Drug Utilization Review Board

Oklahoma Health Care Authority
2401 N.W. 23rd Street, Suite 1A
Oklahoma City, Oklahoma 73107
Ponca Room

Wednesday
November 9, 2011
6:00 p.m.

The University of Oklahoma

Health Sciences Center

COLLEGE OF PHARMACY

PHARMACY MANAGEMENT CONSULTANTS

MEMORANDUM

TO: Drug Utilization Review Board Members

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

SUBJECT: Packet Contents for Board Meeting – November 9, 2011

DATE: November 3, 2011

NOTE: THE DUR BOARD WILL MEET AT 6:00 P.M. THE MEETING WILL BE HELD IN THE PONCA ROOM AT THE OKLAHOMA HEALTH CARE AUTHORITY OFFICES IN SHEPHERD MALL. (NORTH ENTRANCE)

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

Call to Order

Public Comment Forum

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

Update on DUR / MCAU Program – See Appendix B.

Accelerating Utilization of Comparative Effectiveness Findings in Medicaid Mental Health

Action Item – Vote to Prior Authorize Natroba™ Topical Suspension – See Appendix C.

Action Item - Vote to Prior Authorize Biologic Products for the Treatment of Rheumatoid Arthritis, Crohn's Disease, Plaque Psoriasis, and Ankylosing Spondylitis – See Appendix D.

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

Action Item – Vote to Prior Authorize Amturnide® and Edarbi® – See Appendix F.

Action Item – Vote to Prior Authorize Viibryd® – See Appendix G.

30 Day Notice to Prior Authorize Multiple Sclerosis Medications – See Appendix H.

30 Day Notice to Prior Authorize Miscellaneous Products – See Appendix I.

FDA and DEA Updates – See Appendix J.

Future Business

Adjournment

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Oklahoma Health Care Authority
Drug Utilization Review Board
(DUR Board)
Meeting – November 9, 2011 @ 6:00 p.m.

Oklahoma Health Care Authority
2401 N.W. 23rd Street, Suite 1-A
Oklahoma City, Oklahoma 73107
Ponca Room (North Entrance)

AGENDA

Discussion and Action on the Following Items:

Items to be presented by Dr. Muchmore, Chairman:

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

Items to be presented by Dr. Muchmore, Chairman:

2. Public Comment Forum
- A. Acknowledgment of Speakers and Agenda Items

Items to be presented by Dr. Muchmore, Chairman:

3. Action Item – Approval of DUR Board Meeting Minutes – See Appendix A.
- A. October 12, 2011 DUR Minutes – Vote
- B. October 13, 2011 DUR Recommendation Memorandum

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

4. Update on DUR / Medication Coverage Authorization Unit – See Appendix B.
- A. Medication Coverage Activity Audit for October 2011
- B. Pharmacy Help Desk Activity Audit for October 2011

Items to be presented by Dr. Nesser, Dr. Keast, Dr. Muchmore, Chairman

5. Accelerating Utilization of Comparative Effectiveness Findings in Medicaid Mental Health

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

6. Action Item – Vote to Prior Authorize Natroba™ Topical Suspension – See Appendix C.
- A. Current Authorization Criteria
- B. Utilization Details
- C. COP Recommendations

Items to be presented by Dr. Sipols, Dr. Muchmore, Chairman

7. Action Item – Vote to Prior Authorize Biologic Products for the Treatment of Rheumatoid Arthritis, Crohn's Disease, Plaque Psoriasis, and Ankylosing Spondylitis – See Appendix D.

A. COP Recommendations

Items to be presented by Dr. Sipols, Dr. Muchmore, Chairman

8. Action Item – Vote to Prior Authorize Moxeza™ – See Appendix E.

A. COP Recommendations

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

9. Action Item – Vote to Prior Authorize Amturnide® and Edarbi® – See Appendix F.

A. COP Recommendations

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

10. Action Item – Vote to Prior Authorize Viibryd® – See Appendix G.

A. COP Recommendations

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

11. 30 Day Notice to Prior Authorize Multiple Sclerosis Medications – See Appendix H.

A. COP Recommendations

Items to be presented by Dr. Le, Dr. Moore, Dr. Sipols, Dr. Muchmore, Chairman

12. 30 Day Notice to Prior Authorize Miscellaneous Products – See Appendix I.

A. Daliresp®
B. Horizant®
C. Gralise™

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

13. FDA and DEA Updates – See Appendix J.

14. Future Business

A. Annual Review of Statins
B. Annual Review of Antihistamines
C. New Product Reviews
D. Medical Product Reviews

15. Adjournment

Appendix A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES of MEETING of OCTOBER 12, 2011

BOARD MEMBERS:	PRESENT	ABSENT
Brent Bell, D.O., D.Ph.: Vice-Chairman	X	
Mark Feightner, Pharm.D.	X	
Anetta Harrell, Pharm.D.	X	
Evelyn Knisely, Pharm.D.	X	
Thomas Kuhls, M.D.	X	
John Muchmore, M.D., Ph.D.: Chairman	X	
Paul Louis Preslar, D.O., MBA	X	
James Rhymer, D.Ph.		X
Bruna Varalli-Claypool, MHS, PA-C		X
Eric Winegardener, D.Ph.		X

COLLEGE of PHARMACY STAFF:	PRESENT	ABSENT
Metha Chonlahan, D.Ph.; Clinical Pharmacist		X
Karen Egesdal, D.Ph.; SMAC-ProDUR Coordinator/OHCA Liaison	X	
Ronald Graham, D.Ph.; Pharmacy Director	X	
Shellie Keast, Pharm.D, M.S..; DUR Manager	X	
Chris Le, Pharm.D.; Clinical Pharmacist/Coordinator	X	
Carol Moore, Pharm.D.; Clinical Pharmacist	X	
Neeraj Patel, Pharm.D.; Clinical Pharmacist	X	
Lester A. Reinke, Ph.D.; Associate Dean for Graduate Studies & Research	X	
Leslie Robinson, D.Ph.; PA Coordinator	X	
Jennifer Sipols, Pharm.D.; Clinical Pharmacist	X	
Visiting Pharmacy Student(s): Jo'Nel Speegle, Amany Hassan, Manish Mittal, Reid Foster, Anita Mueller	X	

OKLAHOMA HEALTH CARE AUTHORITY STAFF:	PRESENT	ABSENT
Mike Fogarty, J.D., M.S.W.; Chief Executive Officer	X	
Garth Splinter, M.D., M.B.A.; Director of Medicaid/Medical Services	X	
Rebecca Pasternik-Ikard, Deputy State Medicaid Director		X
Nancy Nesser, Pharm.D., J.D.; Pharmacy Director	X	
Lynn Rambo-Jones, J.D.; Deputy General Counsel III	X	
Carter Kimble, MPH/Public Affairs- Information Rep.	X	
Jill Ratterman, D.Ph.; Pharmacy Specialist	X	
Rodney Ramsey; Drug Reference Coordinator	X	
Kerri Wade, Senior Pharmacy Financial Analyst	X	

OTHERS PRESENT:

Eric Garner, Oklahoma Medicaid	Felicia Fuller	David Williams, Forest
Sam Smothers, MedImmune	Tom Arnhart, MedImmune	Jim Chapman, Abbott
Gary Riley, Abbott	Brett Brewer, EMD Serono	Ric Uhles, Forest
Pat Trahan, Taro	Brandi Ezell, Janssen	Mark DeClerk, Lilly
Brad Burgstattler, Elan	Donna Erwin, BMS	Tracy Copeland, DSI
Ben Liniger, Alcon	Vanessa Papion, UCB	Randy McGinley, Bayer
Russ Wilson, JJHCS		

PRESENT FOR PUBLIC COMMENT:

Agenda Item No. 6	Valerie Pennington, Novartis	
Agenda Item No. 7	Gary Riley, Abbott	Ray Cornelison, M.D.
Agenda Item No. 11	James Gilbert	

AGENDA ITEM NO. 1: CALL TO ORDER

1A: Roll Call

Dr. Muchmore 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. Muchmore acknowledged the speakers for public comment:

Agenda Item No. 6 Valerie Pennington, Novartis

Agenda Item No. 7 Gary Riley, Abbott and Ray Cornelison, M.D.

Agenda Item No. 11 James Gilbert

ACTION: NONE REQUIRED

AGENDA ITEM NO. 3: APPROVAL OF DUR BOARD MINUTES

3A: September 14, 2011 DUR Minutes

Dr. Harrell moved to approve as submitted; seconded by Dr. Knisely.

ACTION: MOTION CARRIED

AGENDA ITEM NO. 4: UPDATE ON DUR/MEDICATION COVERAGE AUTHORIZATION UNIT

4A: Retrospective Drug Utilization Review: July 2011

4B: Retrospective Drug Utilization Review Response: May 2011

4C: Medication Coverage Activity Audit: September 2011

4D: Pharmacy Help Desk Activity Audit: September 2011

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

ACTION: NONE REQUIRED

AGENDA ITEM NO. 5: VOTE TO PRIOR AUTHORIZE FIRAZYR®

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

Dr. Bell moved to approve as submitted; seconded by Dr. Harrell.

ACTION: MOTION CARRIED

AGENDA ITEM NO. 6: 60-DAY NOTICE TO PRIOR AUTHORIZE MULTIPLE SCLEROSIS MEDICATIONS

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

For Public Comment; Valerie Pennington: I appreciate the opportunity to briefly address the Board. As you had mentioned, my name is Dr. Valerie Pennington and I am the Novartis field medical person that covers the multiple sclerosis team for this local area, and really we appreciate the fact that fingolimod or Gilenya which has now been on the market for just over a year. And as you know from the review last month, this is the first oral disease modifying therapy that's been approved for the treatment of relapsing forms of multiple sclerosis. So while we are very happy to see that all of the agents in some form or fashion have been included as being available to patients, one thing that we'd like to ask the Board to consider is with regard to the fingolimod prior authorization criteria, that prior auth criteria #1 be reconsidered in terms of the language. What we would ask the Board to consider would be that it state "FDA approved diagnosis" because the current language it appears here is not reflective of the FDA label indication for this compound and so that what we would ask the Board to consider, please, with regard to this particular agent.

Dr. Muchmore: What is the FDA wording?

Dr. Pennington: The FDA wording is that it's approved for relapsing forms of multiple sclerosis and so it's not limited to relapsing remitting in the package labeling and additionally, there's no qualifying information regarding patients having to have one relapse in the previous 12 months. Actually that's not in any of these agents' product labeling, so the potential would exist, for example, I was made aware of a case that currently a patient who is currently attempting to convert from their injectable therapy to fingolimod and they're wanting to change because of needle fatigue, so they're not necessarily, they haven't necessarily had a relapse in the previous 12 months, but yet they've gone to their provider and stated that they no longer will take their injectable therapy and the provider is currently attempting to convert them to fingolimod and so that particular criteria allows for the patient not to convert therapies. So again, just something that we would kindly ask that the Board consider in terms of the language on this particular criteria number. So, I would be happy to answer any other questions that you might have.

Dr. Le: Discussed requested changes to the wording of the criteria for fingolimod/Gilenya.

Dr. Kuhls: I have a question. When you talk about lowest supplemental rebated medication, does that have to be equal to Avonex? Do you understand my question?

Dr. Le: Yeah, or just the lowest.

Dr. Kuhls: Well my big question is when you look at these prices, at least what you got here, some of these are pretty close, right? Betaseron and Avonex. I don't use these drugs, but okay, you're telling me they're all equal, right? So one's going to already be close, so I'm trying to figure out what that full supplemental rebate thing means.
Dr. Le: We're saying if it comes in lower than Avonex.
Dr. Kuhls: Lower?
Dr. Le: I mean, is that what you're saying?
Dr. Kuhls: No, I'm asking …… I'm asking you, what's the plan?
Dr. Nesser: They are very close, we'll just have to see what comes in ……..
Dr. Kuhls: I mean if you look at this you might as well already approve ….
Dr. Nesser: Yeah, but we're not looking at this. We're giving them, the other companies a shot at getting there.
Dr. Kuhls: No, but listen to me. Avonex, right?
Dr. Nesser: Yes.
Dr. Kuhls: Okay, it's on the scale of 1 in price.
Dr. Nesser: Yes.
Dr. Kuhls: Alright? Betaseron, right?
Dr. Nesser: Yes.
Dr. Kuhls: Looks like it's about 1.1 …… I don't what it is.
Dr. Nesser: Yes.
Dr. Kuhls: Right? So that one's already there in many ways, so why don't we just have that one over there? Do you see what I'm saying?
Dr. Muchmore: Well the advantage is you have a 1A and a 1B.
Dr. Knisely: But that's net cost, not whatever they rebate, right? I mean, they could come in lower.
Dr. Kuhls: But Avonex, is this price Avonex right here with your Federal rebate?
Dr. Nesser: Yes.
Dr. Kuhls: That's the one?
Dr. Nesser: Right.
Dr. Kuhls: And all these others are with your rebate, right? So what I'm saying is Betaseron's already there, so why are we supplementing that one? Why don't we …. you see what I'm trying to say?
Dr. Nesser: Right. We're trying to give them the opportunity to participate and cut their price. You know, either one of the other two could do that, so we're just giving them the opportunity. If they don't, then it will, you know, definitely be based on ……..
Dr. Muchmore: Well I think the Board ought to stipulate that when all is said and done we should have both a 1A and a 1B on Tier 1.
Dr. Kuhls: Right and Betaseron's already there.
Dr. Muchmore: Well so if you get no supplemental rebates, that might be the one you add. But there ought to be a 1A and a 1B.
Dr. Le: Well Betaseron looks like it's already there because I used the average price but some of them …….. because it comes in a 20 and a 40 and a lower dose. If they were to use the lower I don't think it would be a low. It's not as low and it looks close but like Nancy said, this will give all the rest the remaining chance to go to Tier 1.
Dr. Kuhls: I don't have any problem trying to get a supplemental rebate down to equal. That's not what I'm arguing. But it looks like you've already got one that's already down there ….
Dr. Muchmore: Let's just take the case where there's no supplemental rebates if that happens. If Extavia doesn't come along with a good supplemental rebate, then …… you've got to have a 1B on Tier 1.
Dr. Kuhls: That's what I'm trying to say.
Dr. Nesser: Yeah, we can do that.
Dr. Kuhls: When if the other two come down to those prices, that's great, I don't have a problem with that. But they have to come down to those prices.
Dr. Nesser: Right, they would have to …….
Dr. Kuhls: But I really think you need a 1B and it looks like from this cost they're about the same already.
Dr. Graham: Nancy, on Avonex, is that, do they have any obligations if they are in Tier 1, automatically? Because like price increases or something may make them ……
Dr. Nesser: Well, the only obligation is through the way the Federal rebate is designed, and if they raise their price more than the CPI index percentage, then they have to pay a CPA penalty, so if they raise their price 10% and the CPI's only 2%, they've got to add 8% to their rebate.
Dr. Muchmore: That's automatic protection?
Dr. Nesser: Yes.
Dr. Muchmore: The thought on the street for whatever reason, even though the literature doesn't support it, they firmly believe that they have an X-brand of 1A, it's not as good as the Rebif brand, so let's see how this plays down.
Dr. Le: And that's been shown because of the once-a-week dosing, it's just not as good when you dose it only once a week.
Dr. Muchmore: They talk about needle fatigue once a week, what about my diabetics, six doses a day?
Dr. Kuhls: Yeah, I don't understand this needle fatigue thing.
Dr. Feightner: Are we allowing, I was going to bring it up, do we want to allow that in? We talked about a lot of that for Gilenya for needle fatigue.
Dr. Muchmore: No we allowed it for prior therapy, not for needle fatigue.
Dr. Bell: Does that mean needle fatigue or does that also mean the side reaction, or, I mean that's kind of a broad ……..
Dr. Le: If the Board wants to define what is acceptable, because currently we don't have it as you have to try this and then you get Gilenya, it's just the interferons have a preferred product and then the copaxone has a hard PA and Gilenya has a hard PA and you meet the criteria and you get it. So they could go straight to Gilenya if they wanted to, first line and if the Board wants to make it that little different, then you're welcome to suggest how we should approach it.

Dr. Muchmore: Fingolimod is a royal pain to initiate. You've got to be monitored for the first six hours for bradycardia. You know, I don't think your MS, you're not going to have a hue and cry for it. It has got the advantage of being oral but it's got significant adverse effects too. I don't have a, I'm not very impressed with needle fatigue treating diabetics all the time, but transitioning from one form to another for whatever reason seems reasonable if they want to go through the song and dance that's required to get started on fingolimod, and if they go off of it for some short period, they have to go through the retesting again.
Dr. Kuhls: So what I'm hearing from you, because I don't know these drugs, is that you don't see anybody first line going for fingolimod.
Dr. Muchmore: Yeah, they do talk to them. They say you know you can take these shots or you can take this oral pill and some people just have such injection aversion they want to go to the oral pill.
(miscellaneous comments from Board members)
Dr. Muchmore: You know there aren't very many people that have this, it's an awful disease. I think we should be relatively loose as long as they meet the diagnostic criteria. (Dr. Le concurred). I'm very comfortable with the way we have this set out as long as we allow for transition. Not everybody once they experience it is going to want fingolimod. A lot of neurologists don't use it at all, but the multiple sclerosis ones are especially attuned to using it.
Dr. Kuhls and Dr. Le discussed and clarified supplemental rebate issues.
ACTION: NONE REQUIRED

AGENDA ITEM NO. 7: 30-DAY NOTICE TO PRIOR AUTHORIZE BIOLOGIC PRODUCTS FOR THE TREATMENT OF RHEUMATOID ARTHRITIS, CROHN'S DISEASE, PLAQUE PSORIASIS, AND ANKYLOSING SPONDYLITIS

For Public Comment; Ray Cornelison, M.D.: I'm a dermatologist and am here to talk to you about the possible decision to put Stelara on the second tier of biologics. The reason I would be opposed to that is I don't think it makes any scientific sense. All four of the biologics are about the same cost; three of the four all have about the same efficacy. So to put Stelara on the second tier doesn't seem to be logical to me and takes away from me and other dermatologists to be able to pick the drug we think is the best, so that's all I have to say. I would like you to consider keeping all the biologics on the same tier and I think that's the proper thing to do.
For Public Comment; Gary Riley: Good evening. My name's Gary Riley. I'm with Abbott Labs representing their clinical evidence and outcomes team. I'm privileged here to come to present to you today. I just want to talk briefly about Humira, adalimumab. And of course all of you look at the product insert to get a comprehensive efficacy and safety review. But I want to talk about the information there is coming from 36 world clinical trials with over 19,000 patients, and over 14 years of clinical experience, an estimated 1.6 million patient years exposed in that information, giving us a nice characterization of safety and efficacy of Humira. Some of the attributes of Humira, consistent efficacy, well characterized safety, convenient, cost efficient maintenance dosing across a broad spectrum of indications. And actually it has the widest breadth of indications among the self-injectable anti-TNF alpha agents. It's currently approved for rheumatoid arthritis, psoriatic arthritis, psoriasis, juvenile idiopathic arthritis down to the age of four, Crohn's disease and psoriasis. Of course, RA, Chrohn's disease and psoriasis make up the majority of the use of Humira. In RA the treatment goals are to inhibit joint destruction, reduce disability, improve clinical signs and symptoms. Humira is FDA indicated with or without methotrexate to inhibit radiographic destruction, improve signs and symptoms in RA and to significantly improve function disability. So all three of the major outcomes you're looking for in RA. Some of the unlabeled attribute there is that there's also improved employment outcomes. There have been two published studies, the PROWD and PREMIER trial, importance fiscally as well in treatment of patients. In Crohn's disease, remission is the primary goal of treatment and Humira is the only self-injection agent FDA approved for both inducing and maintaining clinical remission in Crohn's. The other self-injections don't have both those indications in their label. Hospitalizations, the primary cost driver in Crohn's disease, in our CHARM trial, demonstrated significant reduction of 57% in hospitalizations for patients taking Humira compared to standard therapy. In psoriasis, our REVEAL trial of 16 weeks, we had 7 out 10 patients with a 75% improvement in their plaque psoriasis, close to 5 out of 10 at a 90% improvement in the psoriatic plaques and 1 out of 5 had a total clearing of their psoriatic plaques. Although no head-to-head comparison exists, you can start to see the indirect comparison of clinical trials, Humira stands out for the self-injections. Just finishing up with safety, all TNF inhibitors that are pregnancy category B, the majority of safety comes from our RA clinical trials and the American College of Rheumatology treatment guidelines show no significant difference, no clear distinction among the biologics under the grounds of safety. And all these agents carry a similar box warning for TB, serious infection and malignancy. Humira is a unique among the self-injected TNF alpha inhibitors, with sustained efficacy, proven safety and the broadest scope of indications. I'll take any questions that you have at this time.
Dr. Muchmore: I'd just like to add that these are awful diseases that they are treating and are not brought about by aberrations in lifestyle and it's just remarkable to old geezers like me who remember when we didn't even have DMARDS and now we can actually alter the joint destruction and the bowel destruction in these diseases. I think it's a wonderful thing.
Materials included in agenda packet; presented by Drs. Sipols and Keast.
ACTION: NONE REQUIRED

AGENDA ITEM NO. 8: ANNUAL REVIEW OF PEDICULICIDES AND 30-DAY NOTICE TO PRIOR AUTHORIZE NATROBA™
Materials included in agenda packet; presented by Dr. Keast.
ACTION: NONE REQUIRED

AGENDA ITEM NO. 9: ANNUAL REVIEW OF OCULAR ANTIBIOTICS AND 30-DAY NOTICE TO PRIOR AUTHORIZE MOXEZA™
Materials included in agenda packet; presented by Dr. Sipols.
ACTION: NONE REQUIRED

AGENDA ITEM NO. 10: ANNUAL REVIEW OF ANTIHYPERTENSIVES AND 30-DAY NOTICE TO PRIOR AUTHORIZE AMTURNIDE™ AND EDARBI™

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

AGENDA ITEM NO. 11: ANNUAL REVIEW OF ANTIDEPRESSANTS AND 30-DAY NOTICE TO PRIOR AUTHORIZE VIIBRYD®

For Public Comment; James Gilbert: I was just asked by the company to make a statement in regards to my experience with the medicine and what I've had over the last three months since it's been on the formularies for private insurance. I had treated a lot of treatment-resistant depression and so I've been augmenting most of my antidepressants with either Abilify or Seroquel and we were left with a lot of metabolic issues that go to that and since the Viibryd does work on the 5-HT1A receptor site similar to where the Abilify works and nobody really knows why these drugs do what they do, but that's the current theory. And I thought if we could use this drug that would give us the same type of reaction that we're getting with Abilify plus an SSRI, not only would there not be the metabolic side effect, but you wouldn't have to be paying the big cost of Abilify and Seroquel as a second drug. And right now those are the only two that are FDA approved for augmenting antidepressants. Now we've augmented antidepressants forever trying everything from lithium to Adderall to T-3 Cytomel and I get a lot of treatment resistant depressed patients because that's sort of my sub-category of specialty I guess. Anyway I was just saying that I've used this drug probably on about 15 patients, hard to treat patients, and I've had about a 50% response rate that was possibly into remission. I haven't had them on it long enough to tell you they're for sure in remission, but they certainly are doing better than what they were on before and I didn't have to throw on the Abilify or the Seroquel.
Dr. Muchmore: Dr. Gilbert is a practicing psychiatrist so this is a voice of experience. Any questions?
Dr. Kuhls: Can I ask you about something else?
Dr. Gilbert: Sure.
Dr. Kuhls: I have some psychiatrists in my community that augment depression; they're using this Deplin thing. I know there's not a lot of studies and so on, right, and approvals, but do you have any feeling about that?
Dr. Gilbert: I use that frequently, particularly the 15 mg L-methylfolate and you know, it's supposed to augment monoamines, both dopamine, serotonin, norepinephrine, and when I have a treatment resistant depression, I have a good drug rep that brings me lots of Deplin to try on these patients and I have a significant number, I wouldn't say it's 50%, but 30% of the patients do get improvement and I've had some people that have even done so well that they wanted to get off the drug that was making them impotent and try it by itself, and if they've really succeeded, so I find in a sub-category of patients the Deplin works really well.
Dr. Kuhls: Because the cost of Deplin … .
Dr. Gilbert: Is $62 bucks for … ..
Dr. Kuhls: And what's the cost of this drug? Do you know? $125 … … .. so it's like half the cost, right? Have you had experience on that medicine? What's your feeling Paul?
Dr. Preslar: I've actually seen several patients that have not come back with some of the GI side effects, the libido, weight gain, you know. A lot of times women on this medicine, you know, their biggest thing is weight gain and you get a lot of that with some of the other SSRI's or even the Effexor type things, so … .. I've used it and I've had pretty good, you know, the whole thing comes to if the insurance will cover it. I mean they can't pay, they're not going to pay a $120 or $130 bucks but if I've had resistance on some of the generic Prozac or Zoloft or some of that, it's been pretty efficacious.
Dr. Gilbert: Depends how much Cialis and Viagra they're not using … … .. and you know, women stop drugs because they gain weight. Men stop drugs because it causes sexual side effects. And so, you know, if you've got a drug that's supposed to do less of both of those, then it's something that we will certainly try on patients that are not happy, even though they might be responding fairly well to the regular SSRI.
Dr. Preslar: Have you pushed everyone to the 40 mg, because I've actually kept several on 20 … … ..
Dr. Gilbert: I've done fairly well on, several do quite well on 20.
Dr. Preslar: Yeah and they did respond at 20.
Dr. Muchmore: Well in practice, our tier structure is supposed to allow for the identification of major depressants that do not respond to the Tier 1 medications, and should be able to move on to this one as well as other items in the Tier 3.
Dr. Kuhls: But how … … … .
Dr. Bell: I've had this conversation with Nancy. We can't even put Deplin on the formulary, is that correct?
Dr. Nesser: Because it's not a drug, right? It's a supplement.
Dr. Bell: When you called me you asked me about that.
Dr. Kuhls: I'm just curious, I mean I'm not here promoting it at all, I just have a lot of people using it in the community on some kids.
Dr. Gilbert: It requires a prescription but the insurance won't pay for it because, since it's a natural supplement instead of a drug. So the people that do find that it works, that are willing to pay for it, you know … …
Dr. Kuhls: How is our tier structure set up when you talk in terms of augmentation? Because we're really talking about adding drugs. We're not talking about moving through the tiers, right?
Dr. Bell: Well, there's several ways to augment and you can either, you can use a SSRI if you're getting sexual side effects, you have Wellbutrin, you're, one of the things that interested me is there are a couple of ones that are going generic. I believe it's Cymbalta.
Dr. Preslar: Effexor, venlafaxine is generic.
Dr. Bell: Lexapro's going generic soon. It might be worth looking, pulling the numbers to see how often it's getting augmented with an antipsychotic.
Dr. Kuhls: I don't know if our tier structure does cover the concept of augmentation, of adding Abilify to an antidepressant.

Dr. Le: Are you talking about antidepressant or antipsychotic.
Dr. Kuhls: Both.
Dr. Le: Yes, there are ways for both.
Dr. Bell: But if you go through the antipsychotic cures we have to start with Risperdal.
Dr. Le: No, not for depression because only certain drugs, Abilify and Seroquel XR are and we approve those for augmentation of depression.
Dr. Kuhls: I didn't know we were doing that.
Dr. Le: Yes, we are. It's in the atypical criteria and for the SSRI's there's no edit that stops continuation of therapy, so a lot of people do use one product plus buproprion, you know an SSRI plus a dual-acting, they can.
Miscellaneous comments from the Board members.
Materials included in agenda packet; presented by Dr. Le.
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
Materials included in agenda packet; submitted by Dr. Graham.
A: Annual Review of Statins
B: Annual Review of Narcotics
C: New Product Reviews
D: Medical Product Reviews
ACTION: NONE REQUIRED

AGENDA ITEM NO. 14: ADJOURNMENT: The meeting was adjourned at 7:25 p.m.

The University of Oklahoma
Health Sciences Center
COLLEGE OF PHARMACY
PHARMACY MANAGEMENT CONSULTANTS

Memorandum

Date: October 13, 2011

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

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

Subject: DUR Board Recommendations from Meeting of October 12, 2011

Recommendation 1: Vote to Prior Authorize Firazyr® (icatibant)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends placing a prior authorization on Firazyr® (icatibant) with the following criteria:

1. Documented diagnosis of Hereditary Angioedema (HAE)
2. For acute attacks of Hereditary Angioedema (HAE)

Recommendation 2: Annual Review of Pediculicides

NO ACTION REQUIRED.

The College of Pharmacy recommends continuation of the current Product Based Prior Authorization criteria.

Recommendation 3: Annual Review of Ocular Antibiotics

ACTION TABLED.

Recommendation 4: Annual Review of Antihypertensives

NO ACTION REQUIRED.

The College of Pharmacy recommends continuation of the current Product Based Prior Authorization criteria.

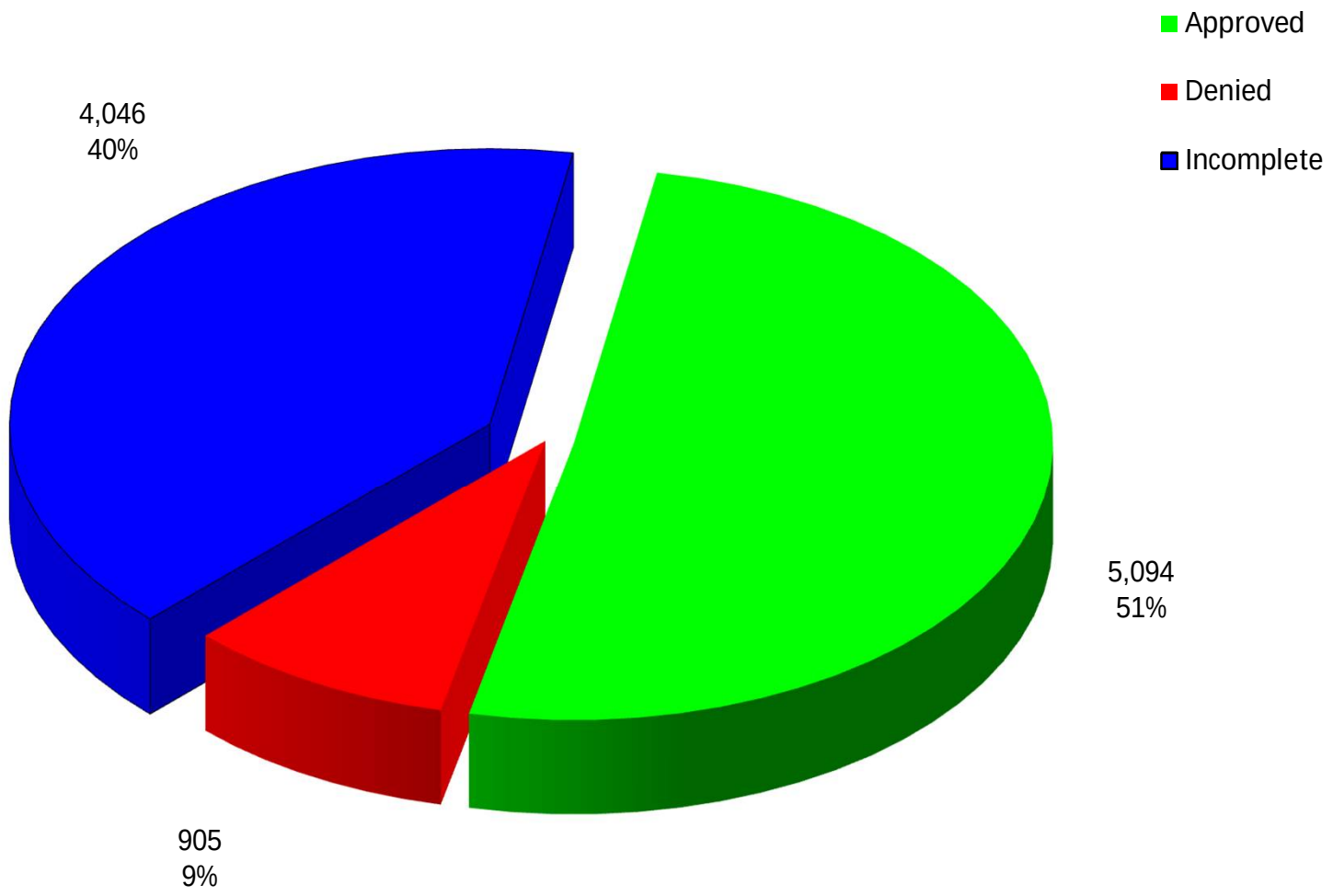
Recommendation 5: Annual Review of Antidepressants

NO ACTION REQUIRED.

The College of Pharmacy recommends continuation of the current Product Based Prior Authorization criteria.

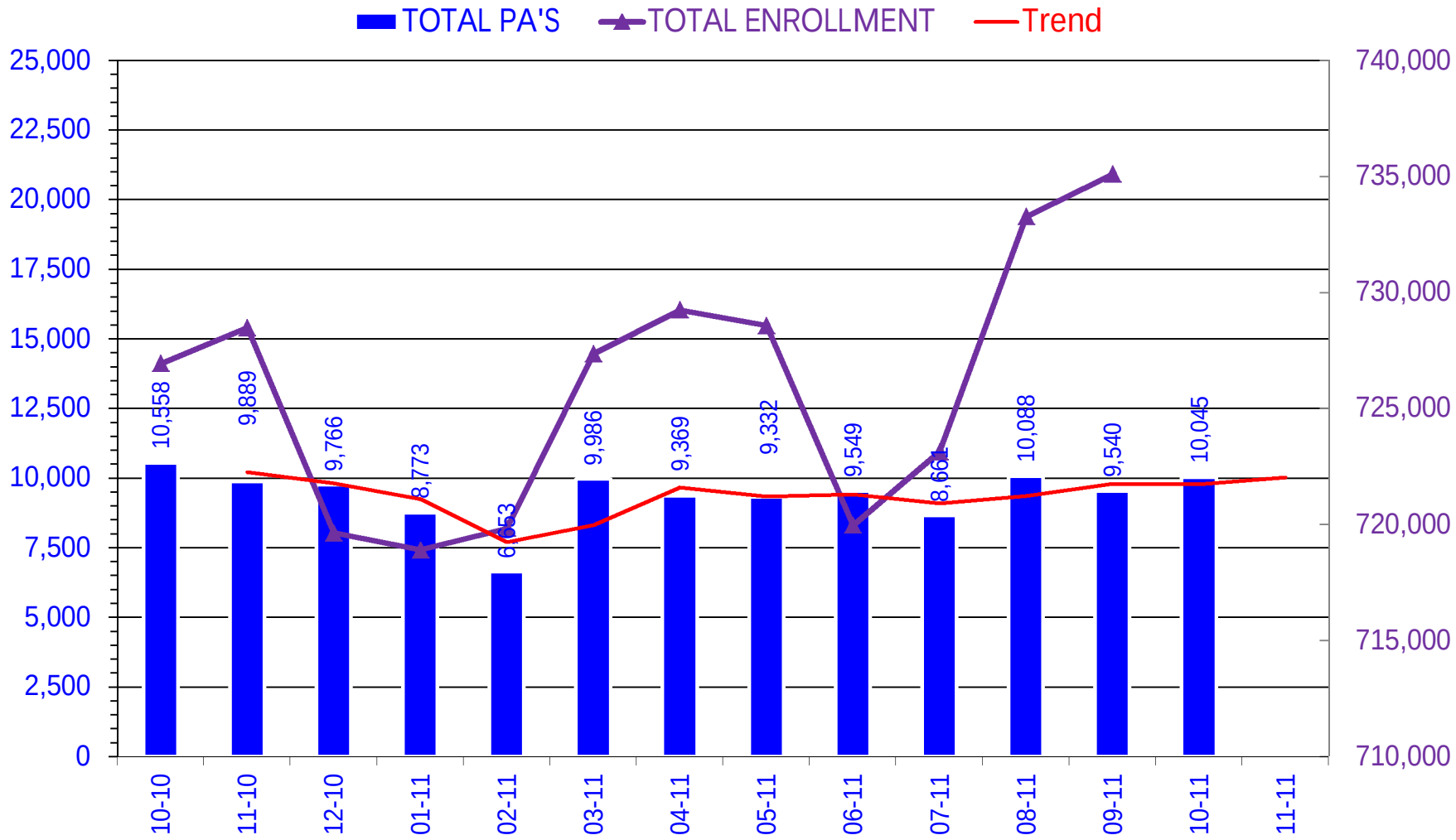
Appendix B

PRIOR AUTHORIZATION ACTIVITY REPORT: October 2011



PA totals include overrides

PRIOR AUTHORIZATION REPORT: October 2010 – October 2011



PA totals include overrides

Prior Authorization Activity

10/1/2011 Through 10/31/2011

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort	423	142	27	254	358
Amitiza	29	6	3	20	238
Anti-Ulcer	452	139	89	224	113
Antidepressant	295	94	18	183	343
Antihistamine	281	174	16	91	336
Antihypertensives	79	22	7	50	353
Antimigraine	94	17	14	63	326
Atypical Antipsychotics	647	361	19	267	348
Benign Prostatic Hypertrophy	5	0	1	4	0
Benzodiazepines	64	36	1	27	239
Bladder Control	51	7	6	38	363
Brovana (Arformoterol)	1	1	0	0	365
Byetta	23	8	3	12	342
Elidel/Protopic	35	14	9	12	89
ESA	89	64	5	20	119
Fibric Acid Derivatives	2	1	0	1	365
Fibromyalgia	155	51	22	82	348
Fortamet/Glumetza	5	2	0	3	363
Forteo	1	0	1	0	0
Glaucoma	27	9	1	17	325
Growth Hormones	53	40	4	9	171
HFA Rescue Inhalers	71	20	2	49	296
Insomnia	90	15	11	64	156
Misc Analgesics	52	9	31	12	232
Muscle Relaxant	151	34	84	33	103
Nasal Allergy	272	81	38	153	129
NSAIDS	154	24	22	108	300
Ocular Allergy	74	15	8	51	93
Ocular Antibiotics	51	15	2	34	15
Opioid Analgesic	281	174	13	94	244
Other	931	320	92	519	256
Otic Antibiotic	48	9	3	36	8
Pediculicides	121	65	6	50	20
Plavix	201	142	0	59	330
Qualaquin (Quinine)	1	0	1	0	0
Singulair	916	496	24	396	244
Smoking Cessation	45	12	1	32	24
Statins	153	99	4	50	354
Stimulant	903	492	63	348	316
Suboxone/Subutex	131	90	2	39	83
Synagis	613	283	177	153	143
Topical Antibiotics	8	2	0	6	18
Topical Antifungals	21	2	0	19	53
Topical Corticosteroids	3	0	0	3	0
Ultram ER and ODT	11	1	3	7	361
Xolair	7	2	4	1	270
Xopenex Nebs	39	15	0	24	338
Zetia (Ezetimibe)	19	6	3	10	361
Emergency PAs	6	6	0	0	
Total	**8,184**	**3,617**	**840**	**3,727**	

Overrides					
Brand	93	70	3	20	288
Dosage Change	596	565	1	30	14
High Dose	6	5	0	1	229
IHS-Brand	4	4	0	0	8
Lost/Broken Rx	90	82	1	7	10
NDC vs Age	19	19	0	0	344
Nursing Home Issue	115	108	0	7	10
Other	33	29	2	2	23
Quantity vs. Days Supply	895	585	58	252	278
Stolen	10	10	0	0	6
Overrides Total	**1,861**	**1,477**	**65**	**319**	
Total Regular PAs + Overrides	**10,045**	**5,094**	**905**	**4,046**	

Denial Reasons	
Unable to verify required trials.	2,841
Lack required information to process request.	1,213
Does not meet established criteria.	868
Requested dose exceeds maximum recommended FDA dose.	3
Drug Not Deemed Medically Necessary	1
Not an FDA approved indication/diagnosis.	1

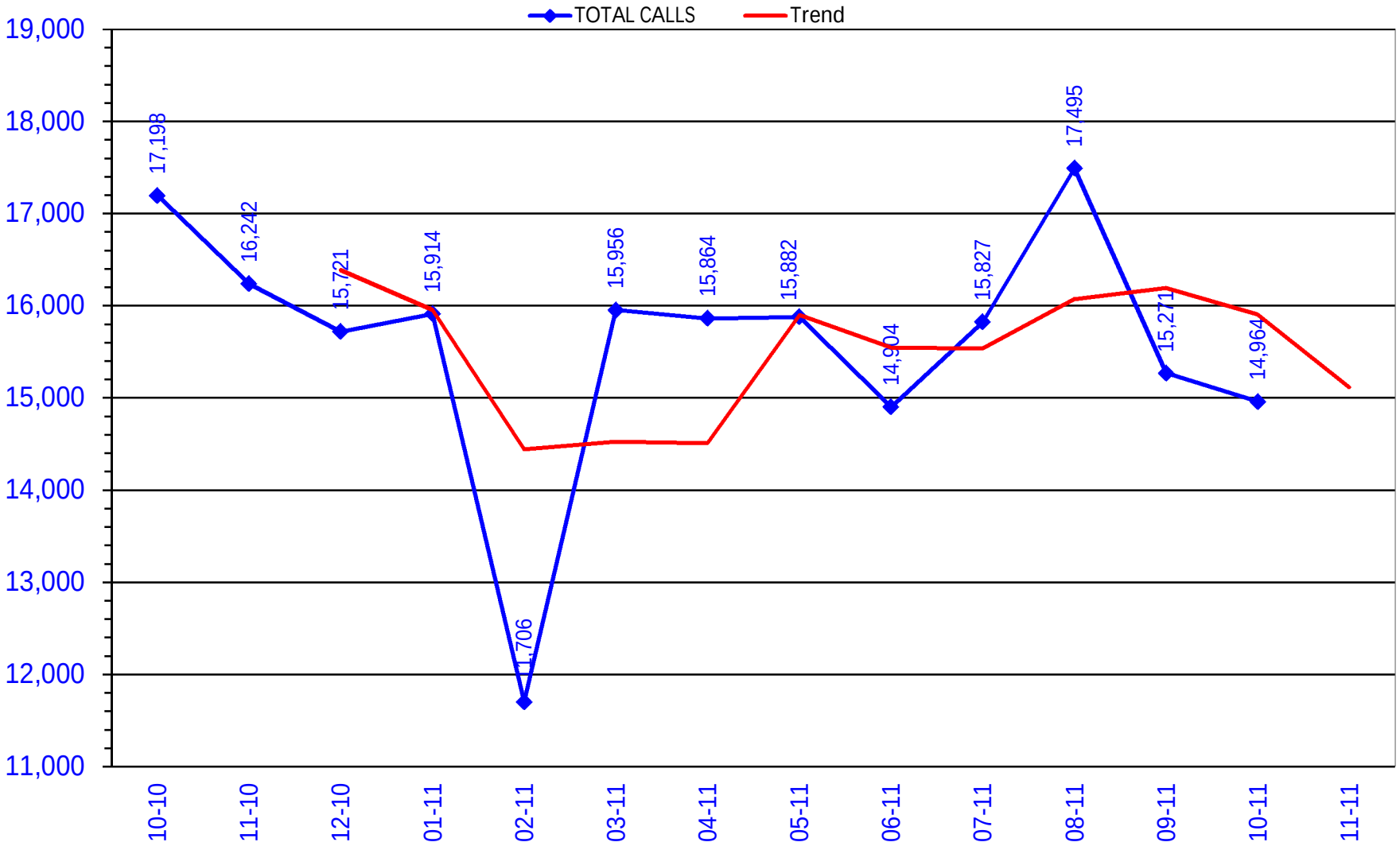
Duplicate Requests: 665

Letters: 2,058

No Process: 516

Changes to existing PAs: 505

CALL VOLUME MONTHLY REPORT:
October 2010 – October 2011



Appendix C

Vote to Prior Authorize Natroba™ (spinosad) Topical Suspension

Oklahoma Health Care Authority
November 2011

Current Prior Authorization Criteria

Approval Criteria:

- **Approval of Tier 2 medication** requires a trial with one Tier 1 medication with inadequate response or adverse effect.
- **Approval of Tier 3 medication** requires trials with all available Tier 2 medication(s) with inadequate response or adverse effect.

Tier 1	Tier 2	Tier 3
Covered OTC Lice Products **Generics with SMAC Pricing**	Supplemental Rebate	Lindane Lotion & Shampoo Crotamiton (Eurax®) Lotion Benzoyl Alcohol (Ulesfia™) Lotion Malathion (Ovide®)

The following restrictions also apply for each individual product based on FDA approval information:

Malathion lotion (Ovide®)

- Member must be at least 6 years old (stated on package label)
- Quantity limit of 60ml for 7 day supply; may be repeated once if needed for current infestation after 7 days from original fill date

Crotamiton lotion (Eurax®)

- Member must be at least 18 years of age
- Quantity limit of 60 grams or milliliters for 30 day supply

Lindane lotion & shampoo

- Member must be at least 13 years old or weigh at least 110 pounds
- Quantity limit of 60ml for 7 day supply
- One 7 day supply per 30 days maximum

Ulesfia™ (benzoyl alcohol) Lotion

- Available only after first-line treatment with an OTC product has failed
- Member must be at least 6 months old
- Due to mechanism of action, requires retreatment after 7 days
- Hair length would be required in order to approve the appropriate number of bottles if requesting more than 2 bottles per treatment (4 bottles for both treatments)

Clinical exception if known resistance to OTC Permethrin and Pyrethrin.

Utilization Details of Pediculicides: Fiscal Year 2011

Chemical Name	Brand Name	Claims	Units	Days	Members	Cost	Cost/ Claim
Permethrin	PERMETHRIN CRE 5%	12,816	767,596	134,753	9,440	$197,246.13	$15.39
Permethrin	PERMETHRIN LOT 1%	10,390	747,005	136,082	6,497	$124,226.11	$11.96
Permethrin	SM LICE LOT TREATMNT	1,564	118,636	19,923	1,020	$22,337.30	$14.28
Permethrin	ACTICIN CRE 5%	394	23,581	4,012	305	$6,052.82	$15.36
Permethrin	LICE TREATME LIQ 1%	190	21,959	3,505	114	$2,889.32	$15.21
Malathion	MALATHION LOT 0.5%	633	37,465	6,441	496	$83,274.34	$131.56
Benzyl Alcohol	ULESFIA LOT 5%	332	127,145	6,848	232	$29,964.10	$90.25
Lindane	LINDANE SHA 1%	39	2,340	452	31	$4,439.99	$113.85
Lindane	LINDANE LOT 1%	21	1,260	204	16	$2,415.90	$115.04
Crotamiton	EURAX CRE 10%	20	1,200	600	17	$1,416.66	$70.83
Crotamiton	EURAX LOT 10%	5	300	150	5	$405.40	$81.08
	Totals	**26,404**	**1,848,487**	**312,940**	**16,924***	**$474,668.07**	**$17.98**

***Total number of unduplicated members**

Conclusion and Recommendations

The College of Pharmacy recommends updating the current Product Based Prior Authorization tier structure as outlined below. Additionally, the College recommends placement of Natroba™ (spinosad) in Tier 3 of the current structure. An age restriction of 4 years or older and a quantity limit of 240 mL every 30 days will also apply.

Tier 1	Tier 2	Tier 3
Covered OTC Lice Products **Generics with SMAC Pricing**	Benzoyl Alcohol (Ulesfia™) Lotion	Lindane Lotion & Shampoo Malathion (Ovide®) Spinosad (Natroba™)

Approval Criteria:

- **Approval of Tier 2 medication** requires a trial with one Tier 1 medication with inadequate response or adverse effect.
- **Approval of Tier 3 medication** requires a trial with one Tier 2 medication with inadequate response or adverse effect.

No changes to individual product restrictions. Crotamiton will not be included in the tier system but will maintain the age and quantity restrictions.

Appendix D

Vote to Prior Authorize Biologic Products for the Treatment of Rheumatoid Arthritis, Crohn's Disease, Plaque Psoriasis, and Ankylosing Spondylitis

Oklahoma Health Care Authority, November 2011

This category was introduced for possible inclusion in the Product Based Prior Authorization program in August 2011. See the August, September and October DUR packets for a more complete discussion of the category. This notice is presented to meet the statutory requirements of 63 O.S. Sec. 5030.5.

Recommendations

The College of Pharmacy recommends pharmacy and medical prior authorization of this class of medications with the following criteria and tier structure :

Tier 2 authorization criteria:

1. FDA approved diagnosis
2. A trial of at least one Tier 1 product in the last 90 days that did not yield adequate relief of symptoms or resulted in intolerable adverse effects.
3. Prior stabilization on the Tier 2 medication documented within the last 100 days.

Tier 3 authorization criteria:

1. FDA approved diagnosis
2. Recent trials of one Tier 1 product and all available Tier 2 medications that did not yield adequate relief of symptoms or resulted in intolerable adverse effects.
3. Prior stabilization on the Tier 3 medication documented within the last 100 days.
4. A unique FDA-approved indication not covered by Tier 2 products.

Biologic Medications		
Tier 1	**Tier 2**	**Tier 3**
DMARDs appropriate to disease state:	Supplemental rebated medications	Abatacept (Orencia®)
Methotrexate		Adalimumab (Humira®)
Hydroxychloroquine		Alefacept (Amevive®)
Sulfasalazine		Anakinra (Kineret®)
Minocycline		Certolizumab pegol (Cimzia®)
Oral Corticosteroids		Etanercept (Enbrel®)
Leflunomide		Golimumab (Simponi®)
Mesalamine		Infliximab (Remicade®)
6-Mercaptopurine		Rituximab (Rituxan®)
Azathioprine		Tocilizumab (Actemra®)
NSAIDs		Ustekinumab (Stelara®)

Appendix E

Vote to Prior Authorize Moxeza™ (moxifloxacin hcl ophthalmic solution)

Oklahoma Health Care Authority, November 2011

Recommendations

The College of Pharmacy recommends the placement of Moxeza™ into Tier 3 of this PBPA category. Current criteria shall apply.

Ophthalmic Antibiotics: Liquids		
Tier 1	**Tier 2**	**Tier 3**
Gentak (Gentamicin)	**Ciloxan Solution (Ciprofloxacin)**	**Vigamox (Moxifloxacin)**
AK-Tob (Tobramycin)	**Ocuflox (Ofloxacin)**	**Moxeza (Moxifloxacin)**
Bleph-10, Na Sulamyd (Na Sulfacetamide)		**Azasite (Azithromycin)**
Polytrim (PolymyxinB/Trimethoprim)		**Besivance (Besifloxacin HCL)**
AK-Spore (Neo/PolyB/Gramacidin)		**Iquix (Levofloxacin)**
		Quixin (Levofloxacin)
		Zymar (Gatifloxacin)
		Zymaxid (Gatifloxacin)

Criteria for a Tier 2 medication:

1. Approved indication/suspected infection by organism not known to be covered by Tier 1 products, or failure of a Tier 1 product.
2. Known contraindication to all indicated Tier 1 medication.
3. Prescription written by optometrists/ophthalmologists, or
4. When used for pre/post-operative prophylaxis.

Criteria for a Tier 3 medication:

1. Approved indication/suspected infection by organism not known to be covered by Tier 2 products, or failure of a Tier 2 product.
2. Known contraindication to all indicated Tier 2 medication.
3. Prescription written by optometrists/ophthalmologists, or
4. When used for pre/post-operative prophylaxis.

Appendix F

Vote to Prior Authorize Amturnide® (aliskiren/amlodipine besylate/HCTZ) and Edarbi® (azilsartan medoxomil)

Oklahoma HealthCare Authority
November 2011

Recommendations

The College of Pharmacy recommends the following changes to the Antihypertensives PBPA category:

1. Placement of Amturnide® (aliskirin/amlodipine/HCTZ) in Tier 3 of the DRI category.
2. Placement of Edarbi™ (azilsartan) into Tier 3 of the ARB category.
3. As ARB patents expire, move generic ARBs to Tier 1 once exclusivity lapses and SMAC is applied.

ARBs (Angiotensin Receptor Blockers) and ARB Combination Products		
Tier-1	**Tier-2**	**Tier-3**
ACE Inhibitor:	amlodopine / valsartan (Exforge®)	candesartan (Atacand®)
benazepril (Lotensin®)	amlodopine / valsartan (Exforge® HCT)	candesartan / HCTZ (Atacand® HCT)
captopril (Capoten®)	amlodipine / olmesartan (Azor™)	eprosartan (Teveten®)
enalapril (Vasotec®)	irbesartan (Avapro®)	eprosartan / HCTZ (Teveten® HCT)
enalaprilat (Vasotec® IV)	irbesartan / HCTZ (Avalide®)	telmisartan/amlodipine (Twynsta)
fosinopril (Monopril®)	valsartan (Diovan®)	telmisartan (Micardis®)
lisinopril (Prinivil®, Zestril®)	valsartan / HCTZ (Diovan HCT®)	telmisartan / HCTZ (Micardis® HCT)
moexipril (Univasc®)	olmesartan (Benicar®)	olmesarten/amlodipine/HCTZ (Tribenzor®)
quinapril (Accupril®)	olmesartan / HCTZ (Benicar HCT®)	**azilsartan (Edarbi™)**
trandolapril (Mavik®)		
ramipril (Altace®)		
ARBs:		
losartan (Cozaar®)		
losartan / HCTZ (Hyzaar®)		

Direct Renin inhibitors (DRI)		
Tier-1	**Tier-2**	**Tier-3**
Tier-1 ACE Inhibitor + Diuretic	ARB + Diuretic	Aliskiren (Tekturna®)
		Aliskiren/HCTZ (Tekturna HCT®)
		Aliskiren/valsartan (Valturna®)
		Aliskiren/amlodipine (Tekamlo®)
		Aliskiren/amlodipine/HCTZ (Amturnide™)

Appendix G

Vote to Prior Authorize Viibryd® (vilazodone)

Oklahoma Health Care Authority, November 2011

Recommendations

The College of Pharmacy recommends the addition of Viibryd® (vilazodone) to Tier 3 of the antidepressants Product Based Prior Authorization Category. The existing criteria will apply.

SSRIs (Selective Serotonin Reuptake Inhibitors)		
Tier 1	**Tier 2**	**Tier 3**
citalopram (Celexa®)	escitalopram (Lexapro®)	
fluoxetine (Prozac®, Sarafem®)	fluoxetine (Prozac Weekly™)	
fluvoxamine (Luvox®)	fluvoxamine (Luvox CR®)	
paroxetine (Paxil®, Paxil CR®)	paroxetine (Pexeva®)	
sertraline (Zoloft®)		
Dual Acting Antidepressants		
Tier 1	**Tier 2**	**Tier 3**
venlafaxine (Effexor®, Effexor XR® Caps)	duloxetine (Cymbalta®)	Venlafaxine ER Tabs®
mirtazapine (Remeron® Tabs & SolTab®)		desvenlafaxine (Pristiq®)
trazodone (Desyrel®)		nefazodone (Serzone®)
bupropion (Wellbutrin®, Wellbutrin SR® & XL®)		bupropion (Aplenzin®)
		trazodone ER (Oleptro®)
		vilazodone (Viibryd®)
Monoamine Oxidase Inhibitors		
Tier 1	**Tier 2**	**Tier 3**
		selegiline transderm patch (Emsam®)
		tranylcypromine (Parnate®)
		phenelzine (Nardil®)
		selegiline (Zelapar®)

Mandatory generic plan applies
Tiers based on FY2011 Supplemental Rebate participation

Tier 2 Authorization Criteria

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

Tier 3 Authorization Criteria

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

Appendix H

30 Day Notice to Prior Authorize Multiple Sclerosis Medications

Oklahoma Health Care Authority
November 2011

This category was introduced for possible inclusion in the Product Based Prior Authorization program in September 2011. See the September and October DUR packets for a more complete discussion of the category. This notice is presented to meet the statutory requirements of 63 O.S. Sec. 5030.5.

Recommendations

The College of Pharmacy recommends the following for the Multiple Sclerosis Category of Medications:

Tier 1	Tier 2
Lowest Supplemental Rebated Interferon β – 1a	Interferon β - 1a (Avonex®)
Lowest Supplemental Rebated Interferon β – 1b	Interferon β - 1a (Rebif®)
	Interferon β - 1b (Extavia®)
	Interferon β - 1b (Betaseron®)

Interferon Prior Authorization Criteria:

1. Documented diagnosis of relapsing remitting MS.
2. Tier-2 medications require failure of the preferred Tier-1 product defined as:
    a. Occurrence of an exacerbation after 6 months.
    b. Significant increase in MRI lesions after 6 months.
    c. Adverse reactions or intolerable side effects.
3. No concurrent use with other therapies.
4. Compliance will be checked for continued approval every 6 months.

Glatiramer Acetate (Copaxone®) Prior Authorization Criteria:

1. FDA approved diagnosis.
2. No concurrent use with other therapies.
3. Compliance will be checked for continued approval every 6 months.

Fingolimod (Gilenya®) Prior Authorization Criteria:

1. Documented diagnosis of relapsing remitting MS with at least one relapse in the previous 12 months.
2. No concurrent use with other therapies.
3. Compliance will be checked for continued approval every 6 months.

Appendix I

30 Day Notice to Prior Authorize Gralise™ (gabapentin)

Oklahoma Health Care Authority
November 2011

Manufacturer	Manufactured by Pantheon Puerto Rico, Inc., for Depomed, Inc.
Classification	Anticonvulsant, Gamma Aminobutyric Acid
Status	Prescription Only

Summary

Gralise™ is a new extended-release formulation of gabapentin indicated for the management of postherpetic neuralgia. It is supplied as 300 mg and 600 mg tablets, and should be titrated to an 1800 mg dose taken once daily with the evening meal. The dose should be decreased in patients with reduced renal function. The tablets should be swallowed whole and not crushed, split, or chewed. Due to this extended-release formulation, Gralise™ is not interchangeable with other gabapentin products.

Gralise™ was developed with a unique patented polymer-based technology which allows controlled drug delivery to the upper gastrointestinal tract. The swelling polymers cause the tablet to be retained in the stomach for approximately 8-9 hours, during which time the drug is steadily delivered to the upper GI tract. The company markets the advantages of this drug delivery system as that it allows for peak plasma levels during the night and provides low rates of side effects.

Gabapentin is a gamma-aminobutyric acid (GABA), analogue. The mechanism of action by which gabapentin exerts its analgesic action is unknown but in animal models of analgesia, gabapentin prevents allodynia and hyperalgesia.

In an 11-week, double-blind, multicenter, placebo-controlled study (n=452), Gralise™ showed a statistically significant reduction in average daily pain score compared to placebo. In clinical trials, the most common adverse events associated with Gralise™ were dizziness (10.9%), somnolence (4.5%), headache (4.2%), and peripheral edema (3.9%).

Cost of therapy of Gralise™ for a dose of 1800 mg/day (three 600 mg tablets) is $169 per month. The cost of therapy with generic gabapentin at the same daily dose is $37.

Recommendations

The College of Pharmacy recommends prior authorization of Gralise™ (gabapentin) with the following criteria:

1. FDA approved indication of postherpetic neuralgia.
2. Must provide documented treatment attempts at recommended dosing or contraindications to at least one agent from two of the following drug classes:
    a. Tricyclic antidepressants
    b. Anticonvulsants
    c. Topical or oral analgesics
3. Must provide a clinically significant reason why the member cannot take the immediate-release formulation of gabapentin.

PRODUCT DETAILS OF GRALISE™ (GABAPENTIN)

FDA-APPROVED IN JANUARY 2011

INDICATIONS:

- Post herpetic neuralgia

DOSAGE FORMS:

- Gralise™ is supplied in 300mg and 600mg oral tablets.

ADMINISTRATION:

- Gralise™ should be titrated to an 1800 mg dose taken orally, once-daily, with the evening meal. Gralise™ tablets should be swallowed whole. Do not crush, split of chew the tablets.

CONTRAINDICATIONS:

- Gralise™ is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

SPECIAL POPULATIONS:

- **Pregnancy:** Pregnancy Category C: Gabapentin has been shown to be fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs, and hind limbs. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the period of organogenesis, or approximately 3 to 8 times the maximum dose of 1800 mg/day given to PHN patients on a mg/m2 basis.
- **Nursing Mothers**: Gabapentin is secreted into human milk following oral administration. A nursed infant could be exposed to a maximum dose of approximately 1 mg/kg/day of gabapentin. Because the effect on the nursing infant is unknown, Gralise™ should be used in women who are nursing only if the benefits clearly outweigh the risks.
- **Pediatric Use:** The safety and effectiveness of Gralise™ in the management of postherpetic neuralgia in patients less than 18 years of age has not been studied.
- **Geriatric Use:** The total number of patients treated with Gralise™ in controlled clinical trials in patients with postherpetic neuralgia was 359, of which 63% were 65 years of age or older. The types and incidence of adverse events were similar across age groups except for peripheral edema, which tended to increase in incidence with age. Gralise™ is known to be substantially excreted by the kidney. Reductions in Gralise™ dose should be made in patients with age-related compromised renal function.
- **Hepatic Impairment:** Because gabapentin is not metabolized, studies have not been conducted in patients with hepatic impairment.
- **Renal Impairment:** Gralise™ is known to be substantially excreted by the kidney. Dosage adjustment is necessary in patients with impaired renal function. Gralise™ should not be administered in patients with CrCL between 15 and 30 or in patients undergoing hemodialysis.

WARNINGS AND PRECAUTIONS:

- **Suicidal Behavior and Ideation:** Antiepileptic drugs (AEDs), including gabapentin, the active ingredient in Gralise™, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.
- **Withdrawal of Gabapentin:** Gabapentin should be withdrawn gradually. If Gralise™ is discontinued, this should be done gradually over a minimum of 1 week or longer (at the discretion of the prescriber).

- **Tumorigenic Potential:** In standard preclinical *in vivo* lifetime carcinogenicity studies, an unexpectedly high incidence of pancreatic acinar adenocarcinomas was identified in male, but not female, rats. The clinical significance of this finding is unknown.

ADVERSE REACTIONS:

- **Common:**
  - Dizziness
- **Other:**
  - Vertigo
  - Diarrhea
  - Dry mouth
  - Constipation
  - Dyspepsia
  - Peripheral Edema
  - Pain
  - Nasopharyngitis
  - Urinary Tract Infection
  - Weight Increase
  - Pain in Extremity
  - Back Pain
  - Somnolence
  - Headache
  - Lethargy

DRUG INTERACTIONS:

- Increase Gabapentin Levels: Cimetidine, Hydrocodone, Morphine, Naproxen
- Decrease Gabapentin Levels: Antacids

PATIENT COUNSELING INFORMATION:

- Advise patients that Gralise™ is not interchangeable with other formulations gabapentin.
- Advise patients to take Gralise™ only as prescribed. Gralise™ may cause dizziness, somnolence, and other signs and symptoms of CNS depression.
- Advise patients not to drive or operate other complex machinery until they have gained sufficient experience on Gralise™ to gauge whether or not it adversely affects their mental and/or motor performance.
- Advise patients who require concomitant treatment with morphine to tell their prescriber if they develop signs of CNS depression such as somnolence. If this occurs the dose of Gralise™ or morphine should be reduced accordingly.
- Advise patients that if they miss a dose of Gralise™ to take it with food as soon as they remember. If it is almost time for the next dose, just skip the missed dose and take the next dose at the regular time. Do not take two doses at the same time.
- Advise patients that if they take too much Gralise™, to call their healthcare provider or poison control center, or go to the nearest emergency room right away.
- **Medication Guide:** Advise patients of the availability of a Medication Guide, and instruct them to read the Medication Guide prior to taking Gralise™.
- **Suicidal Thoughts and Behavior:** Advise patients, their caregivers, and families that AEDs, including gabapentin, the active ingredient in Gralise™, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.
- **Dosing and Administration:** Advise patients that Gralise™ should be taken orally once-daily with the evening meal. Gralise™ tablets should be swallowed whole. Do not split, crush, or chew the tablets.

REFERENCES:

Gralise™Label Information. Depomed Pharmaceuticals Inc. Available online at: http://gralise.com/lib/PDFS/FPI_APR2011.pdf. Last revised April 2011, accessed October 27, 2011.

30 Day Notice to Prior Authorize Horizant® (gabapentin enacarbil)

Oklahoma Health Care Authority
November 2011.

Manufacturer:	**GlaxoSmithKline**
FDA Status:	**Prescription Only**
Approved Indication:	**Restless Legs Syndrome**

Summary of Restless Legs Syndrome[1]

Restless legs syndrome (RLS) is a neurological disorder characterized by throbbing, pulling, creeping, or other unpleasant sensations in the legs and an uncontrollable, and sometimes overwhelming, urge to move them. Symptoms occur primarily at night when a person is relaxing or at rest and can increase in severity during the night. Moving the legs relieves the discomfort. Often called paresthesias (abnormal sensations) or dysesthesias (unpleasant abnormal sensations), the sensations range in severity from uncomfortable to irritating to painful.

As many as 10 percent of the U.S. population may have RLS. Several studies have shown that moderate to severe RLS affects approximately 2-3 percent of adults (more than 5 million individuals). An additional 5 percent appears to be affected by a milder form. Childhood RLS is estimated to affect almost 1 million school-age children, with one-third having moderate to severe symptoms. RLS occurs in both men and women, although the incidence is about twice as high in women. It may begin at any age. Many individuals who are severely affected are middle-aged or older, and the symptoms typically become more frequent and last longer with age.

In most cases, the cause of RLS is unknown. However, it may have a genetic component; RLS is often found in families where the onset of symptoms is before age 40. Specific gene variants have been associated with RLS. Evidence indicates that low levels of iron in the brain also may be responsible for RLS.

Considerable evidence suggests that RLS is related to a dysfunction in the brain's basal ganglia circuits that use the neurotransmitter dopamine, which is needed to produce smooth, purposeful muscle activity and movement. Disruption of these pathways frequently results in involuntary movements. Individuals with Parkinson's disease, another disorder of the basal ganglia's dopamine pathways, often have RLS as well.

Treatment of RLS is directed at relieving symptoms, though treating an associated medical condition such as peripheral neuropathy or diabetes can bring relief. Lifestyle changes that may offer some relief include reducing caffeine, alcohol, and tobacco intake; correcting iron, folate, and magnesium deficiencies; massage, exercise, hot baths, and maintaining good sleep hygiene.

Drug therapy: Dopaminergic agents, used to treat Parkinson's disease, are first line therapy. Pramipexole and ropinirole are FDA approved to treat moderate to severe RLS. Levodopa/ carbidopa has also reportedly given good short-term relief. However, long-term use of these dopaminergic agents is also associated with progressive worsening of symptoms, called

"augmentation", in some patients. With augmentation, symptoms begin earlier in the day and progress to being present all day. Symptoms resolve once the medication is stopped.

Other medications that are used off-label to treat RLS include benzodiazepines, specifically clonazepam and diazepam, opioids, and anticonvulsants such as gabapentin and pregabalin.

Horizant® (gabapentin enacarbil) Summary

Horizant®, extended-release gabapentin enacarbil , a prodrug of gabapentin, was FDA approved in April, 2011 for treatment of moderate-to-severe primary Restless Legs Syndrome in adults. Gabapentin enacarbil undergoes extensive first-pass hydrolysis in enterocytes and the liver, to form gabapentin and other compounds. It is available in a 600 mg tablet for once daily dosing. Doses higher than 600 mg provided no additional benefits, but were associated with increased adverse reactions. The estimated acquisition cost is $3.48 per tab.

The most common adverse reactions are somnolence/sedation and dizziness, therefore caution should be used when driving or operating heavy equipment. As with other antiepileptic drugs, Horizant® can increase the risk of suicide. Horizant® is not interchangeable with immediate release gabapentin due to different kinetics

Cost comparison for 30 day supply

Medication	Estimated Acquisition Cost (EAC)*	State Maximum Allowable Cost (SMAC)*
Pramipexole, 0.1 mg to 0.5 mg daily		$8.37
Ropinirole, 0.25 mg titrated to 4 mg daily		$9.72-$10.92
Carbidopa/levodopa, 100/25 mg to 250/25 mg up to two tabs/day		$18.42
Gabapentin, 300 mg up to tid		$7.62-$14.82
Gabapentin, 600 mg up to tid		$16.32-$40.92
Gabapentin, 800 mg up to tid		$25.92-$69.72
Horizant®, 600 mg once daily	$108.42	

*includes dispensing fee

Recommendations

The College of Pharmacy recommends prior authorizing Horizant® using the following criteria:

1. FDA approved indication of Restless Legs Syndrome
2. Must be 18 years or older
3. Must provide documented treatment attempts at recommended dose with at least two of the following that did not yield adequate relief:
    a. carbidopo/levodapoa
    b. pramipexole
    c. ropinirole
4. Reason that immediate release gabapentin cannot be used.

PRODUCT DETAILS OF HORIZANT® (GABAPENTIN ENACARBIL)[2]
FDA-APPROVED IN APRIL 2011

INDICATIONS:
Horizant® (gabapentin enacarbil) Extended-Release Tablets are indicated for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS) in adults. Horizant® is not recommended for patients who are required to sleep during the daytime and remain awake at night.

DOSAGE FORMS:
Horizant® Extended-Release Tablets, 600 mg, are white to off-white, oval-shaped tablets debossed with "GS LFG". Horizant® Extended-Release Tablets may contain occasional black/grey spots.

ADMINISTRATION:
- The recommended dosage for Horizant® is 600 mg once daily taken with food at about 5 PM. A daily dose of 1,200 mg provided no additional benefit compared with the 600-mg dose, but caused an increase in adverse reactions. If the dose is not taken at the recommended time, the next dose should be taken the following day as prescribed. Tablets should be swallowed whole and should not be cut, crushed, or chewed.
- **Renal Impairment and Hemodialysis:** In patients with compromised renal function (creatinine clearance [CrCl] 30 to 59 mL/min), 600 mg of Horizant® should be administered on Day 1, Day 3, and every day thereafter. Horizant® is not recommended for use in patients with a CrCl <30 mL/min or on hemodialysis because the dose cannot be reduced below 600 mg.

CONTRAINDICATIONS: None

SPECIAL POPULATIONS:
- **Pregnancy:** Pregnancy Category C. There are no adequate and well-controlled studies with Horizant® in pregnant women. In nonclinical studies in rat and rabbits, administration of gabapentin enacarbil was developmentally toxic when administered to pregnant animals at doses and gabapentin exposures greater than those used clinically. Horizant® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- **Labor and Delivery:** The effect of Horizant® on labor and delivery is unknown.
- **Nursing Mothers:** It is not known whether gabapentin derived from Horizant® is secreted in human milk; however, gabapentin is secreted into human milk following oral administration of gabapentin products. Because of the potential for adverse reactions in nursing infants from Horizant®, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother
- **Pediatric Use:** Safety and effectiveness of Horizant® in pediatric patients have not been studied.
- **Geriatric Use :** Of the 515 patients treated with Horizant® in the 3 double-blind, placebo-controlled, 12-week clinical trials for RLS, 11% were 65 to 74 years of age and 1% were 75 years of age and older. Clinical trials of Horizant® did not include a sufficient number of patients 65 years and older to determine whether they respond differently from younger individuals. Gabapentin is known to be almost exclusively excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, the

frequency of dosing may need to be adjusted based on calculated creatinine clearance in these.

- **Renal Impairment:** The dose of Horizant® should be adjusted in patients with renal impairment.

WARNINGS AND PRECAUTIONS:

- **Effects on Driving:** Horizant® causes significant driving impairment. Patients being treated with Horizant® should not drive until they have gained sufficient experience to assess whether Horizant® impairs their ability to drive. However, prescribers and patients should be aware that patients' ability to assess their own driving competence, as well as their ability to assess the degree of somnolence caused by Horizant® can be imperfect. In a 2-week simulated driving study in patients with RLS, a daily 1,200-mg dose of Horizant® caused significant impairment within 2 hours and for up to 14 hours after dosing. The impairment was similar to that caused by the active control, a single oral dose of diphenhydramine 50mg.
- **Somnolence/Sedation and Dizziness:** Horizant® causes somnolence/sedation and dizziness. Patients should be advised not to drive a car or operate other complex machinery until they have gained sufficient experience on Horizant® to assess whether Horizant® impairs their ability to perform these tasks. During the controlled trials in patients with RLS, somnolence/sedation was reported in 20% of patients treated with 600 mg of Horizant® per day compared with 6% of patients receiving placebo.
- **Lack of Interchangeability with Gabapentin**: Horizant® is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles. The same dose of Horizant® results in different plasma concentrations of gabapentin relative to other gabapentin products. The safety and effectiveness of Horizant® in patients with epilepsy have not been studied.
- **Suicidal Behavior and Ideation**: Horizant® (gabapentin enacarbil) is a prodrug of gabapentin, an antiepileptic drug (AED). AEDs increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Because Horizant® is a prodrug of gabapentin, Horizant® also increases this risk. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

ADVERSE REACTIONS: (≥10% and at least 2 times the rate of placebo)

- somnolence
- sedation
- dizziness

DRUG INTERACTIONS:

- Neither gabapentin enacarbil nor gabapentin are substrates, inhibitors, or inducers of the major cytochrome P450 enzymes.
- Gabapentin enacarbil is neither a substrate nor an inhibitor of P-glycoprotein *in vitro.*
- Pharmacokinetic drug-drug interaction studies were conducted to examine the potential for an interaction of gabapentin enacarbil with cimetidine and naproxen. No significant pharmacokinetic interactions were observed.
- No clinically relevant pharmacokinetic interactions are expected between Horizant® and other substrates of organic cation transporter type 2 (OCT2) and monocarboxylate transporter type 1 (MCT-1).

PATIENT COUNSELING INFORMATION:

- **Effects on Driving:** Patients should be told that Horizant® can cause significant driving impairment. Accordingly, they should be advised not to drive a car or until they have gained sufficient experience on Horizant® to assess whether Horizant® impairs their ability to drive. Patients should be told that it is not known how long this effect lasts.
- **Somnolence/Sedation and Dizziness:** Patients should be told that Horizant® can cause significant somnolence and dizziness. This typically resolves within several weeks of initiating treatment. Accordingly, they should be told not to operate dangerous machinery until they have gained sufficient experience on Horizant® to assess whether Horizant® impairs their ability to operate dangerous machinery safely.
- **Suicidal Behavior and Ideation:** Patients, their caregivers, and families should be counseled that Horizant® may increase the risk of suicidal thoughts and behavior, and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.
- **Lack of Interchangeability with Gabapentin:** Patients should be advised that doses of Horizant® and other gabapentin products are not interchangeable.
- **Dosing Instructions:** Patients should be instructed to take Horizant® only as prescribed. Horizant® should be taken once daily with food at about 5 PM. If the dose is not taken at the recommended time, the patient should take the next dose at about 5 PM the following day. Tablets should be swallowed whole and should not be cut, crushed, or chewed.

[1] Restless Legs Syndrome fact sheet http://www.ninds.nih.gov/disorders/restless_legs/detail_restless_legs.htm

[2] Horizant® label information. GlaxoSmithKline: Available Online at: http://us.gsk.com/products/assets/us_Horizant®.pdf

30 Day Notice to Prior Authorize Daliresp® (Roflumilast)

Oklahoma Health Care Authority
November 2011

Manufacturer	Forest Pharmaceuticals, Inc.
Classification	Phosphodiesterase Inhibitor
Status	Prescription Only

Summary[i]

Daliresp® (roflumilast) is indicated as a maintenance treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Roflumilast and its active metabolite (roflumilast N-oxide) are selective inhibitors of phosphodiesterase 4 (PDE4). Roflumilast's inhibition of PDE4 activity leads to accumulation of intracellular cyclic AMP. While the specific mechanism(s) by which roflumilast exerts its therapeutic action in COPD patients is not well defined, it is thought to be related to the effects of increased intracellular cyclic AMP in lung cells.

Roflumilast is marketed under the brand name Daxas® in other countries. The recommended dose is one 500 mcg tablet per day, with or without food. Patients should be informed that Daliresp® is not a bronchodilator and should not be used for the relief of acute bronchospasm.

The first two trials to evaluate efficacy showed roflumilast failed to demonstrate a significant reduction in the rate of COPD exacerbations when compared to placebo. Exploratory analyses of these trials identified a subpopulation of patients with severe COPD associated with chronic bronchitis and COPD exacerbations within the previous year that appeared to demonstrate a better response in the reduction of the rate of COPD exacerbations compared to the overall population. As a result, two subsequent trials were conducted that enrolled patients with severe COPD with chronic bronchitis, who experienced at least one COPD exacerbation in the previous year, and had at least a 20 pack-year smoking history. Both trials showed roflumilast once daily reduced the risk of excacerbation by 17% compared to placebo, which was a significant reduction[ii].

Currently, no treatments aside from lung transplantation have been shown to significantly improve lung function or decrease mortality. The goal of COPD management is to improve a patient's functional status and quality of life by preserving optimal lung function, improving symptoms, and preventing the recurrence of exacerbations. The GOLD[iii] treatment guideline currently recommends the use of the following:

1. Short acting bronchodilators
2. Long acting bronchodilators
3. Inhaled glucocorticoids
4. Long term oxygen therapy – consider surgical options

Theophylline is a non-specific phosphodiesterase inhibitor and is recommended as an adjunctive agent. Roflumilast has just been marketed and has yet to be included in treatment guidelines, but most likely

its place in therapy will be adjunctive. The most common side effects of roflumilast include diarrhea, weight loss, nausea, headache, back pain, flu-like symptoms, insomnia, dizziness, and decreased appetite. Serious adverse effects include mental health problems, including suicidal thoughts and behavior, and weight loss.

The estimated acquisition cost (EAC) of Daliresp® (roflumilast) is $6.07 per tablet which is approximately $182.10 per month.

Recommendations

The College of Pharmacy recommends prior authorization of Daliresp® (roflumilast) with the following approval criteria:

1. Diagnosis of COPD with history of chronic bronchitis; **and**
2. FEV </= 50% of predicted; **and**
3. Smoking history >/= 20 pack-years; **and**
4. Inadequately controlled on LABA therapy (must have 3 or more claims for a LABA-containing product in the previous 6 months)

PRODUCT DETAILS OF DALIRESP® (ROFLUMILAST)

FDA-APPROVED IN FEBRUARY 28, 2011

INDICATIONS: Daliresp® is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.

DOSAGE FORMS:

- Daliresp® is supplied as white to off-white, round tablets, embossed with "D" on one side and "500" on the other side. Each tablet contains 500 mcg of roflumilast.

ADMINISTRATION:

- The recommended dosage for patients with COPD is one 500 mcg tablet per day, with or without food.

CONTRAINDICATIONS:

- Patients with moderate to severe liver impairment (Child-Pugh B or C)

SPECIAL POPULATIONS:

- **Pregnancy Category C**:
  - Teratogenic effects: There are no adequate and well controlled studies of Daliresp® in pregnant women. Daliresp® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- **Labor and Delivery:** Daliresp® should not be used during labor and delivery. There are no human studies that have investigated effects of Daliresp® on preterm labor or labor at term; however, animal studies showed that Daliresp® disrupted the labor and delivery process in mice.
- **Nursing Mothers:** Daliresp® should not be used by women who are nursing.
- **Pediatric Use:** COPD does not normally occur in children. The safety and effectiveness of Daliresp® in pediatric patients have not been established.
- **Geriatric Use:** Based on available data for roflumilast, no adjustment of dosage in geriatric patients is warranted.
- **Hepatic Impairment:** Daliresp® is not recommended for use in patients with moderate or severe liver impairment (Child-Pugh B or C).
- **Renal Impairment:** No dosage adjustment is necessary for patients with renal impairment.

WARNINGS & PRECAUTIONS:

- **Treatment of Acute Bronchospasm:** Daliresp® is not a bronchodilator and should not be used for the relief of acute bronchospasm.
- **Pyschiatric Events including Suicidality:**
  - Treatment with Daliresp® is associated with an increase in psychiatric adverse reactions. In 8 controlled clinical trials 5.9% (263) of patients treated with Daliresp® 500 mcg daily reported psychiatric adverse reactions compared to 3.3% (137) treated with placebo. The most commonly reported psychiatric adverse reactions were insomnia, anxiety, and depression which were reported at higher rates in those treated with Daliresp® 500 mcg daily (2.4%, 1.4%, and 1.2% for Daliresp® versus 1.0%, 0.9%, and 0.9% for placebo, respectively). Instances of suicidal ideation and behavior, including completed suicide, have been observed in clinical trials. Three patients experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) while receiving Daliresp® compared to one patient (suicidal ideation) who received placebo.
  - Before using Daliresp® in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with Daliresp® in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other

mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with Daliresp® if such events occur.

- **Weight Decrease:** Weight loss was a common adverse reaction in Daliresp® clinical trials and was reported in 7.5% (331) of patients treated with Daliresp® 500 mcg once daily compared to 2.1% (89) treated with placebo. 7% of patients who received roflumilast compared to 2% of patients receiving placebo experienced severe (>10% body weight) weight loss. During follow-up after treatment discontinuation, the majority of patients with weight loss regained some of the weight they had lost while receiving Daliresp®. Patients treated with Daliresp® should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of Daliresp® should be considered.
- **Drug Interactions:** major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2. The administration of the cytochrome P450 enzyme inducer rifampicin resulted in a reduction in exposure, which may result in a decrease in the therapeutic effectiveness of Daliresp®. Therefore, the use of strong cytochrome P450 enzyme inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin) with Daliresp® is not recommended.

ADVERSE REACTIONS (Reported in >2%):

- Diarrhea
- Weight decreased
- Nausea
- Headache
- Back pain
- Influenza
- Insomnia
- Dizziness
- Decreased appetite

Adverse reactions at a frequency of 1 to 2% where rates exceed that in the placebo group include:

- Gastrointestinal disorders- abdominal pain, dyspepsia, gastritis, vomiting
- Infections and infestations- rhinitis, sinusitis, urinary tract infection
- Musculoskeletal and connective tissue disorders- muscle spasms
- Nervous system disorders- tremor
- Psychiatric disorders- anxiety, depression

DRUG INTERACTIONS:

- **Drugs that Induce Cytochrome P450 (CYP) Enzymes:** Strong cytochrome P450 enzyme inducers decrease systemic exposure to roflumilast and may reduce the therapeutic effectiveness of Daliresp®. Therefore the use of strong cytochrome P450 inducers (e.g., rifampicin, phenobarbital, carbamazepine, and phenytoin) with Daliresp® is not recommended.
- **Drugs that Inhibit Cytochrome P450 (CYP) Enzymes:** The co-administration of Daliresp® (500 mcg) with CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously (e.g., erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine) may increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit.
- **Oral Contraceptives Containing Gestodene and Ethinyl Estradiol:** The co-administration of Daliresp® (500 mcg) with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased side effects. The risk of such concurrent use should be weighed carefully against benefit.

PATIENT INFORMATION:

- **Bronchospam:** Daliresp® is not a bronchodilator and should not be used for the relief of acute bronchospasm.
- **Pyschiatric Events including Suicidality:**
  - Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with Daliresp® if such events occur.
- **Weight Decrease:** Patients treated with Daliresp® should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of Daliresp® should be considered.
- **Drug Interactions:** The administration of the cytochrome P450 enzyme inducer rifampicin resulted in a reduction in exposure which may result in a decrease in the therapeutic effectiveness of Daliresp®. Therefore, the use of strong cytochrome P450 enzyme inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin) with Daliresp® is not recommended.

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[i] **Daliresp®Label Information. Nycomed GmbH, a subsidiary of Forest Pharmaceuticals, Inc**. Available online at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=39625. Last revised February 2011.

[ii] Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet*. Aug 29 2009;374(9691):685-94.

[iii] http://www.goldcopd.org/

Appendix J

U.S. Department of Health & Human Services

FDA U.S. Food and Drug Administration

Drugs

FDA Drug Safety Communication: Safety review update of Chantix (varenicline) and risk of neuropsychiatric adverse events

Safety Announcement

[10-24-2011] The U.S. Food and Drug Administration (FDA) has reviewed the results from two FDA-sponsored epidemiological studies that evaluated the risk of neuropsychiatric adverse events associated with the smoking cessation drug Chantix (varenicline).

Neither study found a difference in risk of neuropsychiatric hospitalizations between Chantix and nicotine replacement therapy (NRT; e.g., NicoDerm patches). However, both studies had a number of study design limitations, including only assessing neuropsychiatric events that resulted in hospitalization, and not having a large enough sample size to detect rare adverse events (see Data Summary below for more information). Although these two studies did not suggest an increased risk of neuropsychiatric events that result in hospitalization, they do not rule out an increased risk of other neuropsychiatric events with Chantix.

Facts about Chantix (varenicline)

- A prescription medicine used to help adults quit smoking
- Increases the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo.
- Works by blocking the effects of nicotine (from smoking) on the brain.[1]
- From approval in May 2006 through July 2011, approximately 21.8 million Chantix prescriptions were dispensed and approximately 8.9 million patients received Chantix prescriptions from U.S. outpatient retail pharmacies.[2]

Healthcare professionals and patients should continue to follow the recommendations in the physician label and the patient Medication Guide, and to monitor for neuropsychiatric symptoms when prescribing or using Chantix. Based on FDA's assessment of currently available data, the Agency continues to believe that the drug's benefits outweigh the risks and the current warnings in the Chantix drug label are appropriate.

The risk of serious neuropsychiatric events with Chantix is currently highlighted in the Boxed Warning and Warnings and Precautions section of the physician label and in the patient Medication Guide. Such events can include changes in behavior, hostility, agitation, depressed mood, and suicidal thoughts or actions. These warnings were based on postmarketing reports describing changes in mood and behavior during and after Chantix use (see 2008 Public Health Advisory [1] and 2009 Public Health Advisory [2]).

FDA is continuing to evaluate the risk of neuropsychiatric events with Chantix. The drug manufacturer is conducting a large safety clinical trial of Chantix to assess neuropsychiatric adverse events, and results from this study are expected in 2017.

Additional Information for Patients

- Some patients have experienced changes in behavior, hostility, agitation, depressed mood, and suicidal thoughts or actions while using Chantix to help them quit smoking. Some patients had these symptoms soon after they began taking Chantix, and others developed them after several weeks of treatment, or after stopping Chantix.
- Before taking Chantix, patients should inform their healthcare professional if they have ever had depression or other mental health problems.
- If a patient develops agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for them, or if a patient develops suicidal ideation or behavior, they should immediately discontinue Chantix and report these symptoms to their healthcare professional.
- Patients should read the Medication Guide that they get along with their Chantix prescription. It explains the risks associated with the use of Chantix.
- Patients should report serious side effects from the use of Chantix to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of this page.

Additional Information for Healthcare Professionals

- Healthcare professionals should continue to follow the recommendations in the drug label when prescribing Chantix.
- Serious neuropsychiatric adverse events, including, but not limited to, depression, suicidal ideation, suicide attempt, and completed suicide, have been reported in patients taking Chantix.
- Healthcare professionals should ask patients about any history of psychiatric illness, especially depression, prior to initiating treatment with Chantix.
- Healthcare professionals should advise patients and caregivers that the patient should immediately stop taking Chantix and contact a healthcare professional if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior while taking or shortly after discontinuing Chantix.
- Healthcare professionals should encourage patients to read the Medication Guide they receive along with their Chantix prescription.
- Healthcare professionals should report adverse events involving Chantix to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of this page

Data Summary

FDA sponsored two observational studies of neuropsychiatric adverse events with Chantix. One was conducted by the Department of Veterans Affairs '(VA) Center for Medication Safety (VAMedSAFE), and the other by the Department of Defense's (DoD) U.S. Army Medical Command's Pharmacovigilance Center (PVC; hereafter referred to as the 'DoD study').

The VA study was a retrospective cohort study to evaluate the incidence of mental health hospitalizations among veterans using Chantix or nicotine replacement therapy (NRT). Patients starting Chantix or NRT between May 1, 2006 and September 30, 2007, but with no Chantix or NRT use in the previous year, were selected and matched in a 1:1 ratio by use of propensity scores (reflecting demographic characteristics, comorbidities, and psychiatric history). Propensity score matching is

a method of balancing patient characteristics between the treatment groups being compared. The study's main outcome was psychiatric hospitalization, with a coded primary discharge diagnosis for one of a number of psychiatric conditions, including drug-induced mental disorders, schizophrenic disorders, other psychotic disorders, depression, suicide attempts, and other mood disorders. Because the spontaneous adverse event reports for Chantix suggested a relatively short time to onset for psychiatric reactions, psychiatric hospitalizations for selected psychiatric diagnoses were assessed for 30 days after a prescription fill for Chantix or NRT.

The VA study population included 14,131 Chantix users and an equal number of NRT users. Among these patients, there were 16 psychiatric hospitalizations in Chantix-treated patients, and 21 in NRT patients. A Cox proportional hazards analysis showed no statistically significant difference in the risk of psychiatric hospitalization for Chantix users compared to NRT users (hazard ratio [HR] for Chantix/NRT = 0.76; 95% confidence interval [CI] 0.40-1.46). A complementary analysis in a prevalent user cohort of patients who had used NRT in the past before initiating Chantix or refilling an NRT prescription also showed no statistically significant difference in psychiatric hospitalizations between the two treatment groups. Also, the results using time periods longer than 30 days after a prescription fill were similar.

The DoD study was also a retrospective cohort study comparing the acute (30-day) rates of hospitalizations for neuropsychiatric adverse events among new users of Chantix (n=19,933) and NRT patch (n=15,867) who started therapy from August 1, 2006 to August 31, 2007 in the Military Health System. Patients were drawn from active duty military personnel, military retirees, and the dependents of either. Chantix users were matched using propensity scores to NRT users, with subgrouping by concomitant use of the prescription smoking cessation drug bupropion. After propensity score matching, there were 11,978 Chantix users and an equal number of NRT users in the study sample. The main outcome was a primary hospital discharge diagnosis for a neuropsychiatric condition. The following neuropsychiatric diagnoses were identified using ICD-9 codes: drug-induced mental disorders, transient mental disorders, schizophrenia, episodic and mood disorders, delusional disorders, other nonorganic psychoses, anxiety disorders, personality disorders, posttraumatic stress disorder (PTSD), depressive disorders, and suicide attempt.

In the DoD study's propensity score matched samples, there were 18 psychiatric hospitalizations among Chantix users and 16 among NRT users. A Cox proportional hazard analysis did not show a statistically significant difference (HR for Chantix/NRT = 1.13; 95% CI 0.57-2.21). There was also no significant difference in psychiatric hospitalizations for Chantix users compared to NRT users when patients with concomitant bupropion use were excluded (HR = 0.91; 95% CI 0.39-2.14). Most (43) of the 55 neuropsychiatric hospitalizations (18 of the 23 Chantix events and 25 of the 32 NRT events) occurred in patients with a neuropsychiatric diagnosis in the year preceding the Chantix/NRT prescription fill, although such patients were a minority of the cohorts. Among patients with a neuropsychiatric diagnosis in the preceding year, 0.7% of Chantix users and 1.4% of NRT users were hospitalized for psychiatric care.

A strength of both studies was the inclusion of patients with pre-existing psychiatric disorders, since these patients were typically excluded from the clinical trials conducted with Chantix before it was approved (i.e., in premarketing trials).

Although neither study found a measurable increase in psychiatric hospitalizations with Chantix versus NRT, these results should be interpreted with the limitations of both studies in mind. The sample sizes in both studies were too small to assess rare, idiosyncratic events. Focusing on psychiatric hospitalizations is a useful approach for assessing the risk of serious neuropsychiatric adverse events, but it does not allow an assessment of less severe neuropsychiatric events that did not result in a psychiatric hospitalization (in the periods studied). Although the studies did not find a difference in psychiatric hospitalization risk between Chantix and NRT, they do not exclude the possibility that both treatments carry a similar risk. In addition, the VA study did not include PTSD as a reason for psychiatric hospitalization; one published report suggested that patients with PTSD may be more susceptible to the neuropsychiatric adverse effects of Chantix.[3] Also, the DoD study only assessed a 30-day risk period following the fill date of the first qualifying prescription for Chantix or NRT and did not evaluate the rate of neuropsychiatric hospitalizations occurring over a longer duration following a Chantix prescription fill.

Overall, FDA has determined that the current warnings in the Chantix drug label, based on postmarketing surveillance reports, remain appropriate.

FDA is continuing to evaluate the risk of neuropsychiatric adverse events with Chantix. The manufacturer of Chantix, Pfizer, is conducting a large safety clinical trial of Chantix to assess neuropsychiatric adverse events as outcomes. Results from this trial are expected in 2017.

References

1. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US). Drug & Supplements Monograph: Varenicline. Available from: http://www.nlm.nih.gov/medlineplus/druginfo/meds/a606024.html[3]. Accessed September 6, 2011.
2. SDI, Vector One®: National (VONA) and Total Patient Tracker (TPT). May 2006-July 2011. Data extracted September 2011.
3. Campbell AR, Anderson KD. Mental health stability in veterans with posttraumatic stress disorder receiving varenicline. Am J Health Syst Pharm. 2010;67:1832-7.

Related Information

- Public Health Advisory: FDA Requires New Boxed Warnings for the Smoking Cessation Drugs Chantix and Zyban[4]
  7/1/2009
- Public Health Advisory: Important Information on Chantix (varenicline)[5]
  issued 2/1/2008; updated 5/16/2008
- Varenicline (marketed as Chantix) Information[6]

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2. /Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm169988.htm
3. http://www.nlm.nih.gov/medlineplus/druginfo/meds/a606024.html

U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Safety

Stimulant Medications used in Children with Attention-Deficit/Hyperactivity Disorder - Communication about an Ongoing Safety Review

Products involved include: Focalin, Focalin XR (dexmethylphenidate HCl); Dexedrine, Dexedrine Spansules, Dextroamphetamine ER, Dextrostat (dextroamphetamine sulfate); Vyvanse (lisdexamfetamine dimesylate); Desoxyn (methamphetamine); Concerta, Daytrana, Metadate CD, Metadate ER, Methylin, Methylin ER, Ritalin, Ritalin-LA, Ritalin-SR (methylphenidate); Adderall, Adderall XR (mixed salts amphetamine); Cylert (pemoline) and generics.

[UPDATED 11/01/2011] FDA notified the public that a large, recently-completed study in children and young adults treated with medication for Attention-Deficit/Hyperactivity Disorder (ADHD) has not shown an association between use of certain ADHD medications and adverse cardiovascular events. FDA continues to recommend that healthcare professionals prescribe these medications according to the professional prescribing label. See the Data Summary of the FDA Drug Safety Communication for more information.

Audience: Pediatricians, Neuropsychiatric healthcare professionals

[Posted 06/15/2009] FDA notified healthcare professionals that it is providing its perspective on study data published in the American Journal of Psychiatry on the potential risks of stimulant medications used to treat Attention-Deficit/Hyperactivity Disorder (ADHD) in children. This study, funded by the FDA and the National Institute of Mental Health (NIMH), compared the use of stimulant medications in 564 healthy children from across the United States who died suddenly to the use of stimulant medications in 564 children who died as passengers in a motor vehicle accident.The study authors concluded that there may be an association between the use of stimulant medications and sudden death in healthy children. Given the limitations of this study ŝ methodology, the FDA is unable to conclude that these data affect the overall risk and benefit profile of stimulant medications used to treat ADHD in children. FDA believes that this study should not serve as a basis for parents to stop a child ŝ stimulant medication. Parents should discuss concerns about the use of these medicines with the prescribing healthcare professional. Any child who develops cardiovascular symptoms (such as chest pain, shortness of breath or fainting) during stimulant medication treatment should immediately be seen by a doctor.

FDA is continuing its review of the strengths and limitations of this and other epidemiological studies that evaluate the risks of stimulant medications used to treat ADHD in children. FDA and the Agency for Healthcare Research and Quality are sponsoring a large epidemiological study that will provide further information about the potential risks associated with stimulant medication use in children. The data collection for this study will be complete later in 2009.

[11/01/2011 - Drug Safety Communication: Safety Review Update of Medications Used to Treat Attention-Deficit/Hyperactivity Disorder (ADHD) [1] - FDA]

[06/15/2009 - Communication About An Ongoing Safety Review [2] - FDA]
[06/15/2009 - News Release [3] - FDA]
[06/15/2009 - Stimulant Medications Prescribing Information, Medication Guides [4] - FDA]

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4. /Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107918.htm

U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Safety

Birth Control Pills Containing Drospirenone: Possible Increased Risk of Blood Clots

[UPDATED 10-27-2011] FDA notified healthcare professionals of release of the final report of the FDA-funded study that evaluated the risk of blood clots in users of several different hormonal contraceptives. The link is provided below. FDA's review of the results of this study, specifically those results related to drospirenone-containing birth control pills, will be presented and discussed at the joint meeting of the Reproductive Health Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on December 8, 2011.

[UPDATED 09/26/2011] FDA has not yet reached a conclusion, but remains concerned, about the potential increased risk of blood clots with the use of drospirenone-containing birth control pills. FDA has completed its review of the two 2011 studies that evaluated the risk of blood clots for women who use drospirenone-containing birth control pills. FDA is continuing its review of a separate FDA-funded study that evaluated the risk of blood clots in users of several different hormonal birth control products (contraceptives). Preliminary results of the FDA-funded study suggest an approximately 1.5-fold increase in the risk of blood clots for women who use drospirenone-containing birth control pills compared to users of other hormonal contraceptives.

Given the conflicting nature of the findings from six published studies evaluating this risk, as well as the preliminary data from the FDA-funded study FDA has scheduled a joint meeting of the Reproductive Health Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on December 8, 2011 to discuss the risks and benefits and specifically the risk of blood clots of drospirenone-containing birth control pills.

[Posted 05/31/2011]

AUDIENCE: OBGYN, Family Practice, Patient

ISSUE: FDA is aware of two newly published studies that evaluated the risk of venous thromboembolism (VTE) in women who use birth control pills that contain drospirenone. The two recently published studies looked at whether there is a higher risk of blood clots in women taking birth control pills containing the progestin drospirenone when compared to similar women taking birth control pills containing a different progestin called levonorgestrel. These two new studies reported that there is a greater risk of VTE associated with birth control pills that contain drospirenone. This risk is reported to be up to 2 to 3 times greater than the risk of VTE associated with using levonorgestrel-containing pills. Other studies have not reported an increase in risk. The FDA is currently evaluating the conflicting results from these studies and will look at all currently available information to fully assess the risks and benefits of drospirenone-containing birth control pills. FDA will continue to communicate any new safety information to the public as it becomes available. Read the drug safety communication for more information on these studies.

BACKGROUND: Drospirenone is a type of female sex hormone called a progestin. Most birth control pills contain two types of hormones--estrogen and progestin. Birth control pills work by preventing the release of eggs from the ovaries (ovulation) and changing the cervical mucus and the lining of the uterus to prevent pregnancy. Brand names of drospirenone-containing products include Yaz (generics Gianvi and Loryna), Yasmin (generics Ocella, Syeda, and Zarah), Beyaz, and Safyral.

RECOMMENDATION: If your birth control pill contains drospirenone, do not stop taking it without first talking to your healthcare professional. Contact your healthcare professional immediately if you develop any symptoms of blood clots, including persistent leg pain, severe chest pain, or sudden shortness of breath. If you smoke and are over 35 years of age, you should not take combination oral contraceptives because they increase the risk that you could experience serious cardiovascular events, including blood clots.

Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program:

- Complete and submit the report Online: www.fda.gov/MedWatch/report.htm
- Download form [1] or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178

[10/27/2011 - Report: Combined Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints [2] - FDA]
[09/26/2011 – Drug Safety Communication [3] - FDA]
[09/26/2011 – Questions and Answers [4] – FDA]
[05/31/2011 – Drug Safety Communication [5] - FDA]
[05/31/2011 – Questions and Answers [6] - FDA]

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5. /Drugs/DrugSafety/ucm257164.htm
6. /Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm257175.htm

U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Safety

Zyvox (linezolid): Drug Safety Communication - Serious CNS Reactions Possible When Given to Patients Taking Certain Psychiatric Medications

[UPDATED 10/21/2011] The FDA updated information on the potential drug interaction between linezolid and serotonergic psychiatric medications. Not all serotonergic psychiatric drugs have an equal capacity to cause serotonin syndrome with linezolid. Most cases from the FDA's Adverse Event Reporting System (AERS) of serotonin syndrome with linezolid occurred in patients taking specific serotonergic psychiatric drugs, namely a selective serotonin reuptake inhibitor (SSRI) or a serotonin norepinephrine reuptake inhibitor (SNRI). It is unclear at this time whether linezolid administration in patients receiving other psychiatric drugs with lesser degrees of serotonergic activity poses a comparable risk.

FDA will update the public when new information is available.

[Posted 07/26/2011]

AUDIENCE: Infectious Disease, Psychiatry, Family Practice

ISSUE: FDA has received reports of serious central nervous system (CNS) reactions when the antibacterial drug linezolid (Zyvox) is given to patients taking psychiatric medications that work through the serotonin system of the brain (serotonergic psychiatric medications. A list of the serotonergic psychiatric medications that can interact with linezolid can be found in the Drug Safety Communication. Safety information about this potential drug interaction and important drug usage recommendations for emergency and non-emergency situations are being added to the drug labels for serotonergic psychiatric medications and linezolid.

BACKGROUND: Linezolid is used to treat infections, including pneumonia, infections of the skin, and infections caused by a resistant bacterium (Enterococcus faecium). It is a reversible monoamine oxidase inhibitor (MAOI). Although the exact mechanism of this drug interaction is unknown, linezolid inhibits the action of monoamine oxidase A — an enzyme responsible for breaking down serotonin in the brain. It is believed that when linezolid is given to patients taking serotonergic psychiatric medications, high levels of serotonin can build up in the brain, causing toxicity. This is referred to as Serotonin Syndrome — signs and symptoms include mental changes (confusion, hyperactivity, memory problems), muscle twitching, excessive sweating, shivering or shaking, diarrhea, trouble with coordination and/or fever.

A separate Drug Safety Communication (DSC) is being released today for methylene blue due to similar potential drug interactions with serotonergic psychiatric medications and includes drug usage recommendations.

RECOMMENDATION: Linezolid should generally not be given to patients taking serotonergic drugs. However, there are some conditions that may be life-threatening or require urgent treatment with linezolid such as when:

- Linezolid is used to treat vancomycin-resistant Enterococcus faecium (VRE) infections.
- Linezolid is used to treat infections such as nosocomial pneumonia and complicated skin and skin structure infections, including cases caused by methicillin-resistant Staphylococcus aureus (MRSA).

Patients should not stop taking their serotonergic psychiatric medicine without first talking to a healthcare professional. Read the Drug Safety Communication for other specific recommendations for Healthcare Professionals and for Patients.

Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program:

- Complete and submit the report Online: www.fda.gov/MedWatch/report.htm [1]
- Download form [2] or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178

[10/21/2011 - Drug Safety Communication [3] Update - FDA]
[07/26/2011 – Drug Safety Communication [4] - FDA]

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