Drug Utilization Review Board

Oklahoma Health Care Authority

4545 N. Lincoln Suite 124

Oklahoma City, Oklahoma 73105

OHCA Board Room

Wednesday

April 11, 2007

@ 6:00 p.m.

THE UNIVERSITY OF OKLAHOMA

THE UNIVERSITY OF OKLAHOMA

MEMORANDUM

TO: Drug Utilization Review Board Members

FROM: Shellie Gorman, Pharm.D.

SUBJECT: **Packet Contents for Board Meeting – April 11, 2007**

DATE: April 5, 2007

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

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

Call to Order

Public Comment Forum

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

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

Action Item – Vote on Changes to Xopenex® Prior Authorization – **See Appendix C.**

Action Item – Annual Review of Growth Hormone Prior Authorization Category – **See Appendix D.**

Action Item – Annual Review of Smoking Cessation Prior Authorization Category – **See Appendix E.**

30 Day Notice to Prior Authorize Ocular Allergy Medications – **See Appendix F.**

30 Day Notice to Prior Authorize Vyvanse™ – **See Appendix G.**

30 Day Notice to Prior Authorize Flector® – **See Appendix H.**

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

New Products **– See Appendix J.**

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

Future Business

Adjournment

Drug Utilization Review Board

(DUR Board)

Meeting – April 11, 2007 @ 6:00p.m.

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

AGENDA

Discussion and Action on the Following Items:

Items to be presented by Dr. 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. February 15, 2007 DUR Minutes – Vote
B. February 15, 2007 DUR Recommendations Memorandum
C. Provider Correspondence

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

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

A. Retrospective Drug Utilization Review Response for August 2006
B. Medication Coverage Activity Audit for February 2007
C. Medication Coverage Activity Audit for March 2007
D. Help Desk Activity Audit for February 2007
E. Help Desk Activity Audit for March 2007
F. Pharmacotherapy Management Quarterly Report

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

5. Action Item – Vote on Changes to Xopenex® Prior Authorization – See Appendix C.

A. Current Prior Authorization Criteria
B. COP Recommendations
C. Recent Clinical Trials, Levalbuterol vs. Racemic Albuterol

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

6. Action Item – Annual Review of Growth Hormone Prior Authorization Category – See Appendix D.

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

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

7. Action Item – Annual Review of Smoking Cessation Prior Authorization Category – See Appendix E.

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

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

8. 30 Day Notice to Prior Authorize Ocular Allergy Medications – See Appendix F.

A. Product Summary
B. Clinical Trial Summary
C. COP Recommendations

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

9. 30 Day Notice to Prior Authorize Vyvanse™ – See Appendix G.

A. Product Summary
B. Clinical Studies
C. COP Recommendations

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

10. 30 Day Notice to Prior Authorize Flector® – See Appendix H.

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

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

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

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

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

12. New Product Reviews – See Appendix J.

13. FDA and DEA Updates – See Appendix K.

14. Future Business

A. ADHD Tier Changes
B. Anxiolytics
C. Ophthalmic Anti-Infectives
D. Glaucoma Products
E. New Product Reviews

15. Adjournment

Appendix A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES of MEETING of FEBRUARY 15, 2007

BOARD MEMBERS:	PRESENT	ABSENT
Brent Bell, D.O., D.Ph.		X
Mark Feightner, D.Ph.		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.	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	
Kelly Flannigan, Pharm.D../Operations Manager	X	
Shellie Gorman, 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.	X	
Visiting Pharmacy Students: Katie Wise	X	

OKLAHOMA HEALTH CARE AUTHORITY STAFF:	PRESENT	ABSENT
Alex Easton, M.B.A./ Pharmacy Operations Manager		X
Mike Fogarty, J.D., M.S.W./Chief Executive Officer		X
Nico Gomez, Director of Gov't and Public Affairs		X
Lynn Mitchell, M.D., M.P.H/Director of 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	

OTHERS PRESENT:

Christi Davis O'Brien, Amylin	Jason Russell, Novartis	Eardie Houston, Daiichi Sankyo
Alona Vain, McNeil Pediatrics	Phil Sonnenfeld, Inspire	M. Patty Laster, Genentech
Bobby White, UCB Pharma	Aliza Tomlinson, Ortho McNeil Janssen	Laura Mitchell, Purdue Pharma
Rob Baxter, Synagis	Perry Johnson, Graceway Pharma	James McAdams, Daiichi Sankyo
Steve Higgins, TAP Pharmaceuticals	John Omick, Novartis	Richard Ponder, J&J
Jim Dunlap, Eli Lilly	Sam Smothers, MedImmune	Janie Huff, TAP Pharmaceuticals
David Williams, Forest		

PRESENT FOR PUBLIC COMMENT:

Eardie Houston, Pharm.D.; Daiichi Sankyo	Agenda Item 6
Paul S. Thomas, M.D., Warren Clinic	Agenda Item 7
Denise Agee, R.Ph., Ortho McNeil Janssen	Agenda Item 7
Amy Blickensderfer, Pharm.D.	Agenda Item 9
Stan Muenzler, M.D., Inspire Pharma	Agenda Item 10

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

1A: Roll Call

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

ACTION: NONE REQUIRED.

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

Dr. McNeill acknowledged speakers for Public Comment.

ACTION: NONE REQUIRED.

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

3A: January 10, 2007 DUR Minutes

Page 10, Item 8, motion was seconded by Dr. Muchmore instead of Dr. Gourley.

Dr. Knisely moved to approve minutes as corrected; seconded by Dr. Rhymer.

ACTION: MOTION CARRIED.

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

4A: Retrospective Drug Utilization Review Report: September 2006

4B: Retrospective Drug Utilization Review Response: July 2006

4C: Medication Coverage Activity Report: January 2007

4D: Help Desk Activity Report: January 2007

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

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 5: **VOTE ON CHANGES TO ELIDEL®/PROTOPIC® PRIOR AUTHORIZATION**

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

Dr. Kuhls moved to approve and that all PA's by non-dermatologists to be re-reviewed and clients with a current PA can get a 30-day extension to be seen by a dermatologist; seconded by Dr. Muchmore.

ACTION: MOTION CARRIED.

AGENDA ITEM NO. 6: **ANNUAL REVIEW OF HYPERTENSION PBPA CATEGORY**

For Public Comment, Eardie Houston, Pharm.D.: Good evening. My name is Eardie Houston. I'm a medical liason with Daiichi Sankyo. I'm here today to testify on the behalf of Benicar which is also known as olmesartan. I won't take too much of your time speaking about this drug because I know that you're very well familiar with olmesartan, but there is some pretty recent information that I do want to share with you. In patients with Stage II systolic blood pressure respective open label titration study evaluating the safety and efficacy of olmesartan monotherapy and olmesartan in combination with hydrochlorothiazide showed a dose dependent reduction in systolic and diastolic blood pressure when used as either monotherapy or combination therapy. After placebo run-in period patients were started on Benicar 20 and then at three week intervals were titrated to Benicar 40, Benicar hydrochlorothiazide 40/12.5 and then 40/25. Patients exited the study and their last measurement was carried forward at any visit if blood pressure less than 140/90, less than 120/80 was achieved. At week 12, the dose of olmesartan hydrochlorothiazide 40/25 resulted in mean reductions in systolic and diastolic blood pressures of 35 and 14 respectively. This translated to about 70% of patients achieving a blood pressure goal of less than 140/90. I just want to thank you all for your time and ask that you please consider maintaining Benicar on your preferred formulary. Also if you have any questions, I'm available.

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

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 7: **ANNUAL REVIEW OF ADHD/NARCOLEPSY PRIOR AUTHORIZATION**

For Public Comment, Denise Agee, R.Ph.: Hello, my name is Denise Agee. I'm associate director and scientific affairs liasons for Ortho McNeil Janssen's pediatric. I'm here to speak on behalf of Concerta. Concerta is currently, has recently been moved down to tier-2 requiring prior authorization and some of the information that I think should make a difference in making Concerta be considered for a tier-1, on two accounts. One, reduce the abusability related to Concerta versus immediate release methylphenidates and other controlled release products. Composition of the tablet makes it very difficult to extract methylphenidate and snort it. It makes it very difficult to utilize the tablet in means other than an oral route. Additionally a second factor influencing the abusability is pharmacokinetics (unintelligible) a decent amount of work in the past looking at oral versus injectable and inhaled stimulants. We have reinforced that work with a small study n=12 that was published the cover article of the American Journal of Psychiatry March of last year. We replicated (unintelligible) work showing that a 40 mg IR dose of immediate release methylphenidate and a 90 mg dose of OROS methylphenidate had equivalent pharmacokinetic data,

can see pharmacokinetic blood levels; however very different liking and detectability. We've gone on to also looking at likeability versus SODOS methylphenidate which was presented by Dr. Spencer at ENCP in the Fall which did show both the SODOS as well as the OROS were very different from placebo in their detectability and (unintelligible) effect in an oral route. But there was also a significant difference of .05 versus from the SODOS to the OROS methylphenidate. Also we have had some data. We've done, attempted to do some data because we're asking people to pay a premium for our product when there is immediate release methylphenidate, so looking to see what the costs are of our product versus immediate release methylphenidate. Although we can't compare dollar for dollar-wise to the pharmacy budget which as a pharmacist I fully respect, we have demonstrated in a large retrospective analysis, reduced total costs for direct medical costs versus IR methylphenidate, 72% reduction in accident and injuries, a 42% reduction in emergency room visits. That was published in the American Journal of Hospital Pharmacy I think, or Managed Care Pharmacy in 2006. Also demonstrated in comparative, I think it was pharmetrics database retrospective analysis, a reduced total direct medical costs versus Strattera of about $700 and versus Adderall XR of about $113, which again is not much, but when you look at things altogether, having a 12-hour duration of product developed strength in having people persist on treatment can make a difference to total direct medical costs. We acknowledge it doesn't affect your pharmacy budget but it can affect care as a whole. So that said, I just hope you'll take that into consideration when you're making your final decisions.

Dr. Kuhls: I have two quick questions. First one is confusing to me and then the second one is more theoretical. Let me ask the second one first. So what you're saying is we really shouldn't have any immediate methylphenidate release products, tier-1. Is that what you're basically saying?

Dr. Agee: No. It comes down to dollars. I am saying that in this database looking at it, I think it was a California database, Kaiser ... I know Kaiser has decided to do that because when they required a prior auth for a period of time and than a failure of IR methylphenidate and a lot of people are going and filling the script for IR and saying they failed and they couldn't take it three times a day or whatever, and going back to the physician. So it was making their total medical costs go up, so Kaiser has gone to a branded product first for that reason, but everyone has to make, I can't say that should be done universally.

Dr. Kuhls: The second confusing question to me is when I looked at the data for Concerta, can you explain to me why the 36 mg tablet is more expensive than the 18, 27 and 54 mg tablet?

Dr. Agee: I can't speak to pricing at all.

Dr. Kuhls: Doesn't that seem to be totally incredible to you that a 36 mg tablet of Concerta costs more than a 54 mg tablet of Concerta per diem?

Dr. Agee: That's probably because of the day ..... if you're talking about the chart that was on there, I'm betting that might be because of the daycon which was 1.25 at the 36 mg which is because the 72 mg is the maximum dose for adolescents and the most common way for people to get to 36 mg is utilize two 36's. So even though the tablets themselves might be priced very closed to the same. Your daycon is 1.25 so the costs .....

Dr. Kuhls: So you're saying that these numbers are inflated because of all the people that weren't getting 72's at the time? There's a 72 mg tablet.

Dr. Agee: No, there's 18, 36, 54 and 27.

Dr. Kuhls: So that 36 includes the cost of the 54 and 18?

Dr. Agee: No, the daycon is 1.25 which means that more than the average prescrip ..... like there's 1.25 prescriptions, tablets filled in that cost, so it's one tablet plus a quarter of another tablet to come to that cost and we're outside my area of expertise being a science person not a business person, but ....

Dr McNeill: Then it actually comes out to about the same as I figure it here, if you look at the 1.25 units per day.

Dr. Kuhls: So we have that many people on 72 mg, two 36 mg tablets? We have a significant proportion?

Dr. Kuhls: In our clinical trials that was about 30% of the adolescents were on, 30 to 40% of the adolescents were on the 72, so that would make some sense and you'd have a decent amount of uptake of that. Did that help?

Dr. Kuhls: I guess.

For Public Comment, Dr. Paul S. Thomas: My name is Dr. Paul Thomas and I'm a pediatrician in McAlester, Oklahoma. That's a very underserved area of the country, or of the state and certainly my practice and my partner's practice is 80% Medicaid. We have very little psychiatric support. Occasionally Carl Albert sees the others so I found a real need in my practice for Concerta and I wanted to share that with you. One of the reasons I developed kind of an interest is my wife has her doctorate in psychology and helps test and helps me with the diagnosing, but before you know Concerta came out in 2000, we had to use tid Ritalin. And so what happened is that the Ritalin went up and it dropped off and the kids melted down and the teachers went nuts. They gave them again their dose, it went up, it dropped off, and so the kids were always having two meltdowns and the thing that was so great about Concerta was that it has a steady release for a full nine hours, and so I really liked this because I didn't have to dose the kids at school and then the thing that strikes me about ADD is when you make a diagnosis of ADD, it has to be present for six months and it has to be two places .... school and home. And so I think this is the only true 12 hour that we're getting. And one of the things I like is I read a study and it said if you have a child with ADD there's more drinking and more divorce in those families. And if you see them in my office you can understand why. So I really like having this medicine because the parents need help. I want them drinking less, I want them divorcing less and what I also hear is that when the medicine is gone, ten minutes of homework is taking the parents three hours. And so I was really thrilled when I had this Concerta. Now the other thing is that you've got two branded products that I can use and I've had a lot of experience. Focalin and Adderall XR. Focalin is an excellent drug. It's in the beaded system like Adderall so you get a little up and down and you get a little meltdown in the middle, but Focalin in my opinion, when I, 'cause I ask everybody how long does this last, it's gone at the end of the school day. So I'm having to give them a short acting and my Focalin rep will tell me it's a 12-hour drug and they'll show me the thing but the peak of Focalin at nine hours is way down, so I don't think I'm getting twelve hours. And then, the other thing that's important is I've been doing pediatrics for 22 years and I, when I read the driving studies, Adderall and Concerta fix the driving. An ADD kid's driving like an 83-year old if he doesn't have it. And the tid Ritalin person in the study drives worse than no Ritalin at all. And so I really believe that it's cost effective, that it's going to prevent accidents, car wrecks, things like that. Then the other thing is, the reason I start with Concerta over Adderall is I believe that there is an abusability factor. You know, they had a study in pediatrics and it showed that 23% of peers from sixth grade on are asking their kid with

ADD, can I have your medicine for illicit use. And if you study that into the ninth grade, that bumps up 46% of people. And so, you know I know that Adderall has more potential for abuse, you know it's in a beaded system, and Adderall's kind of helped get rid of that because they have the short acting beads were light blue and the long acting were dark, and so the kids were just kind of sorting them out and snorting them. So you know I like to have a less abusable product. And then you know, those are just basically my concerns, is I want twelve hours of ascending peak which you know, and less abusability, and I want the ability to give these kids something where I know that 11:00 they're showing that they're going to be driving better, 'cause that's when these kids are driving. And it was a real asset to my practice and you know, because I've been doing this for many years and when I got 12 hours of you know, the parents were saying, you know, I'm getting homework done, life is better. And I think they're drinking less and divorcing less, but I haven't asked that for sure. But in the studies you know, they do drink more and divorce more in that type of situation. So I felt so strongly that I just wanted to come up and share my concerns that I would like this to be a tier-1.

Dr. Graham: Doctor do you use bid dosing with Concerta?

Dr. Thomas: Very rarely. I would say, I would say I don't. Occasionally if I'm not getting control you know, I'll use a short acting methylphenidate or a short acting Adderall because that's all that's approved in the system. And so I try to look at the peak response at 90 minutes and then titrate, start at 18, 36, 54 and do them at a weekly interval and see what gets me the best response.

Dr. Kuhls: Do you have any data comparing Focalin XR directly versus Concerta, looking at efficacy and the needing for more drug and the second dose of Focalin in the afternoon, comparing the effectiveness?

Dr. Thomas: Well you know, all I can say is I've had several years of experience and I always ask, you know, my patients when they were out. And you know, they generally say well I can tell the drug with you know, Focalin or Ritalin LA, which I consider equivalent, you know, is gone at four or five (o'clock) and most people, you know, will say that you know, that the effect of Adderall XR and Concerta is longer. And I mean, I look at the curves, you know, and Focalin, you know, has that printout where it shows efficacy at 12 hours but it's down around 20-30%, so it's barely separating from placebo at 12 hours.

Dr. Kuhls: As you know, I have a big ADD/ADHD practice myself and I also prescribe a significant amount of Concerta, but I have to say my experience is that with Focalin XR or the patients with Adderall XR, some patients do better on Adderall XR, some patients do better on Focalin XR, some patients do better on Concerta. I'm not sure that the science is there to sit there and say, no Concerta's a much better drug. But it sounds like you're willing to .....

Dr. Thomas: Well I'll just say, you know, clinically I agree with you that some people with Concerta will have more appetite suppression and you can switch them over to the Focalin and you know, they can eat better and, I'm not sure the isomer science is there to make the difference between Ritalin LA and I agree with you, you know, that you need different ones and it's great to have Adderall, but you know, I just try to reserve Adderall and I try to see if Concerta will work first. And then just because of abusability issues, you know, we've all had more late problems on Adderall XR because it's stronger, a little more irritability at the end, and it seems that way to me. I mean, some kids are obviously better, you know, it's just that from my experience you know, I would like to have the ability to go Concerta tier-1, you know. And I like the other two and you know from my experience I would like to have Concerta tier-1 and prior auth the other two (unintelligible) or have all three. You know I realize they're all excellent drugs but I wouldn't mind, you know, like trying to write the prior auth for the others or put a patch. I think that's an interesting thing that fits, but I don't think that should be you know, tier-1 just from the hassle of using it and it fits a certain special niche. But you know, I think Concerta is the only one that has, you know, the oral system with the ascending peak, you know. And if you dose it right, you know, whereas both Adderall and Focalin have the two beaded systems, and I understand Adderall may go to three beaded and get a better peak on Adderall further, so .....

Dr. Kuhls: Well for the public record, we haven't had the presentation yet, but for the public record, I wish that the company would have done their bidding again this year to continue to make it tier-1, but obviously it sounds like they haven't. Last year was tier-1 and it switched, which means that .....

Dr. Thomas: Well you can talk to them. I don't know .....I don't have any idea.

Dr. Kuhls: Well that's what I'm saying ..... that's the real ..... neither do I ..... neither do I. I don't know either. But that ..

Dr. Thomas: I would assume that you know, that I'd look closely at that because I would assume that they would be willing to match what the other two .....

Board Member: I would hope so too, wouldn't you?

Dr. McNeill: And if they do during the course of this year, then they could be moved without any action by us.

Dr. Thomas: They can go back to what they were doing, right?

Dr. Nesser: Right. They already missed the window.

Dr. Kuhls: I understand a lot of that you say. I don't understand what happened with the whole process myself. Nobody on the Board does. We're not allowed to those numbers either.

Dr. McNeill: If you started someone on say, Focalin XR and you have to fail on that in order to wind up with Concerta the way it's proposed here, the way it is here.

Dr. Nesser: Right.

Dr. McNeill: How many days, I missed that. Is it 30 days or what is the fail period? If he started someone on Focalin and so that two weeks and there way no .....

Dr. Kuhls: Well you've got to titrate your dose ..... it takes a period to get the people on the right dose, to get a feel, so you're talking a number of months before you would do that.

Dr. McNeill: Before you could make a decision that Focalin's not .....

Dr. Kuhls: Before you make a decision to go to a second drug.

Dr. Thomas: A lot of people will just give them one dose, say I don't like it and fail them and send it, you know. I don't do that. I think if, you know, it's written that way, you know, then I should try to optimize the dose and try this dose and this dose and this dose which can take two or three months. And then, you know, because I think you have to give it a fair shot. I think that's what you guys want and that's a very reasonable thing.

Dr. Gourley: So the people that you start immediately on Concerta then, you don't really know whether they would have responded to another drug?

Dr. Thomas: Well, I mean, you know, I've been doing this, Concerta's been out since 2000, so there's a lot of ADD kids in McAlester, so I've had a lot of experience on Concerta, Adderall and Focalin. And I know that, you know, my Concerta kids I can get 12 hours. And most of the Focalin people, you know, it's an excellent drug. I get them through a school and then their parents say, well gee, we're spending 10 minutes, you know, three hours to do 10 minutes of homework and then I have to go on the short acting, you know, Ritalin because you can't give a branded plain Focalin a day to get them through the day.
Dr. Gourley: But I thought you said that there were some who respond to one and not another.
Dr. Kuhls: I think that's true and as you know, there are some people that you don't want the longer acting because they don't sleep and so there's some, there's some leeway and some judgement in all of this, but you're, but it's true. I'm not sure the science is there to sit there and say that one drug is definitely better than the other drug. That's ....
Dr. Thomas: I think the science is there that Ritalin, I mean that Concerta gives you a full 12 hours of coverage and all I'm saying is that I, you know, yeah. Some don't want 12 hours but I think everybody should have the chance of 12 hours for their family time, you know. Listening to mother and like my wife when she does counseling, you know. One of her goals, she has to write written goals, is that you will do seven out of ten times what your parents ask you to do, as opposed to two out of ten, you know. And so I think that, you know, gee how fun would that be? Get your book Sally. But maybe if you have the Concerta I think that, you know. Or you've got a 12 hour be it Concerta or Adderall or whatever. If you've got 12 hours they're going to be more compliant. They're going to have better time, you know, with the family over meals, more quality time, and have better bonding. And that's, that's one of the reasons we treat ADD anyway is you know, if you take a non-treated ADD person, you know, they have a 40% chance of growing up to have drug abuse problems or legal problems, getting in trouble, conduct disorders. And if you treat them, you know, you can normalize that, you know. And so I think, you know, it goes back to 15%. It shows that there's a lot of problems in our society that's very protective against further drug abuse or, you know, getting conduct disorder, getting arrested, getting in trouble with the law, so I, you know, that's just why I feel strongly that I would want to start with something that gives me 12 hours of coverage.
Dr. Kuhls: One last quick question . . .2007 . . .do you feel that any child being diagnosed with ADD or ADHD should be started on a immediate release old-fashioned compound, or should everybody be on extended release? Because that was what was basically, the last speaker was talking a lot about immediate release and ....
Dr. Thomas: No, I think, yeah, she was just comparing it. I mean I would definitely think that if you have a true diagnosis I would much rather start them on a Concerta. Give them 12 hours ....
Dr. Kuhls: So at least a long term.
Dr. Thomas: Right, a long term.
Dr. Kuhls: Extended release, right?
Dr. Thomas: Extended release and ....
Dr. Kuhls: I can't see starting somebody on double day, you know, morning and noon dose again. Except for the occasion when you have to use a little Focalin in the afternoons, or ..... I agree with that.
Dr. Muchmore: Isn't the immediate release stuff a major hassle for the school system?
Dr. Thomas: It is.
Dr. Muchmore: I would think that they would just hate to go back to the mid-day dosing.
Dr. Thomas: It's a hassle and it stigmatizes them, you know. I mean, how would you like to be the little kid that, OK, got to get your Ritalin. You know, that's what we had before 2000, you know.
Dr. Kuhls: And the potential for abuse is higher.
Dr. Muchmore: And diversion.
Dr. McNeill: Thank you Dr. Thomas.

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

Dr. Kuhls: Just for the record again, I want to re-state. I use mostly Concerta. There's nothing more that I would like to see than Concerta as being tier-1 because I have a lot of patients on it. For patients where it's on the formularies for insurances, I think it's a good drug and I would love to see it tier-1, however, okay, you have other extended release products on tier-1 that obviously that means they're cheaper. Drugs that are commonly used, Focalin XR, Adderall XR, and so even though I like to use Concerta, I can't see making Concerta tier-1 which costs a lot more when there's not comparative efficacy data and so on. Unfortunately. And I think that's not this DUR Board, DUR's problem. I don't think that is the Health Care Authority's problem. It sounds like that's a pharmaceutical company problem that they don't want to give their drug for a price, it sounds like, that was comparative last year. That's my own opinion. Number two, I agree with you. I think that we need to start weeding out some of these tier-1 immediate release compounds because I think their usefulness in 2007 has decreased tremendously. You have to give them at school twice a day, their potential for abuse is higher, so I would like to see those, some of those products, I think you need one short-acting like Focalin which is a nice short-acting product to use in afternoon and is already tier-1, just to keep one tier-1 short-acting product and move the rest. And so really what I would do is kind of like make for the best of care, use Adderall XR, Focalin XR is tier-1, Focalin is tier-1, move everything to tier-2 and then the third thing I would do is since you really have differences between even Metadate CD and costs compared to, say Concerta right now, you need to start talking about a tier-3. You need to start having it where you have to go through a couple of products to start using a tier-3 drug because you still can do some cost savings with a tier-3 versus a tier-2 so my recommendations are to make a third tier that includes some of the drugs that are now second tier.
Dr. Moore: Well, and we actually do have a third tier, but it just kind of, it's sort of .....
Dr. Kuhls: Yeah, but it's Pemoline and drugs that aren't used.
Dr. Knisely: We still have quite a bit of utilization of the immediate release products, though and if you move those there's going to be some issue with .....
Dr. Kuhls: I think, I think that one of the things we can't do is we can't, we have to grandfather in. We can't take a patient on Concerta now and tomorrow tell them we're switching to Adderall XR. So you're going to have to grandfather ....
(multiple): We do that already.

Dr. Kuhls: So that's not a problem. You're going to have to grandfather because you can't switch products on these kids. But my recommendation is to have Adderall XR as a tier-1, Focalin as tier-1, Focalin XR as tier-2, move all the rest of them to the second tier and then I would make Daytrana as tier-3, Concerta, I hate to do it, but that really probably deserves to be tier-3 compared to Metadate CD and it looks like cost-wise, tell me if I'm not wrong, Ritalin LA probably needs to move to tier-3. But I would base those on just looking at those unit costs.
Dr. McNeill: Can I make a suggestion that, and I like where you're going with this, but maybe allow them an opportunity to structure a 3-tiered system and bring it back at the next meeting . . .
Dr. Kuhls: Based on costs.
Dr. McNeill: . . based on costs, and at the short versus long-acting.
Dr. Kuhls: The one drug that I have difficulty placing second or third tier which people are going to have to put some thought into, is Strattera because Strattera's a different mechanism, you know. That could stay tier-2 but it's more expensive than any of them, so it might be tier-3. So I think you need to put some thought into that, okay? But I really think that we need to be more agressive with costs and I think, you know, until there's scientific data comparing directly Concerta versus Focalin XR or Adderall XR and great comparative studies, I think we're forced to do this even though I don't personally as a physician like doing this. I mean I think that everything that Dr. Thomas said is correct.
Dr. Muchmore: Is most of the use of the IR's tid use or just an afternoon boost use?
Dr. Gourley: It's both.
Dr. Graham: I think when it first, when the long-acting came out, really they were promoted as once-a-day deal, but we saw both of them. It actually just, it increased, you know, it went with the long-acting plus the short-acting. It didn't increase the short-acting.
Dr. Kuhls: I agree with you. It would be nice to table it. I think you need to look at the costs between second and third tier a little more closely and I think you need to look at immediates versus not, but I think coming back and having a new recommendation with this already discussed, I think that's fine. I don't know if the DUR Board has the ability to sit there and say let's give all these companies one more time simply for making the third tier or not. I don't know if we can do that, but that would be nice.
Dr. Nesser: Yeah, that would probably be something that would trigger a second chance.
Dr. Kuhls: I think since we're now making the third tier and even making it harder to use, if some of the pharmaceutical companies want to come back and try to make a third tier first tier, that would be great.
Dr. Muchmore: One more stupid question. Is there a reason why just plain methylphenidate IR or extra amphetamine IR isn't on the tier-1? Not exist? I just saw trade name…
Dr. Moore: Because that's just how they were placed in the tier list.
Dr. Muchmore: Would they be tier-1?
Unknown: Of course, and they're the preferred actually.
Dr. Kuhls: There's a few products that you can but you don't want to have too many short-acting tier-1's available, because I mean we've really got to start decreasing immediate .....
Dr. Muchmore: Certainly you're inviting diversion with the IR's.
Dr. McNeill: Actually I don't think we could take them off tier-1. We have to offer them, but are you saying to move .... to move the IR's other than say Focalin or methylphenidate, to a higher tier.
Dr. Kuhls: Because it's really talking about a PA.
Dr. McNeill: Okay, there's been a motion made to table this until the next meeting.

Dr. Kuhls moved to table to March 14, 2007; seconded by Dr. Gourley.
ACTION: MOTION TABLED.

AGENDA ITEM NO. 8: ANNUAL REVIEW OF AMITIZA®/ZELNORM® PRIOR AUTHORIZATION
Materials included in agenda packet; presented by Dr. Browning.
ACTION: NONE REQUIRED.

AGENDA ITEM NO. 9: ANNUAL REVIEW OF BYETTA®/SYMLIN® PRIOR AUTHORIZATION
For Public Comment, Amy Blickensderfer, Pharm.D.: Good evening. I'm Amy Blickensderfer. I'm a managed care liason for Amylin Pharmaceuticals and I'm here to talk about exenatide and Byetta and pramlintide which is Symlin. With regard to the current criteria, we would request that with regard to Symlin that the current criteria be maintained and with regard to Byetta the current criteria be maintained as well. With the addition of the FDA approval granted in December, Byetta is now approved to be used with TZD's or TZD's plus metformin, along with its' current indication of metformin, a sulfonylurea or the combination of the two. The data that that the FDA reviewed was presented at the ADA in 2006 for the TZD indication. The A1C lowering with TZD's and Byetta or TZD plus metformin and Byetta was similar to what we saw in the original phase 3 trials. 62% of patients achieved the ADA goal of an A1C below 7, and there was virtually an identical risk of hypoglycemia with the use of Byetta plus a TZD or TZD alone. With regard to that I don't really have anything else to share with you. I'd be happy to answer any questions at this time. Thank you.

Materials included in agenda packet; presented by Dr. Gorman.
Discussion among Board members regarding A1C goals and sources of information and recommendations.

Dr. Blickensderfer: With the 7, that tends to be what the FDA will set as far as A1C control, but as Dr. Muchmore indicated, the ACE guidelines are 6.5. We also evaluated that and 40% of the patients were able to achieve ACE guidelines under 6.5. With what we are hearing from the ADA, that recommendation will be moving towards 6.5 as well.

Dr. Muchmore moved to approve recommendations as submitted; seconded by Dr. Kuhls.
ACTION: MOTION CARRIED.

AGENDA ITEM NO. 10: **60-DAY NOTICE AND POTENTIAL ECONOMIC IMPACE OF OCULAR ALLERGY PBPA CATEGORY**

For Public Comment, Stan Muenzler, M.D.: Good evening. I'm here on behalf of Inspire Pharmaceuticals to speak on behalf of Elestat. Elestat, as you may or may not know, is a potent multi-modal drug for ocular allergy. It's antihistaminic, it's mast cell stabilizer, anti-inflammatory. It has no muscarinic effect, so it has great advantages in the use of topical allergy. When I was here in January at the meeting, there were some questions about why there are not large head-to-head studies comparing topical antihistamine mast cell stabilizers and the answer to that apparently is that this is not cost-effective for the drug companies to do that. I want to mention briefly that, and you know this, that the antihistamines alone have only brief effect and have frequent rebound. Mast cell stabilizers alone may take days or weeks to really kick in be effective. If the cost to Medicaid or the State is the same for Zaditor as it is for Elestat, it would seem sensible that the prescribers be allowed to write Elestat because of the advantages it has over the other drugs. Recently more specifically, the fact that it is not muscarinic, it does not cause drying which the other drugs do. This is recently been studied, especially at the Baylor College of Medicine in Houston and we know that conservatively, half of the people with dry eye also, with allergy rather, often have dry eye symptoms that are aggravated by their drops and oral antihistamines. So this would alleviate the problem with induced dry eye and reduce office visits, reduce need for dry eye therapy and reduce costs to the State. I'll take any questions.

Dr McNeill: There has been an addendum to the packet, page 50 make sure you have that. Any questions from the Board?

Dr. Muenzler: I have a handout if anyone wishes. It has the advantages of the drug and also references concerning the drug that were not available on my last visit. Thank you so much.

Materials included in agenda packet; presented by Dr. Gorman.
Board members want to see data for tier-3.
ACTION: NONE REQUIRED.

AGENDA ITEM NO. 11: **UTILIZATION REVIEW OF SELECT TOPICAL PRODUCTS**
Materials included in agenda packet; presented by Dr. Chonlahan.
ACTION: NONE REQUIRED.

AGENDA ITEM NO. 12: **FDA & DEA UPDATES**
Materials included in agenda packet; presented by Dr. Graham.
ACTION: NONE REQUIRED.

AGENDA ITEM NO. 13: **FUTURE BUSINESS**
13A: Annual Reviews
13B: Xopenex® Review
13C: Benzodiazepine Review
13D: 30-Day Notice to PA Ocular Products
13E: New Product Reviews
Materials included in agenda packet; submitted by Dr. Graham.
ACTION: NONE REQUIRED.

AGENDA ITEM NO. 14: **ADJOURNMENT**
The meeting was declared adjourned.

The University of Oklahoma College of Pharmacy

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

Memorandum

Date: February 16, 2007

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

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

Subject: DUR Board Recommendations from Meeting of February 15, 2007.

Recommendation 1: Vote on Changes to Elidel®/Protopic® Prior Authorization

MOTION CARRIED by unanimous approval.

Approval Criteria for the following age groups:

- Elidel® 1% Cream ≥ 2 years of age
- Protopic® 0.03% Cream ≥ 2 years of age
- Protopic® 0.1% Cream ≥ 15 years of age

Clinical Exceptions*:

- ~~Documented adverse effect, drug interaction, or contraindication to topical corticosteroid products.~~
- ~~Atopic dermatitis on the face, neck, or groin where physician does not want to use topical corticosteroids *(regardless of age).*~~
- Prescription by ~~allergist or~~ dermatologist *(regardless of age).*

***Changes only apply to those under FDA approved ages.**

Recommendation 2: Required Annual Review of Hypertension PBPA Category

No Action Required

The College of Pharmacy does not recommend any changes at this time.

Recommendation 3: Required Annual Review of ADHD/Narcolepsy Prior Authorization Category

TABLED by majority approval.

The College of Pharmacy is to review and bring back recommendations for establishing new tier levels for this category.

Recommendation 4: Required Annual Review of Amitiza®/Zelnorm® Prior Authorization Category

No Action Required

The College of Pharmacy does not recommend any changes at this time.

Recommendation 5: Required Annual Review of Byetta®/Symlin® Prior Authorization Category

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the following:

- Continue current criteria for Symlin®.
- Continue current criteria for Byetta® with the addition of thiazolidinediones to the criteria:
  - Patients must have Type 2 diabetes and currently taking metformin, a sulfonylurea, a thiazolidinedione or a combination and have not achieved adequate glycemic control (HbA1C $\geq$ 6.5)
  - Members that have been on a sulfonylurea, metformin, or a thiazolidinedione for 90 of the past 180 days will NOT require prior authorization.

From: slsmith@tulsacoxmail.com [mailto:slsmith@tulsacoxmail.com]
Sent: Thursday, February 08, 2007 3:20 PM
To: Graham, Ronald D. (HSC)
Subject: Medicaid Formulary

Dear Dr. Graham: As a prescriber of Elestat ophthalmic solution I am asking you to consider keeping this excellent mast cell stabilizer on the Oklahoma Medicaid Formulary.

Sincerely,

Steve L. Smith, O.D. slsmith@tulsacoxmail.com

Appendix B

Retrospective Drug Utilization Review Report

Claims Reviewed for August 2006

Module	Drug Interaction	Duplication of Therapy	Drug-Disease Precautions	Dosing & Duration
Limits which were applied	Established, Major, Males Age 41-150	Anti-anxiety Agents, Males and Females, Age 22-32	Contraindicated, Drug Dependence/Abuse, Males and Females, Age 22-45	High dose, Duration, Oxazolidinones, Statins, Males and Females, Age 0-150

Response Summary (Prescriber)
Letters Sent: 137
Response Forms Returned: 56

The response forms returned yielded the following results:

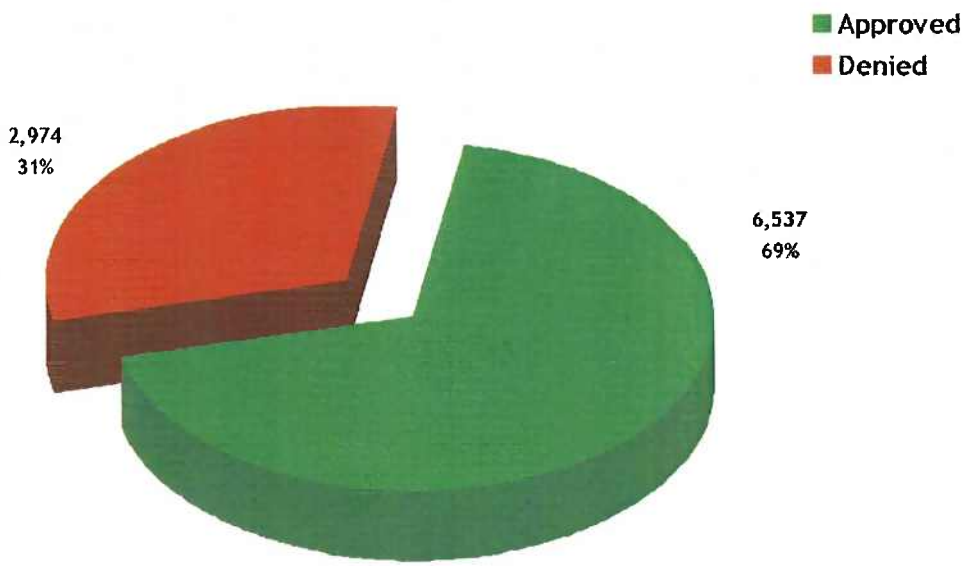
6 (11%)	*Record Error—Not my patient.*
7 (13%)	*No longer my patient.*
2 (4%)	*Medication has been changed prior to date of review letter.*
9 (16%)	*I was unaware of this situation & will consider making appropriate changes in therapy.*
23 (41%)	*I am aware of this situation and will plan to continue monitoring therapy.*
9 (16%)	*Other*

Response Summary (Pharmacy)
Letters Sent: 71
Response Forms Returned: 42

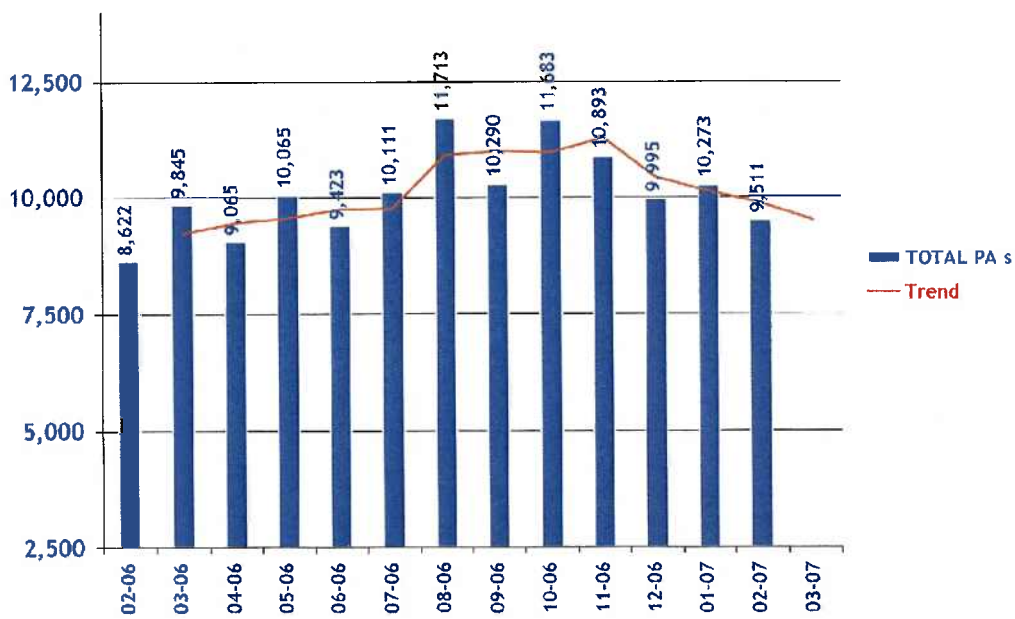
The response forms returned yielded the following results.

0 (0%)	*Record Error—Not my patient.*
6 (14%)	*No longer my patient.*
4 (10%)	*Medication has been changed prior to date of review letter.*
7 (17%)	*I was unaware of this situation & will consider making appropriate changes in therapy.*
18 (43%)	*I am aware of this situation and will plan to continue monitoring therapy.*
7 (17%)	*Other*

PRIOR AUTHORIZATION ACTIVITY REPORT
February 2007



PRIOR AUTHORIZATION REPORT
February 2006 - February 2007



Activity Audit for
February 01, 2007 Through February 28, 2007

	Average Length of Approvals in Days	Approved	Denied	Total
ACE Inhibitors	157	7	11	18
Angiotensin Receptor Antagonist	296	26	59	85
Antidepressant	283	185	486	671
Antihistamine	99	996	518	1513
Antiulcers	18	16	8	24
Anxiolytic	90	3058	392	3450
Calcium Channel Blockers	365	8	47	55
Growth Hormones	167	32	1	33
HTN Combos	292	5	20	25
Hypnotics	88	443	154	597
Nsaids	286	15	67	82
Plavix	353	248	26	274
Stimulant	207	621	265	886
Others	103	870	920	1790
Emergency PAs		7	0	7
Total		**6537**	**2974**	**9511**
Overrides				
Brand	230	24	18	42
Dosage Change	18	245	21	266
High Dose	186	2	1	3
Lost/Broken Rx	14	76	2	78
Nursing Home Issue	15	10	3	13
Other	12	29	9	38
Quantity vs. Days Supply	189	236	155	391
Stolen	7	5	0	5
Wrong D.S. on Previous Rx	2	1	5	6
Overrides Total		**628**	**214**	**842**

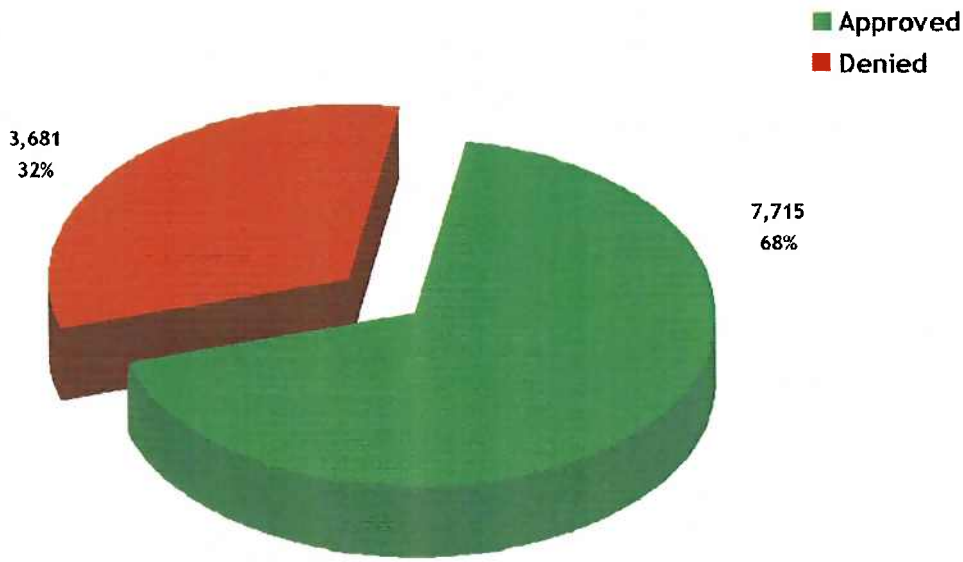
Denial Reasons

Lack required information to process request.	2565
Unable to verify required trials.	1080
Not an FDA approved indication/diagnosis.	182
Does not meet established criteria.	127
Considered duplicate therapy. Member has a prior authorization for similar medication.	113
Member has active PA for requested medication.	74
Requested dose exceeds maximum recommended FDA dose.	57
Medication not covered as pharmacy benefit.	6

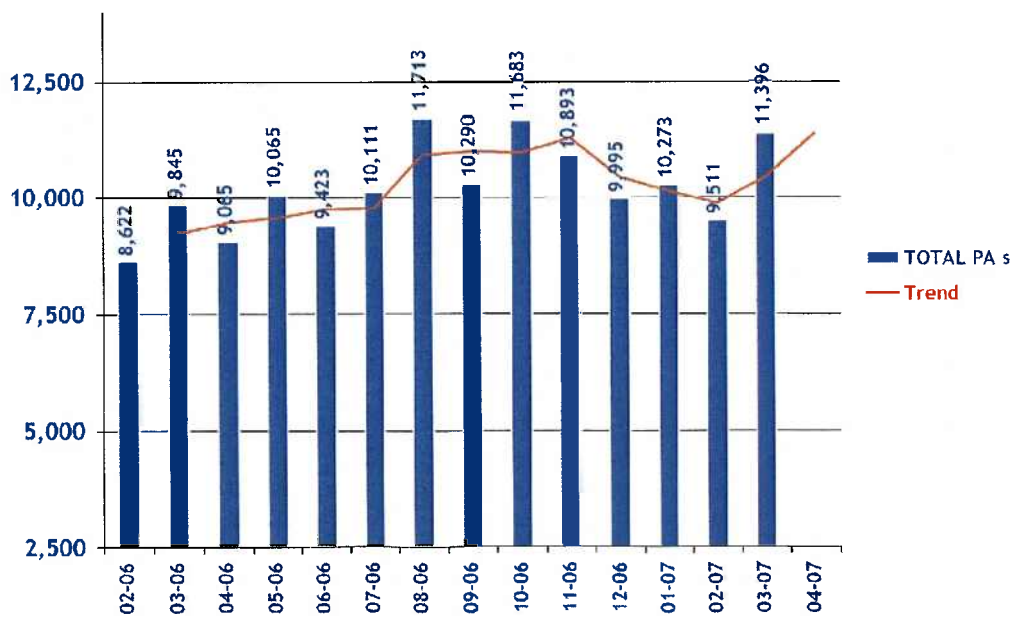
Duplicate Requests	515
* Changes to existing	848

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

PRIOR AUTHORIZATION ACTIVITY REPORT
March 2007



PRIOR AUTHORIZATION REPORT
March 2006 - March 2007



Activity Audit for
March 01, 2007 Through March 31, 2007

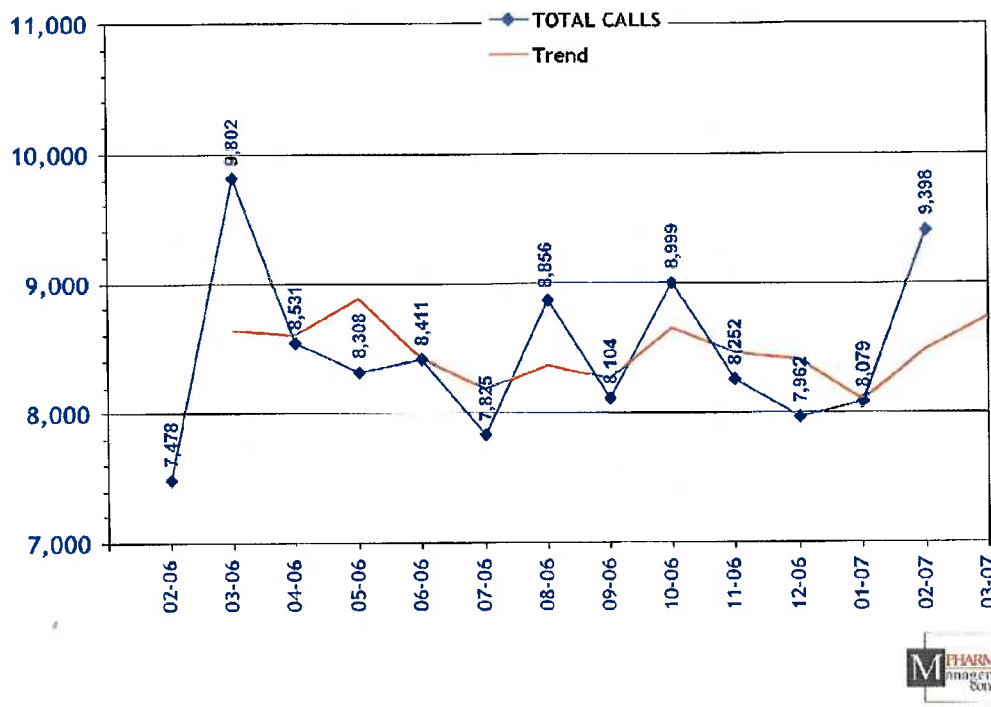
	Average Length of Approvals in Days	Approved	Denied	Total
ACE Inhibitors	164	14	7	21
Angiotensin Receptor Antagonist	365	38	80	118
Antidepressant	274	253	525	778
Antihistamine	102	1322	837	2159
Antiulcers	18	28	3	31
Anxiolytic	93	3691	575	4266
Calcium Channel Blockers	289	18	69	87
Growth Hormones	165	24	1	25
HTN Combos	348	11	28	39
Hypnotics	90	164	46	210
Nsaids	298	16	93	109
Plavix	359	273	31	304
Stimulant	209	760	307	1067
Others	109	1098	1079	2177
Emergency PAs		5	0	5
Total		**7715**	**3681**	**11396**
Overrides				
Brand	158	48	40	88
Dosage Change	19	346	11	357
High Dose	173	3	0	3
Lost/Broken Rx	15	85	13	98
Nursing Home Issue	18	43	4	47
Other	14	27	17	44
Quantity vs. Days Supply	197	240	202	442
Stolen	9	4	1	5
Wrong D.S. on Previous Rx	0	0	4	4
Overrides Total		**796**	**292**	**1088**

Denial Reasons

Lack required information to process request.	3258
Unable to verify required trials.	1295
Not an FDA approved indication/diagnosis.	178
Considered duplicate therapy. Member has a prior authorization for similar medication.	134
Does not meet established criteria.	127
Member has active PA for requested medication.	106
Requested dose exceeds maximum recommended FDA dose.	50
Medication not covered as pharmacy benefit.	15
Duplicate Requests	697
* Changes to existing	911

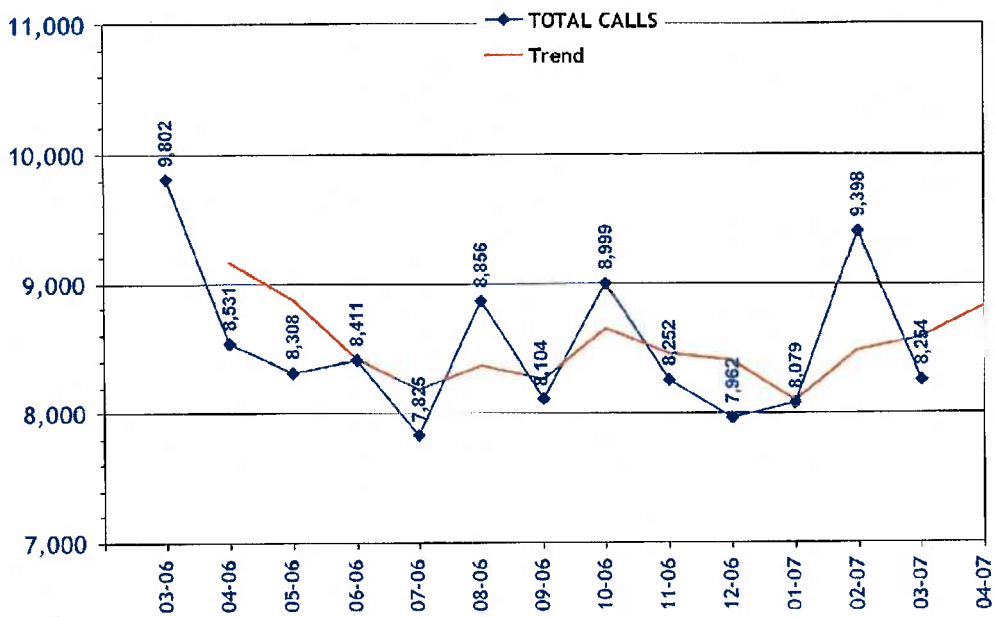
** Changes to existing PA's: Backdates, changing units, end dates, etc.*

CALL VOLUME MONTHLY REPORT
February 2006 - February 2007



PHARMACY Management Consultants

CALL VOLUME MONTHLY REPORT
March 2006 - March 2007



PHARMACY Management Consultants

Pharmacotherapy Management Program
Quarterly Report FY'07
July 2006 – March 2007
Oklahoma Health Care Authority

	MEMBER PROFILES REVIEWED		PRIOR AUTHORIZATIONS				COMMUNICATIONS	
Month	New Members	Established Members	Total	Approved	Denied	Incomplete	Letters	Calls
July 2006	26	13	211	138	20	53	88	34
Aug 2006	27	47	256	136	21	99	187	42
Sept 2006	8	2	229	115	27	87	31	16
Oct 2006	11	20	271	156	19	96	80	31
Nov 2006	25	0	221	105	36	80	54	13
Dec 2006	25	5	212	118	27	67	48	11
Jan 2007	18	12	249	154	23	72	70	9
Feb 2007	13	68	197	109	47	41	215	20
March 2007	26	8	354	197	34	123	92	29
April 2007	-	-	-	-	-	-	-	-
May 2007	-	-	-	-	-	-	-	-
June 2007	-	-	-	-	-	-	-	-
Totals	179	175	2200	1228	254	718	865	205
1st Quarter	61	62	696	389	68	239	306	92
2nd Quarter	61	25	704	379	82	243	182	55
3rd Quarter	57	88	800	460	104	236	377	58
4th Quarter	-	-	-	-	-	-	-	-
Totals	179	175	2200	1228	254	718	865	205

Appendix C

Xopenex® Follow Up From January 2007 Meeting

Oklahoma Health Care Authority
April 2007

Current Prior Authorization Category

Category Criteria for FY'06

Xopenex® (levalbuterol) use in excess of 90 days of therapy in a floating 360-day period will require prior authorization.

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

Quantity limits apply as follows:

- For nebulization – 288units/30 day supply
- For HFA inhaler – 30units/30 day supply

Recommendation

The College of Pharmacy recommends the following change to the Xopenex® prior authorization criteria.

1. Remove the floating 90 days of therapy without a prior authorization for Xopenex® nebs and HFA. Members will still be able to access a 3-day Emergency PA.
2. Approval will be granted for the following reasons:
    a. Members that experienced adverse events with racemic albuterol.
        i. This exception will require a completed MedWatch form along with the prior authorization request. The dosing and duration of racemic albuterol must be provided along with a description of the adverse event/effects.
        ii. The College of Pharmacy will forward all MedWatch forms submitted to the FDA.
        iii. Dose of levalbuterol requested cannot be less than the racemic equivalent documented on the prior authorization request.
    b. Prescription is written by a pulmonologist or asthma/allergy specialist.

Recent Clinical Trials of Levalbuterol vs. Racemic Albuterol

Study	Type	Disease	N =	Inclusion	Drug/Dosing	RAC: LEV	Primary Endpoint	Secondary Endpoint	Results Primary	Results Secondary	Comments
2003 Carl	DB	Asthma	482	1-18 yrs of age; dx asthma; present to ED for exacerbation	RAC 2.5mg or LEV 1.25mg	2:1	Hospital admission rate	Inpt LOS; ED LOS; rate of intensification, # of treatments; requirement for O2; adverse effects	LEV had fewer inpt admissions (p=0.02)	No statistacially significant difference in secondary endpoints	Decision to admit patient was made by ED attending using ED criteria that was not outlined in paper
2003 Lam	Xover	Resp distress; Asthma; COPD	20	18yrs of age or older; expected to stay in unit at least 48h and required B2 agonists every 4h to max resp function	RAC 2.5mg or LEV 1.25mg	2:1	Show no difference in heart rate increases		No difference seen between groups		Power analysis not performed; looked at short term use
2003 Datta	DBPC	COPD	30	dx COPD; stable disease; FEV1 between 45-70% of predicted; FEV1/FVC ration <0.7	RAC 2.5mg; LEV 1.25mg; RAC 2.5mg + IP; or PB	2:1	Change in FEV1	FVC; pulse rate; O2 sat; hand tremor	FEV1 for 3 active treatment groups statistically signficant for first hour; only treatment signficant at 2h was RAC+IP	FVC for 3 active treatment groups statistically signficant at 0.5h, only treatment signficant at 1h was RAC+IP; significant change in pulse for RAC and LEV only at 0.5h; no significant difference in O2 sat, or hand tremor	Only looked at single dose; small population
2004 Pleskow	DBPC	Asthma	362	12 yrs of age or older; nonsmoker; stable moderate-severe asthma (FEV 45-70% of predicted) for > 6mos	TID treatments for 4 weeks: RAC 1.25mg; RAC 2.5mg; LEV 0.63mg; LEV 1.25mg; or PB	1:2:0.5 :1	Differences in pulmonary function (mean peak change in FEV1, % predicted FEV1, and mean AUC FEV1) at Week 0-Day 0 and at the end of Week 4-Day 28		At Week 0-Day 0: LEV 1.25mg significantly better than RAC 2.5mg and 1.25mg in mean peak change FEV1 (p<0.028, p<0.018) and AUC FEV1 (p<0.004, p<0.006); At Week 4-Day 28: LEV 1.25mg better than RAC 1.25mg in mean peak FEV1 (p<0.03)and AUC FEV1 (p<0.031); No significant change between RAC and LEV in % predicted FEV1		Post hoc analysis of previous study; original study not powered to compare active treatment arms

Study	Type	Disease	N =	Inclusion	Drug/Dosing	RAC: LEV	Primary Endpoint	Secondary Endpoint	Results Primary	Results Secondary	Comments
2005 Skoner	DBPC	Asthma	211	2-5 yrs of age; dx of asthma for at least 30 days	TID treatments x 21 days: LEV 0.31mg; LEV 0.63mg; RAC 2.5mg (pts ≥ 33lbs); RAC 1.25mg (pts <33lbs); or PB		Change from baseline in the Pediatric Asthma Questionaire (PAQ)	PEF, rescue medication use, PACQLQ (Pediatric Asthma Caregiver Quality of Live Questionaire), Child Health Status Questionnaire, adverse effects	No statistical significance in difference among treatment groups in PAQ score	No statistically significant difference in secondary endpoints except in overall PACQLQ seen only in pt <33lbs in LEV 0.63mg v. RAC 1.25mg (p<0.02)	LEV dosing NOT weight based
2005 Hardasmalani	DB	Asthma	70	5-21 yrs of age; dx of asthma; presenting to ED for exacerbation	3 q 20min tx: RAC 2.5mg + IP; LEV 1.25mg + IP	2:1	O2 sat; respiratory rate; peak flow rate; need for additional tx; inpatient admission		No statistical significance in difference among treatment groups in all parameters		Small population
2005 Qureshi	DB	Asthma	129	2-14 yrs of age; dx of asthma; presenting to ED for exacerbation with FEV1 less than 70% of predicted or initial asthma score >8	3 q 20min tx with additional allowed at 30-60 min interval: pt <25kg RAC 2.5mg or LEV 1.25mg; pt >25kg RAC 5mg or LEV 2.5mg	2:1	Change from baseline in asthma score and FEV1 after 1st, 3rd, and 5th treatments	# treatments until disposition; ED LOS; rate of hospitalization; adverse events; changes in pulse rate, respiratory rate, and O2 sat	No differences between groups after 1st, 3rd, and 5th treatment	No statistically significant difference in secondary endpoints	
2005 Ralston	DB	Asthma	140	6-18 yrs of age; dx of asthma with ability to use peak flow; PEF < 80% of predicted	Up to six treatments: RAC 5mg + IP for tx 1-3, RAC 5mg for tx 4-6; or LEV 1.25mg all tx	4:1	ED LOS	% change in PEF; % change heart rate; # treatments until disposition; frequency of complications; frequency of adjunctive treatment; frequency of return visits within 72h from ED discharge	No significant difference in ED LOS	No significant difference in secondary outcomes except: more patients in RAC + IP were given adjunctive systemic steroids than in LEV (p=0.014); more increase in heart rate in RAC + IP v. LEV (p≤0.019 for all parameters)	# treatments, dosing interval, adjunct meds, disposition up to treating physican discretion
2006 Nowak	DB	Asthma	627	18 yrs of age or older; dx of asthma ≥6 months; presenting to ED for exacerbation; FEV1 20-55% predicted; O2 sat ≥90% with no more than 6L/min O2; no ther known	3 q 20min tx with additional allowed at 40 min intervals up to 3 additional doses: RAC 2.5mg or LEV 1.25mg	2:1	Time to meet ED discharge criteria (FEV1 ≥ 70% of predicted or 2.1L, plus no wheeze; OR physician decision)	FEV1 change from baseline; proportion of patients hospitalized	No difference seen between groups	FEV1 improvement greater after first dose and cumulatively with LEV v. RAC (p=0.02); no statistical significant differences seen overall with regard to hospitalization or readmission	Most patients discharged based upon subjective clinical improvement; in subset analysis of those patients not taking steroids prior to presentation LEV showed improved FEV1 (p<0.03) and decreased

Study	Type	Disease	N =	Inclusion	Drug/Dosing	RAC: LEV	Primary Endpoint	Secondary Endpoint	Results Primary	Results Secondary	Comments
				nonasthma dx							hospitalization (p=0.03)
2006 Donohue	DBPC	COPD	209	35 yrs of age or older; dx of COPD; baseline FEV1 ≤65% of predicted and >0.7L; FEV1/FVC ≤70%; ≥15 pack-year smoking history; baseline breathlessness severity score ≥2	TID treatments for 6 weeks: RAC 2.5mg; LEV 0.63mg; LEV 1.25mg; or PB	2:0.5:1	FEV1 AUC (0-8hrs) after first dose, 2 weeks, and 6 weeks	excaerbations of COPD; COPD control days; transitional dyspnea index; rescue med use; St. George's Hospital Respiratory Questionnaire; adverse events	All treatments better than placebo	No significant difference in secondary outcomes except: LEV 1.25mg patients used less rescue/supplemental meds than RAC (p≤0.048); statisically significant increases in heart rate compared to PB with LEV 1.25mg (p<0.001)and RAC (p<0.001)	Was not powered to detect difference between active treatment groups
2006 Berger	DBPC	Asthma	173	4-11 yrs of age; stable asthma ≥ 6 months; FEV1 45-80% of predicted with ≥12.5% reversibility with RAC	QID HFA MDI treatments for 28 days: RAC 180mcg; LEV 90mcg; or PB	2:1	peak % change in FEV1 over treatment period	% change in FEV1 AUC (0-6hr); peak % predicted FEV1; QOL, adverse events; rescue med usage	LEV produced significant improvement inpeak % change FEV1 compared to placebo (p<0.001). No significant difference was seen between RAC and PB or RAC and LEV.	No statistacially significant difference in secondary endpoints between the active arms	

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Appendix D

Annual Review of Growth Hormone Prior Authorization Category
Fiscal Year 2006
Oklahoma Health Care Authority
April 2007

Definition of Prior Authorization Category for FY '06
COVERED INDICATIONS

- Classic hGH Deficiency
- Short Stature (including Prader-Willi Syndrome)
- Short Stature associated with chronic renal insufficiency
- Small for Gestational Age (SGA)
- Turner's Syndrome or 45 X, 46 XY mosiacism in males
- Hypoglycemia associated with hGH insufficiency
- AIDS wasting (Serostim only)

Utilization
For the period of July 2005 through June 2006

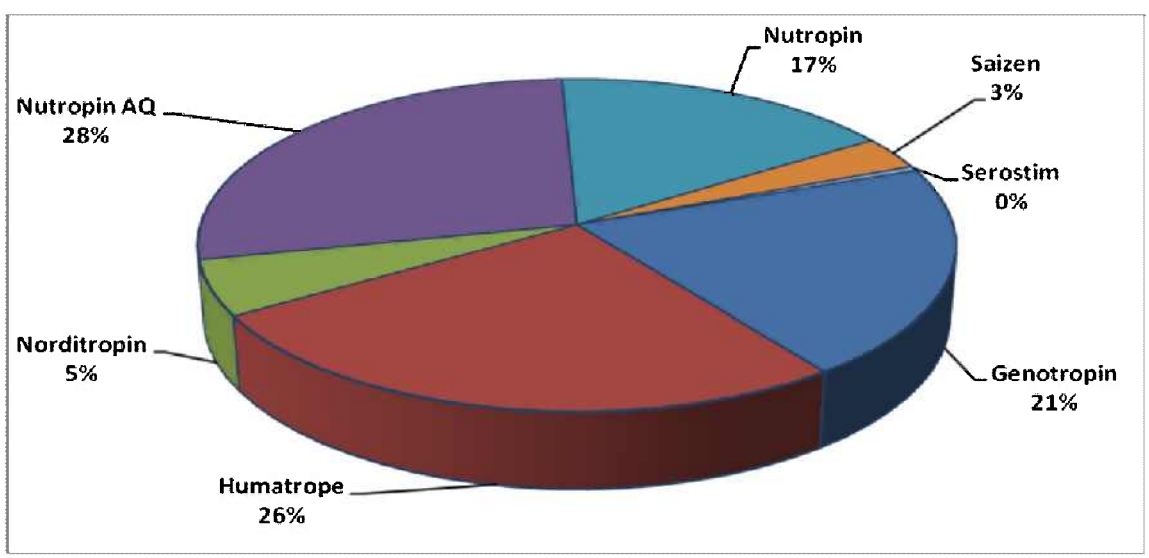
Product	# of Claims	Total Units	Total Days	Units /Day	Total Cost	Total Members	Cost/mg**
Nutropin AQ 5mg/ml	470	3,858	13,417	0.29	$982,024.56	65	$50.91
Norditropin 5mg/1.5ml	59	348	1,666	0.21	$62,071.90	8	$53.56
Norditropin 15mg/1.5ml	64	268	1,816	0.15	$129,066.36	11	$48.16
Humatrope 5 mg	74	705	2,262	0.31	$185,020.19	11	$52.49
Nutropin 5 mg	51	314	1,582	0.20	$60,957.86	7	$38.83
Genotropin 5.8 mg	101	577	2,950	0.20	$142,751.69	11	$42.66
Humatrope 6 mg	120	277	3,289	0.08	$88,648.37	18	$53.33
Humatrope 12 mg	138	505	4,161	0.12	$302,777.91	19	$49.96
Genotropin 13.8 mg	131	587	3,763	0.16	$333,263.40	20	$41.14
Nutropin 10 mg	159	988	4,633	0.21	$524,109.56	21	$53.04
Humatrope 24 mg	58	288	1,751	0.16	$357,568.89	8	$51.73
Genotropin 0.2 mg	8	210	210	1.00	$2,058.73	3	$49.02
Genotropin 0.4 mg	18	504	504	1.00	$10,568.25	2	$52.42
Genotropin 0.6 mg	26	732	756	0.97	$21,707.96	5	$49.43
Genotropin 0.8 mg	20	560	560	1.00	$21,869.04	4	$48.81
Genotropin 1 mg	25	700	702	1.00	$35,280.44	3	$50.40
Genotropin 1.2 mg	15	420	420	1.00	$25,242.30	2	$50.08
Genotropin 1.4 mg	6	168	168	1.00	$11,528.87	1	$49.02
Genotropin 1.6 mg	10	245	245	1.00	$20,006.03	2	$51.04
Genotropin 1.8 mg	12	322	322	1.00	$28,164.42	3	$48.59
Genotropin 2 mg	27	756	756	1.00	$74,799.99	4	$49.47
Saizen 5 mg	6	51	171	0.30	$12,323.55	2	$48.33
Serostim 6 mg	6	72	166	0.43	$15,979.62	1	$36.99
Saizen 8.8 mg	31	272	904	0.30	$102,192.09	6	$42.69
Tev-Tropin 5 mg	0	0	0	0	0	0	$37.58 - EAC
Omnitrope 5.8 mg	0	0	0	0	0	0	$32.39 - EAC
Zorbtive 8.8 mg	0	0	0	0	0	0	$80.00 - EAC
Total	**1,635**	**13,727**	**47,174**	**0.43**	**$3,549,471.98**	**216***	**$48.60*****

*Total unduplicated clients for FY06.
**Cost calculations include dispensing fee, but not rebate information (last 3 products show EAC/mg only).
*** Average of cost/mg.

Total Cost FY '06	**$3,549,471.98**
Total Cost FY '05	*$3,727,007.43*
Total Claims FY '06	**1,635**
Total Claims FY '05	*1,810*
Total Members FY '06	**216**
Total Members FY '05	*215*

	# of Members	# of Claims	Total Units	Total Days	Total Cost	Per Diem
Duals	14	67	766	2,063	$118,265.20	57.33
Non-Duals	202	1,568	12,961	45,111	$3,431,206.78	76.06

Market Share



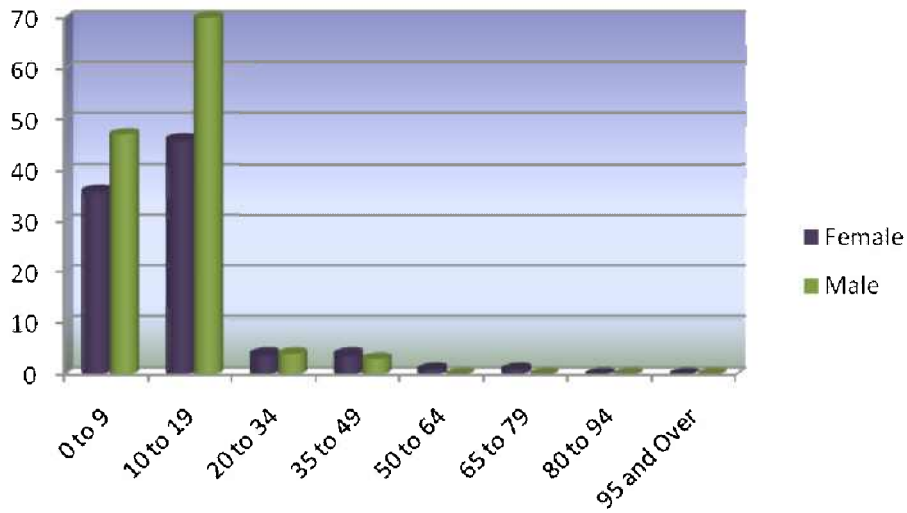
PA Activity

Total petitions submitted in for this category during specified time period: 464

Approved	391
Denied	19
Incomplete	54
D/I subsequently approved	71

Demographics

Claims were reviewed to determine the age/gender of members utilizing this category.



New in FY '07

- In November 2006,Humatrope was given approval from the FDA for the new indication of SHOX (short stature homeobox-containing gene) deficiency
- Omnitrope became available on the market in January 2007
- A new product, Accretropin from Cangene Corp, received an approvable letter from the FDA

Recommendations

The college of pharmacy has the following recommendation(s):

Add SHOX (short stature homeobox-containing gene) deficiency to covered indications and the following criteria[1, 2]

- Chromosomal analysis diagnosing SHOX gene anomaly
- Height below the third percentile on growth chart
- Open epiphyses
- Normal endocrine screen
- No evidence of GH deficiency or insensitivity, tumor activity, diabetes mellitus, history of impaired glucoses tolerance, or other serious illness known to interfere with growth.

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Appendix E

Annual Prior Authorization Review – Smoking Cessation Products
Fiscal Year 2006

Oklahoma Health Care Authority
April 2007

Prior Authorization

- All smoking cessation products are covered, including OTC products
- All smoking cessation products are covered without prior authorization for the first 90 days
- After 90 days of use in a 365 day period, further use of smoking cessation products requires prior authorization
- Criterion for approval of PA after the first 90 days of use: petition must state that the patient is enrolled in a smoking cessation behavior modification program
- Length of approval: PA can be approved for another 90 days.
- After the patient has had 180 days of treatment in a 365 day period, the patient must wait another 180 days before smoking cessation treatment will be covered again.
- Smoking cessation products do not count against either the 6 prescription per month limit or the 3 branded drugs per month limit.

Utilization Fiscal Year 2006

For the period of July 2005 through June 2006, a total of **3,762** members received smoking cessation products through the SoonerCare fee-for-service program.

Product (unit)	# of Claims	Total Units	Total Days	Units/ Day	Total Cost	Total Clients	Per Diem
Zyban (ea)	381	22,222	12,413	1.79	$28,371.45	258	$2.29
Spray (ml)	65	4,006	1,197	3.35	$12,451.97	27	$10.40
Inhalers (cart)	934	207,157	20,871	9.93	$128,958.74	618	$6.18
Patches (ea)	5,520	224,338	126,434	1.00	$477,844.68	3,964	$3.78
Gum (ea)	251	38,418	4,724	8.13	$14,969.57	154	$3.17
Lozenges (ea)	214	33,888	4,133	8.20	$16,798.22	114	$4.06
Total	**7,365**	**530,029**	**169,772**		**$679,394.63**	**3,762***	**$4.00**

*Total unduplicated members for FY05

Total Cost FY '06		**$679,394.63**
	Total Cost FY '05	*$464,320.63*
Total Claims FY '06		**7,365**
	Total Claims FY '05	*4,787*
Per Diem FY '06		**$4.00**
	Per Diem FY '05	*$4.13*
Total Members FY '06*		**3,762**
*unduplicated	*Total Members FY '05**	2,531

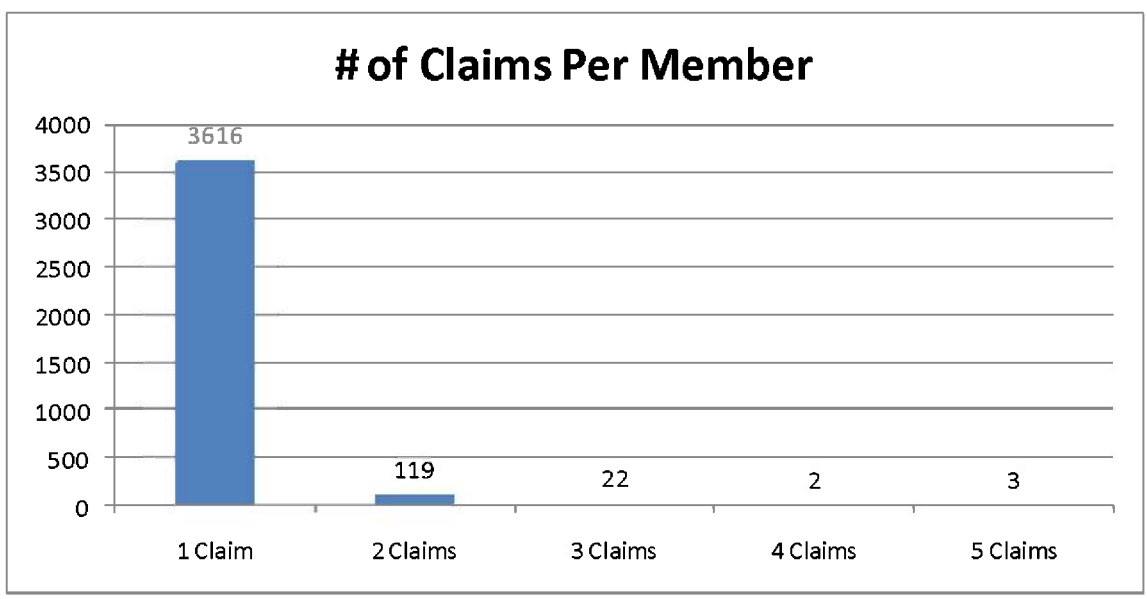
Total petitions submitted for this category during specified time period: 22

Approved 5
Denied 12
Incomplete 5

Demographics

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

Age	Female	Male	Totals
0 to 9	0	0	0
10 to 19	64	43	107
20 to 34	682	98	780
35 to 49	982	363	1,345
50 to 64	807	395	1,202
65 to 79	207	95	302
80 to 94	18	8	26
95 and Over	0	0	0
Totals	**2,760**	**1,002**	**3,762**



For the period of July 2006 through Dec 2006, a total of **1,438** members received Chantix® through the SoonerCare fee-for-service program. Chantix® was approved in May 2006 and the first paid claims were processed in July 2006.

Drug Name		Amount Paid	Days Supply	Quantity	Rxclms Count	Per Diem
CHANTIX	**TAB 0.5MG**	$4,991.53	1,684	2,721	82	$2.96
CHANTIX	**PAK 1MG**	$49,373.31	14,490	27,416	493	$3.41
CHANTIX	**TAB 1MG**	$10,632.07	3,214	5,962	116	$3.31
CHANTIX	**PAK**	$135,560.81	40,935	71,437	1,395	$3.31
Grand Total		**$200,557.72**	**60,323**	**107,536**	**2,086**	**$3.32**

Current News:

Biotechnology research by Zurich-based Cytos and British company Xenova are in early development stages of anti-smoking vaccines. These vaccines would encourage antibodies to bind to nicotine and reduce absorption in the brain, therefore reducing the stimulant effect experienced by smokers.

January 2006 – Patent expiration on Nicotrol Inhaler.

Recommendations

The College of Pharmacy recommends continued monitoring and evaluation of the cost and utilization of this Prior Authorization category.

In addition the College of Pharmacy recommends an educational outreach initiative directed at members who receive prescriptions for smoking cessation products. Staff from the Pharmacy Helpdesk could make outbound calls to encourage these members to contact the Quit Line and/or product specific telephone-based behavior modification support programs. Additionally, these staff members could administer a tobacco cessation survey to these members who have recently received smoking cessation products to evaluate effectiveness of treatment. Educational materials could be mailed to the members with information on available programs.

Appendix F

30 Day Notice to Prior Authorize Ocular Allergy Products

Oklahoma Health Care Authority
April 2007

Product Summary

Class	Product	Indication	Drops per Day
Mast Cell Stabilizer	CROMOLYN SOD SOL 4%	1	1-2 OU QID
	ALOMIDE SOL 0.1% (lodoxamide)	1	1-2 OU up to QID
	ALOCRIL SOL 2% (nedocromil)	2	1-2 OU BID
	ALAMAST DRO 0.1% (pemirolast)	3	1 OU QID
Antihistamine	EMADINE SOL 0.05% (emadastine)	4	1 OU QID
Antihistamine/ Mast Cell Stabilizer	OPTIVAR DRO 0.05% (azelastine)	2	1 OU BID
	ELESTAT DRO 0.05% (epinastine)	3	1 OU BID
	ZADITOR OTC** (ketotifen)	5	1 OU BID
	PATANOL SOL 0.1% (olopatadine)	6	1 OU BID
	PATADAY SOL 0.2% (olopatadine)	7	1 AE QD
Corticosteroid	ALREX SOL 0.2% (loteprednol)	4	1 AE QID

Indications:

1. Treatment of the ocular disorders referred to by the terms vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis.
2. Treatment of *itching* of the eye associated with **allergic conjunctivitis**.
3. Prevention of the *itching* associated with **allergic conjunctivitis**.
4. Temporary relief of the signs and symptoms of **allergic conjunctivitis**.
5. Temporary prevention of *itching* of the eye due to **allergic conjunctivitis**.
6. Treatment of the signs and symptoms of **allergic conjunctivitis**.
7. Treatment of ocular *itching* associated with **allergic conjunctivitis**.

Clinical Trial Summary

Mast Cell Stabilizers

This class inhibits mast cell degranulation and blocks the release of mediators (cytokines, histamines, proteases, etc) from the cell. To obtain maximum efficacy, these products require a loading period where they are applied for several weeks before antigen exposure. Most products in this category are applied four times daily except for nedocromil which can be used twice daily.[1]

- Lodoxamide was found to be more effective than cromolyn sodium (2%).[2] May require up to four weeks of treatment for full symptomatic response.
- Pemirolast was found to be as effective as nedocromil and olopatadine.[3,4]
- Nedocromil was found to be equally efficacious to olopatadine in one study[5] and cromolyn sodium 2% in another.[6]
- Cromolyn sodium was used for many comparisons with other products as it was the first in this class to be marketed. Often the comparison was with 2% and not the 4% commercially available. Cromolyn was found to be similar to levocabastine.[7,8]

Antihistamines

The first class developed for the ophthalmic treatment of allergies, these products exert their effect by preventing histamine release from mast cells in the conjunctiva. Several products in this class are currently available Over-The-Counter combined with a decongestant. They have a rapid onset of action, but a brief duration of action. Prescription products have an increased duration of action up to 4 hours.[1]

- Levocabastine is no longer marketed, but was often used as the comparator agent in many earlier trials.
- Emadastine is selective for the H1-receptor and appears to also affect eosinophil chemotaxis. Emadastine was more efficacious than levocabastine in one clinical trial and was superior to nedocromil in alleviating redness and itching in one antigen challenge model.[9,10,11]

Antihistamine/Mast Cell Stabilizers

The products in this class exhibit a dual action of competitive H1-receptor binding and mast cell degranulation. This dual action provides both rapid onset and long-term control.[1]

- Olopatadine has been shown to be more efficacious than epinastine, nedocromil, azelastine, loteprednol 0.2%, cromolyn sodium (2%) and levocabastine.[12,13,14,15,16,17]
- Ketotifen was shown to be more efficacious than cromolyn sodium, nedocromil and emedastine.[18,19,20]
- Ketotifen and olopatadine were shown to be either equally efficacious or one product more effective than the other in various trials.[21,22,23,24]
- Epinastine is similar or superior to levocabastine, was similar to olopatadine in one trial and non-inferior to ketotifen in another.[25,26,27]
- Most trails were completed with 100 patients or less, were double-blind or double-masked and randomized.

Corticosteroids

These products are used for inflammatory conditions of the eye and although they have shown efficacy in treatment of ocular allergies, they are normally reserved for refractory cases or severe chronic forms. Only one corticosteroid has a single indication for allergic conjunctivitis, loteprednol. Other products have additional indications including post surgical procedures.[1]

NSAIDs

Only one NSAID ocular product has an indication for allergic conjunctivitis, ketorolac. This product also has an indication for post-cataract surgery.[1]

Summary Table of Head-to-Head Trials

(Row Drug vs Column Drug)

→	Cromolyn	Alocril®	Levo-cabastine	Emadine®	Optivar®	Elestat®	Zaditor®	Patanol®	Alrex®
Cromolyn			=/-						
Alomide®	+ (2%)								
Alocril®	= (2%)							=	
Alamast®		=						=	
Emadine®		+	+						
Elestat®			+				=	=	
Zaditor®	+	+		+				=/+	
Patanol®	+ (2%)	+	+		+	+	=/+		+

Recommendations

The College of Pharmacy recommends the addition of the Ocular Allergy class to the Product Based Prior Authorization program. The following Tier-1 drug list has been reviewed and determined to be an acceptable combination for use as initial therapy for the majority of members. The College of Pharmacy recommends this list to the Drug Utilization Review Board based on cost and clinical effectiveness for approval before referral to the Oklahoma Healthcare Authority.

Tier 1	Tier 2
cromolyn sodium	Alomide Alocril® Alamast®
Zaditor OTC	Optivar Elestat® Patanol® Pataday® Ketotifen Emadine® Alrex®

Proposed Criteria for Tier 2 Products:

1. FDA approved diagnosis.
2. A trial of at least one Tier-1 product of a similar type (ie: cromolyn sodium prior to use of a mast cell stabilizer product or OTC ketotifen prior to use of an antihistamine, dual action, or corticosteroid product) for a minimum of two weeks in the last 30 days*.
3. Reason for clinical failure should be noted on the petition.
4. Clinical exceptions granted for products with allergic reaction or contraindication.

* Point-of-Sale Claims system will look for Tier-1 trial and generate automatic approval for Tier 2 product if appropriate trial has been completed.

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Appendix G

30 Day Notice to Prior Authorize Vyvanse™ (lisdexamfetamine dimesylate) Capsules

Oklahoma Health Care Authority
April 2007

Manufacturer	New River Pharmaceuticals, Inc.
Distributer	Shire US, Inc.
Classification	FDA classification: Stimulant Status: C-II Prescription Only

Summary

Vyvanse™ is a once daily prodrug of dextroamphetamine. Lisdexamfetamine dimesylate is rapidly absorbed from the gastrointestinal tract and converted to dextroamphetamine. The drug must be ingested orally in order for activation to occur which may limit its potential for abuse. Vyvanse™ is indicated for treatment of ADHD in children aged 6 to 12 years. The recommended starting dose is 30 mg once daily in the morning. Dosage increases should be done at 20 mg/day on a weekly basis to the maximum dose of 70 mg daily. Afternoon doses should be avoided because of the potential for insomnia.

Clinical Studies

Study One	DB, R, PC, PG for 4 wks	6 to 12 yo, N=290	Vyvanse™ 30, 50, or 70 mg q am	Significant improvement in ADHD rating scale for all doses v placebo; 70 mg numerically superior to 30 and 50 mg.
Study Two	DB, R, PC, XO, 3 wk open label dose titration on Adderall XR® with 2 wk XO	6 to 12 yo, N=53	Adderall XR® same dose as open label; Vyvanse™ 30, 50 or 70; or placebo q am for 1 week each.	Significant difference in behavior based on SKAMP-Deportment scores compared to placebo.

DB=Double-Blind, R=Randomized, PC=Placebo-Controlled, PG=Parallel-Group, XO=Crossover, SKAMP=Swanson, Kotkin, Agler, M..Flynn and Pelham (investigator ratings across 8 sessions of a 12 hour treatment day.

Recommendations

The College of Pharmacy recommends placement of Vyvanse™ in the ADHD Product Based Prior Authorization category. The criteria and tier placement will be determined and presented with new ADHD tier proposal.

Reference

Vyvanse™ Product Information. Shire LLC. 2007.

Appendix H

30 Day Notice to Prior Authorize Flector® (diclofenac epolamine) Topical Patch

Oklahoma Health Care Authority
April 2007

Manufacturer INST Biochem
Classification FDA classification: NSAID
Status: prescription only

Summary

Flector® is a topical analgesic patch containing 1.3% epolamine salt of diclofenac (equivalent to 1% diclofenac sodium) designed for twice a day application which received FDA approval on January 31, 2007. Each patch contains 180mg of diclofenac epolamine in an aqueous base. The high solubility profile both in water and oily solvents and its significant release and absorption of active ingredient through the skin provides a local analgesic and anti-inflammatory effect with minor systemic exposure to diclofenac. Flector® is indicated for topical use only to treat acute pain due to minor strains, sprains and contusions.

Diclofenac Sodium Utilization - Calendar Year 2006

(AWP for Flector® currently unavailable.)

Drug Name	Claims	Units	Days	Total Paid	Per Diem
DICLOFENAC TAB 25MG EC	9	406	186	$ 111.05	$ 0.60
DICLOFENAC TAB 50MG DR	512	31,748	14,029	$ 10,967.27	$ 0.78
DICLOFENAC TAB 50MG EC	396	25,381	11,268	$ 9,184.41	$ 0.82
DICLOFENAC TAB 75MG DR	2,183	128,877	64,938	$ 29,941.42	$ 0.46
DICLOFENAC TAB 75MG EC	388	20,771	10,409	$ 5,424.35	$ 0.52
DICLOFENAC TAB 100MG ER	442	20,034	16,604	$ 18,920.55	$ 1.14
DICLOFENAC TAB 100MG XR	49	1,920	1,605	$ 1,754.08	$ 1.09
DICLOFEN POT TAB 50MG	892	46,536	18,796	$ 11,318.40	$ 0.60
Totals	**4,871**	**275,673**	**137,835**	**$ 87,621.53**	**$ 0.64**

Recommendations

The College of Pharmacy recommends prior authorization of Flector® and placement with the Tier-2 NSAID products. Approval based on clinical documentation of inability to take Tier-1 products and supporting information regarding the medical necessity of topical formulation.

REFERENCE

Flector® Product Information. FDA website: http://www.fda.gov/cder/foi/label/2007/021234lbl.pdf. Accessed 2007.

Appendix I

30 Day Notice to Prior Authorize Qualaquin® (Quinine)

Oklahoma Health Care Authority
April 2007

Manufacturer Mutual Pharmaceutical Company
Classification FDA classification: Antimalarial
Status: prescription only

Summary
Qualaquin®, the only FDA-approved quinine product available for the treatment of malaria, was approved in August 2005. Numerous drug products containing quinine sulfate were marketed without approved applications for malaria and many are used off-label to treat and/or prevent nocturnal leg muscle cramps and related conditions. However, on February 13, 2007 the FDA ordered all firms to cease manufacturing unapproved products containing quinine, including quinine sulfate products and any other salt of quinine due to the various adverse events associated with these products. Because of this, Qualaquin® will soon be the only remaining quinine product on the market.

Risks associated with quinine-containing products
Serious safety concerns, including fatalities, associated with drug products containing quinine are well documented in the literature and in adverse drug events reported. From 1969 through September 11, 2006, the FDA received 665 reports of adverse events with serious outcomes associated with the use of quinine, including 93 deaths. One of the adverse events includes quinine toxicity, a cluster of symptoms that includes tinnitus, dizziness, disorientation, nausea, visual changes and auditory deficits. Serious adverse events include cardiac arrhythmias including torsades de pointes, severe skin reactions, thrombocytopenia and other hematological events, permanent visual and hearing disturbances, hypoglycemia, renal failure and generalized anaphylaxis.

Utilization between 01/01/2007 and 03/21/2007

Drug	Claims	Total units	Total days	Total Cost	Per diem
Qualaquin	18	960	720	$ 3738.70	$ 5.19

Utilization of Products for Treatment of Malaria - Calendar Year 2006

Drug Name	Amount Paid	Days Supply	Quantity	Rx claims Count	Pier diem
CHLOROQUINE TAB 250MG	$608.49	385	349	9	$1.58
ARALEN TAB 500MG	$154.14	30	25	1	$5.14
CHLOROQUINE TAB 500MG	$534.70	251	115	9	$2.13
HYDROXYCHLOR TAB 200MG	$25,211.67	50,918	88,329	1,475	$0.50
LARIAM TAB 250MG	$129.33	28	11	1	$4.62
MEFLOQUINE TAB 250MG	$1,670.17	1,476	173	25	$1.13
PRIMAQUINE TAB 26.3MG	$45.43	21	42	1	$2.16
DARAPRIM TAB 25MG	$869.27	590	1,470	23	$1.47
QUININE SULF CAP 200MG*	$2,276.76	3,315	4,402	90	$0.69
QUININE SULF CAP 325MG*	$14,327.04	37,880	46,725	979$	0.38
QUININE SULF CAP 5GR*	$4,079.23	7,048	9,234	193$	0.58
QUININE SULF TAB 260MG*	$14,293.33	32,986	42,556	927$	0.43
MALARONE TAB 62.5/25	$732.65	180	383	7	$4.07
MALARONE TAB 250-100	$2,411.51	592	462	11	$4.07
Grand Total	**$67,343.72**	**135,700**	**194,276**	**3,751**	**$0.50**

*No longer available

Recommendations

The College of Pharmacy recommends prior authorization of Qualaquin®. Approval would be granted only based on an FDA approved diagnosis of malaria. Off label use for the prevention/treatment of leg cramps and other related conditions will not be covered.

REFERENCE

FDA Updates. Available at: http://www.fda.gov/cder/drug/unapproved_drugs/quinineQA.pdf. Accessed March 26, 2007.

Appendix J

New Product Summaries

Oklahoma Health Care Authority
April 2007

Drug	Manufacturer	Indications	Dosage	Adverse Effects	Contraindications	New Molecular Entity	AWP/ unit
Tykerb (lapatinib) 250mg tablets	GlaxoSmithKline	In combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including anthracycline, a taxane, and trastuzumab	1,250mg (5 tabs) orally once daily on days 1-21 continuously in combination with capecitabine 2,000mg/m^2/day (in 2 doses 12 hours apart) on days 1-14 in a repeating 21 day cycle	Diarrhea, nausea, vomiting, palmar-plantar erythrodysesthisia, rash, and fatigue	none	No	N/A
Tekturna (aliskiren) 150mg & 300mg tablets	Novartis	Treatment of HTN alone or in combination with other agents	150mg daily, may increase to 300mg daily	Dizziness, rash, hyperkalemia, diarrhea, increased creatine kinase, BUN, SCr, and uric acid, cough, abdominal pain, anemia, angina, angioedema, dyspepsia, GERD, gout, myositis, renal stone formation, rhabdomyolysis, seizure, severe hypotension	none	Yes	150mg-$1.95 300mg-$2.46

Vaprisol (conivaptan) 20mg/4mL ampules for injection	Astellas	Treatment of euvolemic hyponatremia in hospitalized patients	20mg IV loading dose followed by 20mg continuous IV infusion over 24 hours. May be continued at this dose for an additional 1-3 days (do not exceed 4 days or 40mg/day)	Headache, thirst, hypokalemia, vomiting, increased urination, diarrhea, hypotension	Hypovolemic hyponatremia, taking statins, ketoconazole, itraconazole, clarithromycin, indinavir, ritonavir	Yes	$315.00
Vyvanse (lisdexamfetamine dimesylate) 30mg, 50mg, 70mg capsules	New River Pharmaceuticals Inc.	Treatment of ADHD in children age 6-12	30mg once daily in the morning, may increase in 20mg/day increments weekly. Max dose is 70mg/day	Upper abdominal pain, decreased appetite, dizziness, dry mouth, irritability, insomnia, nausea, vomiting, decreased weight	Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, glaucoma	Yes	N/A
Lialda (mesalamine) 1.2 gm tablets	Shire	To induce remission in active mild-moderate ulcerative colitis	2.4-4.8gm once daily for up to 8 weeks	Headache, flatulence, increased alanine aminotransferase, alopecia, pruritis	Hypersensitivity to salicylates	No	$3.54
Flector (diclofenac eoplamine) 1.3% topical patch	INST Biochem	Topical treatment of acute pain due to minor strains, sprains and contusions	1 patch to most painful area BID	Pruritis, dermatitis, burning, nausea, somnolence, headache	Hypersensitivity to diclofenac, aspirin, or other NSAIDs. Not for the treatment of perioperative pain in the setting of CABG surgery. Should not be applied to non-intact or damaged skin	No	N/A

Foradil Certihaler (formoterol fumarate) encapsulated formoterol powder for inhalation	Novartis (SkyPharma Production SAS)	Maintenance of asthma and prevention of bronchospasm in adults and children 5 years and older with reversible obstructive airway disease	One 10mcg inhalation every 12 hours (max dose 20mcg/day)	Nasopharyngitis, headache, upper respiratory infection, cough, pyrexia, vomiting, tremor, nasal congestion, rhinitis, viral infection, influenza, bronchitis, back pain, conjunctivitis, rash, dyspepsia, urinary tract infection, diarrhea, muscle cramps, insomnia	Hypersensitivity to any component	No	$1.63
Elestrin (estradiol) gel	BioSante	Moderate to severe vasomotor symptoms associated with menopause	Applied once daily to upper arm	Nasopharyngitis, breast tenderness, metrorrhagia, upper respiratory infection, nausea, vaginal discharge, nipple pain, endometrial hyperplasia	Undiagnosed abnormal genital bleeding, history of breast cancer, estrogen-dependent neoplasia, history of DVT or PE, active or recent arterial thromboembolic disease, liver dysfunction, pregnancy	No	N/A
Invega (paliperidone) 3mg, 6mg, 9mg extended release tablets	Janssen	Treatment of schizophrenia	6mg once daily (range of 3-12mg/day)	Akathisia, extrapyramidal disorder, somnolence, orthostatic hypotension, salivary hypersecretion, dystonia, hypertonia, parkinsonism	Hypersensitivity to paliperidone or risperidone	Yes	N/A

Brovana (arformoterol tartrate) Solution for nebulization	Sepracor	Controlling symptoms of COPD in adults	15 mcg BID	Allergic reactions, chest pain, increased or decreased blood pressure, fast and irregular heartbeat, headache, tremor, nervousness, dry mouth, muscle cramps, nausea, vomiting, dizziness, low or high potassium, hyperglycemia, insomnia	Hypersensitivity to any component	No	$4.61
Zolinza (vorinostat) 100mg Capsules	Merck	Treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent or recurrent disease on or following 2 systemic therapies	400 mg orally once daily (may be reduced to 300mg once daily if patient is intolerant) for 5 days each week	Diarrhea, fatigue, nausea, thrombocytopenia, anorexia, dysgeusia	none	Yes	$60.00
Tirosint (levothyroxine sodium soft caps) 12.5, 25, 50, 75, 100, 125, 150mcg caps	INST Biochem	Hypothyroidism, pituitary TSH suppression	Average 1.7mcg/kg/day given once daily in the morning	Fatigue, increased appetite, weight loss, heat intolerance, fever, excessive sweating, headache, hyperactivity, nervousness, anxiety, irritability, emotional lability, insomnia, tremors, muscle weakness, palpitations,	Untreated subclinical or overt thyrotoxicosis, patients with acute MI, uncorrected adrenal insufficiency,	No	N/A

				tachycardia, arrhythmias, increased pulse and blood pressure, heart failure, angina, MI, cardiac arrest, dyspnea, diarrhea, vomiting, abdominal cramps, elevated LFTs, hair loss, flushing, decreased bone mineral density, menstrual irregularities, impaired fertility			
Tyzeka (telbivudine) tablets	Novartis	Chronic Hepatitis B	600mg orally once daily	Fatigue, malaise, pyrexia, arthralgia, muscle related symptoms, abdominal pain, gastritis, diarrhea, cough, headache	Hypersensitivity to any component	Yes	N/A
Veregen (kune-catechins) topical ointment	Medigene	Topical treatment of external genital and perianal warts in immunocompetent patients age 18 or older	0.5cm strand applied in a thin layer TID not to exceed 16 weeks	Erythema, pruritis, burning, pain/discomfort, erosion/ulceration, edema, induration, rash, vesicular	Hypersensitivity to any component	Yes	N/A

Appendix K

Information for Healthcare Professionals

Linezolid
(marketed as Zyvox)

FDA ALERT [3/16/2007]: FDA is issuing this alert to advise you of new emerging safety concerns about Zyvox (linezolid) from a recent clinical study. This open-label, randomized trial compared linezolid to vancomycin, oxacillin, or dicloxacillin (comparator antibiotics) in the treatment of seriously ill patients with intravascular catheter-related bloodstream infections including those with catheter-site infections. In this study, patients treated with linezolid had a higher chance of death than did patients treated with any comparator antibiotic, and the chance of death was related to the type of organism causing the infection. Patients with Gram positive infections had no difference in mortality according to their antibiotic treatment. In contrast, mortality was higher in patients treated with linezolid who were infected with Gram negative organisms alone, with both Gram positive and Gram negative organisms, or who had no infection when they entered the study.

Linezolid is not approved for the treatment of catheter-related bloodstream infections, catheter-site infections, or for the treatment of infections caused by Gram negative bacteria. If infection with Gram negative bacteria is known or suspected, appropriate therapy should be started immediately. FDA is currently evaluating the new study along with other information about linezolid.

This information reflects FDA's preliminary analysis of data concerning this drug. FDA is considering, but has not reached a final conclusion about, this information. FDA intends to update this sheet when additional information or analyses become available.

To report any serious adverse events associated with the use of linezolid or other medical products, please contact the FDA MedWatch program using the contact information at the bottom of this sheet.

Considerations for Physicians and Other Health Care Professionals

Linezolid is approved for the treatment of vancomycin-resistant *Enterococcus faecium* infections, nosocomial pneumonia, community acquired pneumonia, uncomplicated skin and skin structure infections, and complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis.

Physicians and other healthcare professionals should consider the information from this new study when deciding whether to prescribe linezolid. In this study, mortality was higher in the linezolid arm:

- in patients infected with Gram negative organisms alone,
- in those infected with both Gram positive and Gram negative organisms, and
- in patients in whom no infection was observed when they entered the study.

Linezolid
(marketed as Zyvox)

In patients with only Gram positive infections, however, no difference in mortality was seen between the linezolid and comparator arms.
Physicians and other healthcare professionals are reminded that

- linezolid is not approved for the treatment of catheter-related bloodstream infections or catheter-site infections.
- linezolid is not indicated for the treatment of Gram negative infections. If infection with Gram negative bacteria is known or suspected, appropriate therapy should be started immediately.

Information for the Patient

Physicians and other healthcare professionals should discuss with patients for whom linezolid might be prescribed that new but still uncertain information suggests a higher chance of death for the treatment of catheter-related bloodstream infections including those with catheter-site infections, and for those who have, or may get, infections with types of bacteria other than linezolid's particular target.

Data Summary

Linezolid was studied in an open-label, randomized, clinical trial in patients with intravenous catheter-related bloodstream infections including those with catheter-site infections due to Gram positive bacteria. Patients in the study were randomly assigned to receive either 600 mg linezolid given intravenously or orally every 12 hours, or to one gram vancomycin given intravenously every 12 hours for 7 to 28 days. Patients in the vancomycin arm could have their therapy switched to oxacillin or dicloxacillin if the organism was methicillin-susceptible. Patients could also receive concomitant therapy for Gram negative infections. Patients with intravascular catheters were enrolled in the study if they had signs/symptoms of a catheter site infection or fever/hypothermia with other signs of infection such as hypotension, tachycardia, tachypnea, leukocytosis/leukopenia or elevated bands.

The study included 726 patients 13 years of age or older with catheter-related bloodstream infections including those with catheter-site infections. In the linezolid arm, 151 of the 363 (42%) patients had bacteremia, and in the comparator arm, 136 of the 363 (37%) patients had bacteremia. About 48% of patients were being treated in an intensive care unit and 26% were intubated.

This study showed an increased number of deaths up to 84 days after the first dose of study drug in patients treated with linezolid (78 of 363 [21·5%]) compared to those treated with comparator (58 of 363 [16·0%]). At baseline 34 patients in the linezolid arm and 32 patients in the comparator arm had Gram-negative bacteremia; an additional 28 patients in the linezolid arm

and 17 patients in the comparator arm developed Gram-negative bacteremia during treatment. The greatest imbalance occurred during treatment and within 7 days following discontinuation of study drug with 43/363 (12%) deaths in the linezolid arm versus 22/363 (6%) in the comparator arm.

The following table summarizes deaths by baseline pathogen (all culture sources).

Type of organism	Linezolid N=363	Comparator N=363
	Number died N=78	Number died N=58
Gram positive only	37/222 (16.7%)	37/215 (17.2%)
Gram negative only	4/15 (26.7%)	1/11 (9.1%)
Gram positive and Gram negative	16/46 (34.8%)	7/39 (17.9%)
No organism	20/76 (26.3%)	12/92 (13%)
Other	1/4 (25%)	1/6 (16.7%)

Current Status

Linezolid is not approved by the FDA for the treatment of catheter-related bloodstream infections or catheter-site infections. We are reviewing the information mentioned here, along with other information on the effects of linezolid to further evaluate the observed findings. We have not yet come to any final conclusions about the implications of this new study for linezolid. We intend to continue evaluating all available information and, if the review reveals additional important information to share, we will notify healthcare providers and patients.

FDA News

FOR IMMEDIATE RELEASE
P07-45
March 14, 2007

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888-INFO-FDA

FDA Requests Label Change for All Sleep Disorder Drug Products

The U.S. Food and Drug Administration (FDA) has requested that all manufacturers of sedative-hypnotic drug products, a class of drugs used to induce and/or maintain sleep, strengthen their product labeling to include stronger language concerning potential risks. These risks include severe allergic reactions and complex sleep-related behaviors, which may include sleep-driving. Sleep driving is defined as driving while not fully awake after ingestion of a sedative-hypnotic product, with no memory of the event.

"There are a number of prescription sleep aids available that are well-tolerated and effective for many people," said Steven Galson, M.D., MPH, director of FDA's Center for Drug Evaluation and Research. "However, after reviewing the available post-marketing adverse event information for these products, FDA concluded that labeling changes are necessary to inform health care providers and consumers about risks."

In December 2006, FDA sent letters to manufacturers of products approved for the treatment of sleep disorders requesting that the whole class of drugs revise product labeling to include warnings about the following potential adverse events:

- Anaphylaxis (severe allergic reaction) and angioedema (severe facial swelling), which can occur as early as the first time the product is taken.
- Complex sleep-related behaviors which may include sleep-driving, making phone calls, and preparing and eating food (while asleep).

FDA has been working with the product manufacturers over the past three months to update labeling, notify health care providers and inform consumers of these risks.

Along with the labeling revisions, FDA has requested that each product manufacturer send letters to health care providers to notify them about the new warnings. Manufacturers will begin sending these letters to providers starting this week.

In addition, FDA has requested that manufacturers of sedative-hypnotic products develop Patient Medication Guides for the products to inform consumers about risks and advise them of potential precautions that can be taken. Patient Medication Guides are handouts given to patients, families and caregivers when a medicine is dispensed. The guides will contain FDA-approved information such as proper use and the recommendation to avoid ingesting alcohol and/or other central nervous system depressants. When these Medication Guides are available, patients being treated with sleep medications should read the information before taking the product and talk to their doctors if they have questions or concerns. Patients should not discontinue the use of these medications without first consulting their health care provider.

Although all sedative-hypnotic products have these risks, there may be differences among products in how often they occur. For this reason, FDA has recommended that the drug manufacturers conduct clinical studies to investigate the frequency with which sleep-driving and other complex behaviors occur in association with individual drug products.

The medications that are the focus of the revised labeling include the following 13 products:

Ambien/Ambien CR (Sanofi Aventis)
Butisol Sodium (Medpointe Pharm HLC)
Carbrital (Parke-Davis)
Dalmane (Valeant Pharm)
Doral (Questcor Pharms)
Halcion (Pharmacia & Upjohn)
Lunesta (Sepracor)
Placidyl (Abbott)
Prosom (Abbott)
Restoril (Tyco Healthcare)
Rozerem (Takeda)
Seconal (Lilly)
Sonata (King Pharmaceuticals)

For more information on the sedative hypnotic products and sleep disorders, visit http://www.fda.gov/cder/drug/infopage/sedative_hypnotics/default.htm; www.fda.gov/womens/getthefacts/sleep.html and www.nhlbi.nih.gov/health/dci/Diseases/inso/inso_whatis.html.

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Information for Healthcare Professionals

Interferon Gamma 1-b
(marketed as Actimmune)

FDA ALERT [03/9/2007]: FDA is issuing this alert to advise you of the early termination of the INSPIRE clinical study of Actimmune for idiopathic pulmonary fibrosis (IPF). The study was stopped because an interim analysis showed that patients with IPF who received Actimmune did not benefit. The trial compared survival in patients getting Actimmune or an inactive injection (placebo). An analysis showed that 14.5% of patients treated with Actimmune died as compared to 12.7% of patients treated with placebo. Actimmune is not approved by the FDA to treat IPF.

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

To report any serious adverse events associated with the use of Actimmune or other medical products, please contact the FDA MedWatch program using the contact information at the bottom of this sheet.

Considerations for Physicians and Other Health Care Professionals

Physicians and other healthcare professionals should consider that the INSPIRE study showed no mortality benefit in treating IPF patients with Actimmune. INSPIRE was a clinical trial designed to evaluate survival of patients with mild to moderate IPF treated with Actimmune or placebo. The trial was stopped early because 14.5% of patients treated with Actimmune died as compared to 12.7% of patients treated with placebo. Side effects of Actimmune treatment reported in this study included constitutional symptoms, neutropenia, and possibly pneumonia.

Although Actimmune has not been approved for use in IPF, some patients with IPF may be receiving this product off-label. Physicians and other health care professionals should discuss the results of this trial with their patients receiving Actimmune for IPF and carefully consider whether patients should continue to receive treatment with Actimmune.

Information for the Patient.

Patients being treated with Actimmune for IPF should discuss with their physicians whether they should continue to receive Actimmune treatment.

Data Summary

INSPIRE was a randomized, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of Actimmune in IPF patients with mild to moderate lung function impairment. The primary endpoint was survival time. On February 28, 2007, an independent data monitoring committee (DMC) recommended the early termination of the INSPIRE study due to lack of therapeutic benefit from Actimmune. Among the 826 randomized patients there

Interferon Gamma 1-b
(marketed as Actimmune)

were a total of 115 deaths, 14.5% in the Actimmune group as compared to 12.7% in the placebo group. InterMune concluded that the drug would not show a mortality benefit to IPF patients and stopped the study. In this study, InterMune reported that Actimmune use was associated with several adverse effects, including constitutional symptoms, neutropenia, and possibly pneumonia.

Actimmune is a synthesized version of interferon gamma-1b, a naturally occurring biologic response modifier. Actimmune is FDA-approved to reduce the frequency and severity of infections in patients with chronic granulomatous disease and to delay the progression of severe, malignant osteopetrosis. Both of these hereditary diseases are life-threatening and there are no other FDA-approved treatments. Actimmune is not FDA-approved to treat IPF.

IPF is a chronic progressive interstitial lung disease of unknown etiology. It is characterized by fibrosis of the lung parenchyma. IPF progression is variable and unpredictable. Some patients experience a rapidly progressive fatal course over several months, while others experience a protracted deterioration of lung function. Median survival is 3-5 years from the onset of symptoms.

FDA intends to evaluate the INSPIRE study results and, if the review reveals additional important information to share, will notify healthcare providers and patients.

FDA News

FOR IMMEDIATE RELEASE
P07-33
March 1, 2007

Media Inquiries:
Sandy Walsh, 301-827-6242
Consumer Inquiries:
888-INFO-FDA

FDA Takes Action to Halt Marketing of Unapproved Ergotamine Companies Ordered to Cease Manufacturing and Distribution of Illegal Drugs to Treat Migraine Headaches

The Food and Drug Administration (FDA) today told 20 companies to cease marketing unapproved drug products containing ergotamine tartrate. Ergotamine tartrate products are used to treat vascular headaches, including migraines. As part of the FDA's continued efforts to combat the marketing of unapproved drugs, the agency sent warning letters to eight manufacturers and 12 distributors warning them that they are subject to further enforcement action if they do not stop manufacturing and distributing these products.

The agency urges consumers who are using ergotamine products and have questions or concerns to contact their health care provider. This action does not affect FDA-approved products containing ergotamine, which will remain on the market.

"Unapproved drugs pose real risks to the American public," said Steven Galson, M.D., director of the FDA's Center for Drug Evaluation and Research (CDER). "Because they have not been subject to FDA review, the safety, effectiveness, and quality of such products are unknown. We remain dedicated to tackling this problem through education and outreach, as well as enforcement actions like these. It is central to our mission to ensure a safe and effective drug supply for the American public."

In addition to marketing these products without FDA approval, most of the companies receiving warning letters have omitted from their drugs' labeling critical warnings regarding the potential for serious, possibly fatal, interactions with certain other drugs. Based on recent scientific information, the five marketed, approved versions of ergotamine-containing products have updated their labeling to include a box warning (the strongest agency warning) against using such products when also taking potent CYP 3A4 inhibitors, including some antifungal agents, protease inhibitors, and certain antibiotics. CYP 3A4 is a metabolic enzyme that helps the body eliminate drugs or other chemicals. Serious and life-threatening ischemia (a restriction in blood supply), including death and gangrene, have resulted when such products are used together. Most unapproved versions of the drug do not carry these warnings.

"The warning letters we issued are another example of our commitment to the Unapproved Drugs Initiative. We are taking a sensible, risk-based approach to the problem, and remain dedicated to the goal of getting unapproved drugs off the market," said CDER's Director of Compliance, Deborah M Autor. "Doctors and patients often do not realize that not all drugs that are available on the market are backed by FDA approval. We estimate that less than 2% of prescribed drugs are unapproved. This lack of approval undermines FDA's drug safety efforts. Drugs that skirt the approval process may be unsafe, may not work, and in our experience, often have inadequate labeling."

Companies have 15 days to respond to the FDA with a discontinuation plan for their products. Manufacturers have 60 days to cease manufacturing of new product, and distributors have 180 days to cease further shipment of existing products. Previously manufactured unapproved ergotamine products may still be found on pharmacy shelves for a short period of time.

FDA's actions against unapproved drugs are part of the agency's broader initiative, announced in June 2006, to ensure that consumers and the health care community are provided with established and emerging drug safety information so that they can make the best possible medical decisions about the safe and effective use of drugs.

For additional information, including copies of the Warning Letters (which identify the firms involved and the names of their products), see FDA's Unapproved Drugs Web page, located at http://www.fda.gov/cder/drug/unapproved_drugs.

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Warning Letters for Ergotamine-Containing Drug Products

RSS Feed for FDA News Releases [what's this?]

FDA News

FOR IMMEDIATE RELEASE
P07-26
February 21, 2007

Media Inquiries:
Sandy Walsh, 301-827-6242
Consumer Inquiries:
888-INFO-FDA

FDA Directs ADHD Drug Manufacturers to Notify Patients about Cardiovascular Adverse Events and Psychiatric Adverse Events

The U.S. Food and Drug Administration (FDA) today directed the manufacturers of all drug products approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) to develop Patient Medication Guides to alert patients to possible cardiovascular risks and risks of adverse psychiatric symptoms associated with the medicines, and to advise them of precautions that can be taken.

"Medicines approved for the treatment of ADHD have real benefits for many patients but they may have serious risks as well," said Steven Galson, M.D., MPH, Director, Center for Drug Evaluation and Research (CDER). "In our ongoing commitment to strengthen drug safety, FDA is working closely with manufacturers of all ADHD medicines to include important information in the product labeling and in developing new Patient Medication Guides to better inform doctors and patients about these concerns."

Patient Medication Guides are handouts given to patients, families and caregivers when a medicine is dispensed. The guides contain FDA-approved patient information that could help prevent serious adverse events. Patients being treated with ADHD products should read the information before taking the medication and talk to their doctors if they have any questions or concerns.

ADHD is a condition that affects approximately 3 percent to 7 percent of school-aged children and approximately 4 percent of adults. The three main symptoms are inattention, hyperactivity, and impulsivity. People with ADHD may have difficulty in school, troubled relationships with family and peers, and low self-esteem.

An FDA review of reports of serious cardiovascular adverse events in patients taking usual doses of ADHD products revealed reports of sudden death in patients with underlying serious heart problems or defects, and reports of stroke and heart attack in adults with certain risk factors.

Another FDA review of ADHD medicines revealed a slight increased risk (about 1 per 1,000) for drug-related psychiatric adverse events, such as hearing voices, becoming suspicious for no reason, or becoming manic, even in patients who did not have previous psychiatric problems.

FDA recommends that children, adolescents, or adults who are being considered for treatment with ADHD drug products work with their physician or other health care professional to develop a treatment plan that includes a careful health history and evaluation of current status, particularly for cardiovascular and psychiatric problems (including assessment for a family history of such problems).

As part of the Agency's ongoing regulatory activity, in May 2006 the FDA directed manufacturers of these products to revise product labeling for doctors to reflect concerns about adverse cardiovascular and psychiatric events. These changes were based on recommendations from the FDA Pediatric Advisory Committee and the Drug Safety and Risk Management Advisory Committee. To help patients understand these risks, an additional part of this revised labeling process is the creation of a Patient Medication Guide for each individual product.

The medicines that are the focus of the revised labeling and new Patient Medication Guides include the following 15 products:

- Adderall (mixed salts of a single entity amphetamine product) Tablets
- Adderall XR (mixed salts of a single entity amphetamine product) Extended-Release Capsules
- Concerta (methylphenidate hydrochloride) Extended-Release Tablets
- Daytrana (methylphenidate) Transdermal System
- Desoxyn (methamphetamine HCl) Tablets
- Dexedrine (dextroamphetamine sulfate) Spansule Capsules and Tablets
- Focalin (dexmethylphenidate hydrochloride) Tablets
- Focalin XR (dexmethylphenidate hydrochloride) Extended-Release Capsules
- Metadate CD (methylphenidate hydrochloride) Extended-Release Capsules
- Methylin (methylphenidate hydrochloride) Oral Solution
- Methylin (methylphenidate hydrochloride) Chewable Tablets
- Ritalin (methylphenidate hydrochloride) Tablets
- Ritalin SR (methylphenidate hydrochloride) Sustained-Release Tablets
- Ritalin LA (methylphenidate hydrochloride) Extended-Release Capsules
- Strattera (atomoxetine HCl) Capsules

The draft Patient Medication Guides for each product can be found at http://www.fda.gov/cder/drug/infopage/ADHD/default.htm. For more information please visit www.fda.gov.

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FDA News

FOR IMMEDIATE RELEASE
P07-25
February 21, 2007

Media Inquiries:
Kimberly Rawlings, 301-827-6242
Consumer Inquiries:
888-INFO-FDA

FDA Proposes to Strengthen Label Warning for Xolair

Today the Food and Drug Administration (FDA) announced that it has requested Genentech, Inc. add a boxed warning to the product label for omalizumab, marketed as Xolair. The boxed warning emphasizes that Xolair, used to treat patients with asthma related to allergies, may cause anaphylaxis. Anaphylaxis may include trouble breathing, chest tightness, dizziness, fainting, itching and hives, and swelling of the mouth and throat. In addition, FDA has asked Genentech to revise the Xolair label and provide a Medication Guide for patients to strengthen the existing warning for anaphylaxis.

Xolair was approved in 2003 to treat adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have tested positive for a perennial aeroallergen (pollen, grass or dust) and whose symptoms are inadequately controlled with inhaled steroids. In clinical trials, Xolair decreased the rate of asthma exacerbations, which were defined as a worsening of asthma that required treatment with systemic corticosteroids or a doubling of baseline inhaled corticosteroid dose.

Anaphylaxis was reported following administration of Xolair in clinical trials and was therefore, discussed in the initial product labeling. The cases were reported at a frequency of approximately one in a thousand patients (0.1%). Due to the nature of continued reports in the post-marketing experience, including their life-threatening potential, frequency, and the possibility for the delayed onset of anaphylaxis, FDA has now requested that Genentech, Inc., add the boxed warning and strengthen the existing warning. As the agency gains experience and collects data about a marketed product the determination may be made to strengthen the product label to ensure that consumers are aware of newly identified significant risks.

The strengthened warning includes the possibility of a patient developing anaphylaxis after any dose of Xolair, even if there was no reaction to the first dose. Also, anaphylaxis after administration of Xolair may be delayed up to 24 hours after the dose is given. Health care providers should be prepared to manage life-threatening anaphylaxis following Xolair administration and observe patients for at least two hours after an injection. Following administration of Xolair, patients should also carry and know how to initiate emergency self-treatment for anaphylaxis.

For further information and a copy of the health care professional sheet, go to http://www.fda.gov/cder/drug/infopage/omalizumab/default.htm.

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RSS Feed for FDA News Releases [what's this?]

March 2007

Re: Observation of an Increased Incidence of Fractures in Female Patients Who Received Long-Term Treatment with ACTOS® (pioglitazone HCl) Tablets for Type 2 Diabetes Mellitus

Dear Healthcare Provider:

As part of our continuing efforts to provide appropriate safety information to healthcare providers, Takeda Pharmaceuticals North America, Inc., is informing you of recent safety data concerning pioglitazone-containing products, i.e., ACTOS Tablets, ACTO*plus* met® (pioglitazone HCl and metformin hydrochloride) Tablets, and *duet*act™ (pioglitazone HCl and glimepiride) Tablets. These products are used to treat type 2 diabetes mellitus.

To date, cumulative worldwide postmarketing exposure is more than 7 million patient-years for ACTOS and nearly 40,000 patient-years for ACTO*plus* met.

As part of our ongoing evaluation of all safety information, Takeda has recently undertaken an analysis of its clinical trial database of pioglitazone with a special focus on fractures, comparing patients treated with pioglitazone or a comparator (either placebo or active). The maximum duration of pioglitazone treatment was up to 3.5 years. There were more than 8100 patients in the pioglitazone-treated groups and over 7400 patients in the comparator-treated groups, corresponding to just under 12,000 patient-years exposure per group.

There was no increased risk of fracture identified in men.

However, there were more reports of fractures in female patients taking pioglitazone than those taking a comparator.

The majority of fractures observed in female patients who received pioglitazone were in the distal upper limb (forearm, hand and wrist) or distal lower limb (foot, ankle, fibula and tibia). The fracture incidence calculated was 1.9 fractures per 100 patient-years in the pioglitazone-treated group and 1.1 fractures per 100 patient-years in the comparator-treated group. The observed excess risk of fractures for women in this data set on pioglitazone is therefore 0.8 fractures per 100 patient-years of use.

The explanation for this finding is currently not known. It should also be noted that none of the pioglitazone studies in the database addressed, or were designed to study, the effect on bone, but fractures were collected as adverse events. Due to the limitations of the existing data set, multiple known risk factors for fractures cannot be excluded as confounding variables. Further evaluation of these findings is ongoing.

The risk of fracture should be considered in the care of female patients with type 2 diabetes mellitus who are currently being treated with pioglitazone, or when initiation of pioglitazone treatment is being considered.

TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.
One Takeda Parkway Deerfield, Illinois 60015 Phone: 224-554-6500

Takeda Pharmaceuticals North America, Inc. is committed to providing healthcare providers and patients with up-to-date and accurate information regarding our products. You can assist Takeda in monitoring the safety of our products by reporting adverse reactions to Takeda at 1-877-TAKEDA7 or to the FDA MedWatch program (telephone 1-800-332-1088, fax 1-800-332-0178, online at www.fda.gov/medwatch, or by mail to MedWatch, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852-9787).

Should you have any questions or require additional information, please contact Takeda Pharmaceuticals North America, Inc., information line at 1-877-TAKEDA7.

Sincerely,

Robert Spanheimer, MD
Senior Director, Diabetes, Metabolism
Medical and Scientific Affairs
Takeda Pharmaceuticals North America, Inc.

ACTOS is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. ACTOS is approved for use as monotherapy and in combination with sulfonylureas, metformin, or insulin when diet and exercise plus a single agent do not result in glycemic control.

Important Safety Information

Like other thiazolidinediones (TZDs), pioglitazone can cause fluid retention when used alone or in combination with other antidiabetic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. Patients should be observed for signs and symptoms of heart failure. • In clinical trials, a small number of patients with a history of previously existing cardiac disease were reported to develop congestive heart failure (CHF) when treated with pioglitazone in combination with insulin. Reports of CHF have been received in postmarketing experience in patients with and without previously known heart disease. • Patients with NYHA Class III and IV cardiac status were not studied in pioglitazone clinical trials; therefore, ACTOS is not indicated in these patients. • Patients with systolic heart failure (NYHA Class II) naïve to pioglitazone therapy should be initiated at the lowest approved dose. Patients should be monitored for signs and symptoms of CHF exacerbation.

Reports of hepatitis and of hepatic enzyme elevations to three or more times the upper limit of normal (ULN) have been received in postmarketing experience with pioglitazone. Very rarely, these reports have involved hepatic failure with or without fatal outcome, although causality has not been established. • Liver enzymes, including serum ALT, should be evaluated in all patients at initiation of therapy with ACTOS, and periodically thereafter per the clinical judgment of the healthcare professional. If ALT >2.5X ULN at baseline or if the patient exhibits clinical evidence of active liver disease, do not initiate therapy with ACTOS.

ACTOS may also be associated with hypoglycemia, edema, anemia, weight gain, and/or ovulation in premenopausal, anovulatory women. Adequate contraception should be recommended for premenopausal women. Macular edema has been reported in some diabetic patients receiving TZD therapy, although a causal relationship is unknown. Persons with diabetes should have routine eye exams, and be instructed to immediately report any visual changes to their healthcare provider.

In US placebo-controlled ACTOS monotherapy clinical trials, the most common adverse events (≥5%) were upper respiratory tract infection, headache, sinusitis, myalgia, tooth disorder, aggravated diabetes mellitus, and pharyngitis.

ACTOS should not be used in patients with type 1 diabetes. Management of type 2 diabetes should also include nutritional counseling, weight reduction as needed, and exercise.

Please see accompanying Complete Prescribing Information.

GlaxoSmithKline
Three Franklin Plaza
P.O. Box 13619
Philadelphia, PA 19101-3619

Tel. 215 751 4000
www.gsk.com

February 2007

Re: Clinical Trial Observation of an Increased Incidence of Fractures in Female Patients Who Received Long-Term Treatment with Avandia® (rosiglitazone maleate) Tablets for Type 2 Diabetes Mellitus

Dear Health Care Provider:

As part of ongoing efforts to provide appropriate safety information to Health Care Providers, GlaxoSmithKline (GSK) is informing you of recent safety data concerning rosiglitazone-containing products, i.e., Avandia® (rosiglitazone maleate) Tablets, Avandamet® (rosiglitazone maleate and metformin hydrochloride) Tablets, and Avandaryl™ (rosiglitazone maleate and glimepiride) Tablets. These products are used in treating type 2 diabetes mellitus. To date, cumulative worldwide post marketing exposure is more than nine million patient years for Avandia, one million patient years for Avandamet, and 33,000 patient years for Avandaryl.

Recently, ADOPT (A Diabetes Outcome and Progression Trial) was completed. ADOPT was a randomized, double-blind, parallel group study of patients with recently diagnosed type 2 diabetes mellitus whose progression of diabetes was followed for 4-6 years. The primary goal of the study was to compare glycemic control with rosiglitazone relative to metformin and to glyburide monotherapies in 4,360 randomized patients. The results of ADOPT were published in the *New England Journal of Medicine* (Kahn *et al.*, 2006. N Engl J Med, Vol. 355, No. 23:2427-2443).

A review of the safety data in ADOPT was consistent, in general, with the known safety profile of rosiglitazone. However, significantly more female patients who received rosiglitazone experienced fractures than did female patients who received either metformin or glyburide (see table on the following page). The observed incidence of fractures for male patients in ADOPT was similar among the three treatment groups.

The majority of fractures observed in female patients who received rosiglitazone during ADOPT were in the upper arm (humerus), hand, or foot (see table on the following page). These sites of fracture are different from those associated with post-menopausal osteoporosis (e.g., hip or spine). In ADOPT, the number of female patients with a hip or spine fracture was low and similar among the three treatment groups.

Patients with Fractures in ADOPT

	Rosiglitazone		Metformin		Glyburide	
MALE PATIENTS	811 Males 2766.7 PY		864 Males 2957.6 PY		836 Males 2612.8 PY	
	n (%)	Rate/100 PY	n (%)	Rate/100 PY	n (%)	Rate/100 PY
Experienced a fracture	32 (3.95)	1.16	29 (3.36)	0.98	28 (3.35)	1.07
FEMALE PATIENTS	643 Females 2187.2 PY		590 Females 1948.0 PY		605 Females 1630.8 PY	
	n (%)	Rate/100 PY	n (%)	Rate/100 PY	n (%)	Rate/100 PY
Experienced a fracture *	60 (9.30)	2.74	30 (5.09)	1.54	21 (3.47)	1.29
Lower limb **	36 (5.58)	1.65	18 (3.05)	0.92	8 (1.32)	0.49
Hip	2 (0.31)	0.09	2 (0.34)	0.10	0	0
Foot	22 (3.41)	1.01	7 (1.19)	0.36	4 (0.66)	0.25
Upper limb ***	22 (3.41)	1.01	10 (1.70)	0.51	9 (1.49)	0.55
Hand	8 (1.24)	0.37	4 (0.68)	0.21	1 (0.17)	0.06
Humerus	5 (0.78)	0.23	0	0	0	0
Spine	1 (0.16)	0.05	1 (0.17)	0.05	1 (0.17)	0.06
Other	5 (0.78)	0.23	4 (0.68)	0.21	4 (0.66)	0.25

Rate/100 PY = Patients with Events per 100 Patient Years, n = number of patients

* Some patients experienced fractures in more than one category.

** Other sites of fracture included: ankle, femur, fibula, lower limb (general), patella, and tibia.

*** Other sites of fracture included: clavicle, forearm, radius, upper limb (general), and wrist.

At GSK's request, an independent safety committee reviewed an interim analysis of fractures in another large ongoing, long-term, controlled rosiglitazone clinical trial. The primary purpose of that study is to investigate cardiovascular endpoints in patients with type 2 diabetes mellitus. The results of the preliminary analysis were reported to GSK as being consistent with the observations from ADOPT. The independent safety committee also recommended that the study continue without modification. Final results of this study are anticipated to be available in 2009.

Presently, our understanding of the clinical significance of the findings from these two long-term trials is incomplete, and the mechanism(s) for the observed increase in fractures is uncertain. Further evaluation of these observations is ongoing. GlaxoSmithKline believes the risk of fracture should be considered in the care of patients, especially female patients, with type 2 diabetes mellitus who are currently being treated with rosiglitazone, or when initiation of rosiglitazone treatment is being considered. In these patients, as with all patients with type 2 diabetes mellitus, attention should be given to assessing and maintaining bone health according to current standards of care.

GlaxoSmithKline is committed to providing Health Care Providers and patients with up-to-date and accurate information regarding our products. You can assist GSK in monitoring the safety of our products by reporting adverse reactions to GSK at 1-888-825-5249 or to the FDA MedWatch program (telephone 1-800-332-1088, fax 1-800-332-0178, online at www.fda.gov/medwatch, or by mail to MedWatch, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852-9787).

Should you have any questions or require additional information, please contact your local GlaxoSmithKline information line (1-888-825-5249).

Sincerely,

Alexander R. Cobitz

Alexander R Cobitz, MD, PhD
Senior Director Metabolism
Clinical Development and Medical Affairs
GlaxoSmithKline

Enclosure: Complete Prescribing Information for Avandia® Tablets.

FDA Public Health Advisory
Tegaserod maleate (marketed as Zelnorm)

FDA is issuing this public health advisory to inform patients and health care professionals that the sponsor of Zelnorm (tegaserod maleate), Novartis Pharmaceuticals Corporation, has agreed to stop selling Zelnorm. Zelnorm is being taken off the market because a new safety analysis has found a higher chance of heart attack, stroke, and worsening heart chest pain that can become a heart attack in patients treated with Zelnorm compared to those treated with a sugar pill they thought was Zelnorm.

FDA announces the following, effective immediately:

- At FDA's request, Novartis Pharmaceuticals Corporation has agreed to stop selling Zelnorm.
- Patients being treated with Zelnorm should contact their physician to discuss alternative treatments for their condition.
- Patients who are taking Zelnorm should seek emergency medical care right away if they experience severe chest pain, shortness of breath, dizziness, sudden onset of weakness or difficulty walking or talking or other symptoms of a heart attack or stroke.
- Physicians who prescribe Zelnorm should work with their patients and transition them to other therapies as appropriate to their symptoms and need.

Zelnorm is a prescription medication approved for short term treatment of women with irritable bowel syndrome with constipation and for patients younger than 65 years with chronic constipation. In late February and early March 2007, Novartis Pharmaceuticals gave FDA the results of new analyses of 29 clinical studies of Zelnorm for treatment of a variety of gastrointestinal tract conditions; the data from all the studies were combined to assess the chance of side effects on the heart and blood vessels. In each study, patients were assigned at random to either Zelnorm or a sugar pill they thought was Zelnorm. These 29 studies included 11,614 patients treated with Zelnorm and 7,031 treated with a sugar pill. The average age of patients in these studies was 43 years and most patients—88%--were women.

The number of patients who suffered a heart attack, stroke or severe heart chest pain that can turn into a heart attack was small. However, patients treated with Zelnorm had a higher chance of having any of these serious and life-threatening side effects than did those who were treated with a sugar pill. Thirteen patients treated with Zelnorm (0.1%) had serious and life-threatening cardiovascular side effects; among these, four patients had a heart attack (one died), six had a type of severe heart chest pain which can quickly turn into a heart attack, and three had a stroke. Among the patients taking the sugar pill, only one (or 0.01%) had symptoms suggesting the beginning of a stroke that went away without complication.

There may be patients for whom no other treatment options are available and in whom the benefits of Zelnorm treatment outweigh the chance of serious side effects. FDA will work with Novartis to allow access to Zelnorm for those patients through a special program.

FDA has also indicated to Novartis a willingness to consider limited re-introduction of Zelnorm at a later date if a population of patients can be identified in whom the benefits of the drug outweigh the risks. However, before FDA makes a decision about limited re-introduction, any proposed plan would be discussed at a public advisory committee

re-introduction, any proposed plan would be discussed at a public advisory committee meeting.

Back to Top Back to Tegaserod meleate

PDF requires the free Adobe Acrobat Reader

Date created: March 30, 2007

FDA Public Health Advisory
Pergolide (marketed as Permax)

The FDA is notifying you that the companies that manufacture and distribute pergolide have agreed to withdraw this drug from the market due to the potential for heart valve damage. Two new studies showed that patients with Parkinson's disease who were treated with pergolide had an increased chance of serious damage to their heart valves when compared to patients who did not receive the drug. Pergolide is a member of a class of drugs known as dopamine agonists and is used with levodopa and carbidopa to manage the signs and symptoms (tremors and slowness of movement) of Parkinson's disease.

Patients with Parkinson's disease who are taking pergolide should

- Contact their healthcare professional to discuss alternate treatment options.
- **NOT** stop taking Pergolide without consulting their healthcare professional, since stopping pergolide too quickly can be dangerous and several other effective treatments are available.

Healthcare professionals who prescribe pergolide should consider the following:

- Assess the patient's need for dopamine agonist (DA) therapy. If continued treatment with a DA is necessary, another DA should be substituted for pergolide. There are other dopamine agonists approved for the treatment of Parkinson's disease that are not associated with heart valve damage. Published transition regimens describe the conversion from one DA to another.
- If treatment with a DA is to be discontinued, **pergolide should not be stopped abruptly,** because rapid discontinuation of all dopamine agonist therapies can be dangerous. Instead, gradually decrease the dose of pergolide.
- Patients who will be taken off pergolide should be told that other effective options for treatment exist, including three other DAs that are not associated with damage to heart valves.

In 2006, a boxed warning regarding the risk of serious heart valve damage was added to the labeling for pergolide. The two recent studies, published in *The New England Journal of Medicine* in January 2007, confirm earlier studies that also described this problem. Pergolide is marketed by Valeant under the trade name Permax and sold and manufactured as the generic drug pergolide by Par and Teva.

In light of this additional safety information and the availability of alternative treatments for Parkinson's disease that do not have comparable safety problems, the companies that manufacture and sell pergolide have stopped shipping pergolide for distribution and will, in cooperation with FDA, work to remove from the market both the name brand Permax (pergolide) and the generic versions of pergolide. The effect of this voluntary withdrawal on supplies of pergolide currently in pharmacies will not be immediate. This delay will allow time for healthcare professionals and patients to discuss appropriate treatment options and to change treatments.

One of the drugs that was included in the recent studies showing increased chance of heart

One of the drugs that was included in the recent studies showing increased chance of heart valve problems is Dostinex (cabergoline), another dopamine agonist. This drug is approved in the U.S. for the treatment of hyperprolactinemic disorders (conditions in which there are elevated levels of prolactin in the blood). Dostinex **is not** approved in the U.S. for the treatment of Parkinson's disease. For hyperprolactinemic disorders, a considerably lower dose of Dostinex is used. At these lower doses of Dostinex, there appears to be little chance of heart problems; therefore, Dostinex will remain on the US market for the treatment of hyperprolactinemic disorders.

The FDA is working with the manufacturers of pergolide to determine if it is possible to make the drug available to those few patients who are currently taking pergolide where previous efforts to switch to a different treatment have been unsuccessful, or where efforts subsequent to this advisory to switch therapies are also unsuccessful. In the interim, healthcare professionals and patients should consider all treatment options with the understanding that in the future, the drug may no longer be available.

Back to Top Back to Pergolide

Date created: March 29, 2007

Genentech
IN BUSINESS FOR LIFE

biogen idec

December 2006

IMPORTANT DRUG WARNING
UPDATED SAFETY INFORMATION

Dear Healthcare Professional:

Genentech, Inc. and Biogen Idec, Inc. would like to inform you of important new safety information regarding Rituxan® (rituximab).

- Two cases of progressive multifocal leukoencephalopathy (PML) resulting in death, have been reported in patients receiving Rituxan® for treatment of Systemic Lupus Erythematosus (SLE). Rituxan® is not approved for the treatment of SLE.
- Previously, cases of PML have been reported in patients with lymphoid malignancies during or up to one year after completion of Rituxan®. The majority of patients received Rituxan® in combination with chemotherapy or as part of a hematopoietic stem cell transplant.
- Physicians treating patients with Rituxan® should consider PML in any patient presenting with new onset neurologic manifestations, particularly in patients with SLE, or lymphoid malignancies. Consultation with a neurologist, brain MRI, and lumbar puncture should be considered as clinically indicated.

The current Rituxan® package insert, which contains information on cases of PML in patients with hematologic malignancies, is enclosed for your reference. We are working with the regulatory authorities to update the Rituxan® prescribing information.

Progressive multifocal leukoencephalopathy (PML) is a rare, progressive, demyelinating disease of the central nervous system that usually leads to death or severe disability. PML is caused by activation of the JC virus, a polyomavirus that resides in latent form in up to 80% of healthy adults. JC virus usually remains latent, typically only causing PML in immunocompromised patients. The factors leading to activation of the latent infection are not fully understood. There is no currently accepted screening test for PML.

PML has been reported in the literature in HIV-positive patients, immunosuppressed cancer patients (including those with hematologic malignancies), organ transplant recipients, and patients with autoimmune disease, including SLE, who were not receiving Rituxan. Abnormalities in T cells have been described as important for reactivation of JC virus and PML.

A description of cases of PML in patients with hematologic malignancies treated with Rituxan is included in the current US prescribing information (See WARNINGS: HBV Reactivation with Related Fulminant Hepatitis and Other Viral Infections). There are approximately 23 reports of PML patients with hematologic malignancies treated with Rituxan®; the majority of these patients received Rituxan® in combination with chemotherapy or as part of hematopoietic stem cell transplant. PML has also been reported in the literature in patients with hematologic malignancies receiving chemotherapy or as part of hematopoietic stem cell transplant, who were not receiving Rituxan®.

GENENTECH, 1 DNA WAY, SOUTH SAN FRANCISCO, CA 94080-4990 650.225.1000 *www.gene.com*
BIOGEN IDEC, 5200 RESEARCH PLACE, SAN DIEGO, CA 92122 858.401.8000 *www.biogenidec.com*

JC virus infection with resultant PML and death has been reported in 2 patients with SLE treated with Rituxan®. These patients had longstanding SLE with multiple courses of immunosuppressant therapy prior to receiving Rituxan®, however Rituxan® monotherapy was the last treatment administered prior to the diagnosis of PML. Both patients were diagnosed with PML within 12 months of their last infusion of Rituxan®. PML has also been reported in the literature in patients with SLE receiving prednisone, azathioprine, cyclophosphamide, and other immunosuppressant agents and who were not receiving Rituxan®.

In patients who develop PML, Rituxan® should be discontinued and reductions or discontinuation of concomitant immunosuppressive therapy and appropriate treatment, including antiviral therapy, should be considered. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs.

Rituxan® is indicated for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell, non-Hodgkin's lymphoma (NHL), and for the first line treatment of follicular, CD20-positive, B-cell NHL in combination with CVP chemotherapy. Rituxan® is also indicated for the treatment of low-grade, CD20-positive, B-cell NHL in patients with stable disease or who achieve a partial or complete response following first-line treatment with CVP chemotherapy. Rituxan® is also indicated for the first-line treatment of diffuse large B-cell, CD20-positive, NHL in combination with CHOP or other anthracycline-based chemotherapy regimens. Rituxan® in combination with methotrexate is also indicated to reduce signs and symptoms in adult patients with moderately- to severely- active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies. The safety and effectiveness of Rituxan® for the treatment of SLE has not been established and SLE is not an FDA-approved indication.

Health care professionals should report any serious adverse events possibly associated with the use of Rituxan® to Genentech Drug Safety at 1-888-835-2555. Alternatively, this information may be reported to the FDA's MedWatch reporting system by phone (1-800-FDA-1088), facsimile (1-800-FDA-1078), online at the MedWatch website (www.fda.gov/medwatch), or mailed to MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787.

If you have any questions regarding the use of Rituxan®, please call the Genentech Medical Information/Communications Department at 1-800-821-8590.

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