Drug Utilization Review Board

Oklahoma Health Care Authority
4545 North Lincoln Boulevard, Suite 124
Oklahoma City, Oklahoma 73105
OHCA Board Room

Wednesday
November 12, 2008
6:00 p.m.

THE UNIVERSITY OF OKLAHOMA

MEMORANDUM

TO: Drug Utilization Review Board Members

FROM: Shellie Keast, Pharm.D., M.S.

SUBJECT: **Packet Contents for Board Meeting – November 12, 2008**

DATE: November 5, 2008

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

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

Call to Order

Public Comment Forum

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

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

Action Item – Vote on 2009 DUR Meeting Dates – **See Appendix C.**

Action Item – Vote to Prior Authorize Erythropoiesis Stimulating Agents – **See Appendix D.**

Action Item – Vote to Prior Authorize Protonix® Suspension– **See Appendix E.**

Action Item – Vote to Prior Authorize Patanase® – **See Appendix F.**

Action Item – Vote to Prior Authorize Rescue HFA Products – **See Appendix G.**

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

Glaucoma Intervention Report **– See Appendix I.**

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

Future Business

Adjournment

Drug Utilization Review Board

(DUR Board)

Meeting – November 12, 2008 @ 6:00 p.m.

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

AGENDA

Discussion and Action on the Following Items:

Items to be presented by Dr. McNeill, Chairman:

1. Call To Order

A. Roll Call – Dr. Graham

Items to be presented by Dr. McNeill, Chairman:

2. Public Comment Forum

A. Acknowledgment of Speakers and Agenda Item

Items to be presented by Dr. McNeill, Chairman:

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

A. August 13, 2008 DUR Minutes – Vote
B. September 10, 2008 DUR Minutes – Vote
C. Provider Correspondence

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

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

A. Retrospective Drug Utilization Review for July 2008, August 2008
B. Retrospective Drug Utilization Review Responses for March 2008, April 2008
C. Medication Coverage Activity Audit for September 2008, October 2008
D. Help Desk Activity Audit for September 2008, October 2008

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

5. Action Item – Vote on 2009 DUR Meeting Dates – See Appendix C.

A. COP Recommendations

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

6. Action Item – Vote to Prior Authorize Erythropoiesis Stimulating Agents – See Appendix D.

A. COP Recommendations

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

7. Action Item – Vote to Prior Authorize Protonix® Suspension – See Appendix E.

A. Current PA Criteria
B. COP Recommendations

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

8. Action Item – Vote to Prior Authorize Patanase® – See Appendix F.

A. Product Summary
B. COP Recommendations

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

9. Action Item – Vote to Prior Authorize Rescue HFA Products – See Appendix G.

A. Product Summary
B. Utilization Review
C. COP Recommendations

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

10. Action Item – Vote to Update Antidepressant PBPA Category and Prior Authorize Luvox CR® – See Appendix H.

A. Current PA Criteria
B. COP Recommendations
C. Product Summary

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

11. Glaucoma Intervention Report – See Appendix I.

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

12. FDA and DEA Updates – See Appendix J.

13. Future Business

A. Lock-In Report
B. Oral Antifungal Utilization Review
C. Annual Reviews
D. New Product Reviews

14. Adjournment

Appendix A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES of MEETING of August 13, 2008

BOARD MEMBERS:	PRESENT	ABSENT
Brent Bell, D.O., D.Ph.	X	
Jay D. Cunningham, D.O.		X
Mark Feightner, Pharm.D.		X
Dorothy Gourley, D.Ph.	X	
Evelyn Knisely, Pharm.D.	X	
Thomas Kuhls, M.D.	X	
Dan McNeill, Ph.D., PA-C; Chairman		X
Cliff Meece, D.Ph.; Vice-Chairman	X	
John Muchmore, M.D., Ph.D.	X	
James Rhymer, D.Ph	X	

COLLEGE of PHARMACY STAFF:	PRESENT	ABSENT
Leslie Browning, D.Ph.; PA Coordinator	X	
Metha Chonlahan, D.Ph.; Clinical Pharmacist	X	
Karen Egesdal, D.Ph.; SMAC-ProDUR Coordinator/OHCA Liaison	X	
Shellie Keast, Pharm.D.; DUR Manager	X	
Ronald Graham, D.Ph.; Pharmacy Director	X	
Chris Le, Pharm.D.; Clinical Pharmacist/Coordinator	X	
Carol Moore, Pharm.D.; Clinical Pharmacist	X	
Neeraj Patel, Pharm.D.; Clinical Pharmacist	X	
Lester A. Reinke, Ph.D.; Associate Dean for Graduate Studies & Research		X
Visiting Pharmacy Students: Christy Tran, Valerie Pham	X	

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

OTHERS PRESENT:

Rebecca King, Taro	Randy Clifton, Amgen	Jacque Collier, Abbott
James Lieurence, Abbott	Wayne McGuire, NAMI	David Barton, Schering Plough
Bobby White, UCB	Richard Ponder, J&J	Sue Watson, OBI
Justin Caudle, OBI	Joseph Medina, Sepracor	Carl Rose, Sepracor
Jim Fowler, Astra Zeneca	Krici Mohr, Amgen	Vince Morrison, Forest
Linda Cantu, BMS	Susan Stone, Allergan	William Dozier, Gilead
Bruce Robertson, Eli Lilly	Lean Stewart, Merck	

PRESENT FOR PUBLIC COMMENT:

Agenda Item No. 6: Howard Ozer, M.D.; U. of Oklahoma and Sue Watson, Pharm.D.; Ortho Biotech

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

1A: Roll Call

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

ACTION: NONE REQUIRED.

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

Dr. Meece recognized the speakers for public comment.

Agenda Item No. 6: Howard Ozer, M.D.; U. of Oklahoma and Sue Watson, Pharm.D.; Ortho Biotech

For Public Comment, Howard Ozer, M.D.: Thanks very much for the opportunity to speak to you. My name's Howard Ozer. I'm the Eason Chair and Chief of Hematology and Oncology at the University of Oklahoma and wanted to make a few comments about the erythropoeitic growth factors. I have chaired the national ASCO Committee on white cell growth factors for a number of years and still remain as co-chair. I've also done quite a bit of work in publications and clinical trials both with Amgen that produces Aranesp and with J&J/Ortho that produces Procrit. I know a lot about their use in malignant disease but if you like I could also address their use in chronic kidney disease and HIV. We use these factors to a significant degree in our clinic setting and we find them very useful. They must be used by label and there's been a lot of controversy about their use which primarily results from non-label utilization. When the label is followed, they're extremely valuable to our patients. Typical examples will be patients particularly on, they must be patients on chemotherapy and particularly if they're on platinum-containing chemotherapy which we would use, for example, in lung cancer, GYN malignancies, etc. Those patients develop a very severe anemia that results from lack of native erythropoietin production, and so these products are useful in increasing the serum erythropoietin level and decreasing the transfusion requirement. And that's their primary benefit. There's been lots of efforts made to demonstrate they also improve quality of life and there are some data that support that strongly, but their primary value is in decreasing the need for blood transfusions and those costs. Not everyone benefits. If a patient for example, only needs a transfusion every twelve months or so, there's not much use in keeping them chronically on it but if a patient does require multiple transfusions, they are extremely valuable. The two products that are currently on the market are Procrit, which is administered weekly, and Aranesp, which is a long-acting form and is administered every three weeks. The cost is almost equivalent and there are a couple of studies, and I brought one from 2008 if you'd like to see, that demonstrates that the cost is virtually identical for the two products. We do not find that one product is preferable over the other. They each work. It's simply a matter of patient and physician preference in terms of administration. They are also valuable in other settings where anemia may be severe. So we do use them, obviously, in HIV, obviously in chronic renal disease, where the organ, the juxtaglomerular apparatus is not functioning and erythropoietin is not being produced. But there also are a number of sort of, they're not off-label, but they're what we call compendia listings where we might want to use it in myelodysplastic syndromes. Those are similar to leukemia. It's a failure to produce specifically in this case, red blood cells and those patients may also respond and we find it valuable in that setting. With that, I'll be happy to address any questions that you have. I hope I've been brief and relatively clear.

Board Member Kuhls: Just a quick question. What's your feeling about the importance of if you have a curative cancer that you shouldn't use these products?

Dr. Ozer: I'll give you ..... it's a relatively long answer and I'll try and be as brief as I can. There are data that have been generated from Phase 3 studies, relatively small studies, in which patients with breast cancer, potentially curable, and with head and neck cancer, and then a couple of other trials where there has been a decrease in overall survival in the arm that received the erythropoietin product. And actually there have been three products used in those studies. One was a drug that has never become commercial in this country. We don't know how to explain that. As I look at the data, I'm very skeptical of it. That said, I think that if I had a candidate for chemotherapy that I expected to cure, let's say a small tumor in the breast, who's going to get adjunctive chemotherapy, I would probably prefer to transfuse that patient as opposed to giving an erythropoietin product. So I would make that personal choice. The way the FDA has worded the new black box warning, they still allow appropriate use and you could make the argument that a patient with breast cancer might be curable or might live a long time under other circumstances, but if they had profound anemia, and you expected a relatively short survival, it would still be okay as a physician to try that. But I think if I have a young person and I'm on service this month ..... we have a 29-year old who has a Ewing's sarcoma and that patient is required multiple transfusions and we have elected not to treat that patient with an erythropoietic product for exactly that reason. I think the data are still unclear and I think it'll be three or four more years before some of the trials that are testing this really reveal what's going on.

Board Member Kuhls: We spend so much time dealing with cost versus benefit, and really using these agents, to me, is not a cost issue at all, but probably even more importantly the question, because the question of safety has come up, we're really dealing with this more from the safety aspect than anything else. And so my question to you is very simply, is obviously we want to decrease the amount of off-label use and try to use this medication as safely possible in the State of Oklahoma, like I'm sure you do. None of your patients you decide that morning that you need a ..... this product or whatever, erythropoietin, or whatever. There's always time to get a PA and to make sure that there's somebody at a State level looking that it's being used appropriately, right?

Dr. Ozer: I think that's a fair statement. I don't think that there's emergency use of this compound. I don't think that it's going to deflect a transfusion that is required in three or four days. What it can do is prevent transfusions over a period of several months, so I think there's enough time to have an evaluation.

ACTION: NONE REQUIRED.

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

3A: July 9, 2008 DUR Minutes

Dr. Gourley moved to approve minutes as submitted; seconded by Dr. Bell.

ACTION: MOTION CARRIED.

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

4A: Retrospective Drug Utilization Review Report: April 2008

4B: Retrospective Drug Utilization Review Responses: January 2008

4C: Medication Coverage Activity Audit: July 2008

4D: Help Desk Activity Audit: July 2008

Reports included in agenda packet; presented by Dr. Keast. Board requested to see Lock-In Program reports at future meetings.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 5: **VOTE TO PRIOR AUTHORIZE VOLTAREN® GEL**

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

Dr. Kuhls moved to approve; seconded by Dr. Rhymer.

ACTION: MOTION CARRIED.

AGENDA ITEM NO. 6: **30-DAY NOTICE TO PRIOR AUTHORIZE ERYTHROPOIESIS STIMULATING AGENTS**

For Public Comment, Sue Watson, Pharm.D.: My name is Sue Watson. I'm with, I'm a Pharm.D. with Ortho Biotech, Director of Outcomes Research. We recently had a package update on August 7th so I'm here to answer any questions if you have any label change questions and also just to note in Option 2 that you have, that you'll be discussing, the CKD patients of Dr. Ozer had mentioned, these patients are on these products for the rest of their lives, typically, and they will be getting this product continually until they no longer, when they die. So an 8-week approval of every eight weeks might be quite onerous for CKD patient. I just wanted to mention that. Do you have any questions?

Board Member Kuhls: Other than that, how do you feel about Option 2?

Dr. Watson: I think Option 2 is very in line, it's accurate, it's with the label. You know, my only concern would be number 2 on the eight weeks for CKD patients or ESRD patients. So I guess that would lead you to Option 3, right? Because they would be exempt in Option 3.

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

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 7: **30-DAY NOTICE TO PRIOR AUTHORIZE PATANASE®**

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

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 8: **ANNUAL REVIEW OF ANTIULCER PBPA CATEGORY AND 30-DAY NOTICE TO PRIOR AUTHORIZE PROTONIX® SUSPENSION**

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

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 9: **QUALAQUIN® ANNUAL REVIEW**

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

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 10: **WHITE PAPER ON BIOEQUIVALENT MEDICATIONS**

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

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 11: **FDA & DEA UPDATES**

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

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 12: **FUTURE BUSINESS**

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

12A: Antidepressants
12B: Oral Antifungals Utilization Review
12C: Hemophilia Review
12D: Annual Reviews
12E: Glaucoma Intervention Report
12F: New Product Reviews

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 13: **ADJOURNMENT**

The meeting was adjourned at 7:35 p.m.

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES of MEETING of September 10, 2008

BOARD MEMBERS:	PRESENT	ABSENT
Brent Bell, D.O., D.Ph.		X
Jay D. Cunningham, D.O.		X
Mark Feightner, Pharm.D.		X
Dorothy Gourley, D.Ph.		X
Evelyn Knisely, Pharm.D.		X
Thomas Kuhls, M.D.	X	
Dan McNeill, Ph.D., PA-C; Chairman	X	
Cliff Meece, D.Ph.; Vice-Chairman	X	
John Muchmore, M.D., Ph.D.	X	
James Rhymer, D.Ph	X	

COLLEGE of PHARMACY STAFF:	PRESENT	ABSENT
Leslie Browning, D.Ph.; PA Coordinator	X	
Metha Chonlahan, D.Ph.; Clinical Pharmacist	X	
Karen Egesdal, D.Ph.; SMAC-ProDUR Coordinator/OHCA Liaison		X
Shellie Keast, Pharm.D.; DUR Manager	X	
Ronald Graham, D.Ph.; Pharmacy Director	X	
Chris Le, Pharm.D.; Clinical Pharmacist/Coordinator	X	
Carol Moore, Pharm.D.; Clinical Pharmacist	X	
Neeraj Patel, Pharm.D.; Clinical Pharmacist		X
Lester A. Reinke, Ph.D.; Associate Dean for Graduate Studies & Research	X	
Visiting Pharmacy Students: Jennilee Craig, Clayton Cox	X	

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

OTHERS PRESENT:

Randy Clifton, Amgen	Jacque Collier, Abbott	Mario Freeman, Johnson & Johnson
Justin W. Caudle, Johnson & Johnson	Robert Pearce, TEVA	Susan Stone, Allergan
Jim Dunlap, Eli Lilly	Richard Ponder, Johnson & Johnson	Donna Erwin, BMS
David Barton, Schering-Plough	David Williams, Forest	Jim Fowler, Astra Zeneca
Karina Forrest, NAMI OK	Pam Davis, MHAT	Janie Huff, Takeda
Rebecca King, Taro	Rachel Greene, Merck	Lynne Matzell, Amgen
Linda Cantu, BMS	Brian Shank, Astra-Zeneca	Karen Hanna, Janssen
Monique Lambring, Elan	Pat Trahan, Taro	

PRESENT FOR PUBLIC COMMENT:

(none)

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

1A: Roll Call

Dr. McNeill called the meeting to order. Roll call by Dr. Graham established no quorum present.

ACTION: NONE REQUIRED.

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

There were no speakers for public comment.

ACTION: NONE REQUIRED.

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

3A: August 13, 2008 DUR Minutes

Deferred to October 2008 meeting.

ACTION: DEFERRED TO OCTOBER 2008

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

4A: Retrospective Drug Utilization Review Responses: February 2008

4B: Medication Coverage Activity Audit: August 2008

4C: Help Desk Activity Audit: August 2008

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

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 5: **VOTE TO PRIOR AUTHORIZE ERYTHROPOIESIS STIMULATING AGENTS**

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

Deferred to October 2008 meeting.

ACTION: DEFERRED TO OCTOBER 2008

AGENDA ITEM NO. 6: **VOTE TO PRIOR AUTHORIZE PROTONIX® SUSPENSION**

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

Deferred to October 2008 meeting.

ACTION: DEFERRED TO OCTOBER 2008

AGENDA ITEM NO. 7: **VOTE TO PRIOR AUTHORIZE PATANASE®**

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

Deferred to October 2008 meeting.

ACTION: DEFERRED TO OCTOBER 2008

AGENDA ITEM NO. 8: **GUEST SPEAKER: HEMOPHILIA PRESENTATION**

Materials included in agenda packet; presented by Dr. Sarah M. Hawk, P.A.-C., Oklahoma Center for Bleeding and Clotting Disorders.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 9: **60-DAY NOTICE TO PRIOR AUTHORIZE RESCUE HFA PRODUCTS**

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

ACTION: NONE REQUIRED.

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

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

ACTION: NONE REQUIRED.

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

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

12A: Antidepressants
12B: Oral Antifungal Utilization Review
12C: Glaucoma Intervention Report
12D: Annual Reviews
12E: New Product Reviews

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 12: **ADJOURNMENT**

The meeting was adjourned at 7:10 p.m.

MORTON
Comprehensive Health Services, Inc.

1334 N. Lansing Ave. Tulsa, OK 74106
(918) 587-2171 | (918) 587-8175 (Fax)

September 29, 2008

Shellie Gorman Keast, Pharm. D., M.S.
Dur Manager
Pharmacy Management Consultant
ORI-W4403
P.O. Box 26901
Oklahoma City, OK 73126-0901

Dr. Keast:

As a pediatrician I see a significant number of children with asthma. A great majority of my patients use Ventolin HFA as part of their treatment for acute asthma exacerbations. The counter that is part of Ventolin HFA allows me to track the frequency of use by the patient and helps me in tailoring treatment plans. Ventolin HFA is a valuable and vital part of my practice and I anticipate prescribing it for years to come.

Sincerely,

R. Whittaker, MD

Runako Whittaker, MD
Pediatrician
Morton Health

Generations Family Medical Center
1218 N. Florence Ave.
Claremore, OK 74017

Shellie Gormankeast Pharm D., M.S.
Pharmacy Management Consultants
ORI - W 4403
P.O. Box 26901
Oklahoma City, OK 73126-0901

Dear Shellie:

It is important that Ventalin HFA continue to be available to all of our Medicaid/Sooner Care patients. We prescribe this medication often and feel that it is a valuable asset to our treatment plans. The outstanding feature of the Ventalin HFA is the patient friendly dosage and counter that makes patient error much less likely. This easy format also allows patients to see how much is left and when they need a refill.

The fact that we have many COPD and Asthma patients on state sponsored health insurance that respond well to this medication would lead to many patients that would be left without this treatment option if the prescription was no longer paid for by Medicaid. These patients would not be able to afford this medication on their own and assistance programs do not always cover them. Please continue to note that we support this medication being available to all patients covered by Medicaid/Sooner Care. Thank you for your time in supporting this matter.

Sincerely,

Dr. Larry Lane

ll/arh

WALKER FAMILY PRACTICE, LLC

821 N YORK, SUITE C

MUSKOGEE, OK 74403

918-682-1222

September 24, 2008

To Shellie Gorman Keast Pharm.D., MS:

Please continue to make Ventolin HFA available for patients so I can track their compliance with the dose counter. The counter is a benefit to both the patient and myself to measure control of their asthma. My practice is almost exclusively Medicaid and is beneficial to our patients. If any additional information is needed please do not hesitate to call.

Thank You,

David Walker ARNP

M.V. PRIEST, D.O.
J.R. PRIEST, M.D.

GEMINI
MEDICAL GROUP, INC.

MARY DAGENAIS, P.A.-C

701 Leahy Ave.
Pawhuska, OK 74056
(918) 287-1310

Shellie Gorman Keast, Pharm D, M.S.

DUR manager

Pharmacy Management Consultants

ORI-W4403 P.O. Box 26901

Oklahoma City, OK 73126-0901

September 24, 2008

Dear Ms. Keast:

Please consider this letter of support for Ventolin HFA as preferred rescue medication for Oklahoma Medicaid patients. The product has an excellent long term safety and efficacy profile. As a practicing physician I find it advantageous also because of its dose counter mechanism which gives me an accurate way to measure use of this product.

Please feel free to contact me with any specific questions regarding this matter.

Sincerely,

Michael V. Priest, D.O. FAAFP

M.V. PRIEST, D.O.
J.R. PRIEST, M.D.

GEMINI
MEDICAL GROUP, INC.

MARY DAGENAIS, P.A.-C

701 Leahy Ave.
Pawhuska, OK 74056
(918) 287-1310

Dear Mrs. Kent,

I have been asked to comment on Ventolin HFA for your consideration on formularies. The Albuterol is all the same but the Ventolin is very helpful. This makes it more user friendly to our patients —

Thank you for your kind consideration.

J R Priest, MD
9-24-08

MERCY
EDMOND WESTBROOK

Frank C. Davis, MD
Craig R. Evans, MD
Terrill D. Hulson, MD
David M. James, MD
Sherri A. Tucker, MD

September 22, 2008

To Whom It May Concern:

Simcor, as a powerful combination of both simvastatin and niacin, has the benefits of statin therapy to reduce total and LDL cholesterol, as well as raising HDL cholesterol. Since many of my patients, due to their pre-diabetes, diabetes, and metabolic syndrome have atherogenic lipid profiles (high Total-C, high LDL-C, high triglycerides and low HDL-C), anything I can do to get them to heart-protective goals benefits them and reduces their risks of cardiovascular events. Having only one tablet with variable dosing flexibility really has helped the compliance issue. They only have one co-pay for both medications, which allows them to use their other co-pays for other medications.

I strongly recommend the addition of Simcor to the Oklahoma Medicaid formulary.

Sincerely yours,

Terrill D. Hulson, M.D.

1208 S.W. 15TH ST. ■ EDMOND, OK 73013
405-340-2100 phone ■ **405-340-1184** fax

Susan M. Dimick, M.D., F.A.C.P.

Board Certified Internal Medicine

3317 E. Memorial Rd., Suite 103
Edmond, OK 73013
Phone (405) 475-0100
Fax (405) 475-9275

September 22, 2008

To Whom It May Concern:

This is a notation written in support of Simcor, which combines simvastatin and niacin. Since the use of statins alone in attempt to reduce LDL cholesterol is missing greater than 70% of cardiovascular events, we must be more effective in reduction of residual risk to include treating triglycerides, HDL and lipoprotein(a), non-HDL cholesterol and apolipoprotein B. Since Oklahoma now rates 50th out of the 50 states with regard to incidence of heart disease and since we have such a large American Indian population with insulin resistance, in combination with the more global risk management needed for our growingly obese population in the United State, we must be cognizant of treating more than we can treat with a statin alone. The importance of early intervention in our patients with metabolic syndrome, insulin resistance and diabetes cannot be stressed enough and cannot be addressed with a statin alone. Niacin will allow us to treat virtually all parameters of dyslipidemia, to include HDL, LDL, triglycerides, and non-HDL cholesterol. We are with numerous studies showing that combinations of niacin and statins show a marked reduction in risk compared to statins alone.

This combination is also helpful with regard to copayments and reduces the number of tablets that patients must take to control their problems.

Sincerely,

Susan M. Dimick, M.D., F.A.C.P.
SMD:gp

September 24, 2008

Shellie Gorman Keast, Pharm.D., M.S.

DUR Manager
Pharmacy Management Consultants

ORI-W4403 P.O. Box 26901
Oklahoma City, OK 73126-0901

Dear Ms. Keast,

This letter is for the review of Ventolin HFA.

Ventolin HFA is the only albuterol medication that has a dose counter. I'm sure you are aware that the majority of patients do not know the amount of medication that their inhaler contains. The Ventolin HFA alleviates the risk of the patient using an empty inhaler. The dose counter helps patients know when to refill their Ventolin HFA. The dose counter on Ventolin HFA can also help me accurately track how much albuterol my patients are using.

Thank you for reviewing the Ventolin HFA for the patients.

Sincerely,

Larry Ruffin, DO.

Appendix B

Retrospective Drug Utilization Review Report

Claims Reviewed for July 2008

Module	Drug Interaction	Duplication of Therapy	Drug-Disease Precautions	Dosing & Duration
Total # of messages returned by system when no limits were applied	39,233	57,967	1,061,773	27,338
Limits which were applied	Established, Major, Males and Females, Age 0-18	Males and Females, Age 0-150, Antiplatelet Agents	Contraindicated, Hepatic Disease, Males and Females 41-65	High Dose only, 5710 Benzodiazepines, Males and Females, 0-18
Total # of messages after limits were applied	11	16	367	7
Total # of members reviewed after limits were applied	11	16	281	7

LETTERS			
Prescribers		**Pharmacies**	
Sent	**Responded**	**Sent**	**Responded**
13		2	

Retrospective Drug Utilization Review Report

Claims Reviewed for August 2008

Module	Drug Interaction	Duplication of Therapy	Drug-Disease Precautions	Dosing & Duration
Total # of messages returned by system when no limits were applied	39,922	59,334	1,053,753	29,877
Limits which were applied	Established, Major, Males and Females, Age 19-40	Males and Females, Age 0-150, antiarrhythmics	Contraindicated, Drug Abuse, 0-150 years old, males and females	High Dose only, males and females, 0-150 years old, Substance P/Neurokinin 1 Antagonist (Emend)
Total # of messages after limits were applied	83	3	98	2
Total # of members reviewed after limits were applied	83	3	75	2

LETTERS			
Prescribers		**Pharmacies**	
Sent	**Responded**	**Sent**	**Responded**
72		56	

Retrospective Drug Utilization Review Report

Claims Reviewed for March 2008

Module	Drug Interaction	Duplication of Therapy	Drug-Disease Precautions	Dosing & Duration
Limits which were applied	Established, Major, Males and Females, Age 0-21	Antidepressants-SSRIs, Males and Females, Age 0-21	Contraindicated, Hepatic Disease, Males and Females, Age 0-35	High Dose, Low Dose, Duration, 1623 Zyvox, Males and Females, Age 0-150

Response Summary (Prescriber)
Letters Sent: 98
Response Forms Returned: 62

The response forms returned yielded the following results:

14 (23%)	*Record Error—Not my patient.*
6 (10%)	*No longer my patient.*
6 (10%)	*Medication has been changed prior to date of review letter.*
17 (27%)	*I was unaware of this situation & will consider making appropriate changes in therapy.*
10 (16%)	*I am aware of this situation and will plan to continue monitoring therapy.*
9 (15%)	*Other*

Response Summary (Pharmacy)
Letters Sent: 39
Response Forms Returned: 22

The response forms returned yielded the following results:

1 (5%)	*Record Error—Not my patient.*
2 (9%)	*No longer my patient.*
3 (14%)	*Medication has been changed prior to date of review letter.*
6 (27%)	*I was unaware of this situation & will consider making appropriate changes in therapy.*
7 (32%)	*I am aware of this situation and will plan to continue monitoring therapy.*
3 (14%)	*Other*

Retrospective Drug Utilization Review Report

Claims Reviewed for April 2008

Module	Drug Interaction	Duplication of Therapy	Drug-Disease Precautions	Dosing & Duration
Limits which were applied	Established, Major, Males and Females, Age 22-35	Antidepressants-SSRIs, Males and Females, Age 22-40	Contraindicated, Hepatic Disease, Males and Females, Age 36-45	High Dose only, 3120 Digitalis, Males and Females, Age 0-150

Response Summary (Prescriber)
Letters Sent: 64
Response Forms Returned: 46

The response forms returned yielded the following results:

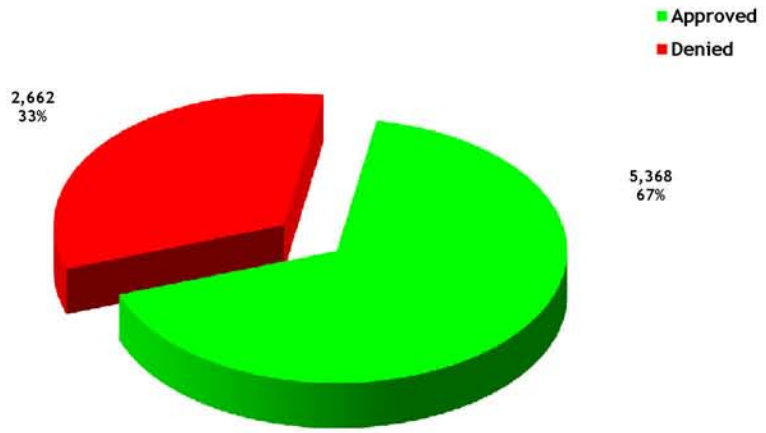
12 (26%)	*Record Error—Not my patient.*
5 (11%)	*No longer my patient.*
1 (2%)	*Medication has been changed prior to date of review letter.*
9 (20%)	*I was unaware of this situation & will consider making appropriate changes in therapy.*
13 (28%)	*I am aware of this situation and will plan to continue monitoring therapy.*
6 (13%)	*Other*

Response Summary (Pharmacy)
Letters Sent: 11
Response Forms Returned: 10

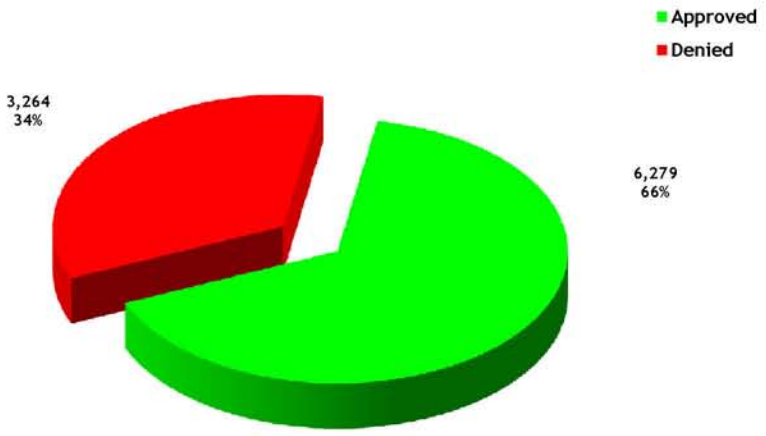
The response forms returned yielded the following results:

0 (0%)	*Record Error—Not my patient.*
1 (10%)	*No longer my patient.*
0 (0%)	*Medication has been changed prior to date of review letter.*
4 (40%)	*I was unaware of this situation & will consider making appropriate changes in therapy.*
4 (40%)	*I am aware of this situation and will plan to continue monitoring therapy.*
1 (10%)	*Other*

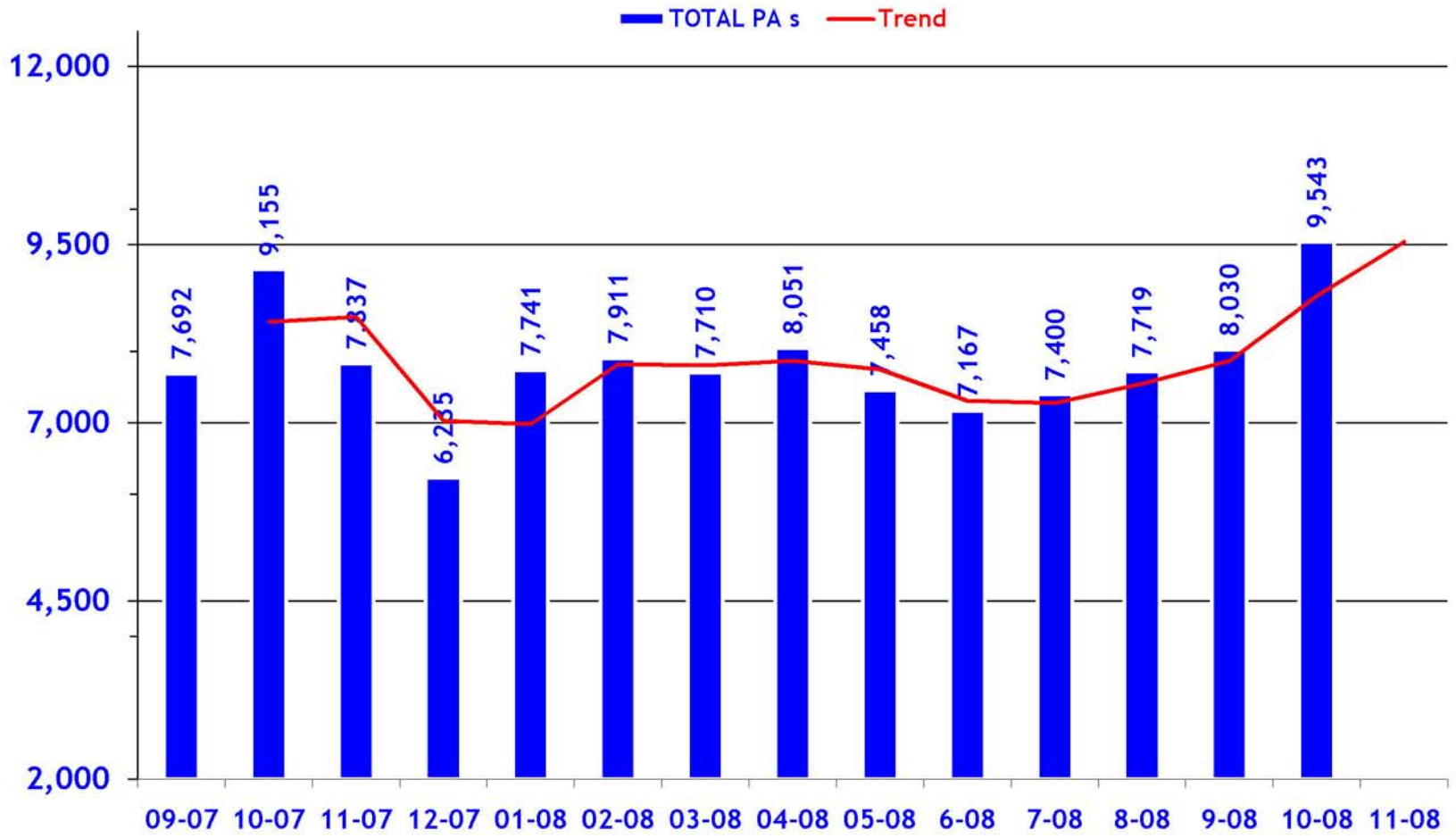
PRIOR AUTHORIZATION ACTIVITY REPORT
September 2008



PRIOR AUTHORIZATION ACTIVITY REPORT
October 2008



PRIOR AUTHORIZATION REPORT
September 2007 – October 2008



Activity Audit for

September 01, 2008 Through September 30, 2008

	Average Length of Approvals in Days	Approved	Denied	Total
ACE Inhibitors	38	11	2	13
Angiotensin Receptor Antagonist	355	31	86	117
Antidepressant	266	222	245	467
Antihistamine	105	267	270	537
Antiulcers	5	16	3	19
Anxiolytic	101	2,912	488	3,400
Calcium Channel Blockers	106	7	7	14
Growth Hormones	181	34	0	34
HTN Combos	220	5	7	12
Insomnia	120	56	85	141
Nsaids	331	31	54	85
Plavix	347	90	21	111
Stimulant	204	659	278	937
Others	89	1,027	1,116	2,143
Emergency PAs		0	0	0
Total		**5,368**	**2,662**	**8,030**
Overrides				
Brand	310	14	7	21
Dosage Change	7	361	40	401
High Dose	163	8	3	11
Lost/Broken Rx	6	71	4	75
Nursing Home Issue	12	58	4	62
Other	23	22	1	23
Quantity vs. Days Supply	160	18	4	22
Stolen	3	2	1	3
Wrong D.S. on Previous Rx	3	1	0	1
Overrides Total		**555**	**64**	**619**

Denial Reasons

Lack required information to process request.	1,765
Unable to verify required trials.	1,270
Considered duplicate therapy. Member has a prior authorization for similar medication.	172
Does not meet established criteria.	168
Not an FDA approved indication/diagnosis.	119
Member has active PA for requested medication.	76
Requested dose exceeds maximum recommended FDA dose.	65
Medication not covered as pharmacy benefit.	14
Drug Not Deemed Medically Necessary	11
Drug Deemed Medically Necessary	1
Duplicate Requests	708
* Changes to existing	702

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

Tuesday, November 4, 2008

Activity Audit for

October 01, 2008 Through October 31, 2008

	Average Length of Approvals in Days	Approved	Denied	Total
ACE Inhibitors	104	12	0	12
Angiotensin Receptor Antagonist	346	26	89	115
Antidepressant	245	213	273	486
Antihistamine	252	262	283	545
Antiulcers	14	10	7	17
Anxiolytic	99	3,158	539	3,697
Calcium Channel Blockers	132	13	5	18
Growth Hormones	168	30	2	32
HTN Combos	217	5	6	11
Insomnia	106	50	109	159
Nsaids	315	48	104	152
Plavix	330	94	13	107
Stimulant	200	625	331	956
Others	113	1,732	1,503	3,235
Emergency PAs		1	0	1
Total		**6,279**	**3,264**	**9,543**
Overrides				
Brand	227	31	5	36
Dosage Change	9	387	28	415
High Dose	210	3	1	4
Lost/Broken Rx	8	72	4	76
Nursing Home Issue	9	91	5	96
Other	24	26	5	31
Quantity vs. Days Supply	116	21	3	24
Stolen	3	5	0	5
Overrides Total		**636**	**51**	**687**

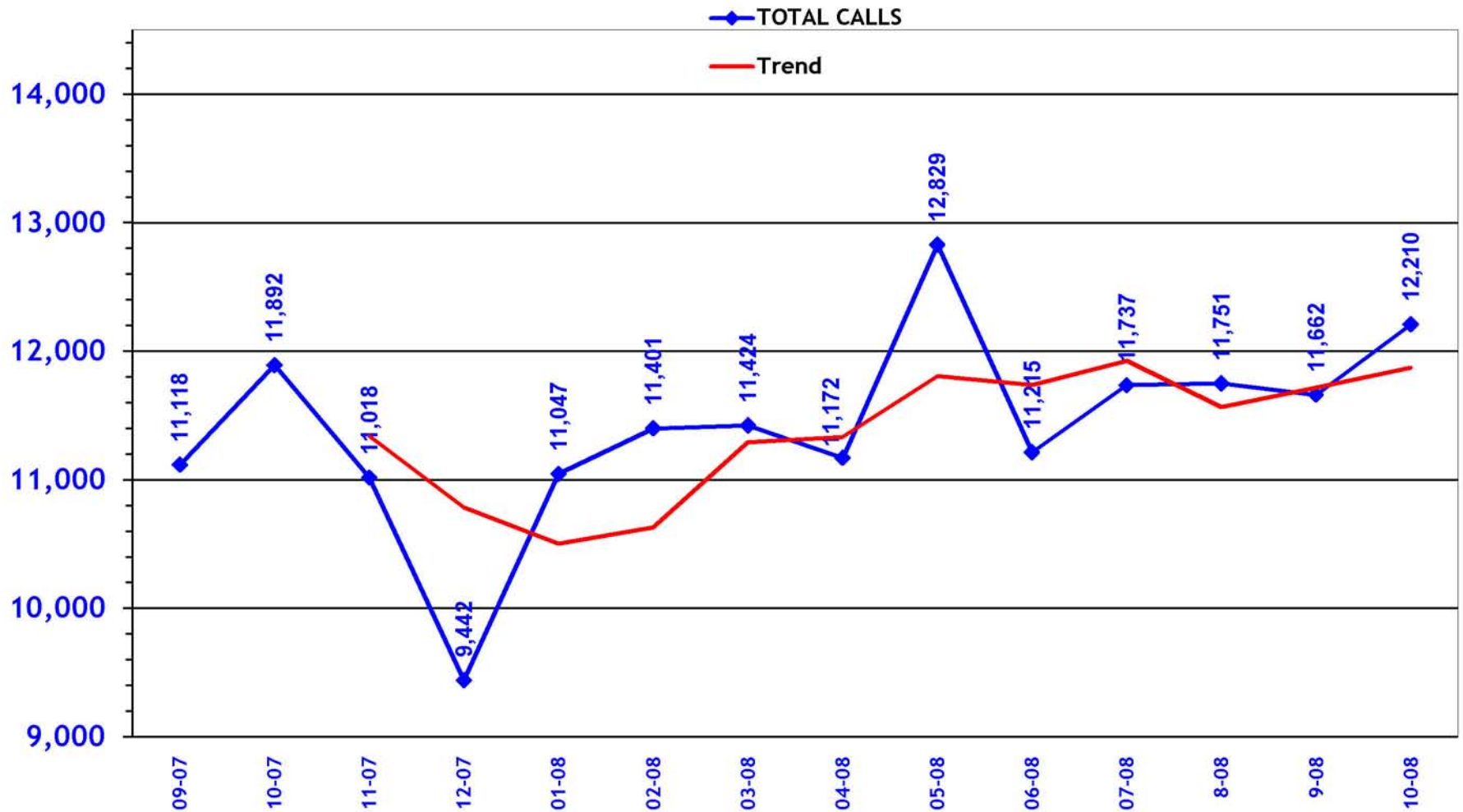
Denial Reasons

Lack required information to process request.	2,373
Unable to verify required trials.	1,553
Does not meet established criteria.	462
Considered duplicate therapy. Member has a prior authorization for similar medication.	198
Not an FDA approved indication/diagnosis.	126
Requested dose exceeds maximum recommended FDA dose.	93
Member has active PA for requested medication.	81
Medication not covered as pharmacy benefit.	15
Drug Not Deemed Medically Necessary	12
Member not approved for TB coverage and/or medication requested not associated with TB symptoms.	1
Drug Deemed Medically Necessary	1
Duplicate Requests	806
* Changes to existing	828

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

Tuesday, November 4, 2008

CALL VOLUME MONTHLY REPORT
September 2007 – October 2008



Appendix C

Vote on 2009 DUR Meeting Dates

Oklahoma Health Care Authority
November 2008

Meetings are held the second Wednesday of each month.

JANUARY 14, 2009

FEBRUARY 11, 2009

MARCH 11, 2009

APRIL 8, 2009

MAY 13, 2009

JUNE 10, 2009

JULY 8, 2009

AUGUST 12, 2009

SEPTEMBER 9, 2009

OCTOBER 14, 2009

NOVEMBER 11, 2009

DECEMBER 9, 2009

Appendix D

Vote to Prior Authorize ESAs

Oklahoma Health Care Authority

November 2008

Recommendations

The College of Pharmacy recommends prior authorization of ESAs with the following criteria:

1. FDA approved indication for specific products.
    a. Treatment of Anemia of Chronic Renal Failure Patients
    b. Treatment of Anemia in Zidovudine-treated HIV-infected Patients
    c. Treatment of Anemia in Cancer Patients on Chemotherapy
        i. Myelosuppressive Chemotherapy-Induced Anemia (Hb 8-10 g/dL) Non-Curative
    d. Reduction of Allogeneic Blood Transfusion in Surgery Patients
2. Most recent Hb levels (and date obtained) should be included on petition. Each approval will be for 8 weeks in duration. Authorization can be granted for up to 8 weeks following the final dose of myelosuppressive chemotherapy in a chemotherapy regimen. Authorization for surgery patients will be for a maximum of 4 weeks.
3. Continuation Criteria:
    a. Continue dose if Hb is ≤ 12.0 g/dL.
    b. If Hb is increasing and approaching 12 g/dL then reduce dose by at least 25%.
    c. If more than 1 g/dL increase (but Hb not greater than upper limits listed below) has occurred in a 2 week period reduce dose by 25 to 50 %.
4. Discontinuation Criteria:
    a. ESRD – Discontinue treatment if Hb is at or above 13.0 g/dL.
    b. All others – Discontinue treatment if Hb is at or above 12 g/dL.
    c. If a minimum increase of 1 g/dL has not been achieved after initial 8 weeks of therapy.
5. Reinitiation Criteria:
    a. If Hb decreases to ≤ 10 g/dL then therapy may be reinitiated at 25 to 50% of the prior dose.

New prior authorization forms for the initial and continuation requests for these medications will be implemented. A copy of these forms will be available at the DUR Board meeting for review. Once the initial request has been submitted and approved, continuation of therapy may occur with submission of the continuation form.

Appendix E

Vote to Prior Authorize Protonix Suspension®

Oklahoma Health Care Authority
November 2008

Anti-Ulcer Medications	
The following products requires prior authorization with a special reason for use: ▪ **ranitidine (Zantac) – effervescent tablets and capsules** ▪ **brand omeprazole 40mg (Prilosec 40mg caps)**	
Tier 1	**Tier 2**
omeprazole (10 and 20 mg caps)	**esomeprazole (Nexium Caps and I.V.)***
omeprazole/antacid (Zegerid Caps)	**omeprazole/antacid (Zegerid Packets)***
lansoprazole (Prevacid) capsules	**lansoprazole (Prevacid ODT and Granules)***
	pantoprazole sodium (Protonix Tabs, Oral Suspension, and I.V.)*

Aqua color indicates Supplemental Rebate Participation
* Special dosage forms require reason for use.

Approval Criteria

- Documented recent trial of a Tier 1 medication with inadequate results or adverse effect, or
- Documented contraindication to the Tier 1 medications, or
- Documented FDA-approved indication for which Tier 1 products are not indicated

Recommendations

The College of Pharmacy recommends placing Protonix® Oral Suspension in Tier 2 of the Anti-ulcers PBPA Category. Approval requires documentation of medical necessity for this dosage form over available Tier 1 products. Quantity limit of 30 packets for 30 days would also be applied.

Appendix F

Vote to Prior Authorize Patanase® (olopatadine hydrochloride)

Oklahoma Health Care Authority
November 2008

Manufacturer	Alcon Laboratories, Inc.
Classification	H_1 receptor antagonist nasal spray
Status:	Prescription Only

Summary

Patanase is a 0.6% (665mcg of olopatadine hydrochloride in each 100-microliter spray) antihistamine nasal spray with selective H1 receptor antagonist activity. It is specifically indicated for symptomatic relief of seasonal allergic rhinitis in patients 12 years of age and older. It is available in a 30.5g bottle that contains 240 actuations. The recommended dose is two sprays per nostril twice a day.

Recommendations

The College of Pharmacy recommends prior authorization of Pantanase® and placement as a Tier 3 nasal allergy product. Approval will be based on the following criteria:

1. The following criteria are required for approval of a Tier 2 product (or a Tier 3 product if no Tier 2 exists):
    a. Documented adverse effect or contraindication to the preferred products.
    b. Failure with at least two Tier 1 medications defined as no beneficial response after at least two weeks each of use during which time the drug has been titrated to the recommended dose (all available Tier 1 corticosteroids should be tried prior to approval of higher Tiered products).
2. The following criteria are required for approval of a Tier 3 product:
    a. All Tier 2 criteria must be met.
    b. Failure with all available Tier 2 products defined as no beneficial response after at least two weeks each of use during which time the drug has been titrated to the recommended dose.
3. Approvals will be for the duration of three months, except for members with chronic diseases such as asthma or COPD, in which case authorizations will be for the duration of one year.

Appendix G

Vote to Prior Authorize Rescue HFA Inhalers

Oklahoma Health Care Authority
November 2008

Recommendations

The College of Pharmacy recommends the addition of the Rescue HFA Inhalers to the Product Based Prior Authorization program. This category is unique in that, pharmacologically, all the agents considered consist of a form of albuterol, in an aerosolized delivery device with hydrofluoroalkane as the propellant. Therefore, the College of Pharmacy recommends initiation of a supplemental rebate offer to all manufacturers involved before arrangement of the products in the tier list. The manufacturer(s) returning the best economic offer will subsequently have their product placed on Tier 1, and all others will be placed on Tier 2. If no supplemental rebate offers are returned then the current lowest priced HFA product will be placed on Tier 1. Once the Tier 1 product(s) have been determined, the College of Pharmacy will perform an educational outreach activity to inform providers of the SoonerCare preferred product(s).

Short Acting B2 Agonists	
Tier 1	**Tier 2**
Best Supplemental Rebate Agreement	**ProAir® HFA**
	Proventil® HFA
	Ventolin® HFA
	Xopenex® HFA

The following is the proposed approval criteria:

1. Approved or clinically accepted indication, and
2. Specific reason member cannot use all available Tier 1 products.

Appendix H

Drug Utilization Review of Antidepressants and Vote to PA Luvox CR®

Oklahoma Health Care Authority
November 2008

Current Prior Authorization of Antidepressants

The following is the current tier structure and prior authorization criteria that has been in effect for this PBPA category since 2005. It is important to note that this category has always fallen under the grandfathering rule and will remain under this rule. This allows a member who is currently stabilized on a medication to remain on that same medication regardless of changes in tier or criteria that may subsequently go into effect. A member is considered stabilized on a medication when claims history suggests continuous usage of the medication in the past 100 days.

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

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

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

Miscellaneous Restrictions of Antidepressants

The following is a table of quantity limits that apply:

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

Fluoxetine 40 mg Capsules

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

Prozac® Weekly

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

Recommendations

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

Criteria for Approval of a Tier 2 Medication:

1. **A documented, recent (within 6 months) trial of a Tier 1 medication at least 4 weeks in duration and titrated to recommended dosing, that did not provide an adequate response. Tier 1 selection can be from any classification.**
2. **Prior stabilization on the Tier 2 medication documented within the last 100 days. A past history of success on the Tier 2 medication will also be considered with adequate documentation.**
3. **A unique FDA-approved indication not covered by Tier 1 products or other products from a different therapeutic class.**
4. **A petition may be submitted for consideration whenever a unique member specific situation exists.**

Criteria for Approval of a Tier 3 Medication:

1. **A documented, recent (within 6 months) trial with a Tier 1 and a Tier 2 medication at least 4 weeks in duration and titrated to recommended dose, that did not provide an adequate response. Tier 1 and Tier 2 selection can be from any classification.**
2. **Prior stabilization on the Tier 3 medication documented within the last 100 days. A past history of success on the Tier 3 medication will also be considered with adequate documentation.**
3. **A unique FDA-approved indication not covered by a lowered tiered product or other products from a different therapeutic class.**
4. **A petition may be submitted for consideration whenever a unique member specific situation exists.**

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

Mandatory generic plan applies.

Available Second Generation Antidepressants

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

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

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

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

† Generic available for all or some dosage forms.

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

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

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

Studies for Major Depressive Disorders*

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

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

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

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

Studies for General Anxiety Disorder (GAD)*

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

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

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

Studies for Pediatric Outpatients with MDD

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

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

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

Studies for Post-Traumatic Stress Disorder*

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

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

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

Studies for Social Anxiety Disorder*

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

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

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

Studies for Obsessive Compulsive Disorder*

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

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

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

Studies for Panic Disorder*

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

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

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

Studies for Dysthymia*

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

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

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

Studies for Pre-Menstrual Dysphoric Disorder*

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

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

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

Studies for Adverse Events

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

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

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

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

Comparison of Adverse Events Among Antidepressants*

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

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

Comparison of Sexual Adverse Effects Among Antidepressants*

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

*Compiled from reported rates in product literature.

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

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[5] Eli Lilly and Company. Package Literature Cymbalta®. January 2005. Available online::http://cymbalta.com/index.jsp.

[6] Forrest Pharmaceuticals, Inc. Package Literature Lexapro®. February 2005. Available online:http://lexapro.com/pdf/lexapro_pi.pdf.

[7] Eli Lilly and Company. Package Literature Prozac®. November 2003. Available online: http://prozac.com/common_pages/prescribing_information.jsp?reqNavId=undefined.

[8] Jazz Pharmaceuticals, Inc. Package Literature Luvox CR®. April 2008. Available Online: **http://www.luvoxcr.com/LUVOX-CR-PI.pdf**

[9] Organon USA, Inc. Package Literature Remeron Soltab®. January 2005. Available online:http://www.remeronsoltab.com/Authfiles/Images/292_73427.pdf.

[10] GlaxoSmithKline Pharmaceuticals. Package Literature Paxil®. March 2004. Available online:http://us.gsk.com/products/assets/us_paxil.pdf.

[11] Pfizer Pharmaceuticals. Package Literature Zoloft®. Available online:http://www.zoloft.com/pdf/ZoloftUSPI.pdf.

[12] Wyeth Pharmaceuticals, Inc. Package Literature Effexor XR®. January 2005. Available online:http://www.effexorxr.com/hcp/index.asp.

Appendix I

Glaucoma Intervention Follow-Up Report

Oklahoma Health Care Authority

November 2008

Introduction

Pharmacy Management Consultants (PMC) has worked with the Oklahoma Health Care Authority (OHCA) to meet the OBRA '90 Retrospective Drug Utilization Review requirements for Oklahoma SoonerCare members since 1993. The findings of these reviews play an important role in shaping the management of healthcare related resources to ensure safe and appropriate utilization of medications. Among the various programs PMC has implemented, provider and member educational outreach programs play a vital role in increasing the appropriate use of medications. A recent review of ophthalmic glaucoma medications identified potential under utilization and/or compliance issues in members with a diagnosis of glaucoma. To address this issue PMC implemented an educational outreach program for both SoonerCare members and physicians. The details of the program are outlined below.

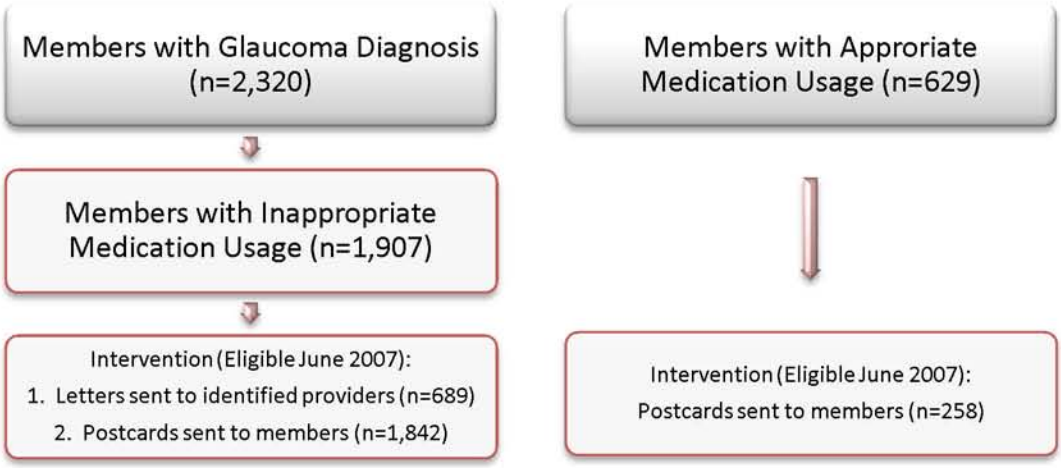
Goal of the Program

- To increase the appropriate utilization of glaucoma medications and eye exams in the Oklahoma SoonerCare population.

Methods for Identification of Members and Providers

- Pharmacy and medical/hospital claims from January 1, 2007 through March 31, 2007 were analyzed to identify members who had a diagnosis of glaucoma but did not have claims for a glaucoma medication or demonstrated noncompliance to medication refills based on submitted day supplies (n=1,907).
- Providers were identified by pulling the providers on the members' claims who had a specialty in the eye care field (n=266 unique prescribers).
- In addition, members who were considered compliant with their glaucoma medication (continuation of therapy during review time period) were also added to the intervention group in an effort to further educate and increase compliance with medications and recommended annual eye exams (n=629).
- Only members who were eligible in June 2007 were included in the intervention.

FIGURE 1. OUTLINE OF INCLUSION CRITERIA



Member and Providers Interventions

- Providers received a letter regarding members under their care who had a diagnosis of glaucoma, but did not have medication claims or apparent medication compliance, as well as a response survey that the providers were encouraged to complete and return to PMC (n=689) (see Figure 2).
- All members received a postcard regarding the importance of regular eye exams and medication compliance (n=2,100) (see Figure 3).

Outcomes Measured

- Pharmacy claims were analyzed to determine if a change in utilization of glaucoma medications for members included in the intervention occurred after the intervention.
- Medical/Hospital claims were analyzed to evaluate number of eye exams in the time periods before and after the intervention.
- Provider survey responses were compiled and reviewed.

Analysis and Results

The proportion of members that had eye exams and glaucoma medication claims before and after the intervention were reviewed and the results are outlined below.

TABLE 1. MEMBERS RECEIVING AT LEAST ONE GLAUCOMA PRESCRIPTION BEFORE AND AFTER INTERVENTION BY TYPE

Intervention Type	Unduplicated Members	At least 1 Rx Prior to Intervention	At least 1 Rx After Intervention	Percent Increase in Members with Rx Usage
Postcards	1,153	77	317	21%
Letters/Postcards	689	2	627	91%
Postcards to Members with Compliant Rx	258	258	258	n/a
Total	**2,100**	**335**	**1,202**	**41% ↑**

Table 1 shows the number of members that had at least one prescription prior to the intervention (although compliance may have been an issue) versus the number of members with at least one prescription after the intervention by intervention type. The overall percent of members with at least one claim increased by 41 %, however 898 members still did not have a glaucoma medication on file. The members who had a prescription after the intervention increased from 15.95 % to 54.24 % and chi-square analysis indicated that there was an association between the intervention and the number of members with a prescription (p. <0.001). Members who had been compliant on medication did not have a change in utilization which indicates that these members continued to be compliant on their regimen. It also appears there was an association between having a claim for a glaucoma medication in the post intervention period given your provider was also sent a letter (p. <0.001).

TABLE 2. MEMBERS HAVING AN EYE EXAM BEFORE AND AFTER THE INTERVENTION

	Eye Exam	No Eye Exam
Prior to Intervention	20	2080
After Intervention	856	1244

The number of eye exams also increased after the intervention (Table 2). Prior to the intervention, only 20 members had received an eye exam. This number had increased to 856 after the intervention. Analysis of these proportions indicated that there was also an association between receiving an eye exam and the intervention (p. <0.001).

TABLE 3. MEMBERS WITH BOTH AN EYE EXAM AND/OR A GLAUCOMA MEDICATION CLAIM AFTER THE INTERVENTION

	Rx	No Rx	Total
Eye Exam	452	424	**876**
No Eye Exam	750	474	**1,224**
Total	**1,202**	**898**	**2,100**

Table 3 shows the number of members after the intervention that received both an eye exam and had at least one claim for a glaucoma medication (452, 21.5 %). The total number of members with both an eye exam and at least one glaucoma medication prior to the intervention was less than 1 %.

TABLE 4. SUMMARY OF PROVIDER RESPONSES TO INTERVENTION LETTER

Provider Letter Responses	
Unaware/Contact Member/Order Exam and Rx	424
No Longer Patient/Not My patient	126
Incomplete	12
Total	**670**

Finally, Table 4 shows a summary of the responses to the letters sent to the providers regarding their patients. A sample of the letter and response page can be found in Attachment 1.

Summary and Conclusion

- The rate of glaucoma medication utilization for members increased 41.28% for an overall rate of 57.2 % after the intervention for these members.
- The proportion of members receiving an eye exam increased by 40.7 %. The number of eye exams increased for both members who received a postcard only and for members who received a postcard and had a letter sent to their provider.
- Approximately 97.2% of provider who were sent letters returned the response form and generally responded favorably to the intervention.

The results of this intervention indicate that it was received favorably and produced a significant increase in utilization of important medications for the members included; however an even higher rate of utilization is desirable. While eligibility was verified prior to final inclusion in the intervention, eligibility for the members may have fluctuated after the intervention causing a lower utilization rate. Total cost to perform this intervention, including personnel time, was approximately $3,000. Overall this intervention appears to be a cost-effective method for increasing utilization and awareness in this disease state.

Recommendations

The College of Pharmacy recommends adding this intervention to the RetroDUR program as an annual or biannual outreach to its members.

FIGURE 1. MAP OF COUNTIES SHOWING NUMBER OF MEMBERS WITH A DIAGNOSIS OF GLAUCOMA WHO ALSO RECEIVED GLAUCOMA MEDICATION – FY06

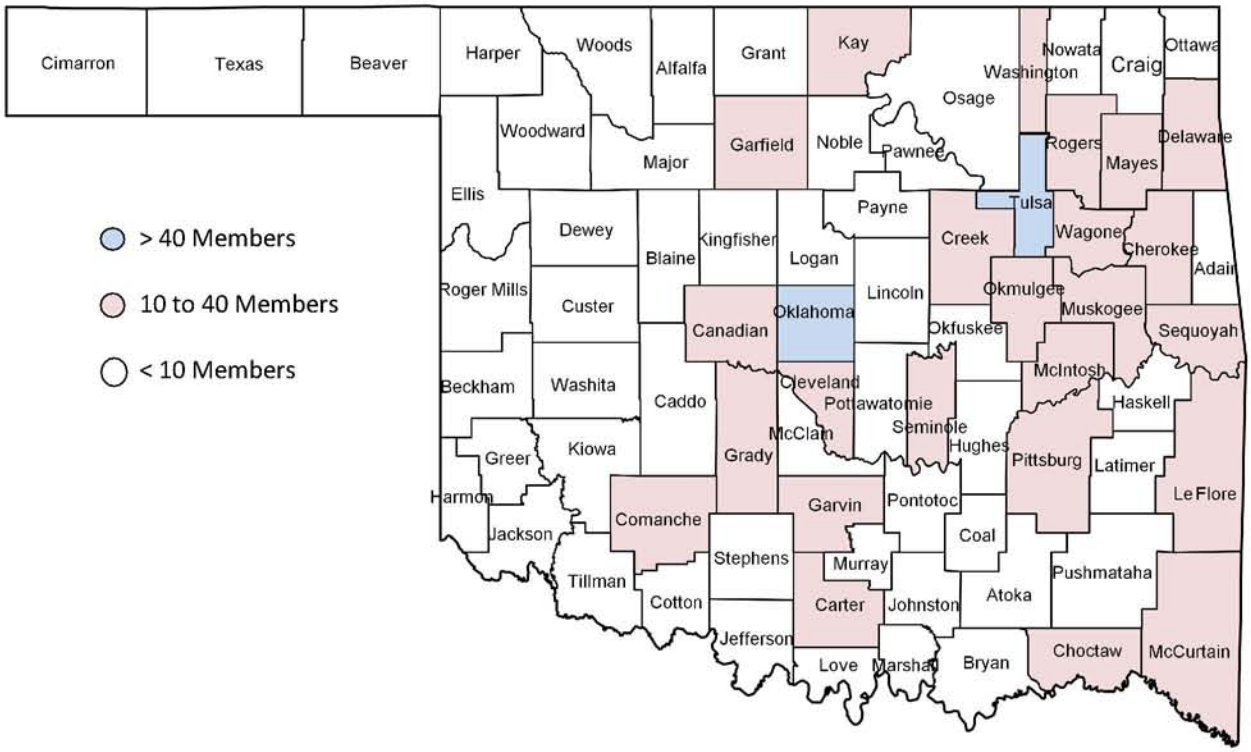
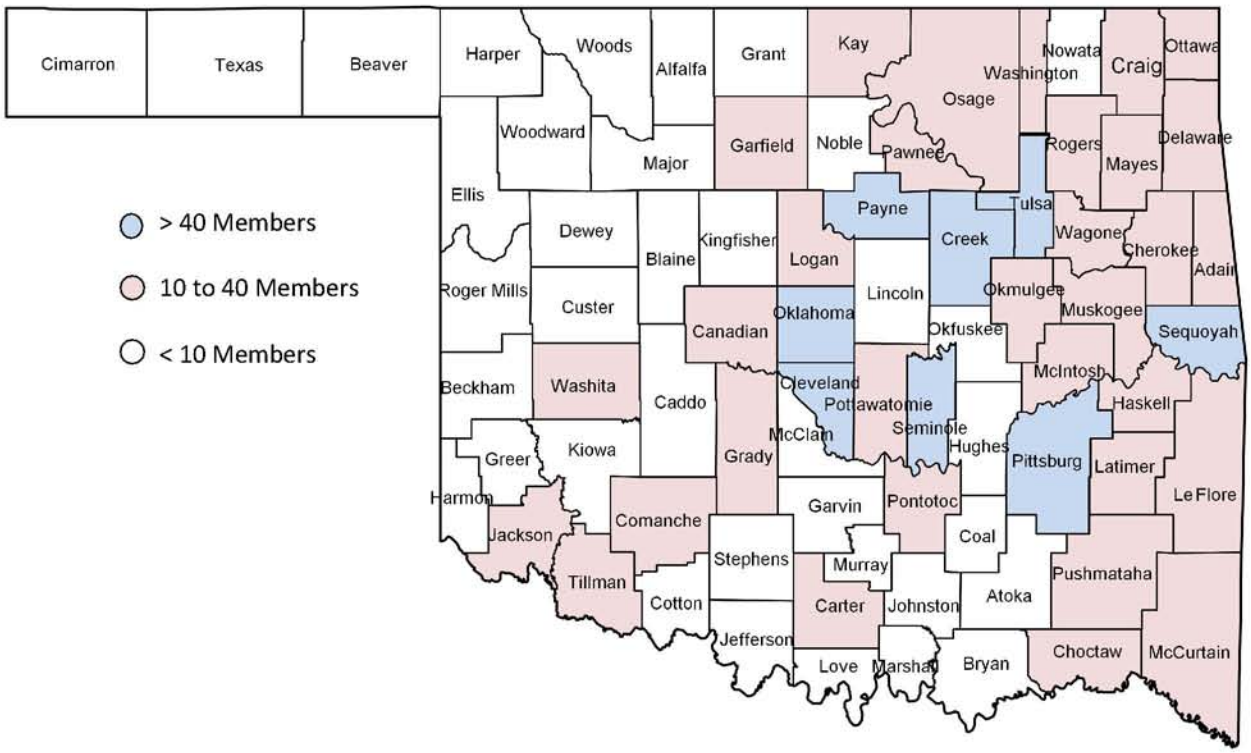


FIGURE 2. MAP OF COUNTIES SHOWING NUMBER OF MEMBERS WITH A DIAGNOSIS OF GLAUCOMA WHO ALSO RECEIVED GLAUCOMA MEDICATION – FY08



ATTACHMENT ONE: COPY OF LETTER AND RESPONSE PAGE SENT TO PROVIDERS

oklahoma health care authority

Oklahoma SoonerCare

Working Together for a Healthier Oklahoma

OKC Metro Area: (405) 522-6205 option 4
Statewide Toll-Free: (800) 522-0114 option 4

Dear Prescriber,

Recent reviews of SoonerCare medical and pharmacy claims revealed some troubling trends as detailed below. We earnestly request your participation to reverse these trends and help promote annual dilated eye examinations and compliance with medical treatment as recommended by the National Eye Institute for those diagnosed and at high risk for glaucoma.

- African-Americans over the age of 40
- Everyone over the age of 60 years of age, especially Mexican Americans
- People with diabetes or family history of glaucoma

To assist you in initiating the educational process and raising glaucoma awareness, patient education materials about glaucoma will be sent to members.

During the review of member diagnosis and medication claim profiles, it was noted that your patient, _____ may have the following concern(s):

1. **Diagnosis of glaucoma in medical claims history but no current medication therapy**

2. **Possible non-compliance with medication therapy. If you have not discontinued medication to treat glaucoma, please counsel the member on the importance of taking medications as prescribed.**

3. **Unable to verify an annual dilated eye examination in members profile as recommended by national guidelines for reevaluation of current medical treatments and status of disease progression.**

Please remember that the findings of the review are based upon the information available in the SoonerCare claims database at the time of review.

We value your response and comments to this information regarding the member's current glaucoma therapy. Please note your comments on the attached provider response form and return the form in the enclosed envelope. This helps us ensure a high standard of quality of care is provided to our members. Thank you for your time and assistance in this review process.

Sincerely,

Oklahoma Health Care Authority

Drug Utilization Review Program
Glaucoma

Provider Response Form

Member Name: Member Id:

Screening Date:

This information is communicated strictly in confidence to the provider for evaluation and response:

- ☐ Not my patient/No longer my patient
- ☐ Medication has been discontinued prior to review letter.
- ☐ I was unaware of this situation and will:
  - ☐ Contact the patient/caregiver
  - ☐ Schedule patient for follow-up
- ☐ Member has had an annual dilated eye examination. Date: _____
- ☐ Other Comments

Prescriber Name Initial(s)

Provider Id: _____

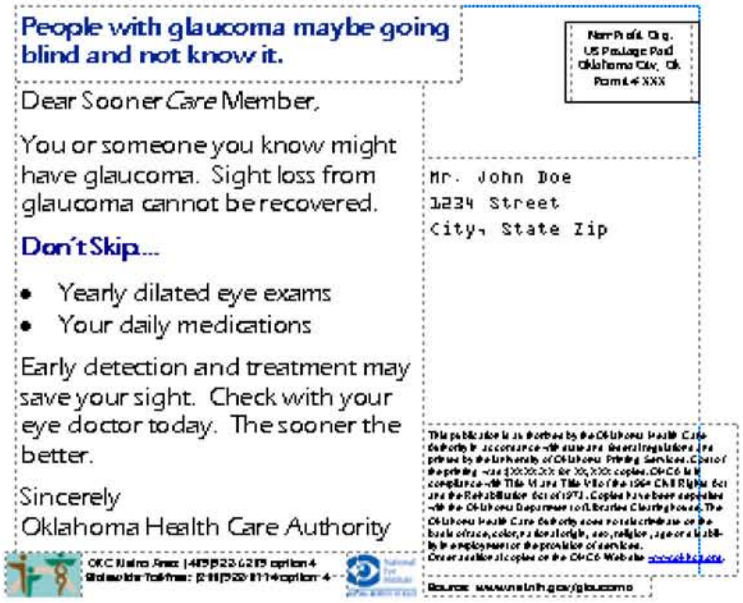
This service is provided to you by the Oklahoma Health Care Authority to ensure high quality of care is provided to members.

Please return this page in the enclosed postage prepaid envelope.

Fax (405) 271-6002 or (866) 335-3331
Pharmacy Management Consultants
P.O.Box 26901; ORI W-4403
Oklahoma City, Oklahoma 73190

ATTACHMENT TWO: EXAMPLE OF POSTCARD SENT TO ALL MEMBERS

Front



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Appendix J

Recall -- Firm Press Release

FDA posts press releases and other notices of recalls and market withdrawals from the firms involved as a service to consumers, the media, and other interested parties. FDA does not endorse either the product or the company.

ETHEX Corporation Voluntarily Recalls Three Lots of Dextroamphetamine Sulfate 5mg Tablets Due to the Potential for Oversized Tablets

Lot Number 77946, 81141 and 81142 NDC #58177-311-04

Contact:
Ann McBride
1-800-321-1705

FOR IMMEDIATE RELEASE -- St. Louis, MO – October 15, 2008 – ETHEX Corporation announced today that it has voluntarily recalled three specific lots (77946, 81141 and 81142) of Dextroamphetamine Sulfate 5 mg tablets, as a precaution, due to the possible presence of oversized tablets. Oversized tablets may contain as much as about twice the labeled amount of the active ingredient. The recalled lots were distributed by ETHEX Corporation under an "ETHEX" label between January 2007 and May 2008. The 5 mg product is an orange round tablet debossed with "ETHEX" and "311" on one side.

If someone were to take a higher than expected dose of Dextroamphetamine Sulfate, then the risk of adverse effects known to be associated with the drug such as tachycardia, hypertension, tremors, decreased appetite, headache, insomnia, dizziness, blurred vision, stomach upset, and dry mouth may be increased.

No report of any oversized Dextroamphetamine Sulfate tablets has been received by ETHEX from any wholesaler, retailer, consumer or caregiver, and ETHEX has not received any report of unexpected side effects or injury related to this product.

ETHEX Corporation is conducting this precautionary, voluntary recall because it found a small number of oversized tablets in lots which had not yet been distributed. These oversized tablets were removed before the lots were distributed.

Please be aware that there are multiple companies in the United States producing and marketing generic versions of Dextroamphetamine Sulfate 5 mg tablets and consumers and their caregivers are encouraged to check their prescriptions to determine the source of their tablets.

Any customer inquiries related to this action should be addressed to ETHEX Customer Service at 1-800-321-1705, or fax to ETHEX Customer Service at 314-646-3751 or sent via email to: customer-service@ethex.com with representatives available Monday through Friday, 8 am to 5 pm CST.

ETHEX Corporation has initiated recall notifications to wholesalers and retailers nationwide who have received any inventory of the recalled lots of this product with instructions for returning the recalled product and, if they have not already done so, they are urged to contact ETHEX as provided above regarding procedures for returning the recalled product. Consumers and their caregivers should not use any Dextroamphetamine Sulfate tablets that appear to be oversized. If consumers have any questions about the recall, they should call the telephone number above, their

physician, their pharmacist or other health care provider.

This recall is being conducted with the knowledge of the U.S. Food and Drug Administration (FDA).

Any adverse reactions experienced with the use of this product, and/or quality problems may also be reported to the FDA's MedWatch Program by phone at 1-800-FDA-1088, by Fax at 1-800-FDA-0178, by mail at MedWatch, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787, or on the MedWatch website at www.fda.gov/medwatch.

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FDA Website Management Staff

FDA News

FOR IMMEDIATE RELEASE
October 15, 2008

Media Inquiries:
Christopher DiFrancesco, 301-827-6242
Consumer Inquiries:
888-INFO-FDA

FDA Creates Web Page with Drug Safety Information for Patients, Health Care Professionals

Consolidates information in one access point

Consumers and health care professionals can now go to a single page on the U.S. Food and Drug Administration's Web site to find a wide variety of safety information about prescription drugs. The Web page, http://www.fda.gov/cder/drugSafety.htm, provides links to information in these categories:

- Drug labeling, including patient labeling, professional labeling, and patient package inserts;
- Drugs that have a Risk Evaluation and Mitigation Strategy (REMS) to ensure that their benefits outweigh their risks;
- A searchable database of postmarket studies that are required from, or agreed to by, drug companies to provide the FDA with additional information about a drug's safety, efficacy, or optimal use;
- Clinicaltrials.gov, a searchable database of clinical trials, including information about each trial's purpose, who may participate, locations, and useful phone numbers;
- Drug-specific safety information, including safety sheets with the latest information about the drug as well as related FDA press announcements, fact sheets, and drug safety podcasts;
- Quarterly reports that list certain drugs that are being evaluated for potential safety issues, based on a review of information in the FDA's Adverse Event Reporting System (AERS);
- Warning Letters, Import Alerts, Recalls, Market Withdrawals, and Safety Alerts;
- Regulations and guidance documents;
- Consumer information about using medications safely and disposing of unused medicines;
- Instructions how to report problems to the FDA through its MedWatch program;
- Consumer articles on drug safety; and
- The FDA's response to the Institute of Medicine's 2006 report on the future of drug safety.

"By placing Web links to these up-to-date resources on a single page, we're helping consumers and health care professionals find drug safety information faster and easier," said Paul Seligman, M.D., M.P.H., associate director of Safety Policy and Communication in the FDA's Center for Drug Evaluation and Research. "This type of communication is aimed at helping consumers and health care professionals make well-informed decisions about medication use."

Establishing such a Web page is one of the requirements of the Food and Drug Administration Amendments Act of 2007, and is among FDA's many efforts to address the safe use of drugs throughout their lifecycle.

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FDA Statement

FOR IMMEDIATE RELEASE
October 8, 2008

Media Inquiries:
Rita Chappelle, 301-827-6242
Consumer Inquiries:
888-INFO-FDA

FDA Statement Following CHPA's Announcement on Nonprescription Over-the-Counter Cough and Cold Medicines in Children

Background: The Consumer Healthcare Products Association (CHPA), an association that represents most of the makers of nonprescription over-the-counter (OTC) cough and cold medicines in children, recently announced that its members are voluntarily modifying the product labels for consumers of OTC cough and cold medicines to state ***"do not use"*** *in children under 4 years of age. Additionally, the manufacturers are introducing new child-resistant packaging and new measuring devices for use with the products.*

The U.S. Food and Drug Administration supports the voluntary actions by CHPA members to help prevent and reduce misuse and to better inform consumers about the safe and effective use of these products for children. The FDA continues to assess the safety and efficacy of these products and to revise its OTC monograph (list of approved ingredients and amounts) for these medicines. Although this new labeling is inconsistent with the current monograph, FDA will not object, under the circumstances presented here, to the new label modification stating "do not use in children under 4," which reflects a more restrictive use of the drugs in children.

The steps that are being taken by CHPA will not affect the availability of the medicines, but this voluntary action will result in a transition period where the instructions for use of some OTC cough and cold medicines in children will be different from others. FDA does not typically request removal of OTC products with previous labeling from the shelves during a voluntary label change such as this one. Therefore, some medicines will have the new recommendation "do not use" for children under 4 years of age, while others will instruct that they not be used for children under 2 years of age. If parents or caregivers have or purchase a product that does not have the voluntarily-modified labeling, FDA recommends that they should adhere to the dosage instructions and warnings on the label that accompanies the medication. They should not, under any circumstances, give adult medications to children. If parents or caregivers have questions or are just not sure about how to use a product, they should consult with their doctor or pharmacist.

Over the last year, FDA has been working on several fronts to address the safe use of nonprescription OTC cough and cold medicines in children.

FDA has held two public meetings to hear from stakeholders and consumers on the issue, most recently, a public hearing that focused on labeling of these products on Oct. 2, 2008. In January of this year, FDA issued a nationwide Public Health Advisory recommending that these products not be used in children under the age of two because of the risk of serious and potentially life-threatening side effects.

Another part of the agency's work includes outreach to other public health agencies, consumer and patient groups companies that manufacture these products, and CHPA.

FDA will continue to work with the Centers for Disease Control and Prevention to monitor the

ongoing use of these products and to develop educational materials for parents and consumers. The Agency will also continue to reach out to the scientific community to obtain more up-to-date information and scientific data about the effects of these products in children so that it can take the appropriate regulatory steps moving forward.

All these areas are vital to support the development and review of data regarding the safe and effective use of these products.

FDA is proceeding with its rulemaking process to update the existing OTC monograph for cough and cold products for children, and will consider input from the recent hearing of Oct. 2. The rulemaking process affords additional opportunity for the submission of data and public comment.

Until all these issues are resolved, FDA continues to recommend to parents and caregivers the following:

- **Do not give children medications labeled only for adults.**
- **Talk to your healthcare professional if you have any questions about using cough or cold medicines in children.**
- **Choose OTC cough and cold medicines with child-resistant safety caps, when available.** After each use, make sure to close the cap tightly and store the medicines out of the sight and reach of children.
- **Check the "active ingredients" section of the DRUG FACTS label of the medicines that you choose.** This will help you understand what symptoms the "active ingredients" in the medicine are intended to treat. Cough and cold medicines often have more than one active ingredient (such as an antihistamine, a decongestant, a cough suppressant, an expectorant, or a pain reliever/fever reducer).
- **Be very careful if you are giving more than one medicine to a child.** If you are giving more than one medicine to a child make sure that they do not have the same type of "active ingredients." If you use two medicines that have the same or similar active ingredients, a child could get too much of an ingredient and that may hurt your child. For example, do not give a child more than one medicine that has a decongestant.
- **Carefully follow the directions for how to use the medicine in the DRUG FACTS part of the label.** These directions tell you how much medicine to give and how often you can give it. If you have a question about how to use the medicine, ask your pharmacist or your doctor. Overuse or misuse of these products can lead to serious and potentially life threatening side effects such as rapid heartbeat, drowsiness, suppression of the respiratory system, seizures and other adverse events.
- **Only use measuring devices that come with the medicine or those specially made for measuring drugs.** Do not use common household spoons to measure medicines for children because household spoons come in different sizes and are not meant for measuring medicines.
- **Understand that using OTC cough and cold medicines does not cure the cold or cough.** These medicines only treat your child's symptom(s) such as runny nose, congestion, fever and aches and do not shorten the length of time your child is sick.

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Early Communication about an Ongoing Safety Review of Tiotropium (marketed as Spiriva HandiHaler)

Update 10/07/2008: FDA's Early Communication About an Ongoing Safety Review issued on March 18, 2008 stated that Boehringer Ingelheim, the maker of Spiriva HandiHaler (tiotropium bromide), had conducted a pooled analysis of 29 trials that suggested a small excess risk of stroke (2 cases per 1000) with tiotropium bromide over placebo. FDA has now received preliminary data from UPLIFT (Understanding the Potential Long-Term Impacts on Function with Tiotropium), a large, 4-year, placebo controlled clinical trial with Spiriva HandiHaler in approximately 6000 patients with chronic obstructive pulmonary disease (COPD). The preliminary results of UPLIFT reported by Boehringer Ingelheim to the FDA showed that there was no increased risk of stroke with tiotropium bromide (Spiriva HandiHaler) compared to placebo.

Two recent publications[1, 2] reported increased risk for mortality and/or cardiovascular events in patients who received tiotropium or inhaled anticholinergics. Both studies examined cardiovascular outcomes. Singh et al.[1] performed a systematic review and meta-analysis of 17 clinical trials enrolling 14,783 patients treated with inhaled anticholinergic drugs used for the treatment of chronic obstructive lung disease. Lee et al.[2] performed a case-control study of 32,130 patients (320,501 controls) treated with inhaled medications, including an anticholinergic, for the treatment of chronic obstructive lung disease.

FDA expects to receive the complete report for UPLIFT in November 2008. Results from this trial will also help to address some issues raised about tiotropium in the two recent publications. Due to the amount of data collected in UPLIFT, a complete review of the results could take several months, at which time FDA will update this communication with the final results of the UPLIFT analysis, as well as all the available data regarding tiotropium and stroke risk.

1. Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease. JAMA 2008; 300 (12): 1439-1450.

2. Lee TA, Pickard S, et al. Risk of Death Associated with Medications for Recently Diagnosed Chronic Obstructive Pulmonary Disease. Annals of Internal Medicine 2008; 149: 380-390.

This information reflects FDA's current analysis of available data concerning this drug. Posting this information does not mean that FDA has concluded there is a causal relationship between the drug product and the emerging safety issue. Nor does it mean that FDA is advising health care professionals to discontinue prescribing this product. FDA is considering, but has not reached a conclusion about whether this information warrants any regulatory action. FDA intends to update this document when additional information or analyses become available.

The manufacturer of Spiriva HandiHaler, Boehringer Ingelheim, recently informed the FDA that ongoing safety monitoring has identified a possible increased risk of stroke in patients who take this medicine. Spiriva HandiHaler contains tiotropium bromide and is used to treat bronchospasm associated with chronic obstructive pulmonary disease (COPD). Additional information is needed to further evaluate this preliminary information about stroke in patients who take Spiriva HandiHaler.

Boehringer Ingelheim reported to the FDA that it has conducted an analysis of the safety data from 29 placebo controlled clinical studies ("pooled analysis"). In 25 of the clinical studies, patients were treated with Spiriva HandiHaler. In the other 4 clinical studies patients were treated with another formulation of tiotropium approved in Europe, Spiriva Respimat. The 29 clinical studies included approximately 13,500 patients with COPD. Based on data from these studies, the preliminary estimates of the risk of stroke are 8 patients per 1000 patients treated for one year with Spiriva, and 6 patients per 1000 patients treated for one year with placebo. This means that the estimated excess risk of any type of stroke due to Spiriva is 2 patients for each 1000 patients using Spiriva over a one year period.

It is important to interpret these preliminary results with caution. FDA has not confirmed these analyses. Pooled analyses can provide early information about potential safety issues. However, these analyses have inherent limitations and uncertainty that require further investigation using other data sources. This early communication is in keeping with FDA's commitment to inform the public about its ongoing safety reviews of drugs.

FDA is working with Boehringer Ingelheim to further evaluate the potential association between Spiriva and stroke. FDA has requested additional information and is currently reviewing post-marketing adverse event reports with Spiriva. In addition, the manufacturer of Spiriva has conducted a large study called UPLIFT (Understanding the Potential Long-Term Impacts on Function with Tiotropium), which is a large four year study that will provide additional long term safety data with Spiriva and additional insight into the risk of stroke or other safety findings with tiotropium. The data from UPLIFT is expected to be available in June 2008. Once Boehringer Ingelheim provides FDA with the UPLIFT study data, FDA will analyze the data and communicate its conclusions and recommendations to the public.

Spiriva HandiHaler is an effective medicine that is indicated for the long-term, once daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Patients should not stop taking Spiriva HandiHaler before talking to their doctor if they have questions about this new information.

The FDA urges both healthcare professionals and patients to report side effects from the use of Spiriva HandiHaler to the FDA's MedWatch Adverse Event Reporting program

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

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PDF requires the free Adobe Acrobat Reader

Date created: March 18, 2008, updated October 7, 2008

Early Communication about an Ongoing Safety Review

Epoetin alfa

This information reflects FDA's current analysis of available data concerning this drug. Posting this information does not mean that FDA has concluded there is a cause and effect relationship between the drug products and the emerging safety issue. Nor does it mean that FDA is advising health care professionals to discontinue prescribing these products. FDA is considering, but has not reached a conclusion about whether this information warrants any regulatory action. FDA intends to update this document when additional information or analyses become available.

FDA has been made aware of preliminary safety findings from a clinical trial conducted in Germany investigating the use of epoetin alfa to treat acute ischemic stroke. The drug used in this investigational study was Eprex, a brand of epoetin alfa not marketed in the United States. Eprex is a member of the class of erythropoiesis stimulating agents (ESAs) that are approved by the FDA for use in the treatment of certain patients with anemia.

Over a period of ninety days after the start of the trial, there were more deaths in the group of patients who received epoetin alfa compared to patients who received the placebo (16% versus 9%). Roughly half of all deaths in both groups occurred within the first seven days after starting the drug, with death from intracranial hemorrhage (bleeding within the brain) occurring among approximately 4% of patients who received epoetin alfa compared to 1% of patients in the placebo group. Treatment of anemia was not a goal of the trial and most patients were not anemic. Additional trial baseline and outcome data are currently being analyzed.

This clinical trial was a double-blind, placebo-controlled, multicenter investigation in 522 adult patients with an MRI-confirmed ischemic stroke in the area of the middle cerebral artery. Patients were randomized to either receive treatment with a placebo or epoetin alfa administered as an intravenous dose of 40,000 units daily for three days. R-tPA, a medication used to help dissolve blood clots, and often used for acute strokes, was also used when clinically indicated. The goal of this clinical trial was to determine whether a relatively high dose of epoetin alfa (40,000 units daily) administered for three days would improve the ability of patients to care for themselves after their strokes (functional outcome).

The clinical trial utilized doses of epoetin alfa that were considerably higher than the doses recommended for the treatment of anemia as described in the FDA-approved labeling for the

product. FDA is aware of other clinical trials using epoetin alfa for potential neuroprotective effects (improving the functional outcomes of patients after stroke). The finding of increased mortality in patients receiving epoetin alfa in the German trial suggests the need to closely monitor patients enrolled in other ongoing trials for adverse outcomes and to evaluate whether the potential benefits for enrolled patients outweigh the risks in these trials.

FDA anticipates the receipt of additional data within the next several weeks. As soon as the review of these data is complete, FDA will communicate our conclusions and recommendations to the public.

This early communication is in keeping with FDA's commitment to inform the public about ongoing safety reviews of drugs. FDA will work with the manufacturers of ESAs and other sponsors of clinical trials to evaluate the clinical parameters associated with the risks and benefits associated with the investigational uses of these products as potential neuroprotective agents.

The FDA urges both healthcare professionals and patients to report side effects from the use of ESAs to the FDA's MedWatch Adverse Event Reporting program

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

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