THE UNIVERSITY OF OKLAHOMA

MEMORANDUM

TO: Drug Utilization Review Board Members

FROM: Ron Graham, D.Ph.

SUBJECT: **Packet Contents for Board Meeting – March 8, 2005**

DATE: March 3, 2005

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

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

Call to Order

Public Comment Forum

New Legislature Update and Budget Issues

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 LUNESTA™ – **See Appendix C.**

Action Item – Vote to Prior Authorize Bladder Control Drugs – **See Appendix D.**

Action Item – Vote to Approve New Quantity Limits – **See Appendix E.**

Antidepressant Product Based Prior Authorization Proposal – **See Appendix F.**

Review of Non-Steroidal Anti-Inflammatory Drugs and Cardiovascular/Thrombotic Events – **See Appendix G.**

Annual Review of Antihistamines – **See Appendix H.**

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

Future Business

Adjournment

Drug Utilization Review Board

(DUR Board)

Meeting – March 8, 2005 @ 6:00p.m.

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

AGENDA

Discussion and Action On the following Items:

Items to be presented by Dr. Whitsett, Chairman:

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

Items to be presented by Dr. Whitsett, Chairman:

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

Items to be presented by Nico Gomez, Dr. Whitsett, Chairman:

3. **New Legislature Update and Budget Issues**

Items to be presented by Dr. Whitsett, Chairman:

4. **Action Item - Approval of DUR Board Meeting Minutes – See Appendix A.**
   A. January 11, 2005 DUR Minutes – Vote
   B. February 8, 2005 DUR Minutes – Vote

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

5. **Update on DUR/MCAU Program – See Appendix B.**
   A. Retrospective Drug Utilization Review Report for November 2004
   B. Medication Coverage Activity Audit for February 2005
   C. Help Desk Activity Audit for February 2005

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

6. **Action Item - Vote to Prior Authorize LUNESTA™ – See Appendix C.**
   A. Product Comparison
   B. COP Recommendation

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

7. **Action Item – Vote to Prior Authorize Bladder Control Drugs – See Appendix D.**
   A. Available Product Information
   B. COP Recommendations
   C. Nursing Home Provider Letter Draft

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

8. **Action Item – Vote to Approve New Quantity Limits – See Appendix E.**
   A. COP Recommendations

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

9. Antidepressant Product Based Prior Authorization Proposal – See Appendix F.

A. Category Review
B. COP Recommendations
C. Economic Impact

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

10. Review of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and Cardiovascular/Thrombotic Events – See Appendix G.

A. Review of Events in Oklahoma Medicaid Population
B. Client Health Outcome Survey – November 2004

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

11. Annual Review of Antihistamines – See Appendix H.

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

13. FDA and DEA Updates – See Appendix I.

14. Future Business

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

15. Adjournment

APPENDIX A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES of MEETING of JANUARY 11, 2005

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

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

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

OTHERS PRESENT:

Scott Mullins, Sanofi	Angela Menchaca, Amgen	Jason Schwier, Amgen
Randy McGinley, Berlex	Mike Cofer, Pfizer	Deron Grothe, Solvay
Jeff West, Chiron	Greg Hoke, Wyeth	Jonathan Klock, GlaxoSmithKline
David Love, Sepracor	Tracy Copeland, Forest	Alex Imhoff, Pharma
Patrick Evans, BMS	Lonna Erwin, BMS	Jorge Nassar, BMS
Mark DeClerk, Lilly	Don Stevens, Novaratis	Richard Ponder, J&J
Warren Piesatt, Pfizer	Roger Enix, Merck	

PRESENT FOR PUBLIC COMMENT:
Samuel Allen, Sepracor; Agenda Item 10

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

1A: Roll Call

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

ACTION: NONE REQUIRED.

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

2A: Acknowledgement of Speakers and Agenda Item

Dr. Whitsett acknowledged speaker for Public Comment.

ACTION: NONE REQUIRED.

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

3A: December 14, 2004 DUR Minutes

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 4: **NEW LEGISLATURE UPDATE AND BUDGET ISSUES**

Reported by Nico Gomez: A new legislature goes to work on February 7, 2005. The House has filed over 1700 Bills, but will have to decrease that number by half before January 20, 2005. The Senate has no limit on the number of Bills that can be filed and there are 1700 Bills filed. Mr. Gomez handed copies of the OHCA budget request. An additional $154 million above current budget base of $482 million is requested to operate this program at maximum efficiency. The top three items of expenditure are Annualization, Maintenance, and Federal and State Mandates. These three items of $97 million are mandatory in order to operate the OHCA for the next year. In October 2005, the State of Oklahoma will lose Federal matching dollars in the amount of 2.27%, a $33 million loss.

ACTION: NONE REQUIRED.

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

5A: Therapy Management Quarterly Report: Second Quarter FY05

Year-to-date totals (July – December 2004) were reported as 576 new clients; 285 established clients; 3,793 total PA's; 1,736 letters to providers; and 464 phone calls to providers; presented by Dr. Flannigan.

5B: Medication Coverage Activity Report: December 2004

The December 2004 activity audit noted total number of petitions submitted was 18,093 including super-PA's and special circumstance PA's. Approval/denial/duplicate percentages were indicated on the reports included in the agenda packet for this meeting; monthly and 2nd Quarter reports presented by Dr. Browning.

5C: Help Desk Activity Report: December 2004

Total calls for December 2004 numbered 18,203 (87.22% pharmacies, 8.43% clients, 2.39% physicians, 1.96% other); monthly and 2nd Quarter reports presented by Dr. Browning.

Dr. McNeill asked for a more defined report on Smoking Cessation. The Annual report is scheduled within the next couple of months. Dr. Whitsett requested more information the proposal from the tobacco trust fund.. Dr. Whitsett asked what other states are doing and maybe give a short report on that. Dr. Whitsett thinks it a good idea to invite someone from the tobacco councils to our meeting. Maybe have this person present something to Board members. Two Board members wanted to acknowledge the outstanding job the pharmacy help desk provides for the pharmacy providers. One statement was related to never having to wait but a few seconds to get through to a customer service representative and the other statement referred to the solving the problem and giving the proper information back to the calling provider in a professional manner.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 6: **UPDATE AND VOTE ON PRIOR AUTHORIZATION STATUS OF ANTIDEPRESSANTS**

Materials included in agenda packet; presented by Dr. Le.
Dr. Robinson moved to approve; motion seconded by Dr. Bell.
Dr. Whitsett asked if all of the SSRI's will get the black box warning? Dr. Le explained that according to the FDA, all antidepressants will get black box warnings. Dr. Whitsett wanted to know how the patient medication guide will get to the patient? Dr. Le stated that she understands that every prescription for these products will require passing out the patient medication guide. Dr. Robinson wanted to know a date that this would take effect. Dr. Whitsett reminded that everyone else besides paroxetine scripts for children are getting it now without prior authorization. Dr. Whitsett wanted to know if there is a safe time after a patient has been on these drugs to not worry too much about this risk of suicide. Dr. Robinson moved to accept COP option 2 recommendation.
ACTION: MOTION CARRIED.

AGENDA ITEM NO. 7: **NEW PRODUCT REVIEW - CYMBALTA®**

Materials included in agenda packet; presented by Dr. Chonlahan. Dr. Whitsett asked about comparable trials? Motion was made by Dr. McNeill to bring back this category to see what can be done as far as prior authorization category for these indications. Dr. Hollen asked to include KI binding affinity and the remission date including the number of weeks. Dr. McNeill asked why we couldn't take all antidepressants as a class for efficacy and toxicity and usage and costs to the state.
ACTION: NONE REQUIRED.

AGENDA ITEM No. 8: **30-DAY NOTICE OF INTENT TO PRIOR AUTHORIZE BLADDER CONTROL DRUGS**

Materials included in agenda packet; presented by Dr. Moore. Dr. McNeill wants to know when it would go into effect? Dr. Nesser said supplemental rebates would go into effect April 1st or by July 1st. Dr. Whitsett wanted to know about usage patterns? Dr. McNeill asked what happens when you have a person who cannot communicate and refuses to take it. As far as a side effect it needs to be opened up a bit. Dr. Whitsett said he would hope that someone would accept that as a side affect. Dr. Whitsett asked if we had the ability to communicate to the nursing homes. Dr. Whitsett asked that a draft of a letter be presented before the Board that would go out to the nursing homes. Grandfathering will be implemented prior to PA requirements.
ACTION: NONE REQUIRED.

AGENDA ITEM NO. 9: **ANNUAL REVIEW OF ANXIOLYTIC/HYPNOTIC PBPA CATEGORY**

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

AGENDA ITEM NO. 10: **30-DAY NOTICE OF INTENT TO PRIOR AUTHORIZE LUNESTA®**

For Public Comment, Samuel Allen: *Thank you Mr. Chairman. I'm here tonight, Dr. Samuel Allen from Sepracor Medicaid Affairs department. I am here to give you a very brief clinical only review of Lunesta®, our new agent which has recently been approved by the FDA. It's not currently on the market, but we expect it will be in the next thirty or sixty days. It has been FDA approved for the use of insomnia in adults and furthermore, it was FDA approved for both sleep onset and maintenance in adults, with no quantity limit thus far. We have 2, 120 patients we reviewed in six clinical trials as submitted in our NDA and one of those was a 12-month study on chronic use of our drug with abrupt discontinuation afterwards to test for withdrawal, addiction, tolerance and we found none of those. The FDA agreed with us so thus our label says we are able to treat chronically. It is an S-isomer of a racemic compound used in Europe, actually, not (unintelligible) of the world for almost twenty years now, and the drug has +20 million patients on it thus far. We licensed the drug, let me rephrase that . . . we took the drug and pulled off the S-isomer and thus received our own unique license . . . got the good half, I guess is the way you say that. The other half was largely inactive at the GABA site. The drug is metabolized primarily by 3A4 of the CYP3450 isoenzyme system. There is a little bit of 2E1 but it's negligible. Metabolite is largely inactive, it's actually two*

metabolites. One is completely inactive, one does have some receptor binding at the therapeutic site but so minimal it's thought to be non-reportable. The differences right now in the market is that we are the only drug that has no quantity limit by the FDA, that is approved both for sleep onset and sleep maintenance, so Ambien and Sonata both are very short half-life drugs, created a niche in the market for us if we could produce a drug that would help us, help a person get a good night's sleep and yet not have any next day side effect carryover effects, thus we think we have succeeded in that. We do not yet know the Schedule, if it will be Schedule IV or not. The FDA suggested we be listed as Schedule IV agent and those data are now at the DEA and apparently there is a debate as to whether it will be a higher Schedule or scheduled at all because of our copious amounts of safety data in long term use. That's my brief introduction. If I have any questions, I'd be happy to address them.

Dr. Whitsett: *Why would it be considered Schedule IV at all?*

Mr. Allen: *Well we don't know. The . . . there's a class . . .*

Dr. Whitsett: *Overdosing . . . feel like some of it ought to be over the counter.*

Mr. Allen: *Actually all the anxiolytic hypnotic sedatives are usually classed affecting the Schedule IV. So we expected it to be Schedule IV. We've only recently learned that it may not be Schedule IV.*

Dr. Swaim: *As of day before yesterday, it was being sold as that.*

Mr. Allen: *Absolutely, we found it out this morning. There was a press release this morning that found out that the DEA has not yet given us our Schedule.*

Dr. Hollen: *Have you had a chance to look through the information that was included in the packet? Was there anything . . .*

Mr. Allen: *I have not. I was the person that was brought in for the clinical presentation and have not seen the data that you have in front of you. It's the label? The 25-page label? Yeah, I'm very familiar with that.*

Dr. Whitsett: *Cost wise? What's . . .*

(unintelligible)

Dr. Whitsett: *. . . per tablet . . . $3.50 a day.*

(unintelligible)

Dr. Hollen: *Okay, but clarify because . . .*

(unintelligible)

Dr. Hollen: *What is your recommended adult dose going to be?*

Mr. Allen: *Recommended adult dose will start out at 2 mg for non-elderly adults, go to 3 mg if needed.*

Dr. Hollen: *If needed?*

Mr. Allen: *If needed.*

Dr. Hollen: *Okay, do you know what your estimated acquisition cost for 2 mg is going to be?*

Mr. Allen: *I cannot say, since the drug's not on the market yet, we haven't . . .*

Dr. Hollen: *So do we know any of the estimated acquisition costs, or do we . . .*

Mr. Allen: *I can't address any . . . issues . . . I'm only here to present clinical data. I'm sorry.*

Dr. Meece: *. . . $3.26 . . . $3.26 . . . 3 mg . . . says $3.26 . . . across the board . . . flat price . . . so it's flat base pricing? Does that sound about . . .*

Mr. Allen: *I know it's flat base pricing. It actually is, I should point out, a different dosing regimen for elderly adults, starting 1 mg and go to 2 mg if needed. It's because their PK kinetics are slightly different. They eliminate a little bit slower, thus the drug tends to be not washed out as quickly.*

Dr. Nesser: *Do you know what the average dose is for the 20 million other users? Since there's a lot of use.*

Mr. Allen: *It's a different drug, it's racemic mixture and actually their main dose is 7.5 mg, but since it's racemic we cut that in half so it would be 3.75 was the average normal maximal dose for the non . . .*

Dr. Whitsett: *I take it drug interactions are not a special issue?*

Mr. Allen: *No. We did quite a few interactions. It does go through 3A4 but it's neither inhibitor nor inducer of the system. It's just broken down by . . we did run it with Ketoconazole which is . . . interactor of 3A4 and it did not change the kinetics Ketoconazole. . . Ketoconazole did increase the area of the curve . . . otherwise we saw no notable interactions. There was a possible other . . . there was . . . pharmacodynamic interaction with olanzepine when it was tested, but it was more in effects of patient sedation and somnolence, which somnolence is means sleeping pill I guess. We have a goodly amount of data. Our next day effect data are excellent.*

Dr. Whitsett: *How are you getting away with that? How does that work?*

Mr. Allen: *How does it work? Well it's a 6-hour half life.*

Dr. Whitsett: *I understand that . . .*

(unintelligible)

Dr. Whitsett: *. . . the next day . . . medications . . . people do have carryover side effects even though theoretically it's gone. It may be out of the plasma but it may still be bound to receptors and leaching off a receptor much slower than it did from the plasma and so a prolonged duration of after effects occur.*

Mr. Allen: *Well that's true of most . . . first of all we're not a benzo. We don't stick to that receptor. We're not chemically related to anything else in that class. It's GABA-A, binds to an alpha sub-unit of GABA-A receptor. It binds to a different sub-unit more so than Ambien does. Ambien tends to be much more at the alpha-1 sub-unit. Our drug binds more at the alpha-3 sub-unit. The alpha-3 sub-unit is localized much more in the actual sleep producing centers instead of the limbic system and/or cortex of the brain where you would get more true sedative effect instead of a sleep inducement effect.*
Dr. Whitsett: *If someone is aroused during the night, do you have difficulty waking them or do they wake up fully alert . . .*
Mr. Allen: *I don't have any data as far as . . . it says in our label very clearly not to take the drug unless you are expecting a good eight hours' sleep, so . . .*
Dr. Whitsett: *So if someone is expected to get up during the night to go to the bathroom, I understand some people do, it would probably be, I don't know that it would be contraindicated . . . what are your contraindications?*
Mr. Allen: *We don't have any.*
Dr. Whitsett: *Don't have any? But if you get up and go to the bathroom two or three times during the night, then you wouldn't recommend it?*
Mr. Allen: *Well, yeah . . . the label plainly says if you . . . expecting a full night's sleep . . . for that matter, that's almost a classic . . . (unintelligible).*
Mr. Allen: *The data actually there is a published paper out there right now by Tom . . . out of the Henry Ford Center up in Michigan . . . (unintelligible) . . . and the number of arousals during the night, as far as the need to go to the restroom decreased significantly in someone whose insomnia is actually treated. That it may be a side effect of someone having to get up and go to the bathroom because they were awake already and . . . (unintelligible).*
Dr. Hollen: *Do we know, what's the half life of Sonata and Ambien? Do we know those?*
Mr. Allen: *Sonata is an hour and a half to two hours. Ambien is right around (untelligible). They're both very short half lifes. That's why neither is indicated for maintenance. They usually wear off . . . the effects wear off (unintelligible).*
Dr. Whitsett: *The onset you said was, onset of action thought to be . . .*
Mr. Allen: *The onset of action is very rapid. C-max is about one hour and our half life is about six hours. It's a very linear curve when you look at the plasma concentrations.*
Materials included in agenda packet; presented by Dr. Browning.
ACTION: NONE REQUIRED.

AGENDA ITEM NO. 11: REVIEW AND DISCUSS MULTIPLE SCLEROSIS MEDICATIONS
Materials included in agenda packet; presented by Dr. Patel. Dr. McNeill asked how these were being filled at retail pharmacies and if administered in the home.
ACTION: NONE REQUIRED.

AGENDA ITEM NO. 12: ANNUAL REVIEW OF ADHD/NARCOLEPSY PBPA CATEGORY
Materials included in agenda packet; presented by Dr. McIlvain. Dr. Hollen asked how many patients on Strattera had shown liver toxicity since it came out? Dr. McIlvain said that two patients had demonstrated this side effect. Dr. Hollen asked if the liver damage was reversible? Dr. Bell said it was. Dr. Whitsett asked how changes for example in black box warnings on a particular drug, do the pharmacist consult with the patient?
ACTION: NONE REQUIRED.

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

AGENDA ITEM No. 14: **FUTURE BUSINESS**

14A: PBPA Annual Reviews
14B: Neurontin™ Follow-Up Review
14C: Zofran® Follow-Up Review
14D: SMAC Update
14E: New Product Reviews
14F: Supplemental Rebate Update

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

ACTION: NONE REQUIRED.

AGENDA ITEM No. 15: **ADJOURNMENT**

The meeting was declared adjourned.

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES of MEETING of February 8, 2005

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

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

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

OTHERS PRESENT:

Marguerite Enlow, BMS	Alan Barrouther, Purdue Pharma	Jonathan Klock, GSK
Greg Novarro, Sepracor	John Niewoehner, Sepracor	Justin Springfield, Sepracor
Joe McIntosh, Novartis	David Dude, BMS	Sandy Rable, Rd Assoc
Angela Menchaca, Amgen	Toby Thompson, Pfizer	Dick Kerr, BMS
Jack Jones, Lilly	Jim Dunlap, Lilly	RaeLynn Herron, KOS
Jason Schwier, Amgen	John Omick, Novartis	Pat Evans, BMS
Richard Ponder, J&J	Janis *(Illegible)*	Don Stevens, Novartis

PRESENT FOR PUBLIC COMMENT:

Marguerite Enlow, PharmD; Item No. 12
Evie Knisely, PharmD; Item No. 8
Niraj Prasad, MD; Item No. 12
Jim Seaboldt, PharmD; Item No. 8
Johnny Roy, MD; Item No. 8

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

1A: Roll Call

Dr. Whitsett called the meeting to order. Roll call by Dr. Graham. There was not a quorum.

ACTION: NONE REQUIRED.

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

2A: Acknowledgement of Speakers and Agenda Item

Dr. Whitsett acknowledged speaker for Public Comment.

ACTION: NONE REQUIRED.

LEGISLATIVE UPDATE

Mr. Gomez, OHCA: *What I asked Ron to hand out is, as I mentioned to you last time, we come to you during the legislative session to give you information on Bills that may or may not affect what you do here, the Oklahoma Health Care Authority, in your role as DUR Board, but we want to make you aware of some Bills that may affect the way we run the pharmacy program as well as the DUR Board. What I've passed out is a list of Bills that we're tracking. I'm not going to go through each one real specifically. I'll just kind of give you a highlight of those. We've also provided you a copy of some of the major Bills if you want to take time to read those later at your leisure. Again, this is just for information purposes only. We're tracking HB 1290 which amends language that restricts the Health Care Authority in negotiation with drug manufacturers by limiting factors to be considered in negotiations. Fiscal impact on this, we estimate about $4.5 million. It limits the authority of the DUR Board to deny or place limitations on the request of any person to make a presentation to the Board and also requires 30-day notice for DUR Board, I believe action items if I read that correctly. So, there's several things in the Bill. You can locate them through the underlined portions of that. HB 1389, let me just go on the record and say this is not a request Bill, but it is interesting and I've talked to the author who said he's picked up this concept out of the State of Maine. This requires manufacturers who dispense under a Federal or State program to submit a written report to the Health Care Authority containing pharmaceutical pricing criteria for each drug. And again, that's modeled after some Maine legislation. It's not one of our ..... Bills but an interesting Bill nonetheless, that would, could affect the day-to-day business of the Agency. HB 1433 is dispense as written. I don't think I need to explain that too much. I think everyone understands what that concept is, but dispense as written as far as brand names go. Based on the SMAC estimated cost of dispensing brand name, exclusively dispensing brand name drugs, we estimate about $48 million in total dollars. That includes Federal dollars, so about a $15 million State share impact on that legislation right now.*

Dr. Whitsett: *Let me interrupt and ask a question because things don't always appear like they seem to be. The dispense as written seems clear and I've not looked at the legislation in a long time, but having read it years ago when the subject came up, it said that the pharmacist was obligated to fill a prescription with the named item when it said dispense as written unless the patient requests and the pharmacist agrees to consider an alternative. So there was an exception in the old law. Now does this do anything to that, or . . . ?*

Dr. Nesser: *This really doesn't do anything to the pharmacy law part, it just says that Medicaid can't require a prior authorization to reimburse at the brand name level. Right now we require that for brand name override. We want to know why and why the generic didn't work and so forth. So this law would just prevent the Health Care Authority from enacting that rule, so it really wouldn't change what's going on with the retail side. It just speaks only to the Health Care Authority.*

Mr. Gomez: *HB 1542, there's about three Bills that I have on your list that deal with cost management council which would allow the State to enter into multi-state agreements. So I threw those in there just so you can see the interest at the legislative level to do some multi-state purchasing or pooling. There's at least three Bills out there that would create such a council. HB 1594 is a prescription drug access for seniors task force, another task force. This one would be staffed by members of the Health Care Authority DHS and have a report to the Legislature or Governor by January 1, 2006.*

Dr. Whitsett: *Which seniors would be affected by this?*

Mr. Gomez: *Right now some of the defining language is not that clear as far as which seniors that would affect.*

Dr. Whitsett: *They would have to be Medicaid seniors?*

Mr. Gomez: *Not necessarily. Not for this task force. They would include us on the council. (HB) 1673 is another multi-state council, multi-state agreement, process, and have the council oversee that. SB 861, prior authorization for drugs for HIV-AIDS-Hepatitis C; this would authorize the DUR to establish protocols for use of drugs used to*

treat HIV-AIDS and Hepatitis C without prior authorization. As I understand it, that's current practice of the DUR, so the Bill, if it were to go through as is, I don't believe would have any effect since it's current practice. Also with the number of clients that would be leaving as a Medicare Part D pharmacy benefit come again, it would even probably have even less impact.
Dr. McNeill: *Is Hepatitis C included in that?*
Mr. Gomez: *Hepatitis C . . .*
Dr. McNeill: *From existing language. I thought it was just HIV.*
Dr. Nesser: *HIV drugs don't count against the script limit, but we don't currently put prior authorization restrictions on drugs in either category, so this legislation only affects the prior authorization, not the script limit.*
Mr. Gomez: *And then SB 896, another cost management council, very similar to HB 1542. SB 959 is the last one I'll leave you with tonight. This Bill amends several sections of the Health Care Authority Act pertaining to the DUR Board, requires the DUR Board to be appointed by elected officials. In other words, the DUR Board would have a portion elected by the Senate Pro Tem, the Speaker of the House, and the Governor's Office. It would require the Chairman to be a physician. There's some restrictions on being able to respond to market changes in regards to prior authorization changes. This one in our analysis has a fiscal impact up to $10 million annually, and these Bills have been on the street, really just over a week, so we're still kind of wading through a lot of the Bills. These are some of the major ones that we've tabbed and will provide you a list of. I've given you copies of four Bills of which I mentioned to you tonight if you would like to look at them at your leisure. Again, this is just for your information. This will probably alter significantly when I meet with you next month because we'll know which one of these Bills has survived the first legislative deadline. Are there any questions?*
Dr. Whitsett: *Perhaps, we'd like to keep track of some of these that have direct implications to our DUR Board and do maybe a follow-up or further review. We'd have a chance perhaps to look at this, but maybe someone could do us a 1-2-3 status and we could track what's happening, what's behind it all.*
Mr. Gomez: *Exactly. That's kind of what I hope to do when the times I visit with you and we'll be, as the Agency, we'll be tracking these closely and we work with our pharmacy division for input and guidance from a policy standpoint as well.*

AGENDA ITEM NO. 3: APPROVAL OF DUR BOARD MINUTES
3A: January 11, 2005 DUR Minutes
ACTION: DEFERRED TO MARCH, 2005 MEETING.

AGENDA ITEM NO. 4: UPDATE ON DUR/MCAU PROGRAM
4A: Retrospective Drug Utilization Review Report for October 2004
Drug Interaction Module, Established, Major, Females Age 21-50 years; 25 client profiles reviewed. Duplication Module, Estrogens, Females, Age 21-50 years; 110 client profiles reviewed. Drug-Disease Level, Contraindicated, with Hypertension or Heart Failure, Females Age 21-50 years, Non-Nursing Home; 136 client profiles reviewed. Dosing & Duration Module, Muscle Relaxants, High Dose Only, Females Age 21-50 years, Non-Nursing Home; 59 client profiles reviewed. Physician response rate was 25%, and 27% response from pharmacists. Material included in agenda packet; presented by Dr. Flannigan.
4B: Medication Coverage Activity Report: January 2005
The January 2005 activity audit noted total number of petitions submitted was 14,188 including super-PA's and special circumstance PA's. Approval/denial/duplicate percentages were indicated on the reports. Material included in agenda packet; presented by Dr. Browning.
4C: Help Desk Activity Report: January 2005
Total calls for January 2005 numbered 15,076 (86.67% pharmacies, 9.05% clients, 1.93% physicians, 2.34% other). Material included in agenda packet; presented by Dr. Browning.
ACTION: NONE REQUIRED.

AGENDA ITEM NO. 5: UPDATE ON SUPPLEMENTAL REBATE PROGRAM
Presented by Dr. Nesser. The first category reviewed are the Proton Pump Inhibitors (PPIs), implemented on July 1st. Rebates are billed after the end of each quarter. Expected quarterly rebate amounts in excess of $200,000 dollars or close to $1 million dollars per year for this particular category. All of the manufacturers in this category

participated in the supplemental rebate program. Basically, all prior authorization restrictions have been removed except for high quantity restrictions. The next category is the SSRI's. As of January 1st, all manufacturers are participating in this program. The first invoices for rebates actually go out at the end of this month. It is expected to reach close to $700,000 dollars per quarter or $2.8 million per year savings. The next category is the Statins. All manufacturers participated in this category also. It is expected to save $340,000 dollars per quarter or $1.3 million dollars per year in this category. In the ARB's category there were 7 out of 8 manufacturers who participated. Expected annual savings should be about $600,000 dollars per year. The other categories are the ACE's and CCB's and Combo's and the NSAIDs, however, there are so many generics in these categories that it is not that beneficial for manufacturers to participate. Expected annual savings should be about $80,000 dollars. Statistically, there are 18 manufacturers participating, over 30 products, and projected savings for this calendar year will be over $6 million dollars. All contracting are done in-house.
Dr. Whitsett asked about other categories such as Growth Hormones. Mike Fogarty expressed his appreciation for this program and the manufacturer's participation and requested feedback from vendors. Greg Novarro, Government Affairs with Sepracor, acknowledged his satisfaction in working with the State of Oklahoma Medicaid program as compared to other state programs. He stated that the healthcare of the client was emphasized first in Oklahoma Medicaid as opposed to only costs.
ACTION: NONE REQUIRED.

AGENDA ITEM NO. 6: STATE MAXIMUM ALLOWABLE COST (SMAC) REPORT
Presented by Mr. Easton. The Oklahoma SMAC was implemented in April of 2000. This program is similar to the Federal Upper Limit (FUL) which was initiated by CMS. For 2004, the SMAC savings were about $47 million dollars and for 2003 it was about $15 million dollars. The large increase in savings in 2004 are due to the additional 150,000 clients transitioned from the HMO's and more assertive management of the SMAC and the increase of generic products on the market.
ACTION: NONE REQUIRED.

AGENDA ITEM No. 7: VOTE TO PRIOR AUTHORIZE LUNESTA™
Materials included in agenda packet; presented by Dr. Browning.
ACTION: DEFERRED TO MARCH, 2005 MEETING.

AGENDA ITEM NO. 8: VOTE TO PRIOR AUTHORIZE BLADDER CONTROL DRUGS
For Public Comment, Jim Seaboldt: *My name is James Seaboldt. I'm with GlaxoSmithKline pharmaceuticals, from the Medical Affairs department. Currently I'm working with the urology and anti-infectives area in that pharmaceutical firm. My background is infectious disease. I am a PharmD. I'm also on staff at the University of New Mexico at Albuquerque currently teaching some pharmacy classes out there. I wanted to just take a minute to maybe address or talk about overactive bladder for a minute. There's a new product that GlaxoSmithKline and Yamanouchi America Pharma is putting out. Basically, let me just give a little bit of background and a prepared statement. Overactive bladder or OAB is a syndrome characterized by urinary urgency with or without urge incontinence. It's usually accompanied by frequency and natri-urea. To put this a little bit into perspective, more than 17 million suffer from OAB in the United States and that accounts for approximately 17% of the adult population and as with many other chronic diseases, the prevalence of OAB increases with advancing age. Often this is thought of mainly a women's health issue, however the National Overactive Bladder Evaluation, or (NOBLE) study, as authored by Stewart et al., 2003, described a syndrome that often affects as many men as women with the component of urge incontinence being one of the main differentiations more often observed in women. Many other health conditions are often observed in patients suffering from overactive bladder. Some of these conditions described in an article by Brown et al., published in the American Journal of Managed Care during 2000 include sleep disturbances, fatigue, urinary tract infections, other skin infections, falls and fractures. Overall the syndrome of overactive bladder also impacts the mental health by an association with depression and maybe more importantly, a fear of embarrassment manifested by the patients. Milson published in the British Journal of Urology in 2001 described that the fear of incontinence displayed by both wet and dry OAB patients often manifested by the patient going to great lengths to avoid risky situations . . . they tend to map locations of lavatories and they tend to change their clothing appearance to accommodate adult diapers or they wear darker colors to hide water staining.*

In the same report, Milson also described that overactive bladder may impact the patient relationships with other people because the disease sufferers are really afraid of that leakage or afraid of, quite frankly, urine smell associated with the disease. So ideally, OAB pharmacologic treatment would include therapy that is efficacious by restoring continence and decreasing urgency, is tolerable with less dry mouth, and a favorable efficacy to adverse event ratio, and provide a high degree of satisfaction so the patients may stay on the medication for long term therapy with symptoms of quality of life improvement over time. Now the new product that I'm here to discuss, VESIcare® or solifenacin succinate is a competitive muscarinic receptor antagonist approved in the USA during November of 2004. The current indications for VESIcare® include the treatment of overactive bladder with symptoms of urge, urinary incontinence, urgency and urinary frequency. VESIcare® is available in two once daily tablet formulations of 5 mg and a 10 mg tablet and the recommended dose of VESIcare® is 5 mg once daily. Now if the 5 mg dose is well tolerated, the dose may be increased to 10 mg once daily. Pharmacologically, VESIcare® is highly protein bound, competitive muscarinic receptor antagonists displaying clinical kinetics consistent with once daily dosing and this agent is metabolized by the liver, primarily by the cytochrome P450 3A4 system, although alternative metabolic pathways do exist. No significant drug-drug interactions have been observed with Warfarin or oral contraceptives, and there seems to be no food effect on efficacy. The half life of VESIcare® is approximately 50 hours. Now turning to the landmark investigations for VESIcare®, briefly, there are four double blind 12-week clinical trials with a 40-week open label extension trial on two of these trials, as published by Burton et al., in Current Medical Research Opinion during 2005. Two pool trials of VESIcare® restore greater than 15% of incontinent patients to continence at week 12 compared to 38% of patients receiving placebo. Now the historical analysis of efficacy in treating OAB includes measures of the median percent change from baseline of incontinence episodes in a 24-hour period. With VESIcare®, trials are analyzed in this manner. At week 12, there is a 100% median decrease percent chance from baseline compared to a 67% median decrease percent chance from baseline in the placebo group. Typical adverse events reported in the pool VESIcare® landmark trials include dry mouth at 10.9% compared to placebo at 3.5, constipation at 5.4% compared to placebo at 1.9, and blurred vision at 3.8% compared to placebo at 2.5. The percent discontinuation due to all adverse events was actually less than the 5 mg VESIcare® arms at 2.8 percent compared to the placebo arm at 3.5. So in summary, VESIcare® was observed to restore continence in more than half of the incontinent patients, significantly reducing continence episodes, significantly improve incontinence frequency, urgency and volume voided, and VESIcare® also reports a favorable tolerability profile with low discontinuation rate due to adverse events. Now as with other anticholinergic agents, VESIcare® is contraindicated in patients with urinary retention, gastric retention, uncontrolled narrow angle glaucoma and patients who have demonstrated hypersensitivity to the drug substance or other components of the product. Any questions?

Dr. Whitsett: *When will that be available?*

Dr.Seaboldt: *It's currently available.*

Dr. Whitsett: *Is it on the shelf?*

Dr.Seaboldt: *Uh-huh.*

Dr. Whitsett: *What's the cost?*

Dr.Seaboldt: *The cost I will have to defer on.*

For Public Comment, Evie Knisely: *Dr. Whitsett, I'd like to let Dr. Roy go. He's with me, he's got a timetable.*

Dr. Whitsett: *Yes, okay. Well he's next on the list. Dr. Roy.*

For Public Comment, Johnny Roy: *Thank you. Hi, I'm Johnny Roy. I'm a urologist. I used to be professor of urology at the University of Oklahoma for 20+ years and I don't want to repeat what the speaker previous to me said. As a urologist, I see a lot of individuals with this syndrome of frequency, urgency and incontinence, better termed as overactive bladder. I'm not here to pitch for anything. All I'm saying is that as a urologist, we see these individuals quite a bit. It's more prevalent in women than in men and I'm called often to see those individuals in the gero-psych units at our hospital or in nursing homes. So when I see them and I try to prescribe for them the old standby, which is the Oxybutynin and Ditropan®, which is a great drug, and I've been using it and I've done research on it 25 years ago or so, and I have even used Bentyl and Probanthine, the old Probanthine before even Oxybutynin came. So I've been in this business for a while. All I can say is that when I'm called to see these older individuals and I try to recommend the old standbys, my recommendation is neglected or rejected by the psychiatrists in the gero-psych units and in nursing home by a family physician stating that these individuals already have dry mouth. They are old, they all have confusion, and you are going to increase their confusion. And as for the tachycardia and angle glaucoma, I'm a urologist. That's outside my jurisdiction. But my recommendation is rejected for fear of increasing confusion and blurring vision and the dry mouth which is quite prevalent in the age group I'm talking about. And that's all I have to say. So all my thing is that we should have some backup to these old standbys regardless of what, I think we do need a backup for these drugs for these individuals.*

For Public Comment, Evie Knisely: *Good evening. My name is Evie Knisely and I'm a Regional Accounts Scientific Associate Director with Novartis, and we've heard a lot about overactive bladder and Dr. Roy talked about the reasoning behind wanting to use one of the newer products as opposed to some of the old standbys, and I'd like to reinforce that. The product that Novartis has just put on the market, actually December 23rd, so we are just getting the product on the shelves right now, and that's Enablex® or darifenacin, which is a once a day long acting product for overactive bladder. What's unique about it is that it's an M3 selective receptor antagonist and to really understand what that means you have to know your muscarinic receptors, think back to medical school or pharmacy school. M1 is in the brain and that deals with cognitive function. M2 is in the cardiovascular system or the heart. M3 is salivary glands, the GI tract and the bladder, so that's the one we really want to focus on. M4 is in the brain but we don't know much about it, and then M5 is in the ciliary's muscles around the eye and handles visual accommodation. So what we're really wanting to do in overactive bladder is target M3 because that's where the detrusor muscle is and the spastic action of the detrusor muscle is what causes overactive bladder. Enablex® is very specific for the M3 so we're getting M3 only and we're not having the side effect profile, cognitive dysfunction, cardiac problems such as QTC prolongation or ciliary's problems that you get if you get M1, M2 or M5 respectively. So we feel like that's a niche for our product. We think that makes our product a good fit for older patients who are the ones that have overactive bladder. And the last point that I want to make is around anticholinergic load and Dr. Roy referred to this as well. The patients in nursing homes do have problems with anticholinergic load. Because they're older they have slower metabolism and elimination of different drugs and many drugs on board because they have many co morbid conditions. They have changes in the muscarinic receptors themselves, the number and the distribution. They have changes in the blood-brain barrier. So these are patients that have problems with anticholinergic medications such as the older agents that have been around awhile, since the generics that you're recommending for Tier 1. One particular study looked at nursing home patients and found that 21 to 32% had two or more anticholinergics on board, 10 to 17% had three or more anticholinergics on board, and 5% had five or more anticholinergics on board. So I urge you to think about putting a drug and making a drug available that won't add to that anticholinergic load in these patients. Thank you.*

Dr. Whitsett: *Dr. Knisely, what kind of costs are we looking at?*

Dr. Knisely: *We actually are very competitively priced. My understanding is that the AWP is running right around $86.00 per month.*

Dr. Whitsett: *What about the difference between the 5 and 10 mg?*

Dr. Knisely: *It's 7.5 and 15 and they will be flat priced, so they won't . . . there'll be no difference in price.*

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

ACTION: DEFERRED TO MARCH, 2005 MEETING.

AGENDA ITEM NO. 9: **ANNUAL REVIEW OF GROWTH HORMONES**

Materials included in agenda packet; presented by Dr. Moore. Dr. Whitsett recalled having criteria set up to demonstrate efficacy and physical progress to document that we were accomplishing our goals for that particular individual and he wanted to know how that was going. Dr. Moore stated she rarely sees a child without an acceptable growth velocity. Dr. Whitsett requested that the College of Pharmacy bring some illustrated results back to the DUR Board for a follow-up report.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 10: **ANNUAL REVIEW OF HYPERTENSIVES**

Materials included in agenda packet; presented by Dr. Le. Dr. Whitsett asked if the College of Pharmacy has looked at how we are doing relative to patients who are diabetics and what percentage of these patients are receiving an ACE Inhibitor? Dr. Le stated that she had not looked at that but she did say there was a 4,000 claims increase in the 2004 ACE Inhibitor class. Dr. Whitsett suggested that we look at that because it is standard of care. Dr. Whitsett asked if more people were coming into Medicaid because of the economy and such? Mr. Fogarty said that the authority still sees an overall trend of about 1% increase per month. Although it is very seasonal and the last couple of months have been fairly stable, he thinks that we will continue to see ½ to 1 percent growth. Mr. Fogarty said that this trend is consistent with other states as well.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 11: **FOLLOW-UP OF ONDANSETRON (ZOFRAN®) UTILIZATION**
Materials included in agenda packet; presented by Dr. Le. (See packet for conclusion and recommendation)
ACTION: NONE REQUIRED.

AGENDA ITEM NO. 12: **ANNUAL REVIEW OF PLAVIX®**
For Public Comment, Niraj Prasad, MD: (Tape stopped). . . *and Plavix combination preferably before. If that's not possible, certainly after the procedure. The one problem that I face with Medicaid patients are that they need preauthorization. You do a procedure say on Friday, put in a stent, and you can't give them Plavix, they can't go home. They often wait for Monday to go home because they can't make alternative arrangements to get Plavix on-board for them. Sometimes you have to go to office or get some samples of Plavix which is not always there, so then the other. . . the hospital would give them free one-week supply which is also sometimes difficult. So this problem we've been facing that we need to have preauthorization for Plavix in these patients. So I would ask the committee members to consider it's my personal belief that Plavix should not be preauthorized for patient undergoing acute coronary intervention and stent because it is life saving. If we don't give them Plavix, they have a stent thrombosis, they die. It's a very deadly complication. So that's why I request from this committee. And second, this new drug porter stents, they require much longer duration of Plavix than the earlier ones. The ordinary metal stents we could do for four to six weeks would be fairly all right. Because this new drug porter stents do not allow healing process to occur and hence some mis-formation can occur as late as six months or nine months. So we currently, our current practice is to give for one year. Certainly nine months. And that's the second . . . the second point to consider. The third point would be for me to voice here the people who have severe peripheral vascular disease would really benefit from Plavix. And in fact American College of Chest Physicians in their guidelines have shown that Plavix be the number one prescription drug for patients with severe peripheral vascular disease because it prevents future bad cardiovascular outcomes in men and that's not there in Medicaid patients, so I would like to add to the request. Thank you.*
Dr. McNeill: *Is the emergency 3-day supply not in place here?*
Dr. Nesser: *No, it should be.*
Dr. McNeill: *So if you did a stent on Friday, they should be able to have access to Plavix Friday, Saturday and Sunday without prior authorization.*
Dr. Prasad: *For our patients in St. Anthony Hospital, if I give them prescription on Friday, they can't get it.*
Dr. Graham: *They should be able to.*
Dr. Whitsett: *If they can't, then there's a violation of our policy for that, because there is an emergency clause and the new policy that's going to be discussed perhaps a little later is that if you had a coronary stent that you placed, writing that on a prescription will let it sail through and fulfill the criteria of the prior authorization.*
Dr. Prasad: *I see. Three days . . . if they get, if they have a prescription on Friday, if they get for three days to Monday, and then to submit a prescription, they're making a week for them to get their things filled.*
Dr. Whitsett: *The pharmacists have it in stock and they can fill it immediately. There should not be a wait. There should not be, and I don't know what's happened to instances in your patients or what you've been told, but there has been communication to the pharmacists around the state and we are in the process of finding who the physicians are that treat our clients, put in stents, so that we can communicate directly with them. But writing that on the bottom of the prescription . . . coronary stent . . . should have their prescription filled in 30 minutes or whatever it takes to fill a prescription.*
Dr. Prasad: *That's good to know that.*
Dr. Whitsett: *That's the way it should be and we've been working towards that and I think to hear what you have said certainly reemphasizes it for people . . . having that immediately and not getting it through mail order.*
Dr. Prasad: *That's good to know that. Because we been so far trying to make sure they get . . . supply . . . before they leave the hospital.*
Dr. Graham: *I would just say it would be good to go ahead and give your patients samples if you have them on hand, just to go through the process, you know, to save them some time. We have pharmacists standing by at the phones that can answer, the overrides for, you know, 72-hour emergency fill, so there shouldn't be a problem . . .*
Dr. Prasad: *Does all the hospitals have their . . . the list of the pharmacists?*
Dr. Graham: *They should. I mean, the pharmacists are the ones that initiate the calls usually. Now you can call the Help Desk if you'd like, but in order for us to give a prior authorization we have to know who the pharmacy is.*
Dr. Prasad: *OK. Do you have any preferred pharmacies or anyone . . .*
Dr. Graham: *Not really. Just any.*
Dr. Whitsett: *You'd mentioned peripheral arterial disease and I think that is one of the criteria that's acceptable. So that . .*

Dr. Whitsett: *So I would hope that the people involved would get the word out that the, our activities are not denying Plavix, that we're not in that business. We, there's a certain process we go through, but I think it is wrong to give misleading information to doctors and getting them upset and it gets everything in a turmoil when false information is spread around, and it's just inappropriate.*

Dr. Enlow: *Well, thanks for your making me aware of that. I haven't seen the piece of paper and I really don't know what you're . . . but I will pass the information on and I thank you for your comments.*

Materials included in agenda packet; presented by Dr. Flannigan. Dr. Whitsett reiterated what the FDA approved indications are for the use of Plavix. He wanted it known that Oklahoma Medicaid actually covers more indications than approved by the FDA. It was recommended that the length of approval per authorization for stent patients should be extended to one year.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 13: **FDA AND DEA UPDATES**

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

ACTION: NONE REQUIRED.

AGENDA ITEM No. 14: **FUTURE BUSINESS**

14A: PBPA Annual Reviews
14B: Neurontin™ Follow-Up Review
14C: Fuzeon® Follow-Up Review
14D: Estrogen Replacement Products Review
14E: Narcotics Follow-Up
14F: New Product Reviews

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

ACTION: NONE REQUIRED.

AGENDA ITEM No. 15: **ADJOURNMENT**

The meeting was declared adjourned.

APPENDIX B

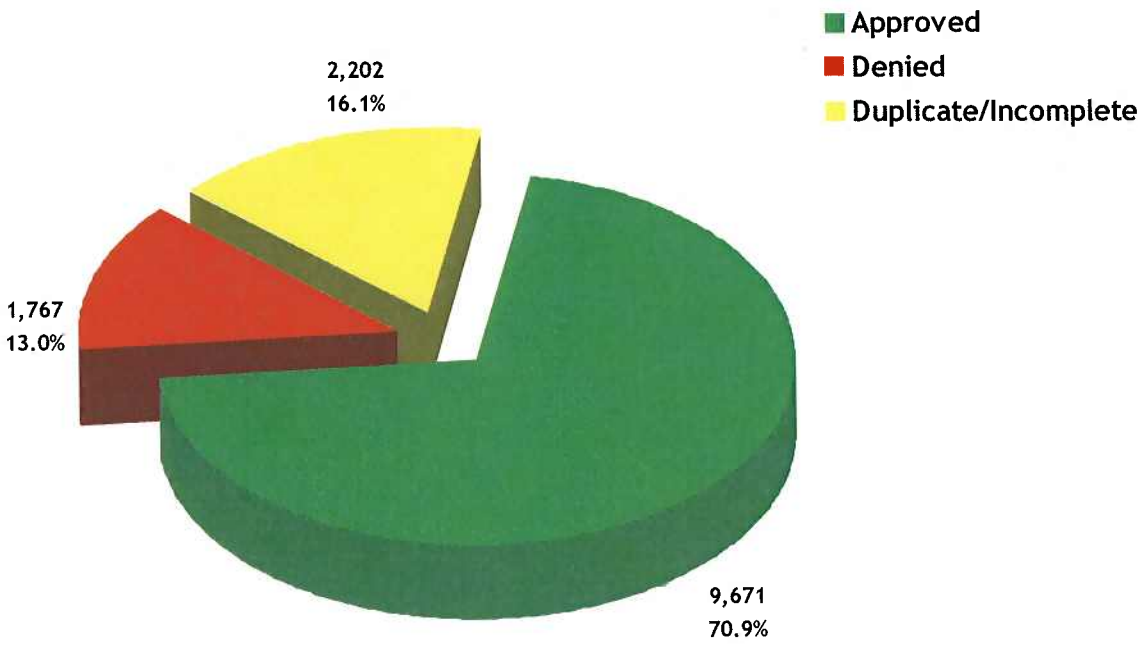
Retrospective Drug Utilization Review Report

Claims Reviewed for November 2004

Module	Drug Interaction	Duplication of Therapy	Drug-Disease Precautions	Dosing & Duration
Total # of messages returned by system when no limits were applied	69,681	54,688	627,195	38,685
Limits which were applied	Established, major, males 21-50 yrs old	Antiplatelet Drugs	Contraindicated, males with heart failure	High dose, platelet aggregation inhibitors
Total # of messages after limits were applied	23	85	303	39
Total # of clients reviewed after limits were applied	41	82	289	39

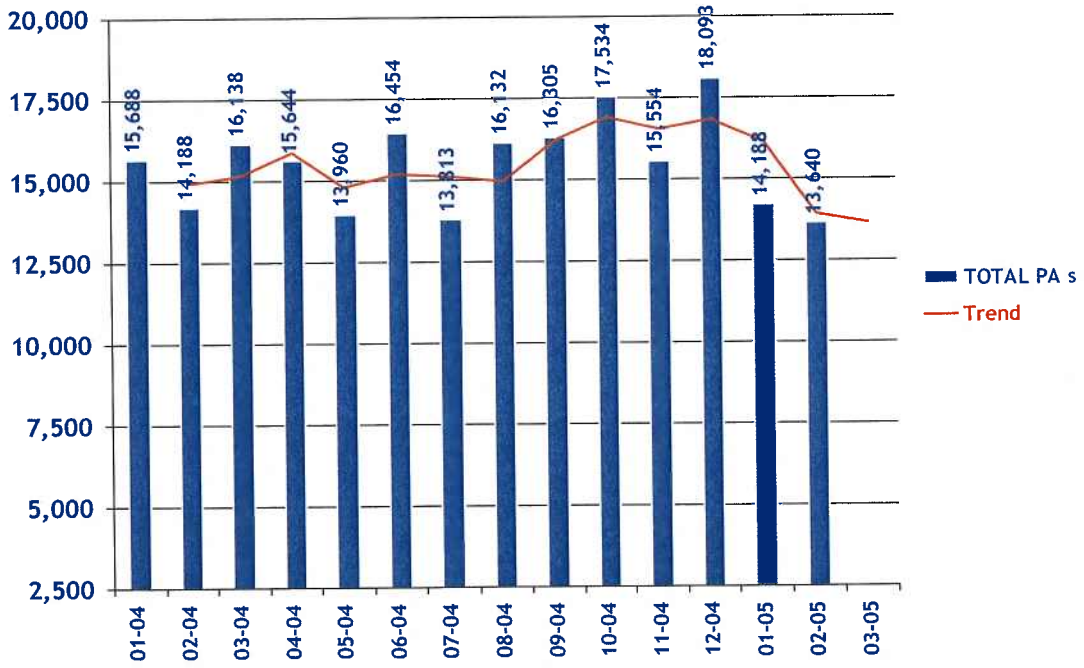
LETTERS			
Prescribers		**Pharmacies**	
Sent	**Responded**	**Sent**	**Responded**
165	48	37	12

PRIOR AUTHORIZATION ACTIVITY REPORT
February 2005



PHARMACY Management consultants

PRIOR AUTHORIZATION REPORT
February 2004 - February 2005



PHARMACY Management consultants

Date Processed: Wednesday, March 02, 2005

Activity Audit for

February 01 2005 Through February 28 2005

Date	Antiulcers app.	Antiulcers den.	Anxiolytic/ Hypnotics app.	Anxiolytic/ Hypnotics den.	Antihistamine app.	Antihistamine den.	Growth Hormones app.	Growth Hormones den.	Stimulant app.	Stimulant den.	Nsaids app.	Nsaids den.	ACE Inhibitors app.	ACE Inhibitors den.	HTN Combos app.	HTN Combos den.	Calcium Channel Blockers app.	Calcium Channel Blockers den.	Plavix app.	Plavix den.	ARB app.	ARB den.	Anti-depressants app.	Anti-depressants den.	Daily Total
App.	15		3641		964		39		1014		104		41		8		99		740		15		171		
Den.		5		318		355		1		218		141		60		4		122		113		9		81	
Average Length of Approvals in Days	48		93		92		157		217		337		189		94		307		277		247		140		

Changes to existing PA's	852
Total (Previous Year)	14188

*** Denial Codes**

762 = Lack of clinical information	10.36%
763 = Medication not eligible	2.21%
764 = Existing PA	5.60%
772 = Not qualified for requested Tier	6.62%
773 = Requested override not approved	11.32%

SUPER PA's

Early Refill Attempts	53322
Dosing Change	539
Lost/Broken Rx	99
Stolen	38
Other	161
Wrong D.S. on Previous Rx	97
Quantity vs. Days Supply	350
Brand	225
– Approved	91
– Denied	63

Monthly Totals

	Number	Percent of Total
Approved	8066	59.13%
Additional PA's	96	0.70%
SUPER PA's	1509	11.06%
Emergency PA's	0	0.00%
Duplicates	537	3.94%
Incompletes	1665	12.21%
Denied *	1767	12.95%
Total	13640	100.00%

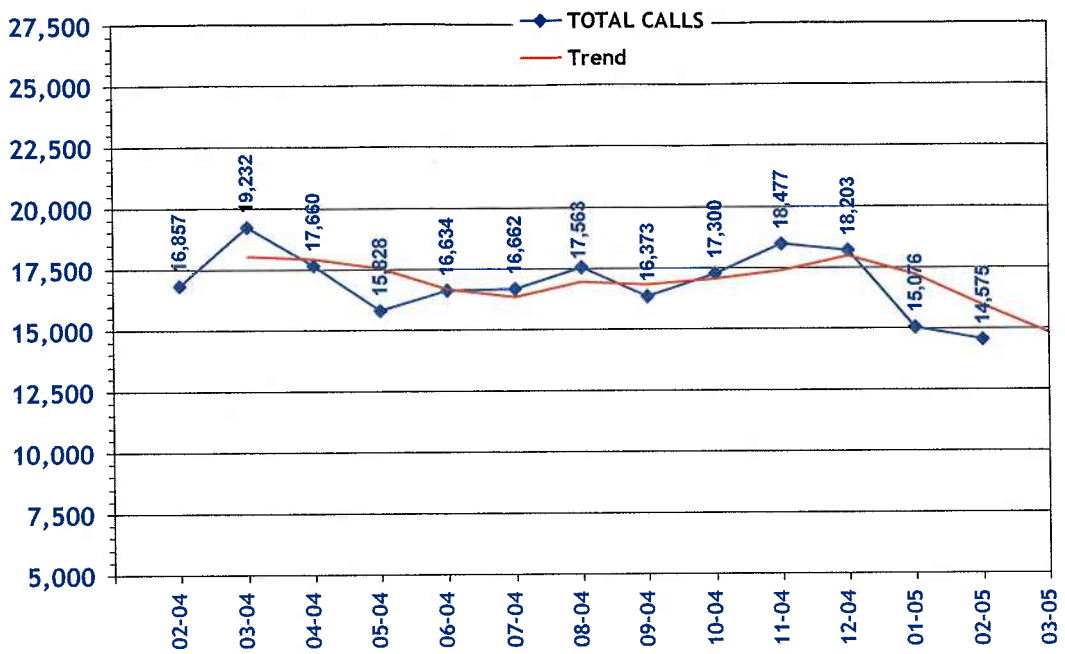
Daily Average of 568.33 for 24 Days

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

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

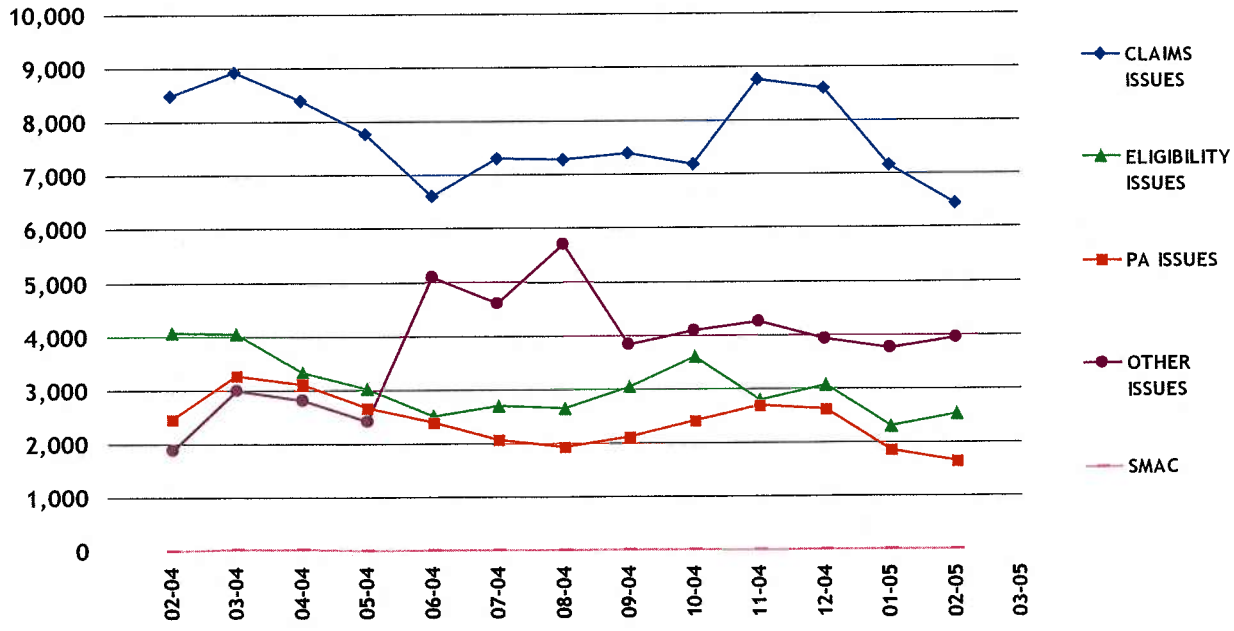
Incompletes: Missing necessary information (NDC, SIG, Diagnosis, etc.)

CALL VOLUME MONTHLY REPORT
February 2004 - February 2005



PHARMACY Management Consultants

CALL VOLUME ISSUES
February 2004 - February 2005



PHARMACY Management Consultants

APPENDIX C

Vote to Prior Authorize LUNESTA™ (eszopiclone)

Oklahoma Medicaid
March 2005

Comparison of LUNESTA™, Ambien®, and Sonata®[1-3]

	LUNESTA™	Ambien®	Sonata®
Not indicated for clients under 18	X	X	X
Dosage adjustment for hepatic impairment	X	X	X
Dosage adjustment in older population	X	X	X
Dosage adjustment with renal impairment			
Sleep Onset	X	X	X
Sleep Duration	X	X	
Sleep Maintenance	X	X	
Renal Excretion	X	X	
Active Metabolites	X		
Tmax affected by food	X	X	X
Contraindications			
Schedule IV	X	X	X
Short term use*		X	X
Long term use*	X		

*All sleep medications recommend limited use for 7-10 days and a re-evaluation before continued use.

Clinical Trials of LUNESTA™ (eszopiclone)

2,700 patients participated in the clinical development program (Phases I-III).[4]

In placebo-controlled clinical effectiveness studies involving approximately 2,120 patients, approximately 1,550 were exposed to LUNESTA™.[4]

Studies assessed safety and efficacy for treatment of insomnia in adult (21-64 years) and elderly (65-86 years).[4]

Completed studies:[4]

- 16 - Phase I studies (n=593) drug interaction and special populations.
- 2 - Phase II studies (n=25) assess next-day residual effects in healthy subjects and those with chronic insomnia.
- 1 - Phase III study in transient insomnia (n=436) using First Night Effect Model in healthy subjects.
- 3 - Phase III studies (n=1,164) in adults with chronic, primary insomnia.
- 2 - Phase III studies (n=526) elderly patients with chronic, primary insomnia.

At the recommended adult dose of 2-3mg and the elderly dose of 1-2mg, the trials showed a significant decrease in sleep latency and improved measures of sleep maintenance (objectively-wake time after sleep onset and subjectively-total sleep time) and no evidence of tolerance or rebound insomnia. [1]

The most common adverse event associated with eszopiclone is unpleasant taste. [5]

LUNESTA™ was approved in mid-December 2004 and was expected to be available in early January 2005. However, there has been a delay in the drug's availability and it is now expected to be available in March 2005. [4]

The manufacturer is conducting additional Phase IIIB/IV studies of LUNESTA™ for the treatment of insomnia in women experiencing the hormonal changes due to perimenopause, in patients experiencing pain associated with rheumatoid arthritis, and a six- month, double-blind, placebo-controlled study in patients with chronic insomnia. [4]

Recommendations

The college of pharmacy has the following recommendation:

- Include LUNESTA™ in prior authorization category with anxiolytics and hypnotics.
- Place quantity limits on LUNESTA™: 30 units for a 30 day supply. Currently quantity limits are in place for Ambien® and Sonata®.

Summary of LUNESTA™ Studies[5-9]

Description	Study Objectives	Population	Drug(s) tested/ Regimens	Number of Subjects (M/F)	Treatment Duration	Conclusion
Randomized, double-blind, placebo controlled	evaluate efficacy and safety of ESZ in First Night Effect of transient insomnia	healthy males and females	single dose ESZ 2mg or 3 mg	n=293	one night	ESZ showed improvements in sleep onset, maintenance (including number of awakenings) quality and reduced morning sleepiness.
Randomized, double-blind, placebo controlled	evaluate efficacy and safety of ESZ in elderly patients with chronic insomnia	patients 65-85 years old diagnosed with primary insomnia	ESZ n=136 PBO n=128	n=264	2 weeks	ESZ 2mg produced consistent statistically significant improvement in both patient-reported measure of sleep (onset and maintenance) and Polysomnography (PSG). Reduced daytime napping and improvements in some QoL domains.
Randomized, double-blind, multi-center, placebo-controlled, followed by 2 nights of single-blind placebo	assess the efficacy and safety of ESZ in adults with chronic primary insomnia	adults	PBO ESZ 2 or 3mg	n=308	6 weeks	Compared to PBO, 3mg dose showed improvements in all areas (time to sleep onset, total sleep and efficiency, maintenance enhanced quality and depth of sleep). 2mg showed improvements in all areas except sleep maintenance. No evidence of tolerance or rebound insomnia or detrimental effects on next-day psychomotor performance using the Digit-Symbol Substitution Test (DSST).
6-month open-label extension phase of previous 6 month, double-blind	long-term efficacy and safety	M/F aged 21-64 sleeping no more than 6.5 hours per night and/or taking longer than 30 minutes to fall asleep	PBO n=111 ESZ n=360 3mg	n=471	6 months	12 months of continued therapy with 3mg ESZ provided and maintained sustained improvement in patient-reported sleep and daytime functioning, was well tolerated and showed no evidence of tolerance or withdrawal.

References

1. LUNESTA™. NDA 21-476 Approved Labeling Test. December 15, 2004.

2. Ambien® package insert.

3. Sonata® package insert.

4. Preliminary Results Show Improvement for Insomnia Patients with Co-Existing Depression Who Were Treated with Sepracor's LUNESTA™ [PR Newswire] Release Date: 1/12/2005.

5. Zammit GK, McNabb L, Caron J, Amato D and Roth T. Efficacy and safety of eszopiclone across 6-weeks or treatment for primary insomnia. *Curr Med Res Opin.* 2004;20(12)1917-1991.

6. Rosenberg R, Jamieson A, Caron J, Roth T. Eszopiclone (ESZ), A novel non-benzodiazepine anti-insomnia agent: efficacy and safety in a model of transient insomnia [Abstract]. *Sleep*. 2002;45:A68-69.

7. Roth T. Krystal A, Walsh J, Roehrs T, Wessel T, Caron J. Twelve months of nightly eszopiclone treatment in patients with chronic insomnia: assessment of long-term efficacy and safety. *Sleep*. 2004;27(suppl.):A260.

8. Erman M, Rosenberg R, Caron J. Polysomnographic and patient-reported evaluation of the efficacy and safety of eszopiclone in elderly subjects with chronic insomnia. *Sleep*.2004;27(suppl.):A257.

9. General Summary for LUNESTA™ (eszopiclone) Tablets.

APPENDIX D

Vote to Prior Authorize Bladder Control Drugs

Oklahoma Medicaid
March 2005

Available FDA Approved Treatment

Drug	How Supplied	Indications
Flavoxate (Urispas®)	100 mg Tablet	Symptomatic relief of dysuria, nocturia, suprapubic pain, urgency, and incontinence due to detrusor instability and hyper-reflexia in elderly with cystitis, urethritis, urethrocystitis, urethrotrigonitis, and prostatitis
Hyoscyamine (Anaspaz®, Cystospaz®, Cystospaz-M®)	0.15 mg Tablet (Cystospaz®), 0.375 mg Capsule, timed release (Cystospaz-M®)	Adjunctive therapy for neurogenic bladder/bowel*
Oxybutynin (Ditropan®, Ditropan XL®, Oxytrol®)	5 mg Tablet (Ditropan®), 5 mg/5 mL syrup (Ditropan®) 5 mg, 10 mg, 15 mg Tablet, extended release (Ditropan® XL): Transdermal system (Oxytrol®): 3.9 mg/ [39 cm^2; total oxybutynin 36 mg]	Antispasmodic for neurogenic bladder (urgency, frequency, urge incontinence) and uninhibited bladder
Tolterodine (Detrol®, Detrol LA®)	1 mg, 2 mg Tablet (Detrol®) 2 mg, 4 mg Caps, extended release (Detrol LA®)	Treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence
Trospium (Sanctura®) (App'd 5/04)	20 mg Tablet - EAC $1.31	Treatment of overactive bladder with symptoms of urgency, incontinence, and urinary frequency
Solifenacin (Vesicare®) (App'd 11/04)	5 mg, 10 mg tablet	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency
Darifenacin (Enablex®) (App'd 12/04)	7.5 mg, 15 mg tablet, extended release	Management of symptoms of bladder overactivity (urge incontinence, urgency, and frequency)

*Also used as adjunctive therapy for peptic ulcers, irritable bowel; treatment of infant colic, GI tract disorders caused by spasm; to reduce rigidity, tremors, sialorrhea, and hyperhidrosis associated with parkinsonism; as a drying agent in acute rhinitis.

Warnings/Side Effects

Drug	Contraindication	Caution	Side Effect
Flavoxate (Urispas®)	Hypersensitivity to flavoxate; pyloric or duodenal obstruction; GI hemorrhage; GI obstruction; ileus; achalasia; obstructive uropathies of lower urinary tract (BPH)	May cause drowsiness, vertigo, and ocular disturbances; administer cautiously in patients with suspected glaucoma	Tachycardia, palpitations, drowsiness, confusion (especially in the elderly), nervousness, fatigue, vertigo, headache, hyperpyrexia, rash, urticaria, constipation, nausea, vomiting, xerostomia, dry throat, dysuria, leucopenia, increased intraocular pressure, blurred vision
Hyoscyamine (Anaspaz®, Cystospaz®, Cystospaz-M®)	Hypersensitivity to belladonna alkaloids or any component of the formulation; glaucoma; obstructive uropathy; myasthenia gravis; obstructive GI tract disease, paralytic ileus, intestinal atony of elderly or debilitated patients, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis; unstable cardiovascular status in acute hemorrhage, myocardial ischemia	Use with caution in children with spastic paralysis. Use with caution in patients with autonomic neuropathy, coronary heart disease, CHF, cardiac arrhythmias, prostatic hyperplasia, hyperthyroidism, hypertension, chronic lung disease, renal disease, and hiatal hernia associated with reflux esophagitis. Use with caution in the elderly, may precipitate undiagnosed glaucoma and/or severely impair memory function (especially in those patients with previous memory problems). May increase the risk of heat prostration.	Palpitations, tachycardia, ataxia, dizziness, drowsiness, headache, insomnia, mental confusion/excitement, nervousness, speech disorder, urticaria, lactation suppression, bloating, constipation, dry mouth, loss of taste, nausea, vomiting, impotence, urinary hesitancy, urinary retention, weakness, blurred vision, cycloplegia, increased ocular tension, mydriasis, allergic reactions, decreased sweating
Oxybutynin (Ditropan®, Ditropan XL®, Oxytrol®)	Hypersensitivity to oxybutynin or any component of the formulation; untreated glaucoma; partial or complete GI obstruction; GU obstruction; urinary retention; megacolon; toxic megacolon	Use with caution in patients with urinary tract obstruction, angle-closure glaucoma (treated), hyperthyroidism, reflux esophagitis (including concurrent therapy with oral bisphosphonates or drugs which may increase the risk of esophagitis), heart disease, hepatic or renal disease, prostatic hyperplasia, autonomic neuropathy, ulcerative colitis (may cause ileus and toxic megacolon), hypertension, hiatal hernia, myasthenia gravis, ulcerative colitis, or intestinal atony. The extended release formulation consists of drug within a nondeformable matrix; following drug release/absorption, the matrix/shell is expelled in the stool. The use of nondeformable products in patients with known stricture/narrowing of the GI tract has been associated with symptoms of obstruction. Caution should be used in elderly due to anticholinergic activity (eg, confusion, constipation, blurred vision, and tachycardia). May increase the risk of heat prostration.	**Oral:** Dizziness, somnolence, xerostomia, constipation, Urination impaired, headache, confusion, insomnia, nervousness, dry skin, skin rash, nausea, dyspepsia, abdominal pain diarrhea, flatulence, gastrointestinal reflux, taste perversion, Post-void residuals increased, urinary tract infection, weakness, blurred vision, dry eyes, rhinitis, dry nasal and sinus membranes. **Transdermal:** Application site reaction, pruritus, xerostomia, diarrhea, constipation, dysuria, erythema, vesicles, rash, vision changes

Drug	Contraindication	Caution	Side Effect
Tolterodine (Detrol®, Detrol LA®)	Hypersensitivity to tolterodine or any component of the formulation; urinary retention; gastric retention; uncontrolled narrow-angle glaucoma; myasthenia gravis	Use with caution in patients with bladder flow obstruction, may increase the risk of urinary retention. Use with caution in patients with gastrointestinal obstructive disorders (ie, pyloric stenosis), may increase the risk of gastric retention. Use with caution in patients with controlled (treated) narrow-angle glaucoma; metabolized in the liver and excreted in the urine and feces, dosage adjustment is required for patients with renal or hepatic impairment. Patients on CYP3A4 inhibitors require lower dose. Safety and efficacy in pediatric patients have not been established.	Dry mouth (35%; extended release 23%), Chest pain, headache (7%; extended release 6%), somnolence (3%; extended release 3%), fatigue (4%; extended release 2%), dizziness (5%; extended release 2%), anxiety (extended release 1%) dry skin, abdominal pain (5%; extended release 4%), constipation (7%; extended release 6%), dyspepsia (4%; extended release 3%), diarrhea, weight gain, dysuria (2%; extended release 1%), arthralgia, abnormal vision (2%; extended release 1%), dry eyes (3%; extended release 3%), bronchitis, sinusitis (extended release 2%)
Trospium (Sanctura®) (App'd 5/04)	Hypersensitivity to trospium or any component of the formulation; urinary retention; gastric retention; uncontrolled narrow-angle glaucoma; myasthenia gravis	Use with caution in patients with bladder flow obstruction, may increase the risk of urinary retention. Use with caution in patients with GI obstructive disorders (eg, pyloric stenosis); may increase the risk of gastric retention. Use with extreme caution in patients with controlled (treated) narrow-angle glaucoma. Use with caution in renal dysfunction; dosage adjustment is required. Monitor closely when used concurrently with other medications that are eliminated by active tubular secretion (eg, digoxin, procainamide, pancuronium, morphine vancomycin, metformin, tenofovir); may increase levels of trospium and/or the coadministered drug. Use caution in Alzheimer's patients. Use caution in patients with moderate-to-severe hepatic dysfunction. Use caution in the elderly (≥ 75 years); increased anticholinergic side effects are seen. Safety and efficacy in pediatric patients have not been established.	Xerostomia, tachycardia, headache, fatigue, dry skin, constipation, abdominal pain, dyspepsia, flatulence, abdominal distention, vomiting, dysgeusia, urinary retention, dry eyes, blurred vision, angioneurotic edema

Drug	Contraindication	Caution	Side Effect
Solifenacin (Vesicare®) (App'd 11/04)	Contraindicated in patients with urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, and in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.	Use with caution in patients with clinically significant bladder outflow obstruction due to risk of urinary retention. Use with caution in patients with decreased gastrointestinal motility. Use with caution in patients being treated for narrow-angle glaucoma. Use with caution in patients with reduced renal function. Doses of VESIcare greater than 5 mg are not recommended in patients with severe renal impairment (CLcr < 30 mL/min). Use with caution in patients with reduced hepatic function. Doses of VESIcare greater than 5 mg are not recommended in patients with moderate hepatic impairment (Child-Pugh B). VESIcare is not recommended for patients with severe hepatic impairment (Child-Pugh C).	Dry Mouth, constipation, nausea, dyspepsia, upper abdominal pain, vomiting, urinary tract infection, influenza, pharyngitis, dizziness, blurred vision, dry eyes, urinary retention, edema lower limb, fatigue, depression, cough, hypertension
Darifenacin (Enablex®) (App'd 12/04)	Hypersensitivity to darifenacin or any component of the formulation; uncontrolled narrow-angle glaucoma; paralytic ileus, GI or GU obstruction	Use with caution with hepatic impairment; dosage limitation is required in moderate hepatic impairment (Child-Pugh Class B). Not recommended for use in severe hepatic impairment (Child-Pugh Class C). Use with caution in patients with clinically-significant bladder outlet obstruction, prostatic hyperplasia (nonobstructive), or urinary retention. Use caution in patients with decreased GI motility, constipation, hiatal hernia, reflux esophagitis, and ulcerative colitis. Use caution in patients with myasthenia gravis. In patients with controlled narrow angle glaucoma, darifenacin should be used with extreme caution and only when the potential benefit outweighs risks of treatment. Safety and efficacy have not been established in pediatric patients.	Xerostomia, constipation Headache, dizziness, dyspepsia, abdominal pain, nausea, diarrhea, urinary tract infection, asthenia, dry eyes, flu-like syndrome, accidental injury, abnormal vision, acute urinary retention, arthralgia, back pain, bronchitis, dry skin, flu-like syndrome, hypertension, pain, peripheral edema, pharyngitis, rash, rhinitis, sinusitis, weight gain, urinary tract disorder, vaginitis, vomiting

Geriatric Effects

Flavoxate: Caution should be used in the elderly due to anticholinergic activity (eg, confusion, constipation, blurred vision, and tachycardia).

Hyoscyamine: Avoid long-term use. The potential for toxic reactions is higher than the potential benefit, elderly are particularly prone to CNS side effects of anticholinergics (eg, confusion, delirium, hallucinations). Side effects often occur before clinical response is obtained. Generally, not recommended because of side effects.

Oxybutynin: Caution should be used in the elderly due to anticholinergic activity (eg, confusion, constipation, blurred vision, and tachycardia). Start with lower doses. Oxybutynin may cause memory problems in the elderly. A study of 12 health volunteers with an average age of 69 showed cognitive decline while taking the drug (*J Am Geriatr Soc*, 1998, L46:8-13).

Tolterodine: Safety and efficacy in patients >64 years was found to be similar to that in younger patients; no dosage adjustment is needed based on age

Trospium: In studies, the incidence of anticholinergic side effects was higher in patients ≥75 years of age as compared to younger adults.

Solifenacin: No dosage adjustment is needed based on age.

Darifenacin: No dosage adjustment is needed based on age.

Recommendations

The College of Pharmacy recommends prior authorizing this class of drugs utilizing the PBPA program. Authorization will be given for 1 year.

- Tier-1 – Detrol®, oxybutynin, hyoscyamine*
- Tier-2 - Detrol LA®, Ditropan XL®, flavoxate, Oxytrol®, Sanctura®, VESIcare®, Enablex®

*hyoscyamine can be used as adjuvant therapy only; by itself, it will not count toward a tier-2

Prior authorization criteria:

In order to get a tier-2 drug, client must meet one of the following criteria:

- tier-1 drug failure (i.e. inadequate clinical response or adverse effect), or
- contraindication to the tier-1 drugs, or
- already stabilized on the tier-2 drug, or
- using the tier-2 drug for a unique indication which the tier-1 drugs lack.

DRAFT

Dear Nursing Home Provider

OHCA will be initiating Product Based Prior Authorization on bladder control drugs. Currently available drugs will be divided into the following tiers:

- Tier-1 – Detrol®, oxybutynin, hyoscyamine*
- Tier-2 - Detrol LA®, Ditropan XL®, flavoxate, Oxytrol®, Sanctura®, VESIcare®, Enablex®

*hyoscyamine can be used as adjuvant therapy only; by itself, it will not count toward a tier-2

Please remind staff involved in direct patient care that the following symptoms are some of the most commonly associated side effects of these drugs:

dry mouth, constipation, dizziness, confusion, weakness, blurred vision , somnolence, impaired urination, urinary tract infection, headache, confusion, and insomnia.

Because these side effects can lead to noncompliance, falls, and other adverse outcomes, particularly in the elderly, it is imperative that they be reported and that steps are taken to alleviate them.

Patients who are stabilized on a Tier-2 medication will be allowed to continue their current treatment without prior authorization.

New Tier-2 drug prescriptions will be subject to the following criteria prior to approval for payment:

- tier-1 drug failure (i.e. inadequate clinical response or adverse effect), or
- contraindication to the tier-1 drugs , or
- need for the tier-2 drug for a unique indication which the tier-1 drugs lack.

Thank you for your continued service to Oklahoma's Medicaid clients. If you have questions, please call the Pharmacy Help Desk at 405-271-6349 or 1-800-831-8921.

Notes:

- Letters could be sent 30 days in advance of the policy going into effect
- Manufacturers will have the opportunity to participate in the supplemental rebate prior to the policy going into effect, and the drugs listed as Tier 1 and 2 will reflect the status after rebate participation

APPENDIX E

QUANTITY LIMITATIONS FOR OKLAHOMA MEDICAID FEE FOR SERVICE

March 2005

The following quantity limits are recommended to insure that prescription claims are submitted to Oklahoma Medicaid using industry standard billing units. The use of standard billing units decreases overpayment of pharmacy claims, auditing and recoupment processes, and federal drug rebate disputes. The standard billing units are developed by the National Council for Prescription Drug Programs (NCPDP). The NCPDP version 5.1 code set is required for all pharmacy transactions to maintain HIPAA compliance.

Drug	Quantity Limits	Comments
Darbopoetin alfa (Aranesp)	4 doses per 28 days	Recommended dosing is one injection weekly.
Anakinra (Kineret)	28 doses per 28 days	Recommended dosing is 100mg SC daily.
Enoxaparin (Lovenox)	60 doses per 30 days	Recommended dosing varies from daily to bid depending on indication.
Fondaparinux (Arixtra)	30 doses per 30 days	Recommended dose is once daily; duration of treatment varies depending on indication.
Filgrastim (Neupogen)	30 doses per 30 days	Recommended dosing is one injection daily.
Glatiramer (Copaxone)	30 doses per 30 days	Recommended dosing is one injection daily.
Interferon beta-1a (Rebif)	12 doses per 30 days	Recommended dosing is one injection three times weekly.
Dalteparin (Fragmin)	30 doses per 30 days	Recommended dose is once daily; duration of treatment varies depending on indication.
Triamcinolone injection	10 mls per 7 days	Amount varies depending on strength of compounded product
Lindane shampoo and lotion	60 mls per 7 days	Recommended dose is one treatment one time using no more than 60 mls.

APPENDIX F

Antidepressant Product Based Prior Authorization Proposal

Oklahoma Medicaid

March 2005

Etiology & Diagnosis of Major Depressive Episode

The etiology of psychiatric illnesses such as depression is not yet fully understood. There is a 3-5 times increased risk of Major Depressive Disorder (MDD) among first degree relatives, which suggests a genetic predisposition. It has also been hypothesized that repetitive episodes of illness due to significant emotional, social, or environmental stressors cause dysfunction of the normal central nervous system (CNS) processes that regulate the balance of neurotransmitters. The resultant imbalances are via alterations in neurotransmitter synthesis, breakdown, and reuptake.[1] Although there are patho-physiological changes in the CNS, currently there are no reliable physiological tests available to diagnose MDD. In the early 1950's, the American Psychiatric Association compiled the first Diagnostic and Statistical Manual of Mental Disorders (DSM). Today the DSM criteria for the diagnosis of psychiatric conditions have become the standard used in clinical trials and practice guidelines for depression. The following are the diagnostic criteria for major depressive episode:

DIAGNOSTIC CRITERIA FOR MAJOR DEPRESSIVE EPISODE	
At least five of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms must be A or B.	
A. Depressed mood most of the day, nearly every day.	▪ Significant weight loss or weight gain when not dieting, or decrease or increase in appetite nearly every day ▪ Insomnia or hypersomnia nearly every day ▪ Psychomotor agitation or retardation nearly every day; observable by others ▪ Fatigue or loss of energy nearly every day ▪ Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day
B. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.	▪ Diminished ability to think or concentrate, or indecisiveness, nearly every day ▪ Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

Treatment of Major Depressive Disorder

Treatment is primarily based upon emergent findings from clinical trials and recommendations agreed upon by consensus within the psychiatry community. There are several effective treatments for MDD such as pharmacotherapy, psychotherapy, the combination of pharmacotherapy plus psychotherapy, or electroconvulsive therapy (ECT).[2] Existing pharmacologic agents used in the treatment of depressive disorders act by influencing the level of certain neurotransmitters in the brain, mainly serotonin, norepinephrine, and dopamine.

The American Psychiatric Association (APA) recommends three phases in the treatment of major depressive episodes.[3]

1. The first phase is the acute phase in which pharmacologic therapy is recommended with or without psychotherapy unless ECT is planned. This phase includes the initiation, titration, and assessment of response to therapy.
2. The continuation phase is the six months following remission in which patients that were treated with antidepressant medications in the acute phase should be maintained on these agents at the stabilized dose to prevent relapse.
3. The final phase in treatment is to determine, by using patient risk factors, whether to maintain the patient on pharmacologic therapy or discontinue treatment. If discontinuation is appropriate then tapering the dose is the best approach to avoid withdrawal symptoms.

Pharmacologic Treatment of Major Depressive Disorder

Although the APA guidelines for treatment of depression do not recommend a specific class of antidepressant, there is a general consensus among clinical psychiatrists that SSRIs are viewed as the first line option for treatment of MDD. For decades, tricyclic anti-depressants (TCAs) were the most commonly prescribed class of antidepressants followed by monoamine oxidase inhibitors (MAOIs). Currently the most commonly prescribed class of antidepressants is the selective serotonin re-uptake inhibitors (SSRIs) due to their more favorable side effect profile.[4] The dual acting antidepressants are relatively new and their place in therapy is emerging as this class is utilized and more clinical data are made available.

Selective Serotonin Reuptake Inhibitors

- SSRIs are selective inhibitors of synaptosomal serotonin reuptake in the brain with a high degree of potency and specificity for the serotonin receptor.
- The most common adverse effects are nausea, somnolence, insomnia, restlessness, asthenia, dyspepsia, and sexual side effects.
- Potentially serious adverse effects are rare with this class of medication and include hyponatremia, activation of mania/hypomania, and seizures.
- Side effects occur upon initiation of the drug and certain effects will decline over time. However, the antidepressive effect may take 3-4 weeks.[5] To decrease side effects, it is recommended to start at half the recommended dose and titrate up to the effective dose as tolerated.
- SSRI's are currently considered first line therapy due to their low incidence of serious adverse effects and safety in overdose compared to TCAs.

Tricyclic Antidepressants

- Tricyclic antidepressants block the reuptake of both norepinephrine and serotonin in the central nervous system. Secondary amines such as desipramine, nortriptyline, and protriptyline, as well as amoxapine and maprotiline, are relatively selective inhibitors of the reuptake of NE.
- The most common adverse effects are anticholinergic effects, sedation, and weight gain.
- Secondary amines, such as nortriptyline and desipramine, are preferred due to less sedation and fewer anticholinergic effects.
- Potentially serious adverse effects include orthostatic hypotension, syncope, hypertension, arrhythmias, AV conduction changes, heart block palpitations, hematologic dyscrasias, and seizures.

- Medication should be initiated at a low dose and titrated within a few days to the optimal effective dose.
- Clinical trials in children and adolescents suggest efficacy of TCAs is at most mediocre, and is generally not recommended as a first line agent in this population.[6]
- Approximately one week's supply of medication may be lethal in overdose situations.

Monoamine Oxidase Inhibitors

- MAOIs block intracellular metabolism of norepinephrine, serotonin, and other biogenic amines, resulting in increased amine concentration in nerve terminals.
- The most common adverse effects are anticholinergic side effects, insomnia, anxiety, weight gain, and sexual side effects.
- Potentially serious adverse effects include liver inflammation, heart attack, stroke, and seizures.
- There are many pharmacologic agents, foods, and food products that must be avoided when taking MAOIs due to a severe reaction known as hypertensive crisis.
- Due to many dietary restrictions and potentially severe side effects, MAOIs are not considered initial agents of choice, and are often reserved for treatment resistant depression.

Review of Dual-Acting Anti-depressants

Mechanism of Action[7]

Some clinical reviews suggest that depression is associated with the alterations in 5-HT\NE levels and/or activity of neurotransmitter receptors.[8,9,10,11] However, depressed patients do not consistently present with these indicators. The dual-acting anti-depressants have a wide range of affinities for blockade of different monoamine transporters and neurochemical receptors. The selectivity of specific neurochemical targets renders these newer anti-depressants with more favorable side-effect profiles while treating specific symptoms of depression. Insufficient data exists to explain binding affinities and causal relationship to improved therapeutic outcomes.

Dual-acting Anti-depressants						
Mechanism	Duloxetine	Venlafaxine	Mirtazapine	Bupropion	Trazodone	Nefazodone
5HT Enhancement	√	√	√		√	
$5HT_{2A}$ Antagonism						√
NE Enhancement	√	√	√	√*		√
α_2 Antagonism			√			
α_1 Antagonism			√		√	√
H_1 Antagonism			√		√	
Muscarinic Antagonism			√			
DA Enhancement				√		

*Active metabolite noradreneric activity

Indications

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

FDA Indications and other Uses Based on Clinical Evidence[12]

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

+++ FDA approved ++ Positive placebo-controlled trial(s) + Positive open trial(s) only - No data or mixed findings

*Diabetic peripheral neuropathic pain

Pharmacokinetics and Bioavailability

- Generally, dosage adjustments should be considered in patients with hepatic or renal impairment.
- Regarding Duloxetine, it appears to be both a substrate and inhibitor of 2D6. This does not mean it inhibits its own metabolism. Duloxetine is a substrate of 1A2 and cigarette smoke may result in increased metabolism.[13,14] It is not recommended to use Duloxetine in patients with ESRD, hepatic impairment, and/or history of alcohol abuse.
- Nefazodone has been linked to life-threatening hepatic failure and should be reconsidered if clinical signs or symptoms suggest liver failure.
- Trazodone is primarily metabolized by the 3A4 hepatic pathway and has the potential of several drug interactions.[15]

	% protein-bound	T_{max} (hours)	Half-life (hours)	Major Metabolic Pathway; Route of Excretion
Duloxetine	90	6	12	1A2, 2D6; urine 70%
Venlafaxine	27	5.5	5	2D6; urine, 87%
Bupropion	88	3-5	21	2B6; urine 87%
Nefazodone	99	1	2-4	liver; urine
Trazodone	85-95	1-2	7-8	3A4; urine
Mirtazapine	85	2	20-40	1A2, 2D6, 3A4; urine, 75%

*Source: Lexi-Comp Online

Adverse Effects

The tolerability of older anti-depressants has limited their use and subsequently led to the development of more selective anti-depressants with more favorable side effect profiles. Ideally, the relief of symptoms of depression without adverse effects promotes long-term efficacy. It is estimated that 44% of those initiated on pharmacotherapy stop treatment after 3 months due to adverse effects.[16] Most studies have shown short-term tolerability but long-term tolerability plays a vital role in patient outcome and treatment adherence.[17] Newer and older anti-depressants did not differ in discontinuation rates but varied significantly in side-effects.[18]

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

*Source: Product Package Inserts[19,20,21,22,23,24]

Safety News

- The request for FDA-approval of an indication for stress urinary incontinence for duloxetine has been withdrawn by the manufacturer due to lack of clinical data.
- The United Kingdom has recently required a change in labeling for venlafaxine (Effexor®) to include a contraindication in patients with heart conditions or hypertension. Prescribing is permitted solely under the supervision of a licensed psychiatrist.

Warnings and Precautions[25,26,27,28,29,30,31]

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

Efficacy and Remission with Dual-Acting Anti-depressants:

The successful treatment of depression with older and newer anti-depressants has been shown with adequate diagnosis, treatment duration, and adherence to treatment regimen. The emergence of clinical challenges of treatment-resistant depression, discontinuation rates due to side effects and long-term remission has supported the need for alternative treatment approaches. Most anti-depressants have similar efficacy and time of onset (requiring at least 4 to 6 weeks to reach therapeutic benefit).[32] In a systematic review funded by the Agency for Healthcare Policy and Research (AHCPR) the newer anti-depressants were shown to be effective with similar efficacy compared to older anti-depressants.[33] With the lack of long-term clinical evidence supporting one agent over another, all anti-depressants should be considered using the clinical guidelines.

Novel therapies have been developed to treat both the emotional and physical symptoms associated with depression. Some evidence suggests a dual mechanism of action may provide relief of a broader range of symptoms. The idea of affecting multiple neurotransmitters is not a novel strategy. TCA's and MAOI's affect several neurochemical pathways but their use has been limited by side-effects. Regarding dual-acting anti-depressants, they have been shown to have a slightly quicker onset of action and a more favorable side-effect profile[34-35] but not increased efficacy.[36-37] Both dual-acting anti-depressants and SSRI's are considered to be as effective as TCA's and MAOI's.[38-39] As compared to the SSRI's, dual-acting anti-depressants have been shown to be similar in efficacy.[40] Selection tends to be a matter of side-effect profile, patient/provider preference and cost-effectiveness. Inconclusive evidence suggests added benefit in selection of one agent over another; therefore, further long-term studies are needed to develop new standards of care for depression.

Remission is defined as long-term resolution of depressive symptoms and is the ultimate goal of therapy. Secondary goals include increasing quality of life and decreasing the economic burden of

depression. Some evidence suggests dual-acting mechanisms may play a major role in long-term remission.[41] Although, a recent open-label study has shown venlafaxine is comparable to the SSRIs in terms of remission rates.[42] Very few long-term head-to-head trials are available comparing SNRIs with SSRIs. Further studies on remission are needed to address long-term efficacy with both newer and older anti-depressants.

Role of Anti-depressants in Diabetic Peripheral Neuropathy:

Diabetes mellitus is a major health concern associated with micro and macro vascular complications. Impaired glucose tolerance causes degradation of neural pathways resulting in somatic system dysfunctions. Consequently, loss of sensory nerve function may result from diabetic peripheral neuropathy (DPN). Clinical manifestations include burning, tingling, and numbness beginning with the lower extremities. The most common symptom presented by diabetic patients is somatic pain. Diabetic Peripheral Neuropathy Pain (DPNP) becomes the focus of symptom management. Glycemic control is the only therapy which can affect the natural course of DPNP[43]. Several pharmacologic treatments have been shown to be effective in treating DPNP which include anti-depressants, anticonvulsants, opioid-like medications and some topical therapies.

Non-pharmacologic

- Management of modifiable risk factors further decreases the incidence of developing DPN which include: smoking, high cholesterol, hypertension, glycemic control, body mass index[44, 45]
- Proper instruction in blood glucose monitoring, utilization of insulin and/or hypoglycemic medications and proper foot care help prevent DPN.

Pharmacologic

- Several clinical reviews and guidelines suggest tricyclic anti-depressants, newer anti-depressants (SSRI/SSNRI), anticonvulsants, opioid-like analgesics, anesthetics, opiates, and topical agents as the order of treatment selection.
- Pharmacologic treatment is highly individualized and should include consideration of patient co-morbidities, side-effect tolerability, and level of treatment adherence and must be properly titrated for adequate duration.

Pharmacologic Treatment Recommendations[46, 47, 48, 49]				
1st Line Medications →				
TCAs: Desipramine*, Nortriptyline*, Amitriptyline**, Clomipramine**, Imipramine**	**Anticonvulsants:** Gabapentin, Pregabalin#	**Opioid-like Analgesic:** Tramadol	**Newer Antidepressants:** Duloxetine#, Bupropion, Venlafaxine	**Topical Agents:** 5 % Lidocaine Patch, 0.075 % Capasaicin
2nd Line Medications →				
Anticonvulsants: Carbamazepine, Topiramate	**SSRIs:** Paroxetine, Sertraline	**Opiate:** Oxycodone cr		
Adjuvant or Alternative				
SSRIs: Citalopram	**Anticonvulsants:** Lamotrigine, Oxcarbazepine	**NSAIDS:** Ibuprofen, Sulindac	**Misc:** Alpha-lipoic Acid, Levodopa	**Newer Antidepressants:** Nefazodone

* Secondary Amines ** Tertiary Amines # FDA-approved DPNP

Further long-term comparative studies are needed to determine the safety and efficacy treatments for DPNP.

Duloxetine (Cymbalta) has received the first FDA-approved indication for treatment of Diabetic Peripheral Neuropathic Pain (DPNP).

Optimizing Therapeutic Outcomes:

Historically, much of the research and development surrounding the treatment of depression has evaluated both primary and secondary outcomes for the acute episodic treatment of depression. Chronic treatment of depression has been shown to assure remission and prevent relapse.[50] Primary outcomes assessed are response rates, discontinuation rates, and discontinuation rates due to side effects. Secondary outcomes assessed are quality of life, suicidality, and functional status. Adherence and compliance to treatment and recommended guidelines are essential to the success of treatment. As stated by APA and AHCPR, the gold standard is full remission and elimination of symptoms.

Minimal or No Response to Treatment

If there is not at least moderate improvement in depressive symptoms after 4-8 weeks the APA Guidelines suggests the following:[51]

1. Investigate the patient's adherence to treatment.
2. Consider drug interactions or sub-therapeutic dosing and alter the dose accordingly.
3. For partial responders at optimal dose, it is recommended to first extend the trial by 2-4 weeks. If severity does not allow for time, consider augmenting the therapy with a non-MAOI antidepressant medication from a different class or an adjuvant medication such as lithium, thyroid hormone, anticonvulsant, or psycho-stimulant.
4. For non-responders on moderate or low doses, it is recommended to increase the dose with proper monitoring of the patient. If there is still a lack of response, consider switching to a non-MAOI antidepressant in the same or different class.
5. If determined to be necessary at any time during treatment, consider adding, changing, or increasing the frequency of psychotherapy.
6. Switch to an MAOI antidepressant.
7. Institute electro-convulsive therapy.

Other Non-pharmacologic Options

- Herbal Therapy
- Phototherapy
- Aroma Therapy

Switching Antidepressants[52]

- Selection of alternative treatment may result from issues pertaining to tolerability, lack of efficacy, compliance, and/or cost issues of initial approach.
- Consideration of tapering and drug interactions should be addressed before switching therapy.
- Studies have shown that patients who initially fail on one SSRI may respond when switched to another SSRI. Medication may be switched with no washout period except in cases with fluoxetine due to the long half life of this drug.
- Switching from an SSRI to a TCA antidepressant has been evaluated in several trials which showed efficacy and may be considered as an effective option. One study showed switching

from a TCA to an SSRI antidepressant and vice versa to be equally efficacious.[53] Discontinuation effects may occur when stopping an SSRI so it is best to cross titrate.
- Any switch to or from an MAOI requires a 10-14 day washout period.

Augmentation and Combination Strategies[54]

- Augmentation strategy is based on combining an antidepressant medication with another agent possessing a different mechanism of action, or different neurotransmitter target, to elicit a synergistic effect. These include lithium, thyroid hormone, anticonvulsant, or psycho-stimulant. Of these, lithium has been demonstrated by clinical trials to be the most efficacious.
- Newer combination strategies include SSRIs with buspirone, pindolol, TCAs, Bupropion, α_2 antagonists, and atypical antipsychotics. These strategies are new and the safety and efficacy of the combination have not been conclusively demonstrated via randomized controlled clinical trials. The risk of serotonin syndrome increases whenever two serotonergic agents are combined.

Recommendations

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

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

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

* Brand-Name Override required where applicable.

** Bristol-Myer Squibb has discontinued marketing of brand name Serzone® due to possible link to hepatic toxicity.

*** Current SSRI tiers based on Supplemental Rebate participation.

Potential Economic Impact

Total Reimbursed for Antidepressants - 2nd Qtr FY '05

Class	Total Claims	Total Reimbursement
Tetracyclic Compounds	6,982	$ 202,449.31
MAO Inhibitors	14	$ 979.05
Modified Cyclics	10,902	$ 111.307.20
SSRI's	55,134	$ 4,027,596.17
Tricyclic Agents	11,725	$ 124,768.61
Misc. Antidepressants	15,110	$ 1,929,887.15
Total	**99,867**	**$ 6,396,987.49**

Client Demographics - 2nd Qtr FY '05

Table 1a. All Clients

Age	Female	Male	Totals
0 to 9	456	984	1,440
10 to 19	3,331	3,279	6,610
20 to 34	4,925	1,464	6,389
35 to 49	6,478	2,931	9,409
50 to 64	6,335	2,409	8,744
65 to 79	5,245	1,606	6,851
80 to 94	4,301	778	5,079
95 and Over	330	35	365
Totals	**31,401**	**13,486**	**44,887**

Table 1b. Clients in a Care Facility

Age	Female	Male	Totals
0 to 9	0	0	0
10 to 19	6	5	11
20 to 34	77	79	156
35 to 49	318	295	613
50 to 64	798	624	1,422
65 to 79	1,844	856	2,700
80 to 94	3,011	577	3,588
95 and Over	289	29	318
Totals	**6,343**	**2,465**	**8,808**

Table 1c. Waiver-Advantage Clients

Age	Female	Male	Totals
0 to 9	0	0	0
10 to 19	0	0	0
20 to 34	14	10	24
35 to 49	123	51	174
50 to 64	310	92	402
65 to 79	280	48	328
80 to 94	111	14	125
95 and Over	0	0	0
Totals	**838**	**215**	**1,053**

Market Analysis - 2nd Qtr FY '05

Table 2a. Product Cost Comparison

Product	EAC	SMAC	Per Diem*
Mirtazapine 7.5 mg	$2.25	N/A	$2.26
Mirtazapine 15 mg	N/A	$0.25	$0.23
Mirtazapine 30 mg	N/A	$0.36	$0.38
Mirtazapine 45 mg	N/A	$0.49	$0.50
Mirtazapine Solutab 15 mg	$2.29	$2.17	$2.28
Mirtazapine Solutab 30 mg	$2.35	$2.17	$2.48
Mirtazapine Solutab 45 mg	$2.51	N/A	$2.49
Remeron® 15 mg	$2.77	N/A	$2.22
Remeron® 30 mg	$2.86	N/A	$2.10
Remeron® 45 mg	$2.91	N/A	$2.00
Remeron® Solutab 15 mg	$2.54	N/A	$2.65
Remeron® Solutab 30 mg	$2.62	N/A	$2.65
Remeron® Solutab 45 mg	$2.79	N/A	$2.73
Nardil® 15 mg	$0.48	N/A	$3.11
Parnate® 10 mg	$0.74	N/A	$2.61
Nefazodone 50 mg	N/A	$0.27	$0.42
Nefazodone 100 mg	N/A	$0.21	$0.54
Nefazodone 150 mg	N/A	$0.33	$0.61
Nefazodone 200 mg	N/A	$0.27	$0.65
Nefazodone 250 mg	N/A	$0.30	$0.60
Serzone® 150 mg	$1.61	N/A	$0.65
Serzone® 200 mg	$1.64	N/A	$1.77
Trazodone 50 mg	N/A	$0.04	$0.08
Trazodone 100 mg	N/A	$0.29	$0.11
Trazodone 150 mg	N/A	$0.31	$0.24
Trazodone 300 mg	N/A	$3.06	$3.33
Desyrel® 150 mg	$2.88	N/A	$2.01
Desyrel® 300 mg	$5.12	N/A	$5.06
Cymbalta® 20 mg	$2.79	N/A	$3.71
Cymbalta® 30 mg	$3.14	N/A	$4.21
Cymbalta® 60 mg	$3.14	N/A	$3.23
Bupropion 75 mg	N/A	$0.21	$0.41
Bupropion 100 mg	N/A	$0.23	$0.63
Bupropion SR 100 mg	N/A	$1.07	$2.09
Bupropion SR 150 mg	N/A	$1.23	$2.57
Bupropion SR 200 mg	$3.32	N/A	$4.07
Wellbutrin® SR 100 mg	$1.86	N/A	$2.48
Wellbutrin® SR 150 mg	$1.99	N/A	$2.40
Wellbutrin® SR 200 mg	$3.69	N/A	$5.35
Wellbutrin® XL 150 mg	$2.82	N/A	$3.29
Wellbutrin® XL 300 mg	$3.73	N/A	$3.69
Effexor® 25 mg	$1.61	N/A	$2.85
Effexor® 37.5 mg	$1.66	N/A	$2.39
Effexor® 50 mg	$1.71	N/A	$2.95
Effexor® 75 mg	$1.81	N/A	$2.82
Effexor® 100 mg	$1.92	N/A	$3.74
Effexor® XR 37.5 mg	$2.68	N/A	$3.56
Effexor® XR 75 mg	$3.00	N/A	$4.23
Effexor® XR 150 mg	$3.27	N/A	$4.34

*Per Diem = Total Reimbursement – Dispensing Fees / Total Days

Table 2b. Market Share and Cost

Product	Total Claims	Total Days	Total Reimbursement	% Market Share	% Cost
Mirtazapine Tabs	6,173	202,031	$ 132,128.58	17.89%	5.89%
Remeron® Tabs	809	25,348	$ 70,320.73	2.24%	3.13%
Nardil® Tab	12	246	$ 814.06	0.02%	0.04%
Parnate® Tabs	2	60	$ 164.99	0.01%	0.01%
Nefazodone Tabs	296	9,816	$ 7,028.40	0.87%	0.31%
Serzone® Tabs	7	214	$ 340.85	0.02%	0.02%
Desyrel® Tabs	7	210	$ 542.55	0.02%	0.02%
Trazodone Tabs	10,581	363,366	$ 103,330.63	32.17%	4.60%
Cymbalta® Caps	695	23,661	$ 85,714.75	2.10%	3.82%
Bupropion Tabs	3,630	119,210	$ 271,186.73	10.56%	12.08%
Wellbutrin® Tabs	301	10,449	$ 50,732.35	0.93%	2.26%
Wellbutrin® XL	2,538	88,429	$ 320,821.77	7.83%	14.30%
Effexor®	871	28,479	$ 81,448.58	2.52%	3.63%
Effexor® XR	7,056	257,850	$ 1,119,421.58	22.82%	49.89%
Total	**32,978**	**1,129,369**	**$ 2,243,996.55**		

Anticipated Market Changes

- Wellbutrin® SR 200 mg first generic approved 12/3/2004. SMAC will be applied when appropriate.
- The patent for Effexor® tablets was first approved in December 1993 and expected to expire in December 2007.
- Cymbalta® was just approved in August 2004 and its current market share is expected to increase rapidly (see table 3).

Table 3	*Claims*	*Cost*
04-Sep	10	$556.79
04-Oct	6	$614.29
04-Nov	152	$19,558.15
04-Dec	537	$65,542.31

Potential Secondary Costs

Overall efficacy has been shown to be equal across the class, but drug selection requires individual patient history including, but is not limited to: other illness/disease risk factors, individual diet restrictions, and drug-drug interaction profiles.

Care will be taken to insure continuation of current therapy for clients stabilized on medications in this category. Current therapy is defined as use of the requested product with in the last 100 days, as evidenced by claims history or prescriber documentation.

Potential Administrative Costs

Based on a potential shift of proposed tier two products to a tier one product of 15%, it is estimated that approximately 5,000 to 9,300 petitions would be required. The proposed tier changes would affect approximately 20% of the total population for this category.

Previously, it has been estimated that total cost per petition to the healthcare system (including cost to physicians, pharmacists, and Medicaid program) is between $6.75 and $12.97. Total cost per petition to the healthcare system is estimated to be between $62,775 and $120,600 annually. Actual administrative cost to the program is projected to be less than $65,000.

Potential Program Savings

Potential savings to the program based on recommended tiers with a potential shift of 15% of market share from tier two to tier one is estimated to be $1,231,000 annually. This is the net ingredient cost savings after accounting for rebates and dispensing fees.

Total Potential Annual Savings

Potential Savings:	$1,231,000.00		$1,231,000.00
Potential Administrative Cost:	120,600.00		62,775.00
Total Potential Annual Program Savings:	**$1,110,400.00**	**to**	**$1,168,225.00**

---

1. **Rakel: Integrative Medicine, 1st ed.,** Copyright © 2003 Elsevier.

2. Williams JW, Jr, Mulrow CD, et al. **A systematic review of newer pharmacotherapies for depression in adults: Evidence report summary: clinical guideline, part 2.** Ann Intern Med, Vol 132(9). May 2000. 743-756

3. Website: **American Psychiatric Association**. Online. Internet. 2004. Available: http://www.psych.org/psych_pract/treatg/pg/Depression2e.book.cfm

4 Kroenke K, West SL, et al. Similar **Effectiveness of Paroxetine, Fluoxetine, and Sertraline in Primary Care.** JAMA 286(23) Dec 2001:2947-55.

5. Gill HS. **The treatment of depression with newer antidepressants: Pharmacology and efficacy versus clinical effectiveness.** J Managed Care Pharm 1999:57-62.

6. Ambrosini PJ. **A Review of Pharmacotherapy of Jajor Depression in Children and Adolescents.** Psychiatric Services, Vol 51(5). May 2000:627-33.

7 Tran PV, Bymaster FP, McNamara RK, Potter WZ. **Dual Monoamine Modulation for Improved Treatment of Major Depressive Disorder.** J Clin Psychopharmacology. 2003;23:78-86.

8 Gjerris A. **Do concentrations of neurotransmitters in lumbar CSF reflect cerebral dysfunction in depression?** Acta Psychiatr Scand Suppl. 1988;345:21-24.

9 Healy D, Leonard BE. Monoamine transport in depression: kinetics and dynamics. J Affect Disord 1987;12:91-103.

10 Garvey MJ, Tuason VB. **Urinary levels of 3-methoxy-4-hydroxy-phenylglycol predict symptom severity in selected patients with unipolar depression.** Psychiatry Res, 1996;62:171-177.

11 Raucoules D, Levy C, Azorin JM, et al. **Plasma levels of MHPG, HVA and total 5-HIAA in depression.** Preliminary study. Encephale 1992;18:611-616.

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

13 Sharma A, Goldberg MJ, Cerimele BJ. **Pharmacokinetics and safety of duloxetine, a dual-serotonin and norepinephrine reuptake inhibitor.** J Clin Pharmacol. 2000;40:161-167.

14 Skinner MH, Kuan H-Y, Pan A, et al. **Duloxetine is both an inhibitor and substrate of cytochrome P4502D6 in healthy volunteers.** Clin Pharmacol Ther. 2003;73:170-177.

15 **Lexi-Comp Online™**, http://www.crlonline.com. Lexi-Comp February 2005.

16 Lin EH, Von Korff M, Katon W, et al. **The role of the primary care physician in patients' adherence to antidepressant therapy.** Med Care 1995;33:67-74.

17 Cassano P, Fava M. **Tolerability issues during long-term treatment with antidepressants.** Ann Clin Psychiatry. 2004;16:15-25.

18 Williams JW, Mulrow CD, Chiquette E, Noel PH, Aguilar C, Cornell J. **A Systematic Review of Newer Pharmacotherapies for Depression in Adults: Evidence Report Summary.** Ann Intern Med. 2000;132:743-756.

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

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

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

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

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

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

25 **Lexi-Comp Online™**, http://www.crlonline.com. Lexi-Comp February 2005.

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

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

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

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

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

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

32 Quitkin FM, Rabkin JG, Markowitz JM, Stewart JW, McGrath PJ, Harrison W. **Use of pattern analysis to identify true drug response.** Arch Gen Psychiatry. 1987;44:259-264.

33. Williams JW, Jr, Mulrow CD, et al. **A systematic review of newer pharmacotherapies for depression in adults: Evidence report summary: clinical guideline, part 2.** Ann Intern Med, Vol 132(9). May 2000. 743-756

34 Montgomery SA. **Rapid onset of action of venlafaxine.** Int Clin Psycholpharmacol. 1995;10(suppl 2):21-27.

35 Nierenberg AA, Kremer C, Reimitz P. **Mirtazapine and the onset of antidepressant action: survival function analysis-response.** Eur Neuropsychopharmacol. 200;10(suppl 3):s265.

36 Anderson IM. **Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability.** J Affect Disord. 2000;58:19-36.

37 Freemantle N, Anderson IM, Young P. **Predictive value of pharmacological activity for the relative efficacy of antidepressant drugs: meta-regression analysis.** Br J Psychiatry. 2000;177:292-302.

38 Anderson IM, Tomenson BM. **Treatment discontinuation with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: a meta-analysis.** BMJ 1995;310:1433-1438.

39 Steffens DC, Krishnan KR, Helms MJ. **Are SSRIs better than TCAs? Comparison of SSRIs and TCAs: a meta analysis.** Depress Anxiety 1997;6:10-18.

40. Williams JW, Jr, Mulrow CD, et al. **A systematic review of newer pharmacotherapies for depression in adults: Evidence report summary: clinical guideline, part 2.** Ann Intern Med, Vol 132(9). May 2000. 743-756

41 Thase ME, Entsuah AR, Rudolph RL. **Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors.** Br J Psychiatry 2001;178(3):234-241.

42 Shelton CI. **Long-term management of major depressive disorder: are differences among antidepressant treatments meaningful?** J Clin Psychiatry. 2004;65 Suppl 17:29-33.

43 Diabetes Control and Complications Trial Research Group. **The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus.** N Engl J Med. 1993;329:977-86.

44 Tanenberg RJ, Pfeifer MA. **Neuropathy: The "forgotten" complication.** Diabetes Forecast 2000;53(12):56-60.

45 Swenson MR. **Diabetic peripheral neuropathy.** Curr Ther Endocrinol Metab 1997;6:458-461.

46 Duby JJ, Campbell RK, Setter SM, White JR, Rasmussen KA. **Diabetic neuropathy: An intensive review.** Am J Health-Syst Pharm. 2004;61:160-173.

47 Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, Bushnell MC, Farrar JT, Galer BS, Haythornthwaite JA, Hewitt DJ, Loeser JD, Max MB, Saltarelli M, Schmader KE, Stein C, Thompson D, Turk DC, Wallace MS, Watkins LR, Weinstein SM. **Advances in Neuropathic Pain: Diagnosis, Mechanisms, and Treatment Recommendations.** Arch Neurol. 2003;60:1524-1534.

48 Goodnick PJ, Mendosa L, Kumar A, Freund B, Devane CL. **Sertraline in Diabetic Neuropathy: Response and Biology.** Psychosomatic Medicine 2000;62:461-462.

49 Goodnick PJ, Breakstone K, Kumar A, Freund B, Devane CL. **Nefazodone in Diabetic Neuropathy: Response and Biology.** Psychosomatic Medicine 2000;62:599-600.

50 Gilbody S, Whitty P, Grimshaw J, Thomas R. **Educational and organizational interventions to improve the management of depression in primary care: a systematic review.** JAMA. 2003;289:3145-3151.

51. Website: **American Psychiatric Association**. Online. Internet. 2004. Available: http://www.psych.org/psych_pract/treatg/pg/Depression2e.book.cfm

52 Nelson JC. **Managing Treatment-Resistant Major Depression.** J Clin Psychiatry 2003;64 (Suppl 1)

53 Thase ME, Rush AJ, et al. **Double-blind Switch Study of Imipramine or Sertraline treatment of Antidepressant-Resistant Chronic Depression.** Archives of General Psychiatry. 59(3). Mar 2002:233-9.

54 Nelson JC. **Managing Treatment-Resistant Major Depression**. J Clin Psychiatry 2003;64 (Suppl 1)

APPENDIX G

Review of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and Cardiovascular/Thrombotic Events

Oklahoma Medicaid
March 2005

Introduction

The Oklahoma HealthCare Authority (OHCA) began Product Based Prior Authorization (PBPA) of the Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in 1999. Many changes have occurred in the NSAID PBPA category since its inception; perhaps the most notable occurred in 2002 after information was released regarding the VIGOR trial. Since that time, attempts have been made to limit clients to the minimum dosage necessary for the Cox-2 Inhibitors (Celebrex®, Vioxx®, Bextra®) due to concerns regarding the unknown extent of cardiovascular risk for these agents. After the voluntary removal of Vioxx® from the world-wide market in September 2004, the Drug Utilization Review (DUR) Board for OHCA requested additional research into the possible effects these medications may have had on the Oklahoma Medicaid clients.

Background of OHCA Pharmacy Program and PBPA Category

The DUR Board has established certain criteria for approval of NSAIDs, in the Oklahoma Medicaid fee-for-service pharmacy program. There are two tiers of drugs in this therapeutic classification. In order for a client to receive a tier-2 medication, the following criteria must be met.

(A) Tier-2 NSAIDs are approved if the individual has had two tier-1 NSAIDs within the current continuous NSAID therapy. This consists of all NSAID claims that have been sequentially acquired within 120 days of each other and provide medication coverage for the current date.
(B) After an individual has received tier-2 NSAID coverage, the individual has tier-1 and tier-2 coverage for the duration of their continuous NSAID therapy.
(C) Individuals who have not acquired an NSAID for 120 days will be considered to have discontinued their NSAID therapy and the previous approval will no longer be in effect.

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

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

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

Table 3. NSAIDS	
Tier 1	Tier 2
diclofenac ER (Voltaren XR®)	diclofenac sodium/misoprostol (Arthrotec®)
diclofenac potassium (Cataflam®)	celecoxib (Celebrex®)
diclofenac sodium (Voltaren®)	indomethacin (Indocin®)
etodolac (Lodine®)	naproxen sodium (Naprelan®)
etodolac ER (Lodine XL®)	piroxicam (Feldene®)
fenoprofen (Nalfon®)	valdecoxib (Bextra®)
flurbiprofen (Ansaid®)	lansoprazole/naproxen (Prevacid® NapraPAC™)
ibuprofen (Motrin®)	
ketoprofen (Orudis®)	
ketoprofen ER (Oruvail®)	
meclofenamate (Meclomen®)	
mefanamic acid (Ponstel®)	
meloxicam (Mobic®)	
nambutone (Relafen®)	
naproxen (Naprosyn®)	
naproxen sodium (Anaprox®)	
naproxen EC (Naprosyn EC®)	
oxaprozin (Daypro®)	
sulindac (Clinoril®)	
tolmetin (Tolectin®)	

Clients are subject to various limitations on their monthly number of prescription claims allowed based on their program. This number was 3, 5, or unlimited from January 2003 to December 2003, but the number was increased to 6, 13 or unlimited in January 2004. These limits mean that not all prescription medications which clients received are reflected in OHCA claims history. Furthermore, over-the-counter (OTC) NSAID products are not a covered benefit. Additionally, attempts were made to maintain clients on the lowest dose possible of all Cox-2 Inhibitors.

Recent National Events and Clinical Trials

The following list of recent events[1] prompted this review of the Oklahoma Medicaid client population by the DUR Board.

- September 30, 2004: voluntary withdrawal of rofecoxib (Vioxx®) from market after reviewing preliminary results from the Adenomatous Polyp Prevention on Vioxx (APPROVE) Study.
- December 09, 2004: addition of "boxed" warning to valdecoxib (Bextra®) strengthening the warning about the risk of life-threatening skin reactions. A bolded warning regarding the contraindication of the use of valdecoxib in patients undergoing coronary artery bypass graft (CABG) surgery was also added.
- December 17, 2004: release of new data from the National Cancer Institute (NCI)- sponsored Adenoma Prevention with Celecoxib (APC) trial demonstrated increased risk of cardiovascular events with celecoxib compared to placebo.
- December 20, 2004: early termination of the National Institute of Health (NIH)- sponsored Alzheimer's Disease Anti-inflammatory Prevention Trial

(ADAPT) after data revealed a 50% increase in heart attacks or strokes in patients treated with naproxen.

- February 16-18, 2004: Meeting of the FDA Advisory Committee on Cox-2 Inhibitors. Panel voted to keep Celebrex® (31-1) and Bextra® (17-13 -2) on the market. A vote to recommend returning Vioxx® to the market was 17-15. The committee agreed that Cox-2 Inhibitors pose risks of heart problems.
- February 18, 2004: Merck indicates it may return Vioxx® to the market.

Prior to the FDA Advisory Committee meeting in February the FDA had the following recommendations for use of available NSAIDs.

- Physicians prescribing Cox-2 Inhibitors should continue to weigh new information as it is available and determine the risks and benefits for individual patients.
- Consumers should use OTC pain medications only as labeled and contact their physician if long-term treatment is required.

Table 4. Review of Cox-2 Inhibitor Trials Related to Cardiovascular (CV) Events[2]

Trial	Drug (Dose)	Disease	CV Event Findings
ADAPT	celecoxib (400 mg qd); naproxen (200 mg bid)	Alzheimer's	Compared with placebo: celecoxib: no difference in rate of CV events; naproxen increased the risk of MI/stroke by 50%.
APC	celecoxib (400 mg or 800 mg qd)	Colorectal cancer	Compared with placebo (6 CV events): 400 mg of celecoxib daily increased risk of major adverse cardiac events by 2.5-fold (15 CV events): risk increase 3.4-fold (20 CV events) among pts on 800 mg.
APPROVe	rofecoxib (25 mg qd)	Colorectal cancer	At 18-months, rate of MI/stroke for rofecoxib vs. placebo; 3.5% vs. 1.9% ($P <$ .001).
CLASS (according to Mukherjee et al review)	celecoxib (400 mg bid) diclofenac (75 mg bid) ibuprofen (800 mg tid)	Arthritis	Rate of MI: celecoxib: 1.6 % diclofenac/ibuprofen: 1.2% in the diclofenac/ibuprofen group among those taking low-dose aspirin P=NS
PreSAP	celecoxib (400 mg qd)	Colorectal cancer	Compared with placebo, preliminary reports suggest use of celecoxib was not associated with increased risk of CV events.
VIGOR	rofecoxib (50 mg qd) naproxen (500 mg bid)	Arthritis	Any thrombotic CV event, rofecoxib vs naproxen: 45 events vs 19 events; $P <$ .002

Methods

The primary objective of this study was to determine if an increased rate of cardiovascular or thrombotic events occurred in Oklahoma Medicaid clients who were using either a traditional NSAID* or a Cox-2 Inhibitor. A secondary objective was to determine if an increase in hypertension diagnoses occurred with these agents.

Medical, hospital, and pharmacy claims for Oklahoma Medicaid clients were the only data available for review to determine any effects that may have been associated with the usage of NSAIDS to the study population. Due to a change of the contracted fiscal agent by OHCA which occurred January 1, 2003, it was decided to use this date as the beginning of the review period. The data prior to this date had different reference points. Therefore it was decided that the period for review would be January 2003 through June 2004.

In order to be included in the study population a client was required to be "continuously eligible for services" throughout the entire study period. Clients who were eligible less than the entire eighteen months were excluded. A total of 81,115 clients were identified as being continuously eligible during the study period. Medical and hospital claims for this population were searched for a diagnosis or procedure code during the time period of January 2003 through June 2003 to establish any pre-existing cardiovascular or thrombotic conditions (with the exception of hypertension) in the population. A total of 3,637 clients were identified as having potential cardiovascular or thrombotic conditions and were then removed from the study population. Clients with a diagnosis of hypertension during this time period were flagged for secondary review.

The remaining 77,518 clients were then divided into three groups based on their prescription claims history:

1. Clients with *Cox-2* prescription claims (regardless of NSAID usage),
2. Clients with *traditional NSAID* prescription claims, and
3. Clients with *no NSAID* prescription claims.

These three groups were then reviewed for cardiovascular/thrombotic events during the study period of July 2003 through June 2004. The following ICD-9 codes were used to identify a cardiovascular/thrombotic (CVT) event on medical or hospital claims for the reviewed clients:

- Myocardial Infarction: 410-412
- Angina: 413
- Chronic Ischemic Heart Disease, Other: 414
- Stroke: 433-434

---

* Traditional NSAIDs are defined as those NSAIDs not classified as a Cox-2 Inhibitor. NSAID includes both traditional and Cox-2 products.

- Transient Ischemic Attack: 435
- Late Effects of CVA: 438
- Thrombosis of Arteries: 444
- Thrombosis of Veins: 453

The three groups were then stratified by age comparable to the Center for Disease Control (CDC) 2002 table of age-adjusted percents of selected circulatory diseases among persons 18 years of age and over. This table is part of the Summary of Health Statistics published in July 2004. The report is the result of the health statistics from the 2002 National Health Interview Survey conducted by the U.S. Census Bureau.

The three groups were then reviewed to determine clients with a diagnosis of hypertension. Clients with a "new" diagnosis (diagnosis not present during the exclusion period) were then compared.

Finally, a Chi-Square test was performed on all groups to determine if a statistically significant difference existed.

Results

Table 1 includes the results of the data collected for the three reviewed groups. A total of 67,910 clients were determined to have no NSAID use during the reviewed time period. Of these clients, 1,522 (2.2 %) were found to have had an event. For the traditional NSAID group a total of 439 (5.4 %) out of 8,136 clients and for the Cox-2 group 191 (13.0%) out of 1,472 clients were determined to have a CVT event. The overall rate of events was 2.78 %. Because of the decreased number of patients with Cox-2 Inhibitor use and no CVT in the 0 to 17 year population, it was not possible to evaluate the frequencies by chi-square analysis. Only the rate of events which occurred in the 18 to 44 year population was found to be statistically significant with a p of 0.0001. In this group the rate of events for both Traditional NSAIDs and Cox-2 Inhibitors were at a higher rate than the overall population. It appears that the rate of cardiovascular/thrombotic events for traditional NSAIDs and Cox-2s become increasingly similar to the rate of events in the No NSAID group as age increased.

Table 2 includes the results of the secondary review of clients without a diagnosis of hypertension during the exclusion period. For the clients with no NSAID use the rate of occurrence was 3.5 %, for traditional NSAIDs the rate was 10.1 %, and for the Cox-2 group the rate was 18.5 %. Again, because of the decreased number of patients with Cox-2 Inhibitor use and no hypertension in the 0 to 17 year population, it was not possible to evaluate the frequencies by chi-square analysis. A statistically significant difference was noted in the 18 to 44 age group and the 45 to 64 age group. The chi-square analysis indicates that clients who are taking an NSIAD (whether a traditional or Cox-2) have a higher

probability of having hypertension and if no NSAID is involved the probability of hypertension decreases. It again appears that the rate of hypertension becomes similar as age increases.

Table 1. Rates of Cardiovascular/Thrombotic Events

Age	No NSAID (n=67,910)	Traditional NSAID (n=8,136)	Cox-2 (n=1,472)	Total (n=77,518)	*P*	CDC 2002[3]	
	# of Events (n)	*# of Events (n)*	*# of Events (n)*	*# of Events (n)*			
0-17	78 (46,570)	9 (2,515)	0 (26)	87 (49,111)	0.0848		
18-44	143 (10,434)	58 (2,577)	6 (133)	207 (13,144)	0.0001		
45-64	605 (6,263)	212 (1,975)	58 (496)	875 (8,734)	0.1687		
65-74	270 (1,845)	77 (497)	33 (249)	380 (2,591)	0.7152		
75+	426 (2,798)	83 (572)	94 (568)	603 (3,938)	0.6156		
	% of Events	*% of Events*	*% of Events*	*% of Events*		*% of Events*	
						CHD	*Stroke*
0-17	0.17	0.36	0.00	0.18		n/a	n/a
18-44	1.37	2.25	4.51	1.57		0.9	0.4
45-64	9.66	10.73	11.69	10.02		7.1	2.5
65-74	14.63	15.49	13.25	14.67		18.7	6.4
75+	15.23	14.51	16.55	15.31		24.5	11.1

Table 2. Rates of Presumed New Onset Hypertension (no ICD-9 present in exclusion period)

Age	No NSAID (n=67,910)	Traditional NSAID (n=8,136)	Cox-2 (n=1,472)	Total (n=77,518)	*P*	CDC 2002[1]
	# of Events (n)	*# of Events (n)*	*# of Events (n)*	*# of Events (n)*		
0-17	102 (46,570)	15 (2,515)	0 (26)	117 (49,111)	0.0008	
18-44	476 (10,434)	214 (2,577)	21 (133)	711 (13,144)	<0.0001	
45-64	982 (6,263)	383 (1,975)	113 (496)	1478 (8,734)	<0.0001	
65-74	350 (1,845)	99 (497)	41 (249)	490 (2,591)	0.5208	
75+	489 (2,798)	110 (572)	97 (568)	696 (3,938)	0.5581	
	% of Events	*% of Events*	*% of Events*	*% of Events*		*% of Events*
0-17	0.22	0.60	0.00	0.24		n/a
18-44	4.56	8.30	15.79	5.41		7.4
45-64	15.68	19.39	22.78	16.92		29.0
65-74	18.97	19.92	16.47	18.91		49.6
75+	17.48	19.23	17.08	17.67		51.8

Discussion

OHCA Client Cox-2 Inhibitor Utilization

Overall the total population of clients OHCA serves can be broken down into three categories: children and pregnant women (74 %); aged, blind, and disabled (20 %); and other (6 %)[4]. The number of clients with no NSAID use who were 17 or under was greater than any other category (69 %). The reverse is true for the Cox-2 Inhibitor group where 55% of users were 65 or older.

Table 5 shows the changes by quarter to the Cox-2 Inhibitor utilization. Vioxx® was removed from the market on the last day of quarter one for fiscal year 2005 (September 30, 2004). There was approximately a 31 % decrease in claims for the subsequent quarter. Table 6 demonstrates the results of attempts to maintain clients on the lowest possible dose of all Cox-2 Inhibitors.

Table 5. Number of claims for Cox-2 Inhibitors January 2004 through December 2004.

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

Table 6. Average dosing based on total units per strength.

Brand	Average Dose	Average Dose for Most Used Strength
Celebrex®	219 mg	274 mg
Vioxx®	34 mg	27 mg
Bextra®	15 mg	11 mg

Study Limitations

Because this study is limited to Medicaid clients, the results of this study may not be applicable to the general Oklahoma population. There are also several aspects to this study which limit its ability to be generalized to other populations. The first is the control of availability to all clients plus the number of monthly claims allowed. Second, clients who were on OTC NSAIDs or daily aspirin therapy cannot be accounted for.

Another limitation is the length of time reviewed. Some data suggests that the rate of events does not increase until after 18 months of continuous use. Additionally, the reduced dosing seen in the study population may also contribute to a lower rate of adverse events. The differences in the age ranges and total number of clients in each group may have affected the outcome of the study.

Also, the overall health of clients in Medicaid populations may be lower when compared to other populations and could affect the rate of events. Table 7 shows the CDC's survey results of rate of events based on an individual's health insurance coverage. A final limitation may be in the data itself as the diagnostic information available may not always be timely or accurate.

Table 7. CDC Survey Results of Health Insurance

	Coronary HD	Stroke	Hypertension
Under 65 years of age			
Private	2.6	0.8	14.2
Medicaid	**7.5**	**5.1**	**26.3**
Other	7.7	4.0	25.0
Uninsured	2.7	0.9	13.3
Over 65 years of age			
Private	21.9	9.0	51.3
Medicaid and Medicare	**24.2**	**11.6**	**58.4**
Medicare only	19.7	7.1	48.0
Other	24.2	9.6	48.8
Uninsured	8.7	2.3	40.5

Conclusion

The data seems to indicate that the rate of cardiovascular or thrombotic events for clients in the Oklahoma Medicaid population who are on a traditional NSAID or Cox-2 Inhibitor do not statistically differ from those with no NSAID use. Differences in ages and total number of clients may limit the ability to determine the effects NSAIDs may be having on the study population. However attempts to limit availability and overall dosing may also have been a positive contributing factor.

---

[1] FDA/Center for Drug Evaluation and Research. Bextra, Celebrex, Vioxx, and naproxen information. Available at: http://www.fda.gov/cder/index.html.

[2] Porter V. *NSAIDs still under surveillance – celecoxib, valdecoxib, and naproxen have been added to the list of suspects.* Medscape Cardiology 2005:9(1). Available at: http://www.medscape.com.

[3] Lethbridge-Cejku M, Schiller JS, Bernadel L. Summary health statistics for U.S. adults: National Health Interview Survey, 2002. National Center for Health Statistics. Vital Health Stat 10(222). 2004.

[4] Oklahoma Health Care Authority. SFY2004 Oklahoma Medicaid Milestones. Available at: http://www.ohca.state.ok.us/general/statistical/fastfacts/2004Milestones.pdf.

Oklahoma Medicaid Drug Utilization Review
Medication Authorization / Client Health Outcome Survey
November 2004

Medication Category: Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Number of surveys mailed	200
Number of survey response forms returned	35
Of the 35 response forms returned,	
Responses indicating change in meds due to PA requirements	21 (60%)
Responses indicating further medical assistance needed	16 (46%)
Responses indicating client required follow-up physician visit	13 (37%)
Responses indicating client required ER treatment*	3 (9%)
Responses indicating client was hospitalized*	1 (3%)

**See following page for follow-up on clients indicating ER treatment or hospitalization.*

The survey conducted in November included supplemental questions regarding use of over-the-counter anti-inflammatory medications for pain in addition to prescription-only NSAIDs.

The supplemental questions yielded the following results:

Number of survey response forms returned	35
Number of responses indicating use of OTC anti-inflammatory product(s) for pain	21 (60%)
Of the 21 responses indicating OTC anti-inflammatory use,	
Responses indicating use of 1 OTC product	15 (71%)
Responses indicating use of 2 OTC products	4 (19%)
Responses indicating use of 3 OTC products	2 (10%)
Responses indicating use of aspirin	8 (38%)
Responses indicating use of ibuprofen	12 (57%)
Responses indicating use of naproxen sodium	6 (29%)
Responses indicating use of other OTC anti-inflammatory	3 (14%)

Follow-up on responses indicating emergency treatment or hospitalization

Client #1 (Arthrotec)

- Client presented at emergency room on 10/28/2004 and was treated for chest pain, abdominal pain, and dyspepsia.
- Petition for Arthrotec was submitted on 10/5/2004 and was disapproved due to lack of information regarding Tier-1 trials or clinical exceptions.
- Petition for Arthrotec was submitted on 11/4/2004 and was disapproved due to lack of information regarding Tier-1 trials or clinical exceptions.

Client #2 (Celebrex)

- Client presented at emergency room on 8/29/2004 and was treated for arthritis and esophageal reflux related diagnoses.
- Client presented at emergency room on 9/16/2004 and was treated for arthritis related diagnosis.
- Client presented at emergency room on 10/14/2004 and was treated for arthritis related diagnosis.
- Petition for Celebrex was received on 8/10/2004 and was disapproved due to lack of information regarding Tier-1 trials or clinical exceptions.
- Petition for Celebrex was received on 9/16/2004 and was disapproved due to lack of information regarding Tier-1 trials or clinical exceptions.
- Petition for Celebrex was received on 10/19/2004 and was disapproved due to lack of information regarding Tier-1 trials or clinical exceptions.

Client #3 (Arthrotec)

- Client presented at emergency room on 2/1/2003 and was treated for headache.
- Client presented at emergency room on 2/4/2003 and was treated for headache.
- Client presented at emergency room on 2/11/2003 and was treated for headache.
- Client was hospitalized on 2/21/2003 and was treated for headache.
- No recent emergency room visit or hospitalization is indicated.
- Petition for Arthrotec was received on 10/19/2004 and was approved based on information regarding prior Tier-1 trials.

APPENDIX H

Prior Authorization Annual Review - Fiscal Year 2004
Non-Sedating Antihistamines (NSA)
Oklahoma Medicaid
March 2005

Current Definition of NSA Prior Authorization Category*

- Legend non-sedating antihistamine only products are covered after a previous trial failure with an over-the-counter antihistamine. A 14 day trial of over-the-counter loratadine is required prior to coverage of a legend only product for all age groups.
    - Trial should have been in the last month and be of adequate dose and duration,
    - Over-the-counter loratadine is a covered benefit for clients under the age of 21 years without prior authorization, and
    - For clients 21 years of age or greater, loratadine is available with prior authorization AFTER documented over-the-counter failure of a non-loratadine product.
- For clients six months to two years of age, cetirizine syrup is available without prior authorization.
- Diagnosis must be for a chronic allergic condition.
- Prior authorization will not be approved for a time period greater than 90 days for clients without a diagnosis which requires continuous coverage.

*Current definition became effective August 2003.

Utilization

For the period of July 2003 through June 2004, a total of 21,279 clients received non-sedating antihistamines products through the Medicaid fee-for-service program.

Product		# of Claims	Total Units	Total Days	Units/Day	Total Cost	Per Diem
Rx	*Solid*	8562	334,681	291,656	1.15	$ 603,249.80	$ 2.07
	Liquid	9594	1,226,299	264,455	4.64	$ 323,327.08	$ 1.22
OTC	*Solid*	20,833	669,482	660,681	0.99	$ 394,208.08	$ 0.60
	Liquid	3,463	470,192	88,847	5.29	$ 54,143.72	$ 0.61
All Products		**42,452**	**2,700,654**	**1,305,639**		**$ 1,374,928.68**	

Total Cost FY '04 **$1,374,928.68**
Total Cost FY '03 *$3,679,540.16*
Total Claims FY '04 **42,452**
Total Claims FY '03 *75,013*
Per Diem FY '04 **$1.05**
Per Diem FY '03 *$1.72*

Market share for select products.

Brand Name	Total Days/ Brand FY '03	% Share/ Brand FY '03	Total Days/ Brand FY '04	% Share/ Brand FY '04
Allegra	255,589	11.98%	90,962	6.97%
Clarinex	68,413	3.21%	9,914	0.75%
Zyrtec	810,663	37.98%	455,235	34.87%
Claritin (OTC)	999,581	46.84%	749,528	57.41%

Total petitions submitted in for this category during FY04: 14,994.

Approved	*7,303*
Denied	5,080
Incomplete	921
Duplicates	1,690

*3,413 denied or incomplete petitions were subsequently approved

Age/Gender FY04

Age	Female	Male	Totals
0 to 10	5,776	6,814	12,590
11 to 20	4,043	3,901	7,944
21 to 34	136	63	199
35 to 49	90	50	140
50 to 64	119	31	150
65 to 79	118	41	159
80 to 94	68	21	89
≥95	5	3	8
Totals	**10,355**	**10,924**	**21,279**

Recommendations

The College of Pharmacy has the following recommendations:

- Continuation of the current criteria and tier structure.
- Continued education to providers regarding available products for this category.

APPENDIX I

FDA Fact Sheet

February 15, 2005

FDA Press Office
301-827-6242

FDA Improvements in Drug Safety Monitoring

On February 15, 2005 , HHS Secretary Mike Leavitt and Acting FDA Commissioner Lester M. Crawford unveiled a new emboldened vision for FDA that will promote a culture of openness and enhanced oversight within the Agency. As part of this vision, FDA will create a new independent Drug Safety Oversight Board to oversee the management of drug safety issues, and will provide emerging information to health providers and patients about the risks and benefits of medicines.

Acting FDA Commissioner Crawford announced specific proposals for immediate and fundamental steps to improve the way the FDA manages drug safety information. These proposals focus on making FDA's review and decision-making processes more independent and transparent.

FDA will enhance the independence of internal deliberations and decisions regarding risk/ benefit analyses and consumer safety by creating an independent Drug Safety Oversight Board (DSB). The DSB will oversee the management of important drug safety issues within the Center for Drug Evaluation and Research (CDER). The DSB will comprise members from the FDA and medical experts from other HHS agencies and government departments (e.g., Department of Veterans Affairs) who will be appointed by the FDA Commissioner. The board also will consult with other medical experts and representatives of patient and consumer groups.

FDA will also increase the transparency of the Agency's decision-making process by establishing new and expanding existing communication channels to provide targeted drug safety information to the public. These channels will be used to help ensure that established and emerging drug safety data are quickly available in an easily accessible form. The increased openness will enable patients and their healthcare professionals to make better-informed decisions about individual treatment options. The Agency is proposing a new "Drug Watch" Web page for emerging data and risk information and increased use of consumer-friendly information sheets written especially for healthcare professionals and patients.

As FDA develops these communications formats, the Agency will be soliciting public input on how FDA should manage potential concerns associated with disseminating emerging information prior to regulatory action. The Agency will issue draft guidance on procedures and criteria for identifying drugs and information for the Drug Watch Web page. In addition, FDA will actively seek feedback from healthcare professionals and patients on how best to make this information available to them.

A cornerstone of all information collection, evaluation, and communication proposals in an age of increasing electronic health information must be a strict adherence to maintaining patient privacy. FDA is committed to maintaining patient privacy as it undertakes these steps.

###

HHS Press Release (Feb. 15, 2005)
Remarks by Acting Commissioner Crawford (Feb. 15, 2005)

Alert for Healthcare Professionals

Adderall and Adderall XR (amphetamine)

FDA Alert [02/09/05]: Sudden Death in Children

Health Canada has suspended marketing of Adderall XR (extended release) from the Canadian market due to concern about reports of sudden unexplained death (SUD) in children taking Adderall and Adderall XR. SUD has been associated with amphetamine abuse and reported in children with underlying cardiac abnormalities taking recommended doses of amphetamines, including Adderall and Adderall XR. In addition, a very small number of cases of SUD have been reported in children without structural cardiac abnormalities taking Adderall. At this time, FDA cannot conclude that recommended doses of Adderall can cause SUD, but is continuing to carefully evaluate these data.

Recommendations

FDA is currently examining the data on these cases occurring in children who are using Adderall as recommended. As a precaution, FDA recommends that Adderall products not be used in children or adults with structural cardiac abnormalities.

Data Summary

A review of the data from the FDA's Adverse Event Reporting System database for the years 1999 through 2003 identified 12 cases of sudden death in pediatric patients (1 to 18 years of age) who were being treated for ADHD with Adderall or Adderall XR (see table for description of cases).

Characteristics of domestic pediatric sudden death cases reported during past five years (n=12)*

Age:	7-16 years (mean 12. years)
Gender:	12 male, 0 female
Suspect drug:	Adderall or Adderall XR
Total daily dose:	10 mg (1), 20 mg (5), 30 mg (1), 40 mg (1), 50 mg (1) , NR (3)
Duration of therapy:	1 day – 8 years (range)
Autopsy:	yes (11), not mentioned or not done (1)
Cardiac structural abnormalities:	aberrant origin of coronary artery (1), idiopathic hypertrophic subaortic stenosis (1), bicuspid aortic valve (1), cardiac hypertrophy (2)
Other risk factors:	unexplained increase or toxic amphetamine level (2), family history of ventricular arrhythmia (1), extreme exercise and dehydration (1)
Concomitant meds:	none mentioned (9), 1 med (3)
Year reported	1999 (0), 2000 (2), 2001 (6), 2002 (2), 2003 (2)

*numbers in parentheses represent count of cases

(Continued on next page)

Alert for Healthcare Professionals

Adderall and Adderall XR (amphetamine)

Five of the 12 pediatric sudden death cases described cardiac risk factors including undiagnosed cardiac abnormalities (e.g., aberrant origin of coronary artery, bicuspid aortic valve, idiopathic hypertrophic subaortic stenosis). Seven occurred in children without such abnormalities, including 1 with a positive family history of ventricular arrhythmia. Several of the cases were complicated by other illness, and very rigorous exercise. Unusual and unexplained accumulation of drug resulting in toxic levels during usual therapeutic dosing also appears to have played a role in several of the pediatric sudden death cases. The rare occurrence of sudden death during stimulant therapy of ADHD deserves continued evaluation. SUD as a possible effect of amphetamines should be considered in the assessment of benefit versus risk during therapeutic decision-making for individual patients. In the pediatric population, potential risk factors include cardiac abnormalities that may be undiagnosed, positive family history for ventricular arrhythmias, and as yet unidentified factors that may cause excessive levels of stimulant to accumulate in children who are taking apparently normal doses.

An update and further analyses of the data are currently in progress.

Questions? Call Drug Information, 1-888-INFO-FDA (automated) or 301-827-4570
Druginfo@cder.fda.gov

Report serious adverse events to FDA's MedWatch at 1-800-FDA-1088; or www.fda.gov/medwatch/report/hcp.htm

U.S. Food and Drug Administration

FDA News

FOR IMMEDIATE RELEASE
P05-07
February 28, 2005

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

FDA Issues Public Health Advisory on Tysabri, a New Drug for MS

The Food and Drug Administration (FDA) today issued a public health advisory to inform patients and health care providers about the suspended marketing of Tysabri (nataluzimab) while the agency and the manufacturer evaluate two serious adverse events reported with its use.

Tysabri, which received accelerated approval from FDA in November 2004, is an innovative treatment that represents a new approach to treating patients with relapsing forms of multiple sclerosis (MS).

"FDA worked with the company to make sure this information, even though preliminary, was given to physicians and patients as soon as possible and supports their decision to voluntarily suspend marketing as well as the use of the product in clinical trials. At the same time, FDA continues to believe Tysabri offers great hope to MS patients," said Dr. Steven Galson, Acting Director, FDA's Center for Drug Evaluation and Research (CDER). "Patients being treated with Tysabri should contact their physician to discuss appropriate alternative treatments while these reports are being evaluated," added Dr. Galson.

FDA received a report from Biogen Idec, the manufacturer of Tysabri, of one confirmed fatal case and one possible case of progressive multifocal leukoencephalopathy (PML) in patients receiving Tysabri for MS. FDA was given preliminary information about these cases by Biogen, Idec on February 18, 2005. Details became available to FDA the next week.

PML is a rare, serious progressive neurologic disease usually occurring in immunosuppressed patients. There is no known effective treatment for PML. Although the relationship between Tysabri and PML is not known at this time, because of the serious and often fatal nature of PML, FDA concurred with the company that the drug be voluntarily withdrawn from marketing and that the use of Tysabri in clinical trials be suspended until more is known.

During the review of Tysabri for marketing approval, FDA conducted an intensive analysis of possible adverse events that might be related to effects of the drug on the immune system. No cases of PML were seen in the clinical trials. However, for any approved therapy, new and unexpected adverse events may occur that were not seen in clinical trials. In the case of Tysabri, required post-marketing studies facilitated the rapid reporting and response to this new information.

According to Biogen, Idec, outside of the approximately 3,000 patients who received the drug in clinical trials, approximately 5,000 additional patients with MS have received Tysabri through their primary physician. Because Tysabri was just recently approved, these patients have only received at most a few doses of Tysabri.

The FDA will maintain close contact with the company during the process of understanding the relationship between Tysabri and these two serious adverse events. The company is working on ways to get additional information soon about the possible risks of PML from the patients who have received Tysabri in the clinical trials.

The FDA urges health care providers and patients to report adverse event information to FDA via the MedWatch program by phone (1-800-FDA-1088), by fax (1-800-FDA-0178) or by the Internet at www.fda.gov/medwatch/index.html.

For further information, the public health advisory can be found on FDA';s website at http://www.fda.gov/cder/drug/advisory/natalizumab.htm.

FDA Public Health Advisory

Seizures in Patients Without Epilepsy Being Treated With Gabitril (tiagabine)

Today the Food and Drug Administration announced that a Bolded Warning will be added to the labeling for Gabitril (tiagabine) to warn prescribers of the risk of seizures in patients without epilepsy being treated with this drug. Gabitril has been approved since 1997 for patients 12 years of age and older as adjunctive therapy (used in addition to other medications) for partial seizures. Recently, the Agency has become aware of reports of the occurrence of seizures in more than 30 patients prescribed Gabitril for conditions other than epilepsy. Most of these uses were in patients with psychiatric illnesses. Such so-called *off label* prescribing is a common practice among physicians. Because of the risk of seizures, however, in addition to adding the Bolded Warning to product labeling, the sponsor has agreed to undertake an educational campaign targeted to healthcare professionals and patients in which such *off label* use will be discouraged.

In addition to the occurrence of isolated seizures, the Agency has received several reports of status epilepticus in patients without epilepsy. Status epilepticus is a particularly dangerous event, in which patients have continuous seizures without regaining consciousness between seizures. In some cases, prescribers have continued to treat with, or actually increased the dose of, Gabitril in patients without epilepsy in whom seizures occurred. Presumably, this was done because the prescribers were unaware of the possibility that Gabitril could cause seizures and they believed that, as a drug approved to treat epilepsy, Gabitril might be beneficial in this situation as well.

Typically, the seizures have occurred soon after the initiation of treatment with Gabitril, or soon after an increase in dose, although some patients experienced seizures after several months of treatment. Some seizures have occurred at very low doses compared to the doses approved for use in patients with epilepsy. Although most of the patients in whom seizures occurred were also taking other medications that may infrequently cause seizures, the temporal relationship to the initiation of treatment with Gabitril or to dose increases in many cases, as well as the number of patients reporting seizures, strongly suggests that the seizures were caused by Gabitril.

Because the system for reporting adverse events is voluntary, the number of reports of adverse reactions that the Agency receives once a drug has been marketed is probably less than the actual number of reactions that have actually occurred. For this reason, it is expected that the number of patients who have experienced a seizure while taking Gabitril is likely to be greater than the number reported, although it is impossible to know what the difference might be.

Because seizures are a serious and potentially life-threatening event and because prescribers are

unlikely to expect that a drug to treat epilepsy can cause seizures in other patients, the Agency has requested that this information be included in a Bolded Warning and announced to healthcare professionals with a *Dear Health Care Practitioner letter* from the sponsor. In addition, as noted above, the sponsor has agreed to undertake an educational campaign in which they will discourage the *off label* use of Gabitril. The Agency will work closely with the sponsor to expedite the adoption and dissemination of the revised label and educational materials.

Healthcare professionals should be aware that the use of Gabitril for any indication other than for partial seizures in patients with epilepsy who are at least 12 years old is an *off label* use, meaning evidence to support the safety and effectiveness for those uses has not been approved by the FDA. For this reason, the labeling for Gabitril will not contain any needed precautions and warnings that might result from such a submission and review. Patients should be aware that the use of Gabitril for the treatment of any condition other than partial seizures is considered *off label* use, and that there is a risk that they may experience a seizure. The risks of seizures should be explained, and patients should report any adverse events promptly to their healthcare professional.

Back to Top Back to Gabitril

Date created: February 18, 2005
