Drug Utilization Review Board

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

Wednesday
August 10, 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 – August 10, 2011

DATE: August 4, 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 August 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 Zuplenz® – See Appendix C.

Action Item – Annual Review of Atypical Antipsychotics – See Appendix D.

30 Day Notice to Prior Authorize Diabetes Medications – See Appendix E.

30 Day Notice to Prior Authorize Berinert®, Cinryze®, and Kalbitor® – See Appendix F.

30 Day Notice to Prior Authorize Xiaflex®– See Appendix G.

Drug Utilization Review of Biologic Products for the Treatment of Rheumatoid Arthritis, Crohn's Disease, Plaque Psoriasis, and Ankylosing Spondylitis – See Appendix H.

FDA and DEA Updates – See Appendix I.

Future Business

Adjournment

Oklahoma Health Care Authority
Drug Utilization Review Board
(DUR Board)
Meeting – August 10, 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. June 8, 2011 DUR Minutes – Vote
- B. June 9, 2011 DUR Recommendation Memorandum
- C. Correspondence

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 April 2011
- B. Retrospective Drug Utilization Review Response for March 2011
- C. Medication Coverage Activity Audit for June, July 2011
- D. Pharmacy Help Desk Activity Audit for June, July 2011

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

5. Action Item – Vote to Prior Authorize Zuplenz® – See Appendix C.
- A. Overview
- B. COP Recommendations

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

6. Action Item – Annual Review of Atypical Antipsychotics – See Appendix D.
- A. Current Authorization Criteria
- B. Utilization Review
- C. Market Update
- D. Adverse Event Questionnaire Responses
- E. COP Recommendations
- F. Utilization Details

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

7. 30 Day Notice to Prior Authorize Diabetes Medications – See Appendix E.

A. COP Recommendations

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

8. 30 Day Notice to Prior Authorize Berinert®, Cinryze®, and Kalbitor® – See Appendix F.

A. Introduction
B. Treatment Options
C. Utilization Data
D. COP Recommendations
E. Product Details

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

9. 30 Day Notice to Prior Authorize Xiaflex® – See Appendix G.

A. Summary of Dupuytren's Contracture
B. Product Summary
C. Utilization Data
D. COP Recommendations

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

10. Drug Utilization Review of Biologic Products for the Treatment of Rheumatoid Arthritis, Crohn's Disease, Plaque Psoriasis, and Ankylosing Spondylitis – See Appendix H.

A. Product Overviews
B. Utilization Review
C. COP Recommendations
D. Utilization Details

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

11. FDA and DEA Updates – See Appendix I.

12. Future Business

A. Utilization Review of Multiple Sclerosis Agents
B. Annual Review of Synagis
C. Annual Review of Ophthalmic Products
D. New Product Reviews

13. Adjournment

Appendix A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES of MEETING of JUNE 8, 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	
Wynn Phung, 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:

Jeff Himmelberg, GlaxoSmithKline	David Mershon, Bristol-Myers Squibb	Janie Huff, Takeda
Jim Dunlap, Eli Lilly	James Osborne, GSK	Kathleen Karnik, OMJ-SA
Russ Wilson, OMJ-PI	Steve Appling, Merck	Andre Johnson, Avanir
Kim Greenberg, Amylin	Jim Chapman, Abbott	Ben Liniger, Alcon
Brad Hayes-Miller, Pharma	Charlene Kaiser, Amgen	Brian Maves, Pfizer
Laura Mitchell, Purdue	Sam Smothers, MedImmune	

PRESENT FOR PUBLIC COMMENT:

Agenda Item No. 6 Chris Schwab, Human Genome Sciences

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 Chris Schwab, Human Genome Sciences

ACTION: NONE REQUIRED

AGENDA ITEM NO. 3: APPROVAL OF DUR BOARD MINUTES

3A: May 11, 2011 DUR Minutes

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

ACTION: MOTION CARRIED

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

4A: Retrospective Drug Utilization Review Response: February 2011

4B: Medication Coverage Activity Audit: May 2011

4C: Pharmacy Help Desk Activity Audit: May 2011

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

ACTION: NONE REQUIRED

AGENDA ITEM NO. 5: VOTE TO PRIOR AUTHORIZE TOPICAL CORTICOSTEROID PRODUCTS

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

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 6: VOTE TO PRIOR AUTHORIZE MISCELLANEOUS PRODUCTS

For Public Comment: Chris Schwab: Good evening. I'm a medical science liaison with Human Genome Sciences and I'm here on behalf of Human Genome Sciences and GlaxoSmithKline to give a brief overview of Benlysta which is the first newly approved treatment for systemic lupus erythematous in over 50 years. Benlysta is a human IgG 1 monoclonal antibody. It is specific for BLyS, or belimumab site stimulator, which is a B-cell survival factor. BLyS is up-regulated in some lupus patients. Benlysta binds to BLyS, which is the active form, keeps it from binding to receptors on B cells and allows B cells to die off, including autoreactive B cells and this prevents them from differentiating them to autoreactive plasma cells which produce autoantibodies which drive part of the disease process in lupus. So Benlysta was studied in three randomized controlled trials, one Phase II and two Phase III, in over 2,100 patients. The two Phase III trials were BLyS-52 and BLyS-76. They enrolled a large number of patients and basically we looked at two doses of Benlysta, 1 mg/kg and 10 mg/kg, compared with placebo. All patients were on standard therapy. These patients were active SLE patients receiving standard therapy of autoantibody positive. And the indication is for these specific patients. Adult patients with active SLE by ACR criteria as well as autoantibody positivity, their ANA or anti-double stranded DNA. The approved dose is 10 mg/kg. In the Phase III trials, the 10 mg/kg dose of Benlysta did result in a significantly higher response rate compared with placebo with the SRI responder index or SLE responder index. As I said, significant in both trials of the 10 mg/kg dose. Looking at subset analyses, we did see a difference, a discrepancy in the African American population in the Phase III trial. They did not seem to respond as well to Benlysta. However, in Phase II, the African Americans did respond to Benlysta similar to the overall population so the FDA said a word of caution should be used, not for safety issues but simply we need more information. In general we saw reduction in steroid use with Benlysta. It was not significant in both trials but there was a general reduction in steroid use with Benlysta compared with placebo. The results are reduction in the risk of severe flares. It was also not significant in both trials, but was generally reduced. As far as some of the cautions in the label to be of concern about, there were a few more deaths with Benlysta than with placebo. There wasn't one cause of these. Infections, suicide and cardiovascular disease were the main causes. There also, as with any biologic . . . . let me back up. It is an infused biologic, one hour of 10 mg/kg, three doses in the first month and then once a month thereafter. There were some infusion reactions, some hypersensitivity reactions, as you might expect. As far as the serious ones, they were rare, but certainly physicians should be aware of this, the potential, and be able to monitor and manage those. As with any biologic immunomodulatory, the risk of infections is definitely a risk for lupus patients. There were some serious infections, 6% with Benlysta compared with 5.2% with placebo and the most common infections were pneumonia, upper respiratory tract infections, cellulitis and those types of things a little more serious. There also were some increased risks of, or increased incidences of psychiatric events with Benlysta. The mechanism of action would not suggest that Benlysta would have an effect on this, we don't really know. There were two suicides in the total of 2,100 patients in all three trials. Two suicides with Benlysta. It is a pregnancy category C. Patients were supposed to be on contraceptive during the trials and it is recommended they be on contraceptives during

treatment as well as four months after, as the half-life of the drug is 19 days. Antibodies such as Benlysta could cross the placenta and could also be found in breast milk, so once again, if a patient does become pregnant and has a child during treatment, they'd need to discuss with their physician about whether they should breastfeed. We do have a pregnancy registry as pregnancies do happen. Live vaccines should not be giving within 30 days and during treatment. Certainly there could be increased risk of subsequent infection from that vaccine. There were no differences in malignancies, however lupus patients do have an increased risk of malignancies and biologics such as Benlysta could increase the risk of some of those malignancies as well. Thank you. I'd be happy to answer any questions or be a resource for you at any time.

Dr. Knisely: Were patients treatment-naïve, or had they been on some of the other common therapies for lupus?

Mr. Schwab: Most patients had been on different therapies. The average time of diagnosis was around five years, so all these were on active therapies. They had to be on stable therapy before beginning trial and this could include NSAID, steroids, antimalarials, immunosuppressants including methotrexate, azathioprine, as well as CellCept and others. Most patients were on about two or more medications at baseline.

Dr. Kuhls: I'm having a hard time understanding when to use this drug. You're telling me there's a lot of risk and so, and there's other treatments that are available, steroids and the whole list that you obviously just got done talking about. So I'm having a hard time as a clinician deciding when do you choose this drug …… . for treatment failure, for somebody who is very severe, or somebody who's relatively naïve because you're talking about a significant risk. Because the way the package insert is, it's like if you're ANA positive and you have lupus, you basically can get it. Right?

Mr. Schwab: That is correct, the patients that are on standard therapy. But for our trials, they had to have fairly moderate disease activity and most patients had at least two or more organ involvement. You know, that could be skin, musculoskeletal, mucocutaneous, and immunologic changes were the most common symptoms. There was some renal involvement and other symptoms. And you are correct. The only classes we excluded that I didn't mention in the testimony, I do need to review, we did not allow severe CNS, severe lupus nephritis as well as concomitant biologic or IV cyclophosphamide use, so those were the main categories we did not look at of not recommended for Benlysta.

Dr. Kuhls: Why did you not pick those categories?

Mr. Schwab: Because those are acute, potentially life-threatening conditions as far as the severe nephritis and CNS. We did allow lesser, less severe forms of CNS and renal involvement, but they require a more aggressive therapy including things like IV cyclophosphamide and steroids and that one could potentially mask the effects of Benlysta as well as just, it's a more difficult patient to manage, and we will be doing a nephritis trial because they are challenging and we get a lot of questions about if it will work for those patients. So it's really, they really had to have active disease, so if it was just mild, maybe skin rash and they're on Plaquenil, maybe a low dose steroid or an NSAID, something like that, I would say that's probably not the right patient, but if they fail that therapy or another therapy, I mean somewhere in there, it depends on where the physician feels comfortable moving that patient as far as if they want to add a steroid, increase a dose, if they want to use an immunosuppressant, but basically once they have the active disease or they have a flare, because these patients' disease wax and wane as you're probably aware, so the goal is to keep those flares under control because those can really increase the risk of morbidity and mortality, as well as the cost, medical cost. Did that help?

Dr. Kuhls: Yeah.

Dr. Muchmore: I think over the next few years we'll have a much better idea of what its' place is in therapy.

Mr. Schwab: Right, I agree. There's no true treatment algorithm, one for lupus patients. It's all across the board.

Dr. Kuhls: Well unfortunately, we've got to make some decisions now despite that.

Dr. Muchmore: The more it's flaring, at least it's plausible that that would be more of a time to use belimumab.

Dr. Kuhls: Have you in your research yet, other than looking at for instance, black Americans, looked at antibody profiles in trying to pick out subsets that this medication is more effective or not or have you looked at what patients have more B-Lymphocyte stimulating protein expression versus others as to do they respond better, have you looked at that?

Mr. Schwab: Right, we are looking at that. And not all patients that respond have elevated BLyS levels. We do know it is in some but as far as the autoantibodies, we do know and we learned this from Phase II, that patients truly do need to be autoantibody positive, because patients can become seronegative and so we would define that as either ANA, and/or anti-double stranded DNA at 30 days before entering the trial. And we also looked at the other autoantibodies such as anti-Smith, anticardiolipin, and things like that. In general those antibodies were reduced in a number of the patients.

Dr. Kuhls: So there's no way down the road that checking the patient's levels in the blood may predict, would give those patients that medication, it looks like that's not going to work.

Mr. Schwab: As far as BLyS levels?

Dr. Kuhls: Yeah.

Mr. Schwab: Correct. There's not a commercially available test …… .

Dr. Kuhls: Right. No I know that now, I said down the road.

Mr. Schwab: Oh, I see. I don't know that. It's not something that, like I said, we did see patients that responded that didn't have elevated BLyS levels. Patients have different sensitivities so really the autoantibody profiles are probably the things that physicians will track. They also look at complement. We saw improvements in complement. So it's those types of things biologically they'll look at to see what's happening there. We can't say it correlates with the clinical activity, but those are the kind of things I know that physicians do track and will look at.

Dr. Kuhls: Okay, then my last question, I'm sorry to prolong but I think it's kind of important. You have responders and non-responders, right?

Mr. Schwab: Right.

Dr. Kuhls: How quickly do patients respond that you decide you've got a response versus patients that never have a response? Do you understand my question?

Mr. Schwab: I'm sorry, repeat it.

Dr. Kuhls: In other words, you give the patient these medicines, right, and you look I guess, at steroid use and some of the others. How quickly do patients respond, how long does it take to see a clinical response, and so is there a time period where you say I don't see any difference in steroid use, I don't see any interest and we better stop this medication? I'm trying to get a feeling for stop points.

Mr. Schwab: Okay, sure. And I know you have the information there but I didn't mention the trial, the primary endpoint was at week 52 of both trials. We did do an additional 24-week period in the BLyS-76. So the primary endpoint was significant in both trials at week 52. That doesn't mean

you have to wait a year to see a response. In BLyS-52, we saw a significant difference as early as week 16, so four months into the trial. Changes in biomarkers changed as early as week 8 significantly, so there are things you can see that do change before that endpoint that we took you to.
Dr. Knisely: When were you collecting data points?
Mr. Schwab: Once a month because as I said after those first three doses in the first month, it's infused once a month thereafter, so they were seen once a month and they checked autoantibody levels, complement, B-cell levels to look at the B-cells changes over time.
Dr. Kuhls: So did you have patients that say at week 24, let's say week 26, did you have patients that didn't respond for the first 26 weeks but then in the second 26 weeks you saw responses?
Mr. Schwab: Yes, there were some patients that were non-responders early on because we did track it over time and then later they did respond. The primary endpoint like I said, was a hard endpoint at week 52, but we did track it and so could pause at endpoint and had to meet all three, but maybe if something wasn't there early on, they did, some did respond later, yes.
Drs. Kuhls, Muchmore: Thank you.
Materials included in agenda packet; presented by Drs. Sipols and Le.
The recommendation for Benlysta prior authorization were modified to include methotrexate to Criteria 1(b)"Documented inadequate response to at least two of the following medications."
Dr. Bell moved to approve with modification noted above; seconded by Dr. Kuhls.
ACTION: MOTION CARRIED

AGENDA ITEM NO. 7: UTILIZATION REVIEW AND 60-DAY NOTICE TO PRIOR AUTHORIZE DIABETES MEDICATIONS
Materials included in agenda packet; presented by Dr. Keast.
ACTION: NONE REQUIRED

AGENDA ITEM NO. 8: ANNUAL REVIEW OF ANXIOLYTIC PRIOR AUTHORIZATION CATEGORY
Materials included in agenda packet; presented by Dr. Keast.
Dr. Kuhls moved to approve as submitted; seconded by Dr. Harrell.
ACTION: MOTION CARRIED

AGENDA ITEM NO. 9: ANNUAL REVIEW OF ANTI-EMETICS AND 30-DAY NOTICE TO PRIOR AUTHORIZE ZUPLENZ™
Materials included in agenda packet; presented by Drs. Phung and Le.
ACTION: MOTION CARRIED

AGENDA ITEM NO. 10: ANNUAL REVIEW OF OTIC ANTIBIOTICS
Materials included in agenda packet; presented by Dr. Moore.
The Board recommended changing PA criteria 3 to require a trial of ofloxacin and dexamethasone drops prior to approval a ciprofloxin combination product.
Dr. Kuhls moved to approve as recommended above; seconded by Dr. Bell.
ACTION: MOTION CARRIED

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: Annual Review of Antipsychotics
B: Utilization Review of Select Biological Agents
C: Utilization Review of Multiple Sclerosis Agents
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: June 9, 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 June 8, 2011

Recommendation 1: Vote to Prior Authorize Topical Corticosteroids

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the addition of the Topical Corticosteroid class of medications to the Product Based Prior Authorization program. The following Tier 1 drug list has been reviewed and determined to be an acceptable combination for use as initial therapy for the majority of members. The College of Pharmacy recommends this list to the Drug Utilization Review Board based on cost and clinical effectiveness for approval before referral to the Oklahoma Healthcare Authority. The following is the proposed Tier list and approval criteria. When Tier 2 products receive a State Maximum Allowable Cost designation and approach the cost of Tier 1 products, they will be moved to Tier 1.

Tier 2 Approval Criteria:

1. Documented trials of ALL Tier 1 topical corticosteroids of similar potency in the past 30 days that did not yield adequate relief.
    a. If Tier 1 trials are completed and do not yield adequate relief, the member must also provide a clinical reason for requesting a Tier 2 in the same potency instead of trying a higher potency.
2. When the same medication is available in Tier 1, a clinical reason must be provided for using a special dosage form of that medication in Tier 2 (foams, shampoos, sprays, kits, etc.).

Topical Corticosteroids	
Tier 1	**Tier 2**
Ultra high to high potency	
Augmented betamethasone dipropionate (Diprolene AF® G,C)	Amcinonide (O)
Betamethasone dipropionate (Diprosone® O)	Augmented betamethasone dipropionate (Diprolene® O, L)
Clobetasol propionate (Temovate® C,G,O,So)	Clobetasol propionate (Clobex® L,Sh,Spr; Olux® F)
Diflorasone diacetate (Apexicon® O, Apexicon E® C)	Desoximetasone 0.25% (Topicort® C,O,) 0.05% (G)
Fluocinonide 0.025% (Lidex® G,C,O)	Fluocinonide 0.01% (Vanos® C)
Halobetasol propionate (Ultravate® C,O)	Flurandrenolide tape (Cordran®)
	Halcinonide (Halog® C,O)
Med/high to medium potency	
Betamethasone dipropionate (Betanate® C,L)	Amcinonide (Cyclocort® C,L)
Betamethasone valerate (Beta-Val® C,O,L)	Betamethasone dipropionate/calcipotriene (Taclonex® O, Sus, Spr)
Fluocinolone acetonide (Synalar® C,O)	Betamethasone valerate (Luxiq® F)
Fluocinonide emollient (Lidex E® C)	Desoximetasone 0.05% (Topicort LP ® C)
Fluticasone propionate (Cutivate® C,O)	Fluticasone propionate (Cutivate® L)
Hydrocortisone valerate 0.2% C	Hydrocortisone butyrate (Locoid® O,C, L; Locoid Lipo C)
Mometasone furoate (Elocon® O,C,L)	Hydrocortisone probutate (Pandel® C)
Triamcinolone acetonide (Kenalog® C,O,L)	Hydrocortisone valerate (Westcort® C,O)
	Prednicarbate (Dermatop® O,C)
	Triamcinolone acetonide (Kenalog® Spr)
Low potency	
Alclometasone dipropionate (Aclovate® C,O)	Coclortolone pivalate (Cloderm® C)
Desonide (LoKara® C,O,L)	Desonide (Desonate® G, Verdeso® F)
Fluocinolone acetonide (So, C; Derma-Smooth®; Derma-Smooth FS® oil)	Desonide/emollient (Desowyn® kit C,O)
Hydrocortisone acetate 2.5% (C,O,L)	Fluocinolone acetonide (Capex® Sh)
Hydrocortisone/urea (U-Cort® C)	Hydrocortisone acetate 2%/aloe (Nucort®, L)
	Hydrocortisone/lidocaine (LidaMantle HC® C)

Recommendation 2: Vote to Prior Authorize Miscellaneous Products

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the following products for Prior Authorization:

A: Benlysta® (belimumab) and Practitioner Administered Drugs

1. The College of Pharmacy recommends prior authorization of Benlysta® (belimumab) for medical claims with the following approval criteria:

    a. FDA approved indication of adults with active, autoantibody-positive, systemic lupus erythematosus already receiving standard therapy.
    b. Documented inadequate response to at least two of the following medications:

i. High-dose oral corticosteroids
ii. Methotrexate
iii. Azathioprine
iv. Mycophenolate
v. Cyclophosphamide

c. Member must not have severe active lupus nephritis or severe active central nervous system lupus.
d. No combination use with biologic therapies or intravenous cyclophosphamide.

2. In order to apply a consistent prior authorization policy to drug products supplied by either a pharmacy or practitioner's office, the College of Pharmacy recommends prior authorization of physician administered medications until these products can be formally reviewed by the DUR Board. The package labeling approved by the Food & Drug Administration (FDA) will be used as the interim criteria. Over the course of the next few months, several of these products will be presented and reviewed.

B: Adcirca® (tadalafil)

The College of Pharmacy recommends prior authorization of Adcirca® (tadalafil) with similar approval criteria to the Revatio® (sildenafil):

1. FDA approved diagnosis of pulmonary arterial hypertension.
2. Medical supervision by a pulmonary specialist and/or cardiologist.
3. Quantity limit of #60 tablets per 30 days will apply.

C: Colcrys® (colchicine) and Uloric® (febuxostat)

The College of Pharmacy recommends prior authorization of Colcrys® (colchicine) and Uloric® (febuxostat) with the following criteria:

Colcrys® (colchicine) will have a free floating 2 days supply of 6 tablets per 365 days. Long term use of Colchicine will require a petition and member must have:

1. Failure of allopurinol defined by persistent gouty attacks with serum urate levels below 6.5mg/dL.
2. Clinical reason why colchicine/probenecid would not be a viable option for the member.
3. Quantity limit of #60 per 30 days will apply for gout.
4. Members with the diagnosis of Familial Mediterranean Fever verified by genetic testing will be approved for up to 2.4mg per day.

Uloric® (febuxostat) approval criteria:

1. Failure of allopurinol defined by persistent gouty attacks with serum urate levels below 6.5mg/dL.
2. Clinical reason why allopurinol is not a viable option for the member.
3. Quantity limit of #30 per 30 days will apply.

D: Miscellaneous Bladder Agents

The College of Pharmacy recommends prior authorization of Urelle®, Prosed DS®, and Darpaz® with the following approval criteria:

1. Recent 14 day trials within the past 30-60 days of:
    a. Urogesic Blue®, and
    b. Utira-C®, Utrona-C®, or Darcalma®

E: Nuedexta™ (dextrmethophan HBr and quinidine sulfate)

The College of Pharmacy recommends prior authorization of Nuedexta™ (dextrmethophan HBr and quinidine sulfate) with the following approval criteria:

1. FDA approved diagnosis of pseudobulbar affect.
2. Member must be 18 years of age or older.
3. Quantity limit of #60 tablets per 30 days will apply.
4. Approvals will be for the duration of a year.

F: Testosterone Products

The College of Pharmacy recommends prior authorization of all testosterone products to ensure safe and appropriate use. The following is the recommended approval criteria:

1. Approved diagnosis:
    a. Testicular failure due to cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome; or orchidectomy.
    b. Idiopathic gonadotropin or luteinizing-hormone-releasing hormone (LHRH) deficiency, or pituitary hypothalamic injury from tumors, trauma, or radiation.
    c. Delayed puberty.
    d. Advanced inoperable metastatic mammary cancer in females 1 to 5 years postmenopausal, or premenopausal women with breast cancer benefitting from oophorectomy and have been determined to have a hormone-responsive tumor.
2. Must include two labs showing pre-medication testosterone level below 300ng/dL (where applicable) and other labs necessary to demonstrate diagnosis.
3. Oral agents are only approved in cases where member cannot use all other available formulations of testosterone.

Recommendation 3: Annual Review of Anxiolytic Prior Authorization Category

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends continuation of the current criteria for this drug category with the following addition:

Add the anxiolytic products to the Ingredient Duplication ProDUR module which is currently set to require prior authorization when claims are attempted for the same ingredient when less than 90 % of the previously submitted day supply has been used. Claims from the same prescriber are exempt under this module.

Recommendation 4: Annual Review of Anti-Emetics Products Prior Authorization Category

NO ACTION REQUIRED.

The College of Pharmacy does not recommend changes to the current criteria.

The DUR Board recommends monitoring and possible educational outreach related to overprescribing in the pediatric population.

Recommendation 5: Annual Review of Otic Antibiotic Product Based Prior Authorization Category

MOTION CARRIED by majority approval.

The College of Pharmacy does not recommend changes to the current criteria.

The DUR Board recommends the following change to the current criteria:

Prior Authorization Criteria

1. Member must have adequate 14-day trial of at least two Tier 1 medications, or
2. Approval may be granted if there is a unique FDA approved indication not covered by Tier 1 products or infection by organism not known to be covered by any of the Tier 1 agents.
3. A ciprofloxacin combination ~~product may be approved when a steroid containing product is required for severe otitis externa and the tympanic membrane is not intact~~ may be approved after a recent 7 to 10 day trial of ofloxacin and dexamethasone 0.1% solution.

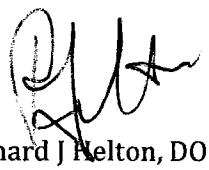
July 27, 2011

Nancy Nesser
Director of Pharmacy Services
Oklahoma Health Care Authority
2401 N.W. 23rd Street, Suite 1-A
Oklahoma City, OK 73107

Dear Mrs. Nesser:

I am writing you today to request a change in protocol with regards to statin therapy in light of the recent FDA simvastatin restrictions and contraindications update. Many patients will be affected by these changes, including those on gemfibrozil, verapamil, and amlodipine. I would like to request that the prior authorization requirement for atorvastatin be removed, in order to get these patients to appropriate LDL goals. I understand there are other statin alternatives available, but these medications do not offer the efficacy and safety offered by atorvastatin. Your consideration in this manner is appreciated.

Sincerely,



Richard J Helton, DO
Helton Rural Health Clinic

Appendix B

RETROSPECTIVE DRUG UTILIZATION REVIEW REPORT
April 2011

MODULE	DRUG INTERACTION	DUPLICATION OF THERAPY	DRUG-DISEASE PRECAUTIONS	DOSING & DURATION
Total # of messages	55,043	66,211	1,133,743	31,454
Limits applied	Established, Major, Males and Females, Age 51-60	Duplication of Benzodiazepines, Age 29-32	Contraindicated, Males and Females, Ulcer, Age 0-150	High Dose, NSAIDs, Males & Females, Age 0-3
Total # of messages after limits were applied	112	119	75	100
Total # of members reviewed	112	107	53	100

LETTERS

Category	Prescribers	Pharmacies	Total Letters
Drug Interaction	4	0	4
Duplication of Therapy	54	20	74
Drug-Disease Precautions	15	0	15
Dosing & Duration	1	1	2
Total Letters Sent	74	21	95

Retrospective Drug Utilization Review Report

Claims Reviewed for March 2011

Module	Drug Interaction	Duplication of Therapy	Drug-Disease Precautions	Dosing & Duration
Limits which were applied	Established, Major, Males and Females, Age 36-50	Benzodiazepines, Age 21-28	Contraindicated, Drug Dependence, Males and Females, Age 0-150	High Dose, NSAIDs, Males and Females, Age 50-150

Response Summary (Prescriber)
Letters Sent: 81
Response Forms Returned: 47

The response forms returned yielded the following results:

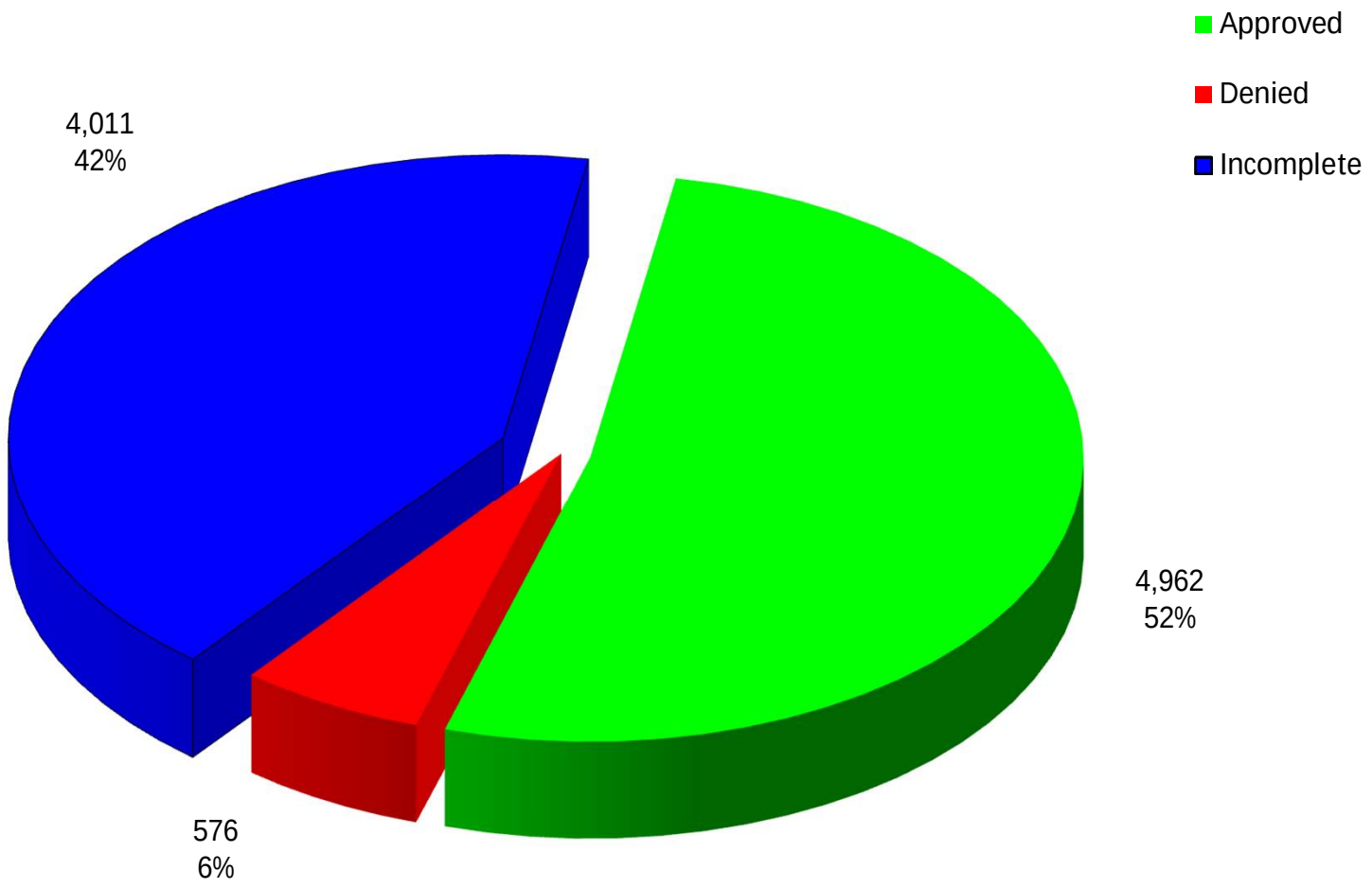
2 (4%)	*Record Error—Not my patient.*
3 (6%)	*No longer my patient.*
4 (9%)	*Medication has been changed prior to date of review letter.*
9 (19%)	*I was unaware of this situation & will consider making appropriate changes in therapy.*
18 (38%)	*I am aware of this situation and will plan to continue monitoring therapy.*
11 (23%)	*Other*

Response Summary (Pharmacy)
Letters Sent: 20
Response Forms Returned: 10

The response forms returned yielded the following results:

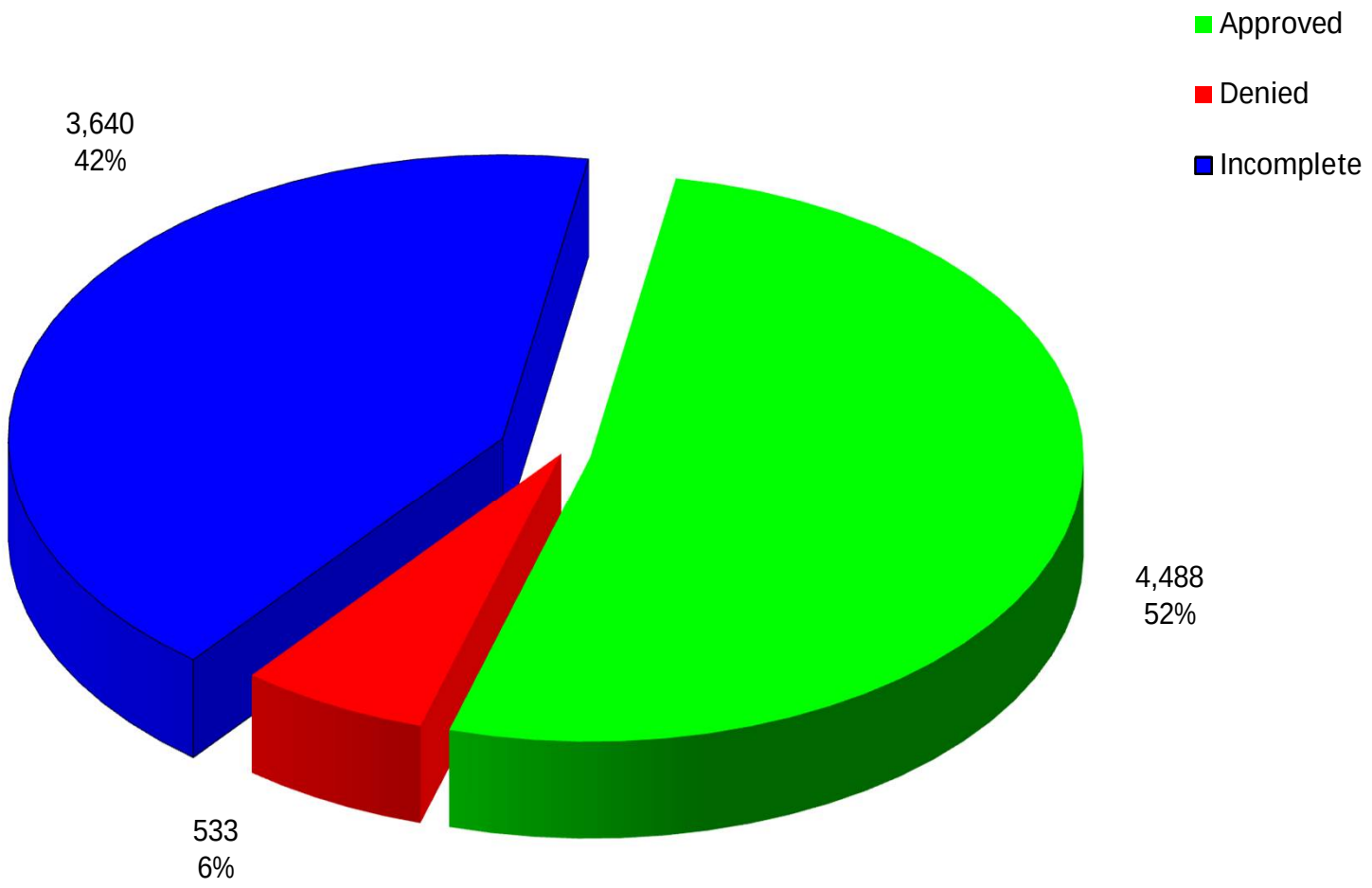
0 (0%)	*Record Error—Not my patient.*
1 (10%)	*No longer my patient.*
0 (0%)	*Medication has been changed prior to date of review letter.*
2 (20%)	*I was unaware of this situation & will consider making appropriate changes in therapy.*
3 (30%)	*I am aware of this situation and will plan to continue monitoring therapy.*
4 (40%)	*Other*

PRIOR AUTHORIZATION ACTIVITY REPORT: June 2011



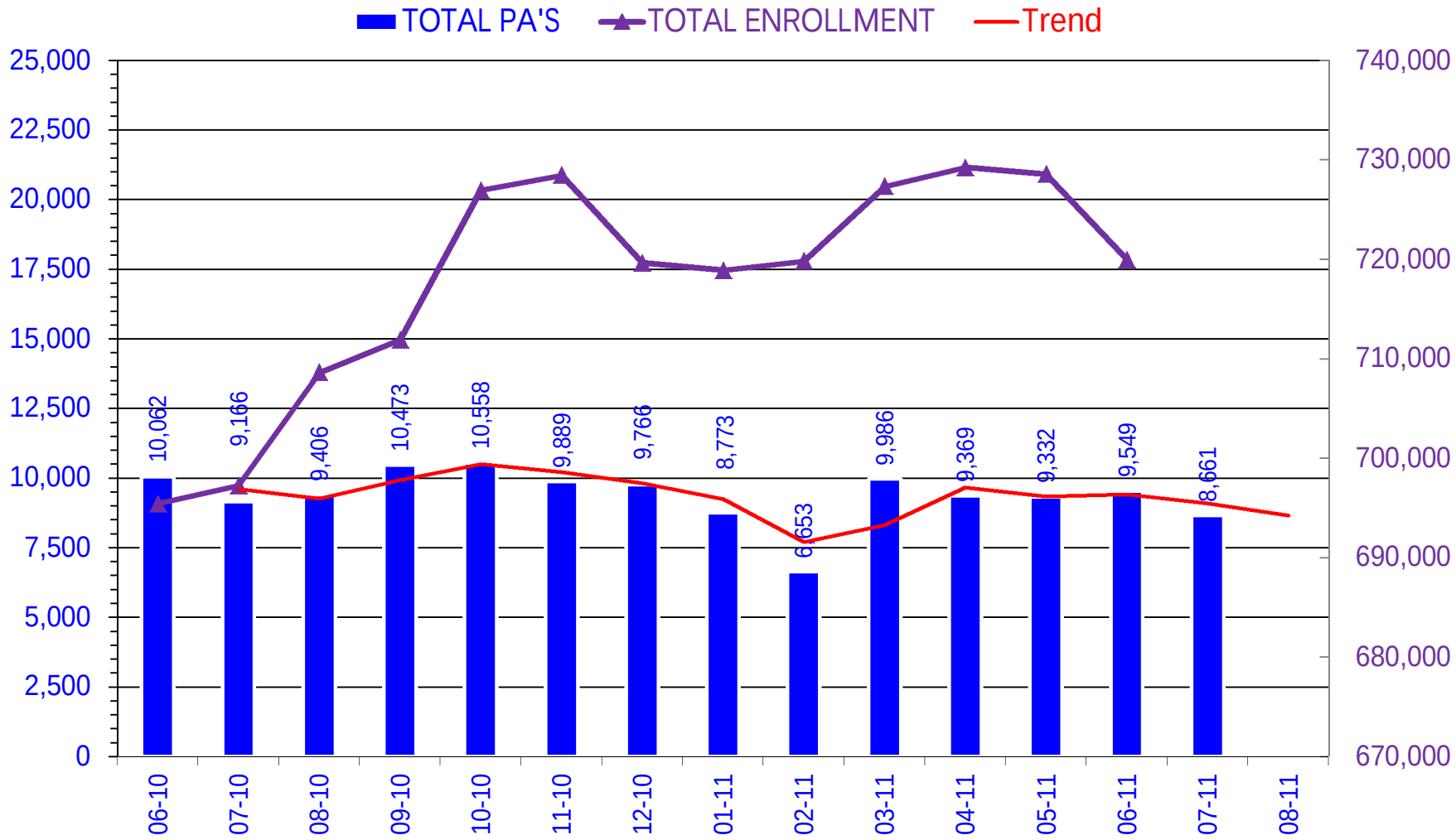
PA totals include overrides

PRIOR AUTHORIZATION ACTIVITY REPORT: July 2011



PA totals include overrides

PRIOR AUTHORIZATION REPORT: June 2010 – July 2011



PA totals include overrides

Prior Authorization Activity

6/1/2011 Through 6/30/2011

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort	380	156	8	216	360
Amitiza	14	7	0	7	204
Anti-Ulcer	719	374	85	260	94
Antidepressant	367	138	8	221	351
Antihistamine	246	146	6	94	340
Antihypertensives	116	27	12	77	308
Antimigraine	79	17	12	50	344
Atypical Antipsychotics	696	351	22	323	350
Benign Prostatic Hypertrophy	4	0	1	3	0
Benzodiazepines	92	43	0	49	192
Bladder Control	69	12	4	53	338
Brovana (Arformoterol)	1	0	0	1	0
Byetta	7	1	2	4	358
Elidel/Protopic	50	24	2	24	92
ESA	149	122	4	23	107
Fibric Acid Derivatives	10	1	1	8	361
Fibromyalgia	154	40	19	95	353
Fortamet/Glumetza	7	0	0	7	0
Forteo	3	1	0	2	361
Glaucoma	14	3	1	10	262
Growth Hormones	67	44	2	21	168
HFA Rescue Inhalers	50	20	3	27	325
Insomnia	83	20	11	52	130
Misc Analgesics	46	6	29	11	270
Muscle Relaxant	158	43	50	65	58
Nasal Allergy	242	69	40	133	114
NSAIDS	164	24	12	128	339
Ocular Allergy	85	13	4	68	169
Ocular Antibiotics	55	15	3	37	20
Opioid Analgesic	315	166	15	134	226
Other	749	232	69	448	202
Otic Antibiotic	91	43	4	44	23
Pediculicides	123	72	3	48	16
Plavix	269	195	0	74	309
Singulair	811	453	23	335	244
Smoking Cessation	86	27	6	53	38
Statins	120	40	4	76	356
Stimulant	913	555	28	330	284
Suboxone/Subutex	200	142	4	54	73
Symlin	3	1	1	1	365
Synagis	1	0	1	0	0
Topical Antibiotics	8	1	0	7	15
Topical Antifungals	20	0	2	18	0
Ultram ER and ODT	2	0	2	0	0
Xolair	6	1	3	2	178
Xopenex Nebs	19	10	0	9	325
Zetia (Ezetimibe)	27	9	1	17	363
Emergency PAs	13	13	0	0	
Total	**7,903**	**3,677**	**507**	**3,719**	

Overrides					
Brand	35	18	5	12	155
Dosage Change	541	516	1	24	9
High Dose	2	2	0	0	195
Ingredient Duplication	10	8	0	2	52
Lost/Broken Rx	112	111	1	0	15
NDC vs Age	8	8	0	0	272
Nursing Home Issue	126	116	2	8	6
Other	28	26	0	2	9
Quantity vs. Days Supply	779	476	59	244	263
Stolen	4	3	1	0	12
Third Brand Request	1	1	0	0	3
Overrides Total	**1,646**	**1,285**	**69**	**292**	
Total Overrides + Regular PAs	**9,549**	**4,962**	**576**	**4,011**	

Denial Reasons

Unable to verify required trials.	3,001
Lack required information to process request.	958
Does not meet established criteria.	558
Drug Not Deemed Medically Necessary	2

Duplicate Requests: 547

Letters: 1,641

No Process: 342

Changes to existing PAs: 504

Prior Authorization Activity

7/1/2011 Through 7/31/2011

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort	301	136	8	157	360
Amitiza	23	6	5	12	225
Anti-Ulcer	372	114	55	203	102
Antidepressant	310	93	18	199	353
Antihistamine	222	148	3	71	353
Antihypertensives	95	20	10	65	301
Antimigraine	72	21	6	45	330
Atypical Antipsychotics	592	308	8	276	350
Benign Prostatic Hypertrophy	4	0	0	4	0
Benzodiazepines	82	43	0	39	233
Bladder Control	53	18	5	30	352
Brovana (Arformoterol)	2	2	0	0	363
Byetta	12	5	2	5	362
Elidel/Protopic	31	13	4	14	115
ESA	132	91	0	41	99
Fibric Acid Derivatives	4	0	1	3	0
Fibromyalgia	168	50	16	102	342
Fortamet/Glumetza	1	0	0	1	0
Forteo	4	1	2	1	361
Glaucoma	24	8	0	16	361
Growth Hormones	41	23	4	14	152
HFA Rescue Inhalers	59	29	6	24	332
Insomnia	113	21	2	90	173
Misc Analgesics	45	4	33	8	103
Muscle Relaxant	157	42	66	49	70
Nasal Allergy	150	50	19	81	90
NSAIDS	137	26	16	95	349
Ocular Allergy	74	15	8	51	161
Ocular Antibiotics	58	13	4	41	8
Opioid Analgesic	307	164	11	132	256
Other	688	206	78	404	214
Otic Antibiotic	107	29	8	70	16
Pediculicides	135	57	12	66	18
Plavix	199	146	2	51	330
Singulair	614	320	18	276	250
Smoking Cessation	43	14	3	26	27
Statins	146	72	1	73	359
Stimulant	821	444	35	342	279
Suboxone/Subutex	89	62	5	22	86
Symlin	2	1	0	1	365
Synagis	1	0	1	0	0
Topical Antibiotics	20	5	2	13	22
Topical Antifungals	21	5	1	15	28
Ultram ER and ODT	9	2	1	6	274
Xolair	10	1	3	6	361
Xopenex Nebs	24	12	2	10	363
Zetia (Ezetimibe)	21	10	0	11	359
Emergency PAs	10	10	0	0	
Total	**6,605**	**2,860**	**484**	**3,261**	

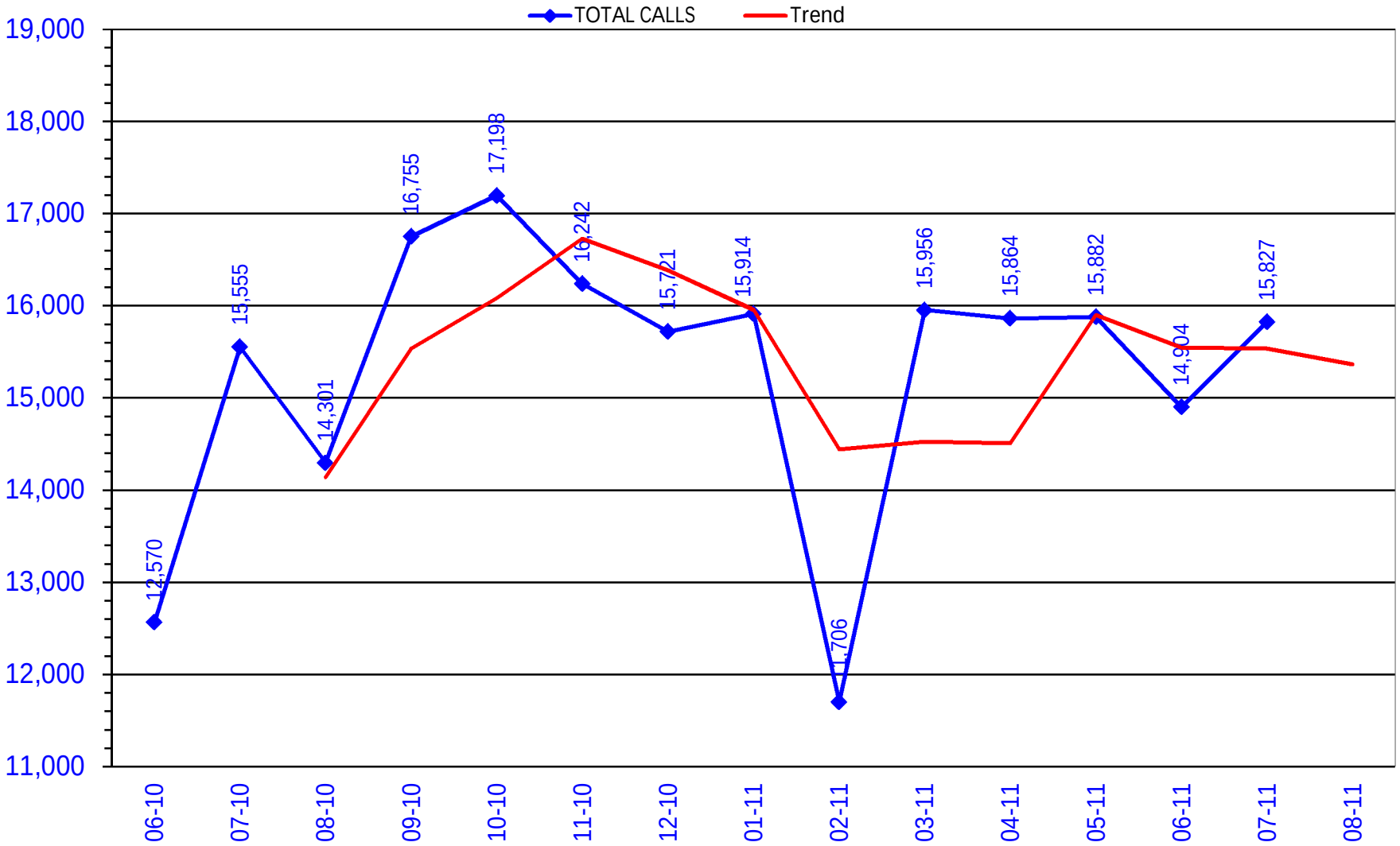
Overrides					
Brand	36	21	2	13	282
Dosage Change	478	466	2	10	7
High Dose	5	5	0	0	172
Ingredient Duplication	14	12	0	2	9
Lost/Broken Rx	111	105	0	6	9
NDC vs Age	8	7	1	0	169
Nursing Home Issue	162	162	0	0	7
Other	24	21	0	3	16
Quantity vs. Days Supply	1,211	822	44	345	261
Stolen	7	7	0	0	4
Overrides Total	**2,056**	**1,628**	**49**	**379**	
Total Regular PAs + Overrides	**8,661**	**4,488**	**533**	**3,640**	

Denial Reasons

Unable to verify required trials.	2,859
Lack required information to process request.	786
Does not meet established criteria.	503
Not an FDA approved indication/diagnosis.	1

Duplicate Requests:	533
Letters:	1,365
No Process:	255
Changes to existing PAs:	450

CALL VOLUME MONTHLY REPORT:
June 2010 – July 2011



Appendix C

Vote to Prior Authorize Zuplenz™ (ondansetron oral soluble film)

Oklahoma HealthCare Authority
August 2011

Zo 'n Go in the SoonerCare Population

A literature search was conducted to detect the origins underlying the medical practice of Zo 'n Go and the possible harmful effects that may result from this practice. Several significant events occurred in the past decade that may have shaped the current usage of ondansetron for the pediatric population presenting in the emergency department:

- In 2002, two trials[1,2] were published showing use of intravenous ondansetron was effective in reducing gastroenteritis related emesis and lowered the rates of intravenous fluid administration and hospital admission in the pediatric population.
- A clinical trial 2006[3] showed that for children with dehydration secondary to vomiting from acute viral gastritis, ondansetron with intravenous rehydration improves tolerance of oral fluids after two hours and reduces the hospital admission rate when compared with intravenous rehydration with or without dexamethasone.
- Also in 2006, the FDA issued an alert notifying healthcare professionals and the public that promethazine should not be given to children less than two years of age because of possible respiratory depression[4].
- In 2009, a meta-analysis[5] was performed to evaluate whether taking antiemetic drugs reduces vomiting and decreases the need for further intervention in children with gastroenteritis without causing significant adverse effects. This meta-analysis resulted in the conclusion that ondansetron therapy decreases the risk of persistent vomiting, the use of intravenous fluid, and hospital admissions in children with vomiting due to gastroenteritis.

Of the clinical trials mentioned, several showed that use of ondansetron was associated with an increased incidence of diarrhea, however the increase was not high compared to placebo and the trials were done in pediatric patients with gastroenteritis, in which vomiting with concurrent diarrhea are commonly present. The most common cause of vomiting in pediatric patients is a stomach or intestinal viral infection. The American Academy of Pediatrics, the European Society of Pediatric Gastroenterology and Nutrition (ESPGAN), and the World Health Organization all recommend oral rehydration solution (ORS) as the treatment of choice for children with mild-to-moderate gastroenteritis.[6] Although hospital admission protocols differ between facilities, severe cases of gastroenteritis resulting in significant dehydration will require hospitalization and rehydration with intravenous fluids.

Conclusion and Recommendations

The College of Pharmacy recommends careful consideration of the risks vs. benefits associated with ondansetron use in the emergency department setting. Educational initiatives may be considered to decrease use of ondansetron in the ER setting; however, this has to be carefully weighed against the increase costs that may occur if it resulted in an increase in hospital admission rates. The College of Pharmacy also 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.

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[1] Ramsook C. et al. **A randomized clinical trial comparing oral ondansetron with placebo in children with vomiting from acute gastroenteritis.** Ramsook C - Ann Emerg Med - 01-APR-2002; 39(4): 397-403

[2] Reeves JJ, Shannon MW, Fleisher GR. **Ondansetron Decreases Vomiting Associated with Acute Gastroenteritis: A Randomized, Controlled Trial.** PEDIATRICS Vol. 109 No. 4 April 2002, pp. e62

[3] Stork CM, Brown KM, Reilly TH, Secreti L, Brown LH. **Emergency department treatment of viral gastritis using intravenous ondansetron or dexamethasone in children.** Acad Emerg Med. 2006 Oct;13(10):1027-33.

[4] http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm109364.htm

[5] DeCamp LR, Byerley JS, Doshi N, Steiner MJ. **Use of antiemetic agents in acute gastroenteritis: a systematic review and meta-analysis.** Arch Pediatr Adolesc Med. 2008 Sep;162(9):858-65

[6] http://emedicine.medscape.com/article/801948-followup#a2645

Appendix D

Annual Review of Atypical Antipsychotics

Oklahoma Health Care Authority, August 2011

Current Prior Authorization and Approval Criteria

Atypical Antipsychotics*

Tier 1	Tier 2**	Tier 3†
risperidone **(Risperdal®)**[₮] clozapine **(Clozaril®)**	aripiprazole **(Abilify®)** iloperidone **(Fanapt™)** quetiapine ER **(Seroquel XR®)** ziprasidone **(Geodon®)**	olanzapine **(Zyprexa®)** quetiapine **(Seroquel®)** paliperidone **(Invega®)** asenapine **(Saphris®)** clozapine **(Fazaclo®)** olanzapine/fluoxetine **(Symbyax®)** lurasidone **(Latuda®)**

***Mandatory Generic Plan Applies**
****Suplemental rebate products**
†May be rebated to Tier 2 status only
[₮]Includes Risperdal Consta

Approval Criteria for Tier 2 Medication:

1. A trial of risperidone, at least 14 days in duration, titrated to recommended dose, that did not yield adequate response or resulted in intolerable adverse effects.

Approval Criteria for Tier 3 Medication:

1. A trial of risperidone, at least 14 days in duration, titrated to recommended dose, that did not yield adequate response or resulted in intolerable adverse effects.
2. A trial of two Tier 2 medications, at least 14 days in duration, titrated to recommended dose, that did not yield adequate response or resulted in intolerable adverse effects.
3. For **aripiprazole and quetiapine extended release, or olanzapine/fluoxetine**: a diagnosis of depression requires current use of an antidepressant, and previous trials with at least two other antidepressants. Tier structure still applies.

Clinical Exceptions:

1. Approvals will be granted for members with clinical conditions for which lower tiered drugs are contraindicated.
2. Approvals will be granted for members whose current regimen includes drugs known to adversely interact with all lowered tiered drugs.
3. Members being released from a hospital and stabilized on a higher tiered medication will be approved.

Utilization Review

For this review the 'Pre' period will be April 1, 2009 through March 31, 2010 and the 'Post' period will be April 1, 2010 through March 31, 2011.

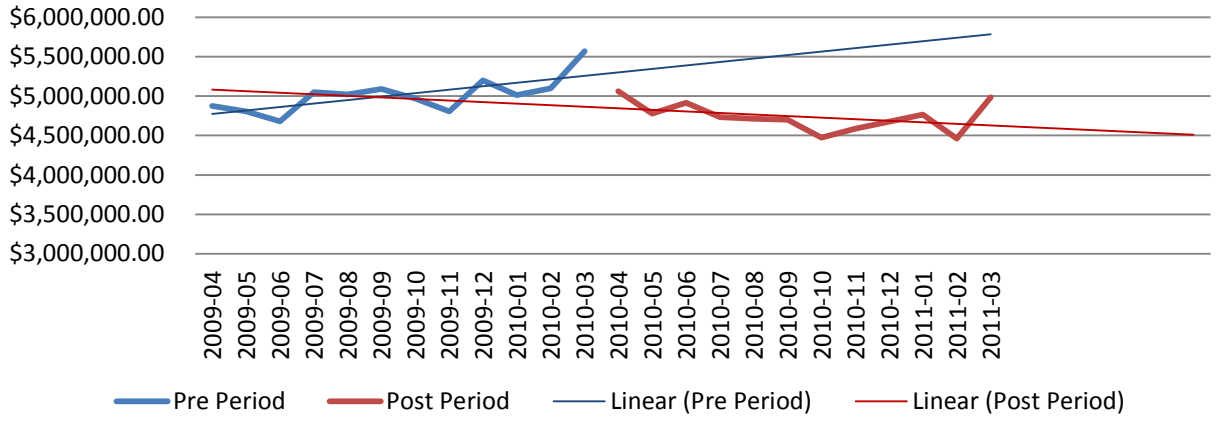
Pre and Post Implementation Comparison

	Total Members*	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
Pre	25,742	178,612	$60,180,228.24	$336.93	$11.00	7,387,533	5,472,749
Post	24,259	173,373	$56,839,182.22	$327.84	$10.77	7,234,864	5,278,012
% Change	**-5.8%**	**-2.9%**	**-5.6%**	**-2.7%**	**-2.1%**	**-2.1%**	**-3.6%**
Change	**-1,483**	**-5,239**	**-$3,341,046.02**	**-$9.09**	**-$0.23**	**-152,669**	**-194,737**

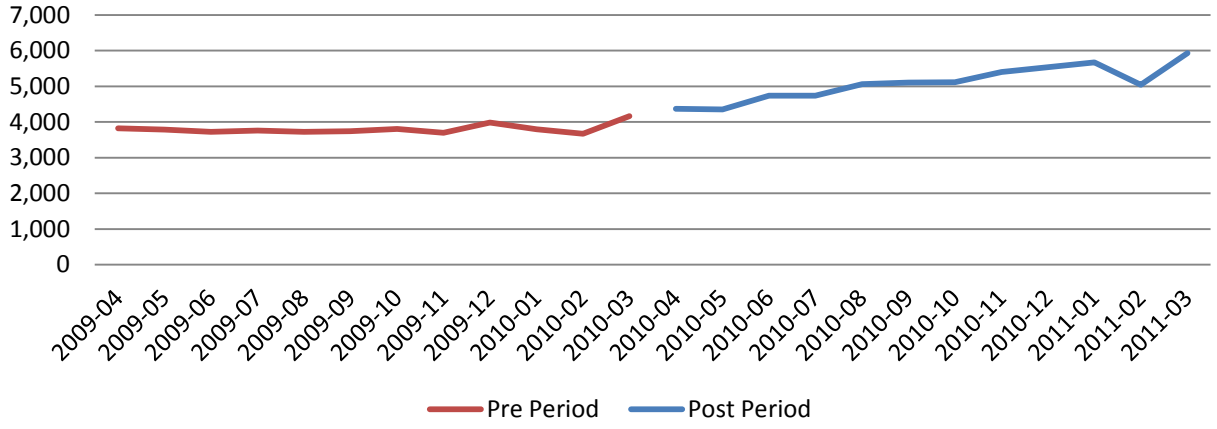
*Unduplicated members

Between FY08 and FY09 this category saw a 17.8% increase in pharmacy reimbursement. Between FY09 and FY10 the increase was only 3.5% due to the introduction of generic risperidone in November 2009 and the start of the PBPA program in April 2010. The estimated total savings for the first year of the PBPA program for this category is just over $9 million based on the difference between the projected monthly trend without the new PBPA program and the actual monthly cost in the post period.

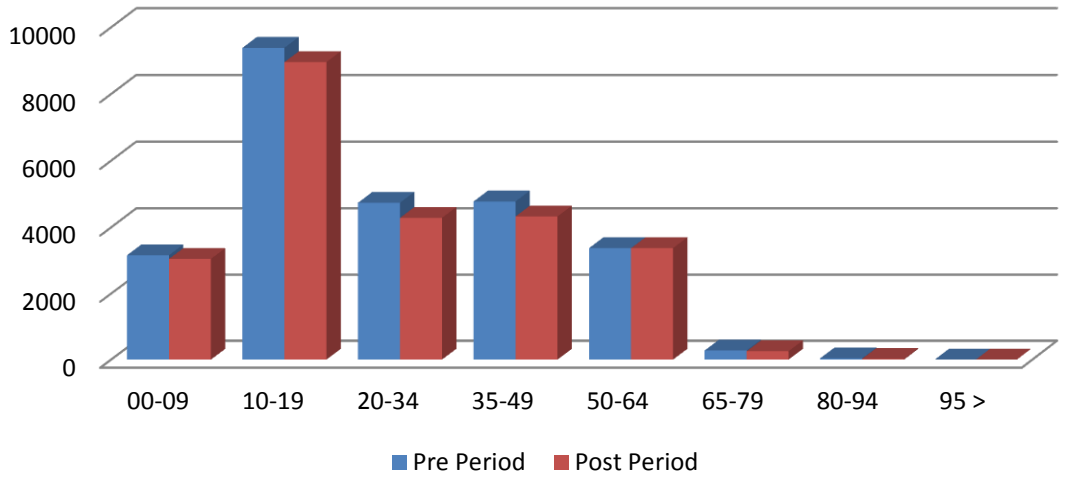
Trend in Pharmacy Reimbursement (Monthly Cost)



Trend in Market Share for Risperidone (Monthly Claims)



Member Demographics

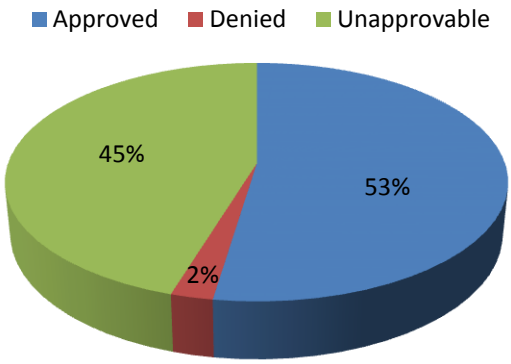


Prior Authorizations

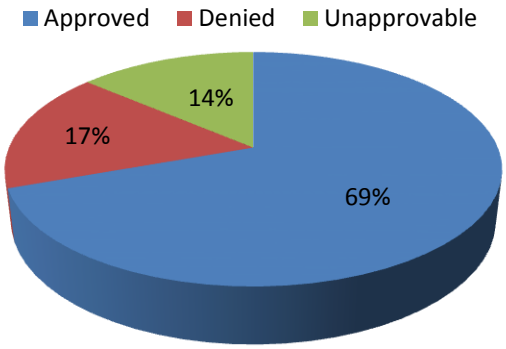
During the review period a total of 9,754 petitions were submitted for this category including step-therapy requests and quantity limit overrides. The point-of-sale system is set to look for claims for lower-tiered products and allow movement to higher tiers when appropriate without manual prior authorization.

Second Opinion Prior Authorizations

Prior to the implementation date of April 1, 2010, 168 children under the age of 5 who had received an atypical antipsychotic in recent months were reviewed. A total of 125 were approved and 43 were denied. After April 1, 2010, a total of 174 requests were reviewed by the OHCA consultant psychiatrist with a total of 121 approved and 53 unapprovable or denied.



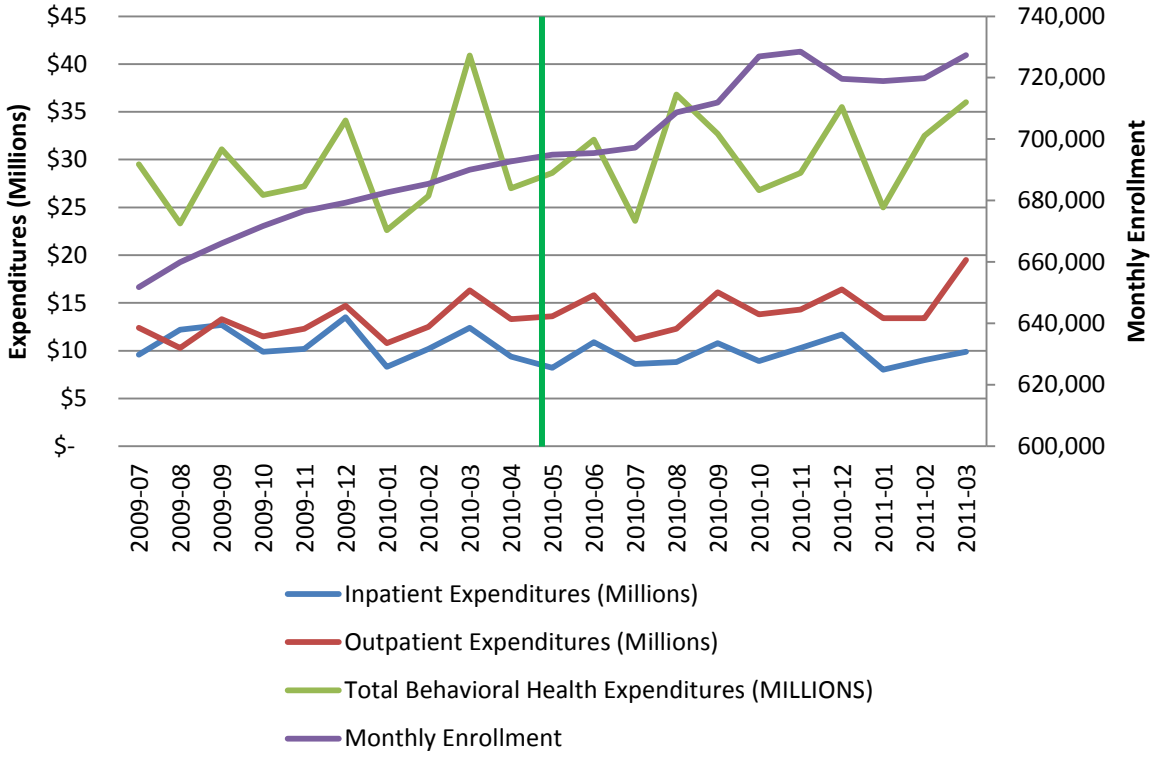
Total Prior Authorizations



Second Opinions

Behavioral Health Data

Trends in behavioral health claims were reviewed to monitor for any unintended consequences of the PBPA program. OHCA tracks behavioral health data on a monthly basis. The data is based on the month the claims were paid and trends may vary from month to month due to sporadic billing and other lump sum payments. The following graphs were compiled from this data for the last two fiscal years (data complete through March 31, 2011). The number of members receiving behavioral health services continues to increase in conjunction with the continued increase in enrollment. The percent of members utilizing services compared to total enrollment for each month has remained consistent at approximately 6.2%. After review of this data, it appears that members are able to access appropriate medication and behavioral health treatments.



The table below shows a snapshot of behavioral health expenditures in the month immediately preceding the implementation of the PBPA category in April 2010 and the same month in 2011. While the overall amount paid has increased for both children and adults, the amount paid per member has actually decreased (3.0% for adults, 6.4% for children).

	Adults			Children		
	$ / Member	Members	Total Paid	$ / Member	Members	Total Paid
March 2010	$ 464	15,489	$ 7,186,166	$ 855	30,906	$ 26,409,937
March 2011	$ 450	16,928	$ 7,613,248	$ 800	34,390	$ 27,522,288

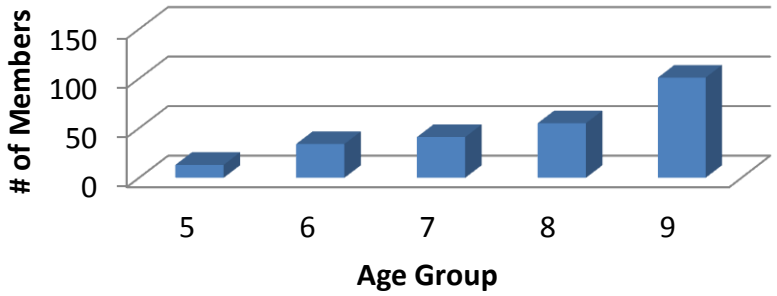
Review of Polypharmacy in Children 5 to 9 Years of Age

Children between 5 and 9 years of age were reviewed for multiple atypical medication usage. A total of 560 members were identified as having more than one atypical prescribed during Calendar Year 2010. Members with greater than 14 days of medication overlap were further reviewed.

	# of Members	Percent (N=3,654)
Total Members 5 to 9 on an Atypical	3,654	N/A
Total Members with any Overlap	560	15.3 %
Overlap > 14 Days	244	6.7 %
Greater than 60 Days of Overlap	123	3.4 %
Greater than Two Medications	33	0.9 %

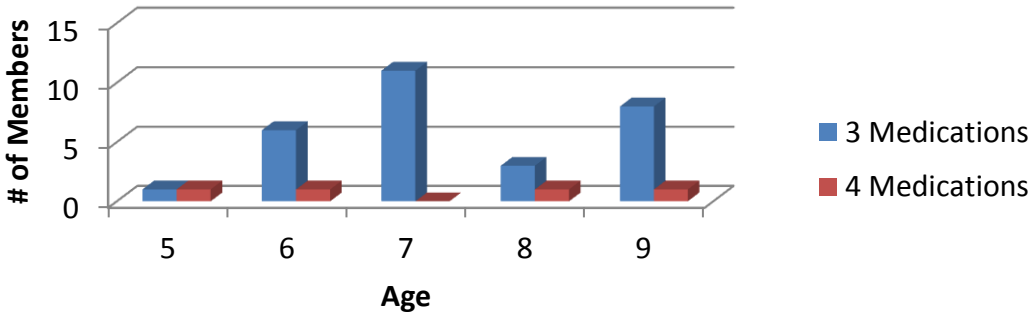
Number of Members with Overlap > 14 Days by Age

The number of members with overlapping atypical therapies increased as age increased. The majority of the overlap days were for less than 60 days potentially indicating that most overlap was for titration purposes.



Number of Members with > 2 Overlapping Medications by Age

Finally, the number of members with three or four medications were reviewed and 19 (59.4 %) had a maximum overlap of all medications for less than or equal to 60 days which may indicate some titration and changing of meds. Eleven members had overlaps of greater than 100 days, however only 7 members in all are currently on more than 2 medications. Two members who are currently still on 3 and 4 medications respectively have been referred for case review.



Review of Members with a Dementia Related Diagnosis

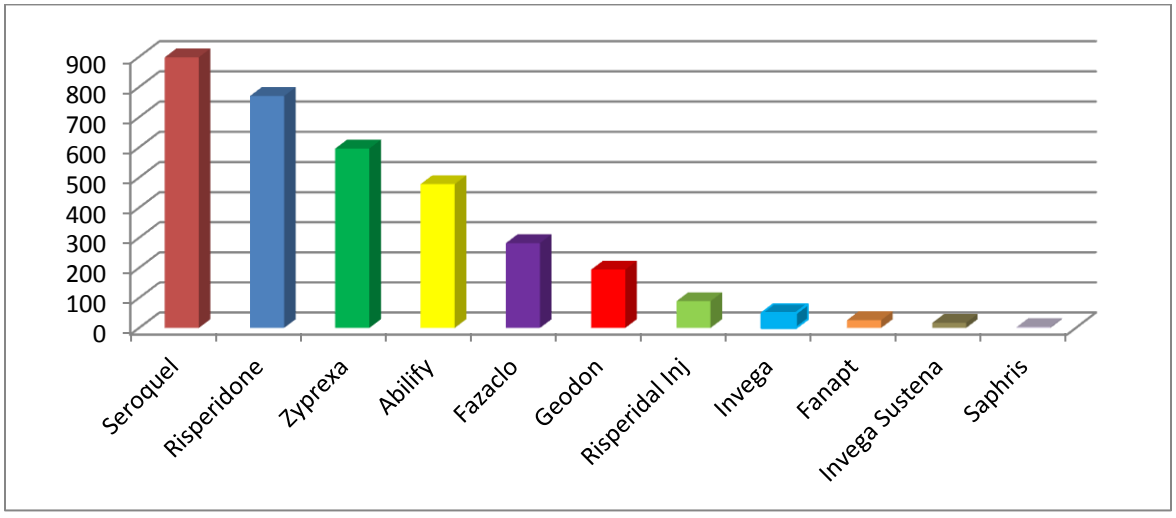
A study was recently published in the American Journal of Psychiatry regarding olanzapine, risperidone, and quetiapine for cognition in patients with Alzheimer's disease. The study authors concluded that cognitive function declined more for those on atypical antipsychotics than those on placebo. They concluded that further cognitive impairment is a risk of treatment with atypicals and should be considered when treating Alzheimer's patients.[1]

In 2005, the FDA issued a black box warning regarding the use of these medications for behavioral disorders in patients with dementia. Recently, the results of a Veteran's Affairs (VA) study showed that the use of these medications in this disease category was 17.7% in 1999, but by 2007, the use had dropped to 12%.[2]

To address these concerns, members with a pharmacy claim for an atypical antipsychotic who also had a claim with an ICD-9 code for a dementia-related or Alzheimer's diagnoses were reviewed. A total of 4,303 members were identified as having possible dementia or Alzheimer's disease. After removing members with both Medicare and Medicaid eligibility (no prescription data available) for 2010, the total number of members with these diagnoses and a claim for an atypical was 279. The percentage of the non-Dual eligibiles with a dementia-related diagnosis and an atypical was 27.2% (279 out of 1,025 non-Dual Eligibles).

Age Group	Any Related Diagnosis	Alzheimer's Disease
<21	13	2
21-35	10	1
36-50	43	4
51-65	162	28
66-80	41	11
>80	10	7

Number of Claims by Product for Members with Dementia/Alzheimer's



Market Update

The following patent expirations are anticipated:

- Zyprexa®: October 2011
- Seroquel®: March 2012
- Geodon®: 2012
- Abilify®: 2014

Adverse Event Monitoring Questionnaire

A total of 2,831 questionnaires were mailed out to current prescribers of atypical antipsychotics who did not respond to the initial mailing. The following table is a summary of the responses received (238) after the second mailing.

Atypical Antipsychotics Prescriber Questionnaire Responses			
Total responses received: 238			
Question	**Yes**	**No**	**N/A**
Is tapering of doses considered when appropriate?	235	3	
Is the possible development of movement disorders monitored?	230	8	
Are weight and BMI being monitored and recorded?	218	20	
Is waist circumference being monitored and recorded monthly? (Adults only). N/A=prescribe to pediatric patients only.	25	165	48
Is blood pressure being monitored and recorded?	227	11	
Is fasting glucose obtained at baseline, after 12 weeks of therapy, and annually?	156	82	
Is fasting lipid profile obtained at baseline, after 12 weeks of therapy, and every 5 years?	151	87	

Conclusion and Recommendations

Criteria

The College of Pharmacy recommends continuation of the Atypical Antipsychotic Product Based Prior Authorization Program. Further review of the current criteria should be performed once additional generics are available on the market.

The incidence of long-term polypharmacy in children 5 to 9 was low. While this is an area of concern, the point-of-sale (POS) limitation of multiple products would hinder the ease of access for Tier 1 products and movement up the Tier structure. The DUR Board may want to consider adding age 5 to the second opinion process as a first step towards addressing this area. For Calendar Year 2010, there were approximately 285 children age 5 on at least one atypical antipsychotic.

For members with a dementia-related diagnosis, the percent of non-Dual members who are on an atypical appears to be higher than the percent from the VA study and should be monitored. A RetroDUR run could be performed bi-annually to address this issue with providers.

Outreach and Education

The College of Pharmacy will begin an educational outreach to prescribers focusing on the two areas from the questionnaires which indicated lower rates of occurrence and can be measured through claims data:

- fasting glucose monitoring
- fasting lipid profile monitoring

Letters will be sent to prescribers of antipsychotics whose members do not have coding in their medical claims indicating that monitoring is being performed. A member list will be included with the letter. The letter will also review all monitoring guidelines for atypical antipsychotics. The current methodology for identifying prescribers for the mailing will be based on a review of the provider's member panel to determine the percentage of members who do not appear to be monitored.

References

[1]Vigen, C. L. P., W. J. Mack, et al. (2011). "Cognitive Effects of Atypical Antipsychotic Medications in Patients With Alzheimer's Disease: Outcomes From CATIE-AD." Am J Psychiatry: appi.ajp.2011.08121844.

[2]JAMA and Archives Journals (2011, February 8). Use of atypical antipsychotics in treatment of dementia declined after FDA warning. *ScienceDaily*. Retrieved July 14, 2011, from http://www.sciencedaily.com/releases/2011/02/110207165440.htm.

Utilization Details for April 1, 2010 through March 31, 2011

Rank Claims	Rank Cost	Product	Claims	Units	Days	Members	Pharmacy Reimbursement
99	100	ABILIFY INJ 9.75MG	1	3	2	1	$33.94
61	60	ABILIFY SOL 1MG/ML	124	15,625	3,593	30	$54,587.45
4	1	ABILIFY TAB 10MG	9,173	282,589	286,380	2,576	$4,456,406.63
7	7	ABILIFY TAB 15MG	6,162	179,657	194,397	1,588	$2,839,820.46
14	6	ABILIFY TAB 20MG	4,437	140,214	140,829	1,081	$3,127,484.31
20	12	ABILIFY TAB 2MG	3,197	97,333	97,404	943	$1,534,431.50
17	8	ABILIFY TAB 30MG	3,606	119,808	121,162	710	$2,665,991.53
5	3	ABILIFY TAB 5MG	9,095	274,840	281,758	2,616	$4,304,470.21
70	67	ABILIFY DISC TAB 10MG	72	2,097	2,200	19	$37,758.64
82	74	ABILIFY DISC TAB 15MG	32	960	960	10	$18,211.98
		Total Aripiprazole	**35,899**	**1,113,126**	**1,128,685**		**$19,039,196.65**
23	36	CLOZAPINE TAB 100MG	2,695	226,898	55,277	222	$219,150.73
66	82	CLOZAPINE TAB 200MG	97	3,822	1,966	12	$9,588.76
49	81	CLOZAPINE TAB 25MG	319	19,231	6,193	40	$9,613.57
78	92	CLOZAPINE TAB 50MG	44	2,239	844	12	$2,115.84
64	50	CLOZARIL TAB 100MG	103	13,010	3,001	12	$86,477.76
		Total Clozapine	**3,258**	**265,200**	**67,281**		**$326,946.66**
77	89	FANAPT PAK	45	360	274	44	$3,436.22
72	69	FANAPT TAB 10MG	61	3,544	1,772	15	$34,036.97
68	65	FANAPT TAB 12MG	82	4,757	2,380	19	$45,070.03
74	71	FANAPT TAB 1MG	54	2,704	1,542	28	$25,575.62
65	62	FANAPT TAB 2MG	98	5,519	2,844	33	$50,389.73
63	61	FANAPT TAB 4MG	107	5,920	3,117	42	$54,480.56
46	39	FANAPT TAB 6MG	367	21,099	10,908	156	$199,627.08
60	51	FANAPT TAB 8MG	161	9,194	4,792	60	$86,039.86
		Total Iloperidone	**975**	**53,097**	**27,629**		**$498,656.07**
19	16	FAZACLO TAB 100MG	3,386	211,747	53,152	239	$1,214,729.93
48	46	FAZACLO TAB 150MG	323	14,289	4,759	52	$118,486.45
50	45	FAZACLO TAB 200MG	302	10,815	4,715	54	$119,361.92
37	49	FAZACLO TAB 25MG	885	47,257	13,508	84	$102,725.42
		Total Clozapine ODT	**4,896**	**284,108**	**76,134**		**$1,555,303.72**
35	30	GEODON CAP 20MG	1,058	46,287	32,000	284	$327,357.33
27	23	GEODON CAP 40MG	2,038	98,244	62,393	484	$696,768.02
25	20	GEODON CAP 60MG	2,181	115,291	66,662	504	$977,525.65
13	10	GEODON CAP 80MG	4,485	257,707	141,135	807	$2,193,022.65
88	91	GEODON INJ 20MG	17	145	133	12	$2,117.54
		Total Ziprasidone	**9,779**	**517,674**	**302,323**		**$4,196,791.19**
75	73	INVEGA TAB 1.5MG	51	1,486	1,501	21	$20,521.75
32	24	INVEGA TAB 3MG	1,329	42,085	40,970	290	$586,893.67
21	11	INVEGA TAB 6MG	3,036	115,748	95,443	552	$1,609,830.66
33	22	INVEGA TAB 9MG	1,196	38,648	38,648	231	$790,889.35
52	35	INVEGA SUST INJ 117/0.75	292	220	8,271	75	$226,496.68
42	26	INVEGA SUST INJ 156MG/ML	459	459	13,037	118	$478,664.29
56	28	INVEGA SUST INJ 234/1.5	240	361	6,805	77	$364,549.93
98	99	INVEGA SUST INJ 39/0.25	1	0	28	1	$261.40
92	86	INVEGA SUST INJ 78/0.5ML	10	5	284	4	$5,304.65
		Total Paliperidone	**6,614**	**199,012**	**204,987**		**$4,083,412.38**
86	77	LATUDA TAB 40MG	20	780	600	15	$11,587.42
89	85	LATUDA TAB 80MG	14	386	401	10	$5,752.40
		Total Lurasidone	**34**	**1,166**	**1,001**		**$17,339.82**
87	87	RISPERDAL INJ 12.5MG	20	38	536	5	$4,826.47
40	37	RISPERDAL INJ 25MG	510	826	11,689	105	$207,220.02
41	31	RISPERDAL INJ 37.5MG	494	811	11,112	77	$304,610.92
31	17	RISPERDAL INJ 50MG	1,362	2,355	33,376	167	$1,189,962.52
85	78	RISPERDAL SOL 1MG/ML	25	1,800	750	3	$10,666.72
93	90	RISPERDAL TAB 0.25MG	9	510	270	1	$2,318.41
90	93	RISPERDAL TAB 0.5MG	13	390	390	5	$1,096.52

Rank Claims	Rank Cost	Product	Claims	Units	Days	Members	Pharmacy Reimbursement
80	83	RISPERDAL TAB 1MG	42	2,957	1,261	9	$9,329.28
73	68	RISPERDAL TAB 3MG	55	3,631	1,678	7	$36,922.07
97	98	RISPERDAL TAB 4MG	1	31	31	1	$422.77
91	88	RISPERDAL M TAB 0.5MG	12	720	360	1	$3,759.86
83	79	RISPERDAL M TAB 1MG	26	1,696	796	4	$10,131.23
38	59	RISPERIDONE SOL 1MG/ML	865	57,300	27,869	175	$57,225.59
96	97	RISPERIDONE TAB 0.25 ODT	2	120	60	1	$481.16
11	52	RISPERIDONE TAB 0.25MG	5,376	251,455	160,810	1,580	$80,696.47
2	38	RISPERIDONE TAB 0.5MG	13,904	598,663	418,005	4,075	$203,045.96
54	76	RISPERIDONE TAB 0.5MG OD	286	12,528	8,402	97	$17,117.33
1	32	RISPERIDONE TAB 1MG	18,282	800,686	559,151	5,144	$278,243.27
44	63	RISPERIDONE TAB 1MG ODT	451	19,817	13,114	145	$46,623.75
3	40	RISPERIDONE TAB 2MG	11,617	499,781	360,146	3,308	$191,630.51
47	57	RISPERIDONE TAB 2MG ODT	358	16,398	10,546	106	$58,531.42
9	44	RISPERIDONE TAB 3MG	6,135	281,610	194,272	1,465	$119,396.38
67	72	RISPERIDONE TAB 3MG ODT	87	3,762	2,651	31	$23,720.75
18	55	RISPERIDONE TAB 4MG	3,432	153,623	114,368	760	$69,819.52
76	70	RISPERIDONE TAB 4MG ODT	48	2,688	1,493	22	$26,258.97
		Total Riperidone	**63,412**	**2,714,196**	**1,933,136**		**$2,954,057.87**
55	47	SAPHRIS SUB 10MG	246	13,020	7,540	84	$117,747.61
59	54	SAPHRIS SUB 5MG	163	8,065	4,860	69	$72,690.94
		Total Asenapine	**409**	**21,085**	**12,400**		**$190,438.55**
6	13	SEROQUEL TAB 100MG	6,588	298,650	205,732	1,451	$1,515,661.84
10	9	SEROQUEL TAB 200MG	5,725	253,700	178,569	1,213	$2,392,803.00
24	29	SEROQUEL TAB 25MG	2,282	117,097	71,042	521	$346,010.08
8	4	SEROQUEL TAB 300MG	6,148	314,181	195,426	1,230	$3,917,220.09
12	5	SEROQUEL TAB 400MG	5,003	242,778	158,410	882	$3,554,451.01
16	21	SEROQUEL TAB 50MG	3,771	174,264	117,907	894	$842,446.57
34	33	SEROQUEL XR TAB 150MG	1,120	35,181	34,590	338	$269,942.10
36	34	SEROQUEL XR TAB 200MG	951	30,469	30,047	308	$261,950.08
26	19	SEROQUEL XR TAB 300MG	2,097	88,232	65,877	561	$1,011,409.33
28	18	SEROQUEL XR TAB 400MG	1,814	78,104	56,349	435	$1,036,831.14
43	53	SEROQUEL XR TAB 50MG	452	18,255	14,462	165	$79,645.30
		Total Quetiapine	**35,951**	**1,650,911**	**1,128,411**		**$15,228,370.54**
71	64	SYMBYAX CAP 12-25MG	62	2,521	2,431	13	$46,174.66
69	56	SYMBYAX CAP 12-50MG	75	3,300	2,970	14	$60,071.84
81	80	SYMBYAX CAP 3-25MG	38	1,140	1,140	10	$10,012.54
62	66	SYMBYAX CAP 6-25MG	113	3,702	3,702	23	$43,906.15
79	75	SYMBYAX CAP 6-50MG	43	1,407	1,407	9	$17,191.58
		Total Olanzepine/Fluoxetine	**331**	**12,070**	**11,650**		**$177,356.77**
84	84	ZYPREXA INJ 10MG	26	211	175	12	$6,955.16
22	14	ZYPREXA TAB 10MG	2,710	88,943	87,673	553	$1,341,391.52
29	15	ZYPREXA TAB 15MG	1,595	57,782	52,030	330	$1,308,183.13
39	43	ZYPREXA TAB 2.5MG	539	16,472	16,472	114	$137,329.46
15	2	ZYPREXA TAB 20MG	4,021	143,470	135,510	655	$4,355,618.04
30	25	ZYPREXA TAB 5MG	1,559	51,254	49,835	351	$512,336.63
53	48	ZYPREXA TAB 7.5MG	290	9,390	9,390	58	$115,651.31
51	42	ZYPREXA ZYDI TAB 10MG	296	9,778	9,373	74	$158,069.03
57	41	ZYPREXA ZYDI TAB 15MG	188	7,578	5,778	42	$178,499.50
45	27	ZYPREXA ZYDI TAB 20MG	409	12,925	12,755	75	$396,408.69
58	58	ZYPREXA ZYDI TAB 5MG	176	5,255	5,219	53	$58,337.19
95	94	ZYPREXA ZYDIS 10MG TAB	2	60	60	2	$953.20
100	96	ZYPREXA ZYDIS 15MG TAB	1	30	30	1	$702.25
94	95	ZYPREXA ZYDIS 5MG TAB	3	75	75	2	$876.89
		Total Olanzepine	**11,815**	**403,223**	**384,375**		**$8,571,312.00**
		Grand Total	**173,373**	**7,234,868**	**5,278,012**		**$56,839,182.22**

Appendix E

30 Day Notice to Prior Authorize Diabetes Medications

Oklahoma Health Care Authority
August 2011

This category was introduced for possible inclusion in the Product Based Prior Authorization program in June 2011. See the June 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.

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 F

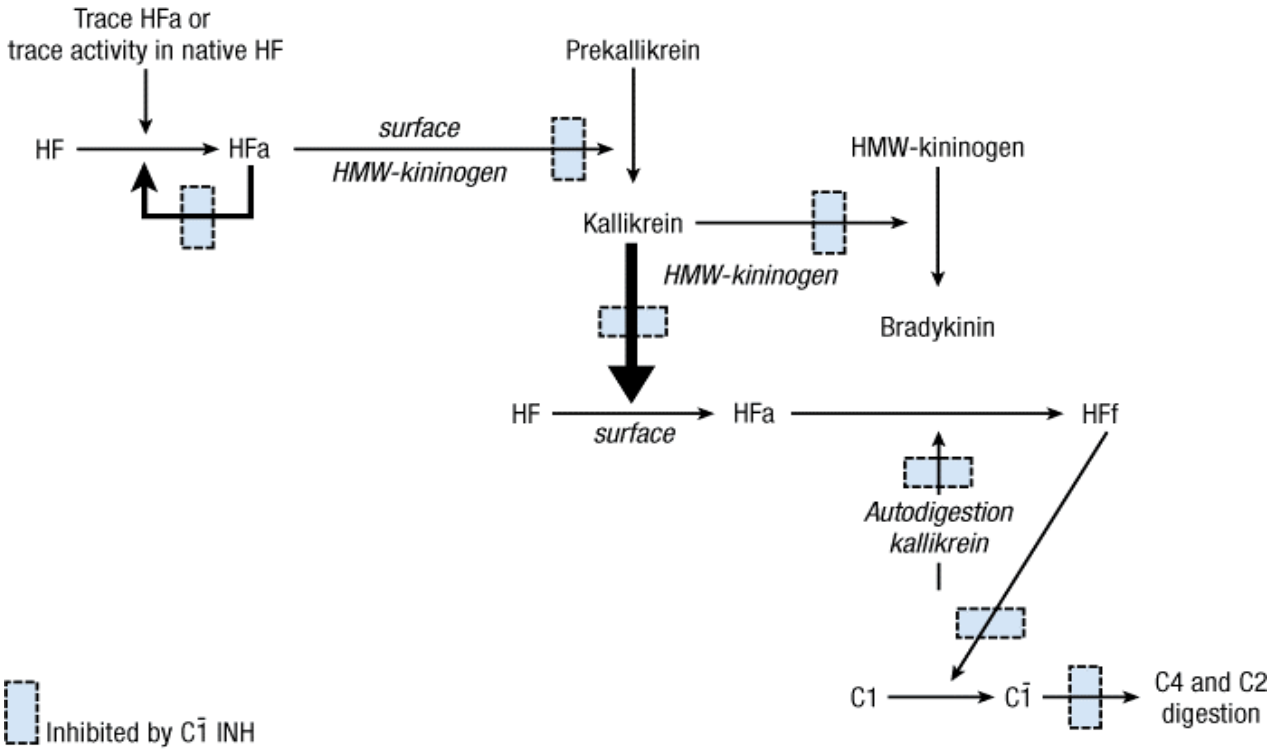
30 Day Notice to Prior Authorize Berinert®, Cinryze® (C-1 Esterase inhibitors) and Kalbitor® (ecallantide)

Oklahoma Health Care Authority, August 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.

Hereditary Angioedema (HAE)[1,2]

- Very rare and potentially life-threatening autosomal dominant condition affecting 1 in 10,000 to 1 in 50,000 people.
- Symptoms include episodes of edema of various body parts, including hands, feet, face, and airways.
- Airway can be compromised by edema, causing death by asphyxiation.
- Swelling in the intestinal wall can cause excruciating abdominal pain, nausea, and vomiting.
- Hereditary angioedema is caused by either low levels or abnormal function of a regulatory protein in the plasma, C1 inhibitor (C1 INH), which exerts control of the complement, fibrinolytic, and kinin-generating pathways. The C1 esterase enzyme, when activated, cleaves two complement products, C4 and C2; without proper inhibition, this leads to low levels of circulating C4 and C2. C1 INH is also a critical modulator of the bradykinin pathway, and decreased C1 INH function leads to increased levels of bradykinin. Increased generation of bradykinin, and not mediators from mast cells or activation of complement, leads to capillary leakage and angioedema.



Source: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ:
Fitzpatrick's Dermatology in General Medicine, 7th Edition: http://www.accessmedicine.com

Treatment Options[1,2,3]

- No treatment – Attacks usually abate in 3 to 4 days even if no medication is given
- Tracheostomy for laryngeal edema
- Mild analgesics for discomfort of severe swelling and abdominal pain
- Attenuated Androgens
  - Danazol
  - Oxandrolone
  - Stanozolol (available as compounded drug)
- Antifibrinolytic agents – off-label use
  - **ε**-aminocaproic acid
  - tranexamic acid (Lysteda™ tabs, Cyklokapron® IV solution)
- Ecallantide – Kalbitor® is a plasma kallikrein inhibitor for treatment of acute attacks
- C1 inhibitors
  - Berinert® – FDA approved for treatment of acute attacks
  - Cinryze® – FDA approved for prophylaxis
- Self-administration training for IV infusions at home
- On-demand treatment for acute attacks - Select hospitals in the state have these drugs (C1 inhibitors and ecallantide) on hand in their emergency rooms for members known to have this condition.

Utilization Data – CY 2010

Brand Name	Claims	Claims per Member	Members	Cost	Cost per claim	Percent cost
Cinryze (C1-INH) 500 units	69	11.5	6	$3,172,262.19	$45,974.81	97.17%
Kalbitor (ecallentide) 10 mg/ml	5	1.67	3	$92,357.30	$18,471.46	2.83%
Totals	**74**	**12.33**	**6**	**$3,264,619.49**	**$44,116.48**	**100%**

Cost Comparison

	EAC/unit	SMAC/unit	Cost per month or per treatment *
Kalbitor®, 30mg/3ml	$2923.20/ml		$8769.60/tx
Berinert® 500 units	$2003.23/vial		$6009.60/tx
Cinryze® 500 units	$2201.60/vial		$4403.20/tx
Danazol, 50 mg cap	$1.41		$155.22/mo
Danazol, 100 mg cap		$1.63	$150.72/mo
Danazol, 200 mg cap		$3.28	$299.22/mo
Stanozolol powder	$25.10/gm		
Methyltestosterone, 10 mg tab**		$5.59	$507.20/mo
ε-Aminocaproic acid 500 mg tab		$2.17	$524.82/mo
Lysteda™ 650 mg tabs	$5.10		$922.02/mo

*weight-based doses for 70 kg person - Berinert® C1 esterase inhibitor - 20 units/kg IV; Cinryze® C1 esterase inhibitor – 1000 units IV q3-4 days for prophylaxis when standard prophylactic treatment fails, is not tolerated, or is contraindicated; Danazol 200 mg bid-tid to response, then reduce 50% q1-3 mo. ε-Aminocaproic acid & Lysteda™ 1 gm po tid-qid. **Men only

Recommendations

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

Criteria for Approval for Cinryze® (C1 esterase inhibitor)

1. Documented diagnosis of Hereditary Angioedema (HAE)
2. For prophylaxis of Hereditary Angioedema (HAE)
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)
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, i.e. 2 treatment per week, or 8 treatments per month.

Criteria for Approval of Kalbitor® (ecallentide):

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

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

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

PRODUCT DETAILS OF KALBITOR® (ECALLANTIDE)[5]

FDA-APPROVED IN 2009

Indication:

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

Dosage Forms:

Kalbitor® is a clear, colorless liquid free of preservatives available in vials containing ecallantide at a concentration of 10 mg/mL.

Administration:

- The recommended dose of Kalbitor® is 30 mg (3 mL), administered subcutaneously in three 10 mg (1 mL) injections. If the attack persists, an additional dose of 30 mg may be administered within a 24 hour period.
- Kalbitor® should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema

Contraindications:

Do not administer Kalbitor® to a patient who has known clinical hypersensitivity to Kalbitor®.

Special Populations:

- **Pregnancy Category C:** There are no adequate and well-controlled trials of Kalbitor® in pregnant women. Kalbitor® has been shown to cause developmental toxicity in rats, but not rabbits. Because animal reproductive studies are not always predictive of human response, Kalbitor® should be used during pregnancy only if clearly needed.
- **Labor and Delivery:** No information is available on the effects of Kalbitor® during labor and delivery.
- **Nursing Mothers:** It is not known whether ecallantide is excreted in human milk. Caution should be exercised when ecallantide is administered to a nursing woman.
- **Pediatric Use:** Safety and effectiveness of Kalbitor® in patients below 16 years of age have not been established.
- **Geriatric Use:** Clinical trials of Kalbitor® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Warnings and Precautions:

- Potentially serious hypersensitivity reactions, including anaphylaxis, have occurred in patients treated with Kalbitor®. In 255 HAE patients treated with intravenous or subcutaneous Kalbitor® in clinical studies, 10 patients (3.9%) experienced anaphylaxis. For the subgroup of 187 patients treated with subcutaneous Kalbitor®, 5 patients (2.7%) experienced anaphylaxis. Symptoms associated with these reactions have included chest discomfort, flushing, pharyngeal edema, pruritus, rhinorrhea, sneezing, nasal congestion, throat irritation, urticaria, wheezing, and hypotension. These reactions occurred within the first hour after dosing.
- Other adverse reactions indicative of hypersensitivity reactions included the following: pruritus (5.1%), rash (3.1%), and urticaria (2.0%).
- Patients should be observed for an appropriate period of time after administration of Kalbitor®, taking into account the time to onset of anaphylaxis seen in clinical trials. Given the similarity in hypersensitivity

symptoms and acute HAE symptoms, patients should be monitored closely in the event of a hypersensitivity reaction.

Common Adverse Effects:

Overall, the most common adverse reactions in 255 patients with HAE were:

- Headache (16.1%)
- Nausea (12.9%)
- Fatigue (11.8%)
- Diarrhea (10.6%)
- Upper respiratory tract infection (8.2%)
- Injection site Reactions (7.4%)
- Nasopharyngitis (5.9%)
- Vomiting (5.5%)
- Pruritus (5.1%)
- Upper abdominal pain (5.1%)
- Pyrexia (4.7%)

Anaphylaxis was reported in 3.9% of patients with HAE. Injection site reactions were characterized by local pruritus, erythema, pain, irritation, urticaria, and/or bruising.

Drug Interactions:

No formal drug interactions studies were performed. No *in vitro* metabolism studies were performed.

Patient Information:

- Patients should be advised that Kalbitor® may cause anaphylaxis and other hypersensitivity reactions.
- Patients should be advised that Kalbitor® should be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema. Patients who have known clinical hypersensitivity to Kalbitor® should be instructed not to receive additional doses of Kalbitor®.
- Patients should be advised to consult the Medication Guide for additional information regarding the risk of anaphylaxis and other hypersensitivity reactions.

PRODUCT DETAILS OF CINRYZE® (C1 ESTERASE INHIBITOR [HUMAN])[6]

FDA-APPROVED IN 2008

Indication:

Cinryze® is a C1 esterase inhibitor indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with Hereditary Angioedema (HAE).

Dosage Form:

Cinryze® is available in single-use vials containing 500 units of lyophilized powder to be reconstituted with 5 ml Sterile Water for Injection

Administration

- The recommended dose of Cinryze® is 1000 units IV every 3 to 4 days, to be infused at a rate of 1 ml/min.
- Patients can be taught by their healthcare provider to self-administer Cinryze® intravenously.

Contraindications:

Cinryze® is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis to the product.

Special Populations:

- **Pregnancy Category C:** No animal data are available. No adequate and well-controlled studies were conducted in pregnant women. It is not known whether Cinryze® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Cinryze® should be given to a pregnant woman only if clearly needed.
- **Labor and Delivery:** The safety and effectiveness of Cinryze® administration prior to or during labor and delivery have not been established. Use only if clearly needed.
- **Nursing Mothers**: It is not known whether Cinryze® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Cinryze® is administered to a nursing woman.
- **Pediatric Use**: The safety and effectiveness of Cinryze® have not been established in neonates, infants, or children. Three of the 24 subjects in Study LEVP2005-1/B were under the age of 18 years (9, 14, and 16 years of age).
- **Geriatric Use**: The clinical study LEVP2005-1/B did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects.

Warnings and Precautions:

Sensitivity

- Severe hypersensitivity reactions may occur. The signs and symptoms of hypersensitivity reactions may include the appearance of hives, urticaria, tightness of the chest, wheezing, hypotension and/or anaphylaxis experienced during or after injection of Cinryze®.
- Because hypersensitivity reactions may have symptoms similar to HAE attacks, treatment methods should be carefully considered.
- In case of hypersensitivity, Cinryze® infusion should be discontinued and appropriate treatment instituted. Epinephrine should be immediately available to treat acute severe hypersensitivity reaction.

Thrombotic Events

- Thrombotic events have been reported in association with C1 esterase inhibitor products when used off-label at high doses. Animal studies have supported a concern about the risk of thrombosis from intravenous administration of C1 esterase inhibitor products.
- In an open label trial further investigating Cinryze® for prevention (n=146) of HAE attacks, 5 serious thrombotic events (including myocardial infarction, deep vein thrombosis, pulmonary embolism and

cerebrovascular accident) occurred. Subjects had underlying risk factors for thrombotic events. Patients with known risk factors for thrombotic events should be monitored closely while taking Cinryze®.

Transmissible Infectious Agents

- Because Cinryze® is made from human blood, it may carry a risk of transmitting infectious agents, e.g. viruses, and, theoretically, the Creutzfeldt-Jakob (CJD) agent. ALL infections thought by a physician possibly to have been transmitted by Cinryze® should be reported by the physician or other healthcare provider to ViroPharma Biologics, Inc. [(877) 945-1000]. The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to the patient.

Common Adverse Effects:

- The most serious adverse events observed in clinical studies of Cinryze® have been death due to non-catheter related foreign body embolus, pre-eclampsia resulting in emergency C-section, stroke, and exacerbation of HAE attacks, none of which have been considered drug related.
- The most common drug related adverse reactions observed at a rate ≥ 5% were upper respiratory tract infection, sinusitis, rash, and headache.

Drug Interactions:

No drug interaction studies have been conducted.

Patient Information:

- Allergic-type Hypersensitivity Reactions: Allergic-type hypersensitivity reactions are possible. Inform patients of the early signs of hypersensitivity reactions [including hives (itchy white elevated patches), tightness of the chest, wheezing, hypotension] and anaphylaxis. Advise patients to discontinue use of Cinryze® and contact their physicians if these symptoms occur.
- Pregnancy: Advise female patients to notify their physician if they become pregnant or intend to become pregnant during their routine prevention with Cinryze®.
- Nursing: Advise patients to notify their physician if they are breastfeeding or plan to breastfeed.
- Usage While Traveling: Based on their current regimen, advise patients to bring an adequate supply of Cinryze® for routine prevention when traveling. Advise patients to consult with their healthcare professional prior to travel.
- Transmissible Infectious Agents: Advise patient that, because Cinryze® is made from human blood, it may carry a risk of transmitting infectious agents, e.g. viruses, and, theoretically, the Creutzfeldt-Jakob (CJD) agent. The risk of transmitting disease has been reduced, but not eliminated, by carefully selecting blood donors, testing donors for infections, and inactivating or removing most viruses during the manufacturing process. Inform patients of the risks and benefits of Cinryze® before prescribing or administering.

PRODUCT DETAILS OF BERINERT® [C1 ESTERASE INHIBITOR (HUMAN)][7]

FDA-APPROVED IN 2009

Indication:

- Berinert® is a plasma-derived C1 Esterase Inhibitor (Human) indicated for the treatment of acute abdominal or facial attacks of hereditary angioedema (HAE) in adult and adolescent patients.
- The safety and efficacy of Berinert for prophylactic therapy have not been established.

Dosage Forms:

Berinert® is available in a single-use vial that contains 500 units of C1 esterase inhibitor as a lyophilized concentrate to be reconstituted with 10 mL of diluent (sterile water) provided.

Administration:

For intravenous use only.

- Store the vial in the original carton in order to protect from light. Store at 2-25°C (36-77°F). Do not freeze.
- Administer 20 units per kg body weight.
- Reconstitute Berinert® prior to use using the diluent (sterile water) provided.
- Administer at room temperature within 8 hours of reconstitution.
- Inject at a rate of approximately 4 mL per minute.
- Do not mix Berinert® with other medicinal products or solutions.

Contraindications:

Do not use in patients with a history of life-threatening immediate hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations.

Special Populations:

- **Pregnancy Category C.** Animal reproduction studies have not been conducted with Berinert. It is not known whether Berinert can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Berinert should be given to a pregnant woman only if clearly needed. In a retrospective case collection study, 20 pregnant women ranging in age from 20 to 35 years received Berinert with repeated doses up to 3,500 units per attack; these women reported no complications during delivery and no harmful effects on their 34 neonates.
- **Labor and Delivery**: The safety and effectiveness of Berinert® administration prior to or during labor and delivery have not been established. Use only if clearly needed.
- **Nursing Mothers**: It is not known whether Berinert® is excreted in human milk. Because many drugs are excreted in human milk, use only if clearly needed when treating a nursing woman.
- **Pediatric Use**: Safety and efficacy of Berinert® in children (ages 0 through 12) have not been established. The clinical studies included an insufficient number of subjects in this age group to determine whether they respond differently from older subjects. The safety and efficacy of Berinert were evaluated in 5 children (ages 3 through 12) and in 8 adolescent subjects (ages 13 through 16).
- **Geriatric Use:** Safety and efficacy of Berinert® in the geriatric population have not been established. Clinical studies with Berinert® included four subjects older than 65 years. The clinical studies included an insufficient number of subjects in this age group to determine whether they respond differently from younger subjects.

Precautions:

Hypersensitivity

- Severe hypersensitivity reactions may occur. Epinephrine should be immediately available for treatment of acute severe hypersensitivity reaction. The signs and symptoms of hypersensitivity reactions may

include hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and/or anaphylaxis during or after injection of Berinert.
- Because hypersensitivity reactions may have symptoms similar to HAE attacks, treatment methods should be carefully considered. In case of suspected hypersensitivity, immediately discontinue administration of Berinert and institute appropriate treatment.

Thrombotic Events

Thrombotic events have been reported in association with Berinert® when used off-label and at higher than labeled doses.1 Animal studies have confirmed the risk of thrombosis from intravenous administration of C1 esterase inhibitor products.

Transmission of Infectious Agents

- Because Berinert® is made from human blood, it may contain infectious agents (e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease [CJD] agent) that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by processes demonstrated to inactivate and/or remove certain viruses during manufacturing.
- Despite these measures, such products may still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products.
- Since 1979, a few suspected cases of viral transmission have been reported with the use of Berinert® outside the US, including cases of acute hepatitis C. From the incomplete information available from these cases, it was not possible to determine with certainty if the infections were or were not related to prior administration of Berinert®.
- The physician should discuss the risks and benefits of this product with the patient before prescribing or administering it to the patient.
- All infections thought by a physician possibly to have been transmitted by Berinert should be reported by lot number, by the physician, or other healthcare provider to the CSL Behring Pharmacovigilance Department at 1-866-915-6958.

Common Adverse Events:

- The most serious adverse reaction reported in subjects enrolled in clinical studies who received Berinert® was an increase in the severity of pain associated with HAE.
- The most common adverse reactions that have been reported in greater than 4% of the subjects who received Berinert® in clinical studies were subsequent HAE attack, headache, abdominal pain, nausea, muscle spasm, pain, diarrhea and vomiting.

Drug Interactions:

No drug interaction studies have been conducted.

Patient Information:

Inform patients to immediately report the following to their physician:

- Signs and symptoms of allergic hypersensitivity reactions, such as hives, urticaria, tightness of the chest, wheezing, hypotension and/or anaphylaxis experienced during or after injection of Berinert®.
- Signs and symptoms of thrombosis, such as new onset swelling and pain in the limbs or abdomen, new onset chest pain, shortness of breath, loss of sensation or motor power, or altered consciousness, vision, or speech.
- Advise female patients to notify their physician if they become pregnant or intend to become pregnant during the treatment of acute abdominal or facial attacks of HAE with Berinert®.
- Advise patients to notify their physician if they are breastfeeding or plan to breastfeed.
- Advise patients to consult with their healthcare professional prior to travel.

- Advise patients that, because Berinert® is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and, theoretically, the Creutzfeldt-Jakob (CJD) agent. Inform patients of the risks and benefits of Berinert before prescribing or administering it to the patient.

REFERENCES

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4. **Kalbitor® Label Information. Dyax Corp.** Available online at: http://www.kalbitor.com/hcp/rems/pdf/KalbitorFullPrescribingInformation.pdf. Last revised 12/2009.
5. **Cinryze® Label Information.** ViroPharma Incorporated. Available online at: www.cinryze.com/documents/cinryze-prescribing-information.pdf. Last revised November 2010.
6. **Berinert® Label Information.** CSL Behring GmbH. Available online at: www.berinert.com/docs/Berinert_pi.pdf. Last revised November 2009.

Appendix G

30 Day Notice to Prior Authorize Xiaflex® (collagenase clostridium histolyticum)

Oklahoma Health Care Authority
July 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.

Manufacturer: Auxilium Pharmaceuticals, Inc.
FDA Status: Prescription Only
Approved Indication: Dupuytren's Contracture

Summary of Dupuytren's Contracture[1,2]

Dupuytren's contracture is a painless thickening and contracture of tissue beneath the skin on the palm of the hand and fingers. In the United States, the prevalence of Dupuytren contracture is about 4% to 6% of the white population.[3] The cause is unknown, but minor injury and/or genetics may play a role in the development of this condition. One or both hands may be affected and the ring finger is affected most often, followed by the little finger. A small, painless nodule develops in the connective tissue on the palm side of the hand and eventually develops into a cord-like band. Dupuytren's contracture progresses slowly and is usually painless, but may cause decrease in motility of the affected finger(s). In severe cases, it's difficult or even impossible to extend the fingers. The condition becomes more common after the age of 40, and occurs more often in men, hence it's sometimes referred to as old man's claw hand.

Surgery may be performed to release the contracture by removing affected fascia. Movement of the finger(s) is usually restored by surgery followed by physical therapy exercises for about 4-6 months. The procedure is not curative in that remaining non-affected fascia may still develop Dupuytren's disease later on, and therefore the patient may need repeat surgery. In addition, the thickened fascia often is near to or wrapped around the digital nerves and arteries, so there is risk of nerve and/or arterial injury. The cost of surgery ranges from $10,000 to $16,000.

Needle aponeurotomy is a minimally invasive technique where the cords are weakened through the insertion and manipulation of a small needle. Once weakened, the offending cords may be snapped by simply pulling the finger(s) straight. This procedure may be done in the office under local anesthesia and offer very rapid return to normal activities without need for rehabilitation. However, the affected tissues are not removed and might start growing again. The cost of this procedure ranges from $700 to $1,000 per finger.

Xiaflex® (collagenase clostridium histolyticum) Summary

Xiaflex® was approved by the FDA in 2010 for the treatment of adult patients with Dupuytren's contracture when there is a palpable cord. Xiaflex® is made from proteinase derived from the bacteria Clostridium histolyticum, which hydrolyzes collagen, resulting in lysis of collagen deposits. Xiaflex must be reconstituted and administered by a healthcare professional experienced in injection procedures of the hand and in the treatment of Dupuytren's contracture. After the injection, a finger extension procedure may be performed if contracture persists. Injections and finger extension procedures may be administered up to 3 times per cord at approximately 4 week intervals. The estimated acquisition cost of Xiaflex® is $3,234.00 per single dose vial, hence the cost per finger may be up to $9,702 per finger, not including physician and other fees.

The most common adverse reactions reported in ≥ 25% of the patients treated with Xiaflex® were peripheral edema (swelling of the injected hand), contusion, injection site reaction, injection site hemorrhage, and pain in the injection extremity. Care must be taken to avoid injecting into tendons, blood vessels, or other collagen-containing structure of the hand, which may result in tendon rupture or ligament damage. The healthcare provider should be prepared to address severe allergic reactions following Xiaflex® injections. Caution should be used when injecting patients with abnormal coagulation or patients who have received anticoagulation medications other than low-dose aspirin within 7 days of the injection.

Utilization

BRAND NAME	CLAIMS	UNITS	DAYS	MEMBERS	COST	PERDIEM	PRESCRIBER SPECIALTY
XIAFLEX INJ 0.9MG	1	1	30	1	$3,432.52	$114.42	Orthopedic Surgeon

Xiaflex® may also be billed by the code J0775, which became active on 1/1/2011. There have been no medical/hospital claims detected in the SoonerCare population for that code since then.

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.

PRODUCT DETAILS OF XIAFLEX® (COLLAGENASE CLOSTRIDIUM HISTOLYTICUM)[4]

FDA-APPROVED IN FEBRUARY 2010

INDICATIONS: Xiaflex® is indicated for the treatment of Dupuytren's contracture with a palpable cord.

DOSAGE FORMS: Xiaflex® is supplied as single-use glass vials containing 0.9mg of collagenase clostridium histolyticum as a sterile, lyophilized powder for reconstitution. Sterile diluent for reconstitution is also provided in a single use glass vial.

ADMINISTRATION:

- Xiaflex® should be administered by a healthcare provider experienced in injection procedures of the hand and in the treatment of Dupuytren's contracture.
- Reconstitute Xiaflex® lyophilized powder with only the supplied diluent prior to use.
- Inject 0.58 mg of Xiaflex® into a palpable Dupuytren's cord with a contracture of a metacarpophalangeal (MP) joint or a proximal interphalangeal (PIP) joint according to the injection procedure.
- Approximately 24 hours following an injection, perform a finger extension procedure if a contracture persists.
- Injections and finger extension procedures may be administered up to 3 times per cord at approximately 4-week intervals.
- Inject only one cord at a time. If a patient has other cords with contractures, inject each cord in sequential order.

CONTRAINDICATIONS: None listed.

SPECIAL POPULATIONS:

- Xiaflex® is categorized as **Pregnancy Category B**, although there are no adequate and well-controlled studies of Xiaflex® in pregnant women.
- It is not known whether collagenase clostridium histolyticum is excreted in human milk.
- The safety and effectiveness of Xiaflex® in pediatric patients less than 18 years old have not been established.

WARNINGS & PRECAUTIONS:

- **Tendon rupture or serious injury to the injected extremity**: Avoid injecting Xiaflex® into tendons, nerves, blood vessels, or other collagen-containing structure of the hand. Injection into these structures may result in possible permanent injury, such as tendon rupture or ligament damage.
- **Patients with abnormal coagulation:** Use with caution, including in patients who have received anticoagulant medications other than low- dose aspirin within 7 days of the injection.
- **Allergic reactions**: Healthcare providers should be prepared to address severe allergic reactions following Xiaflex® injections.

ADVERSE REACTIONS:

- peripheral edema (e.g., swelling of the injected hand)
- contusion
- injection site reaction
- injection site hemorrhage
- pain in the injected extremity

DRUG INTERACTIONS: None listed.

PATIENT INFORMATION:

Advise patients the following before injection

- Serious complications of Xiaflex® injection include tendon rupture or serious ligament damage that may result in the inability to fully bend the finger and may require surgery to correct the complication.
- Xiaflex® injection is likely to result in swelling, bruising, bleeding, and/or pain of the injected site and surrounding tissue.

After the Xiaflex® injections, instruct patients:

- Not to flex or extend the fingers of the injected hand to reduce extravasation of Xiaflex® out of the cord. Not to attempt to disrupt the injected cord by self manipulation. To elevate the injected hand as much as possible until bedtime.
- To promptly contact their physician if there is evidence of infection (e.g., fever, chills, increasing redness or edema), sensory changes in the treated finger, or trouble bending the finger after the swelling goes down (symptoms of tendon rupture).
- To return to their healthcare provider's office the next day for an examination of the injected hand and for a possible finger extension procedure to disrupt the cord.

Following the finger extension procedure(s) and fitting patient with a splint, instruct patients:

- Not to perform strenuous activity with the injected hand until advised to do so.
- To wear the splint at bedtime for up to 4 months.
- To perform a series of finger flexion and extension exercises each day.

[1] http://www.dupuytren-online.info/index.html
[2] http://www.nlm.nih.gov/medlineplus/ency/article/001233.htm
[3] https://online.epocrates.com/u/2923983/Dupuytren+contracture/Basics/Epidemiology
[4] http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/125338lbl.pdf

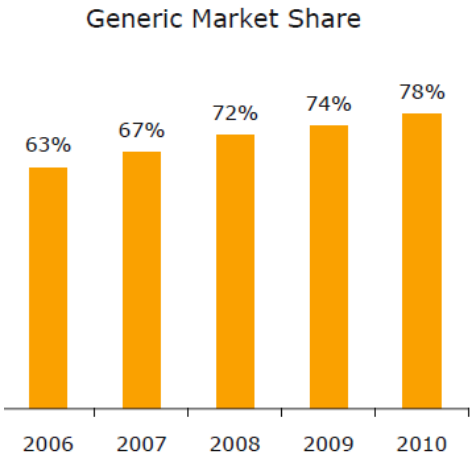
Appendix H

Drug Utilization Review of Biologic Products for the Treatment of Rheumatoid Arthritis, Crohn's Disease, Plaque Psoriasis, and Ankylosing Spondylitis

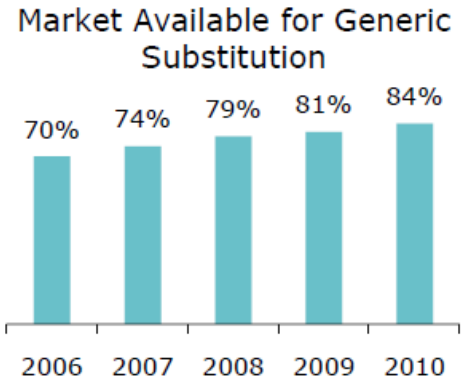
Oklahoma HealthCare Authority
August 2012

Introduction

The landscape of medication utilization and associated costs is poised to undergo a paradigm shift within the next two years. As seen on the chart below, rising costs associated with traditional medications have been slowing down as the generic market share increased through the years and this trend is set to increase significantly with the patent expirations of Lipitor®, Zyprexa®, Levaquin®, and a number of other major blockbuster medications in 2011 and 2012.



Generic market share: percentage of unbranded and branded generic prescriptions dispensed annually.
Source: IMS Health, National Prescription Audit, Dec 2010.[1]



Represents percentage of products at the form level that have a comparable generic available on the market.
Source: IMS Health, National Prescription Audit, Dec 2010.[2]

During this same time period specialty medications accounted for the fastest growing segment of overall drug spending and the sales of these medications are expected to grow at twice the rate of traditional medications by 2013.[3,4,5] The specialty medications include a group of biotech medications which are protein derived, often called biologics. Due to the increase in use of biologic medications, the high costs associated with these medications, and novel agents entering the market, both private and public payors across the nation are focusing on strategies to ensure cost-effective utilization of these products.

In the SoonerCare population, a look at utilization trends for select biologics for the treatment of Rheumatoid Arthritis, Crohn's Disease, Plaque Psoriasis, and Ankylosing Spondylitis showed the following trends:

Calendar Year	Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2006	221	1,714	$2,572,429.49	$1,500.83	$51.61	8,972	49,845
2007	283	2,086	$3,484,413.73	$1,670.38	$57.13	10,008	60,995
2008	294	1,828	$3,340,395.87	$1,827.35	$63.11	8,684	52,929
2009	371	1,929	$3,743,806.02	$1,940.80	$68.02	10,237	55,038
2010	439	2,427	$4,927,903.02	$2,030.45	$71.87	18,432	68,564

Pharmacy Data Only

This review will focus on the agents outlined in the chart[6] below:

Drug name	Mechanism	Dose form	FDA-approved indications				
			Rheumatoid arthritis	Crohn's disease	Plaque psoriasis	Ankylosing spondylitis	Other Indications
Adelimumab (Humira®)	TNF (tumor necrosis factor) blocking	SC	X	X	X	X	Psoriatic arthritis, Juvenile Idiopathic Arthritis
Infliximab (Remicade®)	TNF blocking	IV	X	X	X	X	Psoriatic arthritis, Ulcerative colitis
Etanercept (Enbrel®)	TNF blocking	SC	X		X	X	Psoriatic arthritis, Juvenile Idiopathic Arthritis
Certolizumab pegol (Cimzia®)	TNF blocking	SC	X	X			
Golimumab (Simponi®)	TNF blocking	SC	X			X	Psoriatic arthritis
Rituximab (Rituxan®)	Anti-B-cell	IV	X				Non-Hodgkin's Lymphoma, Chronic Lymphocytic Leukemia, Wegener's Granulomatosis, Microscopic Polyangiitis
Anakinra (Kineret®)	IL-1 (Interleukin-1) receptor antagonist	SC	X				
Abatacept (Orencia®)	Selective T-Cell Costimulation Modulator	IV	X				Juvenile Idiopathic Arthritis
Tocilizumab (Actemra®)	IL-6 receptor antagonist	IV	X				Juvenile Idiopathic Arthritis
Natalizumab (Tysabri®)	Selective adhesion molecule inhibitor	IV		X			Multiple sclerosis
Alefacept (Amevive®)	CD2 receptor antagonist	IV			X		
Ustekinumab (Stelara®)	IL-12,23 receptor antagonist	SC			X		

Biologic medications are relatively new to the armamentum of treatment options in the disease states they are indicated for. Due to the high costs and route of administration, these agents are typically reserved for patients with moderate to severe disease in which traditional pharmacologic options have been exhausted. This review will not include natalizumab (Tysabri®) since the data shows that the most utilization of this medication in the Soonercare population is for multiple sclerosis, which will be covered at a later date.

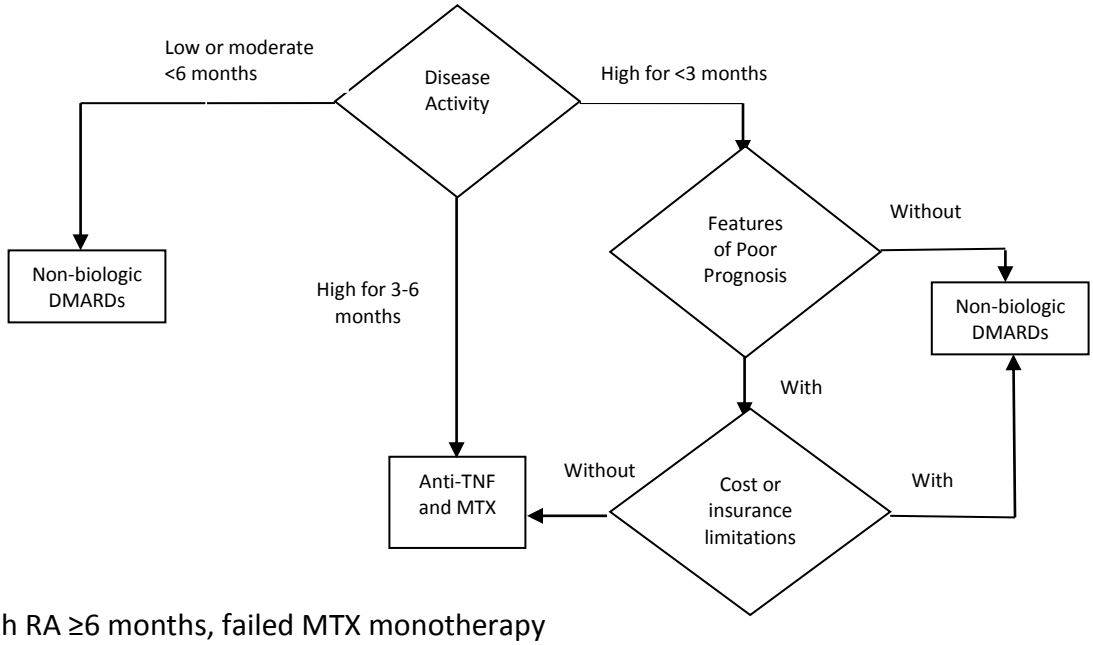
Treatment Guidelines

Rheumatoid arthritis[7]

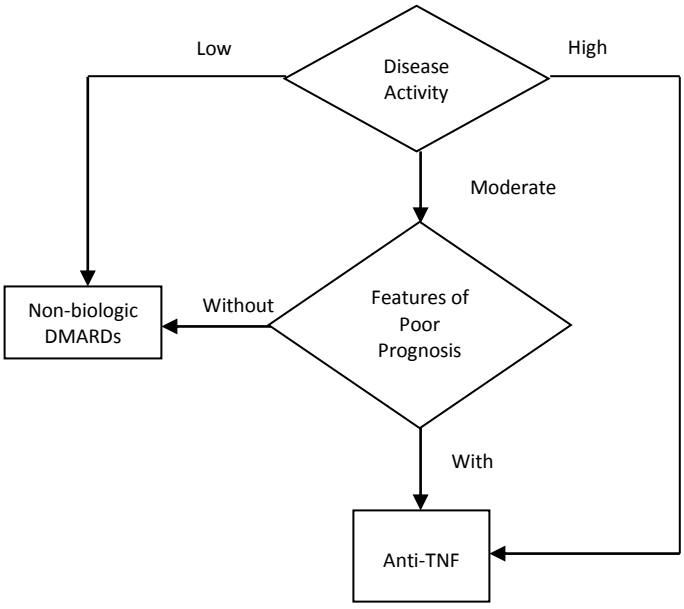
Pharmacotherapy for rheumatoid arthritis generally involves a nonsteroidal anti-inflammatory drug (NSAID) for control of pain, with selective use of low-dose oral or intra-articular glucocorticoids, and initiation of a Disease-Modifying Anti-rheumatic Drug (DMARD). DMARDs are initiated quickly to slow disease progression as early as possible.

Treatment guidelines for newly diagnosed patients published by the American College of Rheumatology (ACR) are divided by disease duration, defined as <6 months, 6-24 months, and >24 months. There are more than 170 possible dual or triple DMARD combinations among the 5 non-biologic drugs considered in the recommendations (methotrexate, hydroxychloroquine, sulfasalazine, minocycline, and leflunomide). For patient-specific circumstances, please consult the tables published by the ACR. Recommendations by the ACR for the use of biologic DMARDs are also initially divided by disease duration for newly diagnosed patients. However, they also include recommendations for members who have failed therapy with non-biologic DMARDs. In general, treatment failure is the sequential administration of nonbiologic DMARDs that have resulted in an inadequate response. DMARDs typically take weeks to months to start working. Also, the guidelines use features of poor prognosis as an important factor in treatment selection. The following indicators were selected as the most important clinical markers of poor prognosis: functional limitation (Health Assessment Questionnaire Disability Index), extraarticular disease (e.g. vasculitis, Sjögren's syndrome, RA lung disease, etc.), rheumatoid factor positivity and/or positive anti-cyclic citrullinated peptide antibodies, and/or bony erosions by radiography. The following flow charts illustrate these recommendations.

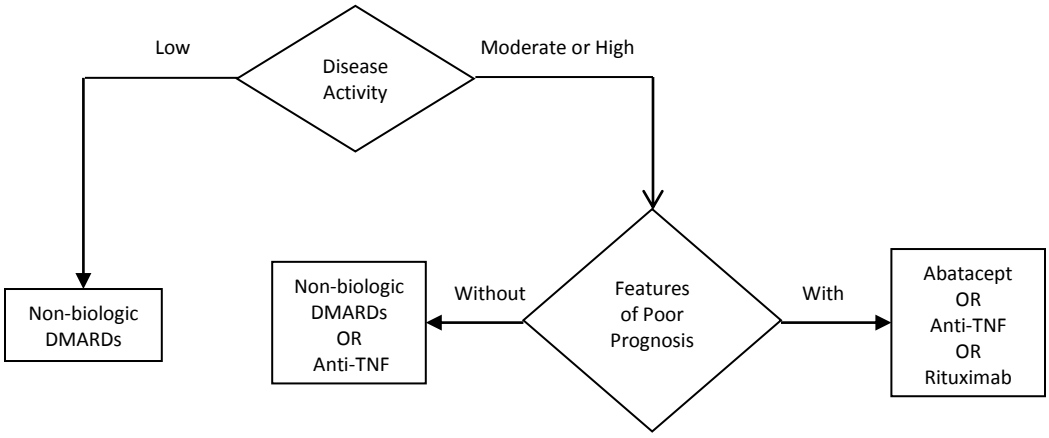
Patients with RA <6 months



Patients with RA ≥6 months, failed MTX monotherapy



Patients with RA ≥6 months, failed MTX combination therapy or sequential therapy with other DMARDs



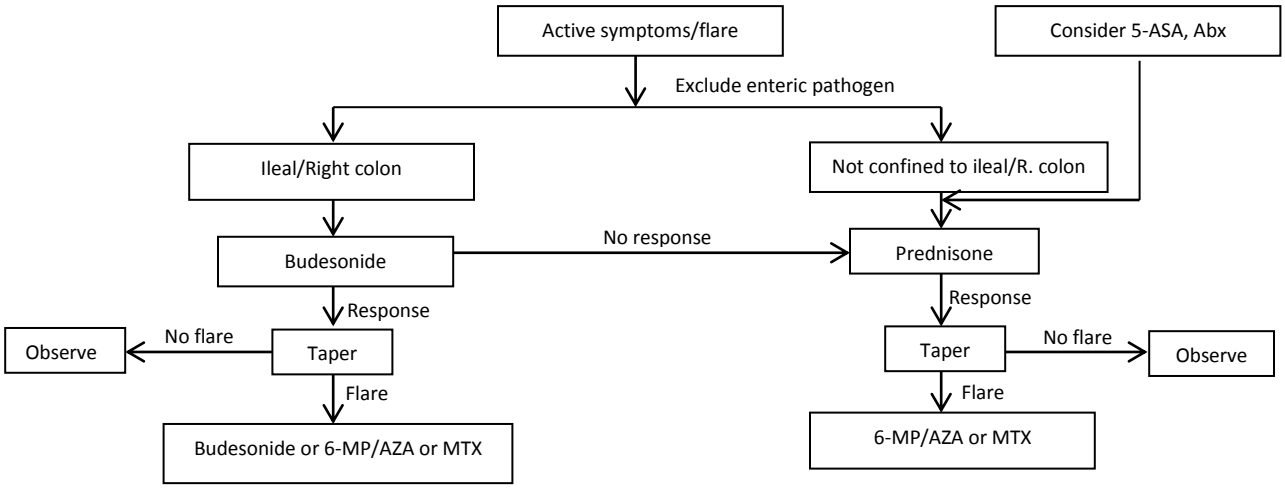
Crohn's Disease[8]

Treatment guidelines have been published by the American College of Gastroenterology in 2009. Therapeutic recommendations depend on the disease location, severity, and complications. The patient's response to initial therapy should be evaluated within several weeks, and treatment for active disease should be continued to the point of symptomatic remission or no further improvement. In general, clinical evidence of improvement should occur within 2-4 weeks and maximal improvement within 12-16 weeks. Patients achieving remission should be considered for maintenance therapy.

Anatomic distribution of disease and disease activity are the factors to be considered when determining appropriate medical therapy for individual patients. Some medications such as sulfasalazine, mesalamine, and enteric-coated budesonide are useful only in specific areas of the GI tract whereas other medications have therapeutic activity throughout the GI tract.

Crohn's Disease Treatment Algorithm

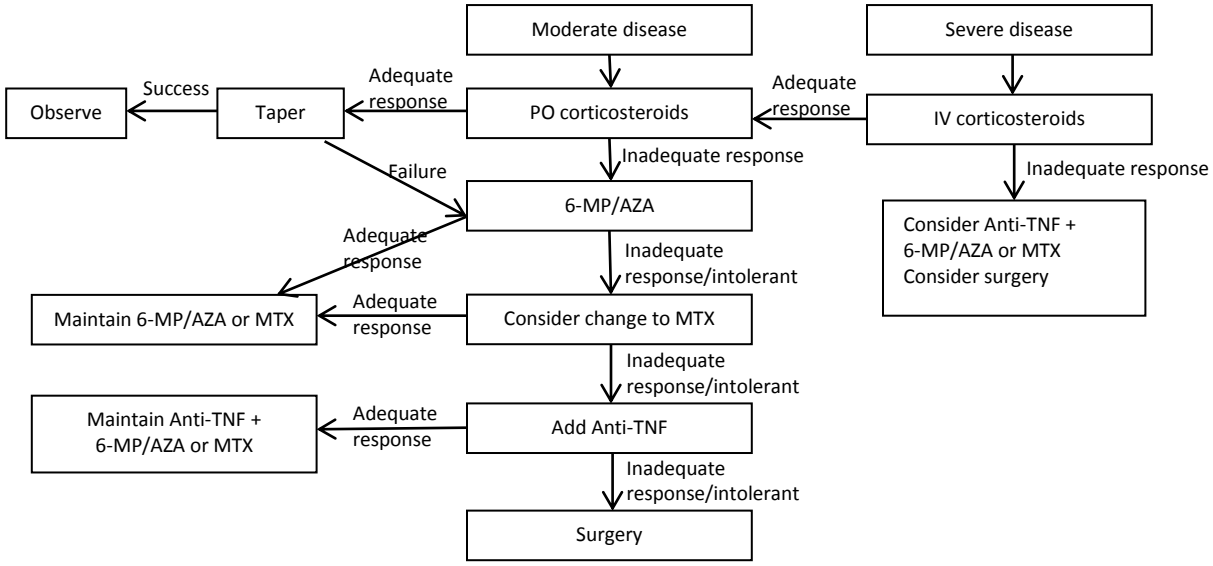
Mild to moderate disease



5-ASA=mesalamine; Abx=antibiotics; 6-MP=6-Mercaptopurine; AZA=azathioprine; MTX=methotrexate

Crohn's Disease Treatment Algorithm

Moderate to severe disease



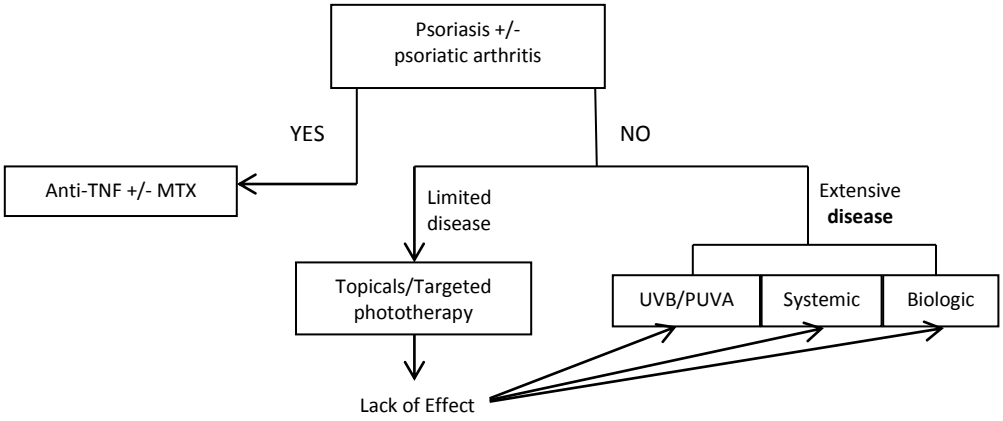
5-ASA=mesalamine; Abx=antibiotics; 6-MP=6-Mercaptopurine; AZA=azathioprine; MTX=methotrexate

Plaque Psoriasis[9]

Psoriasis is a chronic inflammatory disease predominantly affecting the skin and joints. The disease is most commonly seen as plaque psoriasis, which is characterized by disfiguring, scaling, and erythromatous plaques that may be painful or severely pruritic. About 1 in 20 patients with plaque psoriasis also develop psoriatic arthritis, with inflammation affecting the joints.

Treatment guidelines are available from the American Academy of Dermatology and were last updated in 2008. All biologic agents FDA-approved for this condition are for the treatment of moderate-to-severe chronic plaque psoriasis, except for rituximab, which is for severe psoriasis only. The guidelines state that patients with nondeforming psoriatic arthritis without any radiographic changes, loss of range of motion, or interference with tasks of daily living should not automatically be treated with TNF inhibitors. It would be reasonable to treat these patients with nonsteroidal anti-inflammatory agents or to consult a rheumatologist for therapeutic options. Also, patients with limited skin disease should not automatically be treated with systemic therapy if they do not improve, because such treatment may carry more risk than the disease itself.

Plaque Psoriasis Treatment Algorithm

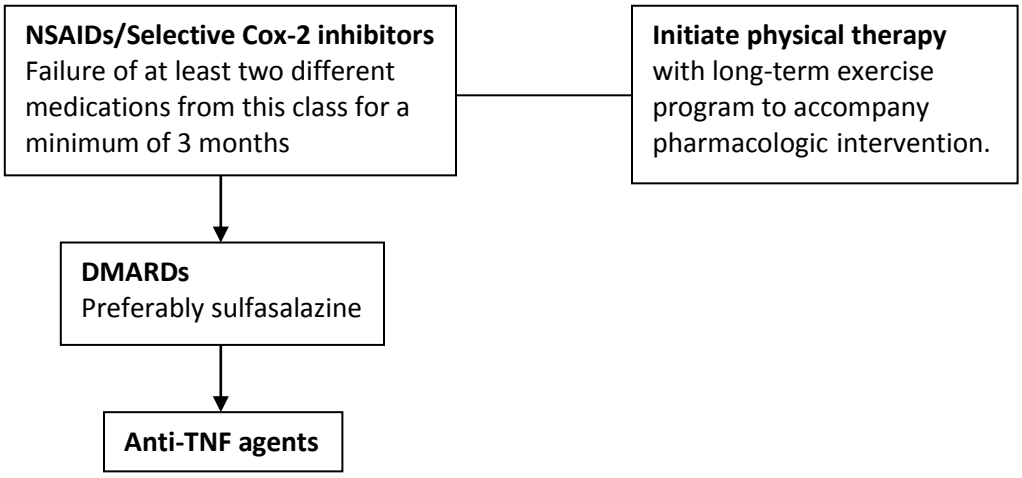


MTX=Methotrexate; UVB=ultraviolet-B;PUVA=psoralen plus ultraviolet-A

Ankylosing Spondylitis[10]

Treatment guidelines have been developed by the Assessments in Spondylitis Working Group (ASAS), published in the Annals of Rheumatic Disease in September 2003. The guidelines for the initiation of anti-TNF therapy require a diagnosis of definitive ankylosing spondylitis (AS) and the presence of active disease for at least four weeks as defined by both a sustained Bath AS Disease Activity Index (BASDAI) of at least 4 and an expert opinion based on clinical features, acute phase reactants, and imaging modalities. Also, the refractory disease should be present, defined by failure of NSAIDs in all AS patients and failure of DMARDs in AS patients with peripheral arthritis. For non-responders to anti-TNF therapy, consideration of whether treatment should be discontinued should be made within 6-12 weeks of treatment. Treatment response is defined as improvement of at least 50% or an increase of at least 2 units (0-10 scale) on the BASDAI, in which case treatment should be continued.

Ankylosing Spondylitis Treatment Algorithm



Utilization of Biologics

Comparison of Calendar Years

Calendar Year	Members	Claims	Cost	Cost/Claim	Perdiem	Units	Days
2009	371	1,929	$3,743,806.02	$1,940.80	$68.02	10,237	55,038
2010	439	2,427	$4,927,903.02	$2,030.45	$71.87	18,432	68,564
Percent Change	**18.30%**	**25.80%**	**31.60%**	**4.60%**	**5.70%**	**80.10%**	**24.60%**
Change	**68**	**498**	**$1,184,097.00**	**$89.65**	**$3.85**	**8,195**	**13,526**

Medical Claims Financial Data: CY 2010

Medications	Claims	Cost
Abatacept	91	$147,639.75
Infliximab	251	$346,299.21
Rituximab	193	$671,223.23
Total Medical Claims:	**535**	**$1,165,162.19**
***Cost for ALL Claims:**		**$6,015,506.04**

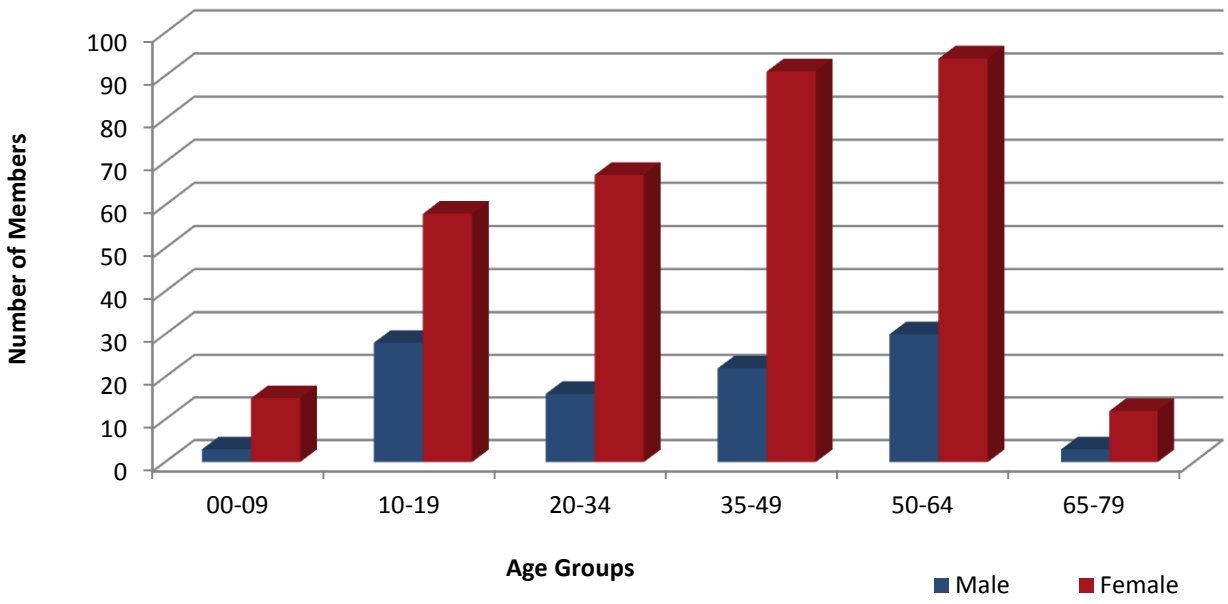
***Pharmacy and medical claims.**

Utilization Details of Pharmacy Claims: CY 2010

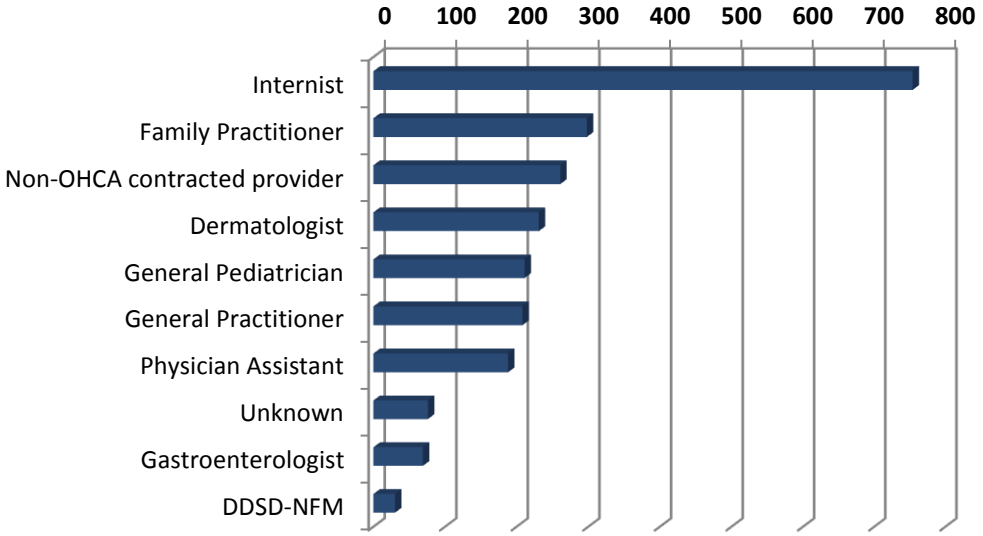
GENERIC NAME	BRAND NAME	CLAIMS	DAYS	MEMBERS	COST	CLAIMS/ MEMBER	COST/ DAY	PERCENT COST
Adalimumab	HUMIRA PEN KIT 40MG/0.8	582	17,068	128	$1,198,277.32	4.55	$70.21	24.32%
Etanercept	ENBREL SRCLK INJ 50MG/ML	506	14,693	104	$1,088,640.77	4.87	$74.09	22.09%
Etanercept	ENBREL INJ 50MG/ML	413	11,422	76	$782,779.77	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*

Demographics of Members Utilizing Biologics: CY 2010



Prescribers of Biologics by Number of Claims: CY2010



Conclusion and Recommendations

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

Tier 2 authorization criteria:

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

Tier 3 authorization criteria:

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

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

[1] IMS Institute for HealthCare Informatics. The Use ofMedicines in theUnited States:Review of 2010. Available online at: http://www.imshealth.com/deployedfiles/imshealth/Global/Content/IMS%20Institute/Static%20File/IHII_UseOfMed_report.pdf
[2] Ibid.
[3] ExpressScripts Drug Trend Report 2010. http://www.express-scripts.com/research/studies/drugtrendreport/2010/dtrFinal.pdf
[4] CuraScript Specialty Drug Trend Report 2008. http://www.curascript.com/bin_web/documents/08DrugTrendReportCuraScript.pdf
[5] http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Specialty%20Pharmaceuticals/Static%20Files/PC_Specialty.pdf
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[10] Braun J, Pham T, Sieper J, Davis J, van der Linden Sj, Dougados M, et al. International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis. Ann Rheum Dis 2003;62:817-24.

Appendix I

U.S. Food and Drug Administration

Drugs

FDA Drug Safety Communication: Serious CNS reactions possible when methylene blue is given to patients taking certain psychiatric medications

Safety Announcement

[07-26-2011] The U.S. Food and Drug Administration (FDA) has received reports of serious central nervous system (CNS) reactions when the drug methylene blue is given to patients taking psychiatric medications that work through the serotonin system of the brain (serotonergic psychiatric medications). Methylene blue is commonly used in diagnostic procedures and is also used to treat a number of medical conditions (see Facts about methylene blue box). A list of the serotonergic psychiatric medications that can interact with methylene blue can be found here.

Although the exact mechanism of this drug interaction is unknown, methylene blue inhibits the action of monoamine oxidase A—an enzyme responsible for breaking down serotonin in the brain. It is believed that when methylene blue is given to patients taking serotonergic psychiatric medications, high levels of serotonin can build up in the brain, causing toxicity. This is referred to as Serotonin Syndrome. Signs and symptoms of Serotonin Syndrome include mental changes (confusion, hyperactivity, memory problems), muscle twitching, excessive sweating, shivering or shaking, diarrhea, trouble with coordination, and/or fever.

Facts about Methylene Blue

- Used to treat methemoglobinemia, vasoplegic syndrome, ifosfamide-induced encephalopathy, cyanide poisoning
- Used as a dye in therapeutic and diagnostic applications
- Is a potent, reversible monoamine oxidase inhibitor (MAOI).

Healthcare professionals and patients may not realize that methylene blue has monoamine oxidase inhibitor (MAOI) properties. Methylene blue should generally not be given to patients taking serotonergic drugs. However, there are some conditions that may be life-threatening or require urgent treatment with methylene blue such as when it is used in the emergency treatment of:

- methemoglobinemia,
- ifosfamide-induced encephalopathy, or
- cyanide poisoning.

Safety information about these potential drug interactions and important drug usage recommendations for emergency and non-emergency situations are being added t the drug labels for serotonergic psychiatric medications. (See Additional Information for Healthcare Professionals)

A separate Drug Safety Communication (DSC) is being released today for linezolid (Zyvox)[1] due to similar potential drug interactions with serotonergic psychiatric medications and includes drug usage recommendations.

Health Canada issued a NOTICE TO HOSPITALS on the association of serotonin toxicity with methylene blue in combination with serotonin reuptake inhibitors on February 16, 2011[2].

Additional Information for Patients

- You may need to temporarily stop taking your serotonergic psychiatric medication if it becomes necessary for you to take methylene blue in certain situations. Your healthcare provider will tell you when to start methylene blue after stopping your serotonergic psychiatric medication.
- Do not stop taking your serotonergic psychiatric medicine without first talking to a healthcare professional.
- Make sure your healthcare professional knows about all the medications you are taking. It is helpful to keep a list of all your current medications in your wallet or another location where it is easily retrieved.
- Contact your healthcare professional immediately if you are taking a serotonergic psychiatric medication and develop any of the following symptoms: mental changes (confusion, hyperactivity, memory problems), muscle twitching, excessive sweating, shivering or shaking, diarrhea, trouble with coordination, and/or fever.
- Discuss any questions or concerns about methylene blue or serotonergic psychiatric medications with your healthcare professional.
- Report any serious 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

- Methylene blue can interact with serotonergic psychiatric medications and cause serious CNS toxicity.
- In emergency situations requiring life-threatening or urgent treatment with methylene blue (as described above), the availability of alternative interventions should be considered and the benefit of methylene blue treatment should be weighed against the risk of serotonin toxicity. If methylene blue must be administered to a patient receiving a serotonergic drug, the serotonergic drug must be immediately stopped, and the patient should be closely monitored for emergent symptoms of CNS toxicity for two weeks (five weeks if fluoxetine [Prozac] was taken), or until 24 hours after the last dose of methylene blue, whichever comes first.
- In non-emergency situations when non-urgent treatment with methylene blue is contemplated and planned, the serotonergic psychiatric medication should be stopped to allow its activity in the brain to dissipate. Most serotonergic psychiatric drugs should be stopped at least 2 weeks in advance of methylene blue treatment. Fluoxetine (Prozac), which has a longer half-life compared to similar drugs, should be stopped at least 5 weeks in advance.
- Treatment with the serotonergic psychiatric medication may be resumed 24 hours after the last dose of methylene blue.
- Serotonergic psychiatric medications should not be started in a patient receiving methylene blue. Wait until 24 hours after the last dose of methylene blue before starting the antidepressant.

- Educate your patients to recognize the symptoms of serotonin toxicity or CNS toxicity and advise them to contact a healthcare professional immediately if they experience any symptoms while taking serotonergic psychiatric medications or methylene blue.
- Report adverse events involving methylene blue or serotonergic psychiatric medications to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page.

Data Summary

FDA has received adverse event reports from the FDA Adverse Event Reporting System (AERS) database of serious central nervous system (CNS) reactions in patients treated with serotonergic psychiatric medications who were administered methylene blue. Additional cases also have been reported in the published literature.[1-3] The reported adverse events include the following: lethargy, confusion, delirium, agitation, aggression, obtundation, and coma. These symptoms were frequently accompanied by neurological symptoms, such as myoclonus, expressive aphasia, hypertonia, and seizures, or autonomic symptoms, such as pyrexia and elevated bloo pressure.

Based on the available information provided in the AERS cases and literature, FDA has concluded that the concomitant administration of a serotonergic psychiatric medication with methylene blue has the potential for a drug interaction causing serotonin syndrome. It appears this potential drug interaction can also occur following the discontinuation of serotonergic psychiatric medications with long half-lives. As a result, methylene blue should generally not be given to patients taking serotonergi drugs unless the benefit is deemed to outweigh the risk.

References

1. Bach KK, Lindsay FW, Berg LS, Howard RS. Prolonged postoperative disorientation after methylene blue infusion during parathyroidectomy. Anesth Analg. 2004;99:1573-4.
2. Kartha SS, Chacko CE, Bumpous JM, Fleming M, Lentsch EJ, Flynn MB. Toxic metabolic encephalopathy after parathyroidectomy with methylene blue localization. Otolaryngol Head Neck Surg. 2006;135:765-8.
3. Sweet G, Standiford SB. Methylene-blue-associated encephalopathy. J Am Coll Surg. 2007;204:454-8.

Tables -Psychiatric medications with serotonergic activity

Selective Serotonin Reuptake Inhibitors (SSRIs)

Generic name	Found in Brand name(s)
paroxetine	Paxil, Paxil CR, Pexeva
fluvoxamine	Luvox, Luvox CR
fluoxetine	Prozac, Sarafem, Symbyax
sertraline	Zoloft
citalopram	Celexa
escitalopram	Lexapro

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Generic name	Found in Brand name(s)
venlafaxine	Effexor, Effexor XR
desvenlafaxine	Pristiq
duloxetine	Cymbalta

Tricyclic Antidepressants (TCAs)

Generic name	Found in Brand name(s)
amitriptyline	Amitid, Amitril, Elavil, Endep, Etrafon, Limbitrol, Triavil
desipramine	Norpramin, Pertofrane
clomipramine	Anafranil
imipramine	Tofranil, Tofranil PM, Janimine, Pramine, Presamine
nortriptyline	Pamelor, Aventyl hydrochloride
protriptyline	Vivactil
doxepin	Sinequan, Zonalon, Silenor
trimipramine	Surmontil

Monoamine Oxidase Inhibitors (MAOIs)

Generic name	Found in Brand name(s)
Isocarboxazid	Marplan
Phenelzine	Nardil
Selegiline	Emsam, Eldepryl, Zelapar
Tranylcypromine	Parnate

Other Psychiatric Medications

Generic name	Found in Brand name(s)
amoxapine	Asendin
maprotiline	Ludiomil
nefazodone	Serzone
trazodone	Desyrel, Oleptro, Trialodine
bupropion	Wellbutrin, Wellbutrin SR, Wellbutrin XL, Zyban, Aplenzin
buspirone	Buspar

vilazodone	Viibryd
mirtazapine	Remeron, Remeron Soltab

Related Information

- Methylene blue injectable in combination with serotonin reuptake inhibitors - Association with serotonin toxicity - Notice to Hospitals [3] [4]
  Health Canada
- FDA Drug Safety Communication: Serious CNS reactions possible when linezolid (Zyvox®) is given to patients taking certain psychiatric medications [5]
  7/26/2011
- FDA Drug Safety Podcast for Healthcare Professionals: Serious CNS reactions possible when methylene blue is given to patients taking certain psychiatric medications [6]
  8/1/2011

Contact Us

- **Report a Serious Problem**
- 1-800-332-1088
- 1-800-FDA-0178 Fax

MedWatch Online [7]

Regular Mail: Use postage-paid FDA Form 3500 [8]

Mail to: MedWatch 5600 Fishers Lane

Rockville, MD 20857

Links on this page:

1. /Drugs/DrugSafety/ucm265305.htm
2. http://hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2011/methylene_blue-bleu_nth-aah-eng.php
3. http://hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2011/methylene_blue-bleu_nth-aah-eng.php
4. /AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm
5. /Drugs/DrugSafety/ucm265305.htm
6. /Drugs/DrugSafety/DrugSafetyPodcasts/ucm266219.htm
7. https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm
8. http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf

U.S. Food and Drug Administration

Drugs

FDA Drug Safety Communication: Multaq (dronedarone) and increased risk of death and serious cardiovascular adverse events

Safety Announcement

[07-21-2011] The U.S. Food and Drug Administration (FDA) is reviewing data from a clinical trial that was evaluating the effects of the antiarrhythmic drug Multaq (dronedarone) in patients with permanent atrial fibrillation. The study was stopped early after the data monitoring committee found a two-fold increase in death, as well as two-fold increases in stroke and hospitalization for heart failure in patients receiving Multaq compared to patients taking a placebo. Currently Multaq is approved for use in a different, but related patient population (see Facts about Multaq box). The approval of Multaq was based on another trial (ATHENA) in which use of Multaq was associated with a decreased number of deaths compared to placebo.[1]

The Permanent Atrial fibriLLAtion Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) [2] study, sponsored by Sanofi Aventis (the maker of Multaq), was being conducted to assess the potential clinical benefit of Multaq in patients over 65 years of age with permanent atrial fibrillation in the reduction of:

- Major cardiovascular (CV) events (stroke, systemic arterial embolism, myocardial infarction or cardiovascular death), or
- Unplanned cardiovascular hospitalization or death from any cause

A critical question is whether and how the unfavorable results of the PALLAS study, obtained in patients with permanent atrial fibrillation, apply to patients who use Multaq for the approved indications (non-permanent atrial fibrillation, also known as paroxysmal or persistent atrial fibrillation). [see Data Summary for more information]

Facts about Multaq

- Used to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors, who are in sinus rhythm or who will be cardioverted [Refer to Multaq label [1]]
- From approval in July 2009 through June 2011, approximately 1 million Multaq prescriptions were dispensed and approximately 241,000 patients received Multaq prescriptions from U.S. outpatient retail pharmacies.[2]

At this time, patients taking Multaq should talk to their healthcare professional about whether they should continue to take Multaq for non-permanent atrial fibrillation. Patients should not stop taking Multaq without talking to a healthcare professional. Healthcare professionals should not prescribe Multaq to patients with permanent atrial fibrillation.

FDA previously issued a Drug Safety Communication (DSC) in January 2011 [3] regarding cases of rare but severe liver injury that have been reported with the use of Multaq.

Today's communication is in keeping with FDA's commitment to inform the public about its ongoing safety review of drugs. FDA will update the public when more information is available.

Additional Information for Patients

- Talk to your healthcare professional about whether you should continue to take Multaq for paroxysmal or persistent atrial fibrillation. Do not stop taking Multaq without talking to your healthcare professional.
- Discuss any questions or concerns about Multaq 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

- Do not prescribe Multaq to patients with permanent atrial fibrillation.
- FDA is evaluating whether and how the preliminary results of the PALLAS study apply to patients taking Multaq for paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL).
- The PALLAS study results are considered preliminary at this time because the data have not undergone quality assurance procedures and have not been completely adjudicated.
- Report adverse events involving dronedarone to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page.

Data Summary

Sanofi Aventis conducted "A randomized, double blind, placebo controlled, parallel group trial for assessing the clinical benefit of dronedarone 400 mg BID on top of standard therapy in patients with permanent atrial fibrillation and additional risk factors" (PALLAS). This study was a large outcome trial intended to evaluate the effectiveness of dronedarone in patients with permanent atrial fibrillation.

The patients eligible to enroll in PALLAS were 65 years or older, in permanent atrial fibrillation (defined by the presence of atrial fibrillation/atrial flutter for at least 6 months prior to randomization without plans to restore sinus rhythm), and had at least one additional cardiovascular (CV) risk criterion.

In July 2011, the data monitoring committee reviewed the preliminary data and concluded that there was a significant excess of CV events in the Multaq group for both co-primary endpoints (CV death/myocardial infarction/stroke/systemic embolism; death/unplanned CV hospitalization) as well as other CV events (see Table 1 below). As a result, the PALLAS study was stopped.

Table 1: Events during the PALLAS study as of June 30, 2011.

	Multaq N=1572 n (%)	Placebo N=1577 n (%)	Hazard Ratio	p-value
CV Death, Myocardial Infarction, Stroke, Systemic Embolism*	32 (2)	14 (0.9)	2.3	0.009
Death, Unplanned CV Hospitalization*	118 (7.5)	81 (5.1)	1.5	0.006
Death	16 (1)	7 (0.4)	2.3	0.065
Myocardial Infarction	3 (0.2)	3 (0.2)	1.0	1
Stroke	17 (1.1)	7 (0.4)	2.4	0.047
Heart Failure Hospitalization	34 (2.2)	15 (1)	2.3	0.008

*coprimary endpoints

Note: These are preliminary data provided by the manufacturer; therefore, the data have not undergone quality assurance procedures and have not been completely adjudicated.

FDA has received and is currently reviewing preliminary results from the PALLAS study and will review the final results when they become available. Because the review is ongoing, FDA has not concluded whether the results of the PALLAS study are applicable to patients taking Multaq for paroxysmal or persistent atrial fibrillation or atrial flutter. However, healthcare professionals should not prescribe Multaq to patients with permanent atrial fibrillation. FDA will update the public when further information is available.

References

1. Hohnloser SH, Crijns HJ, van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med 2009 Feb 12;360(7):668-78.
2. Source: SDI, Vector One®: National (VONA) and Total Patient Tracker (TPT). July 2009 –June 2011. Extracted 7-18-2011.

Related Information

- Multaq (dronedarone) Information [4]
- FDA Drug Safety Communication: Severe liver injury associated with the use of dronedarone (marketed as Multaq) [5]
  1/14/2011
- Permanent Atrial fibriLLAtion Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) study [6]
- Multaq (dronedarone) label (6/21/2011) [7]
- FDA Drug Safety Podcast for Healthcare Professionals: Multaq (dronedarone) and increased risk of death and serious cardiovascular adverse events [8]

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10. http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf

U.S. Food and Drug Administration

Drugs

FDA Drug Safety Communication: Ongoing safety review of oral osteoporosis drugs (bisphosphonates) and potential increased risk of esophageal cancer

Safety Announcement

[07-21-2011] The U.S. Food and Drug Administration (FDA) is continuing to review data from published studies to evaluate whether use of oral bisphosphonate drugs is associated with an increased risk of cancer of the esophagus (esophageal cancer). There have been conflicting findings from studies evaluating this risk.

At this time, FDA believes that the benefits of oral bisphosphonate drugs in reducing the risk of serious fractures in people with osteoporosis continue to outweigh their potential risks.

FDA's review is ongoing and the Agency has not concluded that patients taking oral bisphosphonate drugs have an increased risk of esophageal cancer. It is also important to note that esophageal cancer is rare, especially in women.

The largest studies that FDA has reviewed, thus far, are two epidemiologic studies using one patient database (the U.K. General Practice Research Database or GPRD). One study found no increase in the risk of esophageal cancer.[1] The second study found a doubling of the risk of esophageal cancer among patients who had 10 or more prescriptions of the drugs, or who had taken the drugs over 3 years.[2] Other external researchers investigating this issue, using different patient databases, have reported no increase in risk, or a reduced risk.[3] [See Data Summary for additional information on the studies]

Facts about oral bisphosphonates

- Commonly used for the prevention and treatment of osteoporosis as well as to treat other bone diseases such as Paget's disease. Osteoporosis is a disease that makes bones weak and more likely to break.
- Include: Fosamax (alendronate), Actonel (risedronate), Boniva (ibandronate), Atelvia (risedronate delayed release), Didronel (etidronate), and Skelid (tiludronate).
- May cause irritation of the esophagus. Irritation of the esophagus can lead to esophagitis (inflammation) or esophageal ulcers (sores), which may bleed. The risk of these esophageal events is low when oral bisphosphonates are prescribed appropriately and the specific directions for use are followed by patients.

Patients should talk with their healthcare professionals about the benefits and risks of taking oral bisphosphonates. Patients who take oral bisphosphonates should pay particular attention to the directions for use to minimize any potential adverse events.

FDA will continue to evaluate all available data supporting the safety and effectiveness of bisphosphonate drugs and will update the public when more information becomes available.

Additional Information for Patients

- There is conflicting information on whether oral bisphosphonate drugs can affect your chance of developing esophageal cancer.
- Directions for use of the oral bisphosphonate drug should be followed carefully. All oral bisphosphonate drugs, except Atelvia, should be taken first thing in the morning after awakening, with a full glass of plain water. Atelvia should be taken immediately following breakfast. Do not lie down or eat or drink anything for at least 30 to 60 minutes after taking any oral bisphosphonate drug.
- Talk to your healthcare professional if you develop swallowing difficulties, chest pain, new or worsening heartburn, or have trouble or pain when you swallow. These may be signs of problems of the esophagus.
- You should not take oral bisphosphonates if you have esophageal conditions that delay emptying of the esophagus, or if you cannot stand or sit upright for at least 30 to 60 minutes, or have low calcium levels in your blood.
- Talk to your healthcare professional about the benefits and risks of taking oral bisphosphonates and how long you should expect to take them.
- Discuss any questions or concerns about your oral bisphosphonate drug 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

- FDA has not concluded that taking an oral bisphosphonate drug increases the risk of esophageal cancer and there are conflicting data on this risk.
- There are insufficient data to recommend endoscopic screening of asymptomatic patients.
- Esophagitis and other esophageal events have been reported, particularly in patients who do not follow the specific directions for use of oral bisphosphonates.
- Instruct patients to carefully follow the directions for use of the oral bisphosphonate drug they are prescribed.
- Report adverse events involving bisphosphonate drugs to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page

Data Summary

In January 2009, a case series was published describing reports submitted to the FDA of esophageal cancer in patients prescribed oral bisphosphonates.[4] Since then, several epidemiological studies looking at the association between oral bisphosphonates and esophageal cancer have been published, with discrepant findings. The two largest published studies used data from the U.K.'s General Practice Research Database (GPRD).

One study compared the rate of esophageal cancer in patients taking an oral bisphosphonate to patients not taking an oral bisphosphonate. This study found no increase in the risk of esophageal cancer.[1] Using the same database, a second study found a doubling of the risk of esophageal cancer among patients who had 10 or more prescriptions of oral bisphosphonates, or who had taken the drugs over 3 years.[2]

Other investigators are researching this issue. In a large cohort of Danish patients with fractures, investigators found that bisphosphonate users (who had taken them for a median of 1.5 years) had a significantly reduced risk for esophageal cancer compared to patients with fractures who had not taken any bisphosphonate.[3] Longer term follow-up of alendronate (Fosamax) users and non-alendronate users showed that alendronate users had a higher frequency of endoscopic examination of the esophagus, no greater incidence of esophageal cancer, and no increase in esophageal cancer deaths.[5]

Differences in methodologies in these studies may account for the discrepant findings. Also, since these studies are observational rather than randomized, they are subject to bias and confounding. For example, it is possible that the gastrointestinal side effects of bisphosphonates increase a patient's likelihood of undergoing an endoscopy, which could lead to earlier detection of a cancer or drug discontinuation. At this time, there is not enough information to make definitive conclusions about possible association. FDA's safety review is ongoing. Additional studies conducted in different databases may be warranted.

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1. Cardwell CR, Abnet CC, Cantwell MM, Murray LJ. Exposure to oral bisphosphonates and risk of esophageal cancer. JAMA 2010;304:657-63.
2. Green J, Czanner G, Reeves G, Watson J, Wise L, Beral V. Oral bisphosphonates and risk of cancer of the oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. BMJ 2010;341:doi:10.1136/bmj.c4444.
3. Abrahamsen B, Eiken P, Eastell R. More on reports of esophageal cancer with oral bisphophonate use. N Engl J Med 2009; 360:1789.
4. Wysowski DK. Reports of esophageal cancer with oral bisphosphonate use. N Engl J Med 2009;360:89-90.
5. Abrahamsen B, et. al. The risk of oesophageal and cancer incidence and mortality in alendronate users: a national cohort study. 3rd Joint Meeting of the European Calcified Tissue Society and the International Bone and Mineral Society, May 2011.

Related Information

- Bisphosphonates (marketed as Actonel, Actonel+Ca, Aredia, Boniva, Didronel, Fosamax, Fosamax+D, Reclast, Skelid, and Zometa) Information[1]
- FDA Drug Safety Podcast for Healthcare Professionals: Ongoing safety review of oral osteoporosis drugs (bisphosphonates) and potential increased risk of esophageal cancer[2]

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4. http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf

U.S. Food and Drug Administration

Drugs

An Important FDA Reminder for Parents: Do Not Give Infants Cough and Cold Products Designed for Older Children

In January 2008, manufacturers voluntarily removed over-the-counter (OTC) infant (less than 2 years of age) cough and cold products from the market due to safety concerns. Later in fall of 2008, manufactures also voluntarily re-labeled these cough and cold products to state: "do not use in children under 4 years of age." However, there are concerns that many parents may be giving cough and cold products that remain on the market - those designed for older children - to their infants. FDA reminds all caregivers never to give a child under two years of age any kind of cough and cold product containing decongestants or antihistamines, without seeking the advice of a healthcare provider. These cough and cold products include those that contain the decongestants ephedrine, pseudoephedrine, or phenylephrine, and the antihistamines diphenhydramine, brompheniramine, or chlorpheniramine.

Research shows risks to children

Cough and cold products for children under two years old were voluntarily removed from the market because of on-going safety concerns discussed by the FDA in 2007. These safety concerns revealed that there were many reports of harm, and even death, to children who used these products. These reports of harm occurred when the child received too much medication such as in cases as accidental ingestion, unintentional overdose, or after a medication dosing error. In those reports of harm that lead to a child's death, most of those children were under two years of age.

FDA research indicates that children less than 2 years old appear to be the most susceptible to serious injury when there are no labeled directions for use but rather state "to ask a doctor (healthcare provider) for use." It is not clear if these products are being given to infants under the advice of a healthcare provider or if the recommendation to speak to a healthcare provider leads caregivers to believe that infants are appropriate users of these drugs. For these reasons FDA supports manufactures actions to voluntarily withdraw cough and cold products for children under two years of age from the marketplace. However, cough and cold products fo children older than two years of age were not affected and these products are still sold in pharmacies and other retail outlets today.
Since infant formulations of cough and cold products were voluntarily removed from the market years ago, parents who currently give these products to their infants (less than 2 years of age) may be using cough and cold products designed for older children and modifying the doses, for instance by giving half the recommended amount to the infant than what is recommended for an older child. This can be especially dangerous as dosing adjustments cannot safely be made this way and could add to the existing risk of giving these products to young children.

Alternatives to cough and cold medicines for infants

Parents of infants may not have heard the FDA warnings about cough and cold products in young children issued after the 2007 findings. Physicians are a valuable source of information for parents. Well-informed physicians can offer parents a variety of alternative treatments for infants to help with cough and cold symptoms. For instance, here are some commonly used recommendations:

- A cool mist humidifier helps nasal passages shrink and allow easier breathing (do not use warm mist humidifiers as they can cause nasal passages to swell and make breathing more difficult);
- Saline nose drops or spray keep nasal passages moist and helps avoid stuffiness;
- Nasal suctioning with a bulb syringe either with or without saline nose drops, works especially well for infants less than a year old. Older children often resist it use;
- Acetaminophen or ibuprofen can be used to reduce fever, aches and pains. Parents should carefully read and follow the product's instructions for use label;
- Drinking plenty of liquids will help the child stay well hydrated.

For more information on this subject, please see the following link: http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048682.htm [1]

Links on this page:

1. http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048682.htm

U.S. Food and Drug Administration

News & Events

FDA NEWS RELEASE

For Immediate Release: July 20, 2011
Media Inquiries: Sandy Walsh, 301-796-4669, sandy.walsh@fda.hhs.gov
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FDA approves blood-thinning drug Brilinta to treat acute coronary syndromes
Boxed warning says daily aspirin doses above 100 milligrams decrease effectiveness

The U.S. Food and Drug Administration today approved the blood-thinning drug Brilinta (ticagrelor) to reduce cardiovascular death and heart attack in patients with acute coronary syndromes (ACS).

ACS includes a group of symptoms for any condition, such as unstable angina or heart attack, that could result from reduced blood flow to the heart. Brilinta works by preventing the formation of new blood clots, thus maintaining blood flow in the body to help reduce the risk of another cardiovascular event.

Brilinta has been studied in combination with aspirin. A boxed warning to health care professionals and patients warns that aspirin doses above 100 milligrams per day decrease the effectiveness of the medication.

"In clinical trials, Brilinta was more effective than Plavix in preventing heart attacks and death, but that advantage was seen with aspirin maintenance doses of 75 to 100 milligrams once daily, "said Norman Stockbridge, M.D., Ph.D., director of the Division of Cardiovascular and Renal Products in the FDA's Center for Drug Evaluation and Research.

The boxed warning also says that, like other blood-thinning agents, Brilinta increases the rate of bleeding and can cause significant, sometimes fatal, bleeding. The most common adverse reactions reported by people taking Brilinta in clinical trials were bleeding and difficulty breathing (dyspnea).

Brilinta was approved with a Risk Evaluation and Mitigation Strategy, a plan to help ensure that the drug's benefits outweigh its risks. As part of that plan, the company must conduct educational outreach to physicians to alert them about the risk of using higher doses of aspirin. In addition, Brilinta will be dispensed with a Medication Guide that informs patients of the most important information about the medication. The guide will be distributed each time a patient fills their prescription.

Brilinta is made by AstraZeneca of Wilmington, Del.

For information:

National Heart, Lung and Blood Institute: Heart Attack[1]

Approved Drug: Questions and Answers[2]

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 Communication: Important safety changes to the influenza drug Tamiflu (oseltamivir phosphate) for oral suspension

Safety Announcement

[7-11-2011] The U.S. Food and Drug Administration (FDA) is informing the public of important product safety changes to the influenza drug Tamiflu (oseltamivir phosphate) for oral suspension. These changes are being made to reduce the possibility of prescribing and dosing confusion that can lead to medication errors. FDA has worked with the manufacturer, Genentech (part of the Roche Group), to make these changes.

The changes to Tamiflu oral suspension and the product label include:

- A change to the concentration of Tamiflu from 12 mg/mL to 6 mg/mL. The lower concentration of Tamiflu is less likely to become frothy when shaken, which helps to ensure an accurate measurement. The 12 mg/mL concentration will no longer be marketed after current supplies run out.
- A change in the measurements of the oral dosing device (graphic) from milligrams (mg = weight) to milliliters (mL = volume).
- A change in the dosing table for Tamiflu to include a column for the volume (mL) based on the new 6 mg/mL concentration. (Table 1)
- Revised container labels and carton packaging (graphic).
- Revised compounding instructions for pharmacies to prepare a 6 mg/mL oral suspension from Tamiflu capsules in an emergency situation only if the commercially manufactured Tamiflu for oral suspension is unavailable.

Facts about Tamiflu

- In a class of medications called neuraminidase inhibitors. These drugs work by stopping the spread of the influenza (flu) virus in the body.
- Helps shorten the time you have flu symptoms such as a stuffy or runny nose, sore throat, cough, muscle or joint aches, tiredness, headache, fever, and chills.
- Used to treat some types of flu in adults and children (older than 1 year of age) who have had symptoms for no longer than 2 days. It is also used to prevent some types of flu in adults and children (older than 1 year of age) when they have spent time with someone who has the flu or when there is a flu outbreak.[1]

Genentech[1], the manufacturer of Tamiflu for oral suspension, plans to begin distribution of the new 6 mg/mL product in July 2011. The company has instituted a voluntary Take Back Program for wholesale buyers, distributors and pharmacies to remove the 12 mg/mL product from the marketplace.

There are no quality issues with the 12 mg/mL product—it is still useable through its expiration date. However, FDA encourages participation in the Take Back Program to limit the potential for product confusion.

The 12 mg/mL product will remain in the marketplace and in state or national stockpiles until current supplies expire. Therefore, it is important for healthcare professionals to be aware that a patient may potentially receive either concentration (6 mg/mL or 12 mg/mL) from their pharmacy during the next influenza season (2011-2012). Steps should be taken to avoid the potential for a medication error due to confusion between the two concentrations (see Additional Information sections below).

For complete background information on Tamiflu, please see Tamiflu (oseltamivir phosphate) Information[2].

Additional Information for Patients

- The concentration of Tamiflu for oral suspension is changing and you may get either concentration at your pharmacy during the next flu season.
- The new Tamiflu for oral suspension container label and carton packaging look different from what you may have taken in the past.
- The new oral dosing device is different and the volume (mL) of your dose may differ from past prescriptions.
- Check with a healthcare professional if you have any questions about the dosing directions, how to measure a dose using the new dosing device, or about which concentration of Tamiflu for oral suspension you have.
- Report any side effects you experience or medication errors to your healthcare professional and the FDA MedWatch program using the information in the "Contact Us" box at the bottom of the page.

Additional Information for Healthcare Professionals

- Prescribers should include the new concentration (6 mg/mL) and dose in milliliters on all prescriptions for Tamiflu for oral suspension. A revised dosing chart in Table 1 provides dosing in milliliters, and is included in the revised professional label.
- Prescribers should be aware that pediatric strength Tamiflu capsules (30 mg and 45 mg) are available and have not changed. These capsules can be prescribed for pediatric patients who can swallow capsules. For patients who can not swallow capsules, these can be opened and the capsule contents can be mixed with flavored foods (such as chocolate syrup or caramel topping).
- The new 6 mg/mL product contains an oral dosing device graduated in mL, whereas the old 12 mg/mL product contained an oral dosing device with dose markings in mg.
- It is possible that patients may get either concentration at the pharmacy during the 2011-2012 flu season; patients should be educated about this possibility to avoid medication errors.
- The two versions of the professional label may appear in circulation during the next influenza season (2011-12) and contain different dosing and compounding instructions for the oral suspension.
- Report adverse events or medication errors involving Tamiflu to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page.

Additional Information for Pharmacies

- The most important measure a pharmacy can take is to participate in the Take Back Program and replace the 12 mg/mL concentration of Tamiflu for oral suspension with the new 6 mg/mL concentration.
- Pharmacies should contact their distributor if they have unused/undispensed 12 mg/mL Tamiflu for oral suspension to determine if the product may be returne through the Take Back Program before August 31, 2011.
- Pharmacists should verify that each prescription for Tamiflu for oral suspension contains a concentration (mg/mL) and a dose (mL). If the concentration and dose are not specified, then the pharmacist should clarify the prescription with the prescriber.
- Pharmacists should ensure that the units of measure for the dosing instructions on the bottle match the oral dosing device that is provided (e.g., for the new 6 mg/mL product, the units of measure for both the drug and the device should be in milliliters).
- Pharmacists should ensure that the correct dose, dosing instructions, and oral dosing device are provided for the patient and are consistent with the concentration of Tamiflu for oral suspension (6 mg/mL or 12 mg/mL) that the patient will receive.

Additional Background Information

FDA has worked with Genentech to make these important product safety changes to the Tamiflu for oral suspension product and to address the medication error-prone issues that FDA previously identified and communicated.

FDA issued a Public Health Alert [3] in September 2009 regarding the potential for medication errors with the use of Tamiflu for oral suspension. The agency had received reports of errors where dosing instructions for the patient did not match the dosing dispenser. Additionally, the commercial Tamiflu for oral suspension concentration (12 mg/mL) was different from the concentration of the compounded suspension for emergency use (15 mg/mL when made from Tamiflu 75 mg capsules), which also may have contributed to confusion and medication errors.

FDA issued a Public Health Advisory [4] in December 2009 on the availability of Tamiflu for oral suspension during an overall product shortage. Because the concentration of the marketed Tamiflu for oral suspension has changed to 6 mg/mL, the emergency compounding instructions that FDA provided in 2009 are now being updated to provide a final concentration of 6 mg/mL. This change will align the emergency-compounded final concentration with the new commercially-marketed oral suspension concentration of 6 mg/mL, which may reduce the potential for prescribing and dosing errors. FDA reiterates that this compounded suspension should not be used merely for convenience, or whenthe FDA-approved Tamiflu for oral suspension available.

References

1. U.S. National Library of Medicine. National Institutes of Health. Drug Monograph-Oseltamivir. Available at http://www.nlm.nih.gov/medlineplus/druginfo/meds/a699040.html [5]. Accessed April 15, 2011.

New Tamiflu Dosing Chart (Table 1)

Table 1. Treatment and Prophylaxis Dosing of Oral Tamiflu for Influenza

For Patients 1 Year of Age and Older Based on Body Weight

Weight (kg)	Weight (lbs)	Treatment Dosing for 5 days	Prophylaxis Dosing for 10 days	Volume of For oral suspension (6 mg/mL) for each Dose*	Number of Bottles of For oral suspension to Dispense	Number of Capsules and Strength to Dispense
15 kg or less	33 lbs or less	30 mg twice daily	30 mg once daily	5 mL	1 bottle	10 Capsules 30 mg
16 kg thru 23 kg	34 lbs thru 51 lbs	45 mg twice daily	45 mg once daily	7.5 mL	2 bottles	10 Capsules 45 mg
24 kg thru 40 kg	52 lbs thru 88 lbs	60 mg twice daily	60 mg once daily	10 mL	2 bottles	20 Capsules 30 mg
41 kg or more	89 lbs or more	75 mg twice daily	75 mg once daily	12.5 mL †	3 bottles	10 Capsules 75 mg

* A 10 mL oral dosing dispenser is provided with the oral suspension. In the event that the dispenser provided is lost or damaged, another dosing dispenser may be used to deliver the volume.

†Delivery of this Tamiflu for oral suspension dose requires administering 10 mL followed by another 2.5 mL.

New Oral Dispenser/Syringe Device (10 mL) with markings in mL

New Container Label Photo (6mg/mL)

Old Container Label Photo (12 mg/mL)

Related Information

- Tamiflu (oseltamivir phosphate) Information[6]
- Comunicado de seguridad de medicamentos de la FDA: Cambios importantes de seguridad del medicamento para la influenza Tamiflu (fosfato de oseltamivir) en suspensión oral[7]
- FDA Drug Safety Podcast for Healthcare Professionals: Important safety changes to the influenza drug Tamiflu (oseltamivir phosphate) for oral suspension[8]
  7/11/2011
- Concentration Lowered in Tamiflu Medication[9]
  FDA Consumer Update
- FDA Public Health Alert: Potential Medication Errors with Tamiflu for Oral Suspension[10]
  9/2009
- Public Health Advisory: Availability of Tamiflu for Oral Suspension[11]
  12/2009

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U.S. Food and Drug Administration

Drugs

FDA Drug Safety Communication: Children born to mothers who took Valproate products while pregnant may have impaired cognitive development

Safety Announcement

[6-30-2011] The U.S. Food and Drug Administration (FDA) is informing the public that children born to mothers who take the anti-seizure medication valproate sodium or related products (valproic acid and divalproex sodium) during pregnancy have an increased risk of lower cognitive test scores than children exposed to other anti-seizure medications during pregnancy. This conclusion is based on the results of epidemiologic studies that show that children born to mothers who took valproate sodium or related products throughout their pregnancy tend to score lower on cognitive tests (IQ and other tests) than children born to mothers who took other anti-seizure medications during pregnancy.

In the primary epidemiologic study upon which FDA's conclusion is based, cognitive tests were performed at age three. In supportive studies, cognitive tests were performed at ages five to 16. Cognitive tests are commonly used to assess development in a variety of areas, including intelligence, abstract reasoning, and problem solving.

The long-term effects on cognitive development from exposure to valproate sodium or related products during pregnancy are unknown. It is also not known whether these effects occur when fetal exposure is limited to less than the full duration of pregnancy, such as the first trimester.

FDA has evaluated all available evidence to date, and will be adding information about the risk of lower cognitive test scores to the valproate product labels in the Warnings and Precautions section, the Use in Specific Populations: Pregnancy section, and to the Medication Guides that are being developed for the valproate drug products.

Facts about Valproate

- Valproate products are FDA-approved drugs to treat seizures, and manic or mixed episodes associated with bipolar disorder (manic-depressive disorder), and to prevent migraine headaches. They are also used off-label (for unapproved uses) for other conditions, particularly for other psychiatric conditions.
- Valproate products include: valproate sodium (Depacon), divalproex sodium (Depakote, Depakote CP, and Depakote ER), valproic acid (Depakene and Stavzor), and their generics.

FDA previously warned pregnant women and women of childbearing age about valproate use during pregnancy due to the known risk of birth defects (teratogenic effects) of these products. A teratogen is anything known to cause birth defects during development of an embryo or fetus. Valproate products are assigned to Pregnancy Category D. FDA released an Information for Healthcare Professionals[1] communication in December 2009 on the risk of neural tube birth defects following exposure to valproate products during pregnancy.

The benefits and the risks of valproate sodium and related products should be carefully weighed when prescribing these drugs to women of childbearing age, particularly for conditions not usually associated with permanent injury or death. If the use of valproate is not essential, alternative medications that have a lower risk to the fetus of birth defects and adverse cognitive effects should be considered in pregnant women and women of childbearing age. If the decision is made to use valproate in women of childbearing age, effective birth control should be used. (See Data Summary).

Additional Information for Patients

- Valproate should not be stopped without talking to a healthcare professional, even in pregnant women. Stopping valproate suddenly can cause serious problems. Not treating epilepsy or bipolar disorder (manic-depressive disorder) during pregnancy can be harmful to women and their developing babies.
- If you take valproate during pregnancy, know that there is a higher risk that your child may have birth defects or may score lower on cognitive tests (tests tha measure mental ability and capacity, such as IQ tests) in childhood than if you use another anti-seizure medicine during pregnancy.
- Women of childbearing age who decide to take valproate should use effective birth control (contraception) while taking the drug. Women should talk to their healthcare professionals about the best kind of birth control to use while taking valproate.
- Before you start valproate, you should tell your healthcare professional if you are pregnant or are planning to become pregnant. Healthcare professionals may discuss other treatment options with you.
- You should tell your healthcare professional right away if you become pregnant while taking valproate. You and your healthcare provider should decide if you should continue to take valproate while you are pregnant.
- If you become pregnant while taking valproate, you should talk to your healthcare professional about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect additional information about the safety of antiepileptic drugs during pregnancy. Information about the North American Drug Pregnancy Registry can be found at http://www.massgeneral.org/aed/[2].
- If you took valproate while pregnant, let your child's pediatrician know.
- Valproate passes into breast milk, but its effects on developing babies remain unknown. You should talk to your healthcare professional about the best way to feed your baby if you take valproate.
- You should 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

- Inform women of childbearing age of the increased risk for adverse effects on cognitive development with prenatal valproate exposure.
- Continue to counsel women of childbearing potential taking valproate about the increased risk of major malformations, including neural tube defects, when valproate is used during pregnancy.

- Weigh the benefits and risks of valproate when prescribing this drug to women of childbearing age, particularly when treating a condition not usually associate with permanent injury or death. Alternative medications that have a lower risk of adverse birth outcomes should be considered. Healthcare professionals shoul discuss the relative risks and benefits of appropriate alternative therapies.
- Untreated or inadequately treated epilepsy or bipolar disorder during pregnancy increases the risk of complications in both the pregnant mother and her developing baby.
- If the decision is made to prescribe valproate to women of childbearing age, healthcare professionals should recommend use of effective contraception for women who are not planning a pregnancy.
- Inform patients of the North American Antiepileptic Drug (NAAED) Pregnancy Registry and encourage patients who become pregnant to enroll by calling 1-888 233-2334.
- Report adverse events involving valproate to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page.

Data Summary

Several published epidemiological studies have indicated that children exposed to valproate in utero have lower cognitive test scores than children exposed to either another antiepileptic drug in utero or to no antiepileptic drugs in utero. The largest of these studies is a prospective cohort study conducted in the United States and United Kingdom that found children with prenatal exposure to valproate throughout pregnancy had lower Differential Ability Scale (D.A.S) scores at age 3 (92 [95% confidence interval 88 to 97]) than children with prenatal exposure to the other evaluated antiepileptic drug monotherapy treatments: lamotrigine (101 [95% confidence interval 98 to 104]), carbamazepine (98 [95% confidence interval 95 to 102]) and phenytoin (99 [95% confidence interval 94 to 104]).[1] The D.A.S., which has a mean score of 100 (SD = 15), is a battery of cognitive tests designed for children 2.5 to 17 years of age. The D.A.S. is a measure of cognitive development performed in children who are too young to undergo IQ testing, and generally correlates with IQ scores later in childhood. Although all of the available studies have methodological limitations, the weight of the evidence supports the conclusion that valproate exposure in utero causes subsequent adverse effects on cognitive development in offspring.

References

1. Meador KJ, Baker GA, Browning N, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N Engl J Med 2009;360:1597-605.
2. Gaily E, Kantola-Sorsa E, Hiilesmaa V, et al. Normal intelligence in children with prenatal exposure to carbamazepine. Neurology 2004;62:28-32.
3. Adab N, Jacoby AD, Chadwick D. Additional educational needs of children born to mothers with epilepsy. J Neuro Neurosurg Psychiatry 2001;70:15-21.
4. Adab N, Kini U, Vinten J, et al. The longer term outcome of children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2004;75:1575–83.

Related Information

- FDA Drug Safety Podcast for Healthcare Professionals: Children born to mothers who took Valproate products while pregnant may have impaired cognitive development[3]
  7/1/2011
- Questions and Answers: Children born to mothers who took the anti-seizure medication Valproate while pregnant may have impaired cognitive development[4]
  6/30/2011
- Information for Healthcare Professionals: Risk of Neural Tube Birth Defects following prenatal exposure to Valproate[5]
  12/3/2009
- Valproate Information[6]

Contact Us

- **Report a Serious Problem**
- 1-800-332-1088
- 1-800-FDA-0178 Fax

MedWatch Online[7]

Regular Mail: Use postage-paid FDA Form 3500[8]

Mail to: MedWatch 5600 Fishers Lane

Rockville, MD 20857

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1. /Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm192649.htm
2. http://www.massgeneral.org/aed/
3. /Drugs/DrugSafety/DrugSafetyPodcasts/ucm261653.htm
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6. /Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm192645.htm
7. https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm
8. http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf

U.S. Food and Drug Administration

Safety

Erythropoiesis-Stimulating Agents (ESAs) In Chronic Kidney Disease: Drug Safety Communication - Modified Dosing Recommendations

Epoetin alfa (marketed as Epogen and Procrit) and darbepoetin alfa (marketed as Aranesp)

[Posted 06/24/2011]

AUDIENCE: Nephrology, Oncology

ISSUE: FDA notified healthcare professionals that new, modified recommendations for more conservative dosing of Erythropoiesis-Stimulating Agents (ESAs) in patients with chronic kidney disease (CKD) have been approved to improve the safe use of these drugs. FDA has made these recommendations because of data showing increased risks of cardiovascular events with ESAs in this patient population. The new dosing recommendations are based on clinical trials showing that using ESAs to target a hemoglobin level of greater than 11 g/dL in patients with CKD provides no additional benefit than lower target levels, and increases the risk of experiencing serious adverse cardiovascular events, such as heart attack or stroke.

BACKGROUND: ESAs treat certain types of anemia by stimulating the bone marrow to produce red blood cells and by decreasing the need for blood transfusions. The manufacturer has revised the Boxed Warning, Warnings and Precautions, and Dosage and Administration sections of the labels for the ESAs to include this new information.

RECOMMENDATION: Healthcare professionals should weigh the possible benefits of using ESAs to decrease the need for red blood cell transfusions in CKD patients against the increased risks for serious cardiovascular events, and should inform their patients of the current understanding of potential risks and benefits. Therapy should be individualized to the patient and the lowest possible ESA dose given to reduce the need for transfusions. See the Drug Safety Communication for additional information including a table of key trials and other supporting references. Treatment with ESAs in CKD was discussed at the Cardiovascular and Renal Drugs Advisory Committee, held October 18, 2010. For summary minutes of that Advisory Committee, see link below.

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

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

[06/24/2011 - Drug Safety Communication [3] - FDA]
[06/24/2011 - Press Release [4] - FDA]
[10/18/2010 - Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee [5] - FDA]

Previous MedWatch Alerts:

[02/16/2010 [6]]
[03/12/2008 [7]]
[11/08/2007 [8]]

Links on this page:

1. http://www.fda.gov/MedWatch/report.htm
2. /Safety/MedWatch/HowToReport/DownloadForms/default.htm
3. /Drugs/DrugSafety/ucm259639.htm
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U.S. Food and Drug Administration

Safety

Risperdal (risperidone) and Risperidone: Recall - Uncharacteristic Odor

[Posted 06/20/2011]

AUDIENCE: Pharmacy, Psychiatry, Neurology, Internal Medicine

ISSUE: Ortho-McNeil-Janssen Pharmaceuticals notified healthcare professionals and the public of a recall of specific lots of Risperdal (risperidone) 3mg tablets and risperidone 2mg tablets. The recall stems from consumer reports of an uncharacteristic odor thought to be caused by trace amounts of TBA (2,4,6 tribromoanisole). TBA is a byproduct of a chemical preservative sometimes applied to wood often used in the construction of pallets on which materials are transported and stored. While not considered to be toxic, TBA can generate an offensive odor and a small number of patients have reported temporary gastrointestinal symptoms.

BACKGROUND: The Risperdal lot 0GG904 - which includes approximately 16,000 bottles - was shipped between 8/27/2010 and 2/15/2011. The company believes there are approximately 1,600 bottles of Risperdal from this lot remaining in the marketplace. The risperidone lot OIG175 - which includes approximately 24,000 bottle - was shipped between 11/10/2010 and 1/01/2011. The company believes there are fewer than 1,200 bottles of risperidone from this lot remaining in the marketplace Risperdal (risperidone) is used for the treatment of schizophrenia in adults and adolescents ages 13-17 years, alone or in combination with other medicines (valproate or lithium) in adults for the short-term treatment of bipolar mania; or alone in adults, children and adolescents ages 10-17 years for the short-term treatment of bipola mania and is used for the treatment of irritability associated with autistic disorder in children and adolescents ages 5-16 years.

RECOMMENDATION: Patients should not stop taking their medication. Anyone experiencing an uncharacteristic odor associated with Risperdal 3mg Tablets or risperidone 2mg Tablets should return the tablets to their pharmacist, and contact their healthcare professional if they have questions.

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

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

[06/20/2011 - Press Release [3] - Ortho-McNeil-Janssen]

Links on this page:

1. http://www.fda.gov/MedWatch/report.htm
2. /Safety/MedWatch/HowToReport/DownloadForms/default.htm
3. /Safety/Recalls/ucm259820.htm

U.S. Food and Drug Administration

Drugs

Questions and Answers: FDA announces new requirements for over-the-counter (OTC) sunscreen products marketed in the U.S.

[updated 6/23/2011]

On June 14, 2011 the U.S. Food and Drug Administration (FDA) announced new requirements for sunscreens currently sold over-the-counter (OTC) (i.e. non-prescription). These requirements support the Agency's ongoing efforts to ensure that sunscreens meet modern-day standards for safety and effectiveness. The new requirements, as well as several proposed changes for future rules, are outlined in four regulatory documents that include a Final Rule, a Proposed Rule, an Advance Notice of Proposed Rulemaking, and a Draft Guidance for Industry.

The following questions and answers provide a brief overview of the recent regulatory actions and highlight the most important information for consumers to know when buying and using sunscreen products.

Q1. Why is FDA making changes to how sunscreens are marketed in the United States?

A. FDA is making changes to how sunscreens are marketed in the United States as part of the Agency's ongoing efforts to ensure that sunscreens meet modern-day standards for safety and effectiveness and to help consumers have the information they need so they can choose the right sun protection for themselves and their families. Prior rules on sunscreens dealt almost exclusively with protection against sunburn, which is primarily caused by ultraviolet B (UVB) radiation from the sun, and did not address ultraviolet A (UVA) radiation, which contributes to skin cancer and early skin aging. After reviewing the latest science, FDA determined that sufficient data are available to establish a "broad spectrum" test for determining a sunscreen product's UVA protection. Passing the broad spectrum test shows that the product provides UVA protection that is proportional to its UVB protection.

Sunscreen products that pass the broad spectrum test are allowed to be labeled as "Broad Spectrum." These "Broad Spectrum" sunscreens protect against both UVA and UVB rays. Scientific data demonstrated that products that are "Broad Spectrum SPF 15 [or higher]" have been shown to reduce the risk of skin cancer and early skin aging when used with other sun protection measures, in addition to helping prevent sunburn. Other sun protection measures include limiting time in the sun and wearing protective clothing.

These testing and labeling requirements are necessary to provide consumers with the information they need to make informed choices when selecting sunscreens.

Q2. When will these changes take effect?

A. The Final Rule will take effect by the summer of 2012, but consumers may begin to see changes to sunscreen labels before the effective date.

Q3. What does the SPF value on sunscreen labels indicate?

A. The SPF value indicates the level of sunburn protection provided by the sunscreen product. All sunscreens must be tested according to an SPF test procedure. The test measures the amount of ultraviolet (UV) radiation exposure it takes to cause sunburn when a person is using a sunscreen in comparison to how much UV exposure it takes to cause a sunburn when they do not use a sunscreen. The product is then labeled with the appropriate SPF value indicating the amount of sunburn protection provided by the product. Higher SPF values (up to 50) provide greater sunburn protection. Because SPF values are determined from a test that measures protection against sunburn caused by ultraviolet B (UVB) radiation, SPF values only indicate a sunscreen's UVB protection.

However, sunscreens that pass the new broad spectrum test will have demonstrated that they also provide ultraviolet A (UVA) protection that is proportional to their UVB protection. To pass the broad spectrum test, sunscreens with higher SPF values will provide higher levels of UVA protection as well. Therefore, under the new labe requirements, a higher SPF value for sunscreens labeled "Broad Spectrum SPF [value]" will indicate a higher level of protection from both UVA and UVB radiation.

Q4. Does FDA believe sunscreens are still safe and effective? Do consumers need to throw away the sunscreens they are currently using?

A. The ingredients in FDA-approved sunscreens marketed today have been used for many years, and FDA has no reason to believe these products are not safe and effective when used as directed. Therefore, FDA is not advising consumers to throw away their current sunscreen products.

Sunscreens on the shelf today may have varying levels of ultraviolet A (UVA) radiation protection, but by next year, sunscreens that claim to provide UVA protection, otherwise known as broad spectrum protection, will be required to pass FDA's standardized test. This broad spectrum test will enable consumers to determine the level of UVA protection a sunscreen provides in addition to its ultraviolet B (UVB) radiation protection. This information will allow them to better manage their skin cancer an early skin aging risks. FDA does not want consumers to stop using currently marketed sunscreens in the meantime, as these products still offer sun protection.

It is also important to note that FDA is not questioning the safety of any ingredients used in marketed sunscreens. FDA believes the risk of not using sunscreen is much greater than any potential risk posed by sunscreen ingredients.

Q5. What do consumers most need to know when buying and using sunscreens?

A. Spending time in the sun increases a person's risk of skin cancer and early skin aging.To reduce these risks, consumers should regularly use a Broad Spectrum sunscreen with an SPF value of 15 or higher in combination with other protective measures such as:

- Limiting time in the sun, especially between the hours of 10 AM and 2 PM when the sun's rays are the strongest.
- Wearing clothing to cover skin exposed to the sun (long-sleeved shirts, pants, sunglasses, and broad-brimmed hats) when possible.
- Using a water resistant sunscreen if swimming or sweating.
- Reapplying sunscreen, even if it is labeled as water resistant, at least every 2 hours. (Water resistant sunscreens should be reapplied more often after swimming or sweating, according to the directions on the label.)

Consumers should also be aware that no sunscreens are "waterproof" because all sunscreens eventually wash off. Sunscreens can only be labeled as "water resistant" i they are tested according to the required SPF test procedure. Sunscreens labeled "water resistant" sunscreens will also be required to state whether the sunscreen remains effective for 40 minutes or 80 minutes when swimming or sweating, and all sunscreens will be required to provide directions on when to reapply.

Q6. What are the main points of the new Final Rule?

A. The new final rule includes the following requirements:

- Broad Spectrum designation. Sunscreens that pass FDA's broad spectrum test procedure, which measures a product's ultraviolet A (UVA) protection relative to its ultraviolet B (UVB) protection, may be labeled as "Broad Spectrum SPF [value]" on the front label. For Broad Spectrum sunscreens, SPF values also indicate the amount or magnitude of overall protection. Broad Spectrum SPF products with SPF values higher than 15 provide greater protection and may clain additional uses, as described in the next bullet.
- Use claims. Only Broad Spectrum sunscreens with an SPF value of 15 or higher can claim to reduce the risk of skin cancer and early skin aging if used as directed with other sun protection measures. Non-Broad Spectrum sunscreens and Broad Spectrum sunscreens with an SPF value between 2 and 14 can only claim to help prevent sunburn.
- "Waterproof," "sweatproof" or "sunblock" claims. Manufacturers cannot label sunscreens as "waterproof" or "sweatproof," or identify their products as "sunblocks," because these claims overstate their effectiveness. Sunscreens also cannot claim to provide sun protection for more than 2 hours without reapplication or to provide protection immediately after application (for example-- "instant protection") without submitting data to support these claims and obtaining FDA approval.
- Water resistance claims. Water resistance claims on the front label must indicate whether the sunscreen remains effective for 40 minutes or 80 minutes while swimming or sweating, based on standard testing. Sunscreens that are not water resistant must include a direction instructing consumers to use a water resistant sunscreen if swimming or sweating.
- Drug Facts. All sunscreens must include standard "Drug Facts" information on the back and/or side of the container.

Q7. Does the Final Rule apply to cosmetics and moisturizers containing sunscreen?

A. Yes. All products that claim to provide Broad Spectrum SPF protection are regulated as sunscreen drug products. Therefore, the regulations FDA has developed for OTC sunscreen drug products apply to cosmetics and moisturizers labeled with SPF values.

Q8. What does the Proposed Rule address?

A. The proposed rule, if finalized, would limit the maximum SPF value on sunscreen labels to "50 +" because there is not sufficient data to show that products with SPF values higher than 50 provide greater protection for users than products with SPF values of 50.

The proposed regulation is available for public comment at regulations.gov [1] until September 15, 2011.

Q9. What is the purpose of the Advance Notice of Proposed Rulemaking (ANPR)?

A. The Advance Notice of Proposed Rulemaking (ANPR) allows the public a period of time to comment on regulations FDA may pursue as part of future rulemaking. In developing regulations for over-the-counter (OTC) sunscreens, FDA has not previously specified to which dosage forms the regulations would apply. Therefore, FDA is requesting additional data relating to sunscreen products in specific dosage forms to further our understanding of how dosage forms affect the safety and effectiveness of sunscreen products. For example, the ANPR invites public comment on possible directions for use of and warnings for sunscreen sprays, as well as supporting data o information for sprays and other sunscreen dosage forms including lotions, oils, sticks, gels, butters, ointments, creams, and pastes. The ANPR also explains how interested parties can supply information for FDA to consider other dosage forms, including powders, towelettes, body washes, and shampoos.

Q10. Why is the Advance Notice of Proposed Rulemaking (ANPR) requesting additional data on sunscreen products in the form of sprays?

A. Currently, the record (data and information) about sunscreens in spray dosage forms is not comparable to that for sunscreens in other dosage forms such as oils, creams, and lotions. The manner of application differs significantly between sprays and these other dosage forms. Therefore, we are requesting additional data to address questions of effectiveness and safety that arise from differences in the manner of application.

Q11. What is included in the Draft Guidance for Industry?

A. The Draft Guidance for Industry, entitled "Enforcement Policy – OTC Sunscreen Drug Products Marketed Without an Approved Application (PDF - 83KB) [2]," is an enforcement guidance that includes information to help sunscreen product manufacturers understand how to label and test their products in light of the new Final Rule, the Proposed Rule, and the Advance Notice of Proposed Rulemaking (ANPR).

Q12. Why isn't FDA finalizing all the proposed sunscreen changes under one rule?

A. FDA is finalizing those changes that are based on proposals it made in earlier stages of rulemaking, including a 2007 proposed rule, on which it already received public comment. Those comments also helped to inform the Agency's thinking about additional aspects of sunscreen regulation, which in turn gave rise to the Proposed Rule and Advance Notice of Proposed Rulemaking (ANPR). The regulatory process requires FDA to give public notice and opportunity for comment before finalizing additional changes, which also gives the public and FDA an opportunity to further develop the record (data and information) on safety and effectiveness.

Q13. Where can I find more information on these various regulatory actions?

A. On June 17, 2011, FDA published the new sunscreen Final Rule (PDF - 485KB) [3], the Proposed Rule (PDF - 197KB) [4], the Advance Notice of Proposed Rulemaking (ANPR) (PDF - 187KB) [5] and the notice of availability of the Draft Guidance for Industry (PDF - 217KB) [6] in the Federal Register. The draft guidance entitled "Enforcement Policy – OTC Sunscreen Drug Products Marketed Without an Approved Application" (PDF - 83KB) [7], is also available.

Q14. Where can I find more information on sunscreen use?

A. Additional information about FDA's changes to sunscreen regulations can be found at www.fda.gov/sunscreen[8]. At this link, consumers can see what new sunscreen labels will look like, what types of sun protection various sunscreens will provide, and how to use sunscreens safely and effectively.

In addition, FDA responded to common questions about the new sunscreen regulations submitted by the WebMD community via Twitter and Facebook. These questions and FDA's responses can be found at WebMD Newsroom: FDA's New Sunscreen Rules - FAQ[9].

Related Information

- Sunscreen Information[10]

Links on this page:

1. http://www.regulations.gov/
2. /downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM259001.pdf
3. http://www.gpo.gov/fdsys/pkg/FR-2011-06-17/pdf/2011-14766.pdf
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9. http://blogs.webmd.com/breaking-news/2011/06/fdas-new-sunscreen-rules-faq.html
10. /Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/ucm239463.htm

U.S. Food and Drug Administration

Drugs

Bad Ad Program: 2010-2011 Year End Report

Background

On May 11, 2010, FDA's Center for Drug Evaluation and Research (CDER) launched the Bad Ad outreach program with the goal of encouraging health care professional (HCPs) to recognize and report suspected untruthful or misleading drug promotion.

Led by CDER's Division of Drug Marketing Advertising and Communications (DDMAC), this effort was primarily designed to inform HCPs about what constitutes misleading promotion —from both a legal and clinical perspective — and provide them an easy process for reporting suspected violations to FDA.

Below are key highlights of the program's activities during its first year of operation.

- FDA Commissioner Hamburg kicked off the Bad Ad Program with a letter [1] to more than 33,000 physicians, announcing FDA's efforts to "collaborate with health care professionals to address misleading promotion, wherever it occurs."
- Concurrently, FDA released a press announcement [2] marking the program's launch.
- DDMAC created an informational video [3] about Bad Ad, citing examples of untruthful and misleading promotions. And how to report suspected violations.
- DDMAC created a Bad Ad brochure [4] designed to educate HCPs about prescription drug promotion.
- Throughout the year, DDMAC representatives staffed exhibits at 15 medical conferences across the country, speaking with HCPs about how they can help stop misleading drug promotion. DDMAC representatives also conducted extended presentations at two U.S. teaching hospitals.
- On April 28, 2011, FDA hosted a live Bad Ad webinar [5] for medical and pharmacy professionals with more than 400 attendees.

All of these efforts were intended to raise awareness in the medical community that HCPs can play a valuable role in helping FDA prevent untruthful and misleading prescription drug promotion.

Year One Data

Of the 328 reports of potentially untruthful or misleading promotion, 188 were submitted by HCPs, 116 were submitted by consumers, and 24 were submitted by representatives of regulated industry. Historically, prior to the Bad Ad launch, FDA received an average of about 104 reports per year. This number and diversity of reports received after the Bad Ad program was launched indicates to FDA that the program was successful in raising awareness of untruthful and misleading promotion

Of the 188 reports submitted by HCPs, 87 were identified for a comprehensive review, demonstrating a relatively strong level of knowledge in the medical community about what constitutes misleading promotion. Of the 116 reports submitted by consumers, 24 were identified for a comprehensive review. Of the 24 reports submitte by industry, 14 were identified for a comprehensive review. Many of the other reports helped to focus FDA's surveillance efforts in other ways or were referred to othe FDA Centers (i.e., potentially misleading ads for dietary supplements sent to the Center for Food, potentially misleading ads for devices sent to the Center for Devices and Radiological health, etc.).

During the Bad Ad program's first year, FDA heard some criticisms of anonymous reporting. It was noted by some that anonymous reports could unjustly accuse some promotions of being misleading when in fact they may be appropriately aligned with regulations. For this reason it is noteworthy to mention that of all reports of potentially untruthful or misleading promotion during the first year of the Bad Ad program, only 4% were submitted anonymously.

Although FDA is encouraged by the significant increase in the number of reports of potentially untruthful or misleading drug promotion, the Agency does not view the total number of reports, or number of enforcement actions taken as the primary measures for program success. Instead, FDA's most important measure of success for this program is the heightened sense of awareness of misleading promotion among HCPs throughout the health care community and the likely useful deterrent this awareness has on drug promoters who might run afoul of regulation absent of such messaging.

Future plans

Based on the overwhelmingly positive feedback and response from the medical community, FDA expects to continue and expand its Bad Ad efforts in the coming years Expansion includes the development of a web-based continuing education program. Aligned with the program's primary goal of educating HCPs, FDA will focus additional efforts on students and early career HCPs. FDA will also be actively seeking opportunities to collaborate with the nation's medical, pharmacy, and nursing schools to enhance student education and will continue conducting presentations at U.S. teaching hospitals. Future activities will also include continued attendance of DDMAC representatives at trade shows across the country, including those of the:

- American Academy of Physician Assistants
- American Academy of Nurse Practitioners
- American Academy of Family Physicians
- American Academy of Pediatrics
- American College of Gastroenterology
- American Society of Health System Pharmacists

Highlights of Bad Ad Enforcement Actions

- Derma-Smoothe Warning Letter issued 12/03/2010 [6]. The first action resulting from a Bad Ad complaint was on a particularly egregious website promoting a product for use in a vulnerable population.
- Infergen Warning Letter issued 03/21/2011 [7]. A promotional piece [8] was mailed directly to a clinical pharmacist who was concerned that the information overstated the effectiveness of the promoted product.
- Savella Notice of Violation issued 04/28/2011 [9]. This Bad Ad complaint is representative of the types of promotion we hope to curtail in field-based settings. This regulatory action was supported by a signed statement from a physician outlining violative oral statements that were similar to statements made directly to DDMAC reviewers during the same time period.
- Atelvia Notice of Violation issued 05/05/2011 [10]. This video footage of a violative product detail that occurred in a physician's office was posted to YouTube.com. Of note, is that this violation was reported to Bad Ad when the posted video had less than 20 views. As a result of this early reporting, DDMAC was able to prevent the violative video from being viewed by a much larger audience.
- Vyvanse Warning Letter issued 05/06/2011 [11]. This Bad Ad report came from an astute nurse, who noticed that a promotional piece that was likely viewed everyday by the office's HCPs was misleading in that it was designed to hide the important risk information from plain view.

Thank You

Finally, FDA would like to thank each and every person who took the time to send a report to the Bad Ad Program. The majority of the reports to this program came from HCPs whose contributions have helped ensure the accuracy of the drug information that both HCPs and their patients use to make treatment decisions.

Links on this page:

1. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/DrugMarketingAdvertisingandCommunications/UCM211560.pdf
2. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm211611.htm
3. http://www.youtube.com/user/USFoodandDrugAdmin#p/search/1/SQep0WyIuhg
4. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/PrescriptionDrugAdvertisingandPromotionalLabeling/UCM209847.pdf
5. /AboutFDA/WorkingatFDA/FellowshipInternshipGraduateFacultyPrograms/PharmacyStudentExperientialProgramCDER/ucm247416.htm
6. /Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/ucm259174.htm
7. /Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/ucm259249.htm
8. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM240981.pdf
9. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM253625.pdf
10. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM254562.pdf
11. /Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/ucm259167.htm

U.S. Food and Drug Administration

Safety

Zocor (simvastatin): Label Change - New Restrictions, Contraindications, and Dose Limitations

Simvastatin sold under the brand-name Zocor, as a single-ingredient generic product, and sold in combination with ezetimibe as Vytorin and in combination with niacin as Simcor

[Posted 06/08/2011]

AUDIENCE: Family Practice, Cardiology, Pharmacy

ISSUE: FDA notified healthcare professionals that it is recommending limiting the use of the highest approved dose of the cholesterol-lowering medication simvastatin (80 mg) because of increased risk of muscle damage. Patients taking simvastatin 80 mg daily have an increased risk of myopathy compared to patients taking lower doses of this drug or other drugs in the same class. This risk appears to be higher during the first year of treatment, is often the result of interactions with certain medicines, and is frequently associated with a genetic predisposition toward simvastatin-related myopathy. The most serious form of myopathy, called rhabdomyolysis, can damage the kidneys and lead to kidney failure which can be fatal. FDA is requiring changes to the simvastatin label to add new contraindications (should not be used with certain medications) and dose limitations for using simvastatin with certain medicines.

BACKGROUND: The new changes to the drug labels for simvastatin-containing medicines are based on FDA's review of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial and other data described in the Agency's March 2010 Ongoing safety review of high-dose Zocor (simvastatin) and increased risk of muscle injury. Simvastatin 80 mg should be used only in patients who have been taking this dose for 12 months or more without evidence of muscle injury (myopathy).

RECOMMENDATION: Simvastatin 80 mg should not be started in new patients, including patients already taking lower doses of the drug.

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

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

[06/08/2011 - Drug Safety Communication [3] - FDA]

[06/08/2011 - News Release [4] - FDA]

[06/08/2011 - Consumer Update [5] - FDA

Previous MedWatch Alert

[03/19/2010 [6]]

Links on this page:

1. http://www.fda.gov/MedWatch/report.htm
2. /Safety/MedWatch/HowToReport/DownloadForms/default.htm
3. /Drugs/DrugSafety/ucm256581.htm
4. /NewsEvents/Newsroom/PressAnnouncements/ucm258338.htm
5. /ForConsumers/ConsumerUpdates/ucm257884.htm
6. /Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm205404.htm

U.S. Food and Drug Administration

Safety

5-alpha reductase inhibitors (5-ARIs): Label Change - Increased Risk of Prostate Cancer

Drugs in the 5-ARI class include finasteride and dutasteride. These drugs are marketed under the brand-names Proscar, Propecia, Avodart, and Jalyn

[Posted 06/09/2011]

AUDIENCE: Urology, Family Medicine, Internal Medicine

ISSUE: FDA notified healthcare professionals that the Warnings and Precautions section of the labels for the 5-alpha reductase inhibitor (5-ARI) class of drugs has bee revised to include new safety information about the increased risk of being diagnosed with a more serious form of prostate cancer (high-grade prostate cancer).

BACKGROUND: The new safety information is based on FDA's review of two large, randomized controlled trials—the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial. Proscar, Avodart, and Jalyn are approved to improve symptoms of an enlarged prostate gland (benign prostatic hyperplasia or BPH). Proscar and Avodart are also approved to reduce the risk of urinary retention or surgery related to an enlarged prostate.Propecia is approved to treat male pattern hair loss.

RECOMMENDATION: Prior to initiating therapy with 5-ARIs, perform appropriate evaluation to rule out other urological conditions, including prostate cancer, that might mimic benign prostatic hyperplasia (BPH). See Drug Safety Communication for a Data Summary and additional information.

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

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

[06/09/2011 - Drug Safety Communication [3] - FDA]

[06/09/2011 - Q and A's [4] - FDA]

Links on this page:

1. http://www.fda.gov/MedWatch/report.htm
2. /Safety/MedWatch/HowToReport/DownloadForms/default.htm
3. /Drugs/DrugSafety/ucm258314.htm
4. /Drugs/DrugSafety/ucm258358.htm

U.S. Food and Drug Administration

Safety

Victoza (liraglutide [rDNA origin]) Injection: REMS - Risk of Thyroid C-cell Tumors, Acute Pancreatitis

[Posted 06/13/2011]

AUDIENCE: Endocrinology, Family Practice

ISSUE: Novo Nordisk reminded healthcare professionals of important safety information about Victoza (liraglutide [rDNA origin]) injection required in a Risk Evaluation and Mitigation Strategy (REMS). The letter is being sent because a recent assessment of healthcare providers showed that some primary care providers are not fully aware of the serious risks associated with the use of Victoza.

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Additionally, in clinical trials studying Victoza, there were more cases of pancreatitis in patients treated with Victoza than in patients treated with comparators.

BACKGROUND: FDA may require a REMS for newly or already approved prescription drug product when FDA determines that a REMS is necessary to ensure the benefits of a drug outweigh the risks of the drug. Victoza is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

RECOMMENDATION: Patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation. Although routine monitoring of serum calcitonin is of uncertain value in patients treated with Victoza, if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation.

After initiation of Victoza, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, and which may or may not be accompanied by vomiting).

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

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

[June 2011 - Dear Healthcare Professional Letter [3] - Novo Nordisk]

[May 2011 - Prescribing Information [4] - Novo Nordisk]

Links on this page:

1. http://www.fda.gov/MedWatch/report.htm
2. /Safety/MedWatch/HowToReport/DownloadForms/default.htm
3. /downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM258828.pdf
4. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022341s004lbl.pdf

U.S. Food and Drug Administration

Drugs

FDA Drug Safety Communication: Medication errors resulting from confusion between risperidone (Risperdal) and ropinirole (Requip)

Safety Announcement

[06-13-2011] The U.S. Food and Drug Administration (FDA) is alerting the public to medication error reports in which patients were given risperidone (Risperdal) instead of ropinirole (Requip) and vice versa. In some cases, patients who took the wrong medication needed to be hospitalized.

The FDA determined that the factors contributing to the confusion between the two products include:

1. Similarities of both the brand (proprietary) and generic (established) names
2. Similarities of the container labels and carton packaging
3. Illegible handwriting on prescriptions
4. Overlapping product characteristics, such as the drug strengths, dosage forms, and dosing intervals.

Patients who take Requip, Risperdal, or their generic equivalents are reminded to take note of the name and appearance of their medication, know why they are taking it, and to ask questions when the medication appears different than what they expect.

Healthcare Professionals are reminded to clearly print or spell out the medication name on prescriptions and make certain their patients know the name of their prescribed medication and their reason for taking it.

Facts about Risperidone and Ropinirole

- Risperidone (Risperdal) is an antipsychotic medication used to treat mental illnesses including schizophrenia, bipolar disorder, and irritability associated with autistic disorder.
- Ropinirole (Requip) is a dopamine agonist used in the treatment of Parkinson s disease and Restless Legs Syndrome.

FDA is requesting the manufacturers of Requip (GlaxoSmithKline), Risperdal (Johnson & Johnson), and the generic ropinirole and risperidone products to take the following measures to reduce the potential for confusion between the two products:

- Use of "tall man" lettering on container labels and carton packaging to present the generic names as risperiDONE and rOPINIRole, which may improve the ability of healthcare professionals to distinguish between the two drug names.
- Change individual labels and carton packaging to provide better visual differentiation between the generic products for risperidone and ropinirole in order to reduce the potential for confusion. Currently, the label and packaging features (i.e., similar font size and type, layout, and color) for generic ropinirole and risperidone products make the bottles look similar (See Table 1 below).

Additional Information for Patients

- Check the name of the medication and the appearance of the tablets in the prescription bottle to confirm the medication you receive is what you expect. If something looks different, talk to your pharmacist, and ask to see the original bottle from which the medication was filled.
- Ask your pharmacist to confirm the purpose of the medication. Ask additional questions if the purpose is different from what your healthcare professional told you.
- Report any side effects or medication errors 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

- Be sure to clearly print the drug name on written prescriptions.
- Be sure to spell out the drug name when prescribing over the telephone.
- Counsel patients about their prescribed medication, making sure the patient understands its purpose. Including the medical reason for the medication on the prescription may help ensure the patient gets the correct medication.
- Pharmacists are advised to physically separate the stocks of these two drugs on the shelf or wherever they are stored.
- Pharmacists are advised to confirm the drug name with prescribers if the prescription is not legible or the drug name is not clearly stated.
- Report adverse events or medication errors involving ropinirole or risperidone to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page.

Data Summary

FDA evaluated 226 wrong drug medication errors relating to confusion between risperidone and ropinirole obtained from FDA's Adverse Event Reporting System database and the Institute for Safe Medication Practices. Several cases resulted in adverse events (n=16), including 5 cases that resulted in hospitalization of the patients. The adverse events occurred due to the administration of incorrect medication and included confusion, lethargy, ataxia, hallucinations, tiredness, dizziness, tingling, numbness and altered mental status. In one of the cases reported from outside the United States, a patient was given Risperdal instead of Requip for one month before a care worker noticed the error. Requip was restarted without titration, and one month after Requip was restarted the patient died. It is unclear what role if any, the error had in the death of this patient.

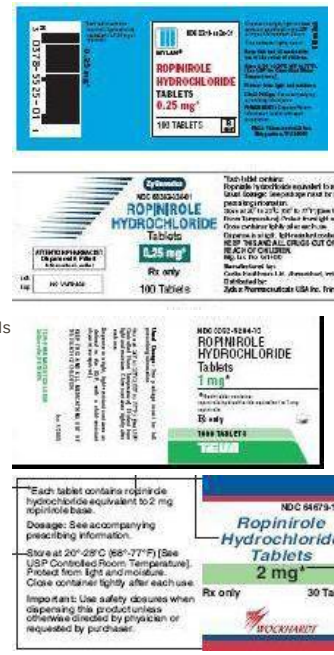
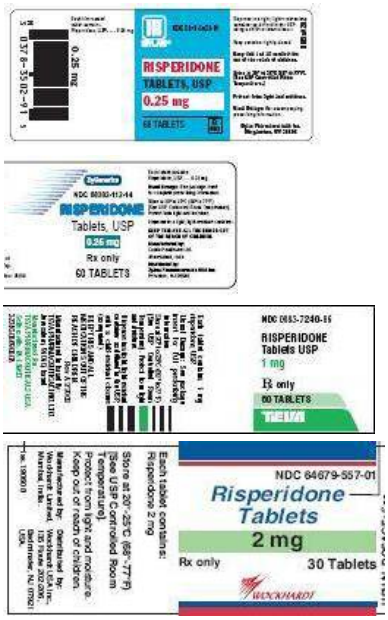
FDA determined the causes of confusion between risperidone and ropinirole are multi-factorial in nature. Contributing factors are orthographic similarity of the proprietary (brand) and established (generic) names, similar container labels and carton packaging, illegible handwriting, and overlapping strengths, dosage forms, and dosing intervals between the two products.

The incidence of confusion between the two products increased considerably after 2006 with the introduction of the generic products, which utilize the established (generic) names on the container labels. Generic risperidone was approved in 2006 and generic ropinirole was approved in 2008. However, FDA cannot rule out the possibility that the proprietary (brand) names also may have contributed to the confusion. All of the cases of confusion between risperidone and ropinirole involved tablet formulations.

In addition to the similarity in names, the products have overlapping characteristics, such as the same dosage form (tablet), frequency of dosing (daily or twice daily) and a numerical similarity in dosage strengths (0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg). It is also possible that the two products are stocked close to one another on pharmacy shelves, whether alphabetized by brand name or generic name. Moreover, some of the generic manufacturers make both products. The use of similar labels and carton packaging within the generic product lines by such manufacturers increases the likelihood of confusion between risperidone and ropinirole. Given similar labels and carton packaging designs used by many generic manufacturers, when this factor is combined with similarities in drug names, overlapping product characteristics, and proximity in stocking within pharmacies, there is considerable potential for product misidentification and medication errors.

Although for most of the cases the reporters did not state the source of the confusion, in two cases they attributed the cause of error to the similarity in the established (generic) names and overlapping strengths. In addition, proximity of the products on the pharmacy shelf and similar packaging were reported as contributing factors in two cases.

Table 1. Ropinirole and Risperidone Product Similarities

Generic name	Ropinirole	Risperidone
Brand name	Requip, Requip XL	Risperdal, Risperdal M-Tab
Strengths	Oral tablet: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg Extended-release tablet (XL): 2 mg, 4 mg, 6 mg, 8 mg, 12 mg	Oral tablet: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg Orally disintegrating tablets (M-tab): 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg
Dosage form	Tablet	Tablet
Dosing intervals	Once daily, Twice daily, or Three times daily	Once daily or Twice daily
Sample Container Labels		

Related Information

- Atypical Antipsychotic Drugs Information [1]
- Ropinirole (marketed as Requip) Information [2]
- FDA Drug Safety Podcast for Healthcare Professionals: Medication errors resulting from confusion between risperidone (Risperdal) and ropinirole (Requip) [3]

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Regular Mail: Use postage-paid FDA Form 3500 [5]

Mail to: MedWatch 5600 Fishers Lane

Rockville, MD 20857

Links on this page:

1. /Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm094303.htm
2. /Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm258819.htm

U.S. Food and Drug Administration

Drugs

FDA Drug Safety Podcast for Healthcare Professionals: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury

Podcast [1]

Welcome, my name is Jennifer Shepherd, a pharmacist in the Division of Drug Information. On June 8, 2011, the Food and Drug Administration issued a Drug Safety Communication recommending limiting the use of the highest approved dose of the cholesterol-lowering medication, simvastatin (80 mg) because of increased risk of muscle damage. Simvastatin 80 mg should be used only in patients who have been taking this dose for 12 months or more without evidence of myopathy. Simvastatin 80 mg should not be started in new patients, including patients already taking lower doses of the drug. In addition to these new limitations, FDA is requiring changes to the simvastatin label to add new contraindications and dose limitations for using simvastatin with certain medicines.

Patients taking simvastatin 80 mg daily have an increased risk of myopathy compared to patients taking lower doses of this drug or other drugs in the same class. This risk appears to be higher during the first year of treatment, is often the result of interactions with certain medicines, and is frequently associated with a genetic predisposition toward simvastatin-related myopathy. Patients with myopathy generally have muscle pain, tenderness or weakness, and an elevation of creatine kinase in the blood. The most serious form of myopathy, called rhabdomyolysis, can damage the kidneys and lead to kidney failure which can be fatal. Rhabdomyolysis is rare hospitalized rhabdomyolysis occurs in 4.9 people out of every 100,000 people exposed to simvastatin for one full year. The average incidence for hospitalized rhabdomyolysis for atorvastatin, pravastatin, or simvastatin is 4.4 people out of every 100,000 people.

FDA has revised the drug labels for simvastatin and Vytorin to include the new dosing restriction for the 80-mg dose. The labels for simvastatin, Vytorin, and Simcor were also revised to include new dosing recommendations when these drugs are used with certain medicines that interact with simvastatin to increase the level of simvastatin in the body. Increasing the levels of simvastatin in the body can increase the risk for myopathy.

In March 2010, FDA announced it was reviewing the safety of simvastatin in the Agency's Ongoing safety review of high-dose Zocor (simvastatin) and increased risk of muscle injury.

At this time, FDA recommends that healthcare professionals should:

1. Maintain patients on simvastatin 80 mg only if they have been taking this dose for 12 or more months without evidence of muscle toxicity.
2. Not start new patients on simvastatin 80 mg.
3. Place patients who do not meet their LDL cholesterol, or LDL-C, goal on simvastatin 40 mg on an alternative LDL-C lowering treatment that provides greater LDL-C lowering.
4. Follow the recommendations in the simvastatin-containing medicines labels regarding drugs that may increase the risk for muscle injury when used with simvastatin.
5. Switch patients who need to be initiated on a drug that interacts with simvastatin to an alternative statin with less potential for the drug-drug interaction.
6. Report adverse events involving simvastatin-containing medicines 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 and background information 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: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury - mp3 (MP3 - 7792KB) [4]
- FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury [5]
  6/8/2011
- FDA: Limit Use of 80 mg Simvastatin [6]
  6/8/2011
- FDA announces new safety recommendations for high-dose simvastatin [7]
  6/8/2011

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Silver Spring, MD 20993

U.S. Food and Drug Administration

Drugs

FDA Drug Safety Communication: 5-alpha reductase inhibitors (5-ARIs) may increase the risk of a more serious form of prostate cancer

Safety Announcement

[6-9-2011] The U.S. Food and Drug Administration (FDA) is informing healthcare professionals that the Warnings and Precautions section of the labels for the 5-alpha reductase inhibitor (5-ARI) class of drugs has been revised to include new safety information about the increased risk of being diagnosed with a more serious form of prostate cancer (high-grade prostate cancer). This risk appears to be low, but healthcare professionals should be aware of this safety information, and weigh the known benefits against the potential risks when deciding to start or continue treatment with 5-ARIs in men.

The new safety information is based on FDA's review of two large, randomized controlled trials—the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial—which evaluated daily use of finasteride 5 mg versus placebo for 7 years and daily use of dutasteride 0.5 mg versus placebo for 4 years, respectively, for the reduction in the risk of prostate cancer in men at least 50 years of age. The trials demonstrated an overall reduction in prostate cancer diagnoses with finasteride 5 mg and dutasteride treatment (see Data Summary below). This overall reduction was due to a decreased incidence of lower risk forms of prostate cancer. However, both trials showed an increased incidence of high-grade prostate cancer with finasteride and dutasteride treatment.

For more information about this safety issue, also refer to the Questions and Answers[1].

Facts about 5-ARIs

- Drugs in this class are finasteride (marketed as Proscar [finasteride 5 mg] and Propecia [finasteride 1 mg]) and dutasteride (marketed as Avodart). Dutasteride is also available in combination with tamsulosin, under the brand-name Jalyn.
- Proscar, Avodart, and Jalyn are approved to improve symptoms of an enlarged prostate gland (benign prostatic hyperplasia or BPH). Proscar and Avodart are also approved to reduce the risk of urinary retention or surgery related to an enlarged prostate.
- Propecia is approved to treat male pattern hair loss.
- Approximately 5 million male patients received a prescription for a 5-ARI between years 2002 to 2009. Of these, nearly 3 million patients were between the ages of 50 to 79 years.[1]

Additional Information for Patients

- Drugs in the 5-ARI class are finasteride and dutasteride. These drugs are marketed under the brand-names Proscar, Propecia, Avodart, and Jalyn.
- Finasteride is available in two different strengths: Proscar 5 mg tablets and Propecia 1 mg tablets.
- Discuss any questions or concerns about 5-ARIs with your healthcare professional.
- Report any side effects you experience to the FDA MedWatch program, using the information at the bottom of the page in the "Contact Us" box.

Additional Information for Healthcare Professionals

- Be aware that 5-ARIs may increase the risk of high-grade prostate cancer.
- Prior to initiating therapy with 5-ARIs, perform appropriate evaluation to rule out other urological conditions, including prostate cancer, that might mimic benign prostatic hyperplasia (BPH).
- Be aware that treatment with 5-ARIs causes an approximate 50% reduction in prostate-specific antigen (PSA) values by 6 months; however, individual patient receiving 5-ARIs may experience varying decreases in PSA values. Therefore, any confirmed increase in PSA while on a 5-ARI may signal the presence of prostate cancer and should be evaluated, even if that PSA is in the normal range of men not taking a 5-ARI.
- Know that 5-ARIs are not approved for the prevention of prostate cancer.
- Report any adverse events involving 5-ARIs to the FDA MedWatch program, using the information at the bottom of the page in the "Contact Us" box.

Data Summary

The PCPT was a randomized, double-blind, placebo-controlled, multicenter trial in 18,882 men age 55 or older with a normal digital rectal examination and PSA levels ≤ 3 ng/mL. Men at higher risk for developing prostate cancer, such as those men with prior prostate biopsies demonstrating high-grade prostatic intraepithelial neoplasia were excluded from the study. The trial compared the use of finasteride 5 mg (n=9423) to placebo (n=9459) for the reduction in the risk of prostate cancer. Treatment was continued for seven years following randomization or until diagnosis of prostate cancer, initiation of treatment for BPH with a 5-ARI, or unacceptable side effects. The study protocol specified that transrectal ultrasound and sextant prostate biopsy were to be performed for an elevation in PSA level or an abnormal digital rectal examination during the study. All participants who were not previously diagnosed with prostate cancer were to undergo transrectal ultrasound and sextant core prostate biopsy after completing 7 years on study.

The results of the PCPT showed that men on the finasteride arm had a 26% overall lower risk of being diagnosed with prostate cancer when compared to the placebo arm ($p<0.0001$). The reduction in risk of prostate cancer was limited to Gleason score (GS) 6 or lower prostate cancers. However, there was an increased incidence of GS 8-10 prostate cancers with finasteride versus placebo (1.8% versus 1.1%, respectively).

The REDUCE trial was a randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of once daily dosing of dutasteride in reducing the risk of biopsy-detectable prostate cancer in men 50-75 years of age considered to be at increased risk for prostate cancer. The trial allocated 8231 men to receive either placebo (n=4126) or dutasteride 0.5 mg (n=4105) once daily for a total of four years. Prostate biopsies were performed at 2 years and 4 years. Unscheduled biopsies in addition to the protocol-mandated Year 2 or 4 biopsies were allowed if clinically indicated at the discretion of the investigator, but were discouraged.

The results of the REDUCE trial showed that men on dutasteride had a 23% overall lower risk of being diagnosed with biopsy detectable prostate cancer when compared to men on placebo ($p<0.0001$). This overall risk reduction was limited to a decrease in GS 6 or lower prostate cancers. In contrast, there was an increased incidence of GS 8-10 cancers with dutasteride versus placebo (1% versus 0.5%, respectively).

Data from the PCPT and REDUCE trials were discussed at the FDA's Oncologic Drugs Advisory Committee, held on December 1, 2010 (for complete safety reviews and background information discussed at this meeting see: December 1, 2010 AC meeting[2]).

References

1. SDI, Vector One®: Total Patient Tracker (TPT). Years 2002-2009. Data extracted 5-24-11.

Related Information

- Questions and Answers: 5-alpha reductase inhibitors (5-ARIs) may increase the risk of a more serious form of prostate cancer[3] 6/9/2011
- December 1, 2010: Oncologic Drugs Advisory Committee Meeting Announcement[4]
- 5-Alpha Reductase Inhibitor Information[5]

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Links on this page:

1. /Drugs/DrugSafety/ucm258358.htm
2. /AdvisoryCommittees/Calendar/ucm230653.htm
3. /Drugs/DrugSafety/ucm258358.htm
4. /AdvisoryCommittees/Calendar/ucm230653.htm
5. /Drugs/DrugSafety/InformationbyDrugClass/ucm258424.htm
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: No increase in risk of cancer with certain blood pressure drugs--Angiotensin Recepto Blockers (ARBs)

Safety Announcement

[06-02-2011] The U.S. Food and Drug Administration (FDA) has completed a review of the potential risk of cancer associated with the class of medications known as angiotensin receptor blockers (ARBs). FDA has concluded that treatment with an ARB medication does not increase a patient's risk of developing cancer. A list of medications containing an ARB is available here.

In July 2010 [1], FDA communicated its intent to conduct a safety review of ARBs after a published meta-analysis of 5 randomized clinical trials reported a small but statistically significant increase in risk of cancer in patients taking an ARB compared to patients not taking an ARB.[1]

Facts about Angiotensin Receptor Blockers (ARBs)

- ARBs are widely used to treat patients with high blood pressure.
- Brand names include Atacand, Avapro, Benicar, Cozaar, Diovan, Micardis, and Teveten, as well as the combination product brand names included in Table 1 below.

To further evaluate the reported link between use of ARBs and cancer, FDA conducted a trial-level meta-analysis of clinical trials in which patients had been randomized to an ARB treatment or a non-ARB treatment. This analysis included 31 trials and approximately 156,000 patients, far more than the approximately 62,000 in the published analysis. FDA's more comprehensive meta-analysis did not show a increased risk of cancer in the patients taking an ARB medication.

Based on our review and analysis of all currently available data regarding this potential safety signal, FDA has concluded that treatment with an ARB medication does not increase the risk of cancer.

Additional Information for Patients

- Do not stop taking your ARB medication without talking to your healthcare professional.
- Discuss any questions or concerns about ARB medications with your healthcare professional.
- Report any side effects you may 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

- Know that FDA's meta-analysis of 31 randomized controlled trials comparing ARBs to other treatment found no evidence of an increased risk of incident (new) cancer, cancer-related death, breast cancer, lung cancer, or prostate cancer in patients receiving ARBs.
- Report adverse events involving ARB medications to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page.

Data Summary

FDA conducted a trial-level meta-analysis of 31 randomized clinical trials to evaluate the risk of incident (new) cancer in patients taking ARBs compared to patients taking non-ARB treatments. The meta-analysis also evaluated the associations between ARBs and the following outcomes individually: cancer-related death, breast cancer, lung cancer, and prostate cancer.

The FDA study is the largest meta-analysis of clinical trials exploring the association between ARBs and cancer conducted to date. The analysis included all drug sponsc -identified randomized clinical trials that met pre-specified criteria (trials that included more than 100 patients and lasted for at least 1 year), including ascertainment c the occurrence of cancer or cancer death as a pre-specified endpoint or adverse event.

The 31 trials included 84,461 patients randomized to ARBs and 71,355 patients randomized to non-ARB comparators, with an average follow-up of 39 months. The rate of incident cancer events in the ARB group was 1.82 per 100 patient-years, and the rate in non-ARB comparators was 1.84 per 100 patient-years. The relative risk of incident cancer in patients taking ARBs was 0.99 (95% confidence interval 0.92 to 1.06). The estimate of risk was similar irrespective of the choice of statistical method (random effects or fixed effects), as well as the choice of comparator arm used in the analysis (all comparators, placebo only, active-comparators only).

FDA also found no evidence of association between ARBs and cancer-related death (relative risk 1.04, 95% confidence interval 0.96 to 1.13), breast cancer (odds ratio 1.06, 95% confidence interval 0.90 to 1.23), lung cancer (odds ratio 1.07, 95% confidence interval 0.89 to 1.29), or prostate cancer (odds ratio 1.05, 95% confidence interval 0.95 to 1.17).

The results from three recently published studies (two meta-analyses[2,3] generally similar to the FDA analysis and an observational cohort study[4]) also do not suggest any increased risk of cancer related to ARB use.

Table 1. Approved Angiotensin Receptor Blockers

Single Ingredient Angiotensin Receptor Blockers

Brand name	Generic name
Atacand	candesartan
Avapro	irbesartan
Benicar	olmesartan
Cozaar	losartan
Diovan	valsartan
Micardis	telmisartan
Teveten	eprosartan

Combination Angiotensin Receptor Blockers

Brand name	Generic name
Atacand HCT	candesartan and hydrochlorothiazide
Avalide	irbesartan and hydrochlorothiazide
Azor	olmesartan and amlodipine
Benicar HCT	olmesartan and hydrochlorothiazide
Diovan HCT	valsartan and hydrochlorothiazide
Exforge	valsartan and amlodipine
Exforge HCT	valsartan, amlodipine, and hydrochlorothiazide
Hyzaar	losartan and hydrochlorothiazide
Micardis HCT	telmisartan and hydrochlorothiazide
Teveten HCT	eprosartan and hydrochlorothiazide
Twynsta	telmisartan and amlodipine
Valturna	valsartan and aliskiren

References

1. Sipahi I, Debanne SM, Rowland DY, Simon DI, Fang JC. Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. The Lancet Oncology 2010;11: 627-36.
2. Bangalore S, Kumar S, Kjeldsen SE, et al. Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324,168 participants from randomized trials. Lancet Oncol 2011;12: 65-82.
3. The ARB Trialists Collaboration. Effects of telmisartan, irbesartan, valsartan, and candesartan, and losartan on cancers in 15 trials. J Hypertens 2011;29: 623-635.
4. Pasternak B, Svanström H, Callréus T, et al. Use of angiotensin receptor blockers and the risk of cancer. Circulation 2011;123: 1729-36.

Related Information

- FDA Drug Safety Communication: Ongoing safety review of the angiotensin receptor blockers and cancer [2]
- FDA Drug Safety Podcast for Healthcare Professionals: No increase in risk of cancer with certain blood pressure drugs--Angiotensin Receptor Blockers (ARBs) [3]

Contact Us

- **Report a Serious Problem**
- 1-800-332-1088
- 1-800-FDA-0178 Fax

MedWatch Online [4]

Regular Mail: Use postage-paid FDA Form 3500 [5]

Mail to: MedWatch 5600 Fishers Lane

Rockville, MD 20857

Links on this page:

1. /Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm218845.htm
2. /Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm218845.htm
3. /Drugs/DrugSafety/DrugSafetyPodcasts/ucm257719.htm
4. https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm
5. http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf

U.S. Food and Drug Administration

Drugs

FDA Statement on the AIM-HIGH Trial

[05-26-2011]

The U.S. Food and Drug Administration (FDA) will conduct a comprehensive review of the results from the clinical trial called the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) once they are available. The AIM-HIGH trial studied whether raising high-density lipoprotein (HDL) or "good" cholesterol levels in patients who have a history of cardiovascular disease and well-controlled low-density lipoprotein (LDL) or "bad" cholesterol levels could lower the rate of major adverse cardiovascular events (MACE). In AIM-HIGH, MACE was defined as cardiovascular death, non-fatal heart attack, ischemic stroke, hospitalizations for acute coronary syndrome in which there is insufficient blood flow to the heart, or revascularization procedures to improve blood flow in the arteries of the heart and brain.

In this trial, all study participants were given standard therapy with simvastatin 40 mg per day, and then randomly assigned to receive either extended-release niacin 1500-2000 mg per day or placebo. In the first year of the trial, the simvastatin dose could be adjusted, or a second LDL cholesterol-lowering drug, ezetimibe 10 mg, could be added, to achieve the target LDL-cholesterol goal of 40-80 mg/dL.

The trial was started in September 2005, but was stopped early due to the lack of incremental benefit on cardiovascular risk reduction in the extended-release niacin plus simvastatin treatment group over simvastatin alone. In addition, a small, unexplained, increase in the rate of ischemic stroke was noted in the simvastatin plus extended-release niacin group compared to the simvastatin alone group (28 strokes [1.6%] vs. 12 strokes [0.7%], respectively). Nine of the ischemic strokes in the simvastatin plus extended-release niacin group occurred in participants who had stopped taking their niacin for at least 2 months and up to 4 years before their stroke. Therefore, it is unclear what role, if any, niacin contributed to this imbalance in ischemic stroke.

At this time, FDA has made no new conclusions or recommendations regarding the use of extended-release niacin alone or in combination with simvastatin or other statins. The Agency will conduct a comprehensive review of the AIM-HIGH trial data as soon as they become available to determine their impac on the approved indications for extended-release niacin.

High-dose niacin is a prescription drug that is used along with diet and exercise to manage cholesterol and fat (triglyceride) levels in the blood. It is also indicated as a monotherapy to lower the risk of heart attacks in patients who have had a heart attack and have high cholesterol. High-dose niacin is available as an extended-release tablet under the brand-name Niaspan, and is also available in combination with simvastatin under the brand-name Simcor, and in combination with lovastatin under th brand-name Advicor.

Healthcare professionals should consider the available clinical information on high-dose extended-release niacin and statin drugs when deciding what cholesterol-lowering medication to prescribe.

Patients should not stop taking their current medications without talking to their healthcare professional.

The Agency will update the public with any new recommendations or conclusions when its review of the AIM-HIGH trial data is complete.

The AIM-HIGH trial was funded by the National Heart, Lung, and Blood Institute (NHLBI). To view the NHLBI's press release, please visit NIH stops clinical trial on combination cholesterol treatment [1].

Related Information

- Simvastatin (marketed as Zocor) Information [2]
- NIH stops clinical trial on combination cholesterol treatment [3]
  NIH Press Release - 5/26/2011

Links on this page:

1. http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?id=2792
2. /Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203669.htm
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