Drug Utilization Review Board

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

Wednesday
September 14, 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 – September 14, 2011

DATE: September 8, 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 September meeting. Material is arranged in order of the Agenda.

Call to Order

Public Comment Forum

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

Update on DUR / MCAU Program – See Appendix B.

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

Action Item – Vote to Prior Authorize Xiaflex® – See Appendix D.

Action Item – Vote to Prior Authorize Berinert®, Cinryze®, and Kalbitor® – See Appendix E.

30 Day Notice to Prior Authorize Firazyr® – See Appendix F.

60 Day Notice to Prior Authorize Biologic Products for the Treatment of Rheumatoid Arthritis, Crohn's Disease, Plaque Psoriasis, and Ankylosing Spondylitis – See Appendix G.

Drug Utilization Review of Multiple Sclerosis Medications – See Appendix H.

Action Item – Annual Review of Synagis® – See Appendix I.

FDA and DEA Updates – See Appendix J.

Future Business

Adjournment

Oklahoma Health Care Authority
Drug Utilization Review Board
(DUR Board)
Meeting – September 14, 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. August 10, 2011 DUR Minutes – Vote
- B. August 11, 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. Retrospective Drug Utilization Review for May 2011
- B. Retrospective Drug Utilization Review Response for April 2011
- C. Medication Coverage Activity Audit for August 2011
- D. Pharmacy Help Desk Activity Audit for August 2011

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

5. Action Item – Vote to Prior Authorize Diabetes Medications – See Appendix C.
- A. COP Recommendations

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

6. Action Item – Vote to Prior Authorize Xiaflex® – See Appendix D.
- A. COP Recommendations

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

7. Action Item – Vote to Prior Authorize Berinert®, Cinryze®, and Kalbitor® – See Appendix E.
- A. Drug Information
- B. COP Recommendations

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

8. 30 Day Notice to Prior Authorize Firazyr® – See Appendix F.

A. Product Summary
B. COP Recommendations
E. Product Details

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

9. 60 Day Notice to Prior Authorize Biologic Products for the Treatment of Rheumatoid Arthritis, Crohn's Disease, Plaque Psoriasis, and Ankylosing Spondylitis – See Appendix G.

A. Member Demographics
B. Market Analysis by Claims and Indication
C. Product Costs
D. Market News and Updates
E. Economic Impact
F. COP Recommendations

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

10. Drug Utilization Review of Multiple Sclerosis Medications – See Appendix H.

A. Treatment of Multiple Sclerosis
B. Utilization Review
C. Market Trends
D. Other Considerations in Treatment of Multiple Sclerosis
E. COP Recommendations

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

11. Action Item – Annual Review of Synagis® – See Appendix I.

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

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

12. FDA and DEA Updates – See Appendix J.

13. Future Business

A. Annual Review of Pediculicides
B. Annual Review of Ophthalmic Antibiotics
C. New Product Reviews
D. Medical Product Reviews

14. Adjournment

Appendix A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES of MEETING of AUGUST 10, 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): Casey Woodson	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	
Howard Pallotta, J.D.; Director of Legal Services		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:		
Donna Erwin, Bristol-Myers Squibb	Ainslie Hatch, Bristol-Myers Squibb	Russ Rainwater, Bristol-Myers Squibb
Monica Iacobucci, AstraZeneca	Eric Gardner, Ventex	Warren Tayes, Merck
Don Kempin, Novo Nordisk	Toby Thompson, Pfizer	Richard Ponder, Johnson & Johnson
Ben Liniger, Alcon	Charlene Kaiser, Amgen	Dave Gibson, Amgen
Jeff Himmelberg, GlaxoSmithKline	Dwayne Dossett, Alkermes	Linda Canto, Bristol-Myers Squibb
Jim Chapman, Abbott	Gary Riley, Abbott	Cher Golding, Mental Health Assoc of Central Okla.
Sam Smothers, MedImmune	James Osborne, GlaxoSmithKline	Cheri Ritchie, Bristol-Myers Squibb
Brian Maves, Pfizer	David Williams, Forest	Jim Dunlap, Eli Lilly
Wayne McLeod, NAMI Oklahoma	David <unreadable>, Janssen	Monica Guillory, Novartis
John Omick, NPC	Tracey Cern, Otsuka	

PRESENT FOR PUBLIC COMMENT:		
Agenda Item No. 6	Julleah Johnson, Asstra Zeneca	
Agenda Item No. 7	Tyrone McBayne, Takeda Pharmaceuticals	Russ Rainwater, Bristol-Myers Squibb
	Harvey Schuck, Merck	Mike Ketcher, Novo Nordisk
Agenda Item No. 10	Courtney Walker, Janssen	David Gibson, Amgen

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 speaker for public comment:

Agenda Item No. 6	Julleah Johnson, Astra Zeneca	
Agenda Item No. 7	Tyrone McBayne, Takeda Pharmaceuticals	Russ Rainwater, Bristol-Myers Squibb
	Harvey Schuck, Merck	Mike Ketcher, Novo Nordisk
Agenda Item No. 10	Courtney Walker, Janssen	David Gibson, Amgen

ACTION: NONE REQUIRED

AGENDA ITEM NO. 3: APPROVAL OF DUR BOARD MINUTES

3A: June 8, 2011 DUR Minutes

Dr. Bell moved to approve as submitted; seconded by Ms. Varalli-Claypool.

ACTION: MOTION CARRIED

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

4A: Retrospective Drug Utilization Review: April 2011

4B: Retrospective Drug Utilization Review Response: March 2011

4C: Medication Coverage Activity Audit: June, July 2011

4D: Pharmacy Help Desk Activity Audit: June, July 2011

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

ACTION: NONE REQUIRED

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

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

Dr. Preslar moved to approve as submitted; seconded by Ms. Varalli-Claypool.

ACTION: MOTION CARRIED

AGENDA ITEM NO. 6: ANNUAL REVIEW OF ATYPICAL ANTIPSYCHOTICS

For Public Comment; Julleah Johnson: Good evening ladies and gentlemen of the DUR committee. My name is Julleah Johnson and I'm with AstraZeneca medical affairs. I'm here to represent Seroquel XR and Seroquel. We have some updates since the last meeting and it all has to do with respect to the safety for both products, Seroquel XR and Seroquel. These are in four general areas. First the non-teratogenic effects on neonates that were exposed to types of Seroquel during the third trimester of pregnancy and labeling was applied to all drugs in the class back in December. Second general change in the label refers to the expanded language, a little bit of expanded language on hyperglycemia, hyperlipidemia and weight gain. And then we have some additional information on QT prolongation as well as hypothyroidism so I'm here just to answer any questions that you might have and if you don't have any ……..

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

Dr. Kuhls moved to approve with the addition of second opinion reviews for 5-year olds; seconded by Ms. Varalli-Claypool.

ACTION: MOTION CARRIED

AGENDA ITEM NO. 7: 30-DAY NOTICE TO PRIOR AUTHORIZE DIABETES MEDICATIONS

For Public Comment; Tyrone McBayne: Good evening ladies and gentlemen. I hope you guys are doing well today. My name is Tyrone McBayne. I'm a clinical science and outcomes manager with Takeda Pharmaceuticals and I'm here representing Actos. As you guys are well aware, Actos has a long track record of servicing the lives of millions of patients with diabetes. However, over the past year or so, the TZ class have garnered significant amount of press. Most of this press has been in relationship to CV, cardiovascular safety, as well as with bladder cancer concerns. Now because of all these concerns I wanted to make myself available here today to answer any questions that you guys may have regarding these concerns. So with that said, if you guys have any questions regarding these concerns …….

Dr. Muchmore: I have a question. Pioglitazone has been shown to be highly effective and useful in pre-diabetes and those with pre-diabetes are a lot less likely to have congestive heart failure, renal failure problems. Is your company applying for FDA approval for the indication pre-diabetes?

Mr. McBayne: As far as I'm aware, no. I'm sure you're familiar with the ACT NOW study and of course pioglitazone is going off patent next year. So as far as I'm aware that's ……..

Dr. Muchmore: Oh, it's going off patent? There'll never be an indication then.

For Public Comment; Russ Rainwater: Good afternoon, or good evening. I'm Dr. Russ Rainwater with Bristol-Myers Squibb and I'm here today just to speak and answer any questions you might have around Onglyza or Kombiglyze which is the combination of once-a-day Metformin XR with saxagliptin. I have reviewed your proposals for over the next couple of months in terms of managing the diabetes class and first of all I want to say, as our company fully supports a generic first policy, both through our clinical trials program with saxagliptin and also our commercial program with our sales reps, how they position our products in the marketplace. First of all, a quick review, a couple of the package insert updates to Onglyza that have occurred over the last few months. Just to review, the Onglyza or saxagliptin is a DPP-4 inhibitor which is indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes and multiple clinical settings (and I refer you to the PI). Of course, important indications of use are should not be used with Type 1 diabetes or the treatment of diabetic ketoacidosis. Our clinical trial program before the product was brought was fairly large. It was over 4,000 patients with Type 2 in multiple settings. This is an add-on to Metformin initial combination with Metformin, in combination with TZD's and also in combination with sulfonylureas, so it has a broad base of clinical applications in Type 2 diabetes. In terms of the effectiveness, if one adds on saxagliptin or Onglyza to Metformin, you can expect reductions in A1C additional to Metformin on the order of .6 with a 2.5 mg dose, .7% reduction with a 5 mg dose, compared to Metformin. In terms of using it in combination with Metformin as initial treatment in treatment naïve patients and those patients in our clinical trial program had A1C's ranging between 8 and 12 and again, using this combination it was very effective in reducing A1C. Clinically meaningful reductions in A1C, fasting plasma glucose and postprandial glucose. In terms of the overall safety profile the discontinuation rates were very similar to what you see with placebo and the overall adverse event profile was very similar to what you saw with placebo. Couple of new information in the PI to bring to your attention is now can be safely, the 2.5 mg dose in patients with renal dysfunction the initial label for Onglyza was for patients who had a creatinine, calculated creatinine clearance of 50 mL/per minute or less would reduce to the 2.5 dose and now with the clinical data that we have, if you have data support showing efficacy and safety in this subpopulation for renal dysfunction. Additionally we've got data now, long term data in combination of saxagliptin and Metformin compared to glipizide and Metformin for a period of a year to a non-inferiority trial showing equal efficacy versus the sulfonylurea without the downside of hypoglycemia. The hypoglycemia that we saw with the glipizide arm was 30%, around 8% with the saxagliptin arm, so it shows the all-around mechanism of DPP-4 as being safe and also being glucose dependent without the propensity of hypoglycemia. We also have the Kombiglyze XR which is the, right now currently, the only DPP-4 with once a day Metformin XR combination that is available in the marketplace. With that, I'd be glad to answer any questions if you have any.

For Public Comment; Harvey Schuck: I want to thank you very much. Dr. Muchmore, Dr. Graham, members of the committee, allowing me to represent Merck and make a few salient points about sitagliptin either with or without Metformin. That's Januvia or Janumet. My colleague from BMS has covered a number of the important points and I don't need to disagree with anything that he said. I think in that sense of it, the information applies to both of these members of the DPP-4 class. I would like to make a couple of points though. Some that apply to the class and some I think that apply uniquely to sitagliptin. First, I'm a Merck physician. Also, I've been ED director and emergency physician for 20 years and my observation is that patients, diabetic patients get into trouble, frequently don't take their medication. Patients in general frequently don't take their medication. But these patients get into trouble because they don't take their medication. One of the principal reasons they don't take their medication is they don't feel good when they take their medication and especially if they take an oral agent and the hypoglycemic episodes, they're much more less likely to take those medications. So sitagliptin which does not produce hypoglycemia unless it's combined with an agent which has a tendency to produce hypoglycemia and then of course, you get only the expect amount of hypoglycemia; but as a monotherapy that does not produce hypoglycemia and in our trials when we compared it to glipizide we did a 52-week trial which was what the pharmacologic companies call non-inferiority trial to show that it was as effective and the efficacy was quite similar but interestingly we have the same results as BMS', that the patients in that trial, about 35% in our trial versus 5%, that is 35% of the patients who were on glipizide had hypoglycemic episodes versus 5% on sitagliptin and if you look at the numbers of hypoglycemic episodes, not just the proportion of patients affected, it's about 12 to 1, so it's safer. Now another important safety feature, and Merck has had Januvia approved since 2006, is that we've had 10,000 patients at our clinical trials. There have been 19 randomized clinical trials, and in those clinical trials we've had at least 5,000 patients that had up to a 2-year exposure to sitagliptin. So if you compare the control groups in those trials on various antihyperglycemic agents versus the sitagliptin arm, you don't find any difference in adverse events, serious adverse events, of cardiac events, GI symptoms, malignancies, pancreatitis or fractures, or decreases in creatinine clearance or diminished hepatic function. So this is a product with a long safety record and another important thing is that we have a trial that justifies the use of sitagliptin with insulin. And these are a particularly difficult group of patients to treat as you might imagine, and in that trial, these patients had an average duration of diabetes of some 12 years, they were on about 50 units a day of insulin and when you added sitagliptin, you're still able to produce an additional 0.6% decrease in their A1-C. Now you know this is a situation where it's very difficult to get additional A1-C lowering in patients who have long-term diabetes who are on insulin. So we have an indication for that. I think it's something that the committee may want to consider. I'd be very happy to answer any questions you might have about sitagliptin, and if I might add, as an emergency physician, I'm highly chagrined to hear that ER doctors are giving antiemetics to young children when in the ER. The standard of care in my humble opinion, in emergency medicine, is to use Odansetron in the emergency department and you may be able to decrease the admission rate but not to give these kids antiemetics. That's, I consider that dangerous. Thanks very much.

For Public Comment; Mike Ketcher: Dr. Muchmore, Dr. Graham, ladies and gentlemen of the committee. Thank you for allowing us the opportunity to comment tonight. Very similar to the previous speakers, I just wanted to acknowledge that I understand how your rebating and pricing works to move the product from Tier 3 to Tier 2, and that it depends upon the rebate structure, etcetera, and I also concur with the previous speakers that the very evidence based algorithm the College of Pharmacy's came up with in support of these medications. The purpose and reason that I wanted to address the committee tonight was to just point out a couple of differences in the clinical development of Victoza or liraglutide relative to the other GLP-1 emetics or DPP-4 inhibitors that are currently on the market. Similar to the previous speakers and the category our clinical development program have also evaluated over several thousand patients, over 4,400 patients in our lead clinical trial program. One of the differences of our lead program relative to the other DPP-4 inhibitor programs, we actually conducted head-to-head randomized controlled clinical trials, the first of which was against the exenatide or Byetta, the second of which is against Januvia or sitagliptin. So the first study I'd like to address is what we call the LEAD-6 study. It's published in The Lancet, included over 500 patients at 132 sites for a

randomized period of 26 weeks. At the end of that 26 week randomized controlled clinical trial period, patients randomized to Victoza or liraglutide compared to exenatide had a significant reduction in A1-C, significantly better reduction in fasting plasma glucose. A greater percentage of patients achieved an ADA goal of less than 7 and a significantly greater percentage of patients achieved the ACE goal of less than 6.5. Also the patients that were randomized to Victoza had a significant improvement in fasting plasma glucose. There was no difference in weight loss, no difference in the rate of hypoglycemia during the randomized phase and those patients at the end of 26 weeks that were randomized to Byetta or exenatide could then go over to an extension study and go on the liraglutide for an additional 14 weeks. One of the most common questions our medical information department receives is, I have a patient on exenatide and may or may not be at the goal I want them to be on, they want to move from twice a day to once a day, they're not tolerating, etc.; how would I switch them from exenatide to liraglutide. The purpose of this study at the end of the 26 weeks was to cross them over, give the patients the option. Those patients that were on exenatide that crossed over to liraglutide at the end of 26 weeks, they subsequently went on to have a significant reduction in A1-C, significant improvement in fasting plasma glucose, and lost more weight than if they were on exenatide throughout the randomized phase. The liraglutide to liraglutide treated patients continue to have improvement in A1-C, they did lose more weight and they had better control of fasting plasma glucose. The second study that is not part of our label at this time, however it's important for the committee to know, when you have randomized controlled trials of active comparators you very rarely get a chance to make those comparisons. The pharmaceutical industry oftentimes will not do head-to-head comparisons and I've heard from previous meetings of this committee that you like this information and request this information. We feel like it's our obligation to provide it to you since you may or may not have received this update. The second study I wanted to talk about is Victoza or liraglutide at both doses, 1.2 or 1.8 mg/day compared to Januvia 100 mg/day. Randomized controlled trial phase was 26 weeks, similar to what I presented with the exenatide study, patients that were randomized to liraglutide had significant improvements in A1-C, fasting plasma glucose, twice as many patients achieved their ADA goal of less than 7, three times as many patients achieved their ACE goal of less than 6.5, with a significant reduction in weight of about 7 ½ pounds, relative to about 2.1 pounds with the oral DPP-4 inhibitor. There was a composite endpoint, a secondary endpoint of this study which was an A1-C of less than 7, no weight gain and no hypoglycemia; 46% of the patients that were randomized to Victoza achieved that versus 14% of the patients that were randomized to sitagliptin or Januvia. There was no difference in the rate of hypoglycemia between the agents. It was hovering around 5%. It's important to point out that in both these studies; all patients were on background Metformin therapy at approved and labeled doses of Metformin. At the beginning of this second study that I'm discussing comparing Victoza to Januvia, there was a difference in GI tolerability for the first 12 to 14 weeks favoring Januvia. At the end of the 26 weeks randomized controlled period there was no difference in the way the patients tolerated liraglutide or sitagliptin. Additionally, this trial was opted for a 26-week extension, which took this data out to 52 weeks and again, to what you saw in the first, to those patients in this study, sitagliptin, the sitagliptin, liraglutide, the liraglutide, they continued out to a year and the durability that was shown at week 26 with the efficacy parameters and safety parameters, I've already verbalized, both post true out at the end of 52 weeks. So in summary, against two agents that are up for evaluation in the Tier 3 class, one from the DPP-4, one from the GLP mimetic, liraglutide was studied. All these trials were published, both of them in The Lancet, demonstrating the efficacy of liraglutide over the active comparators of DPP-4 inhibitors and GLP mimetics. So with that I'll close and be happy to take any questions the committee may have.

Dr. Muchmore: I have one question. Is Novo Nordisk doing any studies on liraglutide in pre-diabetes?

Dr. Ketcher: Novo Nordisk has a clinical program in metabolic syndrome pre-diabetes which would also include obesity or weight loss but I'm not privileged to have any of those results, data, dosing intervals, etc.

Dr. Muchmore: Right, but is there an on-going trial?

Dr. Ketcher: There is numerous trials looking at it specifically in that metabolic syndrome currently underway in the U.S. and ex-U.S.

Dr. Kuhls: What's your comments about liraglutide being better than the other two?

Dr. Muchmore: In that head-to-head study it was a little better. Now will it be better than Bydureon which is the once a week exenatide …. don't know, stay tuned.

Dr. Kuhls: So do you think that's a great improvement that you should consider that different when you're talking about supplemental rebates, or are we talking about relatively very small clinical differences that are statistical but not very important.

Dr. Muchmore: It's a small clinical difference.

Dr. Kuhls: So you think it's a small difference.

Dr. Muchmore: And then this whole scene will you know, rapidly change as new things become available.

Dr. Kuhls: I just want to make sure that when I hear that one drug ……..

Dr. Muchmore: You have a drug that you have to remember to take twice a day, that's been our biggest problem with exenatide is getting people to actually take the stupid drug twice a day instead of once a day.

Dr. Preslar: The other drawback's injectable versus oral.

Dr. Muchmore: Yeah and not everybody's eager to take an injectable.

Dr. Kuhls: Since I don't do these drugs do you think those are factors that we need to take into account before we supplementally rebate them as all equal?

Dr. Muchmore: They all have a choice of DPP-4 or GLP-1 in the second tier, so they don't have to choose injectable if they choose not to.

Dr. Knisely: So they'll be a DPP-4 in Tier 2 as well as a GLP-1 ……

Dr. Muchmore: Right. We separated them so they'll be one of each because where ever possible we like to remember that people have different needs, wants and lifestyles and they are people.

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

ACTION: NONE REQUIRED

AGENDA ITEM NO. 8: 30-DAY NOTICE TO PRIOR AUTHORIZE BERINERT®, CINRYZE® AND KALBITOR®

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

ACTION: NONE REQUIRED

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

AGENDA ITEM NO. 10: DRUG UTILIZATION REVIEW OF BIOLOGIC PRODUCTS FOR THE TREATMENT OF RHEUMATOID ARTHRITIS, CROHN'S DISEASE, PLAQUE PSORIASIS AND ANKYLOSING SPONDYLITIS

For Public Comment; David Gibson: I'd like to thank the Board for a few minutes of your time. It's David Gibson. I'm a microbiologist with medical affairs of Amgen and we really appreciate the depth and detail of the DUR. We want to add a couple of points to it, then answer any questions if I can regarding Etanercept or Enbrel which you have. And the main point, both these points have to do with the fact that this is really one of the anti-TNF's. It's a very unique drug. It works and it does brilliant things. The first point is there are no neutralizing antibodies against this drug so no antibodies formed by the body to reduce the effective dose. You don't have that. The second thing is its' mechanism of action uses natural receptors to bind to the TNF that is monovalent reversible and it's binding as opposed to antibody binding which would be divalent, essentially irreversible. So they're all mixed in there together. I know we're looking at the outcomes but they are very definitely different. This is distinctively different from all the other anti-TNF that has been discussed. So, any questions I can answer or anything?

For Public Comment; Courtney Walker: Good evening. My name is Courtney Walker. I'm a PharmD with Janssen Pharmaceuticals and I'm here on behalf of Remicade, Stelara and Simponi. I yield my time back to the floor unless there are any questions in regards to those products.

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

AGENDA ITEM NO. 11: FDA & DEA UPDATES
Materials included in agenda packet; presented by Dr. Graham.
ACTION: NONE REQUIRED

AGENDA ITEM NO. 12: FUTURE BUSINESS
Materials included in agenda packet; submitted by Dr. Graham.
A: Utilization Review of Multiple Sclerosis Agents
B: Annual Review of Synagis
C: Annual Review of Ophthalmic Products
D: New Product Reviews
ACTION: NONE REQUIRED

AGENDA ITEM NO. 13: ADJOURNMENT: The meeting was adjourned at 7:45 p.m.

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

Memorandum

Date: August 11, 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 August 10, 2011

Recommendation 1: Vote to Prior Authorize Zuplenz™

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends prior authorization of Zuplenz™ (ondansetron) with the following criteria:

1. FDA-approved indication.
2. Must provide a clinically significant reason why the member cannot take all other available formulations of generic ondansetron.

Recommendation 2: Annual Review of Atypical Antipsychotics

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends adding children 5 years of age to the second opinion process.

Appendix B

RETROSPECTIVE DRUG UTILIZATION REVIEW REPORT
May 2011

MODULE	DRUG INTERACTION	DUPLICATION OF THERAPY	DRUG-DISEASE PRECAUTIONS	DOSING & DURATION
Total # of messages	54,498	68,024	1,081,753	29,988
Limits applied	Established, Major, Males and Females, Age 61-150	Duplication of Narcotics, Males and Females, Age 25-26	Contraindicated, Renal Failure, Males and Females, Age 0-150	High Dose and Duration, Males and Female, age 0-150, Oxazolidinones (Zyvox)
Total # of messages after limits were applied	61	177	143	7
Total # of members reviewed	61	151	99	7

LETTERS

Category	Prescribers	Pharmacies	Total Letters
Drug Interaction	0	0	0
Duplication of Therapy	57	2	59
Drug-Disease Precautions	24	0	24
Dosing & Duration	3	0	3
Total Letters Sent	84	2	86

Retrospective Drug Utilization Review Report

Claims Reviewed for April 2011

Module	Drug Interaction	Duplication of Therapy	Drug-Disease Precautions	Dosing & Duration
Limits which were applied	Established, Major, Males and Females, Age 51-60	Benzodiazepines, Age 29-32	Contraindicated, Ulcer, Males and Females, Age 0-150	High Dose, NSAIDs, Males and Females, Age 0-3

Response Summary (Prescriber)
Letters Sent: 74
Response Forms Returned: 25

The response forms returned yielded the following results:

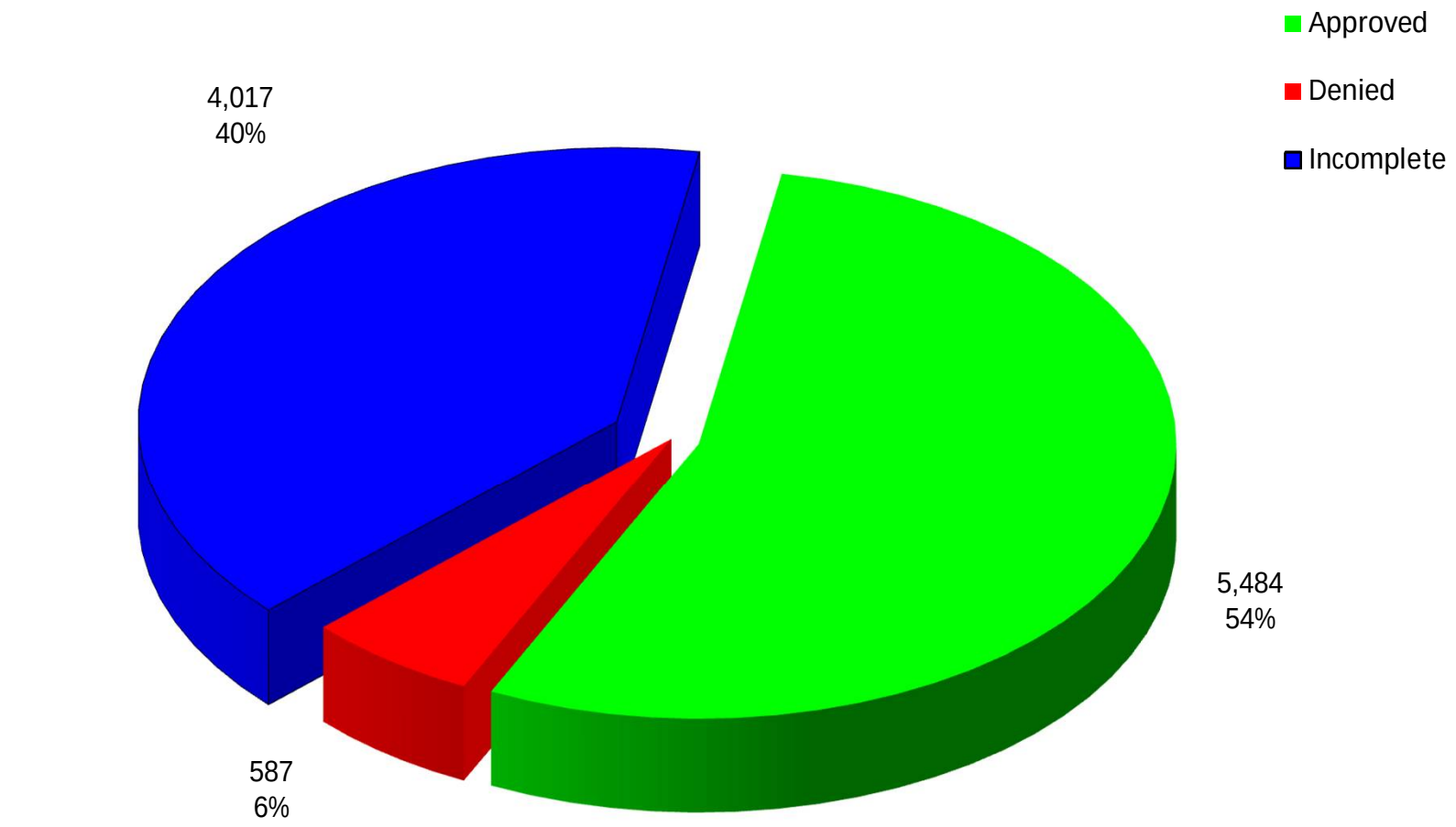
3 (12%)	*Record Error—Not my patient.*
6 (24%)	*No longer my patient.*
2 (8%)	*Medication has been changed prior to date of review letter.*
5 (20%)	*I was unaware of this situation & will consider making appropriate changes in therapy.*
8 (32%)	*I am aware of this situation and will plan to continue monitoring therapy.*
1 (4%)	*Other*

Response Summary (Pharmacy)
Letters Sent: 21
Response Forms Returned: 21

The response forms returned yielded the following results:

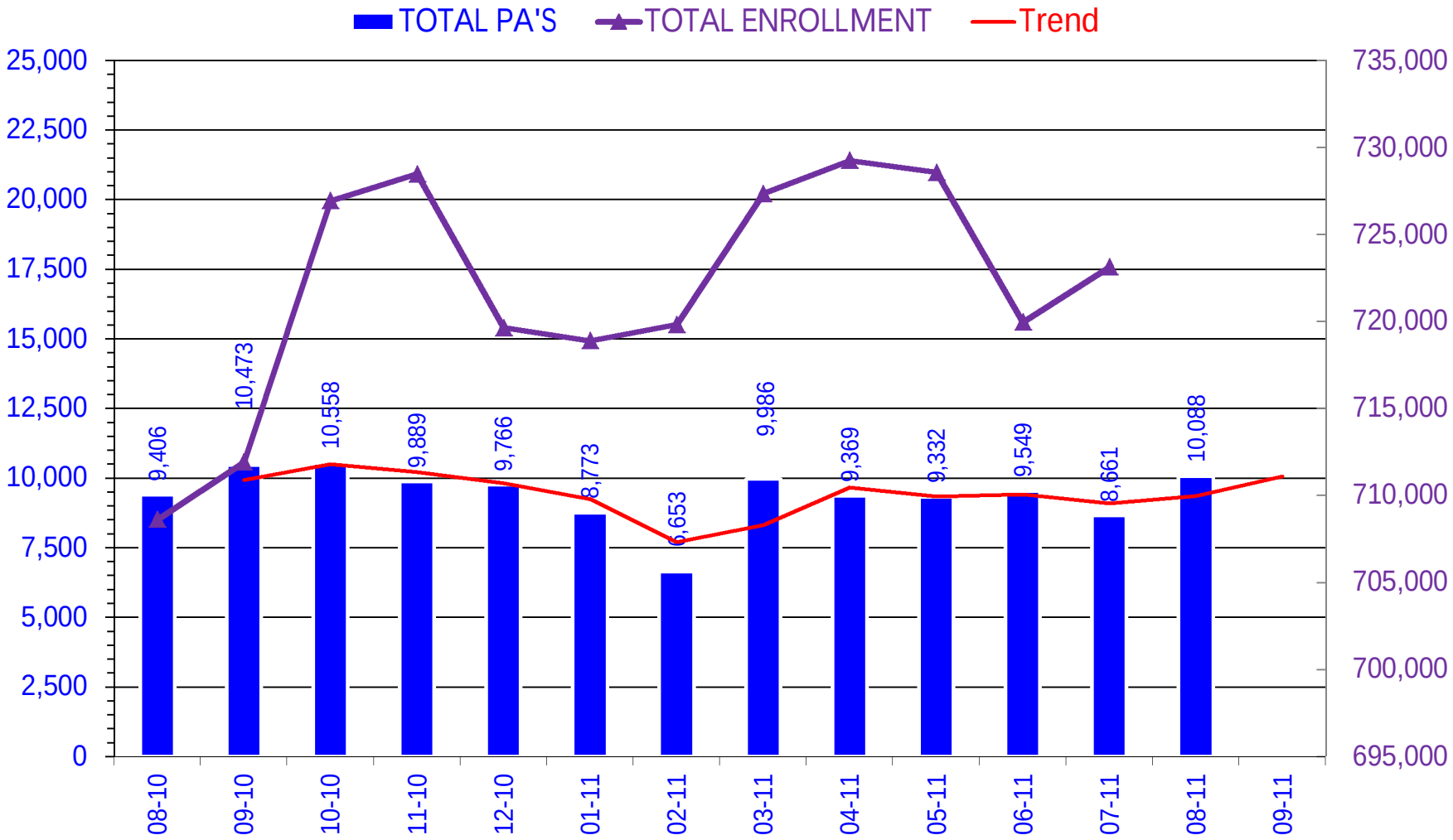
0 (0%)	*Record Error—Not my patient.*
1 (5%)	*No longer my patient.*
0 (0%)	*Medication has been changed prior to date of review letter.*
12 (57%)	*I was unaware of this situation & will consider making appropriate changes in therapy.*
5 (24%)	*I am aware of this situation and will plan to continue monitoring therapy.*
3 (14%)	*Other*

PRIOR AUTHORIZATION ACTIVITY REPORT: August 2011



PA totals include overrides

PRIOR AUTHORIZATION REPORT: August 2010 – August 2011



PA totals include overrides

Prior Authorization Activity

8/1/2011 Through 8/31/2011

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort	324	138	10	176	361
Amitiza	18	4	4	10	248
Anti-Ulcer	472	130	85	257	101
Antidepressant	319	112	15	192	354
Antihistamine	214	139	6	69	329
Antihypertensives	82	23	5	54	306
Antimigraine	96	17	11	68	346
Atypical Antipsychotics	715	405	22	288	358
Benign Prostatic Hypertrophy	10	3	1	6	362
Benzodiazepines	85	53	2	30	189
Bladder Control	62	19	7	36	344
Brovana (Arformoterol)	2	1	1	0	365
Byetta	7	1	0	6	362
Elidel/Protopic	46	27	1	18	95
ESA	106	72	1	33	103
Fibric Acid Derivatives	3	1	0	2	365
Fibromyalgia	182	73	11	98	349
Forteo	1	1	0	0	361
Glaucoma	22	4	0	18	363
Growth Hormones	58	38	0	20	173
HFA Rescue Inhalers	75	27	2	46	305
Insomnia	104	22	13	69	201
Misc Analgesics	37	2	28	7	227
Muscle Relaxant	176	55	59	62	89
Nasal Allergy	219	60	23	136	123
NSAIDS	185	33	14	138	303
Ocular Allergy	77	13	3	61	200
Ocular Antibiotics	53	14	0	39	15
Opioid Analgesic	308	167	20	121	222
Other	1,120	553	69	498	303
Otic Antibiotic	86	20	4	62	19
Pediculicides	125	60	12	53	13
Plavix	246	167	0	79	320
Qualaquin (Quinine)	1	0	1	0	0
Singulair	755	401	27	327	265
Smoking Cessation	62	23	3	36	47
Statins	148	77	3	68	360
Stimulant	935	524	46	365	304
Suboxone/Subutex	167	130	2	35	78
Synagis	1	0	1	0	0
Topical Antibiotics	12	3	1	8	16
Topical Antifungals	17	4	0	13	51
Ultram ER and ODT	7	0	1	6	0
Xolair	16	1	7	8	361
Xopenex Nebs	28	13	0	15	362
Zetia (Ezetimibe)	18	9	0	9	315
Emergency PAs	14	14	0	0	
Total	**7,816**	**3,653**	**521**	**3,642**	

Overrides					
Brand	44	26	5	13	237
Dosage Change	559	542	0	17	6
High Dose	4	4	0	0	76
Ingredient Duplication	8	8	0	0	6
Lost/Broken Rx	119	109	6	4	5
NDC vs Age	9	8	0	1	271
Nursing Home Issue	114	108	0	6	4
Other	42	40	0	2	17
Quantity vs. Days Supply	1,359	973	55	331	272
Stolen	12	11	0	1	11
Third Brand Request	2	2	0	0	3
Overrides Total	**2,272**	**1,831**	**66**	**375**	
Total Regular PAs + Overrides	10,088	5,484	587	4,017	

Denial Reasons	
Unable to verify required trials.	3,263
Lack required information to process request.	767
Does not meet established criteria.	561
Drug Not Deemed Medically Necessary	2

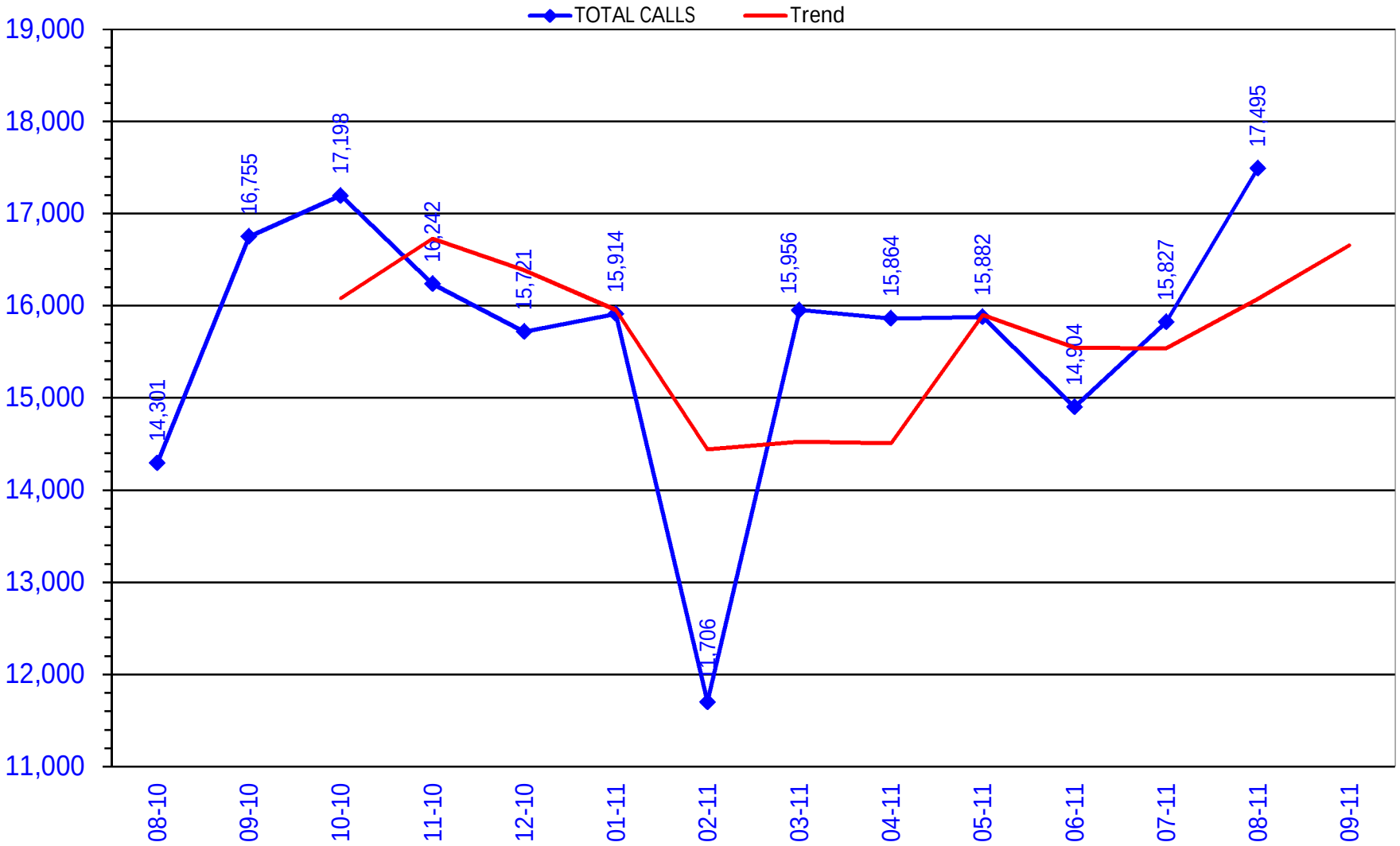
Duplicate Requests: 616

Letters: 1,561

No Process: 346

Changes to existing PAs: 470

CALL VOLUME MONTHLY REPORT:
August 2010 – August 2011



Appendix C

Vote to Prior Authorize Diabetes Medications

Oklahoma Health Care Authority
September 2011

This category was introduced for possible inclusion in the Product Based Prior Authorization program in June 2011. See the June and August 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 addition of the Diabetes Medications to the Product Based Prior Authorization program. The following tiered drug list has been reviewed and determined to be an acceptable combination for use as initial therapy for the majority of members. The College of Pharmacy recommends this list to the Drug Utilization Review Board based on clinical effectiveness and cost for approval before referral to the Oklahoma Healthcare Authority. The following are the recommendations for this category:

1. To qualify for a Tier 2 medication, the member must have a trial of a Tier 1 medication (must include a trial of metformin titrated up to maximum dose), or a clinical reason why a Tier 1 medication is not appropriate.
2. For initiation with dual or triple therapy, additional Tier 2 medications can be approved based on current AACE or ADA guidelines.
3. To qualify for a Tier 3 medication, the member must have tried a Tier 2 medication in the same category and have a documented clinical reason why the Tier 2 medication is not appropriate.
4. To qualify for a Special Prior Authorized medication, the member must be currently stabilized on the requested product or have attempted at least 3 other categories of Tier 2 or Tier 3 medications, or have a documented clinical reason why the requested product is necessary for the member.
    a. For members with steatohepatitis, pioglitazone can be approved after a trial of a Tier 1 medication (must include a trial of metformin titrated up to maximum dose), or a clinical reason why a Tier 1 medication is not appropriate.

Tier 1	Tier 2†	Tier 3	Special PA
Biaguanides Metformin Metformin SR Metformin-Glyburide Metformin-Glipizide Sulfonylureas Glyburide Glyburide Micronized Glipizide Glipizide SR Glimepiride Miscellaneous Chlorpropamide Tolbutamide	Supplementally rebated or best net price product from each class in Tier 3.	DPP-4 Inhibitors Saxagliptin Saxagliptin-Metformin Sitagliptin Sitagliptin-Metformin Linagliptin Glinides Repaglinide-Metformin Repaglinide Nateglinide GLP-1 Agonists Exenatide Liraglutide Alpha-Glucosidase Inhibitors Acarbose Miglitol	Biaguanides Riomet Soln* Metformin Long-Acting‡ Thiazolidinediones Rosiglitazone Pioglitazone Rosiglitazone-Metformin Rosiglitazone-Glimepiride Pioglitazone-Metformin Pioglitazone-Glimepiride Amylinomimetic Pramlintide‡

*No prior authorization required for member 12 and under.
†At least one Tier 2 from each Tier 3 category will be determined based on supplemental rebate or best federal rebate.
‡Special criteria currently apply.

Appendix D

Vote to Prior Authorize Xiaflex® (collagenase clostridium histolyticum)

Oklahoma Health Care Authority
September 2011

Under Oklahoma state law, the OHCA DUR Board must review and make recommendations for any drug subject to prior authorization, whether covered under the pharmacy benefit, the medical benefit, or both. Accordingly, physician administered drugs are brought through the same DUR process as those dispensed by pharmacies.

Recommendations

The College of Pharmacy recommends medical prior authorization of Xiaflex® with the following approval criteria:

1. FDA approved indication of Dupuytren's contracture with palpable cord, functional impairment and fixed-flexion contractures of the metacarpophalangeal (MP) joint or proximal interphalangeal (PIP) joint of 30 degrees or more.
2. Must be 18 years or older.
3. Not a candidate for needle aponeurotomy.
4. Physician must be trained in treatment of Dupuytren's contracture and injections of the hand.
5. Quantity limit of 3 doses (one dose per 4 weeks) per cord.

Appendix E

Vote to Prior Authorize Berinert®, Cinryze® (C-1 Esterase inhibitors) and Kalbitor® (ecallantide)

Oklahoma Health Care Authority, September 2011

Under Oklahoma state law, the OHCA DUR Board must review and make recommendations for any drug subject to prior authorization, whether covered under the pharmacy benefit, the medical benefit, or both. Accordingly, physician administered drugs are brought through the same DUR process as those dispensed by pharmacies.

Drug Information

Cinryze® is a C-1 esterase inhibitor indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with Hereditary Angioedema (HAE).

Berinert® is a plasma-derived C-1 Esterase Inhibitor (Human) indicated for the treatment of acute abdominal or facial attacks of hereditary angioedema in adult and adolescent patients. The safety and efficacy of Berinert for prophylactic therapy have not been established.

Kalbitor® (ecallantide) is a plasma kallikrein inhibitor indicated for treatment of acute attacks of hereditary angioedema (HAE) in patients 16 years of age and older.

Recommendations

The College of Pharmacy recommends prior authorization of the following medications for Hereditary Angioedema:

Criteria for Approval for Cinryze® (C1 esterase inhibitor)

1. Documented diagnosis of Hereditary Angioedema
2. For prophylaxis of Hereditary Angioedema
3. History of at least one or more abdominal or respiratory HAE attacks per month, or history of laryngeal attacks, or three or more emergency medical treatments per year
4. Documented intolerance, insufficient response, or contraindication to
    a. attenuated androgens (e.g. danazol, stanozolol, oxandrolone, methyltestosterone) AND
    b. antifibrinolytic agents (e.g. ε – aminocaproic acid, tranexamic acid) OR
    c. recent hospitalization for severe episode of angioedema
5. Not currently taking an angiotensin converting enzyme (ACE) inhibitor or estrogen replacement therapy.
6. Dosing:
    a. The recommended dose of Cinryze® is 1000 units IV every 3 to 4 days, approximately 2 times per week, to be infused at a rate of 1 ml/min.
    b. Initial doses to be administered in outpatient setting by healthcare provider. Patients can be taught by their healthcare provider to self-administer Cinryze® intravenously.
    c. Quantity limit of 8000 units per month will apply, i.e. 2 treatment per week, or 8 treatments per month.

Criteria for Approval of Berinert® (C1 esterase inhibitor):

1. Documented diagnosis of Hereditary Angioedema
2. For acute attacks of Hereditary Angioedema

Criteria for Approval of Kalbitor® (ecallentide):

1. Documented diagnosis of Hereditary Angioedema
2. For acute attacks of Hereditary Angioedema

Appendix F

30 Day Notice to Prior Authorize Firazyr® (Icatibant)

Oklahoma Health Care Authority, September 2011

Under Oklahoma state law, the OHCA DUR Board must review and make recommendations for any drug subject to prior authorization, whether covered under the pharmacy benefit, the medical benefit, or both. Accordingly, physician administered drugs are brought through the same DUR process as those dispensed by pharmacies.

Firazyr® (icatibant) Summary

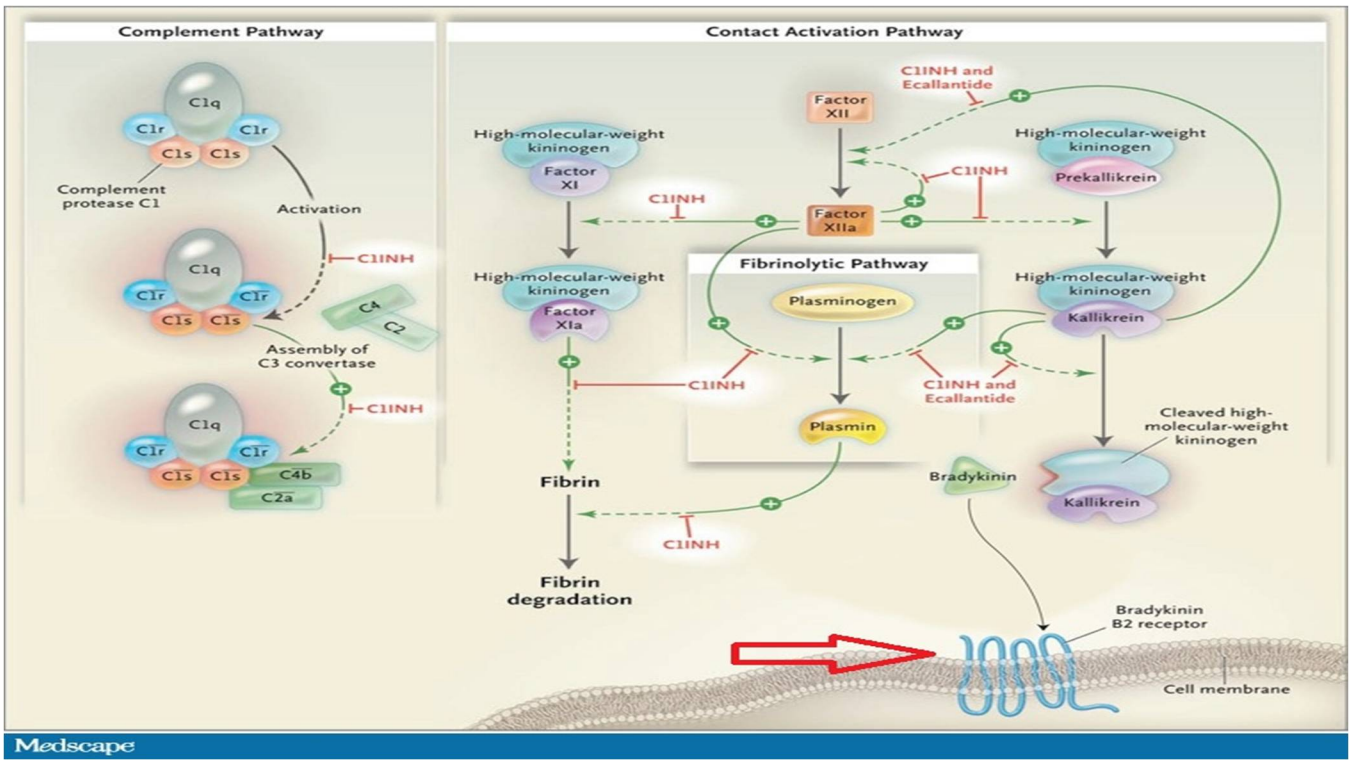
Icatibant is a selective competitive antagonist for the bradykinin B2 receptor located on the cell surface, indicated for treatment of acute attacks of hereditary angioedema. It inhibits bradykinin from binding to B2 receptor and blocks the vasodilation effect that causes the severe edema characteristic of the acute episodic attacks of HAE. The cost per single treatment is $7,184.82 (includes dispensing fee). Patients may be taught to self-administer upon recognition of an HAE attack; however, following treatment of laryngeal attacks patients are advised to seek immediate medical attention.

Recommendations

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)

Hereditary Angioedema Pathway[3]



PRODUCT DETAILS OF FIRAZYR® (ICATIBANT) SUBCUTANEOUS INJECTION[2]

FDA-APPROVED IN 2011

Indications:
Firazyr® (icatibant) is a bradykinin B2 receptor antagonist indicated for treatment of acute attacks of hereditary angioedema (HAE) in adults 18 years of age and older.

Dosage Forms:
Firazyr® (icatibant) is supplied as a single-use, prefilled syringe for subcutaneous administration. Each syringe delivers 3 mL of a sterile solution of icatibant 30 mg (as icatibant acetate).

Administration:

- 30 mg injected subcutaneously in the abdominal area.
- If response is inadequate or symptoms recur, additional injections of 30 mg may be administered at intervals of at least 6 hours.
- Do not administer more than 3 injections in 24 hours.
- Patients may self-administer upon recognition of an HAE attack.

Contraindications: None listed.

Pregnancy Category C

Special Populations:
Pediatric Use:
Safety and effectiveness in pediatric patients below the age of 18 years have not been established.
Nursing Mothers:
Because many drugs are excreted in human milk, caution should be exercised when Firazyr® is administered to a nursing woman. Icatibant is excreted into the milk of lactating rats.
Geriatric Use
Elderly patients demonstrate increased systemic exposure to icatibant. Differences in efficacy and safety between elderly and younger patients have not been identified.

Warnings and Precautions:
Laryngeal attacks: Following treatment of laryngeal attacks with Firazyr®, advise patients to seek immediate medical attention.

Adverse Reactions:
The most commonly reported adverse reactions were injection site reactions, which occurred in almost all patients (97%) in clinical trials. Other common adverse reactions occurring in greater than 1% of patients included pyrexia, transaminase increase, dizziness, and rash.

Drug Interactions:
Formal drug-drug interaction studies were not conducted with Firazyr®. Icatibant metabolism is not mediated by CYP450 enzymes. In vitro study did not show any significant inhibition and/or induction of drug metabolizing CYP450 enzymes; therefore, metabolic drug interactions between Firazyr® and CYP450 substrates, inhibitors and inducers are not expected.

Patient Information:

- Patients may self-administer Firazyr® upon recognition of an HAE attack after training under the guidance of a healthcare professional.
- Patients with laryngeal symptoms should seek medical attention immediately in an appropriate healthcare facility after administration of Firazyr®.
- Injection site reactions are reported in most patients after administration of Firazyr®. Other adverse reactions reported after administration of Firazyr® include pyrexia, increase in transaminases, dizziness, and rash.
- Tiredness, drowsiness, and dizziness have been reported following the use of Firazyr®. Patients should be advised not to drive or use machinery if they feel tired or dizzy.

REFERENCES

1. US Hereditary Angioedema Association at http://www.haea.org
2. Firazyr® Label Information. Shire Orphan Therapies, Inc. Last revised 08/2011. Available online at: http://pi.shirecontent.com/PI/PDFs/Firazyr_USA_ENG.pdf.
3. Zuraw BL. N Engl J Med. 2008;359:1027-1036

Appendix G

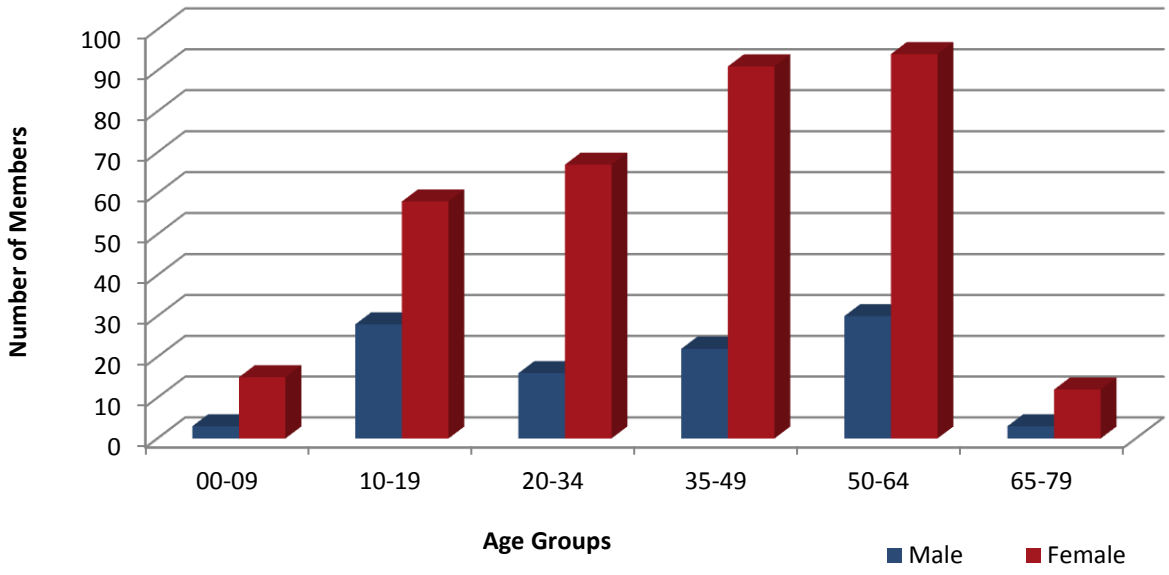
60 DAY NOTICE TO PRIOR AUTHORIZE BIOLOGIC PRODUCTS FOR THE TREATMENT OF RHEUMATOID ARTHRITIS, CROHN'S DISEASE, PLAQUE PSORIASIS, AND ANKYLOSING SPONDYLITIS

OKLAHOMA HEALTH CARE AUTHORITY
SEPTEMBER 2011

This category was introduced for possible inclusion in the Product Based Prior Authorization program in August 2011. See the August DUR packet for a more complete discussion of the category. This notice and statement of potential economic impact are presented to meet the statutory requirements of 63 O.S. Sec. 5030.5.

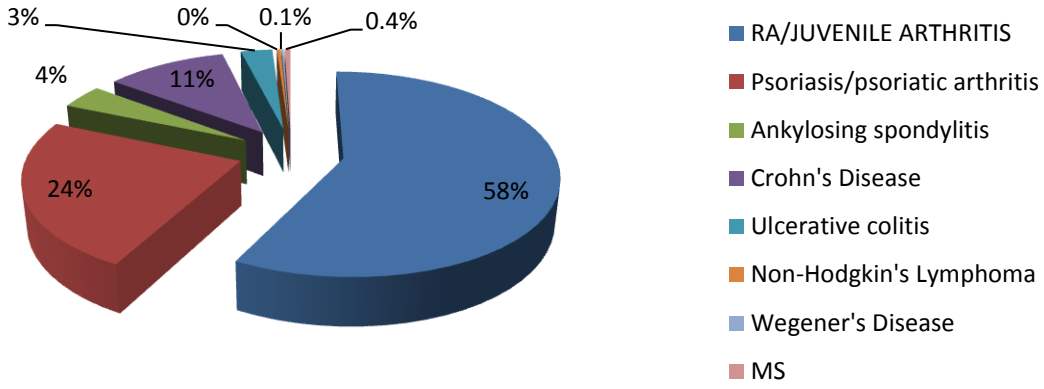
MEMBER DEMOGRAPHICS

In calendar year 2010, there were a total of 439 members utilizing these medications through pharmacy claims, and 116 through medical claims. Within the pharmacy claims, there were 31 waiver and 12 long-term care patients.

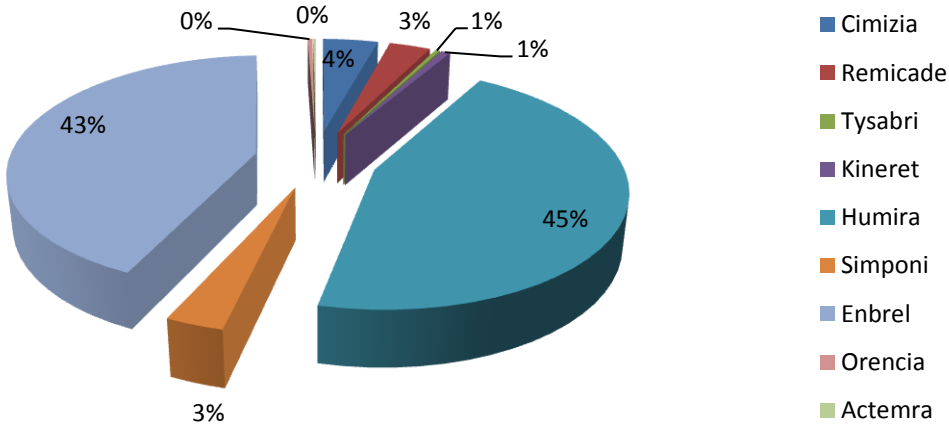


MARKET ANALYSIS BY CLAIMS AND INDICATION

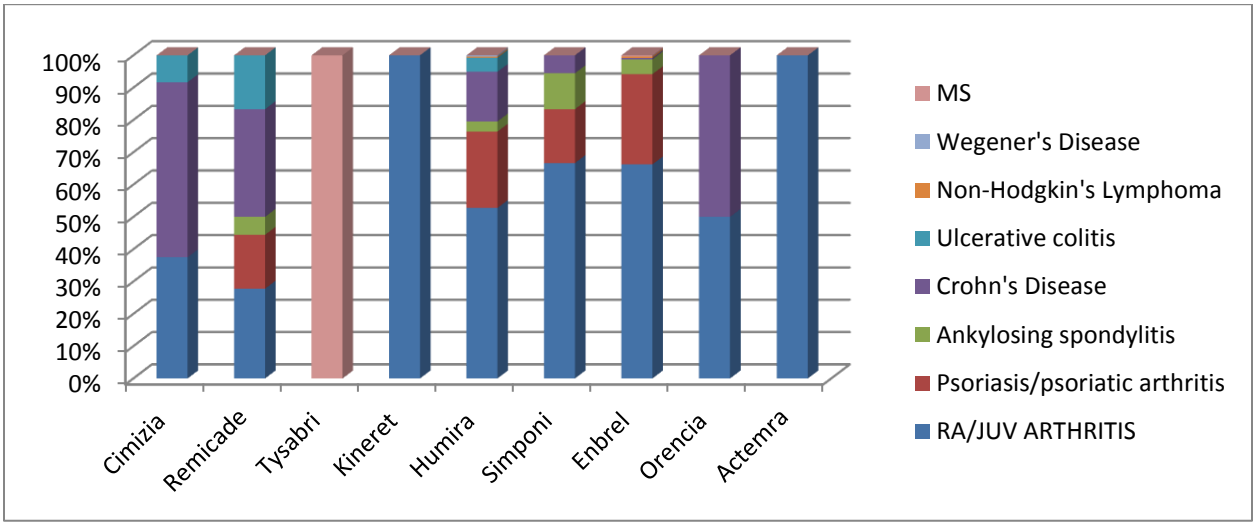
Over half of SoonerCare members taking a biologic medication have a diagnosis of rheumatoid arthritis or juvenile idiopathic arthritis. The other major indications are psoriasis/psoriatic arthritis and Crohn's disease.



The majority of the market share of biologic medications in the SoonerCare population is almost evenly divided between adelimumab (Humira®) and etanercept (Enbrel®).



Review of claims by indication shows that these medications are mostly being utilized for FDA-approved indications.



PRODUCT COSTS

Treatment costs were estimated for the first year of use for each of the FDA-approved indications of these medications. Many treatments include 2-3 loading doses during the first few weeks, and the dosing regimens range from daily (anakinra) up to once every 24 weeks (rituximab). The estimated costs in the chart below are rounded up to the nearest tenth for convenience and the weight-based products are estimated to be for a 100 kg patient. Also, these estimates are for the costs of the medication only, and the actual costs, especially for intravenously-infused medications, may be considerably higher.

Drug name	Average dose	Dose form	Treatment Costs (1st year of therapy)			
			Rheumatoid arthritis	Crohn's disease	Plaque psoriasis	Ankylosing spondylitis
Adelimumab (Humira®)	40mg **SC** q2wks or qwk Plus loading doses required for Crohn's and psoriasis	**SC**	$24,620	$30,290	$25,560	$24,620
Infliximab (Remicade®)	*Start*: 3-5mg/kg **IV** at 0,2,6 wks: then 3-5mg/kg q6-8wks (disease specific)	**IV**	$17,500	$29,160	$17,500	$36,440
Etanercept (Enbrel®)	50mg **SC** qwk; 50mg twice weekly for psoriasis for 1st 3 months	**SC**	$25,360		$31,210	$25,360
Certolizumab pegol (Cimzia®)	*Start*: 400mg **SC** x1 dose wks 0,2,4; then RA:200mg **SC** every other wk; Crohn's: 400mg **SC** q4wk	**SC**	$20,090	$20,090		
Golimumab (Simponi®)	50mg **SC** once monthly	**SC**	$24,610			$24,610
Rituximab (Rituxan®)	1000mg **IV** days 1,15; then q24wks	**IV**	$25,310			
Anakinra (Kineret®)	100mg **SC** q24h	**SC**	$33,730			
Abatacept (Orencia®)	<60 kg, 500mg; 60-100 kg, 750mg; >100kg, 1000mg **IV**; 0,2,4 wks, then q4wks	**IV**	$32,090			
Tocilizumab (Actemra®)	4mg/kg **IV** q4wks; up to 8mg/kg or a max of 800mg/dose	**IV**	$33,360			
Alefacept (Amevive®)	15mg **IM** qwk (for 24 weeks of treatment)	**IM**			$29,870	
Ustekinumab (Stelara®)	≤100 kg, 45mg **SC** wks 0,4 then q12wks >100kg, 45 or 90mg SC wks 0,4 then q12wks	**SC**			$34,760	

MARKETING NEWS AND UPDATES

- The federal government in March 2010 approved the Biologics Price Competition and Innovation Act (BPCIA).
    - Developers of follow-on (biosimilar) biologics must wait 12 years before receiving approval of a drug that is developed by relying on the innovator product data.
- Upcoming patent expirations
    - Enbrel® (etanercept) 2012
    - Kineret® (anakinra) 2013
- FDA has updated the boxed warning for the entire class of TNFα blockers to include the risk of infection from two bacterial pathogens, Legionella and Listeria. Also, the Boxed Warning and Warnings and Precautions sections of the labels for all of the TNFα blockers have been revised so that they contain consistent information about the risk for serious infections and associated disease-causing pathogens.

ECONOMIC IMPACT

POTENTIAL SECONDARY COSTS

Overall efficacy is considered to be similar across the products in this class, but drug selection requires individual patient history which includes, but is not limited to: other illnesses, disease risk factors, and current symptoms.

POTENTIAL ADMINISTRATIVE COSTS

The potential number of petitions which might be required if a Tier 2 product was not chosen initially by the prescriber is estimated to be approximately 600. The total number of members who will be affected by this change is unknown until the final Tier 2 selection has been made.

Previously, it has been theorized that the total cost per petition to the *healthcare system* (includes cost to physicians, pharmacists, and program) is between $7.63 and $14.82. Total cost for prior authorization to the *healthcare system* is estimated to be between $4,578 and $8,892 annually. Anticipated actual administrative cost to the program is projected to be less than $10,000.

POTENTIAL PROGRAM SAVINGS

Potential net ingredient savings to the program after rebates based on the recommended tiers and a potential shift of 50% of market share from Tier 3 to Tier 2 is estimated to be 12% of the CY10 total reimbursement to pharmacies for this category of drugs.

RECOMENDATIONS

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®)

SUMMARY OF PAID CLAIMS CY10

GENERIC NAME	BRAND NAME	CLAIMS	DAYS	MEMBERS	COST	CLAIMS/ MEMBER	COST/ DAY	PERCENT COST
Adalimumab	HUMIRA PEN KIT 40MG/0.8	582	17,068	128	$1,198,277.32	4.55	$70.21	24.32%
Etanercept	ENBREL SRCLK INJ 50MG/ML	506	14,693	104	$1,088,640.77	4.87	$74.09	22.09%
Etanercept	ENBREL INJ 50MG/ML	413	11,422	76	$782,779.77	5.43	$68.53	15.88%
Adalimumab	HUMIRA KIT 40MG/0.8	326	9,041	62	$691,039.51	5.26	$76.43	14.02%
Etanercept	ENBREL INJ 25MG	188	5,536	36	$265,561.40	5.22	$47.97	5.39%
Etanercept	ENBREL INJ 25/0.5ML	89	2,435	16	$129,082.71	5.56	$53.01	2.62%
Certolizumab	CIMZIA KIT 200MG/ML	66	1,862	19	$120,622.42	3.47	$64.78	2.45%
Golimumab	SIMPONI INJ 50MG	64	1,918	15	$114,244.26	4.27	$59.56	2.32%
Infliximab	REMICADE INJ 100MG	55	1,202	16	$206,588.11	3.44	$171.87	4.19%
Anakinra	KINERET INJ	47	1,319	5	$76,932.26	9.4	$58.33	1.56%
Alefacept	AMEVIVE INJ 15MG	25	167	2	$63,789.74	12.5	$381.97	1.29%
Adalimumab	HUMIRA PEN KIT PSORIASI	16	489	11	$54,704.02	1.45	$111.87	1.11%
Certolizumab	CIMZIA KIT	13	366	4	$19,973.37	3.25	$54.57	0.41%
Natalizumab	TYSABRI INJ	12	336	2	$31,447.99	6	$93.60	0.64%
Adalimumab	HUMIRA KIT 20MG/0.4	11	316	4	$18,300.03	2.75	$57.91	0.37%
Adalimumab	HUMIRA PEN KIT CROHNS	10	294	10	$49,682.78	1	$168.99	1.01%
Tocilizumab	ACTEMRA INJ 400/20ML	2	56	1	$5,610.52	2	$100.19	0.11%
Abatacept	ORENCIA INJ 250MG	1	30	1	$4,686.75	1	$156.22	0.10%
Rituximab	RITUXAN INJ 500MG	1	14	1	$5,939.29	1	$424.24	0.12%
	Totals:	**2,427**	**68,564**	**439***	**$4,927,903.02**	**5.53**	**$71.87**	**100.00%**

**Total unduplicated number of members*

Appendix H

Drug Utilization Review of Multiple Sclerosis Medications

Oklahoma Health Care Authority
September 2011

Introduction[1,2]

Multiple Sclerosis (MS) is a neurological disorder where the body's own immune system attacks myelin, the fatty substance that surrounds and protects the nerve fibers in the central nervous system. The nerve fibers themselves can also be damaged. The damaged myelin forms scar tissue (sclerosis), which gives the disease its name. When any part of the myelin sheath or nerve fiber is damaged or destroyed, nerve impulses traveling to and from the brain and spinal cord are distorted or interrupted, resulting in the symptoms of MS.

LESION LOCATION:	SIGNS/SYMPTOMS:
Cerebrum & Cerebellum	Balance problems, speech problems, coordination, tremors
Motor Nerve Tracts	Muscle weakness, spasticity paralysis, vision problems, bladder, bowel problems
Sensory Nerve Tract	Altered sensation, numbness, prickling, burning sensation

Currently, the exact cause of MS remains unknown, but evidence to date point to a combination of factors that may be involved: environmental factors affecting sun exposure, viral and other infections, and a genetic link. Worldwide, MS occurs with much greater frequency above 40° latitude than closer to the equator. MS is at least two to three times more common in women than in men. Multiple sclerosis (MS) affects approximately 400,000 people in the United States. Although there are 4 forms of MS, over 80% of patients with MS are initially diagnosed with relapsing-remitting MS (RRMS). Of these, about 50% will eventually develop secondary progressive MS (SPMS). Although MS can occur in young children and the elderly, most people are diagnosed between the ages of 20 and 50.

Currently, there is no definitive test to diagnose MS. The diagnosis of MS is a partly subjective process, and is best made by an expert who is familiar with the disease and who can interpret imaging and laboratory evidence that can supplement the clinical diagnostic process. In order to make a diagnosis of MS, the physician must:

- Find evidence of damage in at least two separate areas of the central nervous system (CNS), which includes the brain, spinal cord and optic nerves AND
- Find evidence that the damage occurred at least one month apart AND
- Rule out all other possible diagnoses

Other Demyelinating Diseases of in the Central Nervous System
Although MS is the most common demyelination disease; other conditions can damage myelin, including viral infections, side effects from high exposure to certain toxic materials, severe vitamin B_{12} deficiency, autoimmune conditions that lead to inflammation of blood vessels, some rare hereditary disorders, and Guillain-Barré Syndrome. Some of these conditions are self-limiting and some are progressive in nature. Careful and repetitive examinations may be necessary to establish an exact diagnosis among the possible causes of neurologic symptoms.

The requirement remains that there must be no better explanation than MS for the clinical and laboratory findings – other possible diagnoses must be considered and excluded, including other demyelinating disorders. The following are possible tests and procedures that may be used in the diagnosis of MS:

Test/Procedure	Objective
Medical History and Neurologic Exam	Identify any past or present symptoms that might be caused by MS and to gather information about birthplace, family history and places traveled that might provide further clues. The physician also performs a variety of tests to evaluate mental, emotional and language functions, movement and coordination, balance, vision, and the other four senses.
Magnetic Resonance Imaging (MRI)	Detect the presence of MS plaques or scarring lesions in different parts of the CNS (old and new lesions.) The diagnosis of MS cannot be made solely on the basis of MRI because there are other diseases that cause lesions in the CNS that look like those caused by MS. And even people without any disease — particularly the elderly — can have spots on the brain that are similar to those seen in MS.
Visual Evoked Potential (VEP)	Evoked potential (EP) tests are recordings of the nervous system's electrical response to the stimulation of specific sensory pathways (e.g., visual, auditory, general sensory). Because damage to myelin (demyelination) results in a slowing of response time, EPs can sometimes provide evidence of scarring along nerve pathways that does not show up during the neurologic exam. Visual evoked potentials are considered the most useful for confirming the MS diagnosis.
Cerebrospinal Fluid Analysis	Analysis of the cerebrospinal fluid, which is sampled by a spinal tap, detects the levels of certain immune system proteins and the presence of oligoclonal bands. These bands, which indicate an immune response within the CNS, are found in the spinal fluid of about 90-95% of people with MS. But because they are present in other diseases as well, oligoclonal bands cannot be relied on as positive proof of MS.
Blood Tests	While there is no definitive blood test for MS, blood tests can rule out other conditions that cause symptoms similar to those of MS, including Lyme disease, a group of diseases known as collagen-vascular diseases, certain rare hereditary disorders, and AIDS.

Treatment of Multiple Sclerosis

Currently there is no cure for MS. Treatment consists of strategies to modify the course of the disease, treatment of acute exacerbations, manage daily symptoms, improve function and safety, and provide emotional support. Severe exacerbations are treated with high dose corticosteroids to reduce inflammation and possible damage that may occur. Daily symptoms of MS may be managed with medications, self-care techniques, physical therapy, speech/language therapy, etc. Recently dalfampridine (Ampyra®) was approved by the FDA to improve walking in patients with MS. This review will focus mainly on agents indicated to modify the course of the disease. Since MS is a disorder in which the patient's own immune system is the cause of damage and subsequent symptoms, the disease modifying agents are immunomodulators or immunosuppressants in nature, indicated to reduce the frequency of clinical relapses, thereby delaying the accumulation of physical disability.

Medication	Dosing	FDA-Approved Indications
Interferon β - 1a (Avonex®)	30mcg IM Q wk	Relapsing Remitting MS
Interferon β - 1a (Rebif®)	44mcg SQ TIW	Relapsing Remitting MS
Interferon β - 1b (Betaseron®)	0.25mg SQ QOD	Relapsing Remitting MS
Interferon β - 1b (Extavia®)	0.25mg SQ QOD	Relapsing Remitting MS
Glatiramer acetate (Copaxone®)	20mg SQ daily	Relapsing Remitting MS First clinical episode with MRI features consistent with MS
Natalizumab (Tysabri®)	300mg IV infused over 1hr, then Q 4 wks	Relapsing Remitting MS Crohn's Disease (mod - severe)
Mitoxantrone (Novantrone®)	12mg/m2 by IV infused Q 3 months for 24 months	Secondary progressive MS Progressive –relapsing MS Worsening relapsing-remitting MS Acute myeloid leukemia Prostate Cancer
Fingolimod (Gilenya®)	0.5mg PO daily	Relapsing Remitting MS

Efficacy of MS Disease Modifying Drugs

Interferon-beta and glatiramer acetate were the first disease modifying agents approved to modify the disease course of MS. Clinical trials and long term follow-up data[3,4,5,6,7] have shown that use of these agents is associated with approximately 30% reduction in relapse rates, decreases in accumulation of disability and development of lesions visible on magnetic resonance imaging (MRI). However, response to interferon-beta and glatiramer acetate is highly variable, with some patients achieving complete remission and others appear to have no measurable benefit at all. Three large clinical trials[8,9,10] have shown that IFN-beta delays the conversion to clinically definite MS in patients with clinically isolated syndrome. However, this data has not proven to solidify the treat early and treat all concept, although the results were statistically significant, the the magnitude of benefit is clinically small. Consideration should be made by taking into account several factors such as clinical and radiographic disease dissemination and patient's willingness to begin long term parental therapy.

Natalizumab (Tysabri®)[11] is a recombinant humanized IgG4-kappa monoclonal antibody that binds to α4-integrin on immune cells, inhibiting interaction with VCAM-1, which, in turn, inhibits immune cell migration across the blood-brain barrier. Natalizumab was proven effective in a trial of 942 patients that showed a 67% reduction in relapse rate over 2 years when compared to placebo[12]. However, due to the increased risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability, natalizumab is generally recommended for patients who have had inadequate response or are not tolerant of the interferons or glatiramer acetate.

Mitoxantrone (Novantrone®) is an anthracenedione cytotoxic agent with immunosuppressive properties reserved for patients with rapidly worsening MS. Mitoxantrone can cause cardiotoxicities similar to other anthracyclines and the lifetime accumulation dosage should not exceed 140mg/m^2. Immunosuppressive therapies, including cyclophosphamides, are usually recommended for shorter periods of time (3-6 months up to a maximum of 2 years as "induction therapies"), followed by reinstitution of the platform disease-modifying therapy.

Dalfampridine (Ampyra®)[13] is a broad spectrum potassium channel blocker that has been shown in animal studies to increase conduction of action potentials in demyelinated axons through inhibition of potassium channels. Dalfampridine is indicated to improve walking speed/distance in patients with multiple sclerosis (MS). Patients responding to dalfampridine increased walking speed by approximately 25% from baseline in trials as compared to 4.7% to 7.7% with placebo. However, one clinical trial showed only about 35% of the patients who took the medication had a response, and a drug-placebo difference was not established on the patient self-assessment of ambulatory disability.

Fingolimod (Gilenya®) is a sphingosine 1-phosphate receptor (S1P) modulator. Fingolimod blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood to approximately 30% of baseline values. The mechanism by which fingolimod exerts therapeutic effects in multiple sclerosis is unknown, but may involve reduction of lymphocyte migration into the central nervous system. A one year randomized controlled trial showed the annualized relapse rate to be significantly lower in patients treated with fingolimod 0.5 mg than in patients who received interferon beta-1a IM weekly. Fingolimod was shown to induce a dose-dependent reduction in heart rate and has been associated with atrioventricular (AV) conduction delays including 1st or 2nd degree AV block following administration of the initial dose hence the patient should be monitored for 6 hours after the initial dose.

The following are major points taken from the National Multiple Sclerosis Society's Consensus statement regarding treatment:[14]

- The Society recognizes that the factors that enter into a decision to treat are complex and best analyzed by the individual patient's neurologist.
- Initiation of treatment with an interferon beta medication or glatiramer acetate should be considered as soon as possible following a definite diagnosis of MS with active, relapsing disease, and may also be considered for selected patients with a first attack who are at high risk of MS. (A relapse/exacerbation/attack is conventionally defined as the development of new or recurring symptoms lasting at least 24 hours and separated from a previous attack by at least one month.)
- Natalizumab is generally recommended by the Food and Drug Administration (FDA) for patients who have had an inadequate response to, or are unable to tolerate, other multiple sclerosis therapies.
- Treatment with mitoxantrone may be considered for selected relapsing patients with worsening disease or patients with secondary-progressive multiple sclerosis who are worsening, whether or not relapses are occurring.

The full therapeutic effect is believed to occur from 6 months to 1 year after patients begin IFN-beta or GA therapy. Currently, no accepted algorithm for defining and/or managing partial responsiveness in MS patients has been established; however, the following may be indicators of suboptimal or partial therapeutic response to medication[15]:

- The occurrence of more than 1 relapse/year or the failure of a given treatment to reduce the relapse rates from pretreatment levels is considered clinical evidence.
- Patients experiencing incomplete recovery from attacks.
- Patients with recurrent brainstem or spinal cord lesions. There is insufficient consensus to recommend the use of MRI to monitor the individual therapeutic response. However, the presence of a significant increase in T2-weighted MRI lesions while a patient is on therapy is generally agreed to represent a suboptimal response. In clinical trials new T2-weighted MRI

lesion activity was the best predictor of, and significantly correlated with, a poor response to therapy.

The following strategies have been proposed for patients with suboptimal therapeutic responses[16]:

- Increasing the frequency of IFN-beta therapy - studies suggest a greater benefit for the IFN-beta regimens that use higher and more frequent dosing, but only in the first 24 weeks of treatment.
- Switching from one class of therapy to another class – between interferon therapy, glatiramer, and natalizumab.
- Switching to chemotherapeutic agents – mitoxantrone or cyclophosphamide may be considered.

Utilization Trends of Multiple Sclerosis Medications

Five Year Trend in Utilization

Fiscal Year	Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days	cost/ Member
2007	134	1,023	$1,637,132.92	$1,600.33	$53.27	4,911	30,731	$12,217.41
2008	134	1,049	$2,127,909.98	$2,028.51	$67.48	4,864	31,533	$15,879.93
2009	138	972	$2,398,059.09	$2,467.14	$83.31	4,638	28,786	$17,377.24
2010	155	1,044	$2,853,993.47	$2,733.71	$92.00	5,160	31,022	$18,412.86
2011	178	1,216	$3,769,473.93	$3,099.90	$104.09	8,980	36,214	$21,176.82

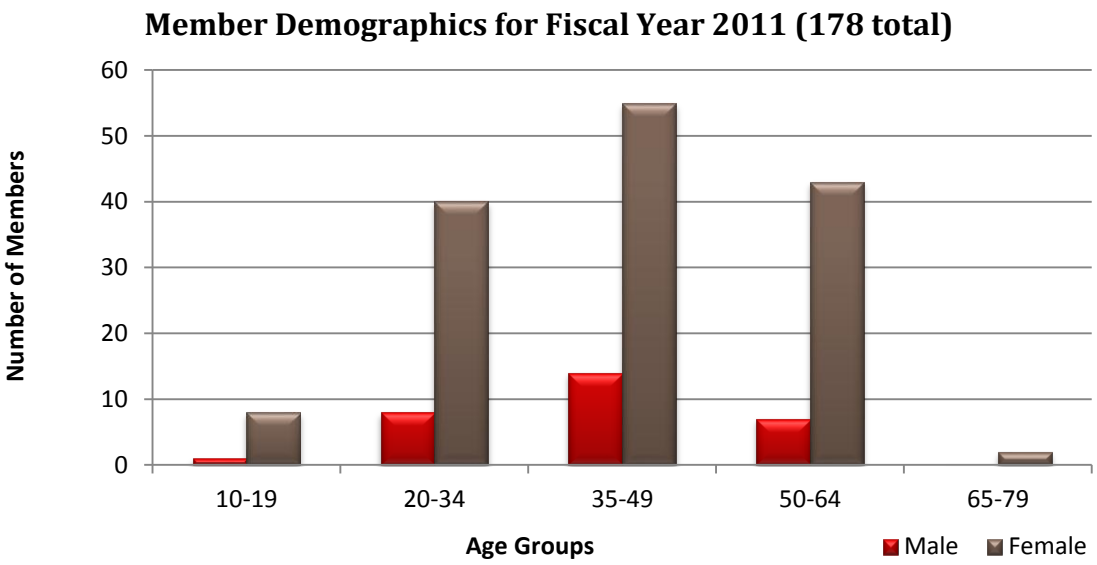
Fiscal Year Comparison

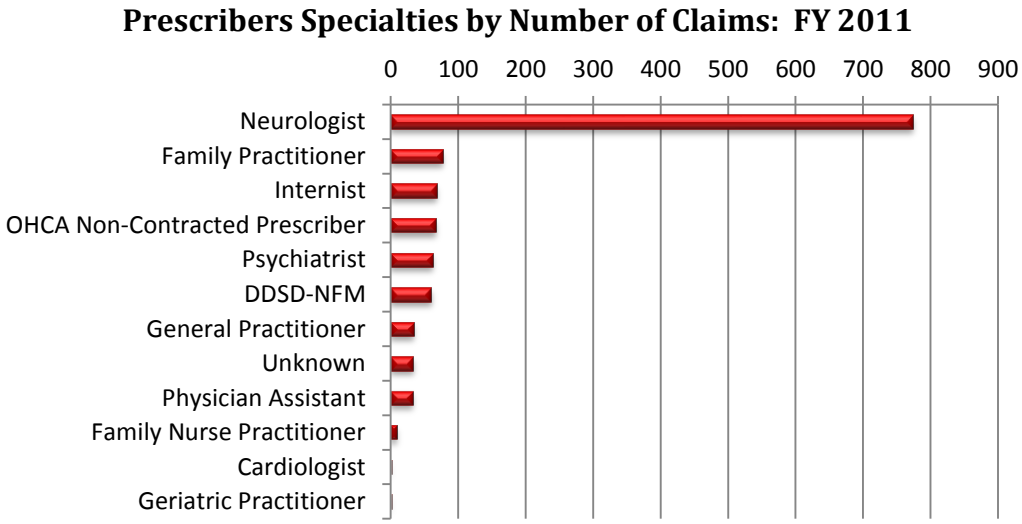
Fiscal Year	Members	Claims	Cost	Cost/Claim	Perdiem	Units	Days
2010	155	1,044	$2,853,993.47	$2,733.71	$92.00	5,160	31,022
2011	178	1,216	$3,769,473.93	$3,099.90	$104.09	8,980	36,214
% Change	**14.80%**	**16.50%**	**32.10%**	**13.40%**	**13.10%**	**74.00%**	**16.70%**
Change	**23**	**172**	**$915,480.46**	**$366.19**	**$12.09**	**3,820**	**5,192**

FY 2011 Utilization Details

GENERIC NAME	BRAND NAME	CLAIMS	MEMBERS	COST	CLAIMS/ MEMBER	COST/ DAY	% COST	UNITS/ DAY
Glatiramer Acetate	COPAXONE KIT 20MG/ML	508	90	$1,743,648.29	5.64	$114.41	46.26%	0.03
Interferon Beta-1a	REBIF INJ 44/0.5	286	41	$809,388.79	6.98	$101.00	21.47%	0.21
Interferon Beta-1b	BETASERON INJ 0.3MG	165	22	$501,165.85	7.5	$103.42	13.30%	0.48
Interferon Beta-1a	AVONEX PREFL KIT 30MCG	130	22	$442,530.54	5.91	$100.21	11.74%	0.14
Dalfampridine	AMPYRA TAB 10MG	55	12	$60,259.60	4.58	$36.52	1.60%	1.93
Interferon Beta-1a	AVONEX KIT 30MCG	18	2	$53,464.53	9	$106.08	1.42%	0.14
Interferon Beta-1a	REBIF INJ 22/0.5	18	3	$49,724.20	6	$98.66	1.32%	0.21
Interferon Beta-1a	REBIF TITRTN SOL PACK	17	17	$46,703.83	1	$91.94	1.24%	0.14
Natalizumab	TYSABRI INJ	11	1	$31,462.42	11	$102.15	0.83%	0.54
Fingolimod	GILENYA CAP 0.5MG	8	4	$31,125.88	2	$138.95	0.83%	1
	Totals	**1,216**	**178***	**$3,769,473.93**	**6.83**	**$104.09**		**0.25**

***Total Number of Unduplicated Members**





Market Trends

Anticipated Patent Expirations – the generic application process for biologic medications is still in development, hence there are no anticipated generic formulations in the near future even when patents expire for these products.

Select Novel Agents Currently in Development for Multiple Sclerosis

Medication	Route Studied	Dosing Regimen Studied	Manufacturer
Cladribine	Oral	10mg tabs for 4-5 day courses, 8-20 days/yr	Merck/EMD Serono
Dimethylfumerate	Oral	Two 120mg caps BID – TID	Biogen Idec
Alemtuzumab	IV Infused	12-24mg QD x 5 days, 12-24mg QD X 3 days at 1 yr	Genzyme
Iaquinimod	Oral	0.6mg caps QD	Teva
Teriflunomide	Oral	7-14mg tabs QD	Sanofi-Aventis
Daclizumab	SQ injection	150mg SQ q4 wks	Biogen Idec

Adapted from Table 1[17]

In addition to new drugs in development, there is also work on existing medications:

- New formulation of Rebif® designed to reduce injection site reactions and antibody formation.
- Pegylated version of Avonex® to be dosed q 2 weeks or q 4 weeks.
- Copaxone® dosed at 40mg SQ 3 times per week.
- Evaluation of Rituximab for secondary progressive MS.
- Cyclophosphamide is in phase III trials to evaluate its use in secondary progressive MS.

Other Considerations in Treatment of Multiple Sclerosis

The management of multiple sclerosis is complicated by a number of factors that sets it apart from management of other disease states. A recent cost-effectiveness analysis[18] raised some discussion among interested parties when published results show that for the interferons, glatiramer acetate, and natalizumab, the incremental cost-effectiveness ratio estimates far exceeded $800,000 per quality-adjusted life year. (No definite cost-effectiveness threshold has been adopted in the United States; however, values between $50,000 and $100,000 per QALY have frequently been applied in the US.[19])

Aside from the high cost of treatments involved, other factors also contribute to complicate the management of multiple sclerosis such as the variable clinical course of the disease, the lack of a clear diagnostic tool and measure of response to treatment, the variability of patient response to treatment, and the morbidity and associated healthcare resource utilization. Due to the number of anticipated new products in the pipeline, many managed care and state Medicaid programs are evaluating ways to better manage this category of medications. Many are going away from the traditional tier approach and using various other methods for these medications. The following is a recent survey of managed care organizations that show other strategies that have been used.

	Avonex®	Betaseron®	Copaxone®	Extavia®	Rebif®	Tysabri®
Prior authorization	61%	58%	56%	53%	56%	66%
Limit use to FDA-approved indications	51%	47%	48%	40%	47%	48%
Quantity limits	42%	40%	42%	37%	39%	29%
Dosage limits	47%	46%	46%	35%	42%	30%
Restricted pharmacy network	31%	29%	30%	27%	30%	25%
Prescribing restricted to specialist	23%	24%	25%	23%	24%	31%
No restrictions	16%	16%	20%	11%	15%	6%
Step therapy	12%	19%	9%	19%	11%	19%
Not covered	5%	6%	2%	17%	6%	11%
Therapeutic interchange	2%	6%	2%	6%	2%	2%
Not applicable	2%	1%	2%	4%	4%	8%

Adapted from Table 2 of the MS Trend Report[20]

State Medicaid programs are also utilizing similar management tools. Many large PBMs are also contracted with states to manage pharmacy benefits for their Medicaid members.

Recommendations

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

Tier 1	Tier 2
Best Net Priced Interferon with Supplemental Rebates	Interferon β - 1a (Avonex®)
	Interferon β - 1a (Rebif®)
	Interferon β - 1b (Betaseron®)
	Interferon β - 1b (Extavia®)

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.

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Appendix I

Annual Review of Synagis® (palivizumab) - Fiscal Year 2011

Oklahoma Health Care Authority
September 2011

Prior Authorization of Synagis® during FY '10

Prior authorization is required for all members who receive Synagis® in an outpatient setting. Synagis® is approved for members who meet the established criteria based on a modified version of the American Academy of Pediatrics (AAP) guidelines.

Current Criteria for Prior Authorization of Synagis®

A. Member Selection. Members must be included in one of the following age groups at the beginning of the RSV season:*

1) Infants and children less than 24 months old with Chronic Lung Disease (CLD) (formerly bronchopulmonary dysplasia) who have required medical treatment (O2, bronchodilator, corticosteroid, or diuretic therapy) for CLD in the 6 months prior to RSV season.
2) Infants up to 24 months old with moderate to severe pulmonary hypertension, cyanotic heart disease, or those on medications to control congestive heart failure.
3) Infants less than 12 months of age, born at 28 weeks gestation or earlier
4) Infants less than 6 months of age, born at 29-31 weeks gestation.
5) Infants less than 12 months of age, born before 35 weeks gestation, with congenital abnormalities of the airway
6) Infants less than 12 months of age, born before 35 weeks gestation, with severe neuromuscular disease
7) Infants, up to 3 months old at the start of RSV season, born at 32-34 weeks gestation, who have one of the following risk factors: (up to three doses only)
    a. Child care attendance
    b. Siblings younger than 5 years of age

* Treatment is authorized for the entire RSV season (as indicated) except for members meeting criteria #7, in which case, a maximum of 3 doses will be authorized. Prescribers may request special consideration for additional doses (up to the end of the RSV season as indicated) on an individual patient basis for members meeting criteria #7.

B. Length of treatment. Synagis® is approved for use only during RSV season. Approval dates were from November 1 through March 31.

C. Units authorized. The maximum duration of therapy is five (5) doses, with a dose to be administered no more often than every 30 days. Infants born at 32-34 weeks gestation will receive a maximum of three doses. Members given doses more frequently than every 30 days will not be authorized for additional doses. Doses administered prior to the member's discharge from a hospital will be counted as one of the approved total.

D. Dose-pooling. To avoid unnecessary risk to the patient, multiple patients are not to be treated from a single vial. Failure to follow this recommendation will result in referral of the provider to the Quality Assurance Committee of the Oklahoma Health Care Authority.

Utilization

For the period of November 1, 2010 through March 31, 2011, a total of 756 SoonerCare members received Synagis® from a pharmacy provider. There were no claims submitted by physicians.

RSV Season	Members	Claims	Cost	Cost/dose	Doses	Units	Days
2009 - 10	812	3,603	$5,955,323.44	$2,174.27	2,739	3,132	107,952
2010 - 11	756	2,998	$5,418,291.70	$2,542.61	2,131	2,616	89,938
Percent Change	-6.90%	-16.80%	-9.00%	16.94%	-22.20%	-16.50%	-16.70%
Change	-56	-605	-$537,031.74	$368.34	-608	-516	-18,014

Claim Type	Cost per Vial
Synagis® 50 mg/0.5 ml vial	$1,095.35
Synagis® 100 mg/ml vial	$2,068.36

Pharmacy Claims

Product	# of Claims	Total Units	Total Days	Total Cost	Total Members
Synagis® 50 mg/0.5 ml vial	955	478	28,646	$4,380,354.74	676
Synagis® 100 mg/ml vial	2,043	2,138	61,292	$1,037,936.96	483
Total	2,998	2,616	89,938	$5,418,291.70	756*

*Total unduplicated members for 10-11

PA Activity

Total petitions - RSV Season 10-11
A total of 1,488 petitions were submitted for consideration of Synagis®.

Approved 851
Denied 270
Incomplete 367

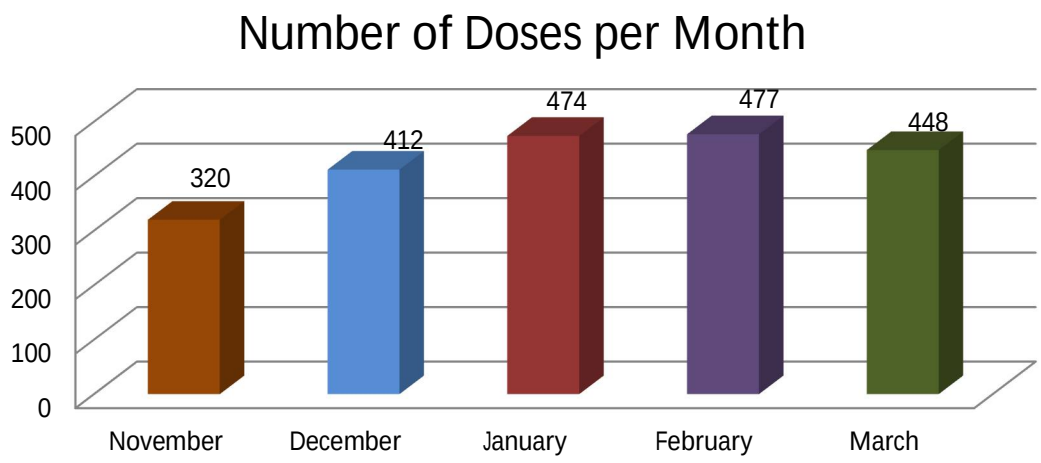
Demographics

Claims were reviewed to determine the age/gender of the members. The 2-year olds were under 24 months at the time of approval.

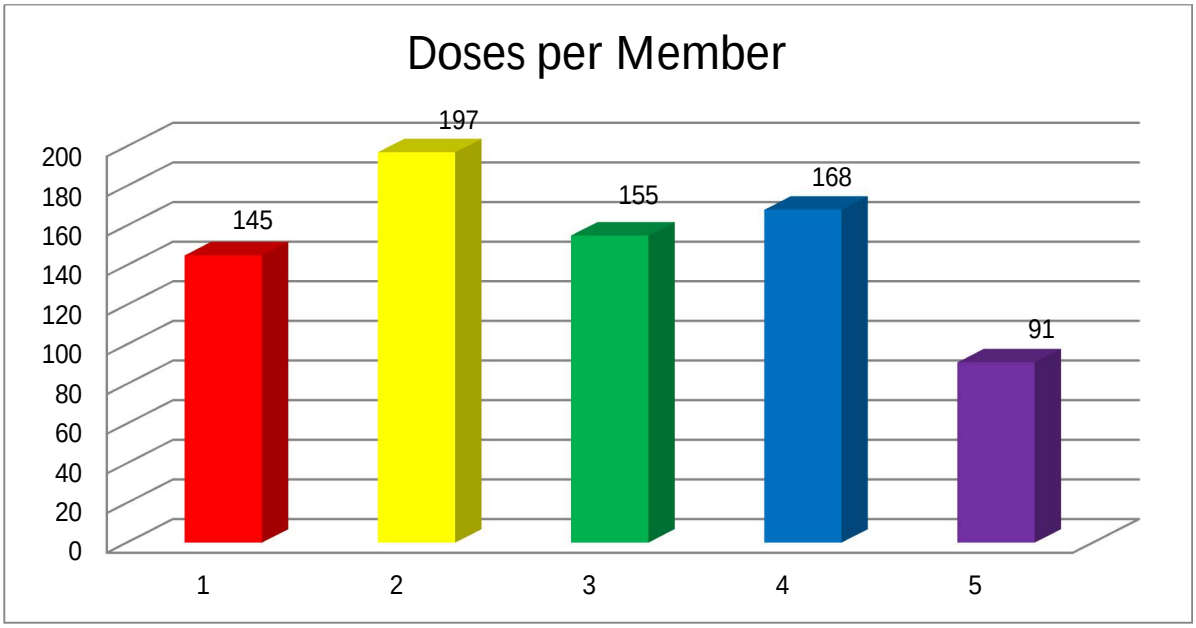
Age	Female	Male	Totals
0	286	322	608
1	56	76	132
2	7	9	16
Totals	349	407	756

Dose Data

A total of 2,131 doses were given through the season. The average cost per dose was $2,542.61. Synagis was limited to 5 doses for the season. Members born at 32-34 weeks gestation received a maximum of 3 doses.

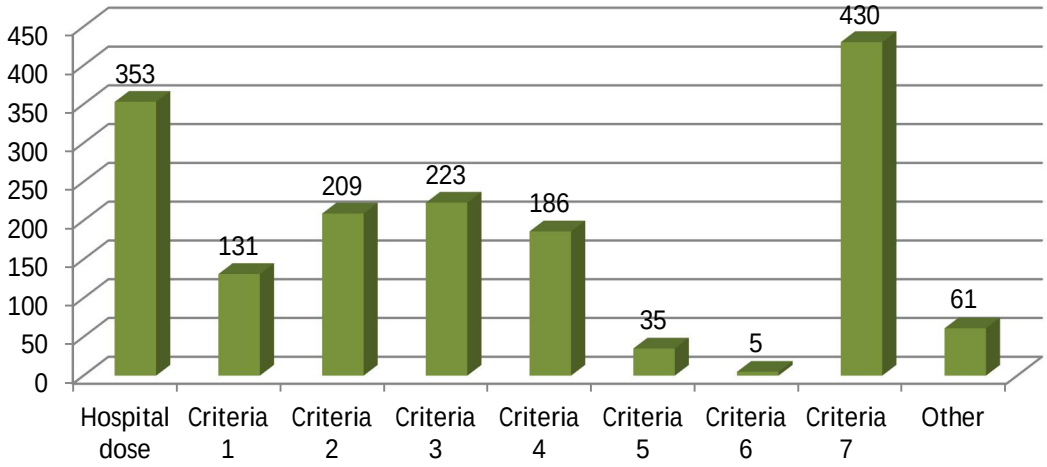


Dosing

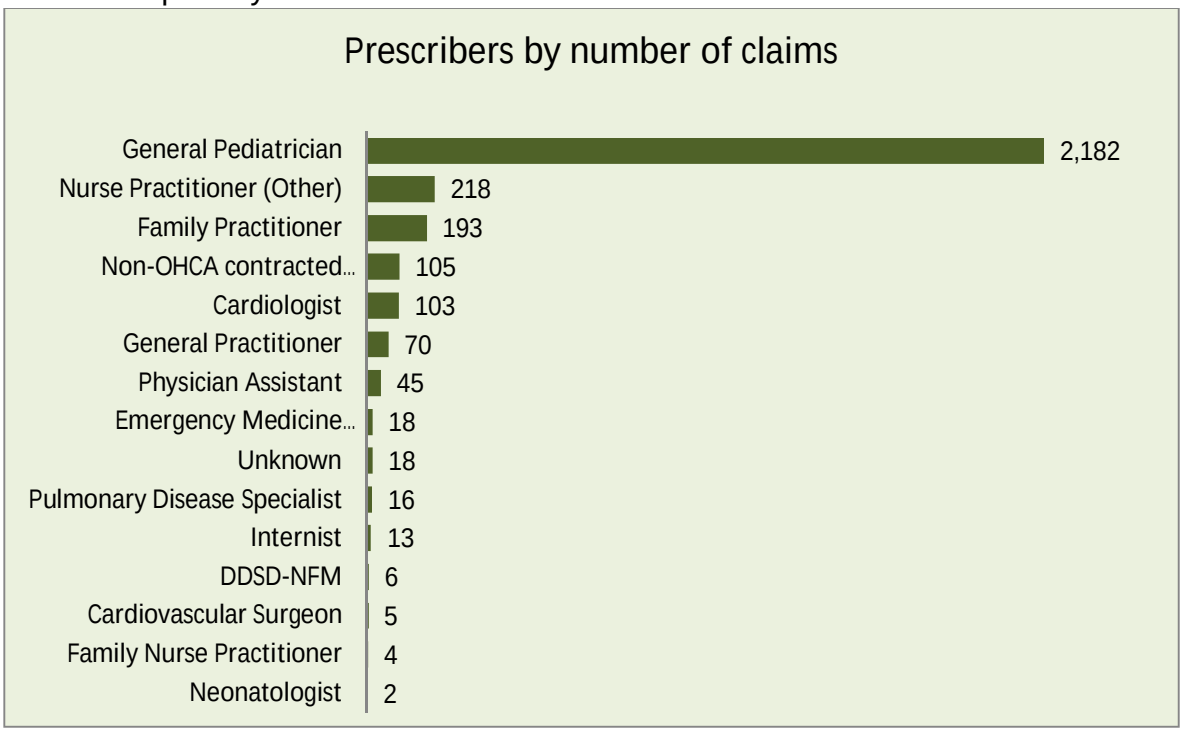


Criteria Totals

The decreased number of doses approved for children born at 32-34 weeks gestation (Criteria 7) helps to explain why the number of members receiving 5 doses is much lower. Doses given in the hospital also decreased the number of doses dispensed. Some members met more than one criterion.



Prescriber Specialty



Discussion

To maximize appropriate referrals, continuity of care, and compliance, the following steps were taken.

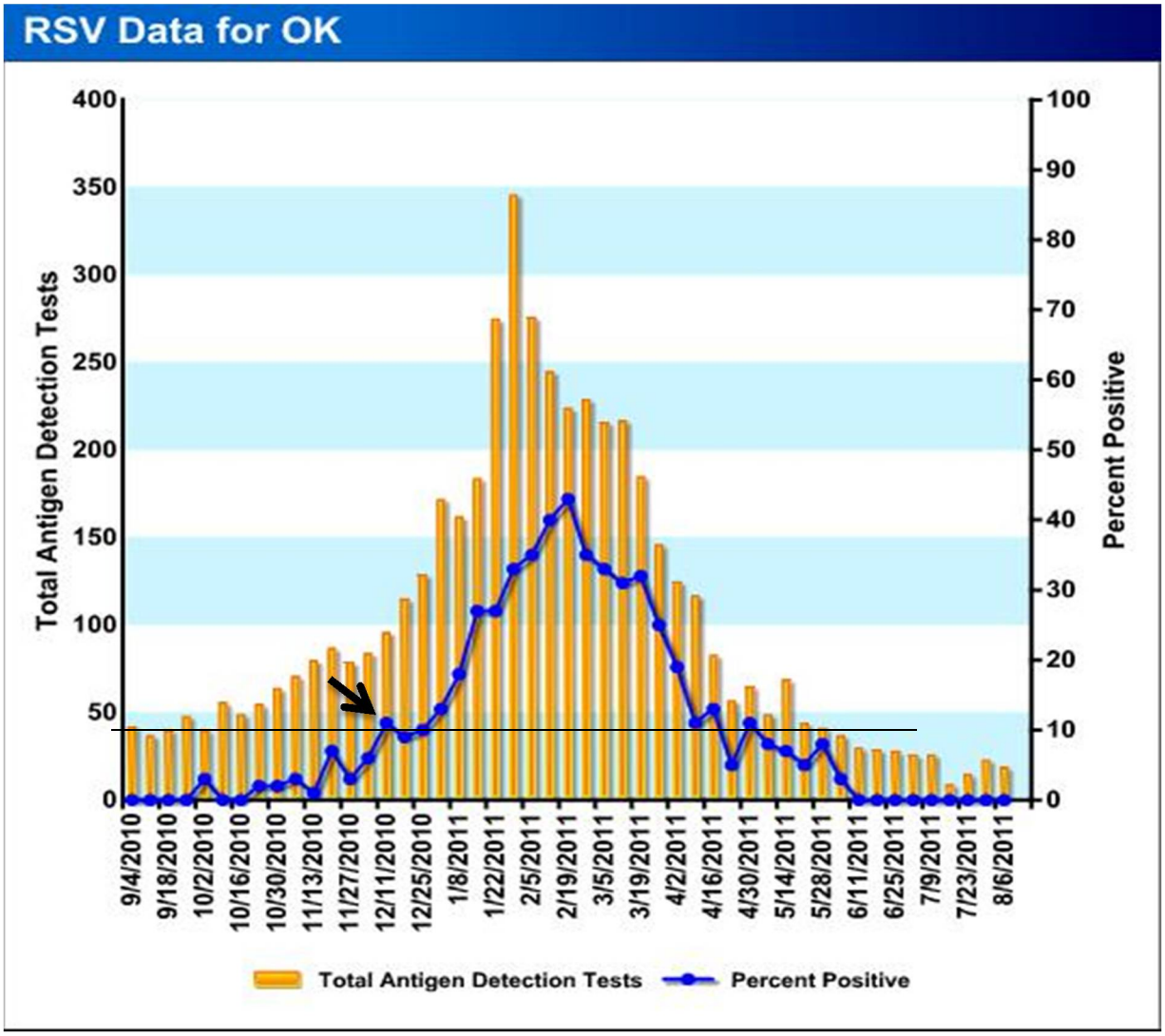
- Starting last season, OHCA Care Management Services was notified by pharmacies and prescribers about infants felt to be at increased risk of noncompliance. Nurse managers contacted the parents to discuss and educate them about the importance of getting Synagis each month, as well as other safety issues. The following message was sent back to the prescriber and the pharmacy with each approved petition:

  For patients at risk of non-compliance, OHCA Care Management Services are available to assist. Please contact them at 877-252-6002.

- Discharge planners at the Neonatal ICU's across the state will be contacted by Medimmune regarding the referral procedure so that there is coordination between the hospital-based neonatologists and the members' PCP.

The 2010-11 RSV season did not reach the epidemic threshold until the first week of January. After the peak in February, there was a gradual decline in cases into March. There was a slight increase in reported cases in mid-March, which corresponds to a winter storm that

occurred in the state. By mid-April, the incidence of RSV had waned and the season was essentially over by the end of the month.



From the National Respiratory and Enteric Virus Surveillance System (NREVSS) at the Centers for Disease Control website: http://www.cdc.gov/surveillance/nrevss/rsv/state.html

Recommendations

The College of Pharmacy recommends no changes to the existing palivizumab authorization criteria.

Appendix J

U.S. Food and Drug Administration

Drugs

FDA Drug Safety Communication: Safety review update of Recombinant Human Growth Hormone (somatropin) and possible increased risk of death

This safety review update is in follow-up to the FDA Drug Safety Communication: Ongoing safety review of Recombinant Human Growth Hormone (somatropin) and possible increased risk of death[1] on 12/22/2010.

[8-4-2011] The U.S. Food and Drug Administration (FDA) is updating the public about its ongoing safety review of recombinant human growth hormone (somatropin) and possible increased risk of death. In December 2010, FDA issued a Drug Safety Communication[2] to inform the public that it was reviewing results from a study conducted in France—the Santé Adulte GH Enfant (SAGhE) study—and other available information on this potential risk. FDA has determined that, at this time, the evidence regarding recombinant human growth hormone and increased risk of death is inconclusive.

In its analysis of the SAGhE study, FDA identified a number of study design weaknesses that limit the interpretability of the study results. FDA also reviewed the medical literature,[1-4] as well as reports from the Agency's Adverse Event Reporting System (AERS). These additional data sources did not provide evidence suggestive of a link between recombinant human growth hormone and an increased risk of death.

Healthcare professionals and patients should continue to prescribe and use recombinant human growth hormone according to the labeled recommendations.

FDA is continuing to review this safety issue and expects to receive additional data from the SAGhE study in Spring 2012. FDA will update the public when new information is available.

References

1. Mills JL, Schonberger LB, Wysowski DK, Brown P, Durako SJ, Cox C, et al. Long-term mortality in the United States cohort of pituitary-derived growth hormone recipients. J Pediatr. 2004;144:430-6.
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3. Bell J, Parker KL, Swinford RD, Hoffman AR, Maneatis T, Lippe B. Long-term safety of recombinant human growth hormone in children. J Clin Endocrinol Metab 2010;95:167-77.
4. Barton JS, Cullen S, Hindmarsh PC, Brook CG, Preece MA. Growth hormone treatment in idiopathic short stature: a preliminary analysis of cardiovascular effects. Acta Paediatr Suppl. 1992;383:35-8.

Related Information

- FDA Drug Safety Communication: Ongoing safety review of Recombinant Human Growth Hormone (somatropin) and possible increased risk of death[3] 12/22/2010
- Somatropin Information[4]
- Comunicado de Seguridad de Medicamentos de la FDA: Actualización de la revisión de seguridad de la hormona de crecimiento humana recombinante (somatropina) y su posible aumento de riesgo de muerte[5]

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6. https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm
7. http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf

U.S. Food and Drug Administration

Drugs

FDA Drug Safety Communication: Updated drug labels for pioglitazone-containing medicines

This update provides a follow-up to the Drug Safety Communication: Update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer[1] issued on 6/15/2011.

[8-4-2011] The U.S. Food and Drug Administration (FDA) is informing the public that the Agency has approved updated drug labels for the pioglitazone-containing medicines to include safety information that the use of pioglitazone for more than one year may be associated with an increased risk of bladder cancer. FDA previously communicated these labeling changes to the public on June 15, 2011 (Drug Safety Communication)[2].

The updated drug labels recommend that healthcare professionals should:

- Not use pioglitazone in patients with active bladder cancer.
- Use pioglitazone with caution in patients with a prior history of bladder cancer.

The updated drug labels recommend that patients should:

- Contact their healthcare professional if they experience any sign of blood in the urine or a red color in the urine or other symptoms such as new or worsening urinary urgency or pain on urination since starting pioglitazone, as these may be due to bladder cancer.

Healthcare professionals and patients can access the latest drug labels for pioglitazone-containing medicines at:

Actos (pioglitazone)[3]

Actoplus Met (pioglitazone/metformin)[4]

Actoplus Met XR (pioglitazone/metformin extended-release)[5]

Duetact (pioglitazone/glimepiride)[6]

Related Information

- FDA Drug Safety Communication: Update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer[7] 6/15/2011
- Pioglitazone HCl (marketed as Actos, Actoplus Met, and Duetact) Information[8]
- Comunicado de Seguridad de Medicamentos de la FDA: Actualización de las etiquetas de los medicamentos que contienen pioglitazona[9]

Labeling and Regulatory History from Drugs@FDA

- Pioglitazone HCL (marketed as Actos) Prescribing and Labeling Information[10]
- Pioglitazone HCl and Metformin HCl (marketed as Actos Met) Prescribing and Labeling Information[11]
- Pioglitazone HCl and Metformin HCl(marketed as Actos Met XR) Prescribing and Labeling Information[12]
- Pioglitazone HCl and Glimepride(marketed as Duetact) Prescribing and Labeling Information[13]

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14. https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm
15. http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf

U.S. Food and Drug Administration

Drugs

Safe Use Initiative: Acetaminophen Toxicity

Acetaminophen is one of the most commonly used medicines in the United States. When used according to the label directions, it has a well-established record of safet and efficacy. Although acetaminophen overdose is very rare in the context of its broad usage, overdose can be toxic and lead to acute liver failure.

Liver injury from acetaminophen overdose remains a serious public health problem despite ongoing regulatory and educational efforts over the past several years to improve the safe use of medicines that contain acetaminophen. Patients can take too much if they take more than the labeled dose of one acetaminophen medicine, or if they take more than one medicine containing acetaminophen (for example, an over-the-counter [OTC] medicine that contains acetaminophen with a prescription medicine that contains acetaminophen).

To prevent acetaminophen overdose, consumers need to be able to read labels and recognize when their medicines contain acetaminophen. The active ingredients in OTC medicines are clearly listed on the label, but the container labels on prescription medicines that contain acetaminophen may not clearly identify acetaminophen as an active ingredient.

Under the leadership of the National Council for Prescription Drug Programs (NCPDP), FDA ś Safe Use Initiative and a broad group of stakeholders came together to form the Acetaminophen Best Practices Task Group, which produced the white paper, "NCPDP Recommendations for Improved Prescription Container Labels for Medicines Containing Acetaminophen (PDF- 974KB)[1]. "(For a list of Task Group members, see Appendix D, "Contributors to this White Paper. ")

These recommendations are intended to make it easier for consumers to: 1) identify that their prescription pain reliever contains acetaminophen, 2) compare active ingredients on their prescription and over-the-counter labels, and 3) take action to avoid taking two medicines with acetaminophen.

The recommendations advocate harmonizing the prescription container labeling with the labeling that already exists for OTC medicines that contain acetaminophen, providing consistency in labeling across all acetaminophen-containing medicines.

The White Paper recommends:

- complete spelling of acetaminophen and all other active ingredients on the pharmacy labels of all acetaminophen-containing prescription medicine, eliminating the use of abbreviations, acronyms or other shortened versions for active ingredients
- a standardized concomitant use and liver pharmacy warning label for these medicines
- formatting and wording on pharmacy container labels consistent with plain language and health literacy principles
- a stakeholder call to action: adopt, implement, adhere, communicate and educate

The Safe Use Initiative will continue to work with stakeholders to encourage adoption, implementation and adherence to these recommendations, to address existing barriers and to encourage education and communication to improve the safe use of acetaminophen medicines.

In addition, the Safe Use Initiative will continue to initiate and participate in collaborative efforts and alternative strategies to help decrease unintentional overdose of acetaminophen-containing medicines.

For more, please go to FDA's Acetaminophen Information[2] page.

Background Information

- NCPDP Recommendations for Improved Prescription Container Labels for Medicines Containing Acetaminophen (PDF) (PDF - 1000KB)[3]
  NABP ś recommendation to boards of pharmacy, July 15, 2010
- FDA and NABP Partner to Help Prevent Acetaminophen Toxicity[4][5]
  November 4, 2010
- FDA's Safe Use Initiative: Reducing Harm Risk From Acetaminophen (PDF - 547KB)[6]
  Pharmacy Today, FDA Update, September 2010
- Prohibition of Acetaminophen Abbreviation (PDF - 20KB)[7]
  Letter from Janet Woodcock, FDA, to Carmen Catizone, NABP about Prohibition of Acetaminophen Abbreviation, July 19, 2010
- NABP Recommends Boards of Pharmacy Prohibit Use of Acetaminophen Abbreviation[8][9]
  NABP ś recommendation to boards of pharmacy (July 15, 2010)
- Letter to State Boards Of Pharmacy on Acetaminophen (PDF - 19KB)[10]
  Letter from Steven Galson, FDA, to state boards of pharmacy, January 22, 2004

Related Information

- Acetaminophen Information[11]
- Using Acetaminophen and Nonsteroidal Anti-inflammatory Drugs Safely[12]
  Consumer Information Materials
- Acetaminophen Awareness Coalition ś Know Your Dose Campaign[13][14]
- Reducing Fever in Children: Safe Use of Acetaminophen[15]
  Consumer Update
- Safe Use Initiative: Preventing Harm from Medicines[16]
  Consumer Update

Contact Us

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12. /Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/SafeUseofOver-the-CounterPainRelieversandFeverReducers/ucm164977.htm
13. http://www.knowyourdose.org/
14. /AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm
15. /ForConsumers/ConsumerUpdates/ucm263989.htm
16. /ForConsumers/ConsumerUpdates/ucm261175.htm

U.S. Food and Drug Administration

Drugs

FDA Drug Safety Communication:Use of long-term, high-dose Diflucan (fluconazole) during pregnancy may be associated with birth defects in infants

Safety Announcement

[8-03-2011] The U.S. Food and Drug Administration (FDA) is informing the public that chronic, high doses (400-800 mg/day) of the antifungal drug Diflucan (fluconazole) may be associated with a rare and distinct set of birth defects in infants whose mothers were treated with the drug during the first trimester of pregnancy This risk does not appear to be associated with a single, low dose of fluconazole 150 mg to treat vaginal yeast infection (candidiasis).

There are several published case reports of birth defects in infants whose mothers were treated with high-dose fluconazole (400-800 mg/day) for serious and life-threatening fungal infections during most or all of the first trimester (see Data Summary below).[1-4] The features seen in these infants are listed in Table 1.

Based on this information, the pregnancy category for fluconazole indications (other than vaginal candidiasis) has been changed from category C to category D. The pregnancy category for a single dose of fluconazole 150 mg to treat vaginal candidiasis has not changed and remains category C.

Pregnancy category D means there is positive evidence of human fetal risk based on human data but the potential benefits from use of the drug in pregnant women with serious or life-threatening conditions may be acceptable despite its risks.

Facts about Diflucan (fluconazole)

- Used to treat yeast infections of the vagina, mouth, throat, esophagus, and other organs.
- Used to treat meningitis caused by a certain type of fungus.
- Used to prevent yeast infections in patients who are likely to become infected because they are being treated with chemotherapy or radiation therapy before a bone marrow transplant.
- The dose of fluconazole for vaginal candidiasis is a single dose of 150 mg and is lower than for other indications.

Healthcare professionals should be aware of the potential risks with long-term, high-dose use of fluconazole and counsel patients if the drug is used during pregnancy or if a patient becomes pregnant while taking the drug.

Additional Information for Patients

- Use of long-term, high-dose (400-800 mg/day) fluconazole during the first three months of pregnancy (first trimester) may be associated with a rare and distinct set of birth defects in infants.
- A single dose of fluconazole 150 mg to treat vaginal yeast infection during pregnancy does not appear to be associated with the birth defects.
- Patients should notify their healthcare professional if they are pregnant or become pregnant while taking fluconazole.
- Side effects from the use of fluconazole should be reported to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page.

Additional Information for Healthcare Professionals

- The pregnancy category for a single 150 mg dose of fluconazole for vaginal candidiasis is category C based on data from animal studies that showed an advers effect on the fetus. There are no adequate and well-controlled studies of fluconazole in pregnant women. Available human data do not suggest an increased risk of congenital anomalies following a single maternal dose of 150 mg.
- The pregnancy category for fluconazole use for indications other than vaginal candidiasis is now category D. A few published case reports describe a rare pattern of distinct congenital anomalies in infants exposed in utero to high-dose maternal fluconazole (400-800 mg/day) during most or all of the first trimester.
- The features seen in these infants include brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease. These effects are similar to those seen in animal studies.
- If fluconazole is used during pregnancy, or if a patient becomes pregnant while taking fluconazole, the patient should be informed of the potential risk to the fetus.
- Adverse events involving fluconazole should be reported to the FDA MedWatch program using the information in the "Contact Us" box at the bottom of this page.

Data Summary

There are several case reports published in the medical literature that describe rare and distinct congenital anomalies in infants whose mothers were treated with chronic high-dose (400-800 mg/day) fluconazole for fungal infections in the first trimester of pregnancy.[1-4] Four reports involved maternal use of chronic high-dose intravenous fluconazole for coccidioidal meningitis and one report involved a human immunodeficiency virus (HIV)-positive mother who received chronic high-dose oral fluconazole for vaginal candidiasis. Cases associated with high-dose fluconazole use all shared some characteristics with the autosomal recessive genetic disorder know as Antley-Bixler syndrome. This combination of congenital anomalies occurs rarely in the general population, and is similar to anomalies seen in animals following in utero fluconazole exposure.

Chronic high-dose fluconazole may be teratogenic in humans when used in the first trimester of pregnancy; however, the magnitude of this potential human teratogeni risk is unknown. The five reports of distinct and rare congenital anomalies following chronic, high-dose in utero exposure to fluconazole suggest a possible drug threshold effect for a fluconazole embryopathy.

The available data in the medical literature do not suggest an association between low-dose oral fluconazole use in the first trimester of pregnancy and congenital anomalies.[5-11] The few published epidemiological studies of in utero exposure to low doses of fluconazole (most patients received a single oral dose of 150 mg) showed

no consistent pattern of anomalies among affected infants; however, most of these studies were too small to accurately detect an increased risk for major birth defects overall.[7, 9-11] In addition, none of these studies were large enough to accurately detect an increased risk for a rare or unique birth defect or syndrome.

Table 1.

Features Seen in Infants Exposed to long-term, high-dose Diflucan (fluconazole) in utero

short, broad head
abnormal looking face
abnormal development of the skullcap
oral cleft (opening in the lip or palate)
bowing of the thigh bones
thin ribs and long bones
muscle weakness and joint deformities
Congenital (present at birth) heart disease

References

1. Lopez-Rangel E, Van Allen MI. Prenatal exposure to fluconazole: an identifiable dysmorphic phenotype. Birth Defects Res A Clin Mol Teratol. 2005;73:919-23.
2. Pursley TJ, Blomquist IK, Abraham J, Andersen HF, Bartley JA. Fluconazole-induced congenital anomalies in three infants. Clin Infect Dis. 1996;22:336-40.
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11. Nørgaard M, Pedersen L, Gislum M, Erichsen R, Søgaard KK, Schønheyder HC, et al. Maternal use of fluconazole and risk of congenital malformations: a Danish population-based cohort study. J Antimicrob Chemother. 2008;62:172-6.

Related Information

- Fluconazole (marketed as Diflucan) Information[1]
- FDA Drug Safety Podcast for Healthcare Professionals: Use of long-term, high-dose Diflucan (fluconazole) during pregnancy may be associated with birth defects in infants[2]
- Comunicado de Seguridad de Medicamentos de la FDA: El uso prolongado de dosis altas de Diflucan (fluconazol) durante el embarazo podría estar asociado co defectos congénitos en infantes[3]

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U.S. Food and Drug Administration

Drugs

FDA Drug Safety Communication: Abnormal heart rhythms associated with high doses of Celexa (citalopram hydrobromide)

Safety Announcement

[8-24-2011] The U.S. Food and Drug Administration (FDA) is informing healthcare professionals and patients that the antidepressant Celexa (citalopram hydrobromide; also marketed as generics) should no longer be used at doses greater than 40 mg per day because it can cause abnormal changes in the electrical activity of the heart. Studies did not show a benefit in the treatment of depression at doses higher than 40 mg per day.

Previously, the citalopram drug label stated that certain patients may require a dose of 60 mg per day.

Changes in the electrical activity of the heart (prolongation of the QT interval of the electrocardiogram [ECG]) - see Data Summary below - can lead to an abnormal heart rhythm (including Torsade de Pointes), which can be fatal. Patients at particular risk for developing prolongation of the QT interval include those with underlying heart conditions and those who are predisposed to low levels of potassium and magnesium in the blood.

Facts about Celexa (citalopram hydrobromide)

- Is in a class of antidepressants called selective serotonin reuptake inhibitors (SSRIs).
- Thought to work by increasing the amount of serotonin in the brain.[1]
- Available as 10 mg, 20 mg, and 40 mg tablets. Also available as an oral solution (10 mg/5 mL).

The citalopram drug label has been revised to include the new drug dosage and usage recommendations, as well as information about the potential for QT interval prolongation and Torsade de Pointes. (See Additional Information for Healthcare Professionals)

Additional Information for Patients

- Do not stop taking citalopram or change your dose without talking to your healthcare professional. Stopping citalopram suddenly can cause unwanted side effects.
- If you are currently taking a citalopram dose greater than 40 mg per day, talk to your healthcare professional about changing your dose.
- Seek immediate care if you experience an irregular heartbeat, shortness of breath, dizziness, or fainting while taking citalopram.
- If you are taking citalopram, your healthcare professional may occasionally order an electrocardiogram (ECG, EKG) to monitor your heart rate and rhythm. An ECG is a test that checks for problems with the electrical activity of your heart.
- Read the Medication Guide for citalopram carefully and discuss any questions you have with your healthcare professional.
- Report any side effects you experience to the FDA MedWatch program using the information in the "Contact Us" box at the bottom of the page.

Additional Information for Healthcare Professionals

- Citalopram causes dose-dependent QT interval prolongation. Citalopram should no longer be prescribed at doses greater than 40 mg per day.
- Citalopram should not be used in patients with congenital long QT syndrome.
- Patients with congestive heart failure, bradyarrhythmias, or predisposition to hypokalemia or hypomagnesemia because of concomitant illness or drugs, are at higher risk of developing Torsade de Pointes.
- Hypokalemia and hypomagnesemia should be corrected before administering citalopram. Electrolytes should be monitored as clinically indicated.
- Consider more frequent electrocardiogram (ECG) monitoring in patients with congestive heart failure, bradyarrhythmias, or patients on concomitant medications that prolong the QT interval.
- 20 mg per day is the maximum recommended dose for patients with hepatic impairment, who are greater than 60 years of age, who are CYP 2C19 poor metabolizers, or who are taking concomitant cimetidine (Tagamet®), because these factors lead to increased blood levels of citalopram, increasing the risk of QT interval prolongation and Torsade de Pointes.
- No dose adjustment is necessary for patients with mild or moderate renal impairment.
- Advise patients to contact a healthcare professional immediately if they experience signs and symptoms of an abnormal heart rate or rhythm while taking citalopram.
- Report adverse events involving citalopram to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page.

Data Summary

FDA has received post-marketing reports of QT interval prolongation and Torsade de Pointes associated with Celexa and its generic equivalents. In addition, FDA has evaluated the results of a thorough QT study assessing the effects of 20-mg and 60-mg doses of citalopram on the QT interval in adults. In this randomized, multi-center, double-blind, placebo-controlled, crossover study, 119 subjects received citalopram 20 mg per day (Day 9), citalopram 60 mg per day (Day 22), and placebo. The overall summary of findings is presented in Table 1

Table 1: Increase in the Corrected QT Interval for Citalopram (FDA Analysis)

Citalopram Dose	Increase in QT Interval (ms)	90% Confidence Interval (ms)
20 mg/day	8.5	(6.2, 10.8)
60 mg/day	18.5	(16.0, 21.0)
40 mg/day	12.6*	(10.9, 14.3)*

*Estimate based on the relationship between citalopram blood concentration and QT interval.

Compared to placebo, maximum mean prolongations in the individually corrected QT intervals were 8.5 and 18.5 milliseconds (ms) for 20 mg and 60 mg citalopram, respectively. For 40 mg citalopram, prolongation of the corrected QT interval was estimated to be 12.6 ms.

As a result of this thorough QT study, FDA has determined that citalopram causes dose-dependent QT interval prolongation and should no longer be used at doses above 40 mg per day. Important safety information about the potential for QT interval prolongation and Torsade de Pointes with drug dosage and usage recommendations are being added to the package inserts of Celexa and its generic equivalents.

References

1. National Center for Biotechnology Information. U.S. National Library of Medicine. PubMed Drug & Supplements Monograph Citalopram. Available at: http://www.nlm.nih.gov/medlineplus/druginfo/meds/a699001.html[1]. Accessed July 20, 2011.

Related Information

- Citalopram (marketed as Celexa) Information[2]
- Citalopram: MedlinePlus Drug Information[3]
- FDA Drug Podcast for Healthcare Professionals: Abnormal heart rhythms associated with high doses of Celexa (citalopram hydrobromide)[4]

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5. https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm
6. http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf

U.S. Food and Drug Administration

News & Events

FDA NEWS RELEASE

For Immediate Release: Aug. 19, 2011
Media Inquiries: Erica Jefferson, 301-796-4988, erica.jefferson@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves Adcetris to treat two types of lymphoma

The U.S. Food and Drug Administration today approved Adcetris (brentuximab vedotin) to treat Hodgkin lymphoma (HL) and a rare lymphoma known as systemic anaplastic large cell lymphoma (ALCL).

Lymphomas are cancers of the lymphatic system. Adcetris is an antibody-drug conjugate that combines an antibody and drug, allowing the antibody to direct the drug to a target on lymphoma cells known as CD30.

Adcetris is to be used in patients with HL whose disease has progressed after autologous stem cell transplant or after two prior chemotherapy treatments for those who cannot receive a transplant. Autologous stem cell transplant is a procedure using a patient's own bone marrow that is designed to repair damaged bone marrow after the use of high chemotherapy doses. Adcetris may also be used in patients with ALCL whose disease has progressed after one prior chemotherapy treatment.

"Early clinical data suggest that patients who received Adcetris for Hodgkin lymphoma and systemic anaplastic lymphoma experienced a significant response to the therapy," said Richard Pazdur, M.D., director of the Office of Oncology Drug Products in the FDA's Center for Drug Evaluation and Research.

According to the National Cancer Institute (NCI), common symptoms of HL include the enlargement of lymph nodes, spleen, fever, weight loss, fatigue, or night sweats. NCI estimates that 8,830 new cases of HL will be diagnosed in the United States in 2011 and about 1,300 people will die from the disease.

Systemic ALCL is a rare malignant tumor (non-Hodgkin lymphoma) that may appear in several parts of the body including the lymph nodes, skin, bones, soft tissue, lungs or liver, according to the NCI.

Adcetris is the first new FDA-approved treatment for HL since 1977 and the first specifically indicated to treat ALCL.

The effectiveness of Adcetris in patients with HL was evaluated in a single clinical trial involving 102 patients. In the single-arm trial, patients were only treated with Adcetris. The study's primary endpoint was objective response rate, the percentage of patients who experienced complete or partial cancer shrinkage or disappearance after treatment. Seventy-three percent of patients achieved either a complete or partial response to the treatment. On average, these patients responded to the therapy for 6.7 months.

The effectiveness of Adcetris in patients with systemic ALCL was evaluated in a single clinical trial in 58 patients. In the single-arm trial, patients were only treated with Adcetris. Similar to the HL trial, the trial's primary endpoint was objective response rate. Of the patients receiving Adcetris for ALCL, 86 percent experienced either a complete or partial response and responded on average for 12.6 months.

The most common side effects experienced with Adcetris were a decrease in infection-fighting white blood cells (neutropenia), nerve damage (peripheral sensory neuropathy), fatigue, nausea, anemia, upper respiratory infection, diarrhea, fever, cough, vomiting, and low blood platelet levels (thrombocytopenia).

Pregnant women should be aware that Adcetris might cause harm to their unborn baby.

The drug is being approved under the FDA's accelerated approval program, which allows the agency to approve a drug to treat a serious disease based on clinical data showing that the drug has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients. The program is designed to provide patient with earlier access to promising new drugs, but the company will be required to submit additional clinical information after approval to confirm the drug's clinical benefit.

Adcetris is marketed by Seattle Genetics of Bothell, Wash.

For more information:

FDA: Office of Oncology Drug Products [1]

NCI: Hodgkin lymphoma [2]

NCI: Non-Hodgkin lymphoma [3]

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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U.S. Food and Drug Administration

News & Events

FDA NEWS RELEASE

For Immediate Release: Aug. 17, 2011
Media Inquiries: Erica Jefferson, 301-796-4988, erica.jefferson@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves Zelboraf and companion diagnostic test for late-stage skin cancer
Second melanoma drug approved this year that improves overall survival

The U.S. Food and Drug Administration today approved Zelboraf (vemurafenib), a drug to treat patients with late-stage (metastatic) or unresectable (cannot be removed by surgery) melanoma, the most dangerous type of skin cancer.

Zelboraf is specifically indicated for the treatment of patients with melanoma whose tumors express a gene mutation called BRAF V600E. The drug has not been studie in patients whose melanoma tests negative for that mutation by an FDA approved diagnostic.

Zelboraf is being approved with a first-of-a-kind test called the cobas 4800 BRAF V600 Mutation Test, a companion diagnostic that will help determine if a patient s melanoma cells have the BRAF V600E mutation.

The BRAF protein is normally involved in regulating cell growth, but is mutated in about half of the patients with late-stage melanomas. Zelboraf is a BRAF inhibitor tha is able to block the function of the V600E-mutated BRAF protein.

"This has been an important year for patients with late-stage melanoma. Zelboraf is the second new cancer drug approved that demonstrates an improvement in overall survival, "said Richard Pazdur, M.D., director of the Office of Oncology Drug Products in the FDA s Center for Drug Evaluation and Research. "In March, we approved Yervoy (ipilimumab), another new treatment for late-stage melanoma that also showed patients live longer after receiving the drug. "

Zelboraf was reviewed under the FDA s priority review program that provides for an expedited six-month review of drugs that may offer major advances in treatment o that provide a treatment when no adequate therapy exists. Zelboraf and the companion BRAF V600E test are being approved ahead of the drug s Oct. 28, 2011 goal date and the companion diagnostics 'Nov. 12, 2011 goal date.

Zelboraf s safety and effectiveness were established in a single international trial of 675 patients with late-stage melanoma with the BRAF V600E mutation who had not received prior therapy. Patients were assigned to receive either Zelboraf or dacarbazine, another anti-cancer therapy. The trial was designed to measure overall surviva (the length of time between start of treatment and death of a patient).

The median survival (the length of time a patient lives after treatment) of patients receiving Zelboraf has not been reached (77 percent still living) while the median survival for those who received dacarbazine was 8 months (64 percent still living).

"Today s approval of Zelboraf and the cobas test is a great example of how companion diagnostics can be developed and used to ensure patients are exposed to highly effective, more personalized therapies in a safe manner, "said Alberto Gutierrez, Ph.D., director of the Office of In Vitro Diagnostic Device Evaluation and Safety in the FDA s Center for Devices and Radiological Health.

The FDA s approval of the cobas 4800 BRAF V600 Mutation Test was based on data from the clinical study that also evaluated the safety and effectiveness of Zelboraf. Samples of a patient s melanoma tissue were collected to test for the mutation.

The most common side effects reported in patients receiving Zelboraf included joint pain, rash, hair loss, fatigue, nausea, and skin sensitivity when exposed to the sun About 26 percent of patients developed a skin-related cancer called cutaneous squamous cell carcinoma, which was managed with surgery. Patients treated with Zelboraf should avoid sun exposure.

Zelboraf is being approved with a Medication Guide to inform health care professionals and patients of Zelboraf s potential risks.

In July 2011, the FDA issued a new draft guidance to facilitate the development and review of companion diagnostics. The guidance, currently available for public comment, is intended to provide companies with guidance on the agency s policy for reviewing a companion diagnostic and the corresponding drug therapy.

Melanoma is the leading cause of death from skin disease. The National Cancer Institute estimated that 68,130 new cases of melanoma were diagnosed in the United States during 2010; about 8,700 people died from the disease.

Zelboraf is marketed by South San Francisco based-Genentech, a member of the Roche Group. The cobas 4800 BRAF V600 Mutation Test is manufactured by Roche Molecular Systems in Pleasanton, Calif.

For more information:

FDA: Office of Oncology Drug Products [1]

FDA: Office of In Vitro Diagnostics [2]

FDA: Draft Guidance – In Vitro Companion Diagnostic Devices [3]

FDA: Approved Drugs: Questions and Answers [4]

NCI: Melanoma [5]

CDC: Skin Cancer [6]

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation s food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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U.S. Food and Drug Administration

Drugs

FDA Drug Safety Podcast for Healthcare Professionals: New contraindication and updated warning on kidney impairment for Reclast (zoledronic acid)

Podcast [1]

Welcome, my name is Steve Jackson, a pharmacist in the Division of Drug Information. On September 1, 2011, the Food and Drug Administration issued a Drug Safety Communication informing the public that FDA has approved an update to the drug label for Reclast, active ingredient zoledronic acid, to better inform healthcare professionals and patients of the risk of renal failure. Renal failure is a rare, but serious, condition associated with the use of Reclast in patients with a history of or risk factors for renal impairment. Cases of acute renal failure requiring dialysis or having a fatal outcome following Reclast use have been reported to FDA.

These labeling changes are being made to the Reclast label only, although zoledronic acid, also sold as Zometa, is approved for treatment of cancer-related indications. Renal toxicity is already addressed in the Warnings and Precautions section of the Zometa label as well as in the Reclast label. Dose reductions for Zometa are provided for patients with renal impairment.

Risk factors for developing renal failure include underlying moderate to severe renal impairment, use of nephrotoxic or diuretic medications at the same time as Reclast or severe dehydration occurring before or after Reclast is given. The risk of developing renal failure in patients with underlying renal impairment also increases with age.

The revised drug label will enhance the safe use of Reclast by providing healthcare professionals updated instructions for prescribing and patient monitoring. The revised label states that Reclast is contraindicated in patients with creatinine clearance less than 35 mL/min or in patients with evidence of acute renal impairment. The label also recommends that healthcare professionals screen patients prior to administering Reclast in order to identify at-risk patients. Healthcare professionals should also monitor renal function in patients who are receiving Reclast.

The Reclast Medication Guide for patients is being updated to contain information about the risk of severe kidney problems. In addition, the manufacturer of Reclast will issue a Dear Healthcare Provider letter to inform healthcare professionals about this risk.

At this time FDA recommends that Healthcare Professionals be aware that:

1. Reclast is contraindicated in patients with creatinine clearance less than 35 mL/min or in patients with evidence of acute renal impairment.
2. Patients should continue to be screened prior to each administration of Reclast to identify those with underlying acute or chronic renal impairment, advanced age, or dehydration. Patients with underlying renal impairment appear to be at highest risk for kidney failure. Reclast should be used with caution in this population.
3. The risk of acute renal failure may increase with underlying renal disease and dehydration secondary to fever, sepsis, gastrointestinal losses, diuretic therapy, etc. The risk of developing renal failure in patients with renal impairment also increases with age.
4. Creatinine clearance should be calculated before each dose of Reclast. Interim monitoring of creatinine clearance should be performed after Reclast dosing in a -risk patients. Creatinine clearance should be calculated based on actual body weight using the Cockcroft-Gault formula.
5. Adverse events with Reclast should be reported to FDA's MedWatch program at www.fda.gov/medwatch [2].

Thank you for listening. The FDA is committed to keeping healthcare professionals informed of the latest safety information. Please read the Drug Safety Communication for the complete Data Summary detailing this communication. A link to this DSC can be found at www.fda.gov/Drugs/DrugSafety [3]. If you have drug questions, you can reach us at druginfo@fda.hhs.gov.

Related Information

- FDA Drug Safety Communication: New contraindication and updated warning on kidney impairment for Reclast (zoledronic acid) [4]
- FDA Drug Safety Podcast for Healthcare Professionals: New contraindication and updated warning on kidney impairment for Reclast (zoledronic acid) mp3 (MP3 - 7868KB) [5]

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4. /Drugs/DrugSafety/ucm270199.htm

U.S. Food and Drug Administration

Drugs

FDA Drug Safety Podcast for Healthcare Professionals: Serious allergic reactions reported with the use of Saphris (asenapine maleate)

Podcast [1]

Welcome, my name is Jennifer Shepherd, a pharmacist in the Division of Drug Information. On September 1, 2011, the Food and Drug Administration issued a Drug Safety Communication warning the public that serious allergic reactions have been reported with the use of the antipsychotic medication Saphris, active ingredient asenapine maleate. The Contraindications, Warnings and Precautions, Adverse Reactions, and Patient Counseling Information sections of the Saphris drug label have been revised to include information about this risk and to inform healthcare professionals that Saphris should not be used in patients with a known hypersensitivity to the drug.

A search of the FDA's Adverse Event Reporting System database identified 52 cases of Type I hypersensitivity reactions with Saphris use. Hypersensitivity reactions car be classified into four categories (Type I to Type IV). Signs and symptoms of Type I hypersensitivity reactions may include anaphylaxis, angioedema, low blood pressure, rapid heart rate, swollen tongue, difficulty breathing, wheezing, or rash. These signs and symptoms are consistent with the reactions reported in the 52 cases Several cases reported multiple hypersensitivity reactions occurring at the same time, with some of these reactions occurring after the first dose of Saphris.

Healthcare professionals should be aware of the risk of hypersensitivity reactions with Saphris and counsel patients who are receiving the drug about how to recognize the signs and symptoms of a serious allergic reaction. Saphris should not be used in patients with a known hypersensitivity to the drug.

At this time, FDA recommends that Healthcare Professionals be aware that:

1. Type I hypersensitivity reactions, including anaphylaxis and angioedema, have been observed in patients treated with Saphris. In several cases, these reaction occurred after the first dose.
2. The hypersensitivity reactions included: anaphylaxis, angioedema, hypotension, tachycardia, swollen tongue, dyspnea, wheezing, and rash.
3. Saphris is contraindicated in patients with a known hypersensitivity to the product.
4. Patients should be educated to recognize the signs and symptoms of a serious allergic reaction and advised to contact a healthcare professional immediately if they experience any of these symptoms while taking Saphris.
5. Adverse events involving Saphris should be reported to the FDA MedWatch program at www.fda.gov/medwatch [2].

Thank you for listening. The FDA is committed to keeping healthcare professionals informed of the latest safety information. Please read the Drug Safety Communication for the complete Data Summary detailing this communication. A link to this DSC can be found at www.fda.gov/Drugs/DrugSafety [3]. If you have drug questions, you can reach us at druginfo@fda.hhs.gov.

Related Information

- FDA Drug Safety Podcast for Healthcare Professionals: Serious allergic reactions reported with the use of Saphris (asenapine maleate) - mp3 (MP3 - 6392KB) [4]
- FDA Drug Safety Communication: Serious allergic reactions reported with the use of Saphris (asenapine maleate) [5]
  9/1/2011
- Atypical Antipsychotic Drugs Information [6]

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