Drug Utilization Review Board

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

Wednesday
January 9, 2013
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: Chris Le, Pharm.D.

SUBJECT: Packet Contents for Board Meeting – January 9, 2013

DATE: January 3, 2013

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 January 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 Linzess™ and Update Amitiza® Criteria – See Appendix C.

60 Day Notice to Prior Authorize Chronic Obstructive Pulmonary Disease Medications – See Appendix D.

Action Item – Annual Review of Antihyperlipidemics and 30 Day Notice to Prior Authorize Vascepa™ and Juxtapid™ – See Appendix E.

Action Item – Annual Review of Osteoporosis Medications and 30 Day Notice to Prior Authorize Binosto™ – See Appendix F.

30 Day Notice to Prior Authorize Xeljanz® – See Appendix G

FDA and DEA Updates – See Appendix H.

Future Business

Adjournment

Oklahoma Health Care Authority
Drug Utilization Review Board
(DUR Board)
Meeting – January 9, 2013 @ 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. Cothran

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. December 12, 2012 DUR Minutes – Vote
B. December 13, 2012 DUR Recommendation Memorandum

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

4. Update on DUR / Medication Coverage Authorization Unit – See Appendix B.

A. Medication Coverage Activity for December 2012
B. Pharmacy Help Desk Activity for December 2012
C. Retrospective Drug Evaluation: Focusing on Safety

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

5. Action Item – Vote to Prior Authorize Linzess™ and Update Amitiza® Criteria – See Appendix C.

A. COP Recommendations

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

6. 60 Day Notice to Prior Authorize Chronic Obstructive Pulmonary Disease Medications – See Appendix D.

A. Utilization Review
B. Cost Comparison
C. Economic Impact
D. Market Analysis
E. COP Recommendations

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

7. Action Item – Annual Review of Antihyperlipidemics and 30 Day Notice to Prior Authorize Vascepa™ and Juxtapid™ – See Appendix E.

A. Current Authorization Criteria
B. Utilization Review
C. Prior Authorization Review
D. Market News and Update
E. Vascepa™ and Juxtapid™ Product Summaries
F. COP Recommendations
G. Utilization Details
H. Vascepa™ and Juxtapid™ Product Details

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

8. Action Item – Annual Review of Osteoporosis Medications and 30 Day Notice to Prior Authorize Binosto™ See Appendix F.

A. Current Authorization Criteria
B. Utilization Review
C. Prior Authorization Review
D. Market News and Update
E. COP Recommendations
F. Utilization Details
G. Binosto™ Product Details

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

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

A. Summary
B. Mechanism of Action
C. Efficacy
D. Safety
E. Cost
F. COP Recommendations
G. Product Details

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

10. FDA and DEA Updates – See Appendix H.

11. Future Business

A. DUR of Oral Corticosteroids
B. Annual Reviews
C. New Product Reviews

12. Adjournment

Appendix A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES of MEETING of December 12, 2012

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
Terry Cothran, D.Ph.; Pharmacy Director	X	
Karen Egesdal, D.Ph.; SMAC-ProDUR Coordinator/OHCA Liaison	X	
Shellie Keast, Pharm.D, M.S.; Clinical Assistant Professor	X	
Chris Le, Pharm.D.; Assisant Director	X	
Mark Livesay, Operations Manager	X	
Carol Moore, Pharm.D.; Clinical Pharmacist	X	
Brandy Nawaz, 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
Jo Nel Weber, Pharm.D.; Clinical Pharmacist	X	
Bethany Holderread, Pharm. D., Clinical Pharmacist	X	
Graduate Students: Amany Hussein, Manish Mittal	X	
Visiting Pharmacy Student(s): n/a		N/A

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

OTHERS PRESENT:		
Audrey Rattan, Otsuka	Tone Jones, Sunovion	Bob Atkins, Biogen
Cheri Ritchie, Otsuka	Jim Fowler, AstraZeneca	Jerrica Dodd, Biogen
David Williams, Forest	Hilary Carter, Otsuka	Roger Enix, Merck
Mai Duong, Novartis	Roger Grotzinger, BMS	CharleneKaiser, Amgen

Eric Gardner, Ventex	Clint Degrier, Novartis	Kathy Phillips, Novo
Flora Micle, Pfizer	Janie Huff, takeda	Sherry Mcloud, Novo
Toby Thompson, Pfizer	Gabriel Pardo, OMRF	
Rodney Nixa, Alcon	Jon Maguire, Glaxo	

PRESENT FOR PUBLIC COMMENT:	
Crystal Henderson	Forest Research Institute
Gabriel Pardo	OMRF

AGENDA ITEM NO. 1: CALL TO ORDER
1A: Roll Call
Dr. Muchmore called the meeting to order. Roll call by Dr. Cothran established the presence of a quorum.
ACTION: NONE REQUIRED

AGENDA ITEM NO. 2: PUBLIC COMMENT FORUM
Agenda Item: Multiple Sclerosis Medications Gabriel Pardo
Agenda Item No. 7 and 8 Crystal Henderson
ACTION: NONE REQUIRED

AGENDA ITEM NO. 3: APPROVAL OF DUR BOARD MINUTES
3A: November 14, 2012 DUR Minutes
3B: November 15, 2012 DUR Recommendation Memorandum
Dr. Harrell moved to approve as submitted; seconded by Ms. Varalli-Claypool
ACTION: MOTION CARRIED

AGENDA ITEM NO. 4: UPDATE ON DUR/MEDICATION COVERAGE AUTHORIZATION UNIT
4A: Medication Coverage Activity: November 2012
4B: Pharmacy Help Desk Activity: November 2012
4C: SoonerCare Atypical Rx Program Update
Reports included in agenda packet; presented by Dr. Keast
ACTION: NONE REQUIRED

AGENDA ITEM NO. 5: VOTE TO PRIOR AUTHORIZE RAYOS®
Materials included in agenda packet; presented by Dr. Moore
Dr. Kuhls moved to approve; seconded by Ms. Varalli-Claypool
ACTION: MOTION CARRIED

AGENDA ITEM NO. 6: VOTE TO PRIOR AUTHORIZE RELISTOR®
Materials included in agenda packet; presented by Dr. Moore.
Dr. Bell moved to approve; seconded by Dr. Rhymer
ACTION: MOTION CARRIED

AGENDA ITEM NO. 7: DRUG UTILIZATION REVIEW OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE MEDICATIONS
For Public Comment: Crystal Henderson
Materials included in agenda packet; presented by Dr. Weber.
ACTION: NONE REQUIRED

AGENDA ITEM NO. 8: ANNUAL REVIEW OF AMITIZA® AND 30 DAY NOTICE TO PRIOR AUTHORIZE LINZESS™
For Public Comment: Crystal Henderson
Materials included in agenda packet; presented by Dr. Le
ACTION: NONE REQUIRED

AGENDA ITEM NO. 9: ANNUAL REVIEW OF SMOKING CESSATION PRODUCTS
Materials included in agenda packet; presented by Le.
Dr. Feightner moved to approve; seconded by Ms. Varalli-Claypool
ACTION: MOTION CARRIED

AGENDA ITEM NO. 10: FDA AND DEA UPDATES
Materials included in agenda packet; presented by Dr. Cothran.
ACTION: NONE REQUIRED

AGENDA ITEM NO. 11: FUTURE BUSINESS
Materials included in agenda packet; submitted by Dr. Cothran
A: Annual Reviews
B: New Product Reviews
C: SAFETY ALERTS
ACTION: NONE REQUIRED

AGENDA ITEM NO. 12: ADJOURNMENT
The meeting was adjourned at 7:02 pm

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

Memorandum

Date: December 12, 2012

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

From: Chris Le, Pharm.D.
Assistant Director
Pharmacy Management Consultants

Subject: DUR Board Recommendations from Meeting of December 12, 2012

Recommendation 1: Vote to Prior Authorize Rayos® (Prednisone, Delayed Release)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Rayos® (prednisone, delayed release).

Approval Criteria:
Approval requires a patient specific, clinically significant reason why the member cannot use immediate release corticosteroid products.

Recommendation 2: Vote to Prior Authorize Relistor® (MethylnaltrexoneBromide)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends prior authorization of Relistor® (methylnaltrexone bromide), with the following criteria:

1. FDA approved indication for the treatment of opioid-induced constipation in patients with severe terminal disease who are receiving only palliative care (life expectancy less than 6 months), and
2. Current use of opioid medications, and
3. Documented treatment attempts with a minimum of three alternate products, excluding bulk forming laxatives, and
4. Mechanical gastrointestinal obstruction has been ruled out.
5. 12 mg single-use vials, syringes or kits will be the preferred products. Criteria for consideration of 8 mg single-use syringes:
    a. Weight range of 38-62 kg, and/or
    b. Caregiver unable to draw up dose from vial.
6. Quantity limit of 30 units per month.

Recommendation 3: Fiscal Year 2012 Annual Review of Smoking Cessation Products

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends removal of the prior authorization requirement for Zyban® (bupropion) and nicotine patches. Member may utilize both products up to 180 days each within a 365 day period. Previous criteria for Chantix™ (varenicline) and other formulations of nicotine replacement products still apply:

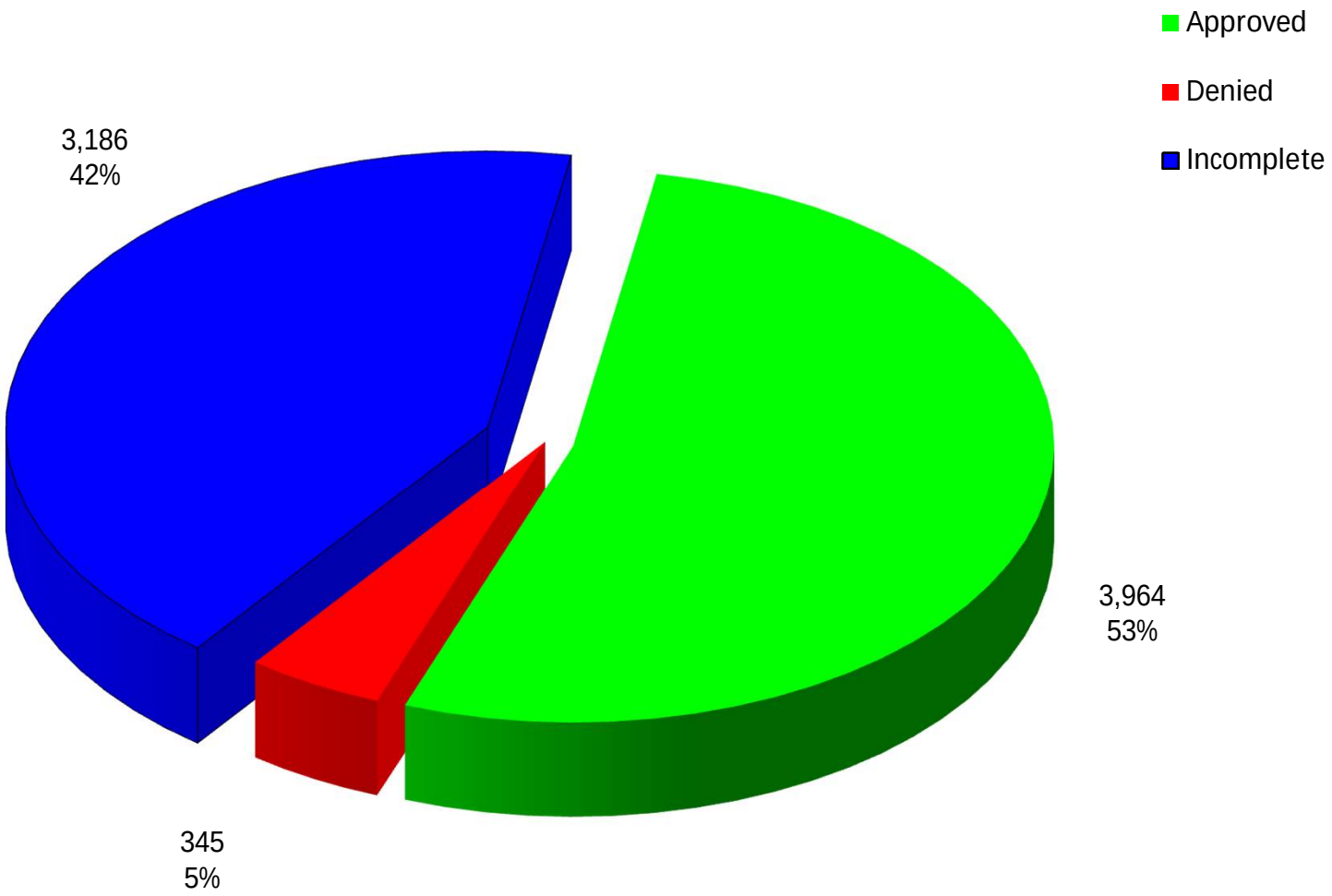
After 90 days of use in a 365 day period, further use of Chantix™ (varenicline) and other formulations of nicotine replacement products require prior authorization.

Criteria for Approval after the First 90 Days:

1. Member must be enrolled in a smoking cessation behavior modification program and the name of the program must be stated on the petition.
2. Petition may be approved for another 90 days.
3. After the member has had 180 days of treatment in a 365 day period, the member must wait another 180 days before smoking cessation treatment will be covered again.
4. Smoking cessation products do not count against the 6 prescription per month limit.
5. Quantity limits apply.

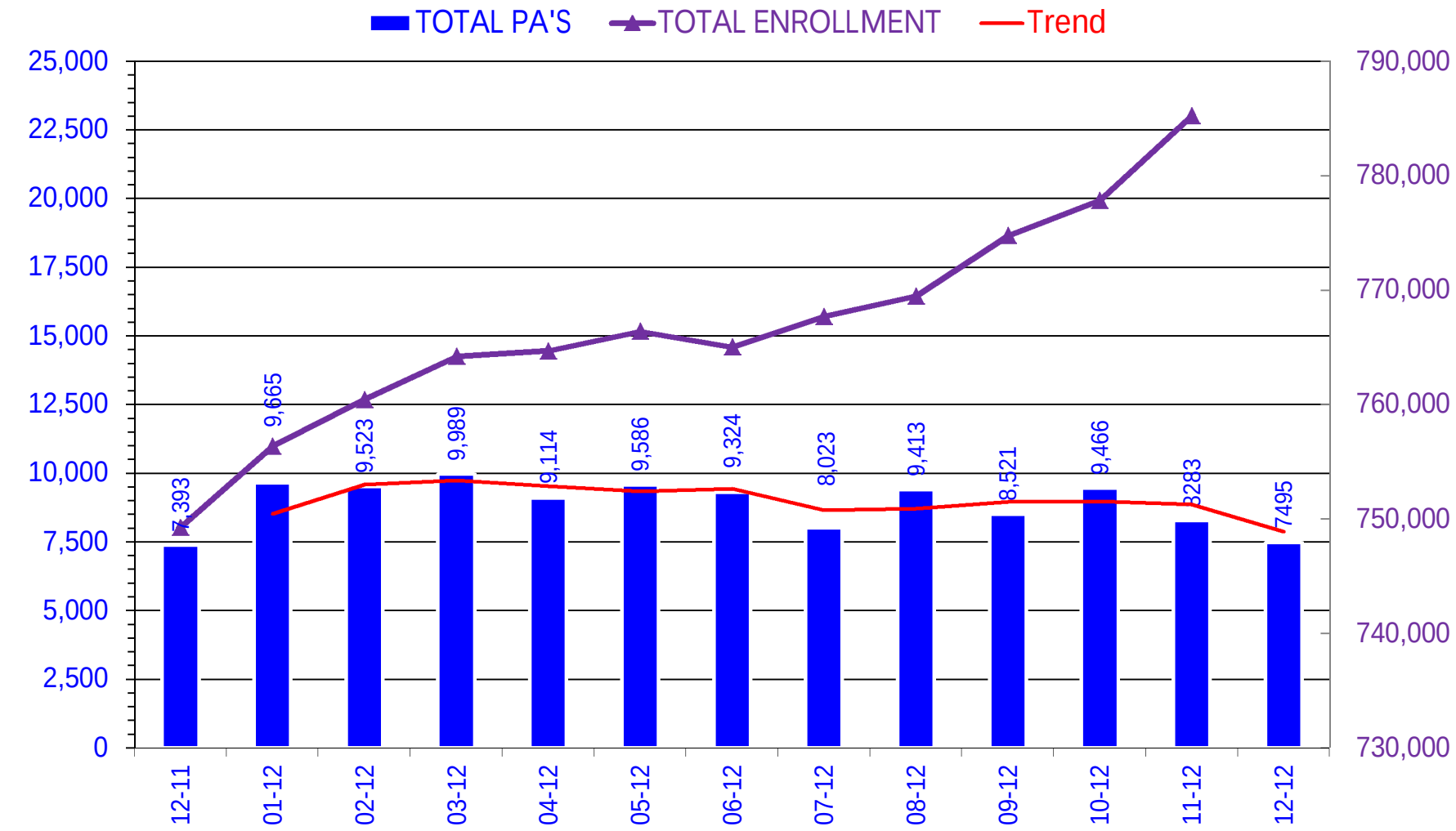
Appendix B

PRIOR AUTHORIZATION ACTIVITY REPORT: December 2012



PA totals include approved/denied/incomplete/overrides

PRIOR AUTHORIZATION REPORT: December 2011-December 2012



PA totals include approved/denied/incomplete/overrides

Prior Authorization Activity

12/1/2012 Through 12/31/2012

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort/Dulera	351	148	4	199	352
Analgesic, Narcotic	320	169	11	140	259
Angiotensin Receptor Antagonist	39	6	2	31	359
Antiasthma	1,002	509	9	484	229
Antibiotic	16	3	1	12	17
Anticoagulant	26	19	2	5	319
Anticonvulsant	57	30	1	26	342
Antidepressant	208	81	6	121	340
Antidiabetic	122	56	4	62	359
Antihistamine	145	113	6	26	351
Antihyperlipidemic	18	4	0	14	359
Antimigraine	78	22	9	47	339
Antiplatelet	27	20	0	7	346
Antiulcers	306	107	35	164	99
Anxiolytic	93	58	2	33	222
Atypical Antipsychotics	365	230	5	130	347
Biologics	35	21	0	14	343
Bladder Control	67	9	2	56	323
Calcium Channel Blockers	12	2	1	9	35
Cardiovascular	81	35	5	41	319
Dermatological	95	23	30	42	114
Endocrine & Metabolic Drugs	129	54	9	66	271
Erythropoietin Stimulating Agents	23	12	2	9	110
Fibromyalgia	137	35	12	90	305
Gastrointestinal Agents	66	30	6	30	177
Glaucoma	10	2	0	8	361
Growth Hormones	85	72	2	11	130
HFA Rescue Inhalers	84	13	3	68	348
Insomnia	67	21	3	43	158
Multiple Sclerosis	19	13	0	6	236
Muscle Relaxant	97	33	25	39	36
Nasal Allergy	95	12	14	69	136
Neurological Agents	43	29	5	9	359
Nsaids	155	29	16	110	332
Ocular Allergy	27	10	3	14	86
Ophthalmic	37	9	3	25	52
Osteoporosis	25	10	0	15	360
Other*	139	26	20	93	253
Otic Antibiotic	34	8	0	26	10
Pediculicide	85	32	2	51	17
Smoking Cess.	34	8	1	25	48
Statins	46	21	2	23	358
Stimulant	606	351	6	249	313
Suboxone/Subutex	131	96	2	33	81
Synagis	175	107	24	44	104
Topical Antifungal	54	1	1	52	85
Topical Corticosteroids	36	1	2	33	86
Vitamin	40	19	15	6	360
Pharmacotherapy	86	67	0	19	83
Emergency PAs	2	2	0	0	
Total	**6,030**	**2,788**	**313**	**2,929**	

* Includes any therapeutic category with less than 10 prior authorizations for the month.

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Overrides					
Brand	46	32	5	9	255
Dosage Change	490	444	4	42	6
High Dose	2	1	0	1	85
Ingredient Duplication	9	8	0	1	6
Lost/Broken Rx	107	101	2	4	4
NDC vs Age	11	11	0	0	219
Nursing Home Issue	97	94	0	3	4
Other	22	20	0	2	4
Quantity vs. Days Supply	659	449	18	192	256
Stolen	8	8	0	0	4
Third Brand Request	14	8	3	3	8
Overrides Total	**1,465**	**1,176**	**32**	**257**	
Total Regular PAs + Overrides	**7,495**	**3,964**	**345**	**3,186**	

Denial Reasons	
Unable to verify required trials.	2,580
Lack required information to process request.	592
Does not meet established criteria.	353

Other PA Activity

Duplicate Requests: 529

Letters: 2,081

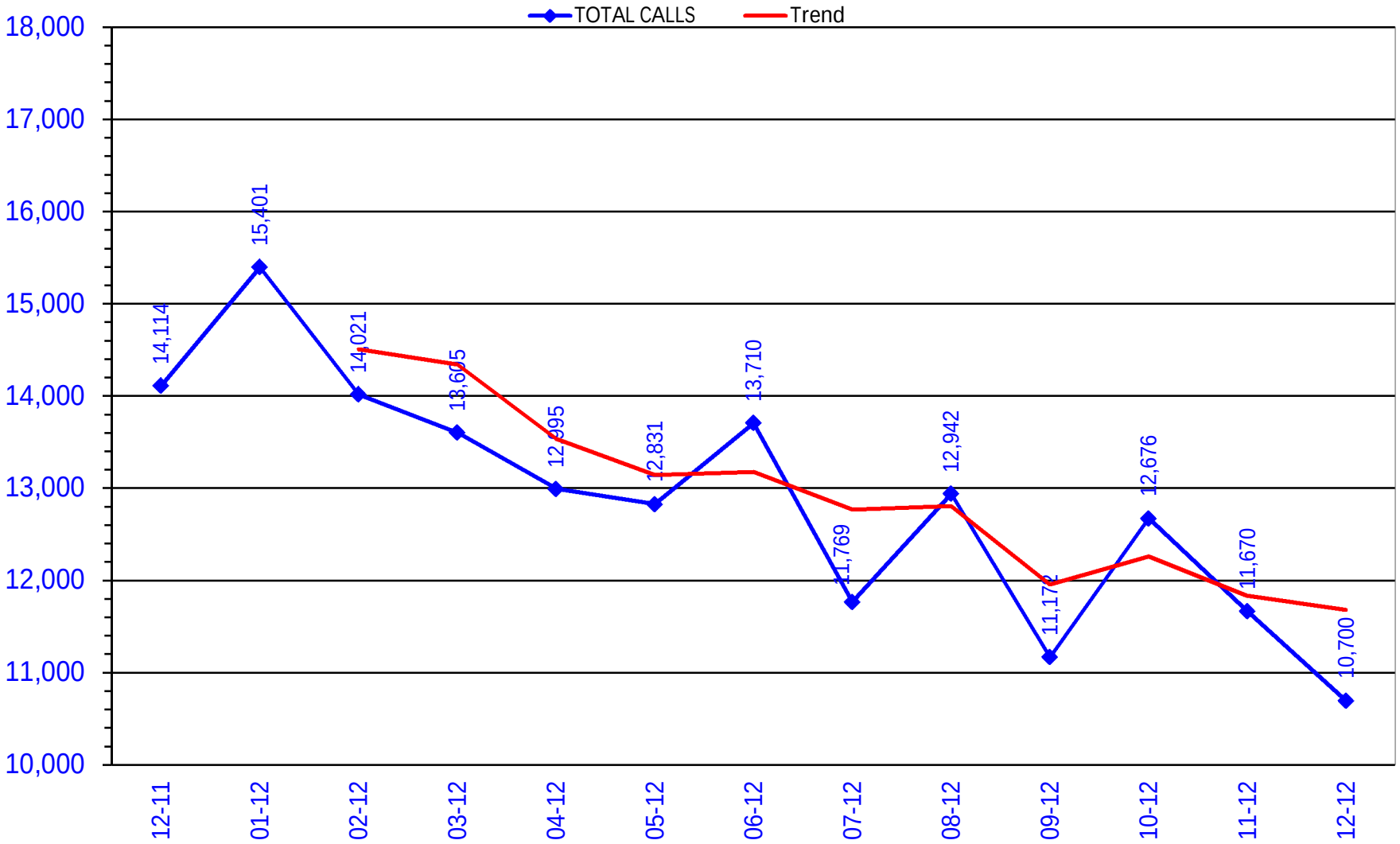
No Process: 205

Changes to existing PAs: 465

Partials: 859

* Includes any therapeutic category with less than 10 prior authorizations for the month.

CALL VOLUME MONTHLY REPORT:
December 2011-December 2012



Retrospective Drug Evaluation: Focusing on Safety

1. Citalopram Safety Intervention Results

2 Combigan® (Brimonidine/Timolol) Utilization in Infant Members

3. Overview of FDA Safety Alerts

1. Citalopram Safety Intervention Results

Oklahoma Health Care Authority
January 2013

Background

In August 2011, FDA issued a Drug Safety Communication (DSC) stating that citalopram should no longer be used at doses greater than **40mg/day** because it could cause potentially dangerous abnormalities in the electrical activity of the heart. Prolongation of the QT interval of the electrocardiogram (ECG) can lead to a risk of an abnormal heart rhythm called Torsade de Pointes, which can be fatal. Citalopram use at any dose is discouraged in patients with certain conditions because of the risk of QT prolongation.

A maximum dose of **20mg/day** is recommended for those with the following conditions:

- Hepatic impairment
- Older than 60 years of age
- CYP2C19 poor metabolizers
- Taking a CYP2C19 inhibitor

Intervention and Results

A quantity limit of one tablet daily was placed on all strengths of citalopram. An additional age restriction was placed on the 40 mg tablet to require a prior authorization for members age 60 years or greater. Information regarding these changes was included in the SoonerCare Provider Update that was sent out at the end of July. Letters were sent to prescribers of members on citalopram doses higher than the FDA recommendations.

Summary of Intervention Results

Members	Pre-Intervention CY 2011	Number of Letters Sent	Number of Responses	Post-Intervention August – October 2012
Total Members ≥60 yrs on Citalopram >20 mg	415	36	19	9
Total Members <60 yrs on Citalopram ≥40 mg	1,197	269	125	63
Totals	1,612	305	144	74

Response Summary

Letters Sent: 305
Response Forms Returned: 144

The response forms returned yielded the following results:

11 (7.6%)	Record Error— Not my patient.
18 (12.5%)	No longer my patient.
31 (21.5%)	Medication has been changed prior to date of review letter.
19 (13.2%)	I was unaware of this situation & will consider making appropriate changes in therapy.
56 (39%)	I am aware of this situation and will plan to continue monitoring therapy.
9 (6.2%)	Other

Recommendations

The College of Pharmacy recommends no further action at this time. The data indicates good prescriber response to the College of Pharmacy's initial intervention letter. Overall utilization of these medications has decreased in the SoonerCare population most likely due to the manufacturer warning, the College of Pharmacy's intervention letter, and the FDA safety alert.

2. Combigan® (Brimonidine/Timolol) Utilization in Infant Members

Oklahoma Health Care Authority
January 2013

Background[i]

On October 11, 2012, the FDA recommended that Combigan® (brimonidine tartrate/timolol maleate) 0.2%/0.5% ophthalmic solution not be prescribed to infants aged 2 years and younger[1]. This recommendation is based on post-marketing reports of adverse reactions. Symptoms of brimonidine overdose, including apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been seen in neonates, infants, and children being treated for congenital glaucoma, or through accidental ingestion. No deaths were reported.

The following new information is being added to the Combigan® drug label:
Combigan is contraindicated in neonates and infants (under the age of 2 years).

Combigan® Utilization in the SoonerCare Population

There has been no use of Combigan® (brimonidine/timolol ophthalmic solution) in SoonerCare children younger than 7 years of age.

Recommendations

The College of Pharmacy recommends the following:

1. Apply an age restriction on Combigan® (brimonidine tartrate/timolol maleate) 0.2%/0.5% ophthalmic solution) for members 2 years and younger. Clinical exception may apply for prescriptions written by ophthalmologists/optometrists.

3. Overview of FDA Safety Alerts

Oklahoma Health Care Authority
January 2013

Introduction[2,3]

The following are recent FDA safety alerts included for the DUR Board's consideration. SoonerCare specific data may be presented where applicable. The College of Pharmacy will make recommendations as well as take recommendations from the DUR Board.

Date	Drug	Issue
12/17/2012	**Xyrem® (sodium oxybate)**	**Increased risk of impaired consciousness and respiratory depression**
Issue Details: The FDA received reports of patients who died while taking Xyrem® along with alcohol or other CNS depressants **FDA Recommendations:** Though the causes of the deaths were inconclusive, the FDA recommends that the label warning should be strengthened regarding these risks.		

Date	Drug	Issue
11/2/2012	**Victrelis® (boceprevir)**	**Hypersensitivity reactions**
Issue Details: Serious acute hypersensitivity reactions (urticaria, angioedema) have been reported when Victrelis® was used in combination with peginterferon alfa and ribavirin. **FDA Recommendations:** In the event of an acute hypersensitivity reaction, combination therapy with peginterferon alfa and ribavirin should be discontinued. Label changes include serious acute hypersensitivity reactions listed in contraindications		

Date	Drug	Issue
10/31/2012	**HMGCoA reductase inhibitor (statin) drugs**	**Risk of immune-mediated necrotizing myopathy (IMNM)**
Issue Details: Rare incidents of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, have been reported with statin use. Symptoms include proximal muscle weakness and elevated serum creatine kinase that persist despite discontinuation of statin. Immunosuppressive agents are effective treatment. **FDA Recommendations:** Label change to include warning about this rare adverse effect. **Follow-up:** Review of 19 members in the SoonerCare population with hospital claims with ICD-9 CM code 359.81 in 2012 did not reveal concomitant use of statin. However, nine of the members are dual eligible so pharmacy claims data was not available for evaluation.		

Date	Drug	Issue
10/26/2012	**Anafranil®(clomipramine) Pamelor® (nortriptyline HCL), Tofranil-PM® (imipramine pamoate), Surmontil® (trimipramine), Norpramin® (desipramine)**	**Risk of serotonin syndrome**
Issue Details: Drugs that impair serotonin metabolism, including MAOIs, Zyvox® (linezolid), and intravenous methylene blue, have been reported to cause potentially life-threatening serotonin syndrome. **FDA Recommendations:** Initiating any of these tricyclic antidepressants in patients currently taking MAOIs, Zyvox® (linezolid), or intravenous methylene blue is contraindicated.		

Date	Drug	Issue
10/9/2012	**Prilosec® (omeprazole), Nexium® (esomeprazole), Vimovo® (naproxen/esomeprazole)**	**Drug interaction**
Issue Details: The active metabolite of the prodrug, clopidogrel, is responsible for all inhibition of platelet aggregation. The listed PPIs inhibit CYP2C19 which is responsible for metabolism of clopidogrel to its active metabolite. **FDA Recommendations:** Concomitant use of clopidogrel with omeprazole, esomeprazole, or naproxen/esomeprazole should be avoided.		

	Drug	Issue
9/28/2012	**Proton pump inhibitors (PPIs)**	**Clostridium difficile associated diarrhea**
Issue Details: The FDA has received observational reports of possible increased risk of Clostridium difficile associated diarrhea with use of proton pump inhibitors, especially in hospitalized patients. **FDA Recommendations:** Health care professionals should prescribe the lowest dose for the shortest duration for the condition being treated.		

References:

[i] http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm327514.htm
[2] http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm_326133.htm
[3] http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm330881.htm

Appendix C

Vote to Prior Authorize Linzess™ (Linaclotide) and Update Amitiza® (Lubiprostone) Criteria

Oklahoma Health Care Authority
January 2013

Recommendations

The College of Pharmacy recommends the prior authorization of Linzess™ (linaclotide) with the following changes to the current criteria for Amitiza® (lubiprostone):

Amitiza® and Linzess™ Prior Authorization Criteria:

1. Members 18 years of age or older with an FDA approved diagnosis, and
    a. Documentation that constipation-causing therapies for other disease states have been discontinued (excluding opioid pain medications for cancer patients).
    b. Documented and updated Colon Screening for members >50 years of age.[1]
2. Documented trials of at least three different types of products that failed to relieve constipation. Trials must be within the past 90 days. Products may be OTC or prescription.
3. Approval will initially be for 12 weeks of therapy. Further approval may be granted if prescriber documents member is responding well to treatment.
4. Quantity limits apply based on maximum recommended daily dose.

[1] Centers for Disease Control and Prevention: Colorectal Cancer Screening Guidelines. Available online at: http://www.cdc.gov/cancer/colorectal/basic_info/screening/guidelines.htm. Page last updated: January 2011

Appendix D

60 Day Notice to Prior Authorize
Chronic Obstructive Pulmonary Disease Medications

Oklahoma HealthCare Authority
January 2013

This category was introduced for possible inclusion in the Product Based Prior Authorization program in December 2012. See the December 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.

Utilization among SoonerCare Members with COPD Diagnosis

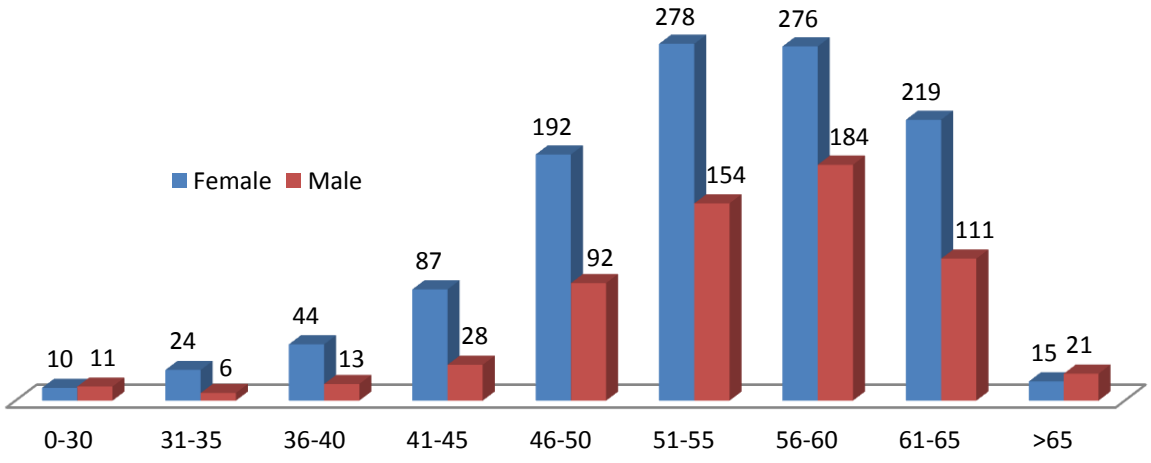
During fiscal year 2012, there were a total of 1,765 members utilizing long acting bronchodilator medications. Within this population there were 309 waiver members and 104 nursing home members.

Utilization Details

Brand Name	Claims	Members	Cost	Unit/Day	Claims/Members	Cost/Day	% Cost
Spiriva®	7,622	1,690	$1,880,215.04	1.00	4.51	8.17	96.25%
Serevent®	164	61	$29,359.00	0.20	2.69	5.93	1.50%
Foradil®	129	30	$21,768.82	1.98	4.30	5.58	1.11%
Perforomist®	18	10	$7,083.36	3.94	1.80	13.49	0.36%
Brovana®	43	14	$15,097.97	3.14	3.07	10.82	0.77%
Total	7,976	1,765*	$1,953,524.19	2.05	3.27	8.80	100.00%

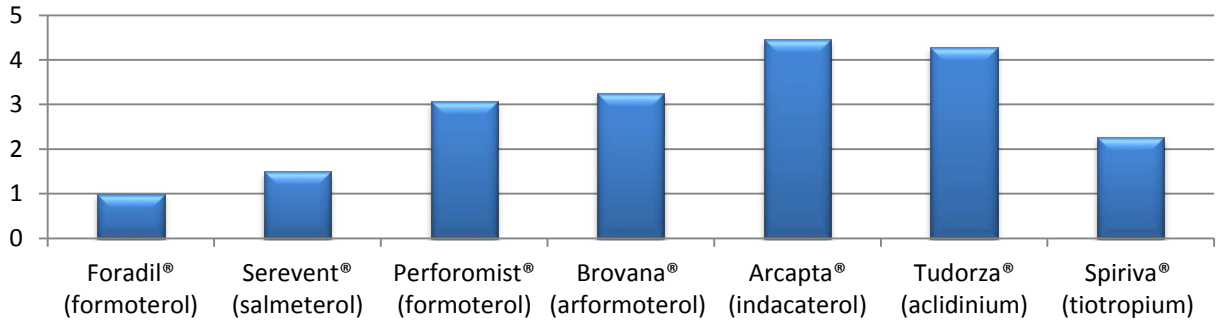
*Total number of unduplicated members.

Member Demographics FY 2012



Cost Ratio Comparison of LAMAs and LABAs

The chart below shows a comparison of medication costs based on cost per device which is designed to last one month. The costs of the products are compared as a ratio to the medication with the lowest monthly cost.



Economic Impact

Potential Secondary Costs

Overall efficacy is considered to be similar across these classes but drug selection requires individual patient history which includes, but is not limited to: lung function tests, disease severity, current symptoms, and risk of exacerbation.

Potential Administrative Costs

Based on potential use of 25% of the final Tier 2 products, it is estimated that approximately 1,800 petitions annually might be required if the step therapy was not initially followed by all members. The proposed Tier changes would affect approximately 1.0% of the current population for this PBPA category.

Previously, it has been theorized that total cost per petition to the *healthcare system* (includes cost to physicians, pharmacists, and program) is between $7.63 and $14.82. Total cost for initial prior authorization of this category to the *healthcare system* is estimated to be between $13,734 and $26,676 annually. Anticipated actual administrative cost to the program is projected to be less than $10,000.

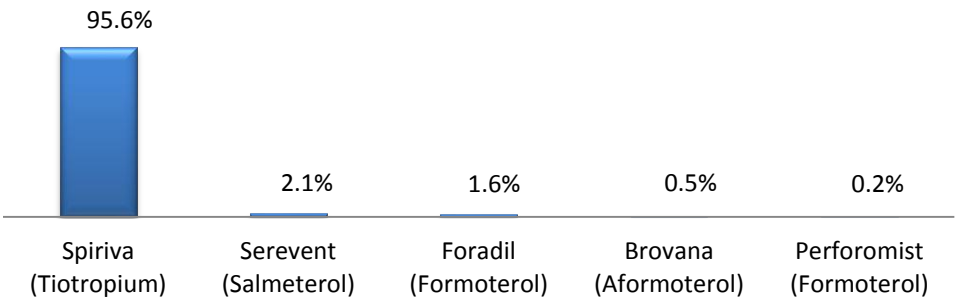
Potential Program Savings

Potential net ingredient savings to the program after rebates based on the recommended Tiers and a potential limited use of new Tier 2 products to 25% of current market share is estimated to be between $250,000 and $500,000 for COPD members annually. Potential savings might also be gained as new products come to market.

Market Analysis

Currently tiotropium has the majority of the market share by claims for this category followed by salmeterol.

Product	Market
Spiriva	95.6%
Serevent	2.1%
Foradil	1.6%
Brovana	0.5%
Perforomist	0.2%
Total	**100%**



The following new products are currently in development:

- **Aclidinium/Formoterol**
  LAMA and LABA combination in phase III trials. (Forrest Labs)
- **Umeclidinium**
  LAMA in phase III trials. (GlaxoSmithKline)
- **Umeclidinium/Vilanterol** (Relovair)
  LAMA and LABA combination in phase III trials.
- **Olodaterol**
  LABA in phase III trials. (Boehringer Ingelheim)
- **Olodaterol/Tiotropium**
  LABA and current LAMA combination in phase III trials.
- **Glycopyrrolate**
  LAMA in phase II trials. (Pearl Therapeutics)
- **Glycopyrrolate/Formoterol**
  LAMA and current LABA combination in phase II trials.

Recommendations

The College of Pharmacy recommends establishing a Product Based Prior Authorization category for long acting bronchodilator medications to ensure appropriate and cost-effective utilization in accordance with current treatment guidelines. The following Tier 1 drug list has been determined to be acceptable 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 Health Care Authority.

Tier 1	Tier 2
Long Acting $Beta_2$ Agonists*	
Serevent® (Salmeterol inhalation powder) Foradil® (formoterol aerosolized powder)	Perforomist® (formoterol nebulizer solution) Brovana® (arformoterol nebulizer solution) Arcapta® (indacaterol inhalation powder)
Long Acting Anticholinergics	
Spiriva® (tiotropium inhalation powder)	Tudorza® (aclidinium inhalation powder)

*Combination agents qualify as Tier 1 agents

Tier-2 Approval Criteria:

1. The member must be age 18 or older, and
2. Have a diagnosis of COPD, chronic bronchitis, or emphysema, and
3. A 4 week trial of at least one LABA and a four week trial of one LAMA within the past 90 days, or
4. A documented adverse effect, drug interaction, or contraindication to all available Tier-1 products.
5. A clinical exception will be made for members who are unable to effectively use hand-actuated devices, such as Spiriva Handihaler® or those who are stable on nebulized therapy.

Appendix E

Fiscal Year 2012 Annual Review of Antihyperlipidemics and 30 Day Notice to Prior Authorize Vascepa™ (Icosapent Ethyl) and Juxtapid™ (Lomitapide)

Oklahoma HealthCare Authority
January 2013

Current Prior Authorization Criteria

Statin Medications and Zetia® (ezetimibe) Prior Authorization Criteria:

For members new to statin therapy to qualify for a Tier 2 medication, there must be:

1. A trial, defined by at least 8 weeks of continuous therapy titrated to recommended dose, of Tier 1 simvastatin or pravastatin that did not yield adequate LDL reduction, but the minimum initiation dosing of the Tier 2 medication may only be at the moderate to high LDL lowering doses (i.e., doses equivalent to or 20 mg rosuvastatin or 40 mg atorvastatin).
2. Documented adverse effect or contraindication to two available lower tiered products.
3. Clinical exception for high risk members hospitalized for recent acute myocardial infarction or acute coronary syndrome for atorvastatin 40 mg or higher and rosuvastatin 20 mg or higher.

To qualify for a Tier 3 medication, there must be:

1. A trial, defined by at least 8 weeks of continuous therapy titrated to recommended dose, of a Tier 2 medication that did not yield adequate LDL reduction.
2. Documented adverse effect or contraindication to two Tier 2 products.
3. Clinical exceptions for Ezetimibe:
    a. Documented active liver disease.
    b. Documented unexplained, persistent elevations of serum transaminases.
    c. Documented statin related myopathy.

Tier-1	Tier-2	Tier-3
atorvastatin (**Lipitor®**)[+]	fluvastatin (**Lescol®, Lescol® XL**)	lovastatin (**Altoprev®**)
simvastatin (**Zocor®**)	pitavastatin (**Livalo®**)	simvastatin/ezetimibe (**Vytorin®**)
lovastatin (**Mevacor®**)	rosuvastatin (**Crestor®**)*	ezetimibe (**Zetia®**)
pravastatin (**Pravachol®**)		simvastatin/niacin (**Simcor®**)
		lovastatin/niacin (**Advicor®**)

*Crestor® 5 mg and Crestor® 10 mg require special reason for use.
[+]Lipitor® (atorvastatin) moved to Tier 1 in June 2012.

Lovaza® (omega-3-fatty acid) Prior Authorization Criteria:

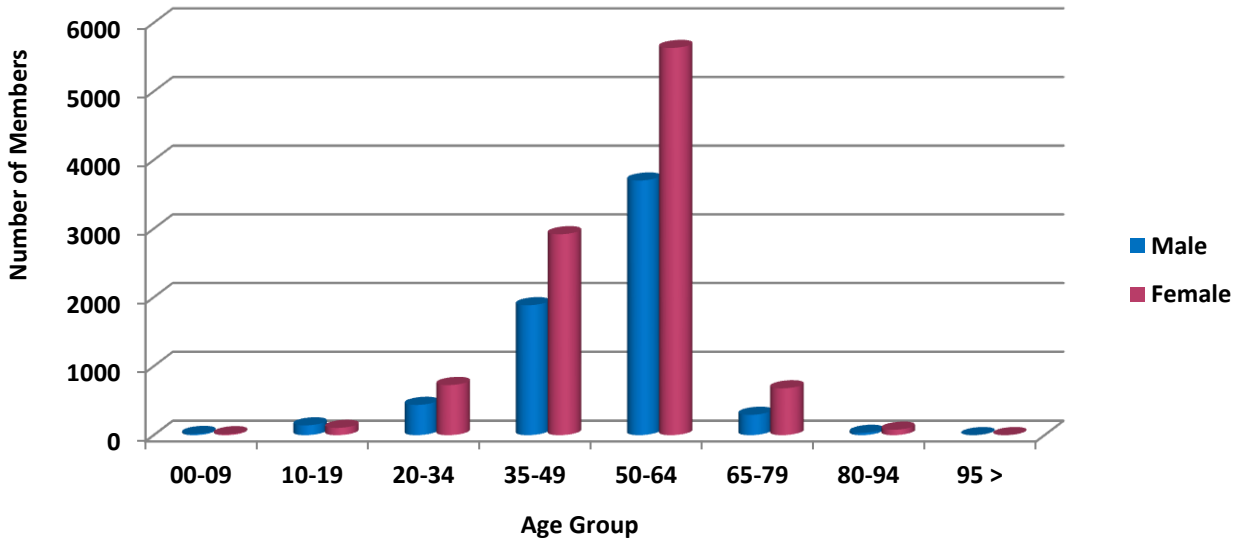
1. Laboratory documentation of severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL).
2. Previous failure with both nicotinic acid and fibric acid medications.

Utilization of Statin Medications, Zetia®, and Lovaza®

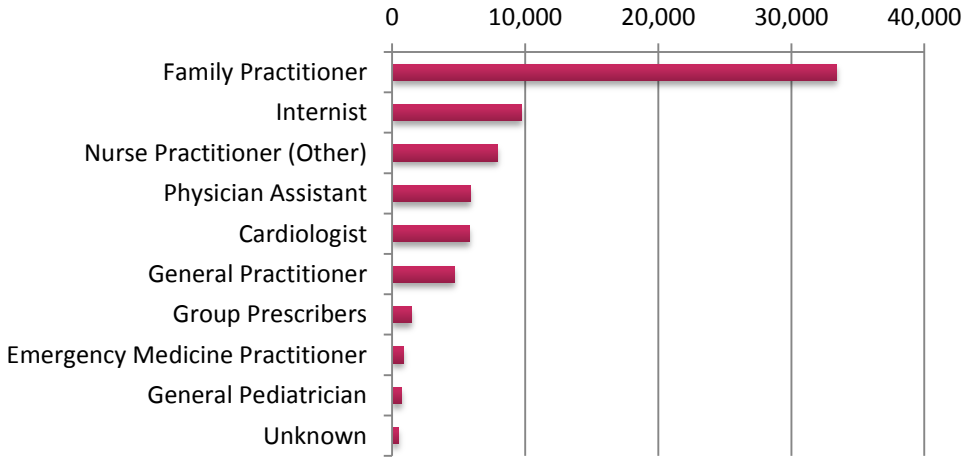
Comparison of Fiscal Year

Fiscal Year	Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2011	15,409	66,212	$2,562,133.11	$38.70	$0.93	2,897,910	2,742,423
2012	16,670	73,294	$2,665,723.45	$36.37	$0.87	3,185,629	3,066,774
% Change	**8.20%**	**10.70%**	**4.00%**	**-6.00%**	**-6.50%**	**9.90%**	**11.80%**
Change	**1,261**	**7,082**	**$103,590.34**	**($2.33)**	**($0.06)**	**287,719**	**324,351**

Demographics of Members Utilizing Statin Medications, Zetia®, and Lovaza®: FY 2012



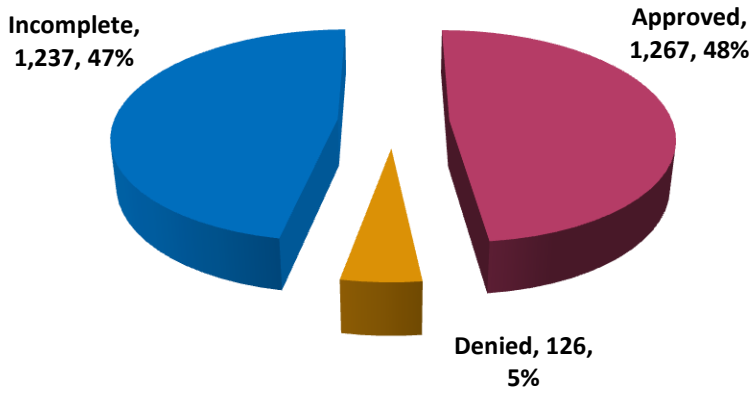
Prescribers of Statin Medications, Zetia®, and Lovaza® by Number of Claims: FY 2012



Prior Authorization of Statin Medications, Zetia®, and Lovaza®

There were a total of 2,630 petitions submitted for this PBPA category during fiscal year 2012. The following chart shows the status of the submitted petitions.

Status of Petitions for Statin Medications, Zetia®, and Lovaza®: FY 2012

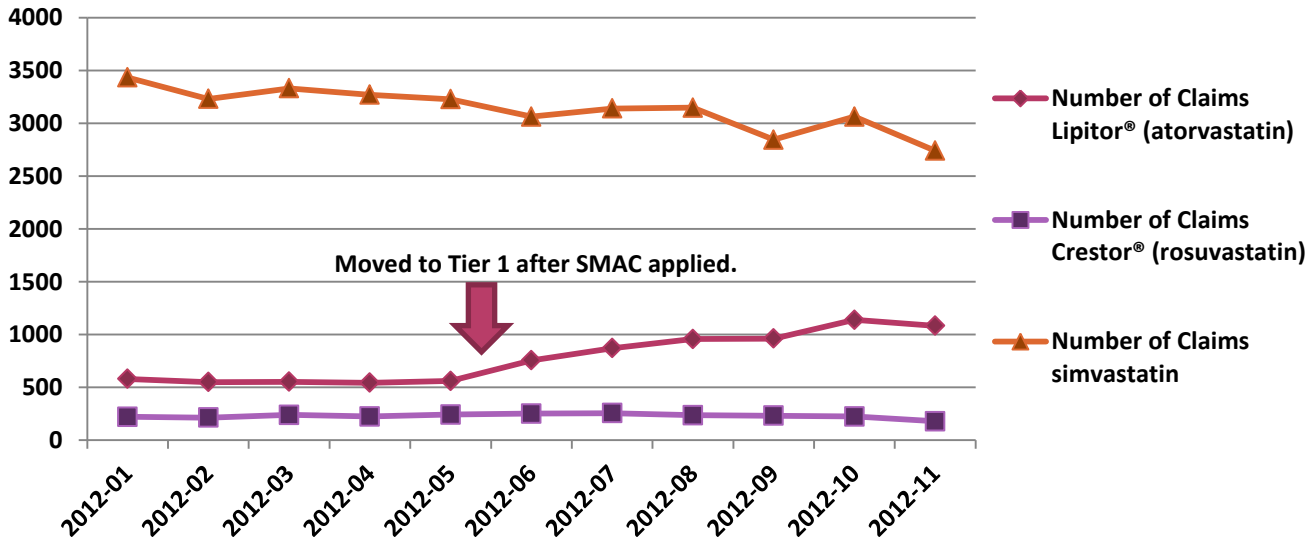


Market News and Update

Anticipated Patent Expirations :

- Lipitor®- Expired December 2011
- Zetia®- September 2013
- Vytorin®- September 2013
- Livalo®- May 2015
- Lovaza®- April 2017
- Crestor®- August 2020

Trend Utilization Report by Number of Claims



Vascepa™ (icosapent ethyl) Summary[1]

- Vascepa™ (icosapent ethyl) is an ethyl ester of eicosapentaenoic acid (EPA), more commonly known as an omega-3 fatty acid, which is indicated as an adjunct to diet to reduce triglyceride levels in adult patients with severe ($\geq$ 500 mg/dL) hypertriglyceridemia.
- Vascepa™ (icosapent ethyl) is available in 1 gram capsules. The daily dose is 4 grams per day taken as 2 capsules twice daily with food. Capsules should be swallowed whole. Patients should not break open, crush, dissolve, or chew Vascepa™ capsules.
- Vascepa™ (icosapent ethyl) is contraindicated in patients with known hypersensitivity to Vascepa™ or any of its components. In patients with hepatic impairment, monitor ALT and AST levels periodically during therapy. Vascepa™ should be used with caution in patients with a known hypersensitivity to fish and/or shellfish.
- Vascepa™ (icosapent ethyl) cost is currently unavailable but is anticipated to be commercially launched in the first quarter of 2013.

Juxtapid™ (lomitapide) Summary[2]

Indication and Dosing (2)

- Juxtapid™ (lomitapide) is a microsomal triglyceride transfer protein inhibitor indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-denisty lipoprotein cholesterol, total cholesterol, apolipoprotein B, and non-high density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia (HoFH).
- Juxtapid™ (lomitapide) is available in 5 mg, 10 mg, and 20 mg capsules. Initial treatment dose is 5 mg once daily and dose may be titrated based on acceptable safety and tolerability. After at least two weeks, dose may be increased to 10 mg daily. After a minimum of four-week intervals, the dose may be increased to 20 mg, 40 mg and up to the maximum recommended dose of 60 mg daily. Patients with end-stage renal disease on dialysis or with baseline mild hepatic impairment should not exceed 40 mg daily.

Efficacy

Juxtapid™ (lomitapide) was evaluated in a single study that evaluated safety and effectiveness of Juxtapid™ in a multinational, single-arm, open-label, 78 week trial involving 29 adults with HoFH. A diagnosis of HoFH was defined by the presence of at least one of the following criteria:

1. Documented functional mutation(s) in both LDL receptor alleles or alleles known to affect LDL receptor functionality, or
2. Skin fibroblast LDL receptor activity <20% normal, or
3. Untreated total cholesterol >500 mg/dL and total triglycerides <300 mg/dL, *and* both parents with documented untreated total cholesterol >250 mg/dL.

Among the 29 patients enrolled in the study, the mean age was 30.7 years (18-55 years), 16 (55%) were men, and 86% were Caucasian. Concomitant lipid-lowering treatments at baseline included one or more of the following:

- statins (93%)
- ezetimibe (76%)
- nicotinic acid (10%)
- bile acid sequestrant (3%)
- fibrate (3%)
- LDL apheresis (62%)

Efficacy was assessed at Week 26 and patients remained in the trial for 52 additional weeks to access long term safety after a total of 78 weeks. Out of 29 patients, twenty-three (79%) patients completed the efficacy endpoint and safety endpoint of the trial. The primary efficacy endpoint was percent change in LDL-C from baseline to Week 26. At Week 26, the mean percent change in LDL-C from baseline was 40%, based on the intent-to-treat population with last observation carried forward for patients who discontinued the study prematurely.

Safety

Juxtapid™ (lomitapide) is contraindicated with the following:

- pregnancy
- concomitant use with strong or moderate CYP3A4 inhibitors
- moderate or severe hepatic impairment
- active liver disease including unexplained persistent abnormal liver function tests

Gastrointestinal adverse reactions occur in 93% of patients and could affect absorption of concomitant oral medication. Females of reproductive potential should have a negative pregnancy test before starting Juxtapid™ and use contraception during treatment. Treatment with Juxtapid™ is only available through the Juxtapid™ Risk Evaluation and Mitigation Strategy (REMS) Program which requires prescribers to go through training, obtain certification, and attest safe patient use by completing a Prescription Authorization Form for each new prescription.

Cost

Juxtapid™ cost is currently unavailable. However, it is anticipated that therapy with Juxtapid™ will be approximately $200,000 - $300,000[3,4] per year.

Conclusion and Recommendations

The College of Pharmacy recommends the following changes:

1. **Prior Authorization of Vascepa™ (icosapent ethyl) with the following Criteria:**
    1. Laboratory documentation of severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL).
    2. Previous failure with both nicotinic acid and fibric acid medications.

2. **Prior Authorization of Juxtapid™ (lomitapide) with the following Criteria:**
    1. FDA approved diagnosis of homozygous familial hypercholesterolemia.
    2. Documented failure of high dose statin therapy (LDL reduction capability equivalent to atorvastatin 40mg or higher)
    3. Prescriber must be certified with the Juxtapid™ REMS program.

3. **Changes to the Statin Medications and Zetia® (ezetimibe) Prior Authorization Criteria and Tiers as follows**:

Tier-1	Tier-2	Special PA
atorvastatin (**Lipitor®**)	rosuvastatin (**Crestor®**)*	lovastatin (**Altoprev®**)
simvastatin (**Zocor®**)		simvastatin/ezetimibe (**Vytorin®**)
lovastatin (**Mevacor®**)		ezetimibe (**Zetia®**)
pravastatin (**Pravachol®**)		simvastatin/niacin (**Simcor®**)
		lovastatin/niacin (**Advicor®**)
		pitavastatin (**Livalo®**)
		fluvastatin (**Lescol®,Lescol® XL**)

*Crestor® 5 mg and Crestor® 10 mg require special reason for use.

Tier 2 Approval Criteria:

1. Trials with both simvastatin and atorvastatin, each consisting of at least 8 weeks of continuous therapy, titrated to recommended dose, that did not yield adequate LDL reduction. The minimum starting dose of the Tier 2 medication may only be at the moderate to high LDL lowering doses (20 mg or 40 mg rosuvastatin).
2. Documented adverse effect or contraindication to all available lower tiered products.
3. Clinical exception for high risk members hospitalized for recent acute myocardial infarction or acute coronary syndrome for rosuvastatin 40 mg.

To qualify for a Special PA medication, there must be:

1. A clinically significant reason why lower tiered medications with similar or higher LDL reduction cannot be used.
    a. Simcor® (simvastatin/niacin) and Advicor® (lovastatin/niacin) will also require a clinically significant reason why the member cannot use the individual products separately.
2. Clinical exceptions for Ezetimibe:
    a. Documented active liver disease.
    b. Documented unexplained, persistent elevations of serum transaminases.
    c. Documented statin related myopathy.

Comparison of LDL Reduction Capability

% LDL Reduction	*Lovastatin (Mevacor®)*	*Pravastatin (Pravachol®)*	*Simvastatin (Zocor®)*	*Atorvastatin (Lipitor®)*	*Rosuvastatin (Crestor®)*	*Pitavastatin (Livalo®)*	*Fluvastatin (Lescol®)*
25-32 %	20mg	20mg	10mg			1 mg	40mg
31-39 %	40mg	40mg	20mg	10mg		2 mg	80mg*
37-45 %		80mg	40mg	20mg	5mg	4 mg	
48-52 %			80mg	40mg	10mg		
55-60 %				80mg	20mg		
60-63 %					40mg		

*Lescol® 40 mg bid and Lescol® XL 80 mg both fall into 31-39% LDL Reduction category.

Utilization Details of Statin Medications, Zetia®, and Lovaza®: Fiscal Year 2012

MEDICATION	CLAIMS	MEMBERS	COST	UNITS/ DAY	CLAIMS/ MEMBER	COST/ DAY	% COST
ADVICOR TAB 1000-20	5	1	$1,315.84	2	5	$8.77	0.05%
ADVICOR TAB 1000-40	4	2	$622.96	1	2	$5.19	0.02%
ADVICOR TAB 500-20MG	23	2	$2,637.07	1	11.5	$3.82	0.10%
SUBTOTAL:	**32**	**5**	**$4,575.87**	**1.33**	**6.17**	**$5.93**	**0.17%**
ATORVASTATIN TAB 10MG	194	85	$13,960.57	1	2.28	$1.93	0.52%
ATORVASTATIN TAB 20MG	407	183	$46,444.97	1	2.22	$2.87	1.74%
ATORVASTATIN TAB 40MG	1,965	682	$289,566.08	1.01	2.88	$3.45	10.86%
ATORVASTATIN TAB 80MG	812	298	$140,570.88	0.99	2.72	$3.78	5.27%
SUBTOTAL:	**3,378**	**1,248**	**$490,542.50**	**1**	**2.53**	**$3.01**	**18.39%**
CRESTOR TAB 5MG	88	26	$16,311.59	0.99	3.38	$4.61	0.61%
CRESTOR TAB 10MG	491	128	$90,539.57	0.99	3.84	$4.72	3.40%
CRESTOR TAB 20MG	1,182	284	$217,537.29	0.97	4.16	$4.58	8.16%
CRESTOR TAB 40MG	777	189	$134,053.37	0.92	4.11	$4.37	5.03%
SUBTOTAL:	**2,538**	**627**	**$458,441.82**	**0.97**	**3.87**	**$4.57**	**17.20%**
LESCOL CAP 20MG	8	3	$2,513.35	1	2.67	$3.49	0.09%
LESCOL CAP 40MG	32	6	$4,191.66	1	5.33	$3.39	0.16%
LESCOL XL TAB 80MG	109	25	$19,300.67	1.01	4.36	$4.55	0.72%
SUBTOTAL:	**149**	**34**	**$26,005.68**	**1**	**4.12**	**$3.81**	**0.97%**
LIPITOR TAB 10MG	84	26	$10,904.59	1	3.23	$3.74	0.41%
LIPITOR TAB 20MG	325	105	$64,199.77	0.98	3.1	$5.23	2.41%
LIPITOR TAB 40MG	1,691	524	$385,690.70	1	3.23	$5.36	14.47%
LIPITOR TAB 80MG	724	232	$168,296.25	0.99	3.12	$5.28	6.31%
SUBTOTAL:	**2,824**	**887**	**$629,091.31**	**0.99**	**3.17**	**$4.90**	**23.60%**
LIVALO TAB 1MG	1	1	$113.46	1	1	$3.78	0.00%
LIVALO TAB 2MG	23	6	$2,732.14	1	3.83	$3.96	0.10%
LIVALO TAB 4MG	21	6	$3,113.46	1	3.5	$3.84	0.12%
SUBTOTAL:	**45**	**13**	**$5,959.06**	**1**	**2.78**	**$3.86**	**0.22%**
LOVASTATIN TAB 10MG	467	159	$3,932.27	1	2.94	$0.18	0.15%
LOVASTATIN TAB 20MG	2,652	733	$22,203.50	1.05	3.62	$0.20	0.83%
LOVASTATIN TAB 40MG	1,895	451	$20,380.81	1.13	4.2	$0.25	0.76%
SUBTOTAL:	**5,014**	**1,343**	**$46,516.58**	**1.06**	**3.59**	**$0.21**	**1.74%**

MEDICATION	CLAIMS	MEMBERS	COST	UNITS/ DAY	CLAIMS/ MEMBER	COST/ DAY	% COST
LOVAZA CAP 1GM	1,290	186	$201,161.71	3.49	6.94	$5.17	7.55%
SUBTOTAL:	**1,290**	**186**	**$201,161.71**	**3.49**	**6.94**	**$5.17**	**7.55%**
PRAVASTATIN TAB 10MG	1,085	340	$9,039.46	1	3.19	$0.21	0.34%
PRAVASTATIN TAB 20MG	5,977	1,913	$53,382.77	1.02	3.12	$0.21	2.00%
PRAVASTATIN TAB 40MG	9,522	2,818	$88,922.33	1.03	3.38	$0.21	3.34%
PRAVASTATIN TAB 80MG	1,635	492	$28,460.91	0.98	3.32	$0.38	1.07%
SUBTOTAL:	**18,219**	**5,563**	**$179,805.47**	**1.01**	**3.25**	**$0.25**	**6.75%**
SIMCOR TAB 500-20MG	11	2	$884.38	1	5.5	$2.68	0.03%
SIMCOR TAB 500-40MG	70	10	$5,414.14	1	7	$2.58	0.20%
SIMCOR TAB 1000-20	20	4	$2,856.21	1	5	$4.76	0.11%
SIMCOR TAB 1000-40	9	2	$1,239.21	1	4.5	$4.59	0.05%
SUBTOTAL:	**110**	**18**	**$10,393.94**	**1**	**5.5**	**$3.65**	**0.39%**
SIMVASTATIN TAB 5MG	113	34	$884.24	1	3.32	$0.21	0.03%
SIMVASTATIN TAB 10MG	3,692	926	$32,553.75	1	3.99	$0.23	1.22%
SIMVASTATIN TAB 20MG	17,205	4,263	$161,798.24	1	4.04	$0.23	6.07%
SIMVASTATIN TAB 40MG	14,645	3,759	$152,043.22	1	3.9	$0.24	5.70%
SIMVASTATIN TAB 80MG	2,835	818	$29,841.83	0.95	3.47	$0.24	1.12%
SUBTOTAL:	**38,490**	**9,800**	**$377,121.28**	**0.99**	**3.74**	**$0.23**	**14.14%**
VYTORIN TAB 10-10MG	31	6	$7,012.53	1	5.17	$4.46	0.26%
VYTORIN TAB 10-20MG	147	29	$31,403.30	1	5.07	$4.19	1.18%
VYTORIN TAB 10-40MG	384	69	$70,976.46	0.99	5.57	$4.33	2.66%
VYTORIN TAB 10-80MG	127	30	$27,794.84	1.02	4.23	$4.45	1.04%
SUBTOTAL:	**689**	**134**	**$137,187.13**	**1**	**5.01**	**$4.36**	**5.14%**
ZETIA TAB 10MG	516	114	$98,921.10	1	4.53	$4.32	3.71%
SUBTOTAL:	**516**	**114**	**$98,921.10**	**1**	**4.53**	**$4.32**	**3.71%**
TOTALS:	**73,294**	**16,670***	**$2,665,723.45**	**1.04**	**4.4**	**$0.87**	**100%**

***Total number of unduplicated members**

Product Information of Vascepa™ (icosapent ethyl)[5]

INDICATIONS: reduction of triglyceride levels in adult patients with severe hypertriglyceridemia (≥500 mg/dL).

DOSAGE FORMS: Vascepa™ is supplied as a 1 gram soft-gelatin capsule.

ADMINISTRATION:

- Use two capsules (1 gram) twice daily with food.
- Swallow the capsule whole. Do not break open, crush, dissolve, or chew.
- Assess lipid levels before initiating therapy.

CONTRAINDICATIONS:

- Known hypersensitivity (e.g., anaphylactic reaction) to Vascepa™ or any of its components.

SPECIAL POPULATIONS:

Pregnancy: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. It is unknown whether Vascepa™ can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Vascepa™ should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

Nursing Mothers: Studies with omega-3-acid ethyl esters have demonstrated excretion in human breast milk. The effect of this excretion is unknown; caution should be exercised when Vascepa™ is administered to a nursing mother. In lactating rats, given oral gavage 14C-ethyl EPA, drug levels were 6 to 14 times higher in milk than in plasma.

Pediatrics: Safety and effectiveness in pediatric patients have not been established.

Geriatrics: Of the total number of subjects in clinical studies of Vascepa™, 33% were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

WARNINGS AND PRECAUTIONS:

- **Monitoring: Laboratory Tests** - In patients with hepatic impairment, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored periodically during therapy with Vascepa™.
- **Fish Allergy:** Vascepa™ contains ethyl esters of the omega-3 fatty acid, eicosapentaenoic acid (EPA), obtained from the oil of fish. It is not known whether patients with allergies to fish and/or shellfish are at increased risk of an allergic reaction to Vascepa™. Vascepa™ should be used with caution in patients with known hypersensitivity to fish and/or shellfish.

ADVERSE REACTIONS:

- **Common adverse reactions:** Arthralgia
- **Other adverse reactions <1% in clinical trials:** Oropharyngeal pain

DRUG INTERACTIONS:

- **Anticoagulants:** Some published studies with omega-3 fatty acids have demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in those studies has

not exceeded normal limits and did not produce clinically significant bleeding episodes. Patients receiving treatment with Vascepa™ and other drugs affecting coagulation (e.g., anti-platelet agents) should be monitored periodically.

PATIENT COUNSELING INFORMATION:

- Vascepa™ should be used with caution in patients with known sensitivity or allergy to fish and/or shellfish.
- Instruct patients to take Vascepa™ as prescribed. If a dose is missed, patients should take it as soon as they remember. However if they miss one day of Vascepa™, they should not double the dose when they take it.
- Patients should be advised that use of lipid-regulating agents does not reduce the importance of appropriate nutritional intake and physical activity.
- Patients should take Vascepa™ capsules whole. Do not break, crush, dissolve, or chew Vascepa™ capsules before swallowing.
- Patient should not change their dose or stop taking Vascepa™ without talking to their doctor.
- Patients should be advised to notify their physicians if they are taking or plan to take any prescription or over-the-counter drugs.
- Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy.
- Patient should notify their physicians if they are breastfeeding or plan to breastfeed.

Product Information of Juxtapid™ (lomitapide)[6]

INDICATIONS: Juxtapid™ is a microsomal triglyceride transfer protein inhibitor indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

DOSAGE FORMS: Juxtapid™ is supplied as 5 mg, 10 mg, and 20 mg capsules.

ADMINISTRATION:

- Before treatment, measure ALT, AST, alkaline phosphatase, and total bilirubin; obtain a negative pregnancy test in females of reproductive potential; and initiate a low-fat diet supplying <20% of energy from fat.
- Initiate treatment at 5 mg once daily. Titrate dose based on acceptable safety/tolerability: increase to 10 mg daily after at least 2 weeks; and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, and up to the maximum recommended dose of 60 mg daily.
- Due to reduced absorption of fat-soluble vitamins/fatty acids: Take daily vitamin E, linoleic acid, alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) supplements.
- Take once daily, whole, with water and without food, at least 2 hours after evening meal.
- Patients with end-stage renal disease on dialysis or with baseline mild hepatic impairment should not exceed 40 mg daily.

CONTRAINDICATIONS:

- Pregnancy.
- Concomitant use with strong or moderate CYP3A4 inhibitors.
- Moderate or severe hepatic impairment or active liver disease including unexplained persistent abnormal liver function test.

SPECIAL POPULATIONS:

- Nursing Mothers: Discontinue drug or nursing.
- Pediatric Patients: Safety and effectiveness not established.

WARNINGS AND PRECAUTIONS:

- Embryo-Fetal Toxicity: Females of Reproductive Potential should have a negative pregnancy test before starting Juxtapid™ and use contraception during treatment.
- Gastrointestinal adverse reactions occur in 93% of patients and could affect absorption of concomitant oral medications.

ADVERSE REACTIONS:

- Common adverse reactions (occurring $\geq$28%):
    - Diarrhea
    - Nausea
    - Vomiting
    - Dyspepsia
    - Abdominal pain

DRUG INTERACTIONS:

- CYP3A4 inhibitors increase exposure to lomitapide. Strong and moderate CYP3A4 inhibitors are contraindicated with Juxtapid™. Patients must avoid grapefruit juice. Do not exceed 30 mg daily of Juxtapid™ when used concomitantly with weak CYP3A4 inhibitors, including atorvastatin and oral contraceptives.
- Warfarin: Lomitapide increases plasma concentrations of warfarin. Monitor international normalized ratio (INR) regularly, especially with Juxtapid™ dose adjustment.
- Simvastatin and lovastatin exposure increase with Juxtapid™. Limit dose when co-administered with Juxtapid™ due to myopathy risk.
- P-glycoprotein (P-gp) Substrates: consider dose reduction of P-gp substrate because of possible increased absorption with Juxtapid™.
- Bile Acid Sequestrants: separate Juxtapid™ dosing by at least 4 hours.

PATIENT COUNSELING INFORMATION:

- Patients should be informed that a registry for patients taking Juxtapid™ has been established in order to monitor and evaluate the long-term effects of Juxtapid™. Patients are encouraged to participate in the registry and should be informed that their participation is voluntary.
- Juxtapid™ can cause both elevations in transaminases and hepatic steatosis. Discuss with the patient the importance of monitoring of liver-related tests before taking Juxtapid™, prior to each dose escalation, and periodically thereafter.
- Patients should be advised of the potential for increased risk of liver injury if alcohol is consumed while taking Juxtapid™. It is recommended that patients taking Juxtapid™ limit consumption to not more than one alcoholic drink per day.

- Juxtapid™ is commonly associated with nausea, vomiting, and abdominal pain. Advise patients to promptly report these symptoms if they increase in severity, persist, or change in the character, as they might reflect liver injury. Patients should also report any other symptoms of possible liver injury, including fever, jaundice, lethargy, or flu-like symptoms.
- Juxtapid™ is only available through a restricted program called Juxtapid™ REMS PROGRAM and therefore, Juxtapid™ is only available from certified pharmacies that are enrolled in the program.
- Juxtapid™ is contraindicated in pregnancy.
- Advise females of reproductive potential that they should have a negative pregnancy test before starting Juxtapid™ and that they should use effective contraception while taking Juxtapid™. If oral contraceptives are initiated while taking Juxtapid™, the dose of Juxtapid™ may require adjustment. Hormone absorption from oral contraceptives may be incomplete if vomiting or diarrhea occurs while taking Juxtapid™, warranting the use of additional contraceptive methods.
- Nursing Mothers: A decision should be made whether to discontinue nursing or discontinue Juxtapid™.
- Discuss with the patient the importance of taking daily supplements that contain 400 international units vitamin E and at least 200 mg linoleic acid, 210 mg alpha-linolenic acid (ALA), 110 mg eicosapentaenoic acid (EPA), and 80 mg docosahexaenoic acid (DHA).
- Inform the patient that gastrointestinal adverse reactions are common with Juxtapid™. These include, but are not limited to, diarrhea, nausea/vomiting, abdominal pain/discomfort, flatulence, and constipation. Strict adherence to a low-fat diet (<20% of total calories from fat) may reduce these reactions.
- Tell the patient that taking Juxtapid™ with food may adversely impact gastrointestinal tolerability; therefore, they should take Juxtapid™ at least 2 hours after the evening meal, swallowing each capsule whole.
- Absorption of oral medications may be affected in patients who develop diarrhea or vomiting. For example, hormone absorption from oral contraceptives may be incomplete, warranting the use of additional contraceptive methods. Patients who develop these symptoms should seek advice from their healthcare provider.
- Tell the patient to omit grapefruit juice from his/her diet while on Juxtapid™.
- Because multiple drug-drug interactions have been described with Juxtapid™, advise the patient to tell their healthcare provider(s) about all medications, nutritional supplements, and vitamins that they are taking or may be taking while taking Juxtapid™.
- If a dose of Juxtapid™ is missed, the normal dose should be taken at the usual time the next day. If dosing is interrupted for more than a week, tell the patient to contact their healthcare provider before restarting treatment.

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[1] Vascepa™ Prescribing Information. Vascepa™ (soft-gelatin capsule) 1gram. Amarin Pharma Inc. Available online at: https://www.vascepa.com/full-prescribing-information.pdf. Last revised: September 2012; Last accessed 11/9/2012.
[2] "Highlights of Prescribing Information: JUXTA PID™." *JUXTAPID REMS Program*. N.p., n.d. Web. 27 Dec. 2012. <http://www.juxtapidremsprogram.com/_pdf/Prescribing_Information.pdf>.
[3] FDA Approves Aegerion's Cholesterol Drug Juxtapid™. Medical News Today. http://www.medicalnewstoday.com/articles/254468.php. December 2012.
[4] Cholesterol Drug Juxtap™ Costs $200K Plus, Has Serious Effects. EmaxHealth. http://www.emaxhealth.com/1275/cholesterol-drug-juxtapid-costs-200k-plus-has-serious-effects. December 2012.
[5] Vascepa™ Prescribing Information. Vascepa™ (soft-gelatin capsule) 1gram. Amarin Pharma Inc. Available online at: https://www.vascepa.com/full-prescribing-information.pdf. Last revised: September 2012; Last accessed 11/9/2012.
[6] "Highlights of Prescribing Information: JUXTA PID™." *JUXTAPID REMS Program*. N.p., n.d. Web. 27 Dec. 2012. <http://www.juxtapidremsprogram.com/_pdf/Prescribing_Information.pdf>.

Appendix F

Fiscal Year 2012 Annual Review of Osteoporosis Medications And 30 Day Notice to Prior Authorize Binosto™ (Alendronate)

Oklahoma HealthCare Authority
January 2013

Current Prior Authorization Criteria

Tier 1*	Tier 2	Tier 3
Alendronate (Fosamax®) Calcium + Vitamin D†	Alendronate + D (Fosamax®+D) Ibandronate (Boniva®) Risedronate (Actonel®)	Zoledronic acid (Reclast®) Teriparatide (Forteo®) Prolia ™ (Denosumab) Risedronate delayed release (Atelvia™)

Mandatory Generic Plan Applies.
***Calcitonin and raloxifene are not included as Tier 1 trials.**
†Must be used at recommended doses in conjunction with Tier 1 bisphosphonate for trial to be accepted unless member has a recent laboratory result showing adequate Vitamin D or member is unable to tolerate calcium. OTC Calcium and Vitamin D are only covered for members with osteoporosis.

1. **Treatment failure with all lower tiered products, or**
2. **Contraindication to all lower tiered products, or**
3. **Allergic reaction to all lowered tiered products, or**
4. **Specific indication not covered by a lower tiered product.**
5. **No concomitant use of bisphosphonate therapy will be approved. No additional bisphosphonate may be approved for 365 days following zoledronic acid infusion.**
6. **Clinical Exceptions:**
   a. **Risedronate** may be approved for members with high risk for gastric side effects.
   b. **Zoledronic acid** may be approved for members with a diagnosis of Paget's disease or for osteoporosis if secondary diagnosis meets criteria below:
      i. Severe esophageal disease (e.g., ulcerations, strictures)
      ii. Inability to take anything by mouth
      iii. Inability to sit or stand for prolonged periods
      iv. Inability to take an oral bisphosphonate for other special medical circumstances that justify the method of administration
   c. **Teriparatide** requires a BMD test (T-score at or below -2.5) within the last month, and a minimum 12 month trial with a bisphosphonate plus adequate calcium and vitamin D, and a 12 month trial of Prolia™ (Denosumab), unless contraindicated, intolerant, or allergic, that did not yield adequate results.
7. **Quantity Limits apply based on FDA maximum doses.**

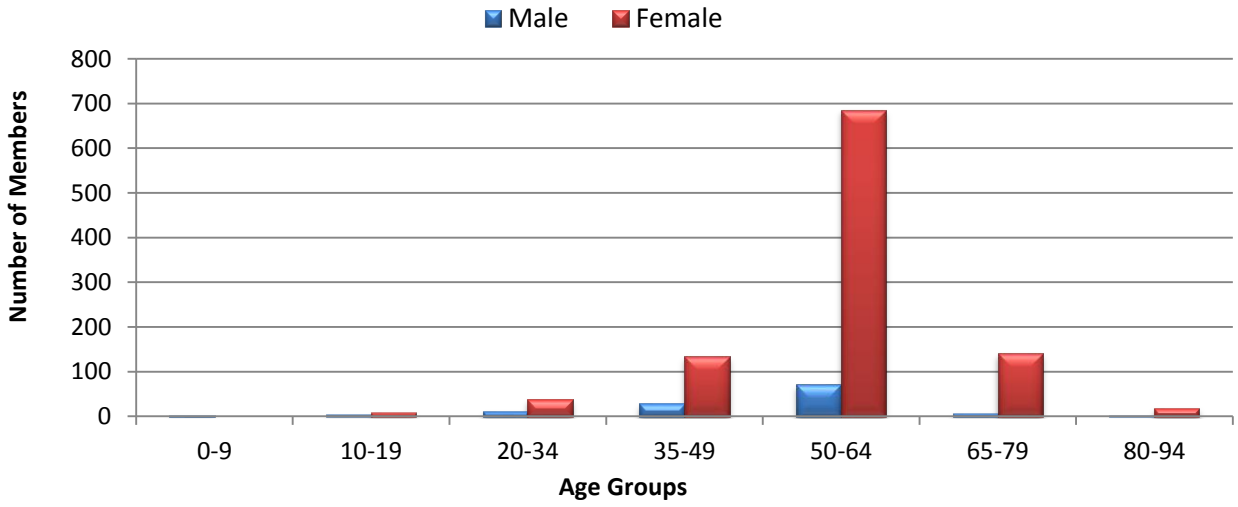
Utilization of Osteoporosis Medications

Comparison of Fiscal Years

Fiscal Year		Members*	Claims	Cost	Cost/Claim
2011	Pharmacy	1,322	6,662	$309,362.12	$46.44
	Medical	7	7	$5,662.46	$808.92
	Total	**1,329**	**6,669**	**$315,024.58**	**$47.23**
2012	Pharmacy	1,133	5,971	$274,449.70	$45.96
	Medical	12	12	$8,163.80	$680.32
	Total	**1,145**	**5,983**	**$282,613.50**	**$47.24**
% Change		**-13.8%**	**-10.3%**	**-10.2%**	**0.0%**
Change		**-184**	**-686**	**-$32,411.08**	**$0.01**

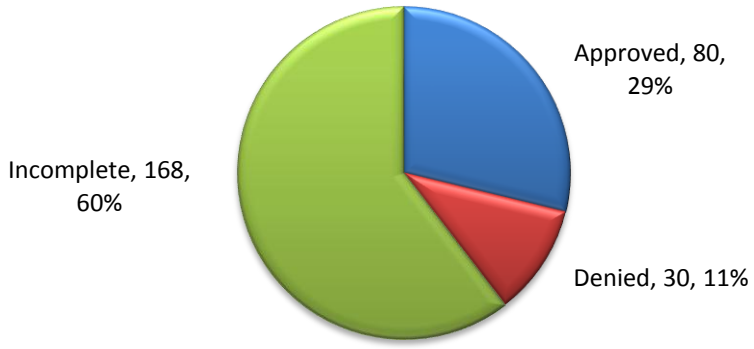
*May be duplications between Pharmacy and Medical claims.

Demographics of Members Utilizing Osteoporosis Medications: FY 2012

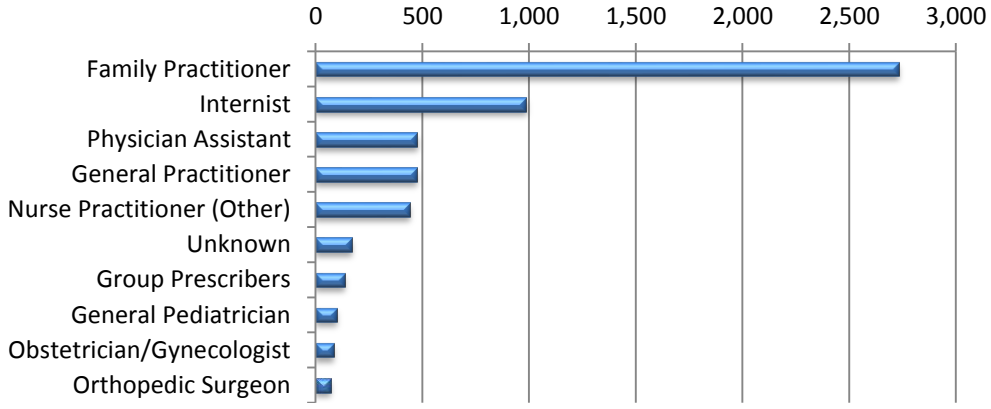


Status of Petitions for Osteoporosis Medications: FY 2012

There were a total of 278 petitions submitted for this category during Fiscal Year 2012. The following chart shows the status of the submitted petitions.



Top 10 Prescribers of Osteoporosis Medications by Number of Claims*: FY 2012



***Pharmacy claims only**

Market News and Update

Patent Expirations:

1. **Boniva®** – patent expired Spring of 2012 and the ibandronate sodium 150mg once monthly tablets currently have a state maximum allowable cost of $113 per tablet.
2. **Actonel®** – patent is anticipated to expire late 2013 or early 2014.
3. **Fosamax +D** – patent is anticipated to expire 2013.

On June 27, 2012, the FDA issued a consumer update regarding the length of bisphosphonate therapy.[1] The update summarizes the review of clinical studies by the FDA which shows that some patients may be able to stop using bisphosphonates after three to five years and still continue to benefit from their use. The studies suggest that patients at low risk of fracture (i.e. younger patients without a fracture history and with a bone mineral density approaching normal) may be good candidates for discontinuation of bisphosphonate therapy after three to five years. Patients at increased risk for fractures (i.e. older patients with a history of fracture and a bone mineral density remaining in the osteoporotic range) may benefit further from continued bisphosphonate therapy. More research is needed on patients' risk of fracture after they stop taking bisphosphonates, and whether taking them again at a later date could prove beneficial.

In September of 2012, Binosto™ (alendronate effervescent tablets) entered the market[2]. It is marketed by Mission Pharmacal. It is an effervescent tablet formulation of alendronate 70mg indicated to be dosed once weekly. The directions are to dissolve the tablet in half a glass of room temperature water, wait at least 5 minutes after the effervescence stops, stir the solution for approximately 10 seconds, and consume contents. Similar to other bisphosphonates, it must be taken 30 minutes before the first food, beverage, or medication of the day and the patient should not lie down for at least 30 minutes after taking Binosto™ and until after the first food of the day. Contraindications, warnings, and adverse events are similar to alendronate oral tablets.

Recommendations

The College of Pharmacy recommends the following :

- Establishment of a Tier for medications with special criteria.
- Placement of Binosto™ into the Special Criteria Tier.
- Placement of Boniva® IV and Actonel® 30mg tablets into the Special Criteria Tier.
- Changes to the Osteoporosis PBPA Category criteria:

Tier 1*	Tier 2	Special Criteria Apply
Alendronate (Fosamax®) Calcium + Vitamin D†	Alendronate + D (Fosamax®+D) Ibandronate (Boniva®) Risedronate (Actonel®)	Teriparatide (Forteo®) Denosumab (Prolia™) Zoledronic Acid (Reclast®) **Ibandronate (Boniva® IV)** Risedronate ER (Atelvia™) **Alendronate (Binosto™)** **Risedronate 30mg Tabs (Actonel®)**

Mandatory Generic Plan Applies.
***Calcitonin and raloxifene are not included as Tier 1 trials.**
†Must be used at recommended doses in conjunction with Tier 1 bisphosphonate for trial to be accepted unless member has a recent laboratory result showing adequate Vitamin D or member is unable to tolerate calcium. OTC Calcium and Vitamin D are only covered for members with osteoporosis.

Tier 2 Approval Criteria:

1. A trial of at least one tier-1 medication, compliantly used for at least 6 months concomitantly with calcium + vitamin D, that failed to prevent fracture, or improve BMD scores, or
2. Hypersensitivity to or intolerable adverse effects with all Tier 1 products.

Special Prior Authorization Criteria

1. **Teriparatide (Forteo)** requires
    a. A Bone Mineral Density test (T-score at or below -2.5) within the last month, and
    b. A minimum 12 month trial with a bisphosphonate plus adequate calcium and vitamin D, and
    c. A 12 month trial of Prolia™ (Denosumab), unless contraindicated, intolerant, or allergic, that did not yield adequate results.
    d. Approval will be for a maximum of 2 years of therapy.
2. **Prolia™, Reclast®, Boniva® IV requires:**
    a. A minimum 12 month trial with a Tier 1 and/or Tier 2 bisphosphonate plus adequate calcium and vitamin D, or
    b. Contraindication to or intolerable adverse effects with Tier 1 and Tier 2 products.
    c. Clinical exceptions may apply for members with
        i. Severe esophageal disease (e.g., ulcerations, strictures)
        ii. Inability to take anything by mouth
        iii. Inability to sit or stand for prolonged periods

iv. Inability to take bisphosphonates orally for other special medical circumstances that justify the method of administration

3. Atelvia™, Binosto™, and Actonel® 30mg Tabs
    a. Patient specific, clinically significant reason why member cannot use all other available Tier 1 and Tier 2 products.

Quantity Limits apply for all products based on FDA recommended maximum doses. No concomitant therapies will be approved.

Utilization Details: FY 2012 Pharmacy Data

CHEMICAL NAME	BRAND NAME	CLAIMS	MEMBERS	COST	CLAIMS/ MEMBER	COST/ DAY	% COST
Alendronate	ALENDRONATE TAB 5MG	68	9	$708.32	7.56	$0.35	0.26%
Alendronate	ALENDRONATE TAB 10MG	121	23	$1,363.85	5.26	$0.36	0.50%
Alendronate	ALENDRONATE TAB 35MG	462	106	$2,923.53	4.36	$0.22	1.07%
Alendronate	ALENDRONATE TAB 40MG	3	2	$240.76	1.5	$2.68	0.09%
Alendronate	ALENDRONATE TAB 70MG	4,382	854	$32,467.99	5.13	$0.26	11.83%
Alendronate – Cholecalciferol	FOSAMAX + D TAB 70-5600	1	1	$96.62	1	$3.45	0.04%
	Subtotals	**5,037**		**$37,801.07**		**$0.26**	**13.79%**
Ibandronate	BONIVA TAB 150MG	389	93	$79,423.03	4.18	$4.33	28.94%
Ibandronate	IBANDRONATE TAB 150MG	85	58	$17,088.23	1.47	$3.81	6.23%
Ibandronate	BONIVA INJ 3MG/3ML	2	1	$920.47	2	$5.48	0.34%
	Subtotals	**476**		**$97,431.73**		**$4.24**	**35.51%**
Risedronate	ACTONEL TAB 5MG	34	3	$2,938.32	11.33	$2.94	1.07%
Risedronate	ACTONEL TAB 30MG	8	2	$5,003.07	4	$10.97	1.82%
Risedronate	ACTONEL TAB 35MG	314	31	$36,955.96	10.13	$4.12	13.47%
Risedronate	ACTONEL TAB 150MG	18	3	$2,198.77	6	$4.07	0.80%
	Subtotals	**374**		**$47,096.12**		**$4.30**	**17.16%**
Zoledronic Acid	RECLAST INJ 5/100ML	6	6	$6,697.28	1	$3.06	2.44%
Teriparatide	FORTEO SOL 600/2.4	70	14	$78,452.74	5	$38.92	28.59%
Denosumab	PROLIA INJ SOL 60MG/ML	8	8	$6,970.76	1	$4.95	2.54%
	Totals	**5,971**	**1,133**	**$274,449.70**	**5.27**	**$1.50**	**100%**

PRODUCT DETAILS OF BINOSTO™ (ALENDRONATE SODIUM)

INDICATIONS: Binosto™ is a bisphosphonate indicated for:

- Treatment of osteoporosis in postmenopausal women.
- Treatment to increase bone mass in men with osteoporosis.

DOSAGE FORMS: 70mg effervescent tablets.

ADMINISTRATION:

- 70 mg Binosto™ effervescent tablet once weekly.
- Dissolve one tablet of Binosto™ in approximately half a glass of plain room temperature water (4 oz). Wait at least 5 minutes after the effervescence stops, stir the solution for approximately 10 seconds and consume contents.
- Must be taken 30 minutes before the first food, beverage, or medication of the day.
- Do not lie down for at least 30 minutes after taking Binosto™ and until after the first food of the day.

CONTRAINDICATIONS:

- Abnormalities of the esophagus which delay emptying such as stricture or achalasia
- Inability to stand/sit upright for at least 30 minutes
- Increased risk of aspiration
- Hypocalcemia
- Hypersensitivity to any component of this product

SPECIAL POPULATIONS:

- Binosto™ is not indicated for use in pediatric patients.
- Binosto™ is not recommended in patients with renal impairment (CrCl <35 mL/min).

WARNINGS AND PRECAUTIONS:

- Severe irritation of upper gastrointestinal mucosa can occur - follow dosing instructions.
- Use caution in patients with active upper GI disease. Discontinue if new or worsening symptoms occur.
- Hypocalcemia can worsen and must be corrected prior to use.
- Severe bone, joint, muscle pain may occur. Discontinue use if severe symptoms develop
- Osteonecrosis of the jaw has been reported.
- Atypical femur fractures have been reported. Evaluate new thigh or groin pain to rule out an incomplete femoral fracture.
- Each tablet contains 650mg sodium, equivalent to 1,650mg NaCl - Use caution in patients on sodium restriction.

ADVERSE REACTIONS: common adverse reactions (incidence ≥ 3%)

- abdominal pain
- acid regurgitation
- constipation
- diarrhea
- dyspepsia
- musculoskeletal pain
- nausea

DRUG INTERACTIONS:

- Calcium supplements, antacids or oral medications containing multivalent cations interfere with absorption of alendronate.
- Aspirin and non-steroidal anti-inflammatory drug use may worsen GI irritation; caution should be used.

PATIENT COUNSELING INFORMATION:

- Patients should be instructed to take supplemental calcium and vitamin D, if daily dietary intake is inadequate. Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as cigarette smoking and/or excessive alcohol consumption, if these factors exist.
- Patients should be instructed that it is necessary to follow all dosing instructions. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking Binosto™ and consult their physician.
- Patients should be instructed that if they miss a dose of once weekly Binosto™, they should take one dose on the morning after they remember. They should not take 2 doses on the same day but should return to taking one dose once a week, as originally scheduled on their chosen day.
- Patients who are prescribed sodium restricted diets should be informed that Binosto™ contains 650mg of sodium which is equivalent to approximately 1,650mg NaCl per tablet.

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[1] **How Long Should You Take Osteoporosis Drugs? FDA Consumer Updates. Accessed online at:** http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm309688.htm. **June 27, 2012. Last accessed 12/18/2012.**

[2] **Binosto™ Prescribing Information. Mission Pharmacal, Inc. Available online at:** http://binosto.com/sites/binosto.com/themes/danlandBinosto/images/binostoPI.pdf. **Last revised: March 2012; Last accessed 12/18/2012.**

Appendix G

30 Day Notice to Prior Authorize Xeljanz® (Tofacitinib)[1]

Oklahoma Health Care Authority
January 2013

Manufacturer	Pfizer, Inc.
Classification	Janus Kinase Inhibitor
Status	Prescription Only

Summary

Xeljanz® (tofacitinib) is a Janus kinase inhibitor indicated for treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other non-biologic disease modifying anti-rheumatic drugs. Xeljanz® should not be used in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine. The recommended dose is 5mg orally twice daily. Xeljanz® is considered to be a small molecular entity and not biologic in nature.

Mechanism of Action

Janus kinase (JAK) inhibitors are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Xeljanz® modulates the signaling pathway, preventing the phosphorylation and activation of STAT. Xeljanz® inhibits the *in vitro* activities of JAK1/JAK2, JAK1/JAK3, and JAK2/JAK2 combinations. However, the relevance of specific JAK combinations to therapeutic effectiveness is not known. The following are also known activities of Xeljanz®:

1. Dose-dependent reductions of circulating CD16/56+ natural killer cells, with estimated maximum reductions occurring at approximately 8-10 weeks after initiation of therapy.
2. Dose-dependent increases in B cell counts.
3. Changes in circulating T-lymphocyte counts and T-lymphocyte subsets (CD3+, CD4+ and CD8+) were small and inconsistent. The clinical significance of these changes is unknown.
4. Total serum IgG, IgM, and IgA levels after 6-month dosing in patients with rheumatoid arthritis were lower than placebo; however, changes were small and not dose-dependent.
5. Rapid decreases in serum C-reactive protein (CRP) were observed and maintained throughout dosing.

Efficacy

Study I

- 6-month monotherapy trial of 610 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a DMARD (nonbiologic or biologic).
- Xeljanz® 5mg or 10mg twice daily vs. placebo.
- At the Month 3 visit, all patients randomized to placebo treatment were advanced in a blinded fashion to a second predetermined treatment of Xeljanz® 5mg or 10mg twice daily.
- The primary endpoints at Month 3 were the proportion of patients who achieved an American College of Rheumatology 20% improvement criteria (ACR20) response, changes in Health Assessment Questionnaire – Disability Index (HAQ-DI), and rates of Disease Activity Score DAS28-4(ESR) less than 2.6.

Study II

- 12-month consisting of 792 patients with moderate to severe active rheumatoid arthritis with inadequate response to a non-biologic DMARD
- Xeljanz® 5mg or 10mg twice daily or placebo added to background DMARD treatment (excluding potent immunosuppressive treatments such as azathioprine or cyclosporine).
- At the Month 3 visit, non-responding patients were advanced in a blinded fashion to a second predetermined treatment of Xeljanz® 5mg or 10mg twice daily.
- At the end of Month 6, all placebo patients were advanced to their second predetermined treatment in a blinded fashion.
- The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, changes in HAQ-DI at Month 3, and rates of DAS28-4(ESR) less than 2.6 at Month 6.

Study III

- 12-month trial consisting of 717 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to methotrexate (MTX).
- Xeljanz® 5mg or 10mg twice daily, adalimumab 40 mg subcutaneously every other week, or placebo added to background MTX.
- Placebo patients were advanced as in Study II. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

Study IV

- 2-year trial with a planned analysis at 1 year in which 797 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to MTX
- Xeljanz® 5mg or 10mg twice daily vs. placebo added to background MTX.
- Placebo patients were advanced as in Study II.
- The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heijde-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

Study V

- 6-month trial consisting of 399 patients with moderate to severe active rheumatoid arthritis with inadequate response to at least one approved TNF-inhibiting biologic agent.

- Xeljanz® 5mg or 10mg twice daily or placebo added to background MTX.
- At the Month 3 visit, all patients randomized to placebo treatment were advanced in a blinded fashion to a second predetermined treatment of Xeljanz® 5mg or 10mg twice daily.
- The primary endpoints at Month 3 were the proportion of patients who achieved an ACR20 response, HAQ-DI, and DAS28-4(ESR) less than 2.6.

Percent Responders from Trials I, IV, and V

	Study I			**Study IV**			**Study V**		
	Monotherapy in Nonbiologic or Biologic DMARD Inadequate Responders[c]			Methotrexate (MTX) Inadequate Responders[d]			TNF Inhibitor Inadequate Responders[e]		
	PBO	Xeljanz® 5 BID	Xeljanz® 10mg BID	PBO + MTX	Xeljanz® 5mg BID + MTX	Xeljanz® 10mg BID + MTX	PBO + MTX	Xeljanz® 5mg BID + MTX	Xeljanz® 10mg BID + MTX
N[a]	122	243	245	160	321	316	132	133	134
ACR20									
Month 3	26%	59%	65%	27%	55%	67%	24%	41%	48%
Month 6	NA[b]	69%	70%	25%	50%	62%	NA	51%	54%
ACR50									
Month 3	12%	31%	36%	8%	29%	37%	8%	26%	28%
Month 6	NA	42%	46%	9%	32%	44%	NA	37%	30%
ACR70									
Month 3	6%	15%	20%	3%	11%	17%	2%	14%	10%
Month 6	NA	22%	29%	1%	14%	23%	NA	16%	16%

Adapted from Table 5 of the Xeljanz Product Label

a. N = number of randomized and treated patients.
b. NA = Not applicable, as data for placebo treatment is not available beyond 3 months in Studies I and V due to placebo advancement.
c. Inadequate response to at least one DMARD (biologic or non-biologic) due to lack of efficacy or toxicity.
d. Inadequate response to MTX defined as the presence of sufficient residual disease activity to meet the entry criteria.
e. Inadequate response to a least one TNF inhibitor due to lack of efficacy and/or intolerance.

The percentages of Xeljanz®-treated patients achieving ACR20, ACR50, and ACR70 responses in Studies I, IV, and V are shown in the table above. It is stated in the product information that similar results were observed with Studies II and III; however, these results were not included. In all trials, patients treated with either Xeljanz® 5mg or 10mg twice daily had higher ACR20, ACR50, and ACR70 response rates versus placebo, with or without background DMARD treatment, at Month 3 and Month 6. Higher ACR20 response rates were observed within 2 weeks compared to placebo.

Improvement in physical functioning was measured by the Health Assessment Questionnaire – Disability Index (HAQ-DI). Patients receiving Xeljanz® 5mg or 10mg twice daily demonstrated greater improvement from baseline in physical functioning compared to placebo at Month 3. The mean (95% CI) difference from placebo in HAQ-DI improvement from baseline at Month 3 in Study III was -0.22

(-0.35, -0.10) in patients receiving 5 mg Xeljanz® twice daily and -0.32 (-0.44, -0.19) in patients receiving 10 mg Xeljanz® twice daily. It is stated in the product information that similar results were observed with Studies I, II, IV and V; however, these results were not included. In the 12-month trials, HAQ-DI results in Xeljanz® -treated patients were consistent at 6 and 12 months. Disease Activity Score DAS28 results were available for Study IV, which showed a greater proportion of patients on Xeljanz® achieved a lower level compared to MTX. However, results for the other studies were not included.

Safety

The most commonly reported adverse reactions during the first 3 months in controlled clinical trials (occurring in greater than or equal to 2% of patients treated with Xeljanz® monotherapy or in combination with DMARDs) were upper respiratory tract infections, headache, diarrhea and nasopharyngitis. The following are major adverse events and precautions:

1. Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections have occurred in patients receiving Xeljanz®.
    a. If a serious infection develops, interrupt Xeljanz® until the infection is controlled.
    b. Prior to starting Xeljanz®, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting Xeljanz®.
    c. Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative.
2. Lymphoma and other malignancies have been observed in patients treated with Xeljanz®.
3. Epstein Barr Virus-associated post-transplant lympho-proliferative disorder has been observed at an increased rate in renal transplant patients treated with Xeljanz® and concomitant immunosuppressive medications.
4. Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were observed in clinical studies with Xeljanz®.
5. Gastrointestinal Perforations - Use with caution in patients that may be at increased risk.
6. Laboratory monitoring - Recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids.
7. Immunizations - Live vaccines should not be given concurrently with Xeljanz®.
8. Severe hepatic impairment – Use not recommended.

Xeljanz® is known to interact with medications that are moderate to potent inhibitors of the Cytochrome P450 CYP3A4 and CYP2C19 enzyme systems. The dose of Xeljanz® should be reduced to 5mg once daily if concomitant use cannot be avoided. There may be a loss of or reduced clinical response when used with potent CYP inducers such as rifampin.

Cost

The estimated wholesale acquisition cost of Xeljanz® is anticipated to be approximately $2,055 for a 30 day supply, which is slightly less than Enbrel® and Humira®, which costs approximately $2,400 per month. Costs for oral immunosupressants such as cyclosporine, azathrioprine, or tacrolimus can range from $16 to $380 per month of therapy.

Recommendations

The College of Pharmacy recommends placement of Xeljanz® (tofacitinib) into Tier 3 of the Biologic Products for the Treatment of Rheumatoid Arthritis, Crohn's Disease, Plaque Psoriasis, and Ankylosing Spondylitis Prior Authorization Category. The existing criteria for this category will apply. In addition, the College also recommends the following safety criteria be met before approval:

1. Negative tuberculosis test or successful treatment of active tuberculosis.
2. Severe hepatic impairment has been ruled out.
3. Approval will be for 12 weeks, after which time, prescriber must confirm performance of the following tests for further approval:
    a. Lymphocytes
    b. Neutrophils
    c. Hemoglobin
    d. Liver enzymes
    e. Lipid panel
    f. Updated tuberculosis test

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

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.

PRODUCT DETAILS OF XELJANZ® (TOFACITINIB)

INDICATIONS AND USE:

- Xeljanz® is an inhibitor of Janus kinases indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other non-biologic disease-modifying antirheumatic drugs (DMARDs).
- Xeljanz® should not be used in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine.

DOSAGE FORMS: 5mg tablets.

ADMINISTRATION: The recommended dose of Xeljanz® is 5 mg twice daily.

CONTRAINDICATIONS: none listed.

SPECIAL POPULATIONS: The dose should be reduced to 5mg once daily in patients with moderate to severe renal impairment and/or moderate hepatic impairment.

WARNINGS AND PRECAUTIONS:

- **Serious Infections** – Do not administer Xeljanz® during an active infection, including localized infections. If a serious infection develops, interrupt Xeljanz® until the infection is controlled.
    - Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in rheumatoid arthritis patients receiving Xeljanz®. The most common serious infections reported with Xeljanz® included pneumonia, cellulitis, herpes zoster and urinary tract infection. Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcus, esophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus, and BK virus were reported with Xeljanz®. Some patients have presented with disseminated rather than localized disease, and were often taking concomitant immunomodulating agents such as methotrexate or corticosteroids.
    - Other serious infections that were not reported in clinical studies may also occur (e.g., histoplasmosis, coccidioidomycosis, and listeriosis).
    - Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were observed in clinical studies with Xeljanz®. The impact of Xeljanz® on chronic viral hepatitis reactivation is unknown. Patients who screened positive for hepatitis B or C were excluded from clinical trials.
- **Lymphomas and other malignancies** have been reported in patients treated with Xeljanz®.
    - In the seven controlled rheumatoid arthritis clinical studies, 11 solid cancers and one lymphoma were diagnosed in 3328 patients receiving Xeljanz® with or without DMARD, compared to 0 solid cancers and 0 lymphomas in 809 patients in the placebo with or without DMARD group during the first 12 months of exposure. Lymphomas and solid cancers have also been observed in the long-term extension studies in rheumatoid arthritis patients treated with Xeljanz®.
    - In Phase 2B, controlled dose-ranging trials in *de-novo* renal transplant patients, all of whom received induction therapy with basiliximab, high dose corticosteroids, and mycophenolic acid products, Epstein Barr Virus-associated post-transplant lymphoproliferative disorder was observed in 5 out of 218 patients treated with Xeljanz® (2.3%) compared to 0 out of 111 patients treated with cyclosporine.
- **Gastrointestinal Perforations** – Use with caution in patients that may be at increased risk.
    - Events of gastrointestinal perforation have been reported in clinical studies with Xeljanz® in rheumatoid arthritis patients, although the role of JAK inhibition in these events is not known.

- Xeljanz® should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis). Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation

- **Laboratory monitoring** –Recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids.
  - **Lymphocytes:**
    - Treatment with Xeljanz® was associated with initial lymphocytosis at one month of exposure followed by a gradual decrease in mean lymphocyte counts below the baseline of approximately 10% during 12 months of therapy. Lymphocyte counts less than 500 cells/mm^3 were associated with an increased incidence of treated and serious infections. Monitor at baseline and every 3 months. Treatment is not recommended when lymphocyte count is < 500 cells/mm^3.
  - **Neutrophils:**
    - Treatment with Xeljanz® was associated with an increased incidence of neutropenia (less than 2000 cells/mm^3) compared to placebo. Avoid initiation of Xeljanz® treatment in patients with a low neutrophil count (i.e., ANC less than 1000 cells/ mm^3). For patients who develop a persistent ANC of 500-1000 cells/ mm^3, interrupt Xeljanz® dosing until ANC is greater than or equal to 1000 cells/mm. In patients who develop an ANC less than 500 cells/ mm^3, treatment with Xeljanz® is not recommended. Monitor neutrophil counts at baseline and after 4-8 weeks of treatment, and every 3 months there-after.
  - **Hemoglobin:**
    - Avoid initiation of Xeljanz® treatment in patients with a low hemoglobin level (i.e. less than 9 g/dL). Treatment with Xeljanz® should be interrupted in patients who develop hemoglobin levels less than 8 g/dL or whose hemoglobin level drops greater than 2 g/dL on treatment. Monitor hemoglobin at baseline and after 4-8 weeks of treatment and every 3 months thereafter. For recommended modifications based on hemoglobin results.
  - **Liver Enzymes:**
    - Treatment with Xeljanz® was associated with an increased incidence of liver enzyme elevation compared to placebo. Most of these abnormalities occurred in studies with background DMARD (primarily methotrexate) therapy. Routine monitoring of liver tests and prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury. If drug-induced liver injury is suspected, the administration of Xeljanz® should be interrupted until this diagnosis has been excluded.
  - **Lipids:**
    - Treatment with Xeljanz® was associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Maximum effects were generally observed within 6 weeks. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined. Assessment of lipid parameters should be performed approximately 4-8 weeks following initiation of Xeljanz® therapy. Manage patients according to clinical guidelines for the management of hyperlipidemia (i.e. NCEP guidelines).
- **Immunizations** – Live vaccines should not be given concurrently with Xeljanz®.
- **Severe hepatic impairment** – Not recommended

ADVERSE REACTIONS:
The most commonly reported adverse reactions during the first 3 months in controlled clinical trials (occurring in greater than or equal to 2% of patients treated with Xeljanz® monotherapy or in combination with DMARDs) were upper respiratory tract infections, headache, diarrhea and nasopharyngitis. See warnings and precautions for other serious reactions.

DRUG INTERACTIONS:

- Potent inhibitors of Cytochrome P450 3A4 (CYP3A4) (e.g., ketoconazole): Reduce dose to 5 mg once daily.
- One or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole): Reduce dose to 5 mg once daily.
- Potent CYP inducers (e.g., rifampin): May result in loss of or reduced clinical response.

PATIENT COUNSELING INFORMATION:

1. Serious infections.
Your healthcare provider should test you for TB before starting Xeljanz®. Your healthcare provider should monitor you closely for signs and symptoms of TB infection during treatment with Xeljanz®. You should not start taking Xeljanz®. if you have any kind of infection unless your healthcare provider tells you it is okay.

Before starting Xeljanz®, tell your healthcare provider if you:

1. are being treated for an infection
2. get a lot of infections or have infections that keep coming back
3. have diabetes, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
4. have TB, or have been in close contact with someone with TB
5. live or have lived, or have traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, or blastomycosis). These infections may happen or become more severe if you use Xeljanz®. Ask your healthcare provider if you do not know if you have lived in an area where these infections are common.
6. have or have had hepatitis B or C
7. think you have an infection or have symptoms of an infection such as:
    a. fever, sweating, or chills
    b. muscle aches
    c. cough
    d. shortness of breath
    e. blood in phlegm
    f. weight loss
    g. warm, red, or painful skin or sores on your body
    h. diarrhea or stomach pain
    i. burning when you urinate or urinating more often than normal
    j. feeling very tired

After starting Xeljanz®, call your healthcare provider right away if you have any symptoms of an infection. Xeljanz® can make you more likely to get infections or make worse any infection that you have.

2. Cancer and immune system problems.

- Xeljanz® may increase your risk of certain cancers by changing the way your immune system works.
- Lymphoma and other cancers can happen in patients taking Xeljanz®. Tell your healthcare provider if you have ever had any type of cancer.
- Some people who have taken Xeljanz® with certain other medicines to prevent kidney transplant rejection have had a problem with certain white blood cells growing out of control (Epstein Barr Virus-associated post-transplant lympho-proliferative disorder).

3. Tears (perforation) in the stomach or intestines.

- Tell your healthcare provider if you have had diverticulitis (inflammation in parts of the large intestine) or ulcers in your stomach or intestines. Some people taking Xeljanz® get tears in their stomach or intestine. This happens most often in people who also take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.
- Tell your healthcare provider right away if you have fever and stomach-area pain that does not go away and a change in your bowel habits.

4. Changes in certain laboratory test results.

Your healthcare provider should do blood tests before you start receiving Xeljanz® and while you take Xeljanz®.

5. Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Xeljanz® and other medicines may affect each other causing side effects. Especially tell your healthcare provider if you take any other medicines to treat your rheumatoid arthritis. You should not take:

1. tocilizumab (Actemra®)
2. etanercept (Enbrel®)
3. adalimumab (Humira®)
4. infliximab (Remicade®)
5. rituximab (Rituxan®)
6. abatacept (Orencia®)
7. anakinra (Kineret®)
8. certolizumab (Cimzia®)
9. golimumab (Simponi®)
10. azathioprine
11. cyclosporine

Or other immunosuppressive drugs while you are taking Xeljanz®. Taking Xeljanz® with these medicines may increase your risk of infection.

[1] **Zeljanz® Prescribing Information. Pfizer, Inc. Available online at:** http://labeling.pfizer.com/ShowLabeling.aspx?id=959. **Last revised: November 2012; Last accessed 12/18/2012.**

Appendix H

FDA & DEA Updates (additional information can be found at http://www.fda.gov/Drugs/default.htm)

FDA NEWS RELEASE

For Immediate Release: Dec. 28, 2012
FDA approves Eliquis to reduce the risk of stroke, blood clots in patients with non-valvular atrial fibrillation

The U.S. Food and Drug Administration today approved the anti-clotting drug Eliquis (apixaban), an oral tablet used to reduce the risk of stroke and dangerous blood clots (systemic embolism) in patients with atrial fibrillation that is not caused by a heart valve problem.

Atrial fibrillation, one of the most common types of abnormal heart rhythm, is an abnormal, irregular, and rapid beating of the heart in which the heart's two upper chambers (atria) do not contract properly, allowing blood clots to form in them. These clots can break off and travel to the brain or other parts of the body.

The safety and efficacy of Eliquis in treating patients with atrial fibrillation not caused by cardiac valve disease were studied in a clinical trial of more than 18,000 patients that compared Eliquis with the anti-clotting drug warfarin. In the trial, patients taking Eliquis had fewer strokes than those who took warfarin.

Patients with prosthetic heart valves should not take Eliquis nor should patients with atrial fibrillation that is caused by a heart valve problem. These patients were not studied in clinical trial. As with other FDA-approved anti-clotting drugs, bleeding, including life-threatening and fatal bleeding, is the most serious risk with Eliquis. There is no agent that can reverse the anti-coagulant effect of Eliquis.

Eliquis will be dispensed with a patient Medication Guide that provides instructions on its use and drug safety information. Health care professionals should counsel patients on signs and symptoms of possible bleeding.

Eliquis is manufactured Bristol-Myers Squibb Company of Princeton, N.J. and marketed by BMS and Pfizer Inc. of New York.

FDA NEWS RELEASE

For Immediate Release: Dec. 31, 2012
FDA approves first anti-diarrheal drug for HIV/AIDS patients

Fulyzaq is the second botanical drug approved by the agency

The U.S. Food and Drug Administration today approved Fulyzaq (crofelemer) to relieve symptoms of diarrhea in HIV/AIDS patients taking antiretroviral therapy, a combination of medicines used to treat HIV infection. Diarrhea is experienced by many HIV/AIDS patients and is a common reason why patients discontinue or switch their antiretroviral therapies. Fulyzaq is intended to be used in HIV/AIDS patients whose diarrhea is not caused by an infection from a virus, bacteria, or parasite. Patients take Fulyzaq two times a day to manage watery diarrhea due to the secretion of electrolytes and water in the gastrointestinal tract.

Derived from the red sap of the Croton lechleri plant, Fulyzaq is the second botanical prescription drug approved by FDA. A botanical drug product is often a complex mixture derived from one or more plant materials with varying degrees of purification. In 2006, the FDA approved the first botanical prescription drug, Veregen (sinecatechins), a treatment for external genital and perianal warts.

Just as for other types of drugs, the safety and efficacy of a botanical drug product are established through clinical trials. In addition, manufacturers of a botanical drug product must ensure rigorous control of raw materials, and good agricultural and collection practices, together with analytical testing of the complex mixture.

The safety and efficacy of Fulyzaq were established in a clinical trial of 374 HIV-positive patients on stable antiretroviral therapy with a history of diarrhea lasting one month or longer. The median number of daily

watery bowel movements was 2.5 per day. Patients who had diarrhea caused by an infection or a gastrointestinal disease were excluded from participating in the trials. Patients were randomly assigned to take Fulyzaq or a placebo twice daily.

The trial was designed to measure clinical response, defined as the number of patients who had two or fewer watery bowel movements weekly. Results showed that 17.6 percent of patients taking Fulyzaq experienced clinical response compared with 8 percent taking placebo. In some patients, a persistent anti-diarrheal effect was seen for 20 weeks.

Before treating patients with Fulyzaq, health care professionals should conduct proper testing to confirm the diarrhea is not caused by an infection or a gastrointestinal disease. Common side effects reported in patients taking Fulyzaq in the clinical trial were upper respiratory tract infection, bronchitis, cough, flatulence, and increased levels of the liver enzyme bilirubin.

Fulyzaq is distributed by Salix Pharmaceuticals, based in Raleigh, N.C. under license from Napo Pharmaceuticals, Inc.

FDA NEWS RELEASE

For Immediate Release: Dec. 31, 2012

On Dec. 28, the U.S. Food and Drug Administration approved Sirturo (bedaquiline) as part of combination therapy to treat adults with multi-drug resistant pulmonary tuberculosis (TB) when other alternatives are not available.

TB is an infection caused by Mycobacterium tuberculosis and is one of the world's deadliest diseases. It is spread from person to person through the air and usually affects the lungs, but it can also affect other parts of the body such as the brain and kidneys. According to the Centers for Disease Control and Prevention, nearly 9 million people around the world and 10,528 people in the United States became sick with TB in 2011.

Multi-drug resistant TB occurs when M. tuberculosis becomes resistant to isonazid and rifampin, two powerful drugs most commonly used to treat TB. Sirturo is the first drug approved to treat multi-drug resistant TB and should be used in combination with other drugs used to treat TB. Sirturo works by inhibiting an enzyme needed by M. tuberculosis to replicate and spread throughout the body.

Sirturo is being approved under the FDA's accelerated approval program, which allows the agency to approve a drug to treat a serious disease based on clinical data showing that the drug has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients. This program provides patients earlier access to promising new drugs while the company conducts additional studies to confirm the drug's clinical benefit and safe use.

The FDA also granted Sirturo fast track designation, priority review and orphan-product designation. The drug demonstrated the potential to fill an unmet medical need, has the potential to provide safe and effective treatment where no satisfactory alternative therapy exists, and is intended to treat a rare disease, respectively.

Sirturo carries a Boxed Warning alerting patients and health care professionals that the drug can affect the heart's electrical activity (QT prolongation), which could lead to an abnormal and potentially fatal heart rhythm. The Boxed Warning also notes deaths in patients treated with Sirturo. Nine patients who received Sirturo died compared with two patients who received placebo. Five of the deaths in the Sirturo group and all of the deaths in the placebo arm seemed to be related to tuberculosis, but no consistent reason for the deaths in the remaining Sirturo-treated patients could be identified.

Sirturo's manufacturer, Janssen Therapeutics, will distribute the drug from a single source and will provide educational materials to help ensure the drug is used appropriately.

Sirturo's safety and effectiveness were established in 440 patients in two Phase 2 clinical trials. Patients in the first trial were randomly assigned to be treated with Sirturo plus other drugs used to treat TB, or a placebo plus other drugs used to treat TB. All patients in the second trial, which is ongoing, received Sirturo plus other

TB drugs. Both studies were designed to measure the length of time it took for a patient's sputum to be free of M. tuberculosis (sputum culture conversion, or SCC).
Results from the first trial showed patients treated with Sirturo combination therapy achieved SCC in a median time of 83 days, compared with 125 days in patients treated with placebo combination therapy. Results from the second trial showed the median time to SCC was 57 days, supporting the efficacy findings of the first trial.
Common side effects identified in the clinical trials include nausea, joint pain, and headache.
Janssen Therapeutics, a division of Janssen Products LP, is based in Titusville, N.J.

FDA NEWS RELEASE

For Immediate Release: Dec. 26, 2012
FDA approves new orphan drug for rare cholesterol disorder

On Dec. 21, the U.S. Food and Drug Administration approved Juxtapid (lomitapide) to reduce low-density lipoprotein (LDL) cholesterol, total cholesterol, apolipoprotein B, and non-high-density lipoprotein (non-HDL) cholesterol in patients with homozygous familial hypercholesterolemia (HoFH). Juxtapid is intended for use in combination with a low fat diet and other lipid-lowering treatments.
HoFH is a rare inherited condition that makes the body unable to remove LDL cholesterol, often called the "bad" cholesterol, from the blood, causing abnormally high levels of circulating LDL cholesterol. In the United States, HoFH occurs in approximately one in one million individuals. For those with HoFH, heart attacks and death often occur before age 30. Juxtapid works by impairing the creation of the lipid particles that ultimately give rise to LDL.
Juxtapid is a capsule taken once a day, without food, and at least two hours after the evening meal. Patients should take supplements that contain fat-soluble vitamins and essential fatty acids daily while taking Juxtapid.
The safety and effectiveness of Juxtapid were evaluated in a clinical trial of 29 patients with HoFH. On average, levels of LDL cholesterol fell by approximately one-half during the first 26 weeks among those who tolerated the drug. Juxtapid carries a Boxed Warning regarding a serious risk of liver toxicity because it is associated with liver enzyme abnormalities and accumulation of fat in the liver, which could potentially lead to progressive liver disease with chronic use. Juxtapid also reduces the absorption of fat-soluble nutrients and interacts with several other medications.
The FDA approved Juxtapid with a Risk Evaluation and Mitigation Strategy (REMS) that consists of elements to ensure safe use including prescriber and pharmacy certification and documentation of safe-use conditions consisting of a prescription authorization form that will be required to accompany each new prescription.
The FDA is requiring three postmarketing studies for Juxtapid: an animal study to evaluate the potential for toxicity in children and teens; a long-term registry of patients with HoFH treated with Juxtapid to determine the long-term safety; and an enhanced pharmacovigilance program to monitor reports of malignancy, teratogenicity, and hepatic abnormalities.
The most common adverse reactions in the clinical trial included diarrhea, nausea, vomiting, indigestion, and abdominal pain.
Juxtapid is marketed by Cambridge, Mass.-based Aegerion Pharmaceuticals Inc.

FDA NEWS RELEASE

For Immediate Release: Dec. 21, 2012
FDA approves Gattex to treat short bowel syndrome

The U.S. Food and Drug Administration today approved Gattex (teduglutide) to treat adults with short bowel syndrome (SBS) who need additional nutrition from intravenous feeding (parenteral nutrition).

SBS is a condition that results from the partial or complete surgical removal of the small and/or large intestine. Extensive loss of the small intestine can lead to poor absorption of fluids and nutrients from food needed to sustain life. As a result, patients with SBS often receive parenteral nutrition.
Gattex is an injection administered once daily that helps improve intestinal absorption of fluids and nutrients, reducing the frequency and volume of parenteral nutrition. It is the third FDA-approved drug to treat adults with SBS receiving nutritional support. Zorbtive (somatropin) and Nutrestore (glutamine) were approved in 2003 and 2004, respectively.
Patients treated with Gattex have a potential increased risk of developing cancer and abnormal growths (polyps) in the intestine, obstructions in the intestine, gallbladder disease, biliary tract disease and pancreatic disease. To ensure that the benefits of Gattex outweigh the potential risks, the drug is being approved with a Risk Evaluation and Mitigation Strategy, consisting of a communication plan and training for prescribers.
Gattex's safety, efficacy and tolerability were evaluated in two clinical trials and two extension studies. Patients in the trials were randomly assigned to receive Gattex or a placebo.
The clinical trials were designed to measure the number of patients who achieved at least 20 percent reduction in the volume of weekly parenteral nutrition after 20 and 24 weeks of treatment (clinical response). Forty-six percent and 63 percent of patients treated with Gattex achieved clinical response, versus 6 percent and 30 percent of patients treated with placebo.
The trials also measured the mean reduction in the volume of parenteral nutrition (liters per week) after 24 weeks of treatment. Results showed a mean reduction in parenteral nutrition of 2.5 L/week and 4.4 L/week in Gattex-treated patients, compared with 0.9 L/week and 2.3 L/week in placebo-treated patients.
The extension studies followed patients treated with Gattex in the clinical trials for an additional 28 weeks. Patients experienced a 4.9 L/week and 5.2 L/week mean reduction in parenteral nutrition after one year of continuous Gattex treatment. Six patients in the extension studies were weaned off parenteral nutrition while on Gattex.
The most common side effects of Gattex identified in clinical trials were abdominal pain, injection site reactions, nausea, headaches, abdominal distension and upper respiratory tract infection.
To study Gattex's long-term safety, the FDA is requiring a postmarket study of SBS patients treated with the drug in a routine clinical setting to further evaluate the drug's potential increased risk to cause colorectal cancer and other conditions. Patients in this study will be followed for at least 10 years.
Gattex is marketed by Bedminster, N.J.-based NPS Pharmaceuticals. Zorbtive is marketed by EMD Serono, based in Rockland, Mass. and Nutrestore is marketed by Torrance, Calif.-based Emmaus Medical Inc.

FDA NEWS RELEASE

For Immediate Release: Dec. 21, 2012
FDA expands Tamiflu's use to treat children younger than 1 year

Parents, health care professionals must ensure proper dosing
The U.S. Food and Drug Administration today expanded the approved use of Tamiflu (oseltamivir) to treat children as young as 2 weeks old who have shown symptoms of flu for no longer than two days.
The drug is not approved to prevent flu infection in this population. In addition, the safety and efficacy of Tamiflu to treat flu infection has not been established in children younger than 2 weeks old.
Tamiflu was approved in 1999 to treat adults infected with flu who have shown symptoms for no longer than two days. It has since been approved to treat flu in children ages 1 year and older who have shown symptoms of flu for no longer than two days, and to prevent flu in adults and children ages 1 year and older.
Although there is a fixed dosing regimen for patients 1 year and older according to weight categories, the dosing for children younger than 1 year must be calculated for each patient based on their exact weight. These children should receive 3 milligrams per kilogram twice daily for five days. These smaller doses will require a different dispenser than what is currently co-packaged with Tamiflu.

Tamiflu is the only product approved to treat flu infection in children younger than 1 year old, providing an important treatment option for a vulnerable population. According to the Centers for Disease Control and Prevention (CDC), children younger than 2 years are at higher risk for developing complications from the flu, with the highest rates of hospitalization in those less than 6 months of age.

The FDA expanded the approved use of Tamiflu in children younger than 1 year based on extrapolation of data from previous study results in adults and older children, and additional supporting safety and pharmacokinetic studies sponsored by both the National Institutes of Health and Roche Group, Tamiflu's manufacturer. Pediatric legislation[1] permits efficacy to be extrapolated from previous study results in adults and older children if the illness being studied and the effects of the drug are sufficiently similar in adult and pediatric patients. Data on how the drug is metabolized in the body (pharmacokinetic data) indicated a dose of 3 mg/kg twice daily provided concentrations of Tamiflu similar to those observed in older children and adults, and is expected to provide similar efficacy in this very young age group.

Almost all of the 135 pediatric patients enrolled in the two safety studies had confirmed flu. Results from these studies showed the safety profile in children younger than 1 year was consistent with the established safety profile of adults and older children. The most common side effects reported with Tamiflu use in this age group include vomiting and diarrhea. Although not seen in the new studies, rare cases of severe rash, skin reactions, hallucinations, delirium, and abnormal behavior have been reported.

The FDA monitors drugs for side effects and believes reporting side effects is important. Health care professionals and patients should report any side effects associated with Tamiflu's use to FDA's MedWatch program[2].

Tamiflu is not a substitute for early, annual flu vaccination, as recommended by the CDC's Advisory Committee on Immunization Practices. CDC recommends all persons aged 6 months and older receive an annual flu vaccine.

Tamiflu is distributed in the United States by South San Francisco-based Genentech, a member of the Roche Group.

FDA NEWS RELEASE

For Immediate Release: Dec. 14, 2012

FDA approves Iclusig to treat two rare types of leukemia

Drug approved 3 months ahead of schedule

The U.S. Food and Drug Administration today approved Iclusig (ponatinib) to treat adults with chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL), two rare blood and bone marrow diseases.

Iclusig is being approved more than three months ahead of the product's prescription user fee goal date of March 27, 2013, the date the agency was scheduled to complete review of the drug application. The FDA reviewed the Iclusig drug application under the agency's priority review program, which provides for an expedited six-month review for drugs that may provide safe and effective therapy when no satisfactory alternative therapy exists, or offer significant improvement compared to marketed products.

Iclusig blocks certain proteins that promote the development of cancerous cells. The drug is taken once a day to treat patients with chronic, accelerated, and blast phases of CML and Ph+ ALL whose leukemia is resistant or intolerant to a class of drugs called tyrosine kinase inhibitors (TKIs). Iclusig targets CML cells that have a particular mutation, known as T315I, which makes these cells resistant to currently approved TKIs.

The FDA approved Bosulif (bosutinib) in September 2012 and Synribo (omacetaxine mepesuccinate) in October 2012 to treat various phases of CML. Marqibo (vincristine sulfate liposome injection) was approved in August 2012 to treat Philadelphia chromosome negative ALL.

Iclusig is being approved under the agency's accelerated approval program, which provides patients earlier access to promising new drugs while the company conducts additional studies to confirm the drug's clinical

benefit and safe use. The therapy was granted an orphan product designation because it is intended to treat a rare disease or condition.

Iclusig's safety and effectiveness were evaluated in a single clinical trial of 449 patients with various phases of CML and Ph+ ALL. All participants were treated with Iclusig.

The drug's effectiveness was demonstrated by a reduction in the percentage of cells expressing the Philadelphia chromosome genetic mutation found in most CML patients, major cytogenetic response (MCyR). Fifty-four percent of all patients and 70 percent of patients with the T315I mutation achieved MCyR. The median duration of MCyR had not yet been reached at the time of analysis.

In accelerated and blast phase CML and Ph+ ALL, Iclusig's effectiveness was determined by the number of patients who experienced a normalization of white blood cell counts or had no evidence of leukemia (major hematologic response or MaHR). Results showed:

- 52 percent of patients with accelerated phase CML experienced MaHR for a median duration of 9.5 months;
- 31 percent of patients with blast phase CML achieved MaHR for a median duration of 4.7 months; and
- 41 percent of patients with Ph+ ALL achieved MaHR for a median duration of 3.2 months.

Iclusig is being approved with a Boxed Warning alerting patients and health care professionals that the drug can cause blood clots and liver toxicity. The most common side effects reported during clinical trials include high blood pressure, rash, abdominal pain, fatigue, headache, dry skin, constipation, fever, joint pain, and nausea.

Iclusig is marketed by ARIAD Pharmaceuticals, based in Cambridge, Mass. Bosulif is marketed by New York City-based Pfizer, and Synribo is marketed by Frazer, Pa.-based Teva Pharmaceuticals. Marqibo is marketed by Talon Therapeutics Inc. based in South San Francisco, Calif.

FDA NEWS RELEASE

For Immediate Release: Dec. 10, 2012

FDA expands Zytiga's use for late-stage prostate cancer

Drug can now be used before treatment with chemotherapy

The U.S. Food and Drug Administration today expanded the approved use of Zytiga (abiraterone acetate) to treat men with late-stage (metastatic) castration-resistant prostate cancer prior to receiving chemotherapy.

The FDA initially approved Zytiga in April 2011 for use in patients whose prostate cancer progressed after treatment with docetaxel, a chemotherapy drug. Zytiga is a pill that decreases the production of male sex hormone testosterone.

In prostate cancer, testosterone stimulates prostate tumors to grow. Drugs or surgery are used to reduce testosterone production or to block testosterone's effects. Some men have castration-resistant prostate cancer, meaning the prostate cancer cells continue to grow even with low levels of testosterone.

The FDA reviewed Zytiga's application for this new indication under the agency's priority review program. The program provides for an expedited six-month review for drugs that may offer major advances in treatment or provide a treatment when no adequate therapy exists.

Zytiga's safety and effectiveness for its expanded use were established in a clinical study of 1,088 men with late-stage, castration-resistant prostate cancer who had not previously received chemotherapy. Participants received either Zytiga or a placebo (sugar pill) in combination with prednisone.

The study was designed to measure the length of time a patient lived before death (overall survival) and the length of time a patient lived without further tumor growth as assessed by imaging studies (radiographic progression-free survival, or rPFS).

Patients who received Zytiga had a median overall survival of 35.3 months compared with 30.1 months for those receiving the placebo. Study results also showed Zytiga improved rPFS. The median rPFS was 8.3 months in the placebo group and had not yet been reached for patients treated with Zytiga at the time of analysis.

The most common side effects reported in those receiving Zytiga include fatigue, joint swelling or discomfort, swelling caused by fluid retention, hot flush, diarrhea, vomiting, cough, high blood pressure, shortness of breath, urinary tract infection, and bruising.
The most common laboratory abnormalities included low red blood cell count; high levels of the enzyme alkaline phosphatase, which can be a sign of other serious medical problems; high levels of fatty acids, sugar, and liver enzymes in the blood; and low levels of lymphocytes, phosphorous and potassium in the blood.
Zytiga is marketed by Horsham, Pa.-based Janssen Biotech Inc.

Safety Announcements

FDA Drug Safety Communication: Pradaxa (dabigatran etexilate mesylate) should not be used in patients with mechanical prosthetic heart valves

[12-19-2012] The U.S. Food and Drug Administration (FDA) is informing health care professionals and the public that the blood thinner (anticoagulant) Pradaxa (dabigatran etexilate mesylate) should not be used to prevent stroke or blood clots (major thromboembolic events) in patients with mechanical heart valves, also known as mechanical prosthetic heart valves. A clinical trial in Europe (the RE-ALIGN trial)[1] was recently stopped because Pradaxa users were more likely to experience strokes, heart attacks, and blood clots forming on the mechanical heart valves than were users of the anticoagulant warfarin. There was also more bleeding after valve surgery in the Pradaxa users than in the warfarin users.

FACTS ON PRADAXA (dabigatran etexilate mesylate)
Pradaxa is a blood-thinning medication used to reduce the risk of stroke and blood clots in patients with a specific condition called non-valvular atrial fibrillation (AF), a common heart rhythm abnormality that causes the upper chambers of the heart, or atria, to beat rapidly and irregularly. Pradaxa is not indicated for patients with atrial fibrillation caused by heart valve problems.

Pradaxa is not approved for patients with atrial fibrillation caused by heart valve problems. FDA is requiring a contraindication (a warning against use) of Pradaxa in patients with mechanical heart valves. Health care professionals should promptly transition any patient with a mechanical heart valve who is taking Pradaxa to another medication. The use of Pradaxa in patients with another type of valve replacement made of natural biological tissue, known as a bioprosthetic valves, has not been evaluated and cannot be recommended. Patients with all types of prosthetic heart valve replacements taking Pradaxa should talk to their health care professional as soon as possible to determine the most appropriate anticoagulation treatment. Patients should not stop taking anticoagulant medications without guidance from their health care professional; stopping Pradaxa or other anticoagulants suddenly can increase the risk of blood clots and stroke.
FDA previously released a Drug Safety Communication[1] about the risk of serious bleeding associated with the use of Pradaxa in patients with non-valvular atrial fibrillation (the population for which the drug is approved). FDA has not changed its recommendations regarding use of Pradaxa in the population for which it is approved.

Safety Announcements

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

This update is in follow-up to the Drug Safety Communications issued on 6/16/2011[1] and 7/22/2011[2].

[12-12-2012] The U.S. Food and Drug Administration (FDA) is informing the public about the results of a large, combined analysis (called a meta-analysis) of clinical trials that compared patients who received the smoking cessation drug Chantix (varenicline) to patients who received a placebo (an inactive treatment). FDA required the manufacturer of Chantix to conduct the meta-analysis to further evaluate the cardiovascular safety of the

drug, and believes it is important to let health care professionals and patients know about the results of this study. FDA first notified the public about a possible increased risk of cardiovascular adverse events with Chantix in its June 2011 Drug Safety Communication (DSC)[3].
A higher occurrence of major adverse cardiovascular events (a combined outcome of cardiovascular-related death, nonfatal heart attack, and nonfatal stroke) was observed in patients using Chantix compared to placebo. These events were uncommon in both the Chantix and placebo groups, and the increased risk was not statistically significant, which means it is uncertain whether the excess risk for the Chantix group was due to the drug or due to chance. However, the data were analyzed many different ways and consistently showed a higher occurrence of events in patients using Chantix, which makes it seem more likely that it is related to the drug and not purely a chance finding (see Data Summary below).
The meta-analysis findings of cardiovascular risk are similar to the findings in the smoking cessation clinical trial of patients with stable cardiovascular disease that was described in FDA's June 16, 2011 DSC[4]. The Warnings and Precautions section of the Chantix label has been updated to include the results of the meta-analysis.
Health care professionals are advised to weigh the risks of Chantix against the benefits of its use. It is important to note that smoking is a major risk factor for cardiovascular disease, and Chantix is effective in helping patients to quit smoking and abstain from it for as long as one year. The health benefits of quitting smoking are immediate and substantial.
Patients taking Chantix should contact their health care professional if they experience new or worsening symptoms of cardiovascular disease, such as chest pain, shortness of breath, calf pain when walking, or sudden onset of weakness, numbness, or difficulty speaking. Patients should also contact their health care professional if they have any questions or concerns about Chantix.

Safety Announcements

FDA Drug Safety Communication: Warning against use of Xyrem (sodium oxybate) with alcohol or drugs causing respiratory depression

[12-17-2012] The U.S. Food and Drug Administration (FDA) is reminding healthcare professionals and patients that the combined use of Xyrem (sodium oxybate) with alcohol or central nervous system (CNS) depressant drugs can markedly impair consciousness and may lead to severe breathing problems (respiratory depression). The use of alcohol with Xyrem is a new contraindication (FDA warns against combined use) added to the Xyrem label, which already contraindicates its use with insomnia drugs. The use of Xyrem with other CNS depressant drugs (drugs that affect the CNS and may lead to breathing problems) such as opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, general anesthetics, and muscle relaxants should generally be avoided.
FDA recently evaluated reports of patients who died while taking Xyrem along with alcohol or other CNS depressants. The cause of these deaths is not clear because the reports contained incomplete information and did not adequately address confounding factors, such as pre-existing sleep apnea and/or chronic obstructive lung disease (COPD) (see Data Summary). Given some of the circumstances noted in the deaths, however, FDA determined that the recommendations in the Xyrem drug label should be strengthened to more strongly remind healthcare professionals and patients of the risks when using Xyrem with CNS depressant drugs or alcohol.
Healthcare professionals are urged to follow the dosing recommendations, contraindications, and boxed warning in the updated Xyrem drug label (PDF - 566KB)[1] and to avoid drug combinations that raise the risk of respiratory depression and death. Patients taking Xyrem should not drink alcohol or take insomnia drugs. The use of Xyrem along with these products or other CNS depressants increases the risk of breathing problems that may lead to loss of consciousness, coma, and death.
The Xyrem drug label (PDF - 566KB)[2] is being revised as follows:

- The addition of the statement: “Patients should not drink alcohol when using Xyrem.” (Contraindications section)
- The addition of a statement recommending that, when concomitant use of Xyrem with a central nervous system depressant is required, a reduction in dose or discontinuation of one or more central nervous system depressants (including Xyrem) should be considered; and a further recommendation that, if short-term opioid treatment is required, interruption of Xyrem treatment should be considered (Warnings and Precautions section)
- The addition of a sentence stating that Xyrem may be dispensed only to patients enrolled in the Xyrem Success Program(Indications and Usage section)
- The addition of an updated summary of risks; a description of the components of the Xyrem Success Program; and details of the website and phone number where further information about Xyrem can be obtained (Warnings and Precautions section)

Current Drug Shortages Index (as of January 2, 2013):

The information provided in this section is provided voluntarily by manufacturers.

Acetylcysteine Inhalation Solution
Acyclovir Sodium Injection (initial posting 11/13/2012)
Alfentanil (Alfenta) Injection (initial posting 1/23/2012)
Amikacin Injection
Amino Acid Products (initial posting 2/14/2012)
Aminophylline (initial posting 12/10/2012) UPDATED 12/28/2012
Ammonium Chloride Injection
Atracurium besylate (initial posting 2/27/2012)
Atropine Sulfate Injection
Bacteriostatic 0.9% Sodium Chloride (initial posting 9/10/2012) UPDATED 12/28/2012
Barium Sulfate for Suspension (initial posting 10/12/2012)
Bismuth subsalicylate/tetracycline hydrochloride/metronidazole (Helidac) Therapy (initial posting 3/8/2012)
Bumetanide Injection (initial posting 6/21/2012) UPDATED 12/28/2012
Bupivacaine Hydrochloride (Marcaine, Sensorcaine) Injection UPDATED 12/28/2012
Buprenorphine hydrochloride (Buprenex) Injection
Butorphanol (Stadol) Injection
Caffeine, anhydrous (125 mg/mL) and Sodium benzoate (125 mg/mL)
Caffeine and Ergotamine Tartrate Tablet (initial posting 3/8/2012)
Calcium Chloride Injection (initial posting 12/11/2012)
Cetrorelix Acetate for Injection (Cetrotide) (initial posting 9/20/2012)
Chloroprocaine (Nesacaine) Injection (initial posting 3/28/2012)
Chromic Chloride Injection
Citric Acid; Gluconolactone; Magnesium Carbonate Solution (Renacidin); Irrigation (initial posting 6/30/2012)
Corticorelin Ovine Triflutate
Daunorubicin Hydrochloride Solution for Injection
Denileukin diftitox (Ontak) injection (initial posting 9/22/2012)
Desmopressin Injection (DDAVP)
Dexrazoxane (Zinecard) Injection
Dextroamphetamine (Dexedrine) Tablets (initial posting 1/12/2012) UPDATED 12/14/2012
Dextrose Injection (initial posting 5/23/2012)
Diazepam Injection UPDATED 12/28/2012
Dipyridamole Injection (initial posting 7/24/2012)
Doxorubicin (adriamycin) lyophilized powder (initial posting 12/2/2011)

Doxorubicin Liposomal (Doxil) Injection
Edetate Calcium Disodium (Calcium Disodium Versenate) Injection (initial posting 10/12/2012)
Epinephrine Injection (initial posting 4/27/2012)
Epinephrine 1mg/mL (Preservative Free) (initial posting 6/21/2012)
Erythromycin Lactobionate Injection (initial posting 6/12/2012) UPDATED 12/28/2012
Ethiodol (ETHIODIZED OIL) ampules
Etomidate (Amidate) Injection (initial posting 2/9/2012) UPDATED 12/28/2012
Fentanyl Citrate (Sublimaze) Injection UPDATED (12/28/2012)
Fluticasone Propionate and Salmeterol (Advair HFA) Inhalation Powder (initial posting date) - 10/17/2012)
Foscarnet Sodium (Foscavir) Injection
Fosphenytoin Sodium (Cerebyx) Injection (initial posting 3/30/2012) UPDATED 12/28/2012
Fospropofol disodium (Lusedra) Injection (initial posting 6/18/2012)
Furosemide Injection (initial posting 6/20/2012) UPDATED 12/28/2012
Gallium Nitrate Injection (Ganite) (initial posting 4/4/2012)
Heparin Sodium Premixes (initial posting 7/5/2012)
Hydromorphone Hydrochloride (Dilaudid) Injection (initial posting 3/7/2012) UPDATED (12/28/2012)
Ibandronate sodium (Boniva) injection (initial posting 6/6/2012)
Intravenous Fat Emulsion UPDATED (12/27/2012)
Isoniazid Tablets UPDATED 1/2/2013
Ketorolac Tromethamine Injection UPDATED 12/28/2012
Leucovorin Calcium Lyophilized Powder for Injection
Leuprolide Acetate Injection
Lidocaine (Xylocaine) Hydrochloride Injection (initial posting date - 2/22/2012) UPDATED 12/28/2012
Lidocaine HCL, 4% Topical Solution (Laryng-O-Jet, LTA kit) (initial posting 5/31/2012)
Liotrix (Thyrolar) Tablets
Lorazepam (Ativan) Injection UPDATED 12/28/2012
Magnesium Sulfate Injection UPDATED 12/28/2012
Mannitol Injection (Osmitrol, Resectisol) Injection (initial posting date - 12/21/2011) UPDATED 12/28/2012
Methadone Injection (initial posting - 11/13/2012)
Methazolamide (Glauctabs, Neptazane) Tablets
Methotrexate Injection
Methoxsalen (Oxsoralen) 1% topical lotion
Methyldopate HCL Injection
Metoclopramide (Reglan) Injection UPDATED 12/28/2012
Midazolam HCL (Versed) Injection
Mitomycin Powder for Injection
Morphine Sulfate Injection UPDATED 12/28/2012
Morphine Sulfate (Astramorph PF, Duramorph, Infumorph) Injection (Preservative Free)
Multi-Vitamin Infusion (Adult and pediatric)
Nalbuphine HCl (Nubain) Injection (initial posting 5/15/2012) UPDATED 12/28/2012
Naloxone (Narcan) Injection (initial posting 2/22/2012) UPDATED 12/28/2012
Naltrexone Oral (Revia) Tablets (initial posting 2/22/2012)
Nefazodone (Serzone) Tablets (initial posting 4/16/2012)
Nitroglycerin Ointment USP, 2% (Nitro-Bid) (Initial posting 10/23/2012)
Norethindrone and Ethinyl Estradiol Tablets, USP (Ovcon 50 Tablets) (initial posting 4/16/2012)
Ondansetron (Zofran) Injection 2 mg/mL UPDATED 12/28/2012
Ondansetron Injection 32 mg/50 mL premixed bags UPDATED 12/28/2012
Oxymorphone Hydrochloride (Opana) Oral Tablet (initial posting 3/19/2012)
Pancuronium Bromide Injection
Papaverine Hydrochloride Injection New!!
Peginterferon Alfa-2a (Pegasys) Injection-Prefilled Syringes (initial posting 3/26/2012)
Pentamidine isethionate inhalant (NebuPent) (initial posting 8/27/2012)

Pentamidine isethionate for injection (Pentam 300) (initial posting 8/27/2012)
Pentostatin for Injection (Nipent) (initial posting 3/21/2012)
Perflutren Lipid Microsphere (DEFINITY) Injection (initial posting 3/23/2012)
Phentolamine Mesylate (Regitine) Injection
Pilocarpine HCL Opthalmic Gel 4% (Pilopine HS) (initial posting 6/1/2012)
Potassium Chloride Injection 2 mEq/mL (initial posting 5/15/2012)
Potassium Phosphate Injection
Procainamide HCL Injection
Prochlorperazine Injection (initial posting 1/30/2012)
Promethazine Injection (initial posting 2/10/2012)
Propofol (Diprivan) Injection (initial posting 4/5/2012)
Secretin Synthetic Human (ChiRhoStim) Injection (ChiRhoStim) (initial posting 6/15/2012)
Selenium Injection
Sodium Acetate Injection (initial posting 3/20/2012) UPDATED 12/28/2012
Sodium benzoate and Sodium phenylacetate (Ammonul) Injection
Sodium Bicarbonate Injection (initial posting 4/4/2012) UPDATED 12/28/2012
Sodium Chloride 0.9% (5.8mL and 20mL) (initial posting 5/4/2012)
Sodium Chloride 23.4%
Succinylcholine (Anectine, Quelicin) Injection (initial posting 8/17/2012) UPDATED 12/28/2012
Sufentanil Citrate (Sufenta) Injection
Sulfamethoxazole 80mg/trimethoprim 160mg/ml injection (SMX/TMP) Bactrim)
Technetium Tc99m Bicisate for Injection (Neurolite) (initial posting 5/4/2012)
Technetium Tc99m Sestamibi Kit for Injection (initial posting 2/14/2012)
Telavancin (Vibativ) Injection
Tetracycline Capsules
Thiotepa (Thioplex) for Injection
Thyrotropin alfa (Thyrogen) injection 1.1mg/vial
Ticarcillin disodium/Clavulanic Potassium Injection (Timentin) (initial posting 8/16/12)
Ticlopidine (Ticlid) Tablets
Tobramycin Solution for Injection
Tromethamine (Tham) Injection (initial posting 5/2/2012)
Viaspan Cold Storage Solution 1000 mL Bag (initial posting 4/16/2012)
Vinblastine Sulfate Injection (initial posting 1/31/2012)
Vitamin A Palmitate (Aquasol A) Injection
Vitamin K1 (Phytonadione) Injectable Emulsion
Zinc Chloride Injection (initial posting 2/15/2012) UPDATED 12/28/2012