Drug Utilization Review Board

Oklahoma Health Care Authority

4545 N. Lincoln Suite 124

Oklahoma City, Oklahoma 73105

OHCA Board Room

Wednesday

July 9, 2008

@ 6:00 p.m.

THE UNIVERSITY OF OKLAHOMA

THE UNIVERSITY OF OKLAHOMA

MEMORANDUM

TO: Drug Utilization Review Board Members

FROM: Shellie Gorman, Pharm.D.

SUBJECT: **Packet Contents for Board Meeting – July 9, 2008**

DATE: July 2, 2008

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

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

Action Item – Vote to Prior Authorize Osteoporosis Medications – **See Appendix C.**

Action Item – Vote to Prior Authorize Topical Antibiotics – **See Appendix D.**

Action Item – Vote to Prior Authorize Auralgan™ – **See Appendix E.**

Action Item – Vote to Prior Authorize Plavix® 300mg – **See Appendix F.**

Action Item – Vote to Prior Authorize Singulair® – **See Appendix G**

Action Item – Vote to Update Antidepressant PBPA Category and Vote to Prior Authorize Pristiq® – **See Appendix H.**

30 Day Notice to Prior Authorize Voltaren® Gel **– See Appendix I.**

30 Day Notice to Prior Authorize Luvox CR® **– See Appendix J.**

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

Future Business

Adjournment

Drug Utilization Review Board

(DUR Board)

Meeting – July 9, 2008 @ 6:00 p.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. McNeill, Chairman:

1. Call To Order

A. Roll Call – Dr. Graham

Items to be presented by Dr. McNeill, Chairman:

2. Public Comment Forum

A. Acknowledgment of Speakers and Agenda Item

Items to be presented by Dr. McNeill, Chairman:

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

A. May 14, 2008 DUR Minutes – Vote
B. May 15, 2008 DUR Recommendations Memorandum
C. Provider Correspondence

Items to be presented by Dr. Keast, Dr. McNeill, Chairman:

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

A. Retrospective Drug Utilization Review for February 2008
B. Retrospective Drug Utilization Review for March 2008
C. Retrospective Drug Utilization Review Responses for November 2007
D. Retrospective Drug Utilization Review Responses for December 2007
E. Medication Coverage Activity Audit for May 2008
F. Medication Coverage Activity Audit for June 2008
G. Help Desk Activity Audit for May 2008
H. Help Desk Activity Audit for June 2008

Items to be presented by Dr. Keast, Dr. McNeill, Chairman

5. Vote to Prior Authorize Osteoporosis Medications – See Appendix C.

A. COP Recommendations

Items to be presented by Dr. Patel, Dr. McNeill, Chairman:

6. Vote to Prior Authorize Topical Antibiotics – See Appendix D.

A. COP Recommendations

Items to be presented by Dr. Moore, Dr. McNeill, Chairman

7. Vote to Prior Authorize Auralgan™ – See Appendix E.

A. Product Summary
B. COP Recommendations

Items to be presented by Dr. Le, Dr. McNeill, Chairman

8. Vote to Prior Authorize Plavix® 300mg – See Appendix F.

A. COP Recommendations

Items to be presented by Dr. Le, Dr. Keast, Dr. McNeill, Chairman

9. Vote to Prior Authorize Singulair® – See Appendix G.

A. Product Summary
B. COP Recommendations

Items to be presented by Dr. Le, Dr. McNeill, Chairman

10. Vote to Update Antidepressants PBPA Category and Vote to Prior Authorize Pristiq® – See Appendix H.

A. Current Antidepressants Criteria
B. Utilization Review
C. COP Recommendations

Items to be presented by Dr. Patel, Dr. McNeill, Chairman

11. 30 Day Notice to Prior Authorize Voltaren® Gel – See Appendix I.

A. Product Summary
B. COP Recommendations

Items to be presented by Dr. Le, Dr. McNeill, Chairman

12. 30 Day Notice to Prior Authorize Luvox CR® – See Appendix J.

A. Product Summary
B. Cost Comparison
C. COP Recommendations

Items to be presented by Dr. Keast, Dr. McNeill, Chairman

13. FDA and DEA Updates – See Appendix K.

14. Future Business

A. Oral Antifungals Review
B. Qualaquin® Annual Review
C. ESA Review
D. Glaucoma Intervention Report
E. Hemophilia Review
F. New Product Reviews

Appendix A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES of MEETING of MAY 14, 2008

BOARD MEMBERS:	PRESENT	ABSENT
Brent Bell, D.O., D.Ph.	X	
Jay D. Cunningham, D.O.		X
Mark Feightner, Pharm.D.	X	
Dorothy Gourley, D.Ph.	X	
Evelyn Knisely, Pharm.D.	X	
Thomas Kuhls, M.D.	X	
Dan McNeill, Ph.D., PA-C; Chairman	X	
Cliff Meece, D.Ph.; Vice-Chairman	X	
John Muchmore, M.D., Ph.D.	X	
James Rhymer, D.Ph	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 Coordinator/OHCA Liaison	X	
Shellie Keast, Pharm.D.; DUR Manager	X	
Ronald Graham, D.Ph.; Pharmacy Director	X	
Chris Le, Pharm.D.; Clinical Pharmacist/Coordinator	X	
Carol Moore, Pharm.D.; Clinical Pharmacist	X	
Neeraj Patel, Pharm.D.; Clinical Pharmacist	X	
Lester A. Reinke, Ph.D.; Associate Dean for Graduate Studies & Research	X	
Visiting Pharmacy Students: (none)		

OKLAHOMA HEALTH CARE AUTHORITY STAFF:	PRESENT	ABSENT
Mike Fogarty, J.D., M.S.W.; Chief Executive Officer		X
Nico Gomez; Director of Gov't and Public Affairs		X
Lynn Mitchell, M.D., M.P.H,; Director of Medicaid/Medical Services	X	
Nancy Nesser, Pharm.D., J.D.; Pharmacy Director	X	
Howard Pallotta, J.D.; Director of Legal Services		X
Lynn Rambo-Jones, J.D.; Deputy General Counsel III	X	
Rodney Ramsey; Drug Reference Coordinator	X	
Jill Ratterman, D.Ph.; Pharmacy Specialist	X	
Kerri Wade, Senior Pharmacy Financial Analyst	X	

OTHERS PRESENT:

Traci Nelson, P&G	Holly Turner, Merck	Paul Davis, MHAT Advocacy
Richard Ponder, J&J	Jim Dunlap, Lilly	Janie Huff, TAP
Charlene Kaiser, Wyeth	Trudie Lerner, Novartis	Susan Stone, Allergan
Tracy Copeland, Daiichi Sankyo	Laura Stewart, Merck	Rebecca Wing, Taro

PRESENT FOR PUBLIC COMMENT:

Fran Kaiser, M.D.; Merck	Agenda Item No. 8
Norman Imes, M.D.; Merch	Agenda Item No. 8
Traci Nelson; Procter & Gamble	Agenda Item No. 10

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

1A: Roll Call

Dr. Meece called the meeting to order. Roll call by Dr. Graham established a quorum.

ACTION: NONE REQUIRED.

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

Dr. McNeill recognized the speakers for public comment.

Fran Kaiser, M.D.; Merck	Agenda Item No. 8
Norman Imes, M.D.; Merck	Agenda Item No. 8
Traci Nelson; Procter & Gamble	Agenda Item No. 10

ACTION: NONE REQUIRED.

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

3A: April 9, 2008 DUR Minutes

Dr. Kuhls moved to approve minutes as submitted; seconded by Dr. Rhymer.

ACTION: MOTION CARRIED.

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

4A: Retrospective Drug Utilization Review Report: January 2008
4B: Retrospective Drug Utilization Review Responses: September 2007
4C: Retrospective Drug Utilization Review Responses: October 2007
4D: Medication Coverage Activity Audit: April 2008
4E: Help Desk Activity Audit: April 2008

Reports included in agenda packet; presented by Dr. Keast.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 5: **VOTE TO PRIOR AUTHORIZE ALLEGRA® SYRUP AND ODT TABLETS AND UPDATE PBPA CATEGORY**

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

Note change to approval criteria "All Tier 2 products must be tried for 14 days each within the last 60 days before a Tier 3 medication can be approved", add "unless no Tier 2 product is available".

Dr. Meece moved to approve as noted; seconded by Dr. Gourley.

ACTION: MOTION CARRIED.

AGENDA ITEM NO. 6: **VOTE TO UPDATE ADHA PBPA CRITERIA**

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

Dr. Muchmore moved to approve as submitted; seconded by Dr. Meece.

ACTION: MOTION CARRIED.

AGENDA ITEM NO. 7: **VOTE ON CRITERIA FOR GRANDFATHERING**

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

Note to add statins to categories to be grandfathered according to dose; 40 mg atorvastatin/Lipitor and 20 mg rosuvastatin/Crestor.

Dr. Gourley moved to approve as noted; seconded by Dr. Kuhls.

ACTION: MOTION CARRIED.

AGENDA ITEM NO. 8: **UTILIZATION REVIEW OF ASTHMA MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE SINGULAIR®**

For Public Comment, Fran Kaiser, M.D.; Merck: Good evening. I'm Dr. Fran Kaiser. I'm an executive medical director with Merck and I'm an adjunct professor of medicine at Saint Louis University. I'm here to talk a little bit about the prior auth that

you're postulating for Singulair. I think it's very important to recognize that lots of individuals have both allergic rhinitis and asthma. While we understand your desire to perhaps curtail some use of Singulair, it's important to recognize that not everybody always gets coded as having asthma since many patients and many physicians would like to avoid that diagnosis, so that the ICD-9 codes that are sometimes used may not always necessarily reflect the true condition of the patient as having asthma. But an unintended consequence of the prior auth that's being proposed for Singulair, which does require a diagnosis of asthma and is one thing for rescue medication is that this will severely disenfranchise anyone we diagnose as an asthmatic patient, especially a very vulnerable population, that is, children who have asthma. Singulair is an effective drug in reducing asthma attacks, reducing the need for rescue medication and improving asthma control. But not every drug works for every single patient and that includes things such as inhaled corticosteroids. Singular has a granular and tablet formulation that can be used after age six months for perennial allergic rhinitis, two years for seasonal allergic rhinitis, and twelve months of age for asthma. The asthma guidelines note that there is a reason for trended medications to be available; consideration of effectiveness domain of relevance to the patient's asthma which includes impairment, risk or both; the patient's history of any possible previous response to therapy; and the ability of the patient and the family to use the medication correctly, as well as adherence to the medication become important. Now one other thing was a little bit troubling also on prior auth for Singulair for allergic rhinitis was that it appears to require a minimum of ten weeks of failed therapy before switching the patient over, which does seem like a rather long period of time for patients to fail. I do wish to mention that the State of Texas had a very similar edit in place for allergic rhinitis that began February of 2008. Realizing the undue burden that it placed on the patients and families just announced this week that they were removing it. I hope that you will consider the same.

For Public Comment, Norman Imes, M.D.; Merck: Good afternoon. Let me thank you for letting me speak to you. I did bring a letter from Jim Claflin, most of you know is a well respected allergist here in town. He was not able to be here this evening but I'd just like to submit this to the Board. I don't want to be redundant, but I looked at the guidelines that have been proposed and it came to mind that we as physicians are asked to practice what we call evidence based medicine; which means that we look at all the evidence and we make a decision about how we're going to evaluate and how we're going to treat disease processes by our best medical evidence that's in the literature. Now fortunately the international society is here available to us and be it allergy, immunology, as in this case, pulmonology, whatever, each international society, each group of specialists, does it for us. We don't have to go out and reinvent the wheel every time we decide we want to treat something. We can just look it up on Medline or we can also look it up on, whatever our best quick facility is to find new information. But the point is that when I looked at these guidelines that would prepare us for allergic rhinitis, they in no way fitted any of the international or national standards for treatment of allergic rhinitis. Which bothers me. Because if I as a physician am trying to teach young physicians to follow these guidelines, then on the other hand I would expect that insurance companies payors would look at the same guidelines and develop protocols and guidelines that are compatible with these international and national experts. So that was the first thing that bothered me. I think the other thing is, I think there's a little bit of a feeling sometime that treatment of allergic rhinitis is not important. I don't know how many of you know me, but I'm also a board certified sleep specialist. And the field of childrens' sleep medicine is a very important field right now because allergic rhinitis has been shown by numerous studies to have adverse effects on children. They have learning disabilities, they have behavioral disabilities, just like you have in patients that have tonsillar and mandible hypertrophy. So it is a very serious problem in children. In addition of course, it can trigger sleep destruction, sleep fragmentation, virtually all the parasomnias can be triggered by allergic rhinitis symptoms. So it is a very important disease in children as well. The main thing I want you to consider is that there are practice guidelines out there on how to approach treatment of allergic rhinitis. Antihistamines are the first drug of choice in patients that have mild or mild and intermittent allergic rhinitis. They are not the first drug that one would use in any other allergic rhinitis patient. Nasal steroids would be the best drug to use. There's also a presumption in here that by switching from one drug to another, be it antihistamines or be it nasal steroids, that you're going to see some kind of beneficial effect. And I think the literature for that is pretty much lacking. Do side effects change? Yes. Does efficacy change? I think that's pretty weak evidence in the literature. So I would not bet on that. The nasal steroids sometimes are going to be duplicated, particularly in children because they're going to be on an inhaled steroid anyway, so you would prefer not to give them nasal steroids. You've got to skip past that to figure algorithm. I think the other thing that's very important to understand is that all of our reactions and all of our responses to these drugs are genetically determined. In asthma we know now that 20 to 40% of patients don't even respond to inhaled corticosteroids, so things that we were taught when we were growing up turned out not to be true. So use of monoleukast has become extremely important as a fall-back drug and also concomitant drug to use with either nasal steroids or inhaled steroids in the treatment of asthma. So again you cannot count on nasal steroids doing the job, you have, and in my opinion, there are really only three drugs that are so-called controller drugs, to cut down inflammation (intelligible) nasal in the nose or inflammation of the lung. That would be your steroids, monoleukast and in the case of the nose, immunotherapy. No other drug is an inflammatory drug so you're looking at decongestants or antihistamines or cromolyn. Those are what I call comfort drugs. They really don't change the underlying disease process. So since we know that so many patients do not respond to corticosteroids, it's very important to have other drugs available to us that you can use when those drugs fail, or to use for serious cases where you need additional medication, more than monotherapy. So I would like you to reconsider that. If we're going to have guidelines, let's make them evidence based, go back to the literature, figure out exactly what is recommended by the international experts and try to use those as the guidelines to treat allergic rhinitis. I'll entertain any questions.

Dr. Kuhls: You know I'm going to ask you a question. You know better than I all the studies comparatively looking at inhaled steroids, whatever asthma drug you want to talk to in comparing that to Singulair, okay? The question here is, is looking at allergic rhinitis, do you have any studies at all that compare Singulair directly with any of the antihistamines that are available or do you have any studies looking at Singulair and comparing them in good trials like you have and you can argue all you want,

asthma is too, you know, what's going on ..... but do you have anything looking at inhaled ..... nasal steroids versus Singulair and allergic rhinitis and compared trials?
Dr. Imes: Yes actually there's quite a bit of literature out there. I've got the references here .....
Dr. Kuhls: Well, I will tell you that I have asked Merck to provide me all the studies that are available in all their literature and all their basis of all their libraries that they have, looking at Singulair versus antihistamines, Singulair looking at nasal steroids, comparing them, and showing that they don't have any studies that are really comparative. And that there's no studies available that I know of that directly compare in large studies, looking, showing that Singulair is more effective, even in the genetically susceptible population of allergic rhinitis, that Singulair works any better than any of the other drugs.
Dr. Imes: Does it work better than the other drugs or ..... which if you look at ..... my point is that if you look at a large population, nasal corticosteroids usually win the race against anything. They're going to print out better than either monoleukast or antihistamines. In fact, some people argue you don't even need the antihistamine if you have them on nasal steroids. But if you take it down another tier, you say is monoleukast better than antihistamines, most of the studies will show monoleukast will, there are studies out there comparing most all the antihistamines and I can give those to you if you want them.
Dr. Kuhls: I would love to see those because Merck hasn't been able to provide those.
Dr. Imes: Okay. I didn't go to Merck. I just pulled those myself.
Dr. Kuhls: So that's going to need to be looked at but I would like to see some really good randomized good controlled trials, like trials you're used to of looking at for asthma and comparing an antihistamine, let's take Zyrtec, let's take Claritin OTC, whatever you want to take and showing me that they're more effective. Because if they're equal effective, then for that reason, we're going to have to look at costs.
Dr. Imes: You will find both. You will find some that say they're equally effective, another study might say that it's more effective. Which is fairly true of medical literature in general ..... but you have to understand also .....
Dr. Kuhls: Well, I'd like to see those studies.
Dr. Imes: ..... that monoleukast is being used not as a substitute for nasal steroids in most cases, it's being used as a add-on or it's being used only in certain cases where the patient's already on corticosteroids, you'd like to keep the dose down. So you're not going to say, well I'm going to use monoleukast as a first line drug. You don't use it, depending upon the circumstances of the patient, but also you have patients who don't tolerate nasal steroids well, you have family members who say I don't want my kid on this. You know all the scenarios. But one of the references I use a lot is, it's up-to-date, which I think is a very authoritary source, up-to-date, you can find the references you're talking about.
Dr. Kuhls: I'd love to see them.
Dr. Imes: Yeah, in fact I've got a copy right here, I'll just give it to you. So yes, the studies are out there and these are a panel of experts and they make the same recommendations I just made to you.
Dr. Kuhls: You need to also, if you look at comparative trials of with Singulair versus Zyrtec and with Claritin and with inhaled nasal steroids, you need to give them to Merck too, because I think they, when they sent me all the information that was available, I didn't get those studies.
Dr. Imes: Oh, well I keep PubMed dialed in on my computer and do my research. Yes it's out there and you're welcome to my copy here of the up-to-date article.
Dr. Kuhls: Okay, yeah I'll take that.
Materials included in agenda packet; presented by Dr. Le.
ACTION: NONE REQUIRED.

AGENDA ITEM NO. 9: **30-DAY NOTICE TO PRIOR AUTHORIZE PLAVIX® 300 MG**
Materials included in agenda packet; presented by Dr. Le.
ACTION: NONE REQUIRED.

AGENDA ITEM NO. 10: **30-DAY NOTICE TO PRIOR AUTHORIZE OSTEOPOROSIS MEDICATIONS**
For Public Comment, Traci Nelson, Procter & Gamble: My name is Traci Nelson and I am a regional account manager for Procter & Gamble Pharmaceutical and I'm just here to speak to you about Actonel which is made for the treatment of osteoporosis. Actonel has the broadest FDA approved osteoporosis indications, indicated for both prevention and treatment of postmenopausal osteoporosis and for prevention and treatment of steroid induced osteoporosis. It is approved for men with osteoporosis as well as for treatment of Paget's disease of the bone. Of the approved osteoporosis therapies, Actonel has the most oral dose dosing options. It is available in 5 mg daily, 35 mg weekly, 75 mg two consecutive days a month and now the newest indication of 150 mg so the newest strength of 150 mg monthly for postmenopausal osteoporosis. Now that you discuss with the board the actual evidence in reducing fractures and begin with the AHRT report on comparative effectiveness of osteoporosis treatment. The report was released December '07. AHRQ, the Agency for Healthcare Research and Quality, is under the Department of Health and Human Services, was established as a mandate for the Medicare Modernization Act of '03. It cited only Actonel and alendronate for having good evidence from the randomized control trials to prevent fractures outside the spine both nonvertebral and hip fractures compared to placebo. It cited only Actonel and alendronate has demonstrated fracture risk reduction in patients treated with steroids. It also cited Actonel as the only bisphosphonate having evidence to reduce the risk of fracture in men. Actonel has an excellent safety GI tolerability safety profile. Actonel was specifically designed

to minimize GI side effects associated with bisphosphonates. Phase 3 results demonstrated that there were no differences in GI adverse events between Actonel treated and placebo groups. Even the patients with active GI disease. It is important to point out that Actonel acts the GI contraindication is not contraindicated in patients with esophageal abnormalities due to stricture or achalasia. Actonel is the only bisphosphonate to have placebo controlled extension studies out to five years. This study demonstrates sustained spine outside the spine fracture efficacy and more importantly, bone safety based on paired biopsy analysis. I would appreciate your consideration of maintaining Actonel with Oklahoma Medicaida a Tier 1 due to Actonel's extensive approved indications, multiple dosing, the strength of its evidence across the entire skeleton, along with its excellent safety data. Thank you. Any questions?
Materials included in agenda packet; presented by Dr. Keast.
ACTION: NONE REQUIRED.

AGENDA ITEM NO. 11: **30-DAY NOTICE TO PRIOR AUTHORIZE TOPICAL ANTIBIOTICS**
Materials included in agenda packet; presented by Dr. Patel.
ACTION: NONE REQUIRED.

AGENDA ITEM NO. 12: **30-DAY NOTICE TO PRIOR AUTHORIZE AURALGAN™**
Materials included in agenda packet; presented by Dr. Moore.
ACTION: NONE REQUIRED.

AGENDA ITEM NO. 13: **FDA & DEA UPDATES**
Materials included in agenda packet; presented by Dr. Keast.
ACTION: NONE REQUIRED.

AGENDA ITEM NO. 14: **FUTURE BUSINESS**
Materials included in agenda packet; submitted by Dr. Graham.
14A: Hemophilia Review
14B: Antidepressant Review
14C: Oral Antifungals Review
14D: New Product Reviews
ACTION: NONE REQUIRED.

AGENDA ITEM NO. 15: **ADJOURNMENT**
The meeting was adjourned at 7:40 p.m.

The University of Oklahoma College of Pharmacy

Pharmacy Management Consultants
ORI W-4403; PO Box 26901
Oklahoma City, OK 73190
(405)-271-9039

Memorandum

Date: May 15, 2008

To: Nancy Nesser, Pharm.D., J.D.
Pharmacy Director
Oklahoma Health Care Authority

From: Shellie Gorman Keast, Pharm.D., M.S.
Drug Utilization Review Manager
Pharmacy Management Consultants

Subject: DUR Board Recommendations from Meeting of May 14, 2008

Recommendation 1: Vote to Prior Authorize Allegra® Syrup and ODT Tablets and Update Prior Authorization Category

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends adding Allegra® Syrup and ODT to the PBPA category as a Tier 3 agent and updating the criteria as follows:

ORAL ALLERGY MEDICATIONS		
Tier 1	**Tier 2**	**Tier 3**
OTC loratadine*	fexofenadine (generic tabs)	desloratadine (Clarinex)
OTC cetirizine*		fexofenadine (Allegra)†
		levocetirizine (Xyzal)‡
* For members 21 years and older, OTC loratadine and OTC cetirizine are available with prior authorization. OTC loratadine and OTC cetirizine do not require PA for members under age 21. †Includes new Allegra syrup and ODT formulations. ‡Xyzal not covered for members under age 6.		

Approval Criteria:

- A 14 day trial each of OTC loratadine and cetirizine within the last month is required before a Tier 2 medication can be approved.
- All Tier 2 products must be tried for 14 days each within the last 60 days before a Tier 3 medication can be approved (unless no age appropriate Tier 2 product exists).
- Diagnosis must be for a chronic allergic condition or asthma.
- Prior authorization will be for 360 days.

Recommendation 2: Vote to Update ADHD PBPA Category

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends moving methylphenidate IR to Tier 1 for doses up to TID, however it will not be counted as a Tier 1 trial (changes in red below).

Tier 1	*Tier 2*	*Tier 3*
methylphenidate SR, ER, and CR *dexmethylphenidate IR (Focalin)* *methylphenidate IR** *Focalin XR* *Concerta* *Adderall XR* *Vyvanse*	*Metadate CD* *Ritalin LA* *Strattera* *amphetamine salt combos†*	*Daytrana* *Desoxyn* *dextroamphetamine* *Dexedrine Spansule* *Provigil*

Blue color denotes current supplemental rebate – individual products would move to Tier 2 if manufacturer chooses to no longer participate in program.
Products can move to lower tiers based on supplemental rebate participation.
*Doses greater than TID will require prior authorization. Does not count as a Tier 1 trial.
†No PA will be required for a once daily dosing of these medications. Doses greater than once daily will require prior authorization.

Recommendation 3: Vote Criteria for Grandfathering

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends establishing specific guidelines for the Product Based Prior Authorization program regarding the grandfathering of medications.

Criteria for Grandfathering of PBPA Categories:

1. A member is considered stabilized on a medication when claims history suggests a minimum compliance rate of 80% in the past 100 days.
2. On categories voted to be grandfathered, the member that is currently stabilized on a medication will still be eligible to receive that medication if it is moved to a higher tier.
3. PBPA categories will not be grandfathered unless the DUR Board votes to apply the grandfathering rule to the category.

The following list shows products recommended for grandfathering:

Medications	Titration Required	Grandfathered
Antidepressants	Yes	Yes
Antifungals (Topical)	No	No
Antihistamines	No	No
Antihypertensives	Yes	Yes
Anti-Ulcer Medications	No	No
Bladder Control Meds	No	No
Fibric Acid Derivatives	No	No
Insomnia Meds	No	No
Muscle Relaxants (excluding Special PAs)	No	No
NSAIDs	No	No
Nasal Allergy Medications	No	No
Narcotic Analgesics	Yes	Yes
Ophthalmic Allergy Products	No	No
Ophthalmic Antibiotics	No	No
Ophthalmic Glaucoma Agents	Yes	Yes
ADHD Medications	Yes	Yes
Statins	Yes (not extensive)	No*

*Unless currently stabilized on atorvastatin 40 mg or rosuvastatin 20 mg or higher.

Oklahoma Allergy® & Asthma Clinic
Founded 1925

(405) 235-0040
www.oklahomaallergy.com

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Meridian Medical Tower
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SOUTH OFFICE:
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NORMAN OFFICE:
Physicians and Surgeons Bldg.
950 North Porter, Suite 101
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EDMOND OFFICE:
Sycamore Square
120 North Bryant, Suite A4
Edmond, Oklahoma

SPECIALIZING IN THE EVALUATION
AND MANAGEMENT OF
ALLERGIES AND ASTHMA
IN ADULTS AND CHILDREN

Charles D. Haunschild, MD*
James H. Wells, MD*
John R. Bozalis, MD*
Warren V. Filley, MD*
James R. Claflin, MD*
Patricia I. Overhulser, MD*
Dean A. Atkinson, MD*
Richard T. Hatch, MD*
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SENIOR CONSULTANTS
Lyle W. Burroughs, MD*
Robert S. Ellis, MD*

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Allergy and Immunology

Joseph A. Schraad, MHA
Chief Executive Officer

Ruth Riddles, BSN MBA CCRC
Clinical Research

Sherry K. Hubbard, RD LD
Clinical Dietitian

Member Institution of
OKLAHOMA Health Center

June 16, 2008

Medicaid Drug Utilization Review Committee

Re: Consideration of Singulair or Pre-authorization in the Pediatric Age Group

Dear Medicaid Drug Utilization Review Committee Members:

As a Medicaid healthcare provider trained in adult and pediatric allergy and immunology and as one of the limited number of allergists in the state of Oklahoma that accept Medicaid patients, I am writing in support of Singulair usage in both allergic rhinitis and bronchial asthma.

Almost 100% of the patients that I see in this age group with allergic rhinitis have been tried on a number of antihistamines and many with nasal steroids for an adequate length of time to declare them a failure when I see them for the first visit. Furthermore, I try to provide patients with a one to two week sample of Singulair with instructions for them to use the sample and not to fill the Singulair prescription if improvement in symptoms has not been noted. A shorter trial of nasal steroids and a number of antihistamines should adequately determine the response to the individual or combination of medications.

My office expends considerable time, effort, and energy on pre-authorizations of medications and this should be streamlined significantly. I could bring patients back on multiple visits and charge for Medicaid visits but I feel this is a waste of Medicaid funds to find effective medications for these very needy patients. Strictly from the standpoint of my office staff's time, requiring pre-authorizations would be much less expensive to do so. However, the cost for the physician services for this approach would be far greater than a speedier pre-authorization of medications.

Most sincerely,

C D Haunschild, MD.

Charles D. Haunschild, M.D.
Diplomate American Board
Allergy and Immunology

CDH:jlc

May 14, 2008

TPAM
Tulsa Pediatric & Adolescent Medicine

Hugh Graham, MD
Joel Gist, MD
Donna Krutka, MD

Dr. Dan McNeal, Ph.D.
Chairman of DUR Board
4545 North Lincoln Blvd., Suite 124
Oklahoma City, Oklahoma 73105

Dear Dr. McNeal:

I am a pediatrician in Tulsa, Oklahoma who is sending you a letter in reference to Singulair. This medication has been available to pediatricians over the last ten years. It has been a remarkable medication, which has served a purpose of helping not only children with asthma, but also with allergic rhinitis. As you may be aware, asthma and allergies in our state account for a very large amount of the clinical problems that we see in our pediatric practice. Children as early as the age of 6 months start having serious problems with the complications of nasal allergies, skin allergies, and respiratory allergies. For a long time, we have tried the medications that were available. The implications of using antihistamines have been a problem for quite a while, including lethargy, sedation, irritability, and sometimes even drying of the oral secretions. When Singulair came along, it provided us with another option to help some of these young children. Oftentimes, both nasal allergies and asthma are coupled together, and Singulair has played a big role in helping to stabilize these children without necessarily the use of nebulizers or aerochambers, which can be quite challenging in younger children.

It is my understanding that you are considering how to handle Singulair in the formulary for the Oklahoma Medicaid Program. It is my hope that you will continue to allow us to use that without changing its prior authorization. This is a critical medication in our practice and in the treatment of many young children, and it would be very disconcerting to not be able to freely prescribe this medication.

1919 S. Wheeling, Suite 304 / Tulsa, OK 74104 / (918) 748-7620 / Fax: (918) 748-7647

TPAM
Tulsa Pediatric & Adolescent Medicine

If I may be of any further help in this matter, please do not hesitate to let me know.

Sincerely,

Donna J. Krutka, M.D.

DJK:pr

Hugh Graham, MD
Joel Gist, MD
Donna Krutka, MD

J. FIELDS, M.D.
E. FOX, M.D.
500 E. Robinson
Doctors Park Suite 2600
Norman, OK 73071
(405) 364-6432

To Whom It May Concern:

The Oklahoma Health Care Authority is considering changing the regulations for which Singulair is prescribed for allergies. Currently no prior authorization is required. As I understand it, the new regulation states a patient must fail on 3 separate antihistamines and 2 nasal steroids before being approved for Singulair. If this is implemented, it could delay a patient up to 10 weeks in getting a medication that has been proven to be very effective in the treatment of allergies.

The Oklahoma Health Care Authority must consider ways for the number of prescriptions written for without a generic equivalent. However, an alternative could be to have a 2 week trial of an antihistamine OR nasal steroid. I think this would better serve the pediatric population of Oklahoma.

Thank you for your consideration in this matter.

Sincerely,

James Fields, MD

J. FIELDS, M.D.
E. FOX, M.D.
500 E. Robinson
Doctors Park Suite 2600
Norman, OK 73071
(405) 364-6432

To Whom It May Concern:

It has come to my attention that the Oklahoma Health Care Authority is considering changing the preferred medication list for the treatment of allergic rhinitis. Currently, providers can prescribe Singulair without a prior authorization; however, it is my understanding the new regulation will require patients to have medication treatment failure prior to authorization of the use of Singulair. According to the new regulation, patients will have to demonstrate treatment failures on 3 separate antihistamines and 2 nasal steroids prior to the approval of Singulair. This will force many patients to wait for up to 10 weeks to receive adequate treatment of their underlying disease process.

Obviously, the rationale is to decrease the number of prescriptions written for a medication that does not have a generic equivalent. I propose that the health care authority consider the use of a 2 week trial of an antihistamine OR nasal steroid prior to authorization of the use of Singulair. I feel that this would allow for both cost containment as well as allow providers continue to give quality, patient focused care.

Thank you for your consideration in this matter.

Sincerely,

Glen Diaz, ARNP, FNP

J. FIELDS, M.D.
E. FOX, M.D.
500 E. Robinson
Doctors Park Suite 2600
Norman, OK 73071
(405) 364-6432

To Whom It May Concern:

Singulair can currently be written without a prior authorization. The Oklahoma Health Care Authority is considering changing the regulations for which this medication is prescribed for allergies. Singulair has been proven to be very effective in the treatment of children with allergies. The new regulation states a patient must fail on 3 separate antihistamines and 2 nasal steroids before being approved for Singulair. By implementing this regulation, it could delay a patient up to 10 weeks in receiving this medication.

A decrease in the number of prescriptions written for medications without a generic equivalent is important for the Oklahoma Health Care Authority to consider. However, an alternative to this regulation could be to have a 2 week trial of an antihistamine OR nasal steroid. I think this would better serve the pediatric population of Oklahoma.

Thank you for your consideration in this matter.

Sincerely,

Eileen Fox

Eileen Fox, MD

J. FIELDS, M.D.
E. FOX, M.D.
500 E. Robinson
Doctors Park Suite 2600
Norman, OK 73071
(405) 364-6432

To Whom It May Concern:

It has been brought to my attention the Oklahoma Health Care Authority is considering changing the regulations for which Singulair is prescribed for allergies. Singulair has been proven to be very effective in the treatment of allergic symptoms. As it stands now, a prescription can be written without a prior authorization, however, the new regulation states a patient must fail on 3 separate antihistamines and 2 nasal steroids before being approved for Singulair. This would delay a patient starting on the medication for up to 10 weeks.

I understand the rationale is to decrease the number of prescriptions written for a medication that is without a generic equivalent. Perhaps requiring a 2 week trial of an antihistamine OR nasal steroid would better serve the pediatric population of Oklahoma.

Thank you for your consideration in this matter.

Sincerely,

Amanda Lowry, ARNP

Amanda Lowry, ARNP, CPNP-PC

South Tulsa Ear Nose & Throat Center, P.C.

Surgery of the Ear, Nose & Throat
Facial Plastic Surgery

Physicians
Michael B. Shaw, D.O.
Thomas V. Nunn, D.O.

4564 South Harvard
Tulsa, Oklahoma
74135
918.459.8824
800.987.6673
918.307.2239 fax

May 20, 2008

Dan McNeill, Ph.D., PA-C
Chair of Drug Utilization Board
4545 North Lincoln Boulevard, Suite 124
Oklahoma City, Oklahoma 73105

Dear Dr. McNeill,

I would like to ask that Singulair be continued on formulary coverage for the Oklahoma Medicaid System. I do not believe that this drug will be over utilized but is invaluable for many patients.

I appreciated consideration in this matter.

Sincerely,

Thomas V. Nunn, D.O.

TVN: cak

Lawton Pediatrics
a service of Comanche County Memorial Hospital

June 23, 2008

To Whom It May Concern:

RE: Proposed changes in Singulair coverage.

It has come to our attention that the Drug Utilization Review board has proposed a 5-tier, 10 week, process when prescribing Singulair for the indication of allergic rhinitis in SoonerCare patients. According to the information we received, the proposed changes will require three antihistamines and two intranasal steroids each being given for two weeks before Singulair can be prescribed.

While it seems prudent to require at least a two-week trial on an antihistamine prior to recommending Singulair, we feel the proposed 5-tier process will make appropriate management of a very common health concern difficult, if not impossible. We further anticipate an increase in the number of patient visits to properly manage the numerous medication changes. This is not only an inconvenience for the patients but will also increase the cost of health care.
We would ask that the proposed changes be reconsidered in lieu of a system that will allow SoonerCare patients to continue to receive the same level of healthcare we now provide our other patients.

Sincerely,

Ed Henson, M.D.
Medical Director

Jacque Gillespie, ARNP

May 25, 2008

Medicaid Drug Utilization Review Committee

TO WHOM IT MAY CONCERN:

Re: Consideration of Singulair or Pre-Authorization in the Pediatric Age Group

Montelukast (Singulair) has been an effective medication for the treatment of respiratory allergic disease for several years. You are aware that it is a specific leukotriene receptor antagonist and is an effective medication to abrogate allergic symptoms that are mediated by the leukotriene pathway of inflammation. You are also aware that there is currently no screening blood test that can prospectively identify patients whose symptoms are caused by leukotriene inflammatory molecules. It is estimated that between 25% and 30% of respiratory allergy sufferers have leukotrienes as their primary mediators. Until such a screening blood test becomes available, physicians have no choice but to try patients on a variety of medications and see which ones work. Montelukast is, and never has been considered, an ultimate third tier medication only to be used if all other appropriate medications, i.e. antihistamines and intranasal steroids, have failed. As you are aware, it is an entirely different category of medication from the antihistamines, decongestants, and corticosteroids.

Singulair should be considered early on for a pharmacotherapeutic option and not as a medication of last resort. To require a trial of Loratadine, Cetirizine, and Fexofenadine for 14 days each plus two trial of intranasal steroids 14 days each before approval of Singulaur is unfair and unreasonable.

The most cost effective way of handling children or adults with respiratory allergic problems is to give them samples of each of the categories of these medications (antihistamines, intranasal steroids, and leukotriene receptor antagonist) for roughly a week to 10 days maximum each, and whichever medication proves the best relief, to then write a prescription for that particular medication. By my calculations 14 days each of 3 different antihistamines plus 14 days each of 2 intranasal steroids adds up to 70 days of medication before you would consider trying Singulair. This, I think, is an unnecessary lengthy period of time and unfair to patients suffering from respiratory allergic symptoms.

I do not understand the concept of requiring preauthorization for a drug such as Singulair whereas it is not required for the antihistamines and intranasal steroid sprays.

In my opinion, this is clearly a case of profiling one type of medication over the others which is not scientifically justified.

If there are any questions regarding this letter, please feel free to contact me.

Sincerely,

John R. Bozalis, M.D.
Diplomate American Board
Allergy and Immunology

JRB:jld

Appendix B

Retrospective Drug Utilization Review Report

Claims Reviewed for February 2008

Module	Drug Interaction	Duplication of Therapy	Drug-Disease Precautions	Dosing & Duration
Total # of messages returned by system when no limits were applied	41,222	64,728	42,296	37,762
Limits which were applied	Established, Major, Males and Females, Age 0-18	Narcotics, Males and Females, Age 26-28	Contraindicated, Males and Females, Age 47-49, Asthma	High Dose only, 7-12 year old, male and females, Abilify and Geodon
Total # of messages after limits were applied	16	155	51	30
Total # of members reviewed after limits were applied	16	124	38	30

LETTERS			
Prescribers		**Pharmacies**	
Sent	**Responded**	**Sent**	**Responded**
86		1	

Retrospective Drug Utilization Review Report

Claims Reviewed for March 2008

Module	Drug Interaction	Duplication of Therapy	Drug-Disease Precautions	Dosing & Duration
Total # of messages returned by system when no limits were applied	39,773	58,827	1,025,118	31,495
Limits which were applied	Established, Major, Males and Females, Age 0-21	Males and Females, 0-21 years of age, Antidepressants-SSRIs	Contraindicated, Hepatic Disease, Males and Females 0-35 years old	High Dose, Low Dose, Duration, 1623 Zyvox, Males and Females 0-150
Total # of messages after limits were applied	35	177	66	8
Total # of members reviewed after limits were applied	35	165	59	8

LETTERS			
Prescribers		**Pharmacies**	
Sent	**Responded**	**Sent**	**Responded**
98		39	

Retrospective Drug Utilization Review Report

Claims Reviewed for November 2007

Module	Drug Interaction	Duplication of Therapy	Drug-Disease Precautions	Dosing & Duration
Limits which were applied	Established, Major, Males and Females, Age 0-18	Narcotics, Males and Females, Age 19-21	Contraindicated, Asthma, Males and Females, Age 22-35	High Dose, Abilify and Geodon, Males and Females, Age 22-43

Response Summary (Prescriber)
Letters Sent: 68
Response Forms Returned: 36

The response forms returned yielded the following results:

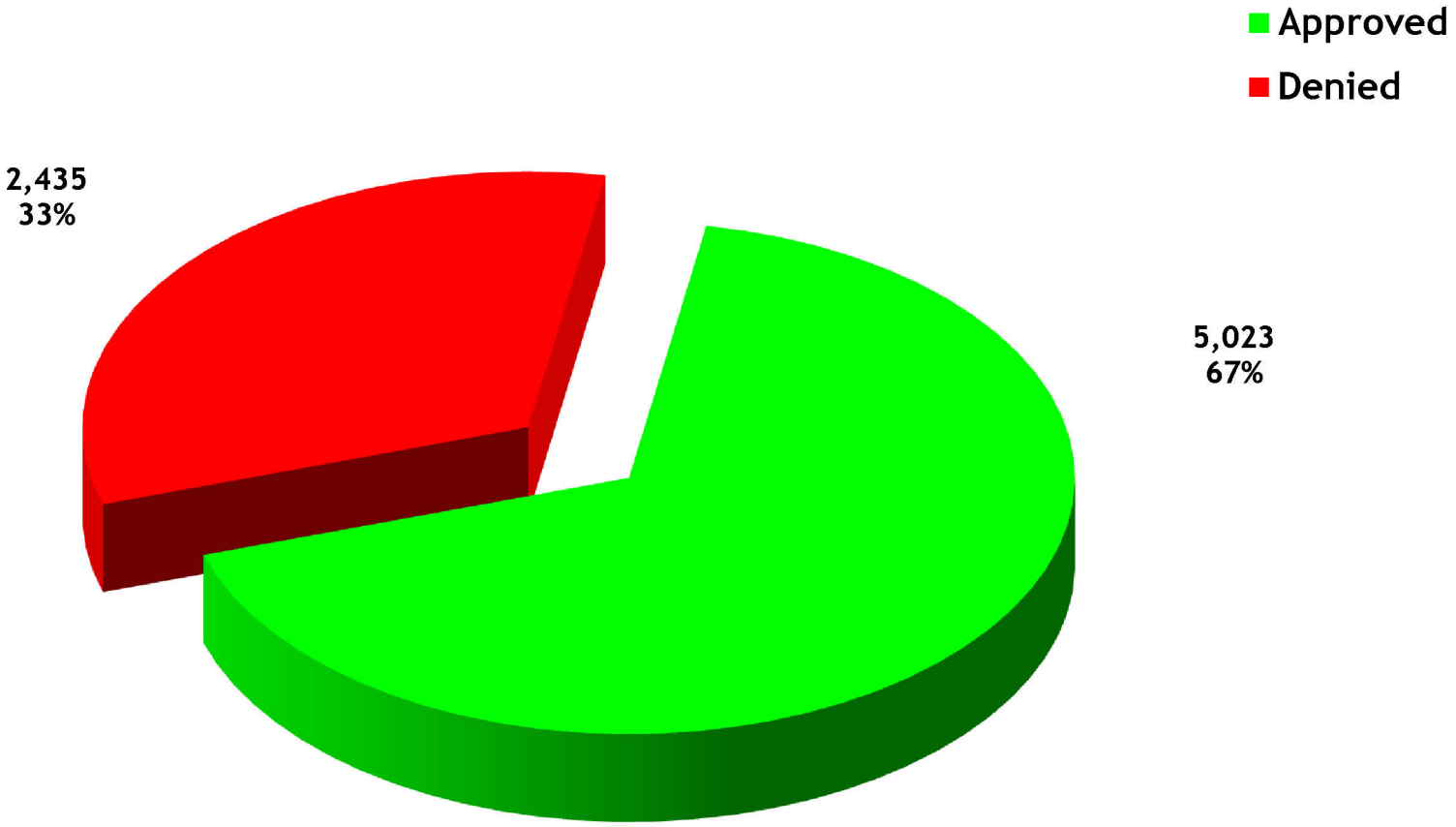
5 (14%)	*Record Error—Not my patient.*
2 (6%)	*No longer my patient.*
3 (8%)	*Medication has been changed prior to date of review letter.*
9 (25%)	*I was unaware of this situation & will consider making appropriate changes in therapy.*
7 (19%)	*I am aware of this situation and will plan to continue monitoring therapy.*
10 (28%)	*Other*

Response Summary (Pharmacy)
Letters Sent: 47
Response Forms Returned: 30

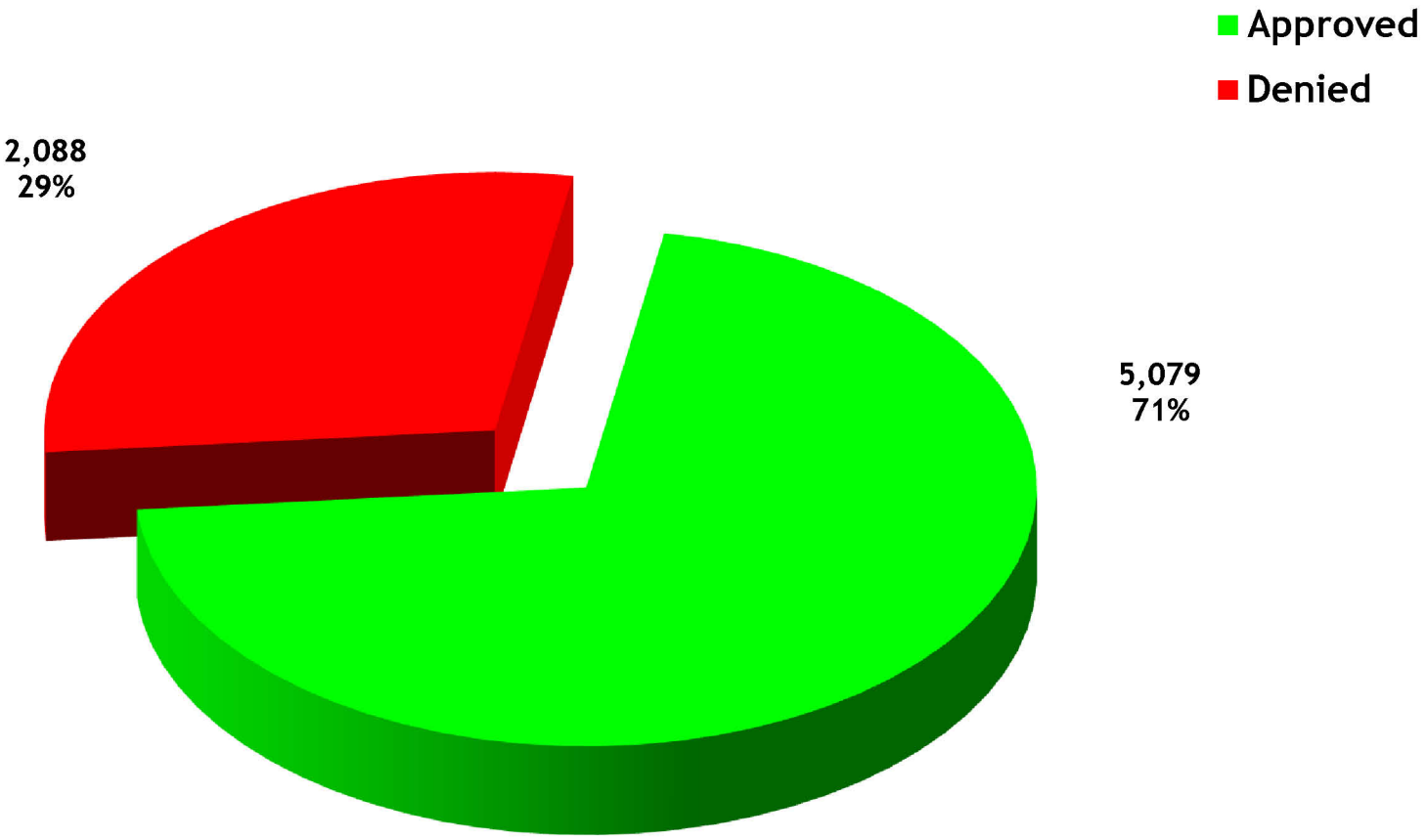
The response forms returned yielded the following results:

0 (0%)	*Record Error—Not my patient.*
3 (10%)	*No longer my patient.*
1 (3%)	*Medication has been changed prior to date of review letter.*
16 (53%)	*I was unaware of this situation & will consider making appropriate changes in therapy.*
4 (13%)	*I am aware of this situation and will plan to continue monitoring therapy.*
6 (20%)	*Other*

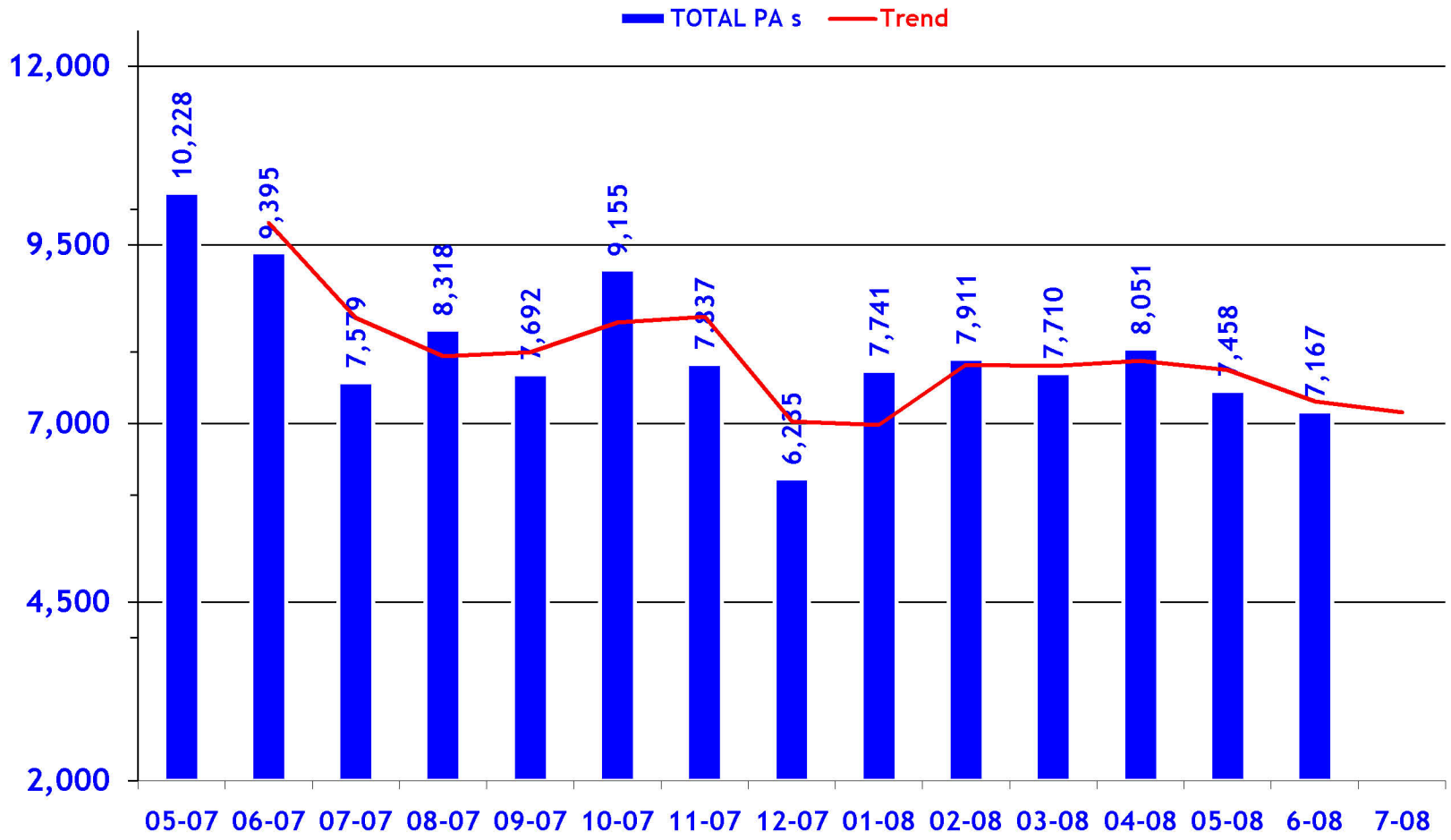
PRIOR AUTHORIZATION ACTIVITY REPORT
May 2008



PRIOR AUTHORIZATION ACTIVITY REPORT
June 2008



PRIOR AUTHORIZATION REPORT
May 2007 – June 2008



Activity Audit for

May 01, 2008 Through May 31, 2008

	Average Length of Approvals in Days	Approved	Denied	Total
ACE Inhibitors	178	13	8	21
Angiotensin Receptor Antagonist	344	90	80	170
Antidepressant	319	452	283	735
Antihistamine	92	362	301	663
Antiulcers	10	12	6	18
Anxiolytic	94	2,325	261	2,586
Calcium Channel Blockers	178	12	1	13
Growth Hormones	174	33	3	36
HTN Combos	364	18	10	28
Insomnia	93	41	16	57
Nsaids	329	46	48	94
Plavix	182	90	17	107
Stimulant	231	560	262	822
Others	102	967	1,139	2,106
Emergency PAs		2	0	2
Total		**5,023**	**2,435**	**7,458**
Overrides				
Brand	232	39	16	55
Dosage Change	12	292	13	305
High Dose	203	9	0	9
Ingredient Duplication	22	9	2	11
Lost/Broken Rx	10	62	11	73
Nursing Home Issue	10	56	3	59
Other	8	32	2	34
Quantity vs. Days Supply	174	36	30	66
Stolen	17	2	0	2
Overrides Total		**528**	**75**	**603**

Denial Reasons

Lack required information to process request.	2,082
Unable to verify required trials.	1,219
Not an FDA approved indication/diagnosis.	172
Considered duplicate therapy. Member has a prior authorization for similar medication.	107
Does not meet established criteria.	96
Requested dose exceeds maximum recommended FDA dose.	40
Member has active PA for requested medication.	19
Medication not covered as pharmacy benefit.	12
Drug Not Deemed Medically Necessary	1
Duplicate Requests	449
* Changes to existing	623

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

Activity Audit for

June 01, 2008 Through June 30, 2008

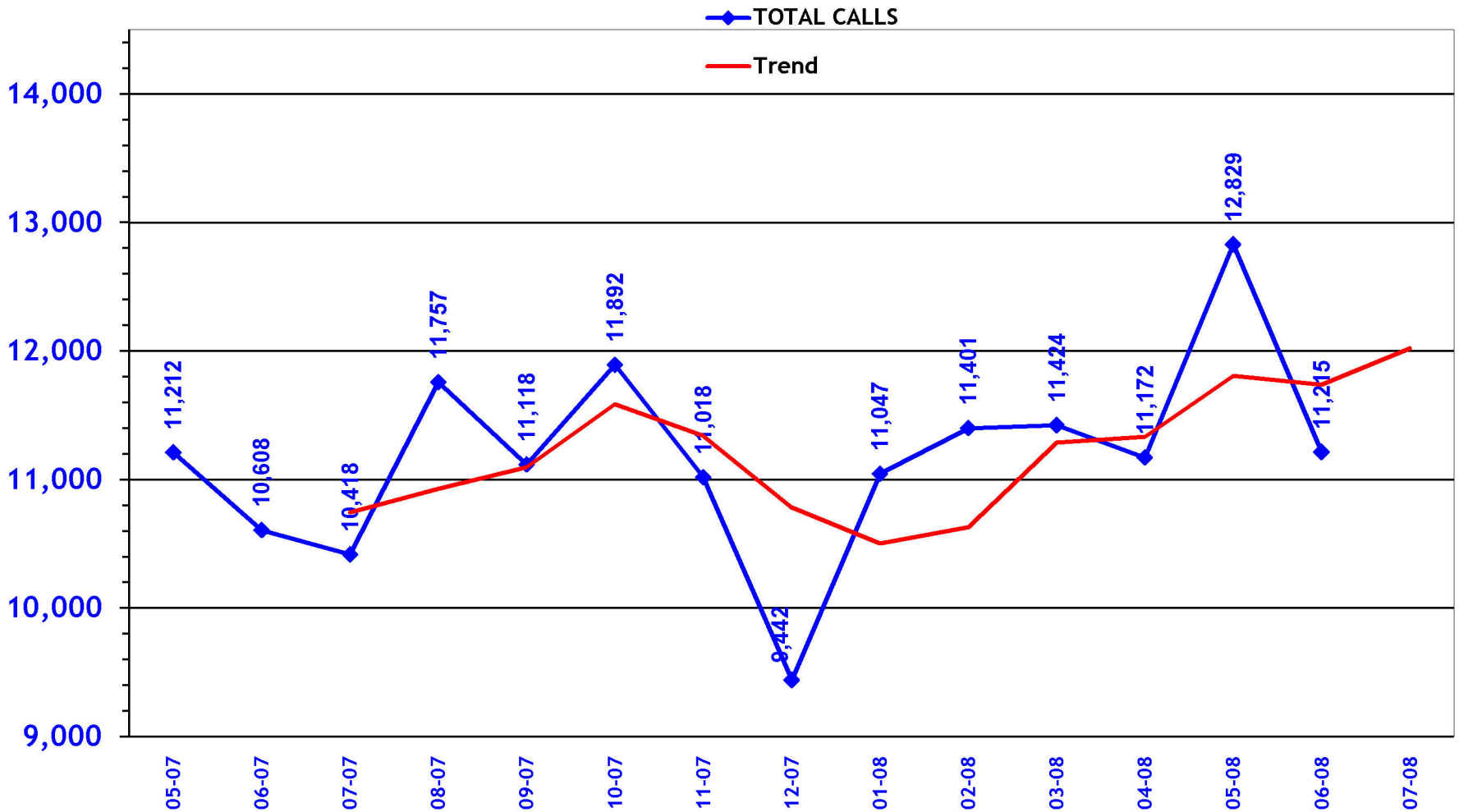
	Average Length of Approvals in Days	Approved	Denied	Total
ACE Inhibitors	109	11	6	17
Angiotensin Receptor Antagonist	358	42	88	130
Antidepressant	282	201	261	462
Antihistamine	91	242	199	441
Antiulcers	3	7	2	9
Anxiolytic	96	3,043	343	3,386
Calcium Channel Blockers	128	7	5	12
Growth Hormones	179	27	3	30
HTN Combos	192	13	11	24
Insomnia	89	36	24	60
Nsaids	241	33	71	104
Plavix	235	103	9	112
Stimulant	223	503	163	666
Others	76	811	903	1,714
Emergency PAs		0	0	0
Total		**5,079**	**2,088**	**7,167**
Overrides				
Brand	178	22	10	32
Dosage Change	13	345	38	383
High Dose	17	2	2	4
Ingredient Duplication	21	14	2	16
Lost/Broken Rx	10	72	4	76
Nursing Home Issue	10	37	2	39
Other	18	48	3	51
Quantity vs. Days Supply	184	14	10	24
Stolen	18	2	0	2
Wrong D.S. on Previous Rx	17	2	0	2
Overrides Total		**544**	**69**	**613**

Denial Reasons

Lack required information to process request.	1,924
Unable to verify required trials.	962
Considered duplicate therapy. Member has a prior authorization for similar medication.	160
Not an FDA approved indication/diagnosis.	154
Does not meet established criteria.	68
Requested dose exceeds maximum recommended FDA dose.	56
Member has active PA for requested medication.	38
Drug Not Deemed Medically Necessary	6
Medication not covered as pharmacy benefit.	2
Duplicate Requests	457
* Changes to existing	608

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

CALL VOLUME MONTHLY REPORT
May 2007 – June 2008



Appendix C

Vote to Prior Authorize Osteoporosis Medications

Oklahoma Health Care Authority
July 2008

This category was introduced for possible inclusion in the Product Based Prior Authorization program in March 2008. See the March, April, and May DUR packets for a more complete discussion of the category. This meets the statutory requirements of 63 O.S. Sec. 5030.5.

Recommendations

The College of Pharmacy recommends adding the Osteoporosis Medications to the Product Based Prior Authorization Program.

Tier 1*	Tier 2	Tier 3
Alendronate (Fosamax)	Alendronate + D (Fosamax+D)	Zoledronic acid (Reclast)
Calcium + Vitamin D†	Ibandronate (Boniva)	Teriparatide (Forteo)
	Risedronate (Actonel)	

*Branded products will require a brand name override. Calcitonin and raloxifene are not included as Tier 1 trials.
†Must be used at recommended doses in conjunction with Tier 1 bisphosphonate for trial to be accepted unless member has a recent laboratory result showing adequate Vitamin D or member is unable to tolerate calcium. OTC Calcium and Vitamin D are only covered for members with osteoarthritis.

Recommended Criteria for Moving to Higher Tiers:

1. Treatment failure with all lower tiered products, or
2. Contraindication to all lower tiered products, or
3. Allergic reaction to all lowered tiered products, or
4. Specific indication not covered by a lower tiered product.
5. No concomitant use of bisphosphonate therapy will be approved. No additional bisphosphonate may be approved for 365 days following zoledronic acid infusion.
6. Clinical Exceptions:
   a. Risedronate may be approved for members with high risk for gastric side effects.
   b. Zoledronic acid will be exempt from prior authorization for a diagnosis of Paget's disease or for osteoporosis if secondary diagnosis meets criteria (see Attachment 2).

Appendix 1

Reclast Coverage Guidelines

Reclast will be covered for postmenopausal osteoporosis in women who have the following secondary diagnoses:

- Severe esophageal disease (e.g., ulcerations, strictures):
  - ICD-9 codes 530.0, 530.20-530.21, 530.3 and 710.1
- Inability to take anything by mouth:
  - ICD-9 codes 530.87, V44.1, V45.72 and V45.75
- Inability to sit or stand for prolonged periods.
  - ICD-9 code V49.84.
- Inability to take an oral bisphosphonate for other special medical circumstances that justify the method of administration:
  - ICD-9 codes 995.29 and V12.79.

http://www.trailblazerhealth.com/Tools/Local%20Coverage%20Determinations/Default.aspx?ID=2084

Appendix 2

Current Forteo Criteria

1. Postmenopausal women at high risk for fractures (T-score at or below -2.5), or that cannot tolerate, are allergic to, or have failed to improve while on other agents.
2. Men with primary or hypogonadal osteoporosis (T-score at or below -2.5), or that cannot tolerate, are allergic to, or have failed to improve while on other agents.
3. No concurrent use of Forteo® with other osteoporosis agents.
4. Minimum 12 month trial with one other agent (unless contraindicated, intolerant, or allergic) and a BMD (T-score at or below -2.5) test within the last month.
5. PA approval for one month's supply per fill for duration of 1 year, with a maximum duration of 2 years.

Appendix 3

Dietary Reference Intakes for Vitamin D (Based on absence of adequate exposure to sunlight.)				
	Life Stage Group	RDA/AI (IU)	UL (IU)	Adverse effects of excessive consumption
Infants	0-6 mo	200	1000	Elevated plasma 25 (OH) D concentration causing hypercalcemia
	7-12 mo	200	1000	
Children	1-3 yrs	200	2000	
	4-8 yrs	200	2000	
Males	9-13	200	2000	
	14-18	200	2000	
	19-30	200	2000	
	31-50	200	2000	
	50-70	400	2000	
	> 70	600	2000	
Females	9-13	200	2000	
	14-18	200	2000	
	19-30	200	2000	
	31-50	200	2000	
	50-70	400	2000	
	>70	600	2000	
Pregnant or Lactating	≤18	200	2000	
	19-30	200	2000	
	31-50	200	2000	

Dietary Reference Intakes for Calcium				
	Life Stage Group	RDA/AI (mg)	Upper Limit (mg)	Adverse Effects of excessive consumption
Infants	0-6 months	210	ND	Kidney stones, hypercalcemia, renal insufficiency, milk alkali syndrome, possible CV risks
	7-12 months	270	ND	
Children	1-3 yrs	500	2500	
	4-8 yrs	800	2500	
Males	9-13 yrs	1300	2500	
	14-18 yrs	1300	2500	
	19-30 yrs	1000	2500	
	31-49 yrs	1000	2500	
	50-70 yrs	1200	2500	
	> 70 yo	1200	2500	
Females	9-13 yrs	1300	2500	
	14-18 yrs	1300	2500	
	19-30 yrs	1000	2500	
	31-50 yrs	1000	2500	
	50-70 yrs	1200	2500	
	>70 yrs	1200	2500	
Pregnant or Lactating	≤18 yrs	1300	2500	
	19-30 yrs	1000	2500	
	31-50 yrs	1000	2500	

United States Department of Agriculture. Dietary Reference Intake Tables. United States Department of Agriculture. http://www.iom.edu/Object.File/Master/7/294/0.pdf. http://www.iom.edu/Object.File/Master/7/296/webtablevitamins.pdf. Published 2001. Accessed March 13, 2008.

Appendix D

Vote to Prior Authorize
Topical Antibiotics

Oklahoma HealthCare Authority, July 2008

Recommendations:

The College of Pharmacy recommends creating a prior authorization category for this group of medications with the following tier structure and criteria:

Tier 1*	Tier 2	Tier 3
Mupirocin Oint 2%	Supplemental Rebated	Bactroban Cream 2%*
Gentamicin Oint 0.1%	Tier 3	Bactroban Nasal Ointment 2%
Gentamicin Cream 0.1%		Centany Kit 2%
Gentamicin Powder		Altabax Oint 1%
Cortisporin Oint 1%†		
Cortisporin Cream 0.5%†		

*Branded products will require a Brand Name Override when generic versions are available.
†Products will remain Tier 1 as long as federal rebate does not change.

Criteria:

- A 5-day trial of a Tier 1 medication within the last month is required before a Tier 2 medication can be approved.
- Member must have a 5-day trial with a Tier 1 and a Tier 2 medication prior to receiving authorization for a Tier 3 medication.
- Clinical exception includes adverse effects with all lowered tiered drugs or unique indication not covered by lower tiered drugs.
- Prior authorization will be for 10 days.

Appendix E

Vote to Prior Authorize Auralgan™

Oklahoma Health Care Authority July 2008

Manufacturer	Deston Therapeutics, LLC.
Classification	Miscellaneous Otic Preparations
Status	Prescription only

Summary[1]

- Auralgan, an otic solution containing 1.4% benzocaine, 5.4% antipyrine, 0.01% acetic acid, 0.01% polycosanol, and glycerin, is the reformulation of the original Auralgan by Ayerst, which contained only antipyrine, benzocaine and glycerin. The new formulation is being marketed for the relief of pain associated with acute otitis externa, removal of cerumen, and as an adjunct to systemic antibiotic to relieve pain and reduce inflammation of acute otitis media.
- Auralgan is available in a 14 mL container with dropper.
- Neither this formulation nor the original Auralgan has FDA approval, so there are no officially approved generics therapeutic equivalents. Generic substitution is not legal.

Recommendations

The College of Pharmacy recommends prior authorization of this product with approval after failed trials of an available generic product containing benzocaine/antipyrine/glycerin, and two (2) trials of oral pain relievers for a duration of 360 days.

1. Pharmacist Letter, May 2008 Vol. 24, Detail-Document 240502,

Appendix F

Vote to Prior Authorize Plavix 300mg

Oklahoma Health Care Authority
July 2008

Recommendations

The College of Pharmacy recommends prior authorization of Plavix® 300mg. Approval Criteria is as follows:

- FDA approved diagnosis of non-ST-segment elevated acute coronary syndrome or ST segment elevated acute myocardial infarction.
- Approval will be for only one dose of 300mg.

Appendix G

Vote to Prior Authorize Singulair®

Oklahoma Health Care Authority
July 2008

Summary of Clinical Evidence Regarding Leukotriene Receptor Antagonists

Asthma

- Inhaled corticosteroids are recommended as the preferred agent of choice for long-term daily control of asthma symptoms by both the NAEPP/NHLBI and the GINA (Global Initiative for Asthma) Guidelines.[1]

- Leukotriene receptor antagonists have also been evaluated as a preferred first- line alternative for inhaled corticosteroids in mild to moderate chronic asthma due to its advantage as an orally administered medication. However, evidence from systematic reviews show patients treated with LTRA were 65% more likely to suffer exacerbations, and LTRA therapy was associated with 160% increase risk of withdrawal due to poor asthma control. Inhaled corticosteroids showed superiority in other outcomes such as improvement in FEV_1, nocturnal awakenings, rescue medication use, symptom-free days, and quality of life.[2,3] As a result, inhaled cortico-steroids remain the preferred first-line therapy of choice, and LTRA are recommended as an alternative option reserved for those who cannot use inhaled corticosteroids.

- For asthmatics who are inadequately controlled with inhaled corticosteroids, evidence from the Cochrane Database of Systematic Review shows that long acting $beta_2$ agonists (LAB_2As) are superior to LTRAs for prevention of exacerbations, improving lung function, and reducing need for rescue medication, while having a lower risk of withdrawal due to any reason.[4]

- For asthmatics who are well controlled by inhaled corticosteroids, daily montelukast may be an option for "step-down therapy." A randomized controlled trial[5] showed that patients with asthma well controlled with the use of twice daily inhaled fluticasone can be switched to once daily fluticasone plus salmeterol without increased rates of treatment failure. Although a switch to montelukast resulted in an increased rate of treatment failure, the rates of clinically significant asthma exacerbations and percentage of symptom free days were similar across treatment groups.

Allergic Rhinitis

- Intranasal corticosteroids are recommended as the preferred agent of choice for reduction of symptoms associated with allergic rhinitis.[6,7] Clinical trials show that LTRAs were effective in reducing symptoms of allergic rhinitis, however, even when used concomitantly with antihistamines, LTRAs were still inferior to intranasal corticosteroids in the treatment of symptoms associated with seasonal allergic rhinitis.[8]

- When compared to antihistamines, there were no significant differences in efficacy, although pooled data slightly favored antihistamines in the reduction of composite nasal symptoms score and increase in quality of life.[9]

- Recently, the LTRA, montelukast, was found to be comparable to pseudoephedrine in reduction of rhinoconjunctival symptoms, except that of nasal congestion, in which pseudoephedrine was found to be superior. [10]

- There has yet to be clinical evidence comparing LTRA with cromolyn or topical antihistamines.

Recommendations

The College of Pharmacy recommends the following options for consideration by the DUR Board for prior authorization of Singulair®:

Option 1:

An edit be put in place to detect a **diagnosis of asthma OR a claim for a an inhaled corticosteroid and a rescue medication** in the member's previous year's claims history. If these are found, the claim for Singulair® will trigger a system-generated prior authorization for one year. For all other claims a manual prior authorization will be required. Members with a diagnosis of asthma and a claim for a rescue medication will receive approval for the duration of one year. For members with a diagnosis of Allergic Rhinitis the following criteria will apply:

- **For members 2 years of age or older** - Trial of an antihistamine and nasal corticosteroid, each 14 days in duration, that has failed to relieve allergic rhinitis symptoms. Agents may be used concomitantly or consecutively within the past 30 days.
- **For members less than two years of age** - Trial of an oral antihistamine, 14 days in duration, that has failed to relieve allergic rhinitis symptoms within the past 30 days.

Option 2:

Singulair® be placed in the Oral Allergy PBPA category as a tier-3 agent. An edit will be put in place to detect a **diagnosis of asthma OR a claim for an inhaled corticosteroid and a rescue medication** in the member's previous year's claims history. If the diagnosis or claims are found, the claim for Singulair® will trigger a system-generated prior authorization for one year. For all other claims a manual prior authorization will be required. Members with a diagnosis of asthma and a claim for a rescue medication will receive approval for the duration of one year. For all other claims a manual prior authorization will be required and the following established criteria for oral allergy products will apply:

ORAL ALLERGY MEDICATIONS		
Tier 1	**Tier 2**	**Tier 3**
OTC loratadine*	**fexofenadine (generic tabs)**	**desloratadine (Clarinex®)**
OTC cetirizine*		**fexofenadine (Allegra®)†**
		levocetirizine (Xyzal®)‡
		montelukast (Singulair®)

* For members 21 years and older, OTC loratadine and OTC cetirizine are available with prior authorization. OTC loratadine and OTC cetirizine do not require PA for members under age 21.
†Includes new Allegra syrup and ODT formulations.
‡Xyzal not covered for members under age 6.

Approval Criteria:

- A 14 day trial each of OTC loratadine and cetirizine within the last month is required before a Tier 2 medication can be approved.
- All Tier 2 products must be tried for 14 days each within the last 60 days before a Tier 3 medication can be approved.
- Diagnosis must be for a chronic allergic condition or asthma.
- Prior authorization will be for 360 days.

Option 3:

In response to discussion by the DUR Board members, this option for prior authorization of Singulair® for both the indications of asthma and allergic rhinitis is presented for review.

- Petitions with a diagnosis of allergic rhinitis will be subject to criteria from Options One or Two listed above or as modified and agreed upon by the DUR Board.
- Petitions with a diagnosis of asthma will be subject to the following suggested criteria as modified and agreed upon by the DUR Board:

    1. Diagnosis of mild or moderate persistent asthma, and/or exercise induced asthma
    2. Trial of inhaled corticosteroid or corticosteroid/LAB_2A therapy within the previous 6 months and reason for trial failure.
    3. Clinical exceptions include: children less than 11 years of age not adequately controlled on compliant inhaled corticosteroid therapy alone, montelukast used as step down therapy, or specific circumstance making inhaled corticosteroid therapy inappropriate for member.

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[1] Bukstein, DA. Jones, CA., et al. **Discussing the Costs of Asthma: Controlling Outcomes, Symptoms, and Treatment Strategies.** American Journal of Managed Care. Vol 11, No 11, SUP. October 2005.

[2] Ng, D. Salvio, F. Hicks, G. **Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children.** Cochrane Database of Systematic Reviews. (2):CD002314, 2004.

[3] Ducharme, FM. Lasserson TJ. Cates, CJ. **Inhaled corticosteroids versus leukotriene antagonists as first-line therapy for asthma: a systematic review of current evidence.** Treatments in Respiratory Medicine. 3(6):399-405, 2004.

[4] Ducharme, FM. Lasserson TJ. Cates CJ. **Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma.** Cochrane Databse of Systematic Reviews. (1):CD003137, 2005.

[5] American Lung Association Asthma Clinical Research Centers. **Randomized Comparison of Strategies for Reducing Treatment in Mild Persistent Asthma.** The New England Journal of Medicine. Vol 356, no 20. May 17, 2007.

[6] Institute for Clinical Systems Improvement (ICSI). **Diagnosis and treatment of respiratory illness in children and adults.** Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2007 Jan. 71 p. [176 references] Available at **http://www.guideline.gov/summary/summary.aspx?doc_id=10622&nbr=005564&string=rhinitis**

[7] Agency for Healthcare Research and Quality. Department of Health and Human Services. **Management of Allergic and Nonallergic Rhinitis.** Available at **http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat1.chapter.117840**

[8] Rodrigo, FJ. Yanez, A. **The role of antileukotriene therapy in seasonal allergic rhinitis: a systematic review of randomized trials.** Annals of Allergy, Ashtma, & Immunology. 96(6):779-86, Jun 2006.

[9] Wilson, AM. O'Byrne, PM. Parameswaran, K. **Leukotriene Receptor Antagonists for Allergic Rhinitis: A Systematic Review and Meta-Analysis.** The American Journal of Medicine. Vol 116; pg 338-344. March 2004.

[10] Nayak A. Langdon RB. **Montelukast in the treatment of allergic rhinitis: an evidence-based review. [Review] [102 refs]** [Journal Article. Research Support, Non-U.S. Gov't. Review] *Drugs. 67(6):887-901, 2007.*

Appendix H

Drug Utilization Review of Antidepressants and Vote to Prior Authorize Pristiq®

Oklahoma Health Care Authority
July 2008

Current Prior Authorization of Antidepressants

The Product Based Prior Authorization program for the class of Antidepressant medications was first reviewed and voted on by the DUR Board in July of 2004. The program initially only included the class of selective serotonin receptor inhibitors (SSRIs). In May of 2005 the PBPA category was expanded to include the following classes with the current criteria:

SSRIs (Selective Serotonin Reuptake Inhibitors)	
Tier-1	**Tier-2**
citalopram (Celexa®)	citalopram suspension (Celexa® suspension)
fluoxetine (Prozac®)	fluoxetine (40mg caps, Sarafem®, Prozac Weekly™)
fluvoxamine (Luvox®)	escitalopram (Lexapro®)
paroxetine (Paxil®, Paxil CR®)	paroxetine (Pexeva®)
sertraline (Zoloft®)	
Dual Acting Antidepressants	
Tier-1	**Tier-2**
bupropion (Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®)	duloxetine (Cymbalta®)
mirtazapine (Remeron®, Remeron SolTab®)	Nefazodone+ (Serzone®)
trazodone (Desyrel®)	venlafaxine (Effexor XR®)
venlafaxine (Effexor®)	
Monoamine Oxidase Inhibitors	
Tier-1	**Tier-2**
	selegiline transderm patch (Emsam®)
	tranylcypromine (Parnate®)
	phenelzine (Nardil®)
	selegiline (Zelapar®)

Mandatory generic plan applies , Current tiers based on Supplemental Rebate participation
+ Brand name Serzone® voluntarily withdrawn from market in June 2004 due to reports of liver toxicity. Generic is still available.

1. Approval of tier-2 medication after a recent (within 6 months) 4 week trial and failure on a tier-1 medication. Tier-1 selection can be from any tier-1 anti-depressant classification.
2. Approval of tier-2 medication with a documented adverse effect, drug interaction, or contraindication to tier-1 products.
3. Approval of tier-2 medication with prior stabilization on the tier-2 medication documented within the last 100 days.
4. Approval of tier-2 medication for a unique FDA-approved indication not covered by any tier-1 products.
5. A petition for a tier-2 medication may be submitted for consideration when a unique member specific situation exists or with a prescription written by a psychiatrist.

Miscellaneous Restrictions of Antidepressants

The following is a table of quantity limits that apply:

Quantity Limits on Antidepressants			
Drug	**Quantity Limits**	**Comments**	**FDA Daily Max**
Mirtazapine (**Remeron**®) Tabs and SolTabs	100 tablets per 100 days	15-45mg QD	45mg
Bupropion (**Wellbutrin**®) Tabs	102 tablets per 34 days	100mg BID – 150mg TID	450mg
Bupropion (**Wellbutrin SR**®) Tabs	100 tablets per 50 days	150mg - 200mg BID	400mg
Bupropion (**Wellbutrin XL**®) sustained release Tabs	100 tablets per 100 days	150mg – 300mg QD	450mg
Venlafaxine (**Effexor**®**)** Tabs	102 tablets per 34 days	25mg -200mg QD	200mg
Venlafaxine (**Effexor XR**®) Caps	100 capsules per 100 days	37.5mg -225 mg QD	225mg
Duloxetine (**Cymbalta**®)	100 tablets per 100 days	20mg-60mg QD	60mg
Citalopram (**Celexa**®) Tabs	100 tablets per 34 days	20mg-40mg QD	60mg
Escitalopram (**Lexapro**®) Tabs	100 tablets per 66 days	10mg-20mg QD	20mg
Fluoxetine (**Prozac**®) Caps/ Tabs	100 capsules/tablets per 34 days	20mg-80mg QD	80mg
Fluoxetine (**Prozac Weekly**®)	4 caps (1 pack) per 28 days	Half life ~ 7 days	90mg weekly
Fluvoxamine (**Luvox**®) tablets	25mg – 100 tablets per 100 days 50mg – 100 tablets per 50 days 100mg - 102 tablets per 34 days	50mg-300mg QD	300mg
Paroxetine (**Paxil**®) Tabs	10, 20mg - 100 tabs per 100 days 30mg – 100 tabs per 50 days 40mg – 100 tabs per 66 days	20mg-50mg QD	50mg
Paroxetine (**Paxil CR**®) Tabs	100 tablets per 100 days	12.5mg-75mg QD	75mg
Sertraline (**Zoloft**®) Tabs	100 tablets per 50 days	25mg-200mg QD	200mg

Fluoxetine 40 mg Capsules

- Fluoxetine 40 mg **capsules** require a prior authorization.
- Fluoxetine 10 and 20 mg capsules are a covered benefit with **no** prior authorization required.
- No specific approval criteria were voted on by the DUR Board. Each request is reviewed on a case by case basis and can be approved if a compelling clinical reason exists, i.e. if the patient is taking 80 mg daily.

Prozac® Weekly

- The quantity limit for Prozac® Weekly is 3 packs of 4 tablets each (12 week supply).
- Members currently stabilized on Prozac® Weekly should be continued.
- New start members must meet all of the following criteria:
    - Member must have been stabilized on 20 mg daily of fluoxetine for at least 12 weeks.
    - Start date should be 7 days after the last daily dose.
    - Member must have a compelling clinical reason for use of this convenience only product. This product should not be approved for patients in nursing homes or assisted living centers (because medications are administered to patients, so compliance/convenience should not be an issue).
    - Prior authorization can be given for a 12 week supply per petition.

Utilization of Antidepressants

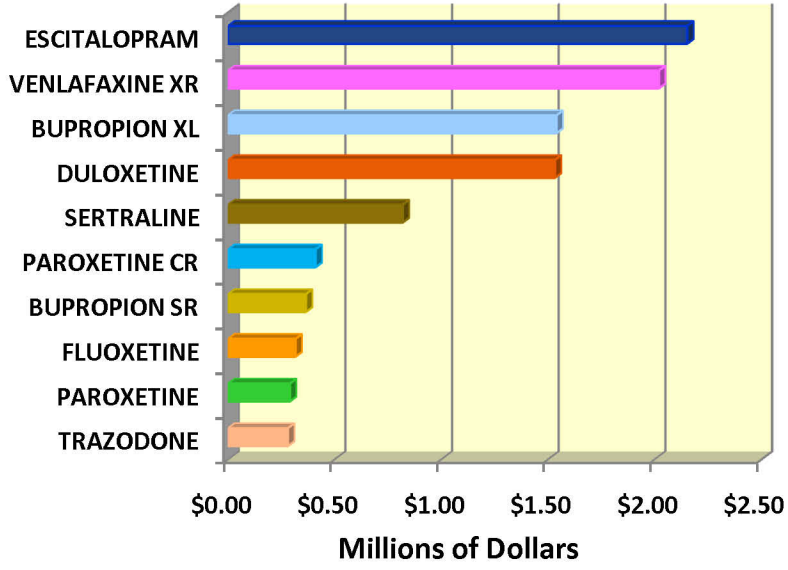
Summary of Antidepressant Utilization for Calendar Year 2007

Class of Antidepressant	Claims	Members	Units	Days	Cost	Perdiem	Units/Day	Claims/Mem	% Cost
Dual Acting	92,966	19,325	3,787,276	3,086,765	$6,136,970.52	$1.99	1.23	4.81	57 %
SSRIs	141,165	32,935	5,499,553	4,706,668	$4,243,728.38	$0.90	1.17	4.29	40 %
Tricyclics	24,736	6,642	1,320,722	831,180	$324,127.73	$0.39	1.59	3.72	3 %
MAOIs	70	17	2,250	2,103	$31,034.88	$14.76	1.07	4.12	0.2 %
Totals	258,937	47,578	10,609,801	8,626,716	$10,735,861.51	1.23	5.44	$1.24	100

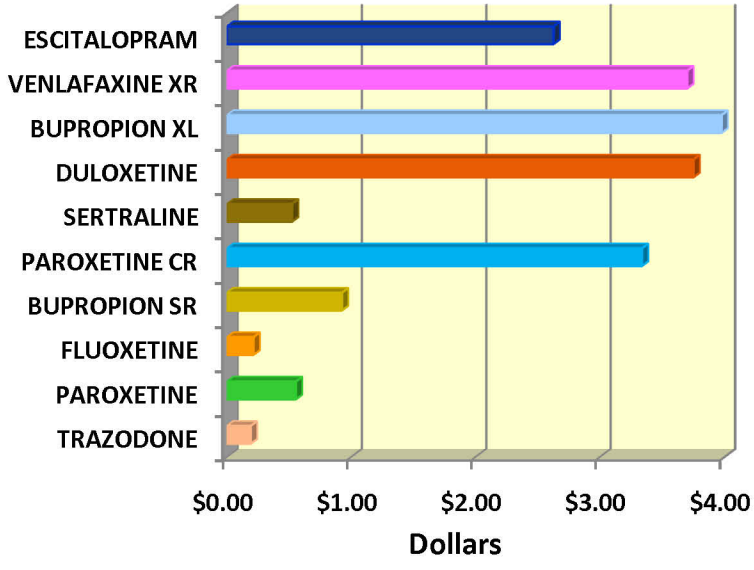
Trends in Utilization of Antidepressants

Calendar Year	Members	Claims	Cost	Cost/Claim	Perdiem	Units	Days
2006	48,435	251,252	$15,116,055.37	$60.16	$1.77	10,443,971	8,522,832
2007	47,578	258,937	$10,735,861.51	$41.46	$1.24	10,609,801	8,626,716
Change	-853	7,707	-$4,379,748.70	-$18.70	-$0.53	166,705	104,552
Percent Change	-1.8 %	3.1 %	-29 %	-31 %	-30 %	1.6 %	1.2 %

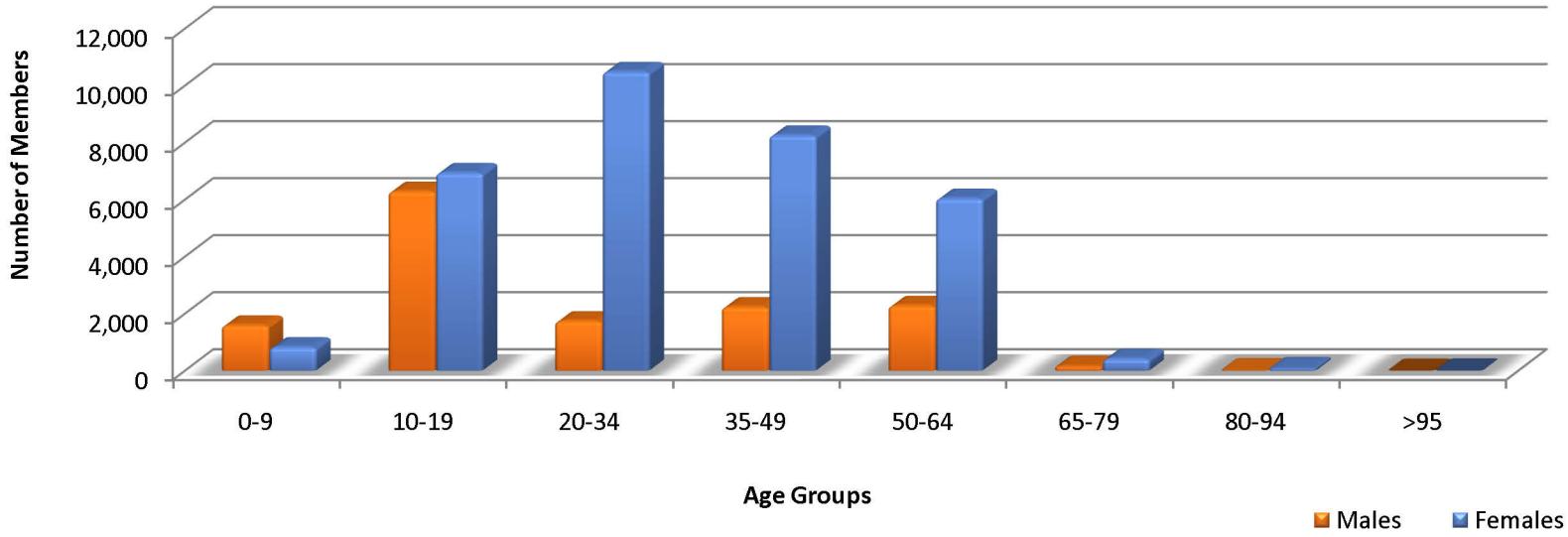
Top 10 Agents by Cost



Cost/Unit



Demographics of Members Utilizing Antidepressants: CY2007

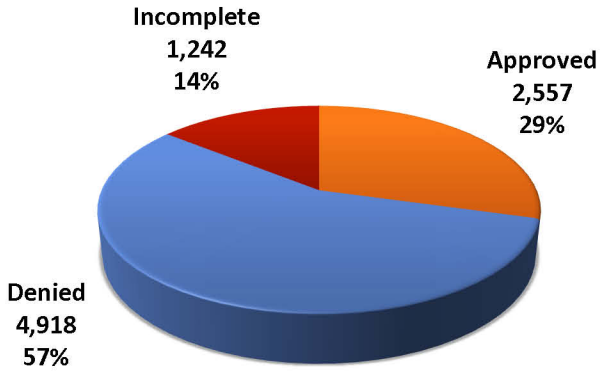


Age Groups	0-9	10-19	20-34	35-49	50-64	65-79	80-94	>95
Males	1,590	6,283	1,736	2,229	2,274	153	25	0
Females	825	6,939	10,485	8,254	6,039	419	91	9

Prior Authorization of Antidepressants

There are two types of computer edits implemented at the point of sale for the antidepressant category. One edit detects stabilization on a tier-2 medication via recent continuous claims for the tier-2 medication, in which case, the medication would be grandfathered for that member. The other edit detects a tier-1 medication in the claims history according to criteria, in which case, a prior authorization is automatically generated for that member, and the claim is paid. If the edits detects neither, then a manual prior authorization is required. For the calendar year 2007, there were a total of 9,422 petitions received for this category. The following chart shows the status of all the petitions received, including early refill override and quantity limit override petitions.

Status of Petitions Received for Calendar Year 2007



Available Second Generation Antidepressants

Generic Name	US Trade Name*	FDA Indications**	Dosage Forms**	Dosing Range	Frequency
Fluoxetine†	Prozac® Prozac Weekly® Sarafem®	MDD (adult/peds) OCD PMDD Panic disorder	10, 20, 40 mg caps; 10 my tabs; 4 mg/ml solution 90 mg pellets (weekly)	10-80 mg 90 mg (weekly)	QD-BID Q weekly
Sertraline†	Zoloft®	MDD (adult) OCD Panic DO PTSD PMDD SAD	25, 50, 100 mg tabs; 20 mg/ml solution	25-200 mg	QD
Paroxetine†	Paxil® Paxil CR®	MDD (adult) OCD Panic DO SAD GAD PTSD PMDD††	10, 20, 30, 40 mg tabs; 2 mg/ml solution; 12.5, 25, 37.5 mg CR tabs	10-60 mg 12.5-75 mg	QD
Citalopram†	Celexa®	MDD	10, 20, 40 mg tabs; 1, 2 mg/ml solution	20-60 mg	QD
Fluvoxamine†	Luvox® Luvox CR®	OCD (≥ 8 yo/adults)	25, 50, 100 mg tabs	50-300 mg	QD-BID
Escitalopram	Lexapro®‡	MDD GAD	10, 20 mg tabs 1 mg/ml solution	10-20 mg	QD
Duloxetine	Cymbalta®	MDD DPNP**	20, 30, 60 mg caps	40-60 mg	QD-BID
Venlafaxine†	Effexor® Effexor XR®	MDD GAD††† Panic DO SAD †††	25, 37.5, 50, 75, 100 mg tabs; 37.5, 75, 150 mg XR caps	75-375 mg (IR) 75-225 mg (XR)	BID-TID QD
Desvenlafaxine	Pristiq®	MDD	50, 100 mg extended- release tabs	50-100 mg	QD
Bupropion†	Wellbutrin® Wellbutrin SR® Wellbutrin XL®	MDD Seasonal affective DO	75, 100 mg tabs; 50, 100, 150, 200 mg SR tabs; 150, 300, mg XL tabs	100-450 mg 150-400 mg 150-450 mg 150-300 mg	TID BID QD
Mirtazapine†	Remeron®	MDD	15, 30, 45 mg tabs; 15, 30, 45 mg orally disintegrating tabs	15-45 mg	QD
Nefazodone***†	Serzone®	MDD	50, 100, 150, 200, 250 mg tabs	200-600 mg	BID

* CR, SR, XL, and XR are registered trademarks referring to controlled, sustained, or extended-release dosage forms

** **GAD**-generalized anxiety disorder; **MDD**- major depressive disorder; **OCD**-obsessive compulsive disorder; **PTSD**-post-traumatic stress disorder; **PMDD**-premenstrual dysphoric disorder; **DPNP**-diabetic peripheral neuropathic pain; **SAD**-social anxiety disorder

*** Withdrawn from the US market effective June 14, 2004

† Generic available for all or some dosage forms.

†† Only Paxil CR® (not Paxil®) is approved for the treatment of PMDD

††† Only Effexor XR® is approved for the treatment of GAD and Social Anxiety Disorder

‡ Lexapro was denied approval for social anxiety disorder 3/30/2005

Studies for Major Depressive Disorders*

Author, Year	Interventions	N	Results	Quality Rating
SSRI versus SSRIs				
Burke et al., 2002	Citalopram vs. Escitalopram	491	No differences	Fair
Colonna et al., 2005	Citalopram vs. Escitalopram	357	Significantly more responders and remitters in the escitalopram group at 8 wks but not 24 wks	Fair
Lader et al., 2005	Citalopram vs. Escitalopram (pooled data)	1321	Greater efficacy of escitalopram in reducing sleep disturbance	Fair
Lepola et al., 2003, 2004	Citalopram vs. Escitalopram	471	Significantly more responders and remitters in the escitalopram group	Fair
Moore et al., 2005	Citalopram vs. Escitalopram	280	Significantly more responders and remitters in the escitalopram group	Fair
Patris et al., 1996	Citalopram vs. Fluoxetine	357	Faster onset of citalopram	Fair
Ekselius et al., 1997	Citalopram vs. Sertraline	400	No differences	Good
Dalery et al., 2003	Fluoxetine vs. Fluvoxamine	184	Faster onset of fluvoxamine	Fair
Rapaport et al., 1996	Fluoxetine vs. Fluvoxamine	100	No differences	Fair
Cassano et al., 2002	Fluoxetine vs. Paroxetine	242	Faster onset of paroxetine	Fair
Chouinard et al., 1999	Fluoxetine vs. Paroxetine	203	No differences	Fair
De Wilde et al., 1993	Fluoxetine vs. Paroxetine	100	Faster onset of paroxetine	Fair
Gagiano et al., 1993	Fluoxetine vs. Paroxetine	90	No differences	Fair
Schone et al., 1993	Fluoxetine vs. Paroxetine	108	Faster onset of paroxetine	Fair
Fava et al., 1998	Fluoxetine vs. Paroxetine	128	No differences	Fair
Bennie et al., 1995	Fluoxetine vs. Sertraline	286	No differences	Fair
Boyer et al., 1998	Fluoxetine vs. Sertraline	242	No differences	Fair
Fava et al., 2002	Fluoxetine vs. Sertraline	284	No differences	Fair
Finkel et al., 1999	Fluoxetine vs. Sertraline	75	Faster onset of sertraline	Fair
Sechter et al., 1999	Fluoxetine vs. Sertraline	238	No differences	Fair
Newhouse et al., 2000	Fluoxetine vs. Sertraline	236	No differences	Fair
Kroenke et al., 2001	Fluoxetine vs. Sertraline vs. Paroxetine	601	No differences	Fair
Aberg-Wistedt et al.,2000	Paroxetine vs. Sertraline	353	No differences	Fair
Kiev et al., 1997	Paroxetine vs. Fluvoxamine	60	No differences	Fair
Nemeroff et al., 1995	Sertraline vs. Fluvoxamine	97	No differences	Fair
Franchini et al., 1997, 2000	Sertraline vs. Fluvoxamine	64	No differences	Fair
Dual Acting versus SSRIs				
Detke et al., 2004	Duloxetine vs. Paroxetine	367	No Differences	Fair
Goldstein et al., 2002	Duloxetine vs. Paroxetine	173	No Differences	Fair
Hong et al., 2003	Mirtazipine vs. Fluoxetine	133	No Differences	Fair
Schatzberg et al., 2002	Mirtazipine vs. Paroxetine	255	Faster onset of mirtazapine	Fair
Benkert et al., 2000	Mirtazipine vs. Paroxetine	275	Faster onset of mirtazapine	Fair
Behnke et al., 2003	Mirtazipine vs. Sertraline	346	Faster onset of mirtazapine	Fair
Bielski at al., 2004	Venlafaxine vs. Escitalopram	198	No Differences	Fair
Montgomery et al., 2004	Venlafaxine vs. Escitalopram	293	No Differences	Fair
Allard et al., 2004	Venlafaxine vs. Citalopram	151	No Differences	Fair
Costa e Silva et al., 1998	Venlafaxine vs. Fluoxetine	382	No Differences	Fair
Alves et al., 1999	Venlafaxine vs. Fluoxetine	87	Faster onset of venlafaxine	Fair
Tylee et al., 1997	Venlafaxine vs. Fluoxetine	341	No Differences	Fair
Dierick et al., 1996	Venlafaxine vs. Fluoxetine	314	Significantly higher response rate for venlafaxine	Fair
De Nayer et al., 2002	Venlafaxine vs. Fluoxetine	146	Significantly greater improvement for venlafaxine	Fair
Rudolph et al., 1999	Venlafaxine vs. Fluoxetine	301	No Differences	Fair
Silverstone et al., 1999	Venlafaxine vs. Fluoxetine	368	No Differences	Fair
Ballus et al., 2000	Venlafaxine vs. Paroxetine	84	No Differences	Fair
McPartlin et al., 1998	Venlafaxine vs. Paroxetine	361	No Differences	Fair
Mehtonen et al., 2000	Venlafaxine vs. Sertraline	147	Significantly higher response rate for venlafaxine	Good
Sir et al., 2005	Venlafaxine vs. Sertraline	163	No Differences	Good

(con't) Other Dual Acting Antidepressants versus SSRIs				
Nieuwstraten et al., 2001	Buproprion vs. SSRIs (SR)	1,332	No Differences	Good
Panzer et al., 2005	SSRIs vs. other 2nd generation antidepressants (SR)	NR	No Differences in patients with comorbid anxiety	Fair
Feighner et al., 1991	Buproprion vs. Fluoxetine	123	No Differences	Fair
Coleman et al., 2001	Buproprion vs. Fluoxetine	456	No Differences	Fair
Weihs et al., 2000	Buproprion SR vs. Paroxetine	100	No Differences	Fair
Coleman et al., 1999	Buproprion vs. Sertraline	364	No Differences	Fair
Croft et al., 1999	Buproprion vs. Sertraline	360	No Differences	Fair
Kavoussi et al., 1997	Buproprion vs. Sertraline	248	No Differences	Fair
Rush st al., 1998	Nefazodone vs. Fluoxetine	125	No Differences	Fair
Baldwin et al., 1996, 2001	Nefazodone vs. Paroxetine	206	No Differences	Fair
Feiger et al., 1996	Nefazodone vs. Sertraline	160	No Differences	Fair
DeMartinis et al., 2007[306]	Desvenlafaxine vs. placebo	480	Significantly greater improvement in the 100mg and 400mg group than placebo, but not the 200mg group.	NR
Septien-Velez et al., 2007[308]	Desvenlafaxine vs. placebo	375	Significantly greater improvement in both the 200mg and 400mg groups than placebo.	NR
Liebowitz et al., 2008[332]	Desvenlafaxine vs. placebo	447	Significantly greater improvement in 50mg group than placebo, but not the 100mg group.	NR
Study 333-EU CSR Wyeth 2007	Desvenlafaxine vs. placebo	485	Significantly greater improvement in both the 50mg and 100mg groups than placebo.	NR

*Adapted from Table 6. Oregon Health and Science University. Drug Class Review on Second Generation Antidepressants. 2006. Available online at: http://www.ohsu.edu/drugeffectiveness/reports/documents/SG%20Antidepressants%20Final%20Report%20u3.pdf

- **Overall, effectiveness and efficacy were similar and the majority of trials did not identify substantial differences among drugs.**
- **The only exception is the comparison of citalopram to escitalopram, in which available trials showed escitalopram to be more effective than citalopram. However, all available trials were conducted by the manufacturer of escitalopram.**
- **For all the other comparisons, discontinuation rates and response and remission rates assessed on multiple diagnostic scales did not differ substantially when taking all the evidence into consideration.**

Studies for General Anxiety Disorder (GAD)*

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus SSRIs				
Ball et al., 2005[104]	Paroxetine vs. Sertraline	55	No difference	Fair
SSRIs versus Placebo				
Davidson et al., 2004[106]	Escitalopram vs. Placebo	315	Significantly greater improvement in QoL for escitalopram	Fair
Pollack et al., 2001[110]	Paroxetine vs. Placebo	331	Significantly greater reduction in SDS for paroxetine	Fair
Rickels et al., 2003[109]	Paroxetine vs. Placebo	566	Significantly greater reduction in SDS for paroxetine	Fair
Allgulander et al., 2004[114] Dahl et al., 2005[115]	Sertraline vs. Placebo	378	Significantly greater improvement in HAM-A total score; HAM-A psychic and somatic factors, QoL, and work productivity	Fair
Meoni et al., 2004[112, 113]	Venlafaxine XR vs. Placebo	1,839	Significantly greater reduction in psychic and somatic scores for venlafaxine	Fair

*Table 12. Oregon Health and Science University. Drug Class Review on Second Generation Antidepressants. 2006. Available online at: http://www.ohsu.edu/drugeffectiveness/reports/documents/SG%20Antidepressants%20Final%20Report%20u3.pdf

- **Placebo-controlled trials showed general efficacy of the agents in the treatment of GAD.**
- **Evidence is insufficient to compare one second-generation antidepressant to another for treating GAD.**

Studies for Pediatric Outpatients with MDD

Author, Year	Interventions	N	Results	Quality Rating
Systemic Review				
Whittington et al., 2004	Citalopram vs. Placebo Fluoxetine vs. Placebo Paroxetine vs. Placebo Sertraline vs. Placebo Venlafaxine vs. Placebo (SR)	2,145	Only fluoxetine had favorable risk-benefit profile	Fair
SSRIs versus Placebo				
Wagner et al., 2004	Citalopram vs. Placebo	174	Significantly greater efficacy for citalopram	Fair
March et al., 2004	Fluoxetine plus CBT vs. Fluoxetine vs.CBT vs. Placebo	439	Greater improvement on the CDRS-R for fluoxetine plus CBT compared to fluoxetine alone, CBT alone, or placebo	Good
Keller et al., 2001	Paroxetine vs. Imipramine vs. Placebo	275	No differences	Fair
Wagner et al., 2003	Sertraline vs. Placebo	376	Significantly greater efficacy for sertraline	Fair
SNRIs versus Placebo				
Mandoki et al., 1997	Venlafaxine vs. Placebo	40	No differences	Fair

*Table 11. Oregon Health and Science University. Drug Class Review on Second Generation Antidepressants. 2006. Available online at:
http://www.ohsu.edu/drugeffectiveness/reports/documents/SG%20Antidepressants%20Final%20Report%20u3.pdf

- **Available published evidence is insufficient to compare one second-generation antidepressant to another in pediatric outpatients with MDD.**
- **The systematic review of published and unpublished data suggests that only fluoxetine has a favorable risk-benefit profile in pediatric populations.**

Studies for Post-Traumatic Stress Disorder*

Author, Year	Interventions	N	Results	Quality Rating
SSRI versus SSRIs				
Tucker et al., 2005[150]	Citalopram vs. Sertraline	59	No difference in efficacy	Fair
Other Dual Acting Antidepressants versus SSRIs				
McRae et al., 2004[151]	Sertraline vs. Nefazodone	37	No difference in efficacy	Fair
SSRIs versus Placebo				
Conner et al., 1999[156]	Fluoxetine vs. Placebo	54	Significantly greater efficacy of fluoxetine	Fair
Marshall et al., 2001[155]	Paroxetine vs. Placebo	563	Significantly greater efficacy of paroxetine	Fair
Brady st al., 2000[152,154,157,158]	Sertraline vs. Placebo	187	Significantly greater efficacy of sertraline	Fair
Davidson et al., 2001[153]	Sertraline vs. Placebo	208	Significantly greater efficacy of sertraline	Fair

*Table 15. Oregon Health and Science University. Drug Class Review on Second Generation Antidepressants. 2006. Available online at:
http://www.ohsu.edu/drugeffectiveness/reports/documents/SG%20Antidepressants%20Final%20Report%20u3.pdf

- **There is one head-to-head trial comparing sertraline to nefazodone. Placebo-controlled trials showed general efficacy of fluoxetine, paroxetine, and sertraline in the treatment of PTSD.**
- **Significant differences in population characteristics make this evidence insufficient to identify differences between treatments based on placebo-controlled evidence.**

Studies for Social Anxiety Disorder*

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus SSRIs				
Lader, et al., 2004	Escitalopram vs. Paroxetine vs. Placebo	839	No difference between active treatments; escitalopram and paroxetine significantly better than placebo	Fair
Dual Acting Antidepressants versus SSRIs				
Allgulander et al., 2004	Venlafaxine ER vs. Paroxetine vs. Placebo	436	No difference between active treatments; venlafaxine and paroxetine significantly better than placebo	Fair
Liebowitz et al., 2005	Venlafaxine ER vs. Paroxetine vs. Placebo	440	No difference between active treatments; venlafaxine and paroxetine significantly better than placebo	Fair
SSRIs versus Placebo				
Van der Linden et al., 2000	Fluvoxamine vs. Placebo Paroxetine vs. Placebo Sertraline vs. Placebo (SR)	1,482	No differences between active treatments	Fair
Kasper et al., 2005	Escitalopram vs. Placebo	358	Significantly greater efficacy of escitalopram	Fair
Montgomery et al., 2005	Escitalopram vs. Placebo	372	Significantly lower risk of relapse for escitalopram	Fair
Koback et al., 2002	Fluoxetine vs. Placebo	60	No difference in efficacy	Fair
Stein et al., 1999	Fluvoxamine vs. Placebo	92	Significantly greater efficacy of fluvoxamine	Fair
Westenberg et al., 2004	Fluvoxamine CR vs. Placebo	300	Significantly greater improvement for fluvoxamine CR	Fair
Muehlbacher et al., 2005	Mirtazapine vs. Placebo	66	Significantly greater efficacy of mirtazapine	Fair
Stein et al., 1998	Paroxetine vs. Placebo	187	Significantly greater improvement in social life and work domains for paroxetine	Fair
Baldwin et al., 1999	Paroxetine vs. Placebo	290	Significantly greater improvement in social life and work domains for paroxetine	Fair
Stein et al., 2002	Paroxetine vs. Placebo	323	Significant reduction in relapse for paroxetine	Fair
Lepola et al., 2004	Paroxetine CR vs. Placebo	370	Significantly greater improvement in SDS for paroxetine CR	Fair
Van Ameringen et al., 2001	Sertraline vs. Placebo	204	Significantly greater improvement in SDS for sertraline	Fair
Liebowitz et al., 2003	Sertraline vs. Placebo	415	Significantly greater improvement in SDS and QoL for sertraline	Fair
Blomhoff et al., 2001	Sertraline vs. Placebo	387	Significantly greater improvement in SDS and mental health for sertraline	Fair

*Table 16. Oregon Health and Science University. Drug Class Review on Second Generation Antidepressants. 2006. Available online at: http://www.ohsu.edu/drugeffectiveness/reports/documents/SG%20Antidepressants%20Final%20Report%20u3.pdf

- **There were three head-to-head trials that compared one second-generation antidepressant to another for the treatment of social anxiety disorder. These trials suggest no differences in efficacy for escitalopram vs. paroxetine and venlafaxine ER vs. paroxetine.**
- **Indirect evidence from a meta-analysis of placebo-controlled trials provides evidence that there is no difference in efficacy between fluvoxamine, paroxetine, and sertraline.**

Studies for Obsessive Compulsive Disorder*

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus SSRIs				
Bergeron et al., 2002[125]	Fluoxetine vs. Sertraline	150	No differences	Fair
Other second-generation antidepressants versus SSRIs				
Denys et al., 2003[120, 126, 140]	Venlafaxine vs. Paroxetine	150	No differences	Fair
SSRI versus SSRI plus another second-generation antidepressant				
Pallanti et al., 2004[121]	Citalopram vs. Citalopram plus Mirtazapine	49	No differences at 12 weeks	Fair
SSRIs versus Placebo				
Piccinelli et al., 1995[122]	SSRIs vs. Placebo (SR)	1,076	Significantly greater efficacy of SSRIs	Fair
Ackerman et al., 2002[123]	SSRIs vs. Placebo (SR)	530	No differences among SSRIs	Fair
Stein et al., 1995[124]	SSRIs vs. Placebo (SR)	516	No differences among SSRIs	Fair
Montgomery et al., 2001[128]	Citalopram vs. Placebo	401	Significantly greater efficacy of citalopram	Fair

*Table 13. Oregon Health and Science University. Drug Class Review on Second Generation Antidepressants. 2006. Available online at: http://www.ohsu.edu/drugeffectiveness/reports/documents/SG%20Antidepressants%20Final%20Report%20u3.pdf

- **Two fair head-to-head studies provide evidence that there is no difference in efficacy between fluoxetine and sertraline or venlafaxine and paroxetine.**
- **Other evidence is insufficient to draw conclusions about comparative efficacy between one second-generation antidepressant and another.**

Studies for Panic Disorder*

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus SSRIs				
Bandelow et al., 2004[143]	Paroxetine vs. Sertraline	225	No difference	Fair
Stahl et al., 2003[141]	Citalopram vs. Escitalopram vs. Placebo	366	No difference	Fair
SSRIs versus Placebo				
Asnis et al., 2001[146]	Fluvoxamine vs. Placebo	188	Significantly greater efficacy of fluvoxamine	Fair
Black et al., 1993[149]	Fluvoxamine vs. Placebo	75	Significantly greater efficacy of fluvoxamine	Fair
Hoehn-Saric et al., 1993[145]	Fluvoxamine vs. Placebo	50	Significantly greater efficacy of fluvoxamine	Fair
Pohl et al., 1998[147]	Sertraline vs. Placebo	168	Significantly greater efficacy of sertraline	Fair
Bradwejin et al., 2005[148]	Venlafaxine ER vs. Placebo	361	Significantly greater efficacy of sertraline except of sertraline in percentage of patients free from panic attacks	Fair

*Table 14. Oregon Health and Science University. Drug Class Review on Second Generation Antidepressants. 2006. Available online at: http://www.ohsu.edu/drugeffectiveness/reports/documents/SG%20Antidepressants%20Final%20Report%20u3.pdf

- **One fair head-to-head study provides evidence that efficacy does not differ between citalopram and escitalopram.**
- **In other trials, significant differences in study design and outcome selection make this evidence insufficient to identify differences between treatments.**

Studies for Dysthymia*

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus Placebo				
Barrett et al., 2001 Williams et al., 2000	Paroxetine vs. Placebo vs. Behavioral therapy	656	Significantly more responders for paroxetine in patients older than 60 years	Fair
Devanand et al., 2005	Fluoxetine vs. Placebo	90	No differences in response rates and quality of life	Good
Thase et al., 1996	Sertraline vs. Imipramine vs. Placebo	412	Significantly more responders for sertraline than placebo	Fair
Ravindran et al., 2000	Sertraline vs. Placebo	310	Significantly more responders and remitters for sertraline	Fair
Vanelle et al., 1997	Fluoxetine vs. Placebo	111	Significantly more responders for fluoxetine	Fair

*Table 10. Oregon Health and Science University. Drug Class Review on Second Generation Antidepressants. 2006. Available online at: http://www.ohsu.edu/drugeffectiveness/reports/documents/SG%20Antidepressants%20Final%20Report%20u3.pdf

- **Placebo-controlled trials showed general efficacy of the agents in the treatment of Dysthymia.**
- **There were no head to head trials, and from the available trials, significant differences in population characteristics make the evidence insufficient to identify differences between treatments.**

Studies for Pre-Menstrual Dysphoric Disorder*

Author, Year	Interventions	N	Results	Quality Rating
SSRIs versus SSRIs				
Dimmock et al., 2000	5 SSRIs vs. Placebo (SR)	904	Significantly greater efficacy of SSRIs	Good
Wyatt et al., 2004	5 SSRIs vs. Placebo (SR)	844	Significantly greater efficacy of SSRIs	Fair
SSRIs versus Placebo				
Freeman et al., 2001	Venlafaxine vs. Placebo	157	Significantly greater efficacy of venlafaxine	Fair
Steiner et al., 2005	Paroxetine CR vs. Placebo	373	Significantly greater efficacy of paroxetine	Fair
Freeman et al., 2004	Sertraline vs. Placebo	167	Significantly greater efficacy of sertraline; no differences between intermittent and continuous treatment	Fair
Halbreich et al., 2002	Sertraline vs. Placebo	281	Significantly greater efficacy of sertraline	Fair

*Table 6. Oregon Health and Science University. Drug Class Review on Second Generation Antidepressants. 2006. Available online at: http://www.ohsu.edu/drugeffectiveness/reports/documents/SG%20Antidepressants%20Final%20Report%20u3.pdf

- **The agents were shown to be generally effective compared to placebo, however, no studies with a high degree of generalizability was found from which any conclusions could be drawn.**
- **There is one trial examining the efficacy of intermittent (e.g., luteal phase only) sertraline therapy against continuous sertraline therapy. Both sertraline groups improved significantly compared to placebo. Premenstrual dosing did not differ in efficacy from continuous dosing. A subgroup analysis in a good meta-analysis reported similar results.**

Studies for Adverse Events

Author, Year	Interventions	N	Results	Quality Rating
Tolerability and Discontinuation				
Brambilla et al., 2005	Fluoxetine vs. SSRIs (SR)	NR	No difference in discontinuation rates because of adverse events	Good
Greist et al., 2004	Pooled analysis: Duloxetine vs. Paroxetine vs. Fluoxetine	2345	No difference in nausea between Duloxetine and Paroxetine, and Duloxetine and Fluoxetine	NA
Haffmans et al., 1996	Fluvoxamine vs. Paroxetine	217	Significantly more diarrhea and nausea with Fluvoxamine	Fair
Kiev et al., 1997	Fluvoxamine vs. Paroxetine	60	Significantly more sweating with Paroxetine	Fair
Mackay et al., 1997, 1999	Prescription Event Monitoring	≥60,000	Venlafaxine had highest rate of nausea and vomiting; Paroxetine highest rate of sexual side effects; among SSRIs, most overall adverse events with Fluvoxamine	NA
Meijer et al., 2002	Sertraline vs. SSRIs (OS)	1251	Significantly more diarrhea with Sertraline	Fair
Rapaport et al., 1996	Fluvoxamine vs. Fluoxetine	100	Significantly more nausea with Fluoxetine	Fair
Suicidality				
Didham et al., 2005	SSRIs	57,000	No difference in suicide or self-harm among Citalopram, Fluoxetine, and Paroxetine	Fair
Fergusson et al., 2005	SSRIs vs. Placebo (SR)	87,650	Higher risk of suicide attempts for SSRI-treated patients	Good
Gunnell et al., 2005	2bd gen, AD vs. Placebo (SR)	40,000	No difference in adults	Good
Jick et al., 2004	Case-control; database review	159,810	No differences	NA
Jick et al., 1995	Open cohort; database review	172,598	Significantly higher risk of suicide with Fluoxetine and Mianserin compared to Dothiepin	NA
Khan et al., 2003	Data review	NR	No differences	NA
Lopez-Ibor 1993	Database review	4,686	No differences	NA
Martinez et al., 2005	Database review	146,095	No differences	NA
Pederson et al., 2005	Retrospective cohort study	4,091	Higher rate of self-harm in Escitalopram than in placebo	Fair
Sexual Dysfunction				
Nieuwstraten et al., 2001	Bupropion vs. SSRIs (SR)	1,332	Significantly higher rate of sexual satisfaction in Bupropion group	Good
Clayton et al., 2002	Cross-sectional survey	6,297	Highest risk for Paroxetine and Mirtazapine; lowest risk for Bupropion	NA
Coleman et al., 2001	Bupropion vs. Fluoxetine	456	Significantly more sexual adverse events with Fluoxetine	Fair
Coleman et al., 1999	Bupropion vs. Sertraline	364	Significantly more sexual adverse events with Sertraline	Fair
Croft et al., 1999	Bupropion vs. Sertraline	360	No differences	Fair
Ekselius et al., 2001	Citalopram vs. Sertraline	308	No differences	Fair
Landen et al., 2005	Citalopram vs. Paroxetine	119	No differences	Good
Segraves et alk., 2000	Bupropion vs. Sertraline	248	Significantly more sexual adverse events with Sertraline	Fair
Montejo et al., 2001	Prospective cohort study	1,022	Highest incidence of sexual dysfunction for Citalopram, Paroxetine, and Venlafaxine; lowest for Mirtazapine and Nefazodone	Fair
Changes in Weight				
Maina et al., 2004	Open-label SSRIs	149	Highest weigh gain with Paroxetine, Fluvoxamine, and Citalopram	Fair
Fava et al., 2000	Fluoxetine vs. Paroxetine vs. Sertraline	284	Highest weigh gain with Paroxetine	Fair
Benkert et al., 2000	Mirtazapine vs. Paroxetine	275	Significant weight gain with Mirtazapine	Fair
Schatzberg et al., 2002	Mirtazapine vs. Paroxetine	255	Significant weight gain with Mirtazapine	Fair

Cardiovascular Events (cont'd)				
Thase et al., 1998	Post hoc analysis	3,744	Significantly higher diastolic blood pressure with Venlafaxine	NA
Thase et al., 2005	Post hoc analysis	1,873	Greater change in heart rate with Duloxetine than for Fluoxetine and Paroxetine	NA
Other Adverse Events				
Buckley et al., 2005	Database analysis	47,329	Highest rate of fatal toxicity for Venlafaxine	NA
Coogan et al., 2005	Case-control	4,996	No association between breast cancer and SSRIs	Fair
Dunner et al., 1998	Prospective observational	3,100	Rate of seizures for bupropion within range of other antidepressants	Fair
Johnston et al., 1991	Prospective observational	3,341	Rate of seizures for bupropion within range of other antidepressants	NA
Whyte et al., 2003	Prospective observational	538	Seizures more common in Venlafaxine overdose than TCA or SSRI overdose	Good

* Table 19. Oregon Health and Science University. Drug Class Review on Second Generation Antidepressants. 2006. Available online at: http://www.ohsu.edu/drugeffectiveness/reports/documents/SG%20Antidepressants%20Final%20Report%20u3.pdf

- **Fair to good evidence from multiple randomized controlled head-to-head trials and retrospective data analyses of prescription event monitoring documents show that side-effect profiles differ among the drugs.**
- **Venlafaxine had a significantly higher rate of nausea and vomiting in multiple trials; paroxetine frequently led to higher sexual side effects; mirtazapine to higher weight gains; and sertraline to a higher rate of diarrhea than comparable second-generation antidepressants.**
- **A retrospective review of prescription event monitoring data provides fair evidence that, among SSRIs, fluvoxamine has the highest mean incidence of adverse events.**
- **Pooled estimates from efficacy trials suggest that venlafaxine has a statistically significantly higher rate of discontinuation because of adverse events than do SSRIs as a class. However, overall discontinuation rates do not differ significantly between venlafaxine and SSRIs.**

Comparison of Adverse Events Among Antidepressants*

Chemical Name	Headache	Nausea	Dizziness	Diarrhea	Insomnia	Weight
Buproprion	27%	15%	13%	9%	16%	NR
Citalopram	5%	12%	NR	7%	6%	NR
Desvenlafaxine	21%	24%	12%	10%	11%	1.5% (loss)
Duloxetine	NR (14%-DPNP)	25%	10%	10%	10%	-0.5kg to 1.1kg
Escitalopram	14%	15%	NR	9%	9%	NR
Fluoxetine	17%	19%	7%	12%	14%	4% (gain)
Fluvoxamine	27%	32%	14%	16%	34%	NR
Mirtazapine	12%	4%	12%	9%	8%	14% (gain)
Paroxetine	21%	18%	11%	9%	14%	10% (gain)
Sertraline	20%	20%	8%	15%	15%	8% (gain)
Venlafaxine	13%	31%	16%	6%	11%	NR

*Mean incidence calculated from randomized controlled trials; method and extent of adverse event assessment varied among studies and pooled incidence should be interpreted with caution. Adapted from Table 18. Oregon Health and Science University. Drug Class Review on Second Generation Antidepressants. 2006. Available online at: http://www.ohsu.edu/drugeffectiveness/reports/documents/SG%20Antidepressants%20Final%20Report%20u3.pdf

Comparison of Sexual Adverse Effects Among Antidepressants*

Chemical Name	Brand Name	Decreased Libido	Impotence /Erectile Dysfunction	Ejaculation Disorder	Anorgasmia
Buproprion[2]	Wellbutrin XL®	3%	"Infrequent" (1/1000)	"Infrequent" (1/1000)	NR
Citalopram[3]	Celexa®	4%	3%	6%	1%
Desvenlafaxine[4]	Pristiq®	4-5%	3-6%	0-1%	1-3%
Duloxetine[5]	Cymbalta®	1-6%	4%	3%	2-4%
Escitalopram[6]	Lexapro®	3-6%	2-3%	9-12%	2-3%
Fluoxetine[7]	Prozac®	3-11%	2-7%	2-7%	NR
Fluvoxamine[8]	Luvox CR®	4-8%	2%	11%	4-5%
Mirtazapine[9]	Remeron®	"Increased libido" (Infrequent)	"Infrequent" (1/1000)	"Infrequent" (1/1000)	NR
Paroxetine[10]	Paxil®	6-15%	2-9%	13-28%	2-9%
Sertraline[11]	Zoloft®	1-11%	"Frequent" (1/100)	7-19%	NR
Venlafaxine[12]	Effexor XR®	3-9%	4-10%	11-16%	2-8%

*Compiled from reported rates in product literature.

Conclusions

- Currently, all commonly used SSRIs and dual acting antidepressants are available as tier-1, except Lexapro®, Cymbalta®, and Effexor XR®, which are also the major cost drivers for this class.
- Overall, the costs have decreased, even while utilization has increased for this category. This is due mainly to the loss of patents and availability of generics for the majority of the chemical entities in this category.
- The comparative safety and efficacy of available agents have been reviewed and re-assessed periodically. Overall, effectiveness and efficacy of agents reviewed were found to be similar and the majority of trials did not identify substantial differences among drugs. Discontinuation, response, and remission rates assessed were not found to be substantially different when taking all the evidence into consideration.
- The available clinical evidence shows variability in adverse effect profiles, however, this has been taken into account and various drugs were either tier-1 due to its unique advantages or clinical exceptions were made.

Recommendations

The progressive implementation of this PBPA category through the years have allowed for substantial savings to the program while minimally affecting availability of treatment options for the members. Many drug categories, after a certain number of years, may evolve into a generic only category, however, this does not seem to be the case. In looking forward, it is anticipated that in the coming years as medications continue to lose their patents and become generically available, the costs will be replaced by newer patented agents.

As a result, the College of Pharmacy recommends the following three tiered structure. In order to be considered for tier-1 or tier-2, new treatment options must have a proven advantage in safety, efficacy, or cost, over the numerous agents currently available. The class will be periodically reviewed and medications may be moved according to availability of emerging treatment options and comparative cost/benefit profile.

Criteria for Approval of a tier 2 Medication:

1. Documented recent (within 6 months) trial of a tier-1 medication at least 4 weeks in duration and titrated to recommended dose, that has failed to produce adequate response. Tier-1 selection can be from any classification.
2. Prior stabilization on the tier-2 medication documented within the last 100 days.
3. A unique FDA-approved indication not covered by tier-1 products.
4. A petition may be submitted for consideration whenever a unique member specific situation exists.

Criteria for Approval of a tier 3 Medication:

1. Documented recent (within 6 months) trial with a tier-1 and a tier-2 medication at least 4 weeks in duration and titrated to recommended dose, that has failed to produce adequate response. Tier-1 and tier-2 selection can be from any classification.
2. Prior stabilization on the tier-3 medication documented within the last 100 days.
3. A unique FDA-approved indication for which the lower tiered medications lack.
4. A petition may be submitted for consideration whenever a unique member specific situation exists.

SSRIs (Selective Serotonin Reuptake Inhibitors)		
Tier-1	Tier-2	Tier-3
citalopram (Celexa®)	Supplemental Rebated T-3	citalopram suspension (Celexa® susp)
fluoxetine (Prozac®, Sarafem®)		fluoxetine (40mg caps, Prozac Weekly™)
fluvoxamine (Luvox®)		escitalopram (Lexapro®)
paroxetine (Paxil®, Paxil CR®)		paroxetine (Pexeva®)
sertraline (Zoloft®)		
Dual Acting Antidepressants		
Tier-1	Tier-2	Tier-3
venlafaxine (Effexor®)	Supplemental Rebated T-3	desvenlafaxine (Pristiq®)
trazodone (Desyrel®)		venlafaxine (Effexor XR®)
mirtazapine (Remeron®, Remeron SolTab®)		duloxetine (Cymbalta®)
bupropion (Wellbutrin®, Wellbutrin SR®)		bupropion (Wellbutrin XL®)
		nefazodone (Serzone®)
Monoamine Oxidase Inhibitors		
Tier-1	Tier-2	Tier-3
		selegiline patch (Emsam®)
		tranylcypromine (Parnate®)
		phenelzine (Nardil®)
		selegiline (Zelapar®)

Mandatory generic plan applies

[1] Oregon Health and Science University. Drug Class Review on Second Generation Antidepressants. 2006. Available online at: **http://www.ohsu.edu/drugeffectiveness/reports/documents/SG%20Antidepressants%20Final%20Report%20u3.pdf**

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Appendix I

30 Day Notice to Prior Authorize Voltaren® Gel (Diclofenac Sodium)

Oklahoma Health Care Authority
July 2008

Manufacturer	Novartis
FDA Classification	NSAID
Status	prescription only

Summary

Voltaren® is a topical analgesic gel 1% diclofenac sodium indicated for the relief of pain of osteoarthritis of joints amenable to topical treatment, such as the knees and of the hands. It has not been evaluated for use in the spine, hip or shoulder.
Dosage for the lower extremities is 4g to affected area 4 times daily (no more than 16g to a single joint daily) and for upper extremities is 2g to affected area 4 times daily (no more than 8g to a single joint daily). Total dose should not exceed 32g per day, over all affected areas.

Diclofenac Sodium Utilization- Calendar Year 2007

DRUG NAME	CLAIMS	UNITS	DAYS	MEMBERS	COST	UNITS/ DAY	CLAIMS/ MEM	COST/ DAY	PERCENT COST
DICLOFENAC TAB 75MG DR	2,445	220,025	70,611	1,192	$32,941.99	3.12	2.05	$0.47	44.98%
DICLOFEN POT TAB 50MG	821	41,977	16,583	545	$9,742.86	2.53	1.51	$0.59	13.30%
DICLOFENAC TAB 50MG DR	522	31,852	14,013	302	$7,437.65	2.27	1.73	$0.53	10.15%
DICLOFENAC TAB 100MG ER	416	19,629	14,179	153	$14,902.47	1.38	2.72	$1.05	20.35%
DICLOFENAC TAB 50MG EC	349	21,606	9,853	193	$4,678.23	2.19	1.81	$0.47	6.39%
DICLOFENAC TAB 75MG EC	193	10,282	5,219	128	$2,014.88	1.97	1.51	$0.39	2.75%
DICLOFENAC TAB 100MG XR	46	1,690	1,510	16	$1,293.58	1.12	2.88	$0.86	1.77%
DICLOFENAC TAB 25MG EC	17	1,110	465	9	$221.65	2.39	1.89	$0.48	0.30%
DICLOFENAC POW SODIUM	1	72	30	1	$8.51	2.4	1	$0.28	0.01%
Voltaren® Gel (EAC= $0.24/gram**								**$7.68**	
Totals	**4,810**	**348,243**	**132,463**	**2,389***	**$73,241.82**	**2.63**	**2.01**		

**Unduplicated Members*
*** Based on maximum dose application of 32grams/day*

Recommendations

The College of Pharmacy recommends prior authorization of Voltaren® Gel and placement in the Tier-2 NSAID product. Approval will be based on clinical documentation of inability to take tier-1 products and supporting information regarding the medical necessity of topical formulation.

REFERENCE

Voltaren® Gel Product Information. Novartis Pharmaceuticals. October 2007. Available online at: http://www.voltarengel.com/index.html

Appendix J

LUVOX CR® (FLUVOXAMINE ER)

OKLAHOMA HEALTHCARE AUTHORITY
JULY 2008

Manufacturer	Eli Lilly and Company
Pharmacologic Category	Selective Serotonin Reuptake Inhibitor (SSRI)
Status	Prescription only

SUMMARY

Pharmacological data

Fluvoxamine ER is a selective serotonin (5-HT) reuptake inhibitor (SSRI). SSRIs are believed to relieve symptoms by blocking the reuptake of serotonin. This leaves more serotonin available in the brain. As a result, this enhances neurotransmission. Fluvoxamine has no significant affinity for histamine, alpha and beta adrenergic, muscarininc or dopaminergic receptors.

Therapeutic Indications

Fluvoxamine ER is indicated for the treatment of **social anxiety disorder**, also known as social phobia and the treatment of obsessions of compulsions in patients with **obsessive compulsive disorder** (OCD).

Cost Comparison

	AWP	EAC	SMAC	Monthly Cost*
Fluvoxamine 25mg tabs	$2.29	$2.02	$0.49	$29.40 - $176.40
Fluvoxamine 50mg tabs	$2.56	$2.25	$0.38	$22.80 - $68.40
Fluvoxamine 100mg tabs	$2.62	$2.31	$0.40	$24.00 - $36.00
Luvox CR 100mg Caps	$4.06	$3.58		$107.40 - $322.20
Luvox CR 150mg Caps	$4.06	$3.58		$214.80

*Maximum dose of 300mg per day for 30 days

RECOMMENDATIONS

The College of Pharmacy recommends placement of this product in Tier-3 of the Antidepressants PBPA category.

PHARMACOLOGIC INFORMATION

Absorption
In the single-dose crossover study, mean Cmax was 38% lower and relative bioavailability was 84% for LUVOX CR Capsules versus immediate-release fluvoxamine maleate tablets.

Distribution
Approximately 80% of fluvoxamine is bound to plasma protein, mostly albumin, over a concentration range of 20 ng/mL to 2000 ng/mL.

Metabolism
Fluvoxamine maleate is extensively metabolized by the liver; the main metabolic routes are oxidative demethylation and deamination. Nine metabolites were identified following a 5 mg radiolabelled dose of fluvoxamine maleate, constituting approximately 85% of the urinary excretion products of fluvoxamine. The main human metabolite was fluvoxamine acid which, together with its N-acetylated analog, accounted for about 60% of the urinary excretion products. A third metabolite, fluvoxethanol, formed by oxidative deamination, accounted for about 10%. Fluvoxamine acid and fluvoxethanol were tested in an in vitro assay of serotonin and norepinephrine reuptake inhibition in rats; they were inactive except for a weak effect of the former metabolite on inhibition of serotonin uptake (1-2 orders of magnitude less potent than the parent compound). Approximately 2% of fluvoxamine was excreted in urine unchanged.

Elimination
Following a 14C-labelled oral dose of fluvoxamine maleate (5 mg), an average of 94% of drug-related products was recovered in the urine within 71 hours. After administration of a 100 mg, single oral dose of LUVOX CR Capsules, the mean plasma half-life of fluvoxamine in healthy male and female volunteers was 16.3 hours. In elderly patients administered immediate-release fluvoxamine maleate tablets, the clearance of fluvoxamine was reduced by about 50%; therefore, LUVOX CR Capsules should be slowly titrated during initiation of therapy.

Dosage Forms Available
100 mg and 150 mg capsules for oral administration. LUVOX CR capsules should not be crushed or chewed.

Dosage range
The recommended starting dose for LUVOX CR Capsules in adult patients is 100 mg once per day. LUVOX CR Capsules should be administered, with or without food, as a single daily dose at bedtime. In the controlled clinical trials establishing the effectiveness of LUVOX CR Capsules in social anxiety disorder and OCD, patients were titrated in 50 mg increments within a dose range of 100 mg/day to 300 mg/day. Consequently, the dose should be increased in 50 mg increments every week, as tolerated, until maximum therapeutic benefit is achieved, not to exceed 300 mg per day.

Pregnancy/Nursing: Pregnancy Risk Factor C
Fluvoxamine is secreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants from LUVOX CR Capsules, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Known adverse effects/toxicities
Commonly Observed Adverse Events: LUVOX CR Capsules have been studied in two controlled trials of social anxiety disorder (N = 279) and one trial of OCD (N = 124). In general, adverse event rates were similar in the two data sets as well as in a study of pediatric patients with OCD treated with immediate-release fluvoxamine maleate tablets. The most commonly observed adverse events associated with the use of LUVOX CR Capsules and likely to be drug-related (incidence of 5% or greater and at least twice that for placebo) for patients in social anxiety disorder and in OCD derived were: abnormal ejaculation, anorexia, anorgasmia asthenia, diarrhea, nausea, somnolence, sweating and tremor. In addition, the following events occurred in the social anxiety disorder population: dyspepsia, dizziness, insomnia, and yawning. In the OCD population, the following additional events occurred: accidental injury, anxiety, decreased libido,

myalgia, pharyngitis, and vomiting . In a study evaluating immediate-release fluvoxamine maleate tablets in pediatric patients with OCD, the following additional events were identified using the above rule: agitation, depression, dysmenorrhea, flatulence, hyperkinesia, and rash.

Special precautions/warnings

LUVOX CR carries the suicidality and antidepressant drugs black box warning. This warning states that antidepressants increase the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies in major depressive disorder (MDD) and other psychiatric disorders.

Co-administration of alosetron, tizanidine, thioridazine, or pimozide with LUVOX CR Capsules is contraindicated. The use of MAO inhibitors used in combination with LUVOX CR Capsules, or within 14 days of discontinuing treatment with LUVOX CR Capsules is contraindicated. LUVOX CR Capsules are contraindicated in patients with a history of hypersensitivity to fluvoxamine maleate or any of the excipients.

Thioridazine administration produces a dose-related prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias, and sudden death. It is likely that this experience underestimates the degree of risk that might occur with higher doses of thioridazine. Moreover, the effect of fluvoxamine may be even more pronounced when it is administered at higher doses. Therefore, LUVOX CR Capsules and thioridazine should not be co-administered

Benzodiazepines metabolized by hepatic oxidation (e.g., alprazolam, midazolam, triazolam, etc.) should be used with caution because the clearance of these drugs is likely to be reduced by fluvoxamine. The clearance of benzodiazepines metabolized by glucuronidation (e.g., lorazepam, oxazepam, temazepam) is unlikely to be affected by fluvoxamine.

The development of a potentially life-threatening serotonin syndrome may occur with LUVOX CR Capsules treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs that impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

REFERENCES

1. Luvox CR® Prescribing Information. Jazz Pharmaceuticals. June 2008. Available online at: http://www.jazzpharmaceuticals.com/content/news/documents/LUVOX_CR.pdf

Appendix K

FDA News

FOR IMMEDIATE RELEASE
June 30, 2008

Media Inquiries:
Sandy Walsh, 301-827-3418
Consumer Inquiries:
888-INFO-FDA

FDA Approves First Generic Risperidone to Treat Psychiatric Conditions

The U.S. Food and Drug Administration today approved the first generic versions of Risperdal (risperidone) tablets. Risperdal is an antipsychotic drug used for the treatment of schizophrenia, bipolar disorder, and other psychiatric conditions.

"This generic drug approval is another example of the FDA's efforts to increase access to safe and effective generic drugs as soon as the law permits," said Gary Buehler, director of the FDA's Office of Generic Drugs in the Center for Drug Evaluation and Research.

Varying strengths of risperidone tablets, manufactured by TEVA Pharmaceuticals USA, have been approved. Specific information about the strengths approved can be found at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

The labeling of the generic risperidone may differ from that of Risperdal because some uses of the drug are protected by patents and exclusivity.

The generic risperidone products will have the same safety warnings as Risperdal, including a Boxed Warning that cautions that older patients with dementia-related psychosis treated with atypical anti-psychotic drugs are at increased risk of death compared with those taking placebo. Risperdal, and other antipsychotic medications, are not FDA-approved to treat dementia-related psychosis. The decision to use antipsychotic medications in the treatment of patients with symptoms of dementia is left to the discretion of the physician. Such use is often called "off-label" use and falls within the practice of medicine.

For more information, see
Consumer Education: Generic Drugs

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Information for Healthcare Professionals
Antipsychotics

FDA ALERT [6/16/2008]: FDA is notifying healthcare professionals that both conventional and atypical antipsychotics are associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis.

In April 2005, FDA notified healthcare professionals that patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death. Since issuing that notification, FDA has reviewed additional information that indicates the risk is also associated with conventional antipsychotics.

Antipsychotics are not indicated for the treatment of dementia-related psychosis.

This information reflects FDA's current analysis of data available to FDA concerning these drugs. FDA intends to update this sheet when additional information or analyses become available.

To report any unexpected adverse or serious events associated with the use of these drugs, please contact the FDA MedWatch program and complete a form on line at http://www.fda.gov/medwatch/report/hcp.htm or report by fax to 1-800-FDA-0178, by mail using the postage-paid address form provided on line, or by telephone to 1-800-FDA-1088.

FDA is requiring the manufacturers of conventional antipsychotic drugs to add a *Boxed Warning* and *Warning* to the drugs' prescribing information about the risk of mortality in elderly patients treated for dementia-related psychosis similar to the *Boxed Warning* and *Warning* added to the prescribing information of the atypical antipsychotic drugs in 2005.* See the last page of this document for a list of conventional and atypical antipsychotic drugs.

Considerations for Healthcare Professionals

- Elderly patients with dementia-related psychosis treated with conventional or atypical antipsychotic drugs are at an increased risk of death.
- Antipsychotic drugs are not approved for the treatment of dementia-related psychosis. Furthermore, there is no approved drug for the treatment of dementia-related psychosis. Healthcare professionals should consider other management options.
- Physicians who prescribe antipsychotics to elderly patients with dementia-related psychosis should discuss this risk of increased mortality with their patients, patients' families, and caregivers.

Background Information and Data

Previously, in April 2005, FDA informed healthcare professionals and the public about the increased risk of mortality in elderly patients receiving atypical antipsychotic drugs to treat dementia-related psychosis (April 2005 Public Health Advisory and Information for Healthcare Professionals). At that time, the analyses of 17 placebo-controlled trials that enrolled 5377 elderly patients with dementia-related behavioral disorders revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g. pneumonia) in nature. Based on this analysis, FDA requested that the manufacturers of atypical antipsychotic drugs include information about this risk in a *Boxed Warning* and the *Warnings* section of the drugs' prescribing information.

Recently, two observational epidemiological studies[1,2] were published that examined the risk of death in patients who were treated with conventional antipsychotic drugs.

Gill et al.[1] performed a retrospective cohort study in Ontario, Canada of 27,259 adults, 66 years of age or older, with a diagnosis of dementia between April 1997 and March 2002. The investigators compared the risk for death with use of an atypical antipsychotic versus no antipsychotic and the risk for death with use of a conventional antipsychotic versus an atypical antipsychotic. They found that atypical antipsychotics were associated with increased mortality as compared to no antipsychotic use as early as 30 days and persisting until study end at 180 days. The investigators found that conventional antipsychotic use showed a marginally higher risk of death compared with atypical antipsychotic use. The causes of death were not reported in this study.

Schneeweiss et al.[2] performed a retrospective cohort study in British Columbia, Canada of 37,241 adults, 65 years of age or older, who were prescribed conventional (12,882) or atypical (24,359) antipsychotic medications for any reason between January 1996 and December 2004. The investigators compared the 180-day all cause mortality with use of a conventional antipsychotic versus an atypical antipsychotic. They found that the risk of death in the group of patients treated with conventional antipsychotic medications was comparable to, or possibly greater than, the risk of death in the group of patients treated with atypical antipsychotic medications. The causes of death with the highest relative risk were cancer and cardiac disease.

FDA considers that the methodological limitations in these two studies preclude any conclusion that conventional antipsychotics have a greater risk of death with use than atypical antipsychotics. FDA has determined, however, that the overall weight of evidence, including these studies, indicates that the conventional antipsychotics share the increased risk of death in elderly patients with dementia-related psychosis that has been observed for the atypical antipsychotics. The prescribing information for all antipsychotic drugs will now include the same information about this risk in a *Boxed Warning* and the *Warnings* section.

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*FDA is requiring the manufacturers to make these changes to the prescribing information for these drugs under its new authority to require safety label changes provided in Title IX of the FDA Amendments Act of 2007 (creating new section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act).

References

1. Gill SS et al. Antipsychotic drug use and mortality in older adults with dementia. Ann Intern Med. 2007;146:775-786

2. Schneeweiss S et al. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. CMAJ. 2007;176:627-632.

Conventional Antipsychotic Drugs	Atypical Antipsychotic Drugs
Compazine (prochlorperazine)	Abilify (aripiprazole)
Haldol (haloperidol)	Clozaril (clozapine)
Loxitane (loxapine)	FazaClo (clozapine)
Mellaril (thioridazine)	Geodon (ziprasidone)
Moban (molindone)	Invega (paliperidone)
Navane (thiothixene)	Risperdal (risperidone)
Orap (pimozide)	Seroquel (quetiapine)
Prolixin (fluphenazine)	Zyprexa (olanzapine)
Stelazine (trifluoperazine)	Symbyax (olanzapine and fluoxetine)
Thorazine (chlorpromazine)	
Trilafon (perphenazine)	

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Date created: June 16, 2008

Early Communication About an Ongoing Safety Review of Tumor Necrosis Factor (TNF) Blockers (marketed as Remicade, Enbrel, Humira, and Cimzia)

FDA is investigating the possible association between the use of medicines known as tumor necrosis factor (TNF) blockers and the development of lymphoma and other cancers in children and young adults. These individuals were treated with TNF blockers for Juvenile Idiopathic Arthritis (JIA), Crohn's disease or other diseases. JIA is the new name for what was called Juvenile Rheumatoid Arthritis (JRA).

FDA is investigating approximately 30 reports of cancer in children and young adults. These reports were submitted to FDA's Adverse Event Reporting System over a ten-year interval, beginning in 1998 after approval of the first TNF blocker, and extending through April 29, 2008. These reports described cancer occurring in children and young adults who began taking TNF blockers (along with other immuno-suppressive medicines such as methotrexate, azathioprine or 6-mercaptopurine), when they were ages 18 or less, to treat Juvenile Idiopathic Arthritis (JIA), Crohn's disease or other diseases. Approximately half the cancers were lymphomas and included both Hodgkin's and non-Hodgkin's lymphoma. Lymphoma is a cancer of the cells in the immune system. Lymphoma is not a recognized complication of JIA or of Crohn's disease. Other cancers reported included leukemia, melanoma, and solid organ cancers. While cancers are known to occur in children and young adults, the reports of these events in children and young adults receiving TNF blockers are of concern and deserve further investigation. Long-term studies are necessary to provide definitive answers about whether TNF blockers increase the occurrence of cancers in children because cancers may take a long time to develop and may not be detected in short-term studies.

TNF blockers suppress the immune system by blocking the activity of TNF, a substance in the body that can cause inflammation and lead to immune system-related diseases. There are currently four TNF blockers available in the United States. Remicade, Enbrel, Humira, and Cimzia are each approved to treat one or more of a number of immune system diseases including JIA, rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, Crohn's disease, and ankylosing spondylitis. Remicade is approved for use in children to treat Crohn's disease. Enbrel and Humira are approved for use in children to treat JIA.

FDA has been aware of the possible association between the use of TNF blockers and the development of cancer. The prescribing information for all four TNF blockers warns about the possible risk of cancer. FDA is also aware of the risk of hepatosplenic T cell lymphoma in children and young adults with Crohn's disease treated with Remicade and immunosuppressive drugs such as azathioprine or 6-mercaptopurine. This risk was described in the Remicade prescribing information in 2006.

FDA has asked the makers of the TNF blockers approved for use in children (Remicade, Enbrel, and Humira) to provide information about all cases of cancer reported in children taking TNF blockers. The maker of Cimzia is required to conduct a study to assess long-term risks of the product, including lymphoma and other cancers. This study will begin in 2009 and take about 10 years to complete. FDA has contacted medical experts to assess the potential association between TNF blockers and cancers, including lymphoma, and to determine if there are children and young adults with JIA and Crohn's disease who may be at

particular risk for developing a lymphoma or other cancer.

This early communication is in keeping with FDA's commitment to inform the public about its ongoing safety reviews of drugs. FDA will communicate the conclusions and any resulting recommendations to the public after it completes its evaluation of the new information within about six months. At the current time, the FDA believes that the potential benefits of the use of TNF blockers outweigh the potential risks in certain children and young adults having one of the diseases for which the TNF blockers are approved to treat. Until the evaluation is completed, healthcare providers, parents, and caregivers should be aware of the possible risk of lymphoma and other cancers in children and young adults when deciding how to best treat these patients.

The FDA urges both healthcare professionals and patients to report side effects from the use of Remicade, Enbrel, Humira, and Cimzia, to the FDA's MedWatch Adverse Event Reporting program.

- by reporting online at www.fda.gov/medwatch/report.htm;
- by returning the postage-paid FDA form 3500 available in PDF format at www.fda.gov/medwatch/getforms.htm to 5600 Fishers Lane, Rockville, MD 20852-9787;
- by faxing the form to 1-800-FDA-0178; or
- by phone at 1-800-332-1088.

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Date created: June 4, 2008

FDA News

FOR IMMEDIATE RELEASE
May 30, 2008

Media Inquiries:
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Consumer Inquiries:
888-INFO-FDA

FDA Advises Patients to Switch to HFA-Propelled Albuterol Inhalers Now

CFC-propelled inhalers no longer available as of Dec. 31, 2008

The U.S. Food and Drug Administration today issued a public health advisory to alert patients, caregivers and health care professionals to switch to hydrofluoroalkane (HFA)-propelled albuterol inhalers because chlorofluorocarbon (CFC)-propelled inhalers will not be available in the United States after Dec. 31, 2008.

CFC-propelled albuterol inhalers are being phased out because they are harmful to the environment by contributing to depletion of the ozone layer above the Earth's surface.

Three HFA-propelled albuterol inhalers have been approved by the FDA: Proair HFA Inhalation Aerosol, Proventil HFA Inhalation Aerosol, and Ventolin HFA Inhalation Aerosol. In addition, an HFA-propelled inhaler containing levalbuterol, a medicine similar to albuterol, is available as Xopenex HFA Inhalation Aerosol.

"Concern about the environment stimulated the need to phase out CFCs," said Janet Woodcock, M.D., director of the FDA's Center for Drug Evaluation and Research. "The FDA wants to emphasize that HFA-propelled albuterol inhalers are safe and effective replacements for CFC-propelled albuterol inhalers."

Albuterol inhalers are used to treat bronchospasm (wheezing) in patients with asthma and chronic obstructive pulmonary disease (COPD), which includes chronic bronchitis and emphysema. Patients use albuterol inhalers to deliver medicine directly into the lungs.

The FDA is urging patients to talk with their health care professionals now about switching to HFA-propelled albuterol inhalers. These products are safe and effective replacements for CFC-propelled albuterol inhalers.

Manufacturers have been increasing production of HFA albuterol inhalers, so an adequate supply is available now.

HFA-propelled albuterol inhalers may taste and feel different than the CFC-propelled albuterol inhalers. The spray of an HFA-propelled albuterol inhaler may feel softer than that of a CFC-propelled albuterol inhaler. Patients must also prime and clean HFA-propelled albuterol inhalers. Doing so prevents buildup of the drug in the inhalation device, and buildup can block the medicine from reaching the lungs. Each HFA-propelled albuterol inhaler has different priming, cleaning, and drying instructions, and patients should read and understand the instructions first before using the inhaler.

The phaseout of CFC-propelled inhalers is the result of the Clean Air Act and an international environmental treaty, the Montreal Protocol on Substances that Deplete the Ozone Layer. Under this treaty, the United States has agreed to phase out production and importation of ozone depleting substances including CFCs. No CFC-propelled albuterol inhalers may be produced,

marketed or sold in the United States after Dec. 31, 2008.

For more information:
http://www.fda.gov/cder/mdi/albuterol.htm

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