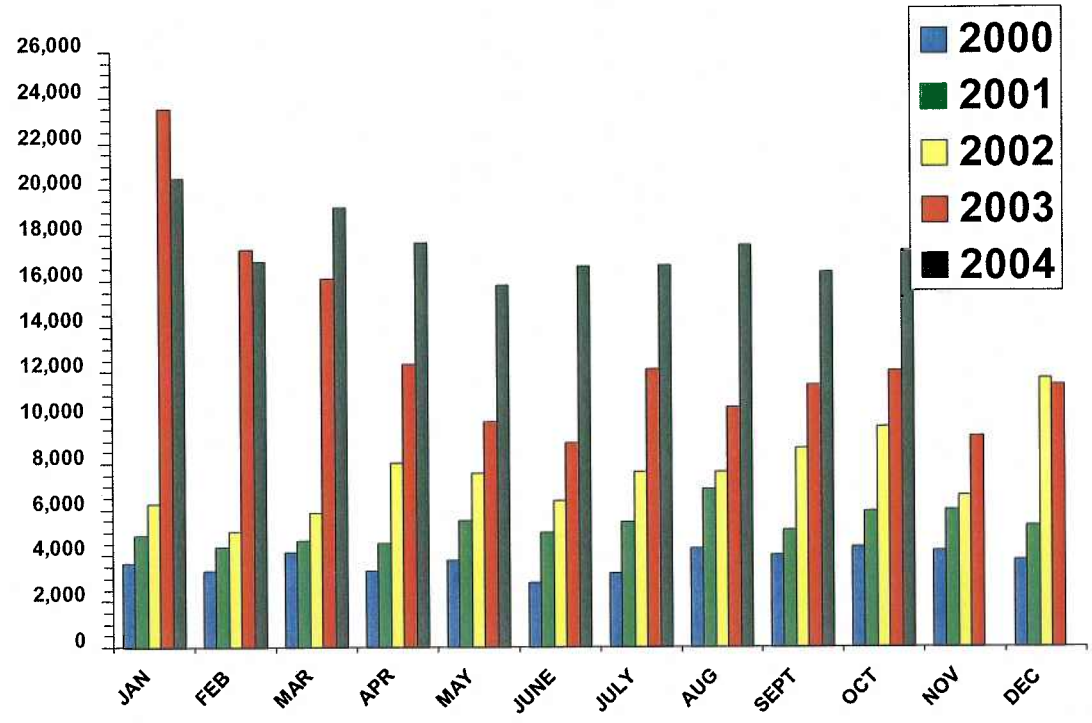
Monthly Totals

MONTH	1999 Total	2000 Total	2001 Total	2002 Total	2003 Total	2004 Total
January	* 0	3,697	4,905	6,295	23,499	20,498
February	* 0	3,335	4,393	5,049	17,354	16,857
March	* 0	4,157	4,668	5,858	16,081	19,232
April	* 0	3,337	4,556	8,047	12,378	17,660
May	* 0	3,804	5,540	7,586	9,836	15,828
June	* 0	2,820	4,982	6,368	8,917	16,634
July	* 0	3,242	5,465	7,651	12,126	16,662
August	3,883	4,333	6,881	7,629	10,454	17,563
September	2,360	4,015	5,145	8,664	11,449	16,373
October	1,963	4,398	5,912	9,608	12,102	17,300
November	1,721	4,216	6,011	6,627	9,178	
December	2,475	3,804	5,314	11,710	11,461	
Calendar Year Total	**12,402**	**45,158**	**63,772**	**91,092**	**154,835**	**174,607**

* Help Desk Call Center implemented in August 1999.

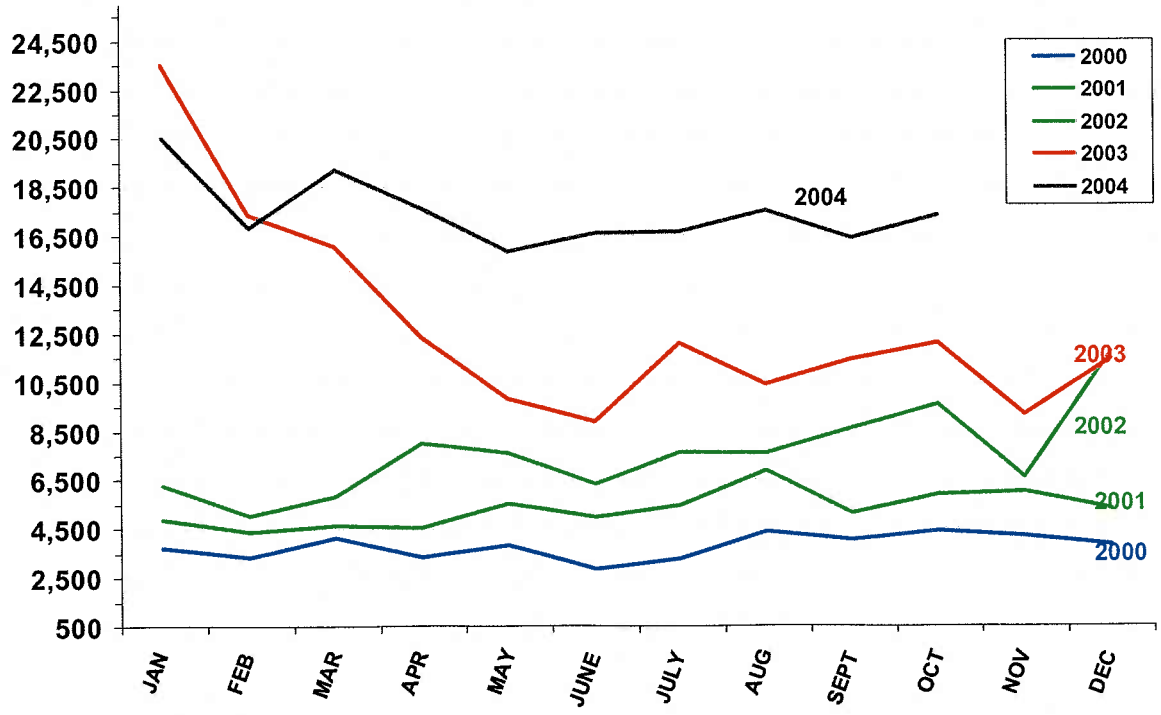
Monthly Call Volume

Calendar Years 2000-2004

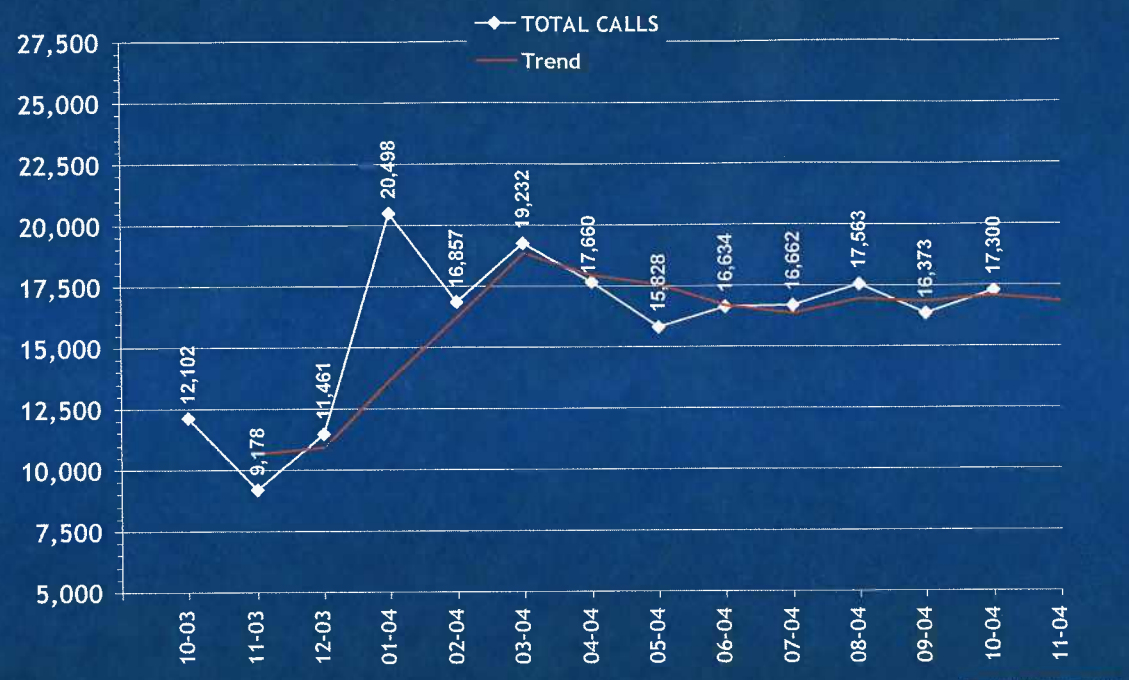


Monthly Call Volume

Calendar Years 2000-2004

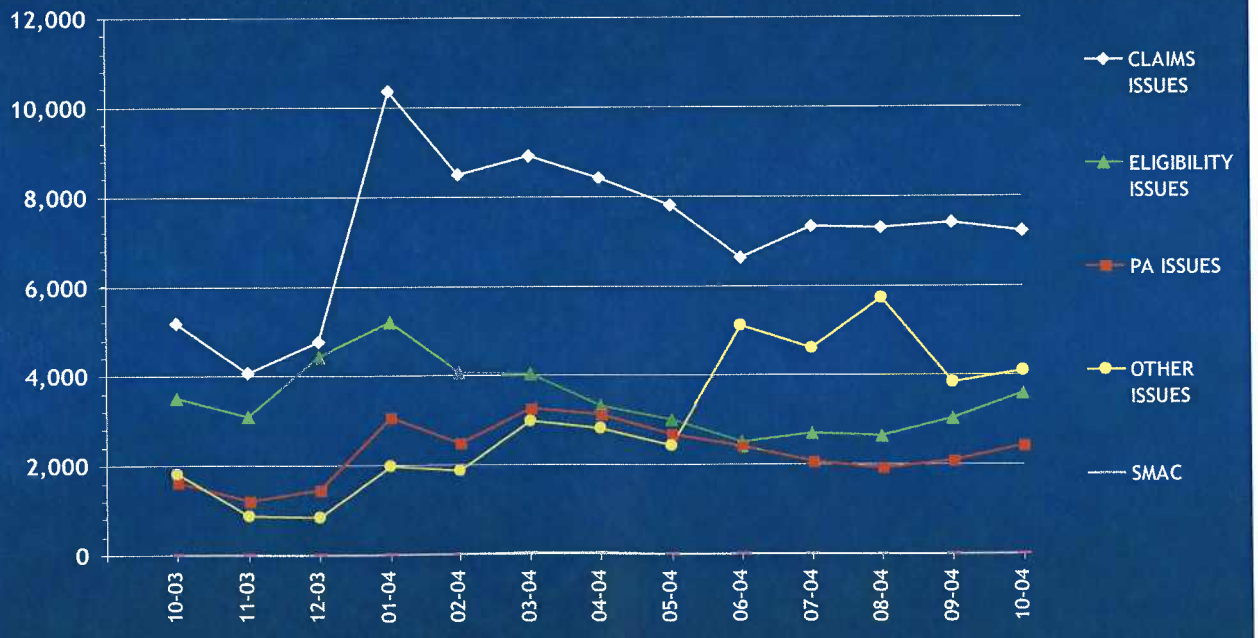


CALL VOLUME MONTHLY REPORT
October 2003 - October 2004



PHARMACY Management Consultants

CALL VOLUME ISSUES
October 2003 - October 2004



PHARMACY Management Consultants

APPENDIX C

(30) Day Notice to Vote on Prior Authorization Changes ADHD/Narcolepsy Drugs – Change to Step Therapy

Oklahoma Medicaid
November 2004

Product Based Prior Authorization

With respect to the ADHD/narcolepsy medications, there are two tiers of medications in the therapeutic category. A failed trial with a tier-1 ADHD medication or a clinical exception to a tier-1 trial is required before a tier-2 ADHD medication can be approved.

Medication	Age Groups	PA Requirements
Ritalin, Ritalin SR, Dexedrine, Dexedrine Spansule, Adderall	Children up to 21 years old	No PA required
	Adults	PA required – Diagnosis of ADHD or narcolepsy.
Ritalin LA, Concerta, Metadate CD, Focalin, Adderall XR, Strattera	Children and Adults	PA Required – Requires failed trial with Ritalin, Dexedrine or Adderall. Diagnosis of ADHD or narcolepsy.
Desoxyn and Cylert	Children and Adults	PA Required – Requires failed trial with Ritalin and Dexedrine. Diagnosis of ADHD or narcolepsy.

Current Process:

Tier 1 drugs are set in the computer system to pay without PA for clients up to 21 years of age; PA is required for adult clients. Tier 2 drugs are set to require a PA for all ages. Providers must submit a new PA petition every time the drug dosing strength changes.

Suggested Change in the Process:

- Tier 1 stimulants would be in the step therapy edit as Tier 1 and on the drug file as PA for over 21 years old.
- Tier 2 stimulants would be in the step therapy edit as Tier 2 and on the drug file as PA for over 21 years old.
- Strattera would continue to have a PA on the drug file for all ages. This would provide a means to monitor concurrent use of stimulants and Strattera.
- Quantity limits of one unit per day would be placed on the Tier 2 drugs. Any quantity greater than this would require a PA.

How this would affect clients:

- Adults: The process would stay the same as it currently is for adult clients - all drugs in this category would require a PA, including all dosing strength changes.

- Children up to 21 years old: Everything would stay the same except the following: when the pharmacy tries to run a claim for a tier-2 drug in this category, the computer would look into the client's Medicaid claims history. If the computer finds any drug in this category in the claims history, the computer would allow the tier-2 ADHD/narcolepsy drug claim to pay without requiring a PA, as long as the claim does not exceed the quantity limit. If the claim does exceed the quantity limit, PA would be required.

Advantage:

Once a tier-2 drug in this category has been approved for a patient, providers would be able to change the dosage and strength of the drug without having to submit a new PA petition. This would reduce the number of PA petitions that providers have to submit and the COP's PA unit has to process.

Disadvantage:

The computer system would allow clients to get more than one tier-2 drug at a time. It would allow clients to get several strengths of the same drug or several different drugs in this category, and clients could use this duplication to exceed the 1.5 times the FDA approved maximum dose limit currently in place. OHCA will make every effort to program the system so that it won't allow such duplication.

APPENDIX D

Prior Authorization Annual Review - Fiscal Year 2004
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
Oklahoma Medicaid
November 2004

Product Based Prior Authorization

With respect to the non-steroidal, anti-inflammatory drugs (NSAIDs), there are two tiers of drugs in this therapeutic classification.

(A) Tier-2 NSAIDs are approved if the individual has had two tier-1 NSAIDs within the current continuous NSAID therapy. This consists of all NSAID claims that have been sequentially acquired within 120 days of each other and provide medication coverage for the current date. The current continuous NSAID therapy shall then be retrospectively reviewed up to a maximum of 360 days for tier-1 NSAIDs.

(B) After an individual has received tier-2 NSAID coverage, the individual has tier-1 and tier-2 coverage for the duration of their continuous NSAID therapy.

(C) Individuals who have not acquired an NSAID for 120 days will be considered to have discontinued their continuous NSAID therapy and the previous approval will no longer be in effect.

The clinical exceptions for the non-steroidal, anti-inflammatory drugs in tier-2 are demonstrated by the following conditions:

(A) history of upper GI bleeding; or
(B) history of NSAID-induced ulcer, or
(C) active peptic ulcer disease, or
(D) concurrent use of warfarin, or
(E) concurrent chronic use of oral corticosteroids, or
(F) chronic NSAID therapy in elderly or debilitated patients, or
(G) diagnosis of gout – indomethacin only.

These clinical conditions are demonstrated by the documentation sent by the prescribing physician and pharmacist.

NSAIDS	
(Arthritis Medications or Non-Steroidal Anti-Inflammatory Drugs)	
Tier 1	**Tier 2**
diclofenac ER (Voltaren XR®)	diclofenac sodium/misoprostol (Arthrotec®)
diclofenac potassium (Cataflam®)	celecoxib (Celebrex®)
diclofenac sodium (Voltaren®)	indomethacin (Indocin®)
etodolac (Lodine®)	naproxen sodium (Naprelan®)
etodolac ER (Lodine XL®)	piroxicam (Feldene®)
fenoprofen (Nalfon®)	valdecoxib (Bextra®)
flurbiprofen (Ansaid®)	lansoprazole/naproxen (Prevacid® NapraPAC™)
ibuprofen (Motrin®)	
ketoprofen (Orudis®)	
ketoprofen ER (Oruvail®)	
meclofenamate (Meclomen®)	
mefanamic acid (Ponstel®)	
meloxicam (Mobic®)	
nambutone (Relafen®)	
naproxen (Naprosyn®)	
naproxen sodium (Anaprox®)	
naproxen EC (Naprosyn EC®)	
oxaprozin (Daypro®)	
sulindac (Clinoril®)	
tolmetin (Tolectin®)	

Changes during Fiscal Year 2004

December 9, 2003: addition of lansoprazole/naproxen (Prevacid® NapraPAC™) to tier-2 status.

Changes for Fiscal Year 2005

July 1, 2004: meloxicam (Mobic®) was moved to a tier-1 status due to a supplemental rebate agreement,

September 30, 2004: voluntary withdrawal of rofecoxib (Vioxx®) from market.

Utilization – Fiscal Year 2004

For the period of July 2003 through June 2004, a total of 53,621 clients received non-steroidal, anti-inflammatory drugs through the Oklahoma Medicaid fee-for-service program.

Tier	# of Claims	Total Units	Total Days	Units /Day	Total Cost	Total Clients	Cost /Client	Cost /Claim
Tier-1	102,989	6,024,016	2,565,002	2.35	$1,930,843.12	45,574	$ 42.37	$ 18.75
Liquids	4,166	1,497,193	44,653	33.53	$ 90,891.94	2,313	$ 39.30	$ 21.82
Tier-2	37,143	1,804,869	1,386,305	1.30	$4,539,524.97	7,748	$ 585.90	$ 122.22
Liquids	65	10,050	1,803	5.57	$ 8,256.49	13	$ 635.12	$ 127.02
Total	**144,363**	**9,336,128**	**3,997,763**	**2.34**	**$6,569,516.52**	**53,621***	**$ 122.52**	**$ 45.51**

*Total unduplicated clients for FY04

Total Cost FY '04	**$6,569,516.58**
Total Cost FY '03	*$6,464,720.31*
Total Claims FY '04	**144,363**
Total Claims FY '03	*128,624*
Total Clients FY '04	**53,621**
Total Clients FY '03	*41,349*
Per Diem FY '04	**$1.64**
Per Diem FY '03	*$1.79*

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

Age	Female	Male	Totals
0 to 9	1,147	1,181	2,328
10 to 19	8,082	4,813	12,895
20 to 34	9,961	1,024	10,985
35 to 49	5,504	2,216	7,720
50 to 64	4,990	2,254	7,244
65 to 79	5,593	1,745	7,338
80 to 94	4,056	740	4,796
95 and Over	281	34	315
Totals	**39,614**	**14,007**	**53,621**

Claims were also divided into the two available tiers and reviewed by age and gender.

Tier-1 Claims

Age	Female	Male	Totals
0 to 9	1,142	1,179	2,321
10 to 19	8,054	4,793	12,847
20 to 34	9,894	989	10,883
35 to 49	5,195	2,065	7,260
50 to 64	4,149	1,967	6,116
65 to 79	3,970	1,400	5,370
80 to 94	2,374	516	2,890
95 and Over	175	25	200
Totals	**34,953**	**12,934**	**47,887**

Tier-2 Claims

Age	Female	Male	Totals
0 to 9	7	2	9
10 to 19	83	39	122
20 to 34	151	53	204
35 to 49	543	267	810
50 to 64	1,271	443	1,714
65 to 79	2,063	463	2,526
80 to 94	1,982	262	2,244
95 and Over	122	10	132
Totals	**6,222**	**1,539**	**7,761**

Review of Cox-2 Inhibitor Utilization

Market Share for Cox-2 Inhibitors July 2003 through June 2004.

Brand Name	Total Cost/ Brand FY '04	% Share/ Brand FY '04	Total Cost/ Brand FY '03	% Share/ Brand FY '03
Celebrex®	$ 2,682,463.87	61.34%	$ 2,674,577.76	61.20%
Vioxx®	$ 1,239,720.49	28.35%	$ 1,314,738.18	30.46%
Bextra®	$ 450,665.77	10.31%	$ 326,361.69	7.56%

A review of Cox-2 Inhibitor claims revealed the following usage.

Medication	Units/Day	# of Clients
Celebrex® 100 mg Capsule	1.64	480
Celebrex® 200 mg Capsule	1.37	3,602
Celebrex® 400 mg Capsule	1.00	2
Vioxx® 12.5 mg Suspension	5.71	6
Vioxx® 25 mg Suspension	5.42	7
Vioxx® 12.5mg Tablet	1.11	357
Vioxx® 25 mg Tablet	1.07	2,162
Vioxx®50 mg Tablet	0.95	123
Bextra® 10 mg Tablet	1.13	934
Bextra® 20 mg Tablet	0.92	49

Vioxx® usage July 2003 through June 2004

Strength	# of Claims	Total Units	Total Days	Total Cost	Total Clients
Vioxx® 12.5 mg Tab	1,569	59,598	53,482	$162,854.22	357
Vioxx® 25 mg Tab	8,968	375,774	352,600	$1,027,148.41	2,162
Vioxx® 50 mg Tab	265	10,517	11,027	$41,461.37	123
Vioxx® 12. 5 mg Suspension	34	5,400	945	$4,439.37	6
Vioxx® 25 mg Suspension	31	4,650	858	$3,817.12	7
Total	**10,867**	**455,939**	**418,912**	**$1,239,720.49**	**2,542***

*Total unduplicated clients for FY04

Age	Female	Male	Totals
0 to 9	3	2	5
10 to 19	31	19	50
20 to 34	50	20	70
35 to 49	185	77	262
50 to 64	397	143	540
65 to 79	575	167	842
80 to 94	640	93	733
95 and Over	33	7	40
Totals	**2,014**	**528**	**2,542**

Recommendations

The college of pharmacy has the following recommendations for this prior authorization category:

1. **Consideration by the Drug Utilization Review Board to make changes to the current criteria for approval of Cox-2 Inhibitors.**
2. **Patient information letters to be sent to previous Vioxx® clients regarding the voluntary recall of this product.**

APPENDIX E

Omeprazole Powder for Oral Suspension (Zegerid™)

Oklahoma Medicaid
November 2004

Manufacturer's Main Selling Point (from Zegerid.com):
"Until now, all oral PPIs were delayed release. PPIs are acid labile and rapidly degrade in the presence of gastric acid. To protect the drug from degradation in the stomach, delayed-release PPIs are formulated as enteric-coated granules or as enteric-coated tablets. Enteric coating delays release, which delays absorption and bioavailability. Initial acid suppression effect occurs in 2 to 6 hours.
Zegerid is the first immediate-release oral PPI. A novel formulation protects Zegerid from acid degradation and allows immediate release of omeprazole. Immediate release results in peak plasma levels of Zegerid in ~30 minutes. Immediate-release Zegerid provides 24-hour acid control."

Indications:

- *Duodenal Ulcer*: short-term treatment of active duodenal ulcer.
- *Gastroesophageal Reflux Disease (GERD)*: heartburn and other symptoms
- associated with GERD.
- *Erosive Esophagitis*: short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy.
- *Maintenance of Healing of Erosive Esophagitis*: maintain healing of erosive esophagitis.

Dosing:
One 20 mg single-dose packet once-daily, on an empty stomach one hour prior to a meal. Directions for use: Empty packet contents into a small cup containing 2 tablespoons of water. Do not use other liquids or foods. Stir well and drink immediately. Refill cup with water and drink.

Precautions & Adverse Effects:
The most frequently reported adverse events with Zegerid are headache, diarrhea and abdominal pain. Symptomatic response to therapy does not preclude the presence of gastric malignancy. Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long term with omeprazole.
Zegerid contains 460mg sodium per dose in the form of sodium bicarbonate (1680mg/20mEq), which should be taken into consideration for patients on a sodium-restricted diet. Sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia. Sodium
bicarbonate should be used with caution in patients with Bartter's syndrome, hypokalemia, and respiratory alkalosis. Long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome.

Cost:
Average Wholesale Price (AWP): $4.86 per packet.
AWP of Prilosec OTC 20 mg tablet: $0.68 per tablet.

Cost comparison:

	Estimated Acquisition Cost (EAC)	State Maximum Allowable Cost (SMAC)	Daily Dose	Monthly Dose* (30 day supply)
Zegerid® 20 mg Suspension	$4.28 per packet	$0.00	20 mg	$128.40
Omeprazole 20 mg	$3.65 per capsule	$1.86	20 mg	$ 55.80
Prevacid® Suspension	$4.37 per packet	$0.00	30 mg	$131.10
Prevacid® Solutab	$3.03 per tablet	$0.00	30 mg	$ 90.90

*SMAC pricing used where appropriate. No rebate information was incorporated.

Related products under development by the manufacturer:
Zegerid™ Powder for Oral Suspension 40mg (expected to be through FDA review by the end of 2004)
Zegerid™ Chewable Tablets
Zegerid™ Capsules

Current tiers

Anti-Ulcer Medications	
Tier 1	**Tier 2**
Prilosec OTC & generic rx omeprazole	ranitidine (Zantac) - all forms except tablets
esomeprazole magnesium (Nexium)	brand rx omeprazole (Prilosec)
lansoprazole (Prevacid) capsules	rabeprazole sodium (Aciphex)
pantoprazole sodium (Protonix)	lansoprazole (Prevacid) – tablets & granules

Zegerid is currently not covered because its manufacturer does not have a rebate agreement with OHCA. This could change.

Recommendation

Place all Zegerid products on tier-2 status.

APPENDIX F

Drug Utilization Review of Linezolid (Zyvox®)

Oklahoma Medicaid
November 2004

Introduction:

Zyvox® is a synthetic antibacterial agent belonging to a new class of antibiotics called oxazolidinones. Zyvox® inhibits bacterial protein synthesis by preventing the formation of a functional 70S bacterial ribosomal unit. Zyvox® is the only drug of its kind to be approved since the release of Vancomycin for the treatment of MRSA infections. This new medication is currently the last line of defense for Vancomycin resistant infections and should be used prudently to reduce development of drug-resistant bacteria. Zyvox® should be reserved for infections caused by susceptible organisms that are resistant to conventional antibiotics. Empiric use should be followed by proper culture and sensitivity, after which, treatment should be adjusted accordingly.

FDA Approved Indications:

- **Vancomycin-Resistent *Enterococcus faecium*** infections, including cases with concurrent bacteremia.
- **Nosocomial pneumonia** caused by ***Staphylococcus aureas*** (methicillin-susceptable and resistant strains), or ***Streptococcus pneumoniae*** (including multi-drug resistant strains-MDRSP.)
- **Community-acquired pneumonia** caused by ***Staphylococcus aureas*** (methicillin-susceptable strains only), or **Streptococcus pneumoniae** (including MDRSP)
- **Complicated skin and skin structure infections**, including diabetic foot infections without concomitant osteomyelitis, caused by ***Staphylococcus aureas*** (methicillin-susceptable and resistant strains), ***Streptococcus pyogenes***, or ***Streptococcus agalactiae.***
- **Uncomplicated skin and skin structure infections** caused by***Staphylococcus aureus*** (methicillin-susceptible only), or ***Streptococcus pyogenes.***

Dosing and Administration:

- Formulations available include oral tablet, oral suspension, and IV solution.
- Dosing adjustments are not necessary when converting from IV to oral.
- Indicated for twice daily dosing (every 12 hours) for 10-14 days or up to 28 days when necessary.
- Can be dosed up to three times daily in pediatrics.
- No dosing adjustments are necessary in renal and hepatic insufficiency.
- Oral formulation can be taken with or without food.

Monitoring:

- Complete blood counts (CBCs) should be monitored weekly as myelosuppression, including anemia, leukopnia, pancytopenia, and thrombocytopenia has been reported in patients receiving Zyvox® (~2.4 %.)

Trends in Utilization of Zyvox®

	Fiscal Year 2003	Fiscal Year 2004	Percent Change	
Total Claims	**141**	**284**	**Increased**	**101 %**
Zyvox® 600mg Tab	112	265	Increased	136 %
Zyvox® 600mg Oral Suspension	8	10	Increased	25.0 %
Zyvox® 2mg/ml IV Solution	21	9	Decreased	57.1 %
Total Cost	**$ 201,854.92**	**$ 415,304.45**	**Increased**	**106 %**
Zyvox® 600mg Tab	$ 192,887.92	$ 402,322.60	Increased	109 %
Zyvox® 600mg Oral Suspension	$ 4,752.19	$ 9,890.83	Increased	108 %
Zyvox® 2mg/ml IV Solution	$ 4,214.81	$ 3,091.02	Decreased	26.6 %
Cost per Claim	**$ 1,564.77**	**$ 1,462.33**	**Decreased**	**6.5 %**
Zyvox® 600mg Tab	$ 1,722.21	$ 1,518.20	Decreased	11.8 %
Zyvox® 600mg Oral Suspension	$ 594.02	$ 989.08	Increased	66.5 %
Zyvox® 2mg/ml IV Solution	$ 468.31	$ 343.45	Decreased	26.6 %

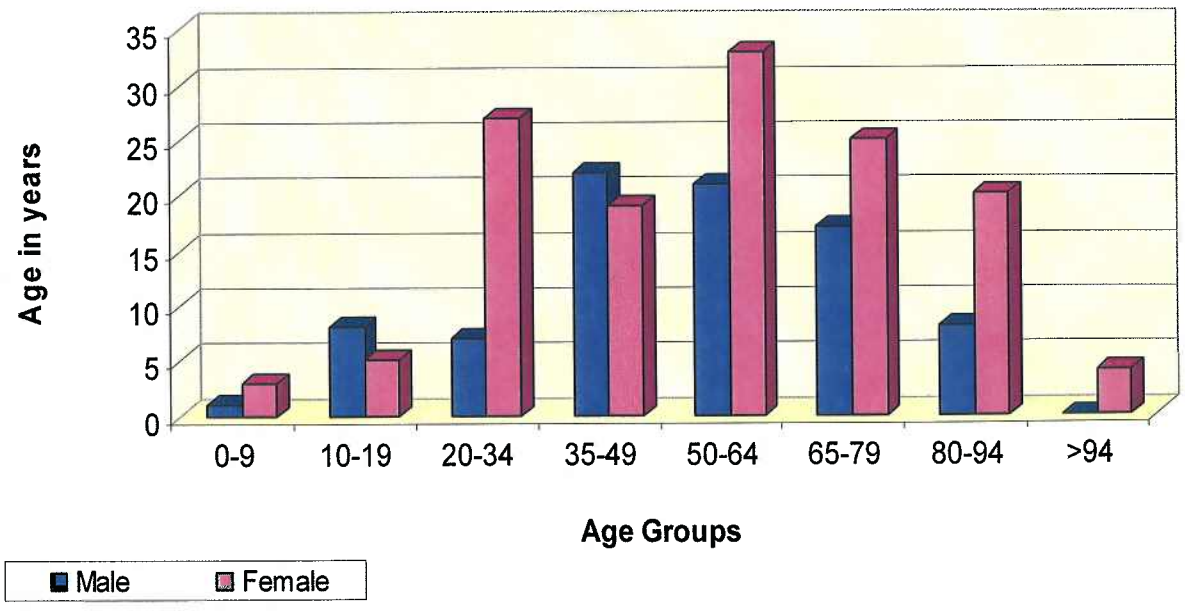
Utilization of Zyvox® During Fiscal Year 2004

For the period of July 2003 through June of 2004, a total of 220 clients received Zyvox® through the Medicaid fee-for-service program.

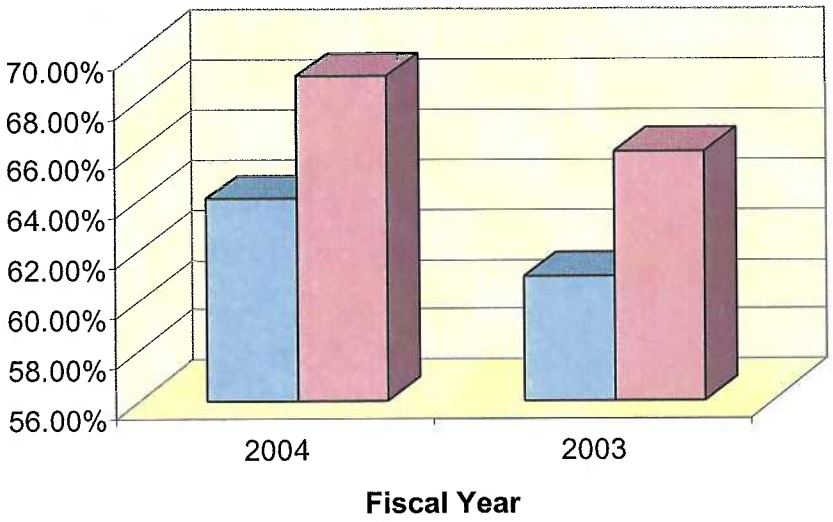
	Claims	Cost	Quantity/Claim	Days/Claim	Cost/Claim	PerDiem
Zyvox® 600mg Tab	265	$ 402,322.60	27 tabs /claim	13.6 days	$ 1,518.20*	$ 111.38
Zyvox® 600mg Oral Susp	10	$ 9,890.83	525 ml/claim	11.8 days	$ 989.08	$ 83.82
Zyvox® 2mg/ml IV Sol	9	$ 3,091.02	1,366 ml/claim	2.3 days	$ 343.45	$ 147.19

* Total cost divided by by total claims, EAC is $56.69 per 600mg tablet

Client Demographics



Percent of Zyvox® claims in relation to Hospitalization Discharge and/or Presence in Care Facility



[i]

Data about the severity of the infection or the presence of culture and sensitivity is not readily available via client's claims data. However, hospitalization or residence in a care facility may indicate severity of client's condition, or an increased likelihood of a nosocomial infection caused by resistant strains. Furthermore, culture and sensitivity assays are more readily available at these institutions. This graph shows the percentage of Zyvox® prescriptions filled in the community setting by clients that were previously discharged from the hospital or were at a care facility.

Discussion

The information available indicates that a majority of the Zyvox® recipients had severe disease prior to receiving Zyvox® due to their presence in a hospital or care facility. These clients were in an institution where culture and sensitivity and CBCs were more readily available. Lastly, the days per claim are mostly within the recommended 10-14 days or less.

Conclusion

The College of Pharmacy recommends no action at this time as it appears that Zyvox® is being used appropriately.

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[i] Pharmacia & Upjohn Pharmaceuticals. Package literature Zyvox®. July 2004

APPENDIX G

BLADDER CONTROL DRUGS – DRUG UTILIZATION REVIEW
Oklahoma Medicaid - November 2004

Mechanisms of Action

Bethanechol: Stimulates cholinergic receptors in the smooth muscle of the urinary bladder and gastrointestinal tract resulting in increased peristalsis, increased GI and pancreatic secretions, bladder muscle contraction, and increased ureteral peristaltic waves.

Flavoxate: Synthetic antispasmotic with similar actions to that of propantheline; it exerts a direct relaxant effect on smooth muscles via phosphodiesterase inhibition, providing relief to a variety of smooth muscle spasms; it is especially useful for the treatment of bladder spasticity, whereby it produces an increase in urinary capacity.

Oxybutynin: Direct antispasmodic effect on smooth muscle, also inhibits the action of acetylcholine on smooth muscle (exhibits 1/5 the anticholinergic activity of atropine, but is 4-10 times the antispasmodic activity); does not block effects at skeletal muscle or at autonomic ganglia; increases bladder capacity, decreases uninhibited contractions, and delays desire to void; therefore, decreases urgency and frequency.

Hyoscyamine: Blocks the action of acetylcholine at parasympathetic sites in smooth muscle, secretory glands and the CNS; increases cardiac output, dries secretions, antagonizes histamine and serotonin

Tolterodine: Competitive antagonist of muscarinic receptors. In animal models, tolterodine demonstrates selectivity for urinary bladder receptors over salivary receptors. Urinary bladder contraction is mediated by muscarinic receptors. Tolterodine increases residual urine volume and decreases detrusor muscle pressure.

Lexi-Comp Online™

Oklahoma Medicaid Utilization FY 2003 & FY 2004

Summary Table

Year	Claims	Units	Days	Clients	Amount Paid
FY 2003	35,274	1,883,324	1,164,327	81,124	$2,932,051.60
FY 2004	35,565	1,831,117	1,212,922	84,506	$3,370,916.98
% Change 2003 to 2004	**0.82%**	**-2.8%**	**4.2%**	**4.2%**	**16%**

Summary Table

Year	$/Day	$/Unit	$/Client
FY 2003	$2.58	$1.60	$446.81
FY 2004	$2.79	$1.85	$471.69
% Change 2003 to 2004	**8.1%**	**15.63%**	**5.57%**

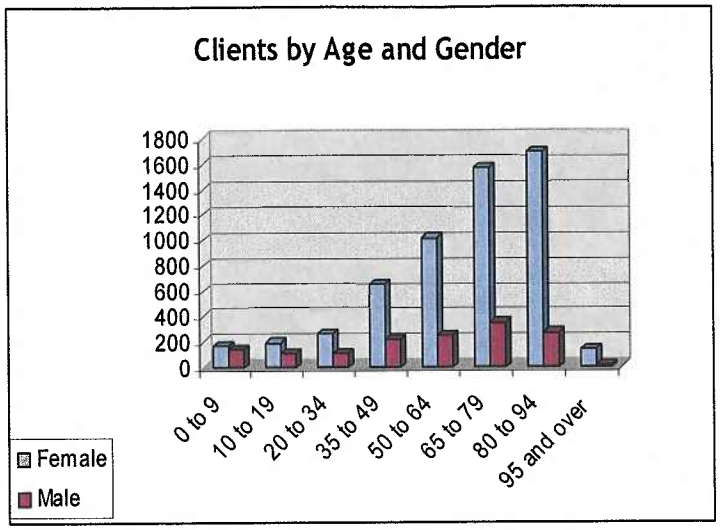
BLADDER CONTROL DRUGS – DRUG UTILIZATION REVIEW

Oklahoma Medicaid - November 2004

Drug Name	FY 2003	FY 2004	$ Change 2003-2004	% Change 2003-2004
Bethanechol 5 mg tab	0	$479.42	$479.42	100%
Bethanechol - Urecholine 5 mg tab	$493.81	$105.63	-$388.18	-78.61%
Bethanechol 10 mg tab	0	$4,627.00	$4,627.00	100%
Bethanechol - Urecholine 10 mg tab	$6,497.72	$7,475.76	$978.04	15.05%
Bethanechol 25 mg tab	$121.23	$22,014.54	$21,893.31	18059%
Bethanechol - Duvoid 25 mg tab	0	$6.39	$6.39	100%
Bethanechol - Urecholine 25 mg tab	$100,016.71	$98,135.96	-$1,880.75	-1.9%
Bethanechol 50 mg tab	0	$9,345.31	$9,345.31	100%
Bethanechol - Urecholine 50 mg tab	$10,566.34	$17,684.76	$7,118.42	67.37%
Bethanechol powder	$5.71	0	-$5.71	-100%
Flavoxate 100 mg tab	0	$8,951.30	$8,951.30	100%
Flavoxate - Urispas 100 mg tab	$68,243.05	$40,175.17	-$28,067.88	-41.13%
Oxybutynin -Oxytrol 3.9 mg/24hr transdermal patch	$730.96	$52,302.63	$51,571.67	7055.3%
Oxybutynin - Ditropan 5 mg tab	$4,312.24	$4,496.65	$184.41	4.28%
Oxybutynin 5 mg tab	$65,410.50	$45,901.28	-$19,509.22	-29.83%
Oxybutynin - Ditropan 5 mg/5 ml syrup	$1,221.61	$807.14	414.47	33.93%
Oxybutynin 5 mg/ 5 ml syrup	$8,710.70	$9,843.48	$1,132.78	13%
Oxybutynin powder	0	$118.50	$118.50	100%
Oxybutynin - Ditropan XL 5 mg tab	$374,154.79	$384,384.51	$10,229.72	2.7%
Oxybutynin - Ditropan XL 10 mg tab	$430,026.41	$536,396.69	$106,370.28	24.74%
Oxybutynin - Ditropan XL 15 mg tab	$112,766.71	$149,401.86	$36,625.15	32.48%
Hyoscyamine - Cystospaz 0.15 mg tab	$2,396.02	$1,105.43	-$1,290.59	-53.86%
Hyoscyamine 0.15 mg tab	$80.50	$497.79	$417.29	518.37%
Hyoscyamine - Hyospaz 0.15 mg tab	$146.11	$33.76	-$112.36	-76.9%
Tolterodine - Detrol 1 mg tab	$62,979.95	$54,012.63	-$8,967.32	-14.24%
Tolterodine - Detrol 2 mg tab	$500,090.49	$334,572.05	-$165,518.44	-33.1%
Tolterodine - Detrol LA 2 mg cap	$125,287.81	$158,646.99	$33,359.18	26.63%
Tolterodine - Detrol LA 4 mg cap	$1,057,772.20	$1,432,394.35	$374,622.15	35.42%
Totals	**$2,932,051.60**	**$3,370,916.98**	**$438,865.38**	**15.97%**

BLADDER CONTROL DRUGS – DRUG UTILIZATION REVIEW
Oklahoma Medicaid - November 2004

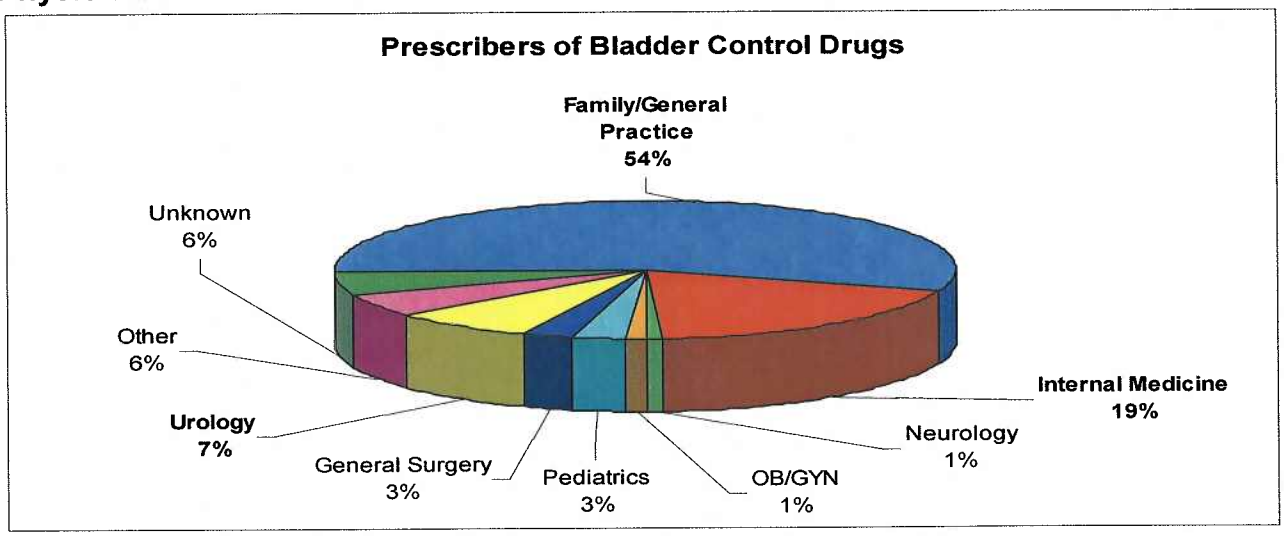
Client Demographics - FY 2004



Age	Female	Male	Total
0 to 9	168	138	306
10 to 19	195	107	302
20 to 34	268	113	381
35 to 49	648	214	862
50 to 64	1018	247	1265
65 to 79	1566	352	1918
80 to 94	1687	272	1959
95 and over	140	13	153
FY 04 Total	**5690**	**1456**	**7146**

The majority of patients are middle-aged and older women, particularly those who are postmenopausal, as the effects of estrogen diminish. Men are more apt to take the drugs for benign prostatic hypertrophy (BPH).

Physicians



Discussion:

- The number of clients increased in FY 04 as HMO clients moved into the fee for service program
- Review of claims shows a shift to the extended release products, including the newly formulated transdermal oxybutynin, which accounts for the 16% increase in cost.
- There are three new drugs for bladder control coming out later this year; Sanctura (trospium), Enablex (darifenacin), and Vesicare (solifenacin).

Recommendations:

The College of Pharmacy recommends the following action.

- Continue to monitor this class of drugs.
- Review the new drugs as they come on the market.
- Consider prior authorization of the new drugs as the older drugs go off patent.

APPENDIX H

Thirty Day Notice – Intent to Prior Authorize
Estimated Economic Impact
Xopenex® (levalbuterol)
Oklahoma Medicaid
November 2004

Proposed Prior Authorization Criteria

Xopenex® (levalbuterol) use in excess of 90 days of therapy in a floating 360 day period will require prior authorization. The current quantity limit of 288units/30 days supply would still apply.

1. In the prior authorization request, the prescriber should explain why the client is unable to use long acting bronchodilators and/or inhaled corticosteroid (ICS) therapy for long-term control per NAEPP guidelines.
2. Clinical exceptions will be made for clients with COPD.

Estimated Economic Impact

Utilization for July 2003 through June 2004

	Clients	*Cost*	*Claims*	*Days/ Client**	*Cost/ Client/ Day*	*Cost/ Claim*	*Cost/ Day*	*Cost/ Client*	*Claims/ Client*
</= 3 Claims	4,144	$ 706,979.08	5,841	22.45	7.60	$121.04	$ 7.66	$ 170.60	1.41
> 3 Claims	565	$ 531,058.07	4,510	125.14	7.51	$117.75	$ 9.40	$ 939.93	7.98
COPD </= 3 Claims	196	$ 46,343.36	289	31.66	7.47	$160.36	$ 8.35	$ 236.45	1.47
COPD> 3 Claims	98	$ 123,869.42	900	169.25	7.47	$137.63	$ 9.29	$ 1,263.97	9.18
Total	**5,003**	**$1,408,249.93**	**11,540**	**37.29**	**7.55**	**$122.03**	**$ 8.40**	**$ 281.48**	**2.31**

*Days/Client = (Units÷ 9.6ml/daily) ÷ Clients
**Cost/Client/Day = Cost/Client ÷ Days/Client

Projected Program Savings/Cost Calculations

	Clients[1]	*Current Reimbursement*	*PA Cost*[2]	*Clients Approved*[3]	*90 Day No PA*[4]	*Post 90 Day*[5]	*Projected Savings*[6]
No PA	4,144	$ 706,979.08	$ 0.00	4,144	$ 706,979.08	$ 0.00	$ 0.00
Need PA	565	$ 531,058.07	$(7,163.31)	188	$ 381,934.81	$49,620.13	$92,339.82
COPD No PA	196	$ 46,343.36	$ 0.00	196	$ 46,343.36	$ 0.00	$ 0.00
COPD PA	98	$ 123,869.42	$(1,271.06)	98	$ 65,868.69	$58,001.04	$(1,271.37)
Totals	**5,003**	**$1,408,249.93**	**$(8,434.37)**	**4,626**	**$ 1,201,125.94**	**$107,621.17**	**$90,566.64**

[1]Clients divided by those with less than or equal to 3 claims for the year for COPD and no COPD.
[2]The average cost for processing petitions is calculated at $6.75 per petition with the maximum cost at $12.97 per petition. The maximum cost was used in the estimation of administrative costs.
[3]Approved clients based on those requiring less than 90 days of therapy and an approximate approval rate of 1/3 for clients with a duration of therapy greater than 90 days.
[4]Cost for clients with less than 90 days of therapy.
[5]Cost for clients with greater than 90 days of therapy.
[6]Projected Savings = Current Reimbursement – Pre and Post 90 Day Cost + PA Cost.

APPENDIX I

FDA Public Health Advisory
October 15, 2004

Suicidality in Children and Adolescents Being Treated With Antidepressant Medications

Today the Food and Drug Administration (FDA) directed manufacturers of all antidepressant drugs to revise the labeling for their products to include a boxed warning and expanded warning statements that alert health care providers to an increased risk of suicidality (suicidal thinking and behavior) in children and adolescents being treated with these agents, and to include additional information about the results of pediatric studies. FDA also informed these manufacturers that it has determined that a Patient Medication Guide (MedGuide), which will be given to patients receiving the drugs to advise them of the risk and precautions that can be taken, is appropriate for these drug products. These labeling changes are consistent with the recommendations made to the Agency at a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Drugs Advisory Committee on September 13-14, 2004.

The drugs that are the focus of this new labeling language are all drugs included in the general class of antidepressants; they are listed at the end of this Advisory.

The risk of suicidality for these drugs was identified in a combined analysis of short-term (up to 4 months) placebo-controlled trials of nine antidepressant drugs, including the selective serotonin reuptake inhibitors (SSRIs) and others, in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders. A total of 24 trials involving over 4400 patients were included. The analysis showed a greater risk of suicidality during the first few months of treatment in those receiving antidepressants. The average risk of such events on drug was 4%, twice the placebo risk of 2%. No suicides occurred in these trials. Based on these data, FDA has determined that the following points are appropriate for inclusion in the boxed warning:

- Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with MDD and other psychiatric disorders.
- Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.
- Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.
- Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber.

- A statement regarding whether the particular drug is approved for any pediatric indication (s) and, if so, which one(s).

Among the antidepressants, only Prozac is approved for use in treating MDD in pediatric patients. Prozac, Zoloft, Luvox, and Anafranil are approved for OCD in pediatric patients. None of the drugs is approved for other psychiatric indications in children.

Pediatric patients being treated with antidepressants for any indication should be closely observed for clinical worsening, as well as agitation, irritability, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. This monitoring should include daily observation by families and caregivers and frequent contact with the physician. It is also recommended that prescriptions for antidepressants be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

In addition to the boxed warning and other information in professional labeling on antidepressants, MedGuides are being prepared for all of the antidepressants to provide information about the risk of suicidality in children and adolescents directly to patients and their families and caregivers. MedGuides are intended to be distributed by the pharmacist with each prescription or refill of a medication.

FDA plans to work closely with the manufacturers of all approved antidepressant products that are the subject of today"s letters to optimize the safe use of these drugs and implement the proposed labeling changes and other safety communications in a timely manner. The labeling changes at issue will be posted on FDA's website http://www.fda.gov/cder/drug/antidepressants/default.htm.

• Anafranil (clomipramine HCl) • Aventyl (nortriptyline HCl) • Celexa (citalopram HBr) • Cymbalta (duloxetine HCl) • Desyrel (trazodone HCl) • Effexor (venlafaxine HCl) • Elavil (amitriptyline HCl) • Lexapro (escitalopram oxalate) • Limbitrol (chlordiazepoxide/amitriptyline) • Ludiomil (Maprotiline HCl) • Luvox (fluvoxamine maleate) • Marplan (isocarboxazid) • Nardil (phenelzine sulfate) • Norpramin (desipramine HCl) • Pamelor (nortriptyline HCl) • Parnate (tranylcypromine sulfate)	• Paxil (paroxetine HCl) • Pexeva (paroxetine mesylate) • Prozac (fluoxetine HCl) • Remeron (mirtazapine) • Sarafem (fluoxetine HCl) • Serzone (nefazodone HCl) • Sinequan (doxepin HCl) • Surmontil (trimipramine) • Symbyax (olanzapine/fluoxetine) • Tofranil (imipramine HCl) • Tofranil-PM (impiramine pamoate) • Triavil (Perphenaine/Amitriptyline) • Vivactil (protriptyline HCl) • Wellbutrin (bupropion HCl) • Zoloft (sertraline HCl) • Zyban (bupropion HCl)

Back to Top Back to Antidepressants

Date created: October 15, 2004

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Ajit Shetty, M.D.
CEO
Janssen Pharmaceutica, Inc.
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

RE: NDA # 19-813
Duragesic® (fentanyl transdermal system) CII
MACMIS # 12386

WARNING LETTER

Dear Dr. Shetty,

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional file card (DR-850) for Duragesic® (fentanyl transdermal system) submitted by Janssen Pharmaceutics, Inc. (Janssen) under cover of Form FDA 2253. The file card makes false or misleading claims about the abuse potential and other risks of the drug, and includes unsubstantiated effectiveness claims for Duragesic. The file card thus misbrands the drug under Section 502(a) of the Federal Food, Drug, and Cosmetic Act (Act) 21 U.S.C. 352(a). By suggesting that Duragesic has a lower potential for abuse compared to other opioid products, the file card could encourage the unsafe use of the drug, potentially resulting in serious or life-threatening hypoventilation.

Background

According to the approved product labeling (PI), Duragesic is a transdermal system providing continuous systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours. Duragesic is indicated in 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. The Indications and Usage section of the PI states: "Duragesic should not be used in the management of acute or postoperative pain because serious or life-threatening hypoventilation could result (see BOX

WARNING and CONTRAINDICATIONS)." The boxed warning and contraindications sections further discuss the risk of serious or life-threatening hypoventilation. This risk is also addressed in the warnings and precautions sections of the PI.

Duragesic has the potential for abuse. The Drug Abuse and Dependence section of the PI states, in pertinent part:

Fentanyl is a Schedule II controlled substance and can produce drug dependence similar to that produced by morphine. DURAGESIC® (fentanyl transdermal system) therefore has the potential for abuse. Tolerance, physical and psychological dependence may develop upon repeated administration of opioids.

False or Misleading Safety Claims

The file card presents the prominent claim, "Low reported rate of mentions in DAWN data," along with Drug Abuse Warning Network (DAWN) data comparing the number of mentions for Fentanyl/combinations (710 mentions) to other listed opioid products, including Hydrocodone/combinations (21,567 mentions), Oxycodone/combinations (18,409 mentions), and Methadone (10,725 mentions). The file card thus suggests that Duragesic is less abused than other opioid drugs.

This is false or misleading for two reasons. First, we are not aware of substantial evidence or substantial clinical experience to support this comparative claim. The DAWN data cannot provide the basis for a valid comparison among these products. As you know, DAWN is not a clinical trial database. Instead, it is a national public health surveillance system that monitors drug-related emergency department visits and deaths. If you have other data demonstrating that Duragesic is less abused, please submit them.

Second, Duragesic is not as widely prescribed as other opioid products. As a result, the relatively lower number of mentions could be attributed to the lower frequency of use, and not to a lower incidence of abuse. The file card fails to disclose this information.

The information from the Drug Abuse and Dependence section of the PI, which appears in a footnote on the opposite page of the spread (entitled "Favorable side-effect profile") is not sufficient to make the claim truthful and non-misleading. The footnote does not substantiate the claim. Nor does it set forth qualifying information about the frequency of prescribing of the compared opioids.

In addition, on the page entitled "Favorable side-effect profile," the file card presents the claim, "Minimizes the potential for local GI side effects by avoiding GI absorption," along with a table entitled, "Adverse experiences in patients with cancer," that shows a 14 percent rate of constipation with Duragesic and a 0 percent discontinuation rate because of constipation. This combination of text and graphics is false or misleading, in that it suggests that Duragesic is associated with less constipation, nausea, and vomiting than oral opioids, which are absorbed by the GI tract. We are not aware of substantial evidence or substantial clinical experience to support this comparative claim.

Unsubstantiated Effectiveness Claims

The file card states, on page four, "Demonstrated effectiveness in chronic back pain with additional patient benefits." The referenced study, (Simpson RK Jr, Edmondson EA, Constant CF, Collier C. Transdermal fentanyl as treatment for chronic low back pain. J Pain Symptom Manage. 1997; 14:218-224.) conducted by Simpson et al., is inadequate to support this claim, because it was an open-label, single-arm trial with no control group. We are not aware of substantial evidence or substantial clinical experience to support this claim.

On pages 4 and 5, the file card includes the claims, "86% of patients experienced overall benefit in a clinical study based on: pain control, disability in ADLs, quality of sleep," "All patients who experienced overall benefit from DURAGESIC would recommend it to others with chronic low back pain," " Significantly reduced nighttime awakenings," and "Significant improvement in disability scores as measured by the Oswestry Disability Questionnaire and Pain Disability Index." To support these claims, the file card again cites the Simpson et al. trial. For the reasons noted above, this uncontrolled study is inadequate to support such claims. We are not aware of substantial evidence or substantial clinical experience to support these claims.

On pages 6 and 7, the file card includes the claims, "Long-term effects: 12-month open-label study," "Significant improvement in physical functioning summary score," and "Significant improvement in social functioning," along with figures illustrating these claims. To support these claims, the tile card cites a study (Milligan K, Lanteri-Minet M, Borchert K, et al. Evaluation of long-term efficacy and safety of transdermal fentanyl in the treatment of chronic noncancer pain. J Pain. 2001;2:197-204.) conducted by Milligan et al. This open-label, uncontrolled study is not adequate in design to show an analgesic effect. The data from this study are not substantial evidence or substantial clinical experience to support such outcomes claims. We are not aware of substantial evidence or substantial clinical experience to support these claims.

On pages 8 and 9, the file card includes the claims, "Improved patient outcomes: Open-label, crossover comparison study, " "Significant improvement in physical functioning summary score," and "Significant improvement in social functioning," along with figures comparing data for Duragesic and sustained release oral morphine. To support these claims, the file card cites the study (Allan L, Hays H, Jensen N-H, et al. Radomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain BMJ. 2001;322:1154-1158) conducted by Allan et al.. An open-label study cannot minimize bias in the reporting of subjective response in the SF-36, a general healthcare questionnaire. It is therefore not sufficient to support the cited claims. We are not aware of substantial evidence or substantial clinical experience to support these claims.

Finally, the file card prominently presents the claims, "1,360 loaves.. .and counting," "Work, uninterrupted, " "Life, uninterrupted, " "Game, uninterrupted," " Chronic pain relief that supports functionality, " "Helps patients think less about their pain," and "Improvements in physical and social functioning." These outcome claims are misleading because they imply that patients will experience improved social or physical functioning or improved work productivity when using

Duragesic. Janssen has not provided references to support these outcome claims. We are not aware of substantial evidence or substantial clinical experience to support these claims.

Conclusions and Requested Actions

The file card makes false or misleading safety claims and unsubstantiated effectiveness claims for Duragesic. The file card thus misbrands Duragesic in violation of the Act. 21 U.S.C. 352(a).

DDMAC requests that Janssen immediately cease the dissemination of promotional materials for Duragesic the same as or similar to those described above. Please submit a written response to this letter on or before September 17, 2004, describing your intent to comply with this request, listing all promotional materials for Duragesic the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a plan of action to disseminate truthful, non- misleading, and complete information to the audience (s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to MACMIS # 12386 in addition to the NDA numbers. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Duragesic comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,
{See appended electronic signature page}
Thomas W. Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/S/

Thomas Abrams
9/2/04 04:32:52 PM

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Department of Health and Human Services

Public Health Service
Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Seth H.Z. Fischer
President
Ortho-McNeil Pharmaceutical, Inc
1000 Route 202, P.O. Box 300
Raritan, NJ 08869-0602

Re: NDA # 20-505,20-844
Topamax® (topiramate) Tablets
Topamax® (topiramate capsules) Sprinkles
MACMIS # 12547

WARNING LETTER

Dear Mr. Fischer:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a sales aid (2T10971), two case study flashcards (02T113 and 02T114), and a website (www.topamax.com) for Topamax® (topiramate) submitted by Ortho-McNeil Pharmaceutical, Inc. (Ortho-McNeil) under cover of Form FDA 2253. These promotional materials omit risk information about Topamax, in violation of the Federal Food, Drug, and Cosmetic Act (Act). 21 U.S.C. 352(a), (n), 321(n). These materials raise serious public health concerns because they encourage the unsafe use of Topamax, including, particularly, in pediatric patients.

Background

The Indications and Usage section of the approved product labeling (PI) for Topamax states:

> **Epilepsy**
>
> TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated as adjunctive therapy for adults and pediatric patients ages 2 - 16 years with partial onset

seizures, or primary generalized tonic-clonic seizures, and in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome.

Migraine

TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated for adults for the prophylaxis of migraine headache. The usefulness of TOPAMAX® in the acute treatment of migraine headaches has not been studied.

TOPAMAX is associated with numerous risks. According to the Warnings and Precautions/Information for Patients sections of the PI:

Oligohidrosis and Hyperthermia

Oligohidrosis (decreased sweating), infrequently resulting in hospitalization, has been reported in association with TOPAMAX® use. Decreased sweating and an elevation in body temperature above normal characterized these cases. Some of the cases were reported after exposure to elevated environmental temperatures.

The majority of the reports have been in children. Patients, especially pediatric patients, treated with TOPAMAX® should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather. Caution should be used when TOPAMAX® is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity.

Patients, especially pediatric patients, treated with TOPAMAX® should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather.

According to the Warnings section:

Metabolic Acidosis

Hyperchloremic, non-anion gap, metabolic acidosis (i.e. decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is associated with topiramate treatment. This-metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of topiramate on carbonic anhydrase. Such electrolyte imbalance has been observed with the use of topiramate in placebo-controlled clinical trials and in the post-marketing period. Generally, topiramate-induced metabolic acidosis occurs early in treatment although cases can occur at any time during treatment. Bicarbonate decrements are usually mild-moderate (average decrease of 4 mEq/L at daily doses of 400 mg in adults and at approximately 6 mg/kg/day in pediatric patients); rarely, patients can experience severe decrements to

values below 10 mEq/L. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or drugs) may be additive to the bicarbonate lowering effects of topiramate.

In adults, the incidence of persistent treatment-emergent decreases in serum bicarbonate (levels of <20 mEq/L at two consecutive visits or at the final visit) in controlled clinical trials for adjunctive treatment of epilepsy was 32% for 400 mg/day, and 1% for placebo. Metabolic acidosis has been observed at doses as low as 50 mg/day. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in these trials was 3% for 400 mg/day, and 0% for placebo. Serum bicarbonate levels have not been systematically evaluated at daily doses greater than 400 mg/day.

In pediatric patients (< 16 years of age), the incidence of persistent treatment-emergent decreases in serum bicarbonate in placebo-controlled trials for adjunctive treatment of Lennox-Gastaut Syndrome or refractory partial onset seizures was 67% for TOPAMAX (at approximately 6 mg/kg/day), and 10% for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in these trials was 11% for TOPAMAX and 0% for placebo. Cases of moderately severe metabolic acidosis have been reported in patients as young as 5 months old, especially at daily doses above 5 mg/kg/day.

The incidence of persistent treatment-emergent decreases in serum bicarbonate in placebo-controlled trials for adults for prophylaxis of migraine was 44 % for 200 mg/day, 39 % for 100 mg/day, 23 % for 50 mg/day, and 7 % for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value < 17 mEq/L and > 5 mEq/L decrease from pretreatment) in these trials was 11 % for 200 mg/day, 9 % for 100 mg/day, 2 % for 50 mg/day, and < 1 % for placebo.

Some manifestations of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk for fractures. Chronic metabolic acidosis in pediatric patients may also reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated.

Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering). If the decision is made

to continue patients on topiramate in the face of persistent acidosis, alkali treatment should be considered.

Omission of Material Fact

The promotional materials promote the use of Topamax in adults and children, and make safety and tolerability claims. For example, page one of the Sales Aid and a section of the website entitled "Physician Information," present the following claims:

- "The established worldwide safety record of Topirimate"
- "Well Tolerated"

The materials include some risk information, but fail to present any information about the risks of oligohidrosis, hyperthermia, and metabolic acidosis. For example, a section of the website entitled "Fact Sheet," includes only the following risk information:

- "When TOPAMAX® (5 to 9 mg/kg/day) was taken in clinical trials in combination with traditional AEDs, the most common side effects in children were excessive drowsiness, loss of appetite, fatigue, nervousness, difficulty with concentration/attention, weight loss, aggressive reaction to stimuli and memory difficulties. However, when they occurred, these effects were typically transient."
- "When TOPAMAX® (200 to 400 mg/day) was taken in clinical trials in combination with traditional AEDs, the most common side effects were sleepiness, dizziness, poor coordination, speech difficulties, slowed thinking (psychomotor slowing), blurred or double vision, memory difficulties and changes in sensation. However, when they occurred, these effects were generally temporary."

Additionally, the two Case Study Flashcards make the claim:

- In combination with other traditional antiepileptic drugs (AEDs), the most common side effects of TOPMAX in adults (200 to 400 mg/day) were somnolence, dizziness, ataxia, speech disorders and related problems, psychomotor slowing, abnormal vision, difficulty with memory, paresthesia, and diplopia; and in children (5 to 9 mg/kg/day), somnolence, anorexia, fatigue, nervousness, difficulty with concentration/attention, weight decrease, aggressive reaction, and memory difficulty.

Oligohidrosis and hyperthermia are very serious risks whose negative impact may be mitigated with appropriate monitoring. It is also noteworthy that the majority of reports of these adverse reactions have been in children. Metabolic acidosis is a very serious risk whose manifestations may include hyperventilation, cardiac arrhythmias or stupor. Monitoring in this case, measurement of serum bicarbonate, is quite important. Therefore, we view these adverse reactions of Topamax to be material when promoting the drug. Because the materials omit material risk information, they are false or misleading.

Conclusion and Requested Action

The sales aid, two case study flashcards, and website omit important risk information for Topamax® in violation of the Act. 21 U.S.C. 352(a), (n) & 321(n).

DDMAC requests that Ortho-McNeil immediately cease the dissemination of promotional materials for Topamax® the same as or similar to those described above. Please submit a written response to this letter on or before September 29, 2004 describing your intent to comply with this request, listing all promotional materials for Topamax® the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a plan of action to disseminate truthful, nonmisleading, and complete information to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857, facsimile at (301) 594-6771. In all future correspondence regarding this matter, please refer to MACMIS ID # 12547 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Topamax® comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violation discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

(See appended electronic signature page]

Thomas W. Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising and Communications

cc:
William C. Weldon
CEO
Johnson & Johnson Pharmaceutical
Research & Development, L.L.C.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/S/
