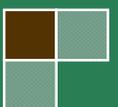




Drug Utilization Review Board

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

Wednesday
March 13, 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 – March 13, 2013

DATE: March 7, 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 March 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 Chronic Obstructive Pulmonary Disease Medications – See Appendix C.

Action Item – Vote to Prior Authorize Select Oral Corticosteroid Medications – See Appendix D.

Action Item – Annual Review of Diabetes Medications and 30 Day Notice to Prior Authorize Juvisync[®], Bydureon[®], Jentadueto[®], Janumet XR[®], Nesina[®], Kazano[®], and Oseni[®] – See Appendix E.

Action Item – Annual Review of Anticoagulant Medications and 30 Day Notice to Prior Authorize Eliquis[®] – See Appendix F.

30 Day Notice to Prior Authorize Kuvan[®] – See Appendix G.

30 Day Notice to Prior Authorize Gattex[®] – See Appendix H.

FDA and DEA Updates – See Appendix I.

Future Business

Adjournment

Oklahoma Health Care Authority
Drug Utilization Review Board
(DUR Board)
Meeting –March 13, 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. February 14, 2013 DUR Minutes – Vote
 - B. February 14, 2013 DUR Recommendation Memorandum

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

4. **Update on DUR / Medication Coverage Authorization Unit – See Appendix B.**
 - A. Medication Coverage Activity for February 2013
 - B. Pharmacy Help Desk Activity for February 2013
 - C. SoonerCare Atypical Rx Program Update

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

5. **Action Item – Vote to Prior Authorize Chronic Obstructive Pulmonary Disease Medications – See Appendix C.**
 - A. COP Recommendations

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

6. **Action Item - Vote to Prior Authorize Select Oral Corticosteroid Medications – See Appendix D.**
 - A. COP Recommendations
 - B. Utilization Details

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

7. **Action Item – Annual Review of Diabetes Medications and 30 Day Notice to Prior Authorize Juvisync[®], Bydureon[®], Jentaduetto[®], Janumet XR[®], Nesina[®], Kazano[®], and Oseni[®] – See Appendix E.**
 - A. Current Authorization Criteria
 - B. Utilization Review
 - C. Prior Authorization Review
 - D. Market News and Update
 - E. Cost Comparisons
 - F. COP Recommendations
 - G. Utilization Details
 - H. Product Details

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

8. **Action Item –Annual Review of Anticoagulant Medications and 30 Day Notice to Prior Authorize Eliquis[®] – See Appendix F.**
 - A. Current Authorization Criteria
 - B. Utilization Review
 - D. Prior Authorization Review
 - E. Market News and Update
 - F. COP Recommendations
 - G. Product Details

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

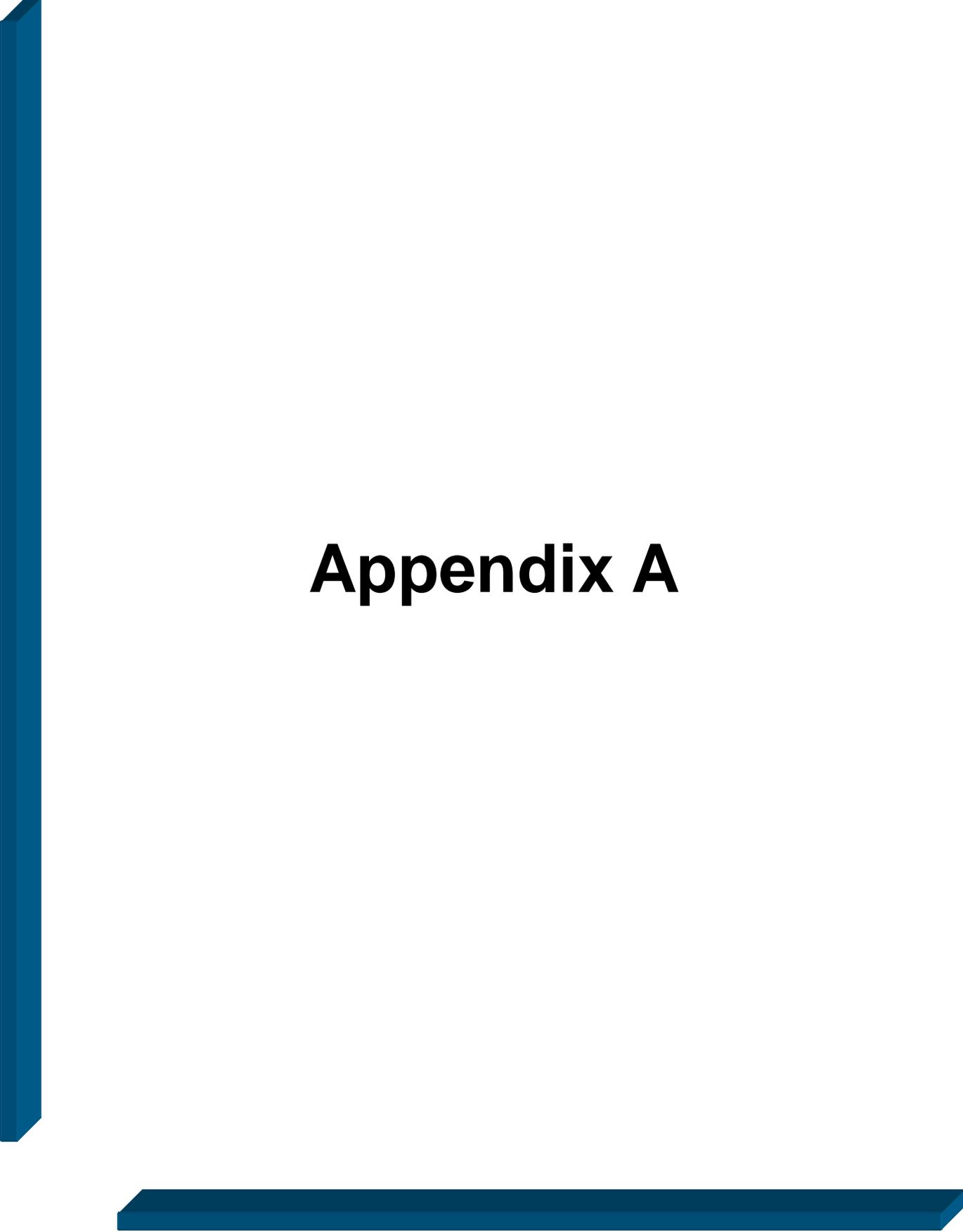
9. **30 Day Notice to Prior Authorize Kuvan[®] – See Appendix G.**
 - A. Introduction and Product Summary
 - B. COP Recommendations
 - C. Product Details

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

10. **30 Day Notice to Prior Authorize Gattex[®] – See Appendix H.**
 - A. Introduction and Product Summary
 - B. Cost Comparison
 - C. COP Recommendations
 - D. Product Details

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

11. **FDA and DEA Updates – See Appendix I.**
12. **Future Business**
 - A. Fiscal Year 2012 Review
 - B. New Product Reviews
 - C. Annual Reviews
13. **Adjournment**



Appendix A

OKLAHOMA HEALTH CARE AUTHORITY
 DRUG UTILIZATION REVIEW BOARD MEETING
 MINUTES of MEETING OF FEBRUARY 13, 2013

BOARD MEMBERS:	PRESENT	ABSENT
Brent Bell, D.O., D.Ph.: Vice-Chairman	X	
Mark Feightner, Pharm.D.	X	
Anetta Harrell, Pharm.D.		X
Evie 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
Bethany Holderread, Pharm. D.; Clinical Pharmacist	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	
Graduate Students: Amany Hussein, Manish Mittal	X	
Visiting Pharmacy Student(s): Khiem Bui; Michael Schraad	X	

OKLAHOMA HEALTH CARE AUTHORITY STAFF:	PRESENT	ABSENT
Nico Gomez, Chief Executive Officer		X
Garth Splinter, M.D., M.B.A.; Medicaid Director		X
Sylvia Lopez, M.D., FAAP, Chief Medical Officer	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
Jennie Melendez, 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:		
Roger Grotzinger, BMS	Clint Degner, Novartis	Mark DeClerk, Lilly
Jim Fowler, AstraZeneca	Mark Kaiser, Otsuka	Larry Curtis, Forest
David Williams, Forest	Charlene Kaiser, Amgen	Brad Burgstahler
Gregory Klingman, Pfizer	Toby Thompson, Pfizer	Brad Clay, Amgen
Brian Maves, Pfizer	Kim Loneragan, Otsuka	

PRESENT FOR PUBLIC COMMENT:	
Chris Hurst	Pfizer

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 NO 7: Speaker: Chris Hurst

ACTION: NONE REQUIRED

AGENDA ITEM NO. 3: APPROVAL OF DUR BOARD MINUTES

3A: January 9, 2013 DUR Minutes

3B: January 10, 2013 DUR Recommendation Memorandum

Dr. Preslar 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: January 2013

4B: Pharmacy Help Desk Activity: January 2013

4C: Retrospective Drug Evaluation: Duplication of Narcotic Therapy

4D: Vote on Brimonidine Safety Recommendations.

Reports not in packet, but on slide; presented by Dr. Le.

Dr. Winegardner moved to approve; seconded by Dr. Bell

ACTION: MOTION CARRIED

AGENDA ITEM NO. 5: UPDATE ANTIHYPERLIPIDEMICS PRIOR AUTHORIZATION CRITERIA, AND PRIOR AUTHORIZE VASCEPA™ AND JUXTAPID™

5A: COP Recommendations

Materials included in agenda packet; presented by Dr. Brandy Nawaz

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 6: VOTE TO PRIOR AUTHORIZE BINOSTO™ AND UPDATE OSTEOPOROSIS MEDICATION PRIOR AUTHORIZATION CRITERIA MEDICATIONS

6A: COP Recommendations

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

Ms. Varalli-Claypool moved to approve; seconded by Dr. Winegardner.

ACTION: MOTION CARRIED

AGENDA ITEM NO. 7: VOTE TO PRIOR AUTHORIZE XELJANZ ®

7A: COP Recommendations

For Public Comment: Chris Hurst

Dr. Le clarifies recommended criteria from the board "the board recommends removing (f.) from criteria #3 ...updated tuberculosis test to be required at one year... Dr. Muchmore states "to obtain a second year of therapy... Dr. Le states "yes...to obtain approval".

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

Dr. Bell moved to approve; seconded by Dr. Preslar.

ACTION: MOTION CARRIED

AGENDA ITEM NO. 8: FY12 ANNUAL REVIEW OF NARCOTIC ANALGESICS

8A: Background and Statistics Update

8B: Current Authorization Criteria and Tier Structure

8C: Utilization review

8D: Prior Authorization Review

8E: COP Recommendations

Dr. Le states "DUR recommendations are to survey doctors, put extended release in tier one, lower immediate release to #120, prescriber profiling".

Materials included in agenda packet; presented by Dr. Le

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 9: 30 DAY NOTICE TO PRIOR AUTHORIZE CHRONIC OBSTRUCTIVE PULMONARY DISEASE MEDICATIONS

9A: COP Recommendations

Materials included in agenda packet; presented by Dr. Weber

ACTION: NONE REQUIRED

AGENDA ITEM NO. 10: 30 DAY NOTICE TO PRIOR AUTHORIZE MISCELLANEOUS CORTICOSTEROID PRODUCTS

10A: Summary

10B: COP Recommendations

Dr. Muchmore "can we possibly make some proposals for possible time limit and age limit, and not necessarily 30 day to discuss for next month".

Materials included in agenda packet; presented by Dr. Moore

ACTION: NONE REQUIRED

AGENDA ITEM NO. 11: FDA AND DEA UPDATES

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

ACTION: NONE REQUIRED

AGENDA ITEM NO. 12: FUTURE BUSINESS

Materials included in agenda packet; submitted by Dr. Cothran

A: Annual Reviews

B: New Product Reviews

ACTION: NONE REQUIRED

AGENDA ITEM NO. 13:

ADJOURNMENT

The meeting was adjourned at 7:42



The University of Oklahoma

Health Sciences Center

COLLEGE OF PHARMACY

PHARMACY MANAGEMENT CONSULTANTS

Memorandum

Date: February 14, 2013

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 February 13, 2013

Recommendation 1: Vote to Apply Age Restriction on Brimonidine Products

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends:

Apply age restriction on brimonidine combination products (Combigan®) and single products (Alphagan-P®) for members 2 years and younger. Use will require a demonstration of clinical necessity not met with other available alternatives.

Recommendation 2: Vote to Update Antihyperlipidemics Prior Authorization Criteria and Prior Authorize Vascepa™ (icosapent ethyl) and Juxtapid™ (Iomitapide)

MOTION CARRIED by unanimous approval.

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 \geq 500 mg/dL), and controlled diabetes (fasting glucose <150 mg/dL at the time of triglycerides measurement and HgA₁C <7.5%), and
 2. Previous failure with both nicotinic acid and fibric acid medications.

These criteria will also apply for Lovaza® (omega-3-fatty-acid).

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

Changes to the Antihyperlipidemics Product Based 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)

Tier 2 approval criteria:

1. A trial with atorvastatin, consisting of at least 8 weeks of continuous therapy, titrated to 40 mg, which 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 rosuvastatin or higher), or
2. Documented adverse effect or contraindication to all available lower tiered products, or
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.
 - i. 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:
 - i. Documented active liver disease, or
 - ii. Documented unexplained, persistent elevations of serum transaminases, or
 - iii. Documented statin related myopathy.

Recommendation 3: Vote to Prior Authorize Binosto™ (Alendronate) and Update Osteoporosis Product Based Prior Authorization Criteria

MOTION CARRIED by unanimous approval.

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, or
 - c. A 12 month trial of Prolia™ (Denosumab), unless contraindicated, intolerant, or allergic, that did not yield adequate results.
 - d. The diagnosis of non-healing fracture may be approved for six months.
 - e. 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 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.
- b. Members with diagnosis in history of Paget's disease will not require prior authorization.

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

Recommendation 4: Vote to Prior Authorize Xeljanz® (Tofacitinib)

MOTION CARRIED by unanimous approval.

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, successful treatment of active tuberculosis, or close evaluation and appropriate treatment of latent 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
4. Subsequent approvals will be for the duration of one year. Yearly approvals require performance of repeat tuberculosis test.

Recommendation 5: Annual Review of Narcotic Analgesics Product Based Prior Authorization Category

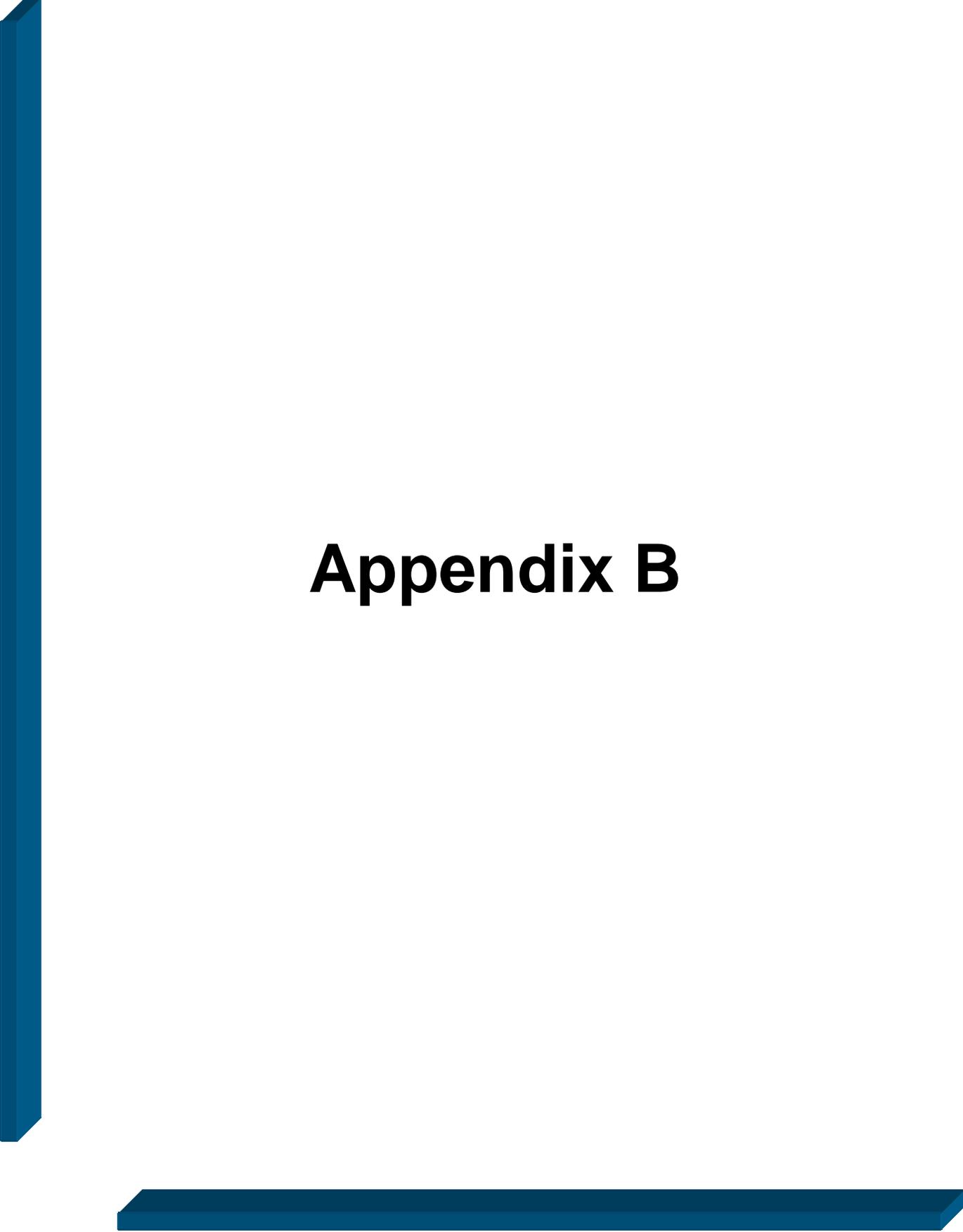
MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the following:

1. Apply an age restriction on oral liquid narcotic analgesic products for all members older than 12 years of age.
2. Apply an age restriction on oral solid dosage forms of narcotic analgesic products for all members younger than 10 years of age.

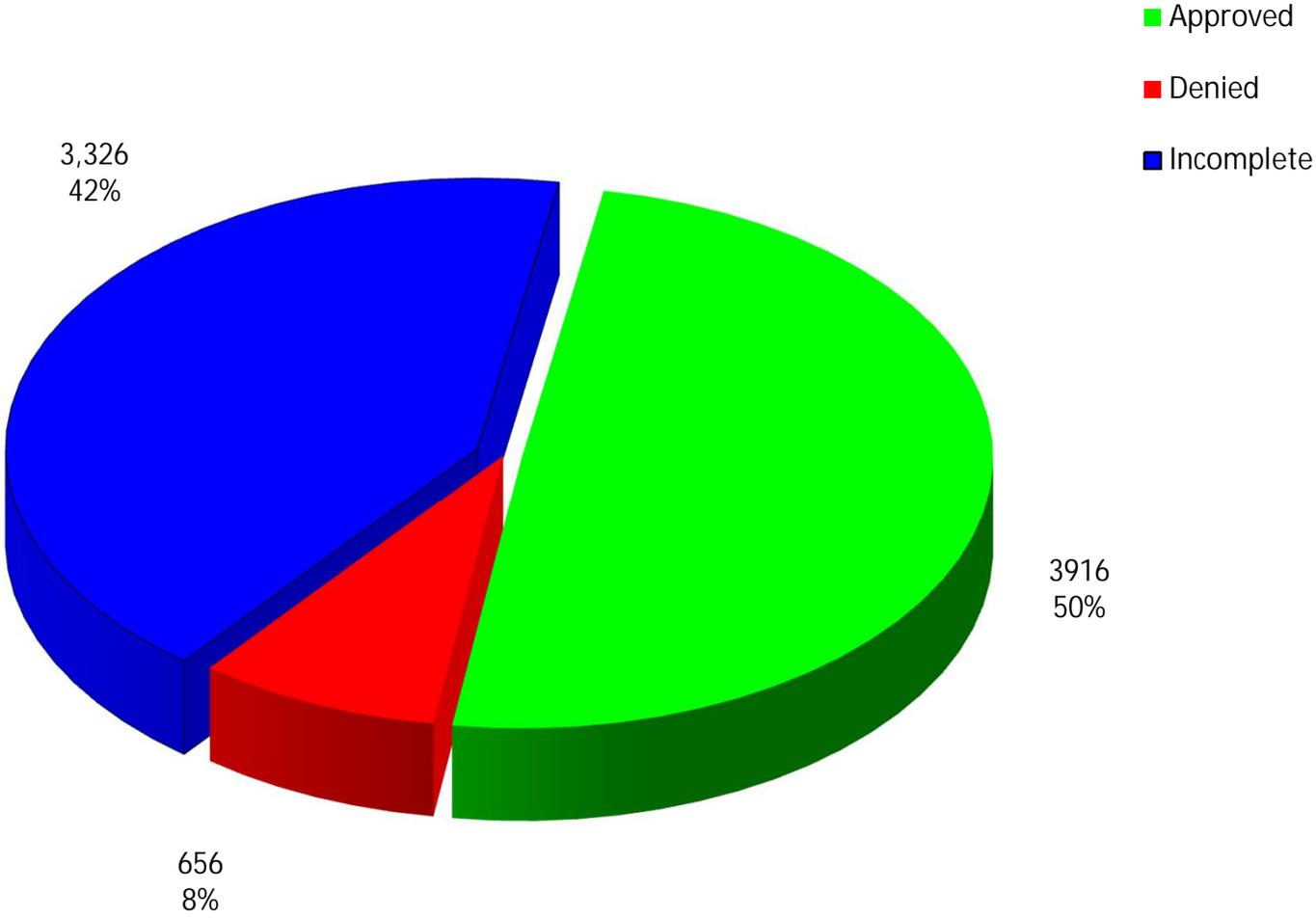
In addition, the DUR Board recommended evaluation of the following:

- Quantity limit of #120 per 30 days supply for all immediate release products
- Placement of morphine sulfate extended release (MS ER) on Tier 1
- Survey prescribers for preference of extended release vs. immediate release use
- Identification of members with diagnosis of chronic pain
- Prescriber profiling according to region, percent of narcotic claims, quantities prescribed



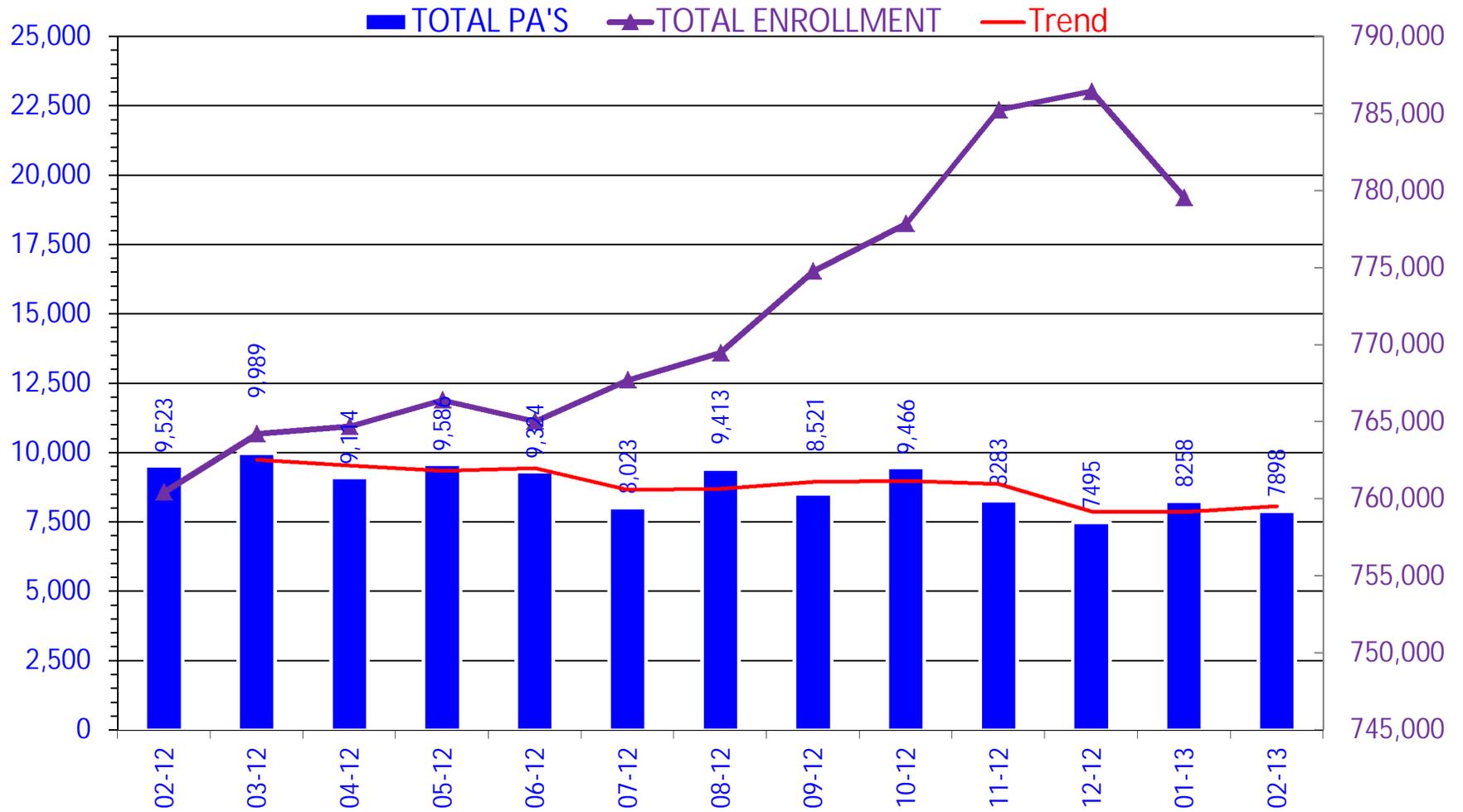
Appendix B

PRIOR AUTHORIZATION ACTIVITY REPORT: February 2013



PA totals include approved/denied/incomplete/overrides

PRIOR AUTHORIZATION REPORT: February 2012- February 2013



PA totals include approved/denied/incomplete/overrides

Prior Authorization Activity

2/1/2013 Through 2/28/2013

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort/Dulera	403	187	11	205	354
Analgesic, Narcotic	386	177	22	187	260
Angiotensin Receptor Antagonist	51	12	9	30	360
Antiasthma	1,011	523	26	462	233
Antibiotic	27	6	0	21	83
Anticoagulant	45	26	1	18	290
Anticonvulsant	63	30	3	30	347
Antidepressant	260	73	31	156	348
Antidiabetic	207	112	11	84	359
Antifungal	10	4	1	5	11
Antigout	15	9	0	6	360
Antihistamine	165	118	6	41	357
Antimigraine	69	28	8	33	334
Antiplatelet	15	11	0	4	352
Antiulcers	282	90	39	153	93
Anxiolytic	74	48	8	18	203
Atypical Antipsychotics	400	253	11	136	342
Benign Prostatic Hypertrophy	14	0	4	10	0
Biologics	58	33	3	22	350
Bladder Control	60	8	12	40	359
Calcium Channel Blockers	10	3	0	7	168
Cardiovascular	47	18	2	27	307
Dermatological	117	23	47	47	100
Endocrine & Metabolic Drugs	109	54	11	44	262
Erythropoietin Stimulating Agents	36	19	5	12	101
Fibromyalgia	184	52	26	106	352
Gastrointestinal Agents	72	26	7	39	141
Glaucoma	19	7	1	11	258
Growth Hormones	87	76	5	6	166
HFA Rescue Inhalers	86	26	6	54	359
Insomnia	88	16	14	58	182
Multiple Sclerosis	16	5	0	11	157
Muscle Relaxant	145	49	32	64	52
Nasal Allergy	161	17	43	101	213
Neurological Agents	41	28	1	12	350
Nsaids	134	22	16	96	351
Ocular Allergy	50	11	6	33	159
Ophthalmic	51	10	1	40	10
Osteoporosis	27	10	3	14	358
Other*	140	20	9	111	267
Otic Antibiotic	38	13	0	25	14
Pediculicide	78	28	9	41	12
Prenatal Vitamins	13	0	2	11	0
Smoking Cess.	18	6	0	12	67
Statins	87	31	6	50	342
Stimulant	492	268	26	198	318
Suboxone/Subutex	136	109	2	25	76
Synagis	82	52	14	16	44

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

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Topical Antibiotic	13	2	3	8	8
Topical Antifungal	112	1	50	61	84
Topical Corticosteroids	40	1	8	31	20
Vitamin	59	22	31	6	320
Pharmacotherapy	62	41	4	17	86
Emergency PAs	2	2	0	0	
Total	6,467	2,816	596	3,055	

Overrides

Brand	30	22	4	4	341
Dosage Change	359	321	2	36	7
High Dose	4	4	0	0	359
IHS-Brand	1	1	0	0	358
Ingredient Duplication	14	12	0	2	63
Lost/Broken Rx	103	98	3	2	4
NDC vs Age	3	3	0	0	4
Nursing Home Issue	145	136	0	9	7
Other	26	16	4	6	3
Quantity vs. Days Supply	693	456	37	200	264
Stolen	1	0	1	0	0
Temporary Unlock	5	4	1	0	28
Third Brand Request	47	27	8	12	47

Overrides Total	1,431	1,100	60	271	
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Total Regular PAs + Overrides	7,898	3,916	656	3,326	
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Denial Reasons

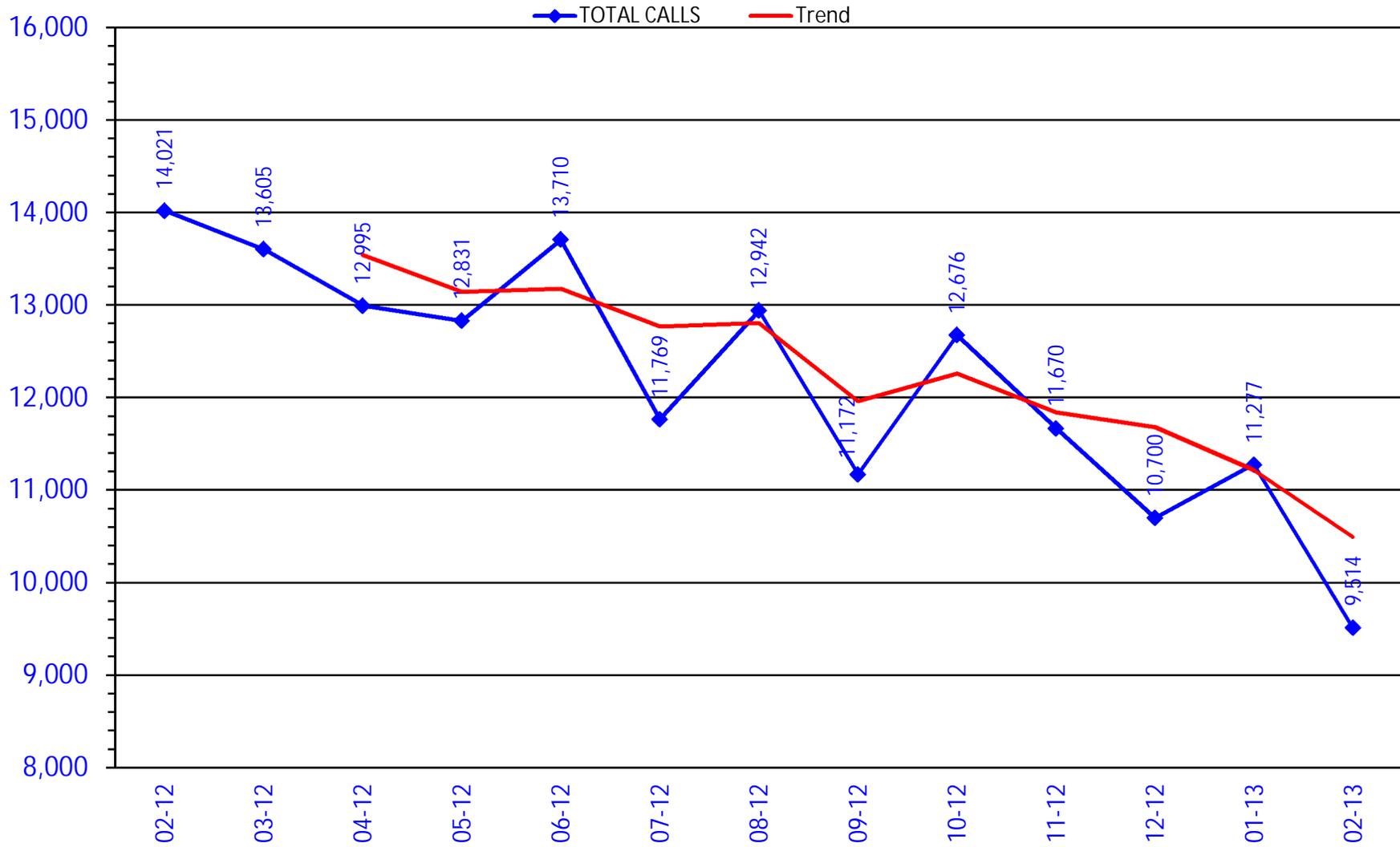
Unable to verify required trials.	2,451
Lack required information to process request.	828
Does not meet established criteria.	673

Other PA Activity

Duplicate Requests	553
Letters	2,330
No Process	388
Changes to existing PAs	511
Partials	813

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

CALL VOLUME MONTHLY REPORT: February 2012- February 2013



SoonerCare Atypical Rx Program Update

*Oklahoma Health Care Authority
March 2013*

Physician Response to Third Mailing: Adherence to Atypical Antipsychotics

A total of 771 prescribers were listed on paid pharmacy claims for atypical antipsychotics between June 1, 2012 and December 31, 2012. A total of 6,710 members were reviewed for adherence to their atypical antipsychotic. Adherence was defined as having a medication possession ration (MPR) of > 0.80 . This value was obtained by dividing the number of days a medication was available to a member, by the number of days in the review period. In order to be included in the mailing, a member had to have an MPR of ≤ 0.60 .

There were 4,105 members flagged as having an MPR of less than 0.80 and 1,362 members with an MPR of ≤ 0.60 who were included in the mailing. Packets were mailed to 200 prescribers in January 2013. The packets included information regarding the 1,362 individual members flagged and an optional individual member response page which allows the prescriber to provide feedback. Because some prescribers had multiple members, the maximum number of members included in a single packet was 10 in order to keep the volume manageable for the individual prescriber. We received responses for 456 members.

Summary of Mailing

Letters/Physicians	#
Total Letters Mailed	200
Members	
Total Members Included	1,362
Total Responses Received	456

Prescriber Response Summary

Q#	Response	Total*
Q1	Not my patient.	10
Q2	No longer my patient.	85
Q3	Medication has been changed prior to date of review letter.	58
Q4	I was unaware of this situation and will consider making appropriate changes in therapy.	44
Q5	I am aware of this situation and will plan to continue monitoring this therapy.	180
Q6	I am continuing this medication from an original psychiatric prescription.	46
Q7	Other, comments.	154

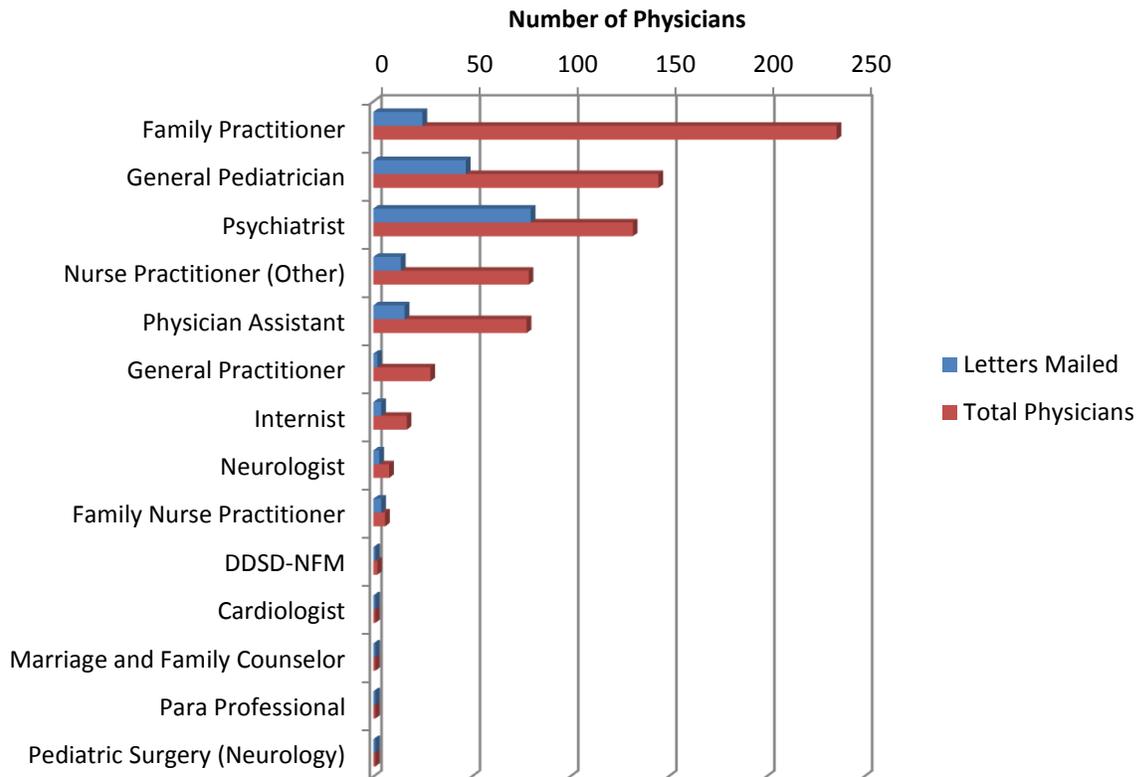
*Members can be included in multiple categories.

Summary of Additional Comments Provided

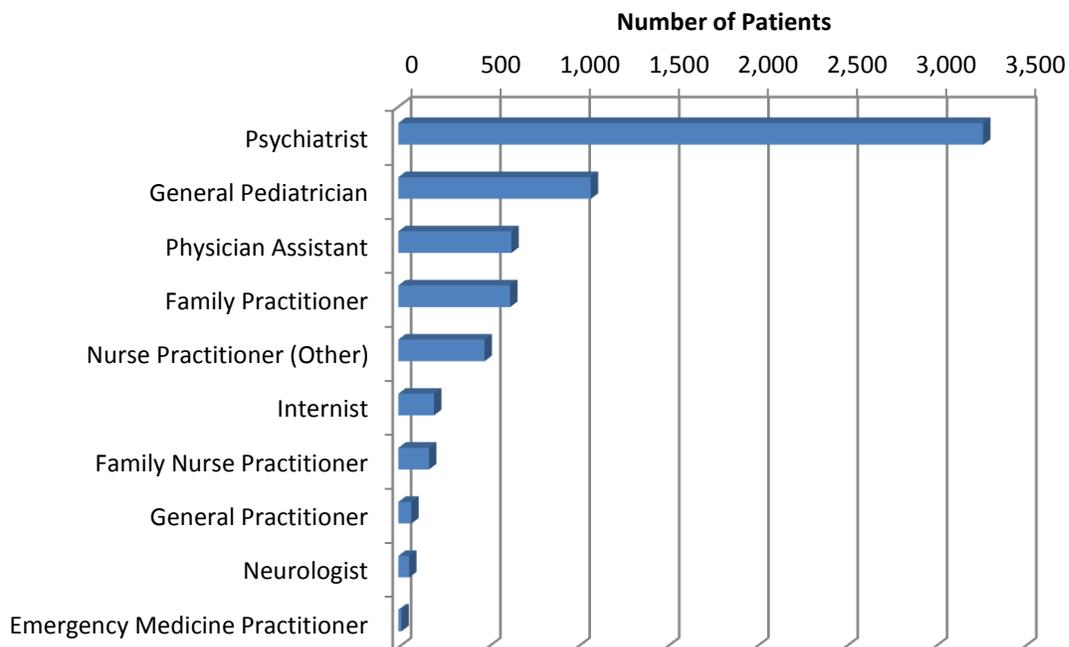
Comment Category	Total*
Patient has missed appointments/reports non-compliance/dropped out of treatment	34
Drug discontinued/medication change/lack of efficacy	25
Dose adjustment	14
One-time fill or used 'as needed'	14
Patient specific information provided	13
Doctor no longer seeing patient/admitted to inpatient	11
Diagnosis or current medications or regimen provided	10
Patient reports consistent use/doing well	8
Attempts to wean medication unsuccessful	7
Continuing medications from previous prescriber	3

*Members can be included in multiple categories, single categories not included.

Total Physicians versus Letters Mailed by Prescriber Specialty



Top Ten Prescriber Specialties by Number of Members Reviewed



Next Mailing – March 2013

The next mailing is planned for the end of March and will address metabolic monitoring for all members (see attachment 1). For this project, metabolic monitoring will be determined by the presence of a CPT code for metabolic panels, glucose testing, A1cs, lipid panels, cholesterol or triglycerides. The review period will be for one year and will be prevalent in nature (not based on a new start of an atypical antipsychotic). Members will be eligible for inclusion in the mailing if they do not have any metabolic or glucose testing during the year. Members with a diagnosis of hyperlipidemia will be included if they do not have any lipid testing during the year. Because it is not recommended that members with a normal lipid profile be monitored each year, members without any lipid testing will be not be included in the mailing if they have received metabolic testing. Initial review of the metabolic metric indicate that approximately 75% of the members < 21 years of age included in the review were eligible to receive a letter (had not received monitoring). The mailing will be limited to 200 unique prescribers not included in the last two mailings where possible.

Attachment 1: Metabolic Monitoring Insert for March Mailing

Recommended Metabolic Monitoring of Atypical Antipsychotics

Atypical antipsychotics are associated with undesirable metabolic effects and can potentially perpetuate cardiovascular complications.¹ In 2003, the Food and Drug Administration required a class warning be added to product labeling for all atypical antipsychotics. This warning described an increased risk of hyperglycemia and diabetes mellitus, including the potential for extreme hyperglycemia associated with ketoacidosis, hyperosmolar coma, or death. Monitoring is vital in minimizing adverse drug events and improving therapeutic outcomes.²

Weight Gain

Baseline weight should be obtained upon initiation of therapy, and reassessed at 4, 8, and 12 weeks. Other key monitoring parameters include, body mass index (BMI) and abdominal waist circumference.³ It is recommended that nutrition and physical activity counseling be provided for all patients who are overweight or obese.^{4,5}

Glucose Monitoring

Studies have shown up to a fourfold increased rate of diabetes among children exposed to atypical antipsychotics in comparison with children not exposed.⁶ Baseline fasting plasma glucose should be obtained upon initiation of atypical antipsychotic therapy, and reassessed at 3 months and yearly thereafter.⁴ Routine monitoring of A₁C levels is also advised. The increased risk of diabetes with these agents is an important drug safety and public health issue.

Dyslipidemia

Baseline lipid profiles should be obtained upon initiation of therapy, and reassessed at 3 months for evaluation of atypical antipsychotic associated cardiovascular risk. Repeated testing at 5-year intervals is recommended for individuals with a normal lipid profile.⁴ High risk individuals may require lipid-lowering agents to decrease the threat of cardiovascular malignancies.⁵

References

1. [Nasrallah HA](#). Atypical Antipsychotic-Induced Metabolic Side Effects: Insights from Receptor-Binding Profiles. *Mol Psychiatry*. 2008 Jan;13(1):27-35. Epub 2007 Sep 11.
2. Rosack J. FDA to require diabetes warning on antipsychotics. *Psychiatr News*. 2003; 38(20):1.
3. Ackerman S and Nolan L. Bodyweight gain induced by psychotropic drugs: incidence, mechanisms, and management. *CNS Drugs*. 1998 Feb; 9(2):135-51.
4. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologist, North American Association for the Study of Obesity. *Diabetes Care*. 2004 Feb;27(2):596-601.
5. Correll CU, Manu P, Olshansky V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA*. 2009; 302(16):1765–1773.
6. Andrade S, Lo J, Roblin D, et al. Antipsychotic medication use among children and risk of diabetes mellitus. *Pediatrics*. 2011 Dec; 128(6):1135-41.

Post this page for future reference!

Metabolic Monitoring CPT Codes

Metabolic panels, glucose testing, and A1c

80048 Basic metabolic panel
80050 General health panel
80053 Comprehensive metabolic panel
82947 Glucose; quantitative, blood (except reagent strip)
82948 Glucose; quantitative, blood (reagent strip)
82950 Glucose; post glucose dose (includes glucose)
82951 Glucose; tolerance test (GTT), three specimens (includes glucose)
83036 Glycohemoglobin (A1c)

Lipids

80061 Lipid panel
82465 Cholesterol, serum or whole blood, total
83700 Lipoprotein, blood; electrophoretic separation and quantitation (form. 83715)
83701 Lipoprotein, blood; high resolution fractionation... (form. 83716)
83704 Lipoprotein, blood; quantitation of lipoprotein particle numbers...
83715 Lipoprotein, blood; electrophoretic separation and quantitation
83716 Lipoprotein, blood; high resolution fractionation...
83721 Lipoprotein, direct measurement, LDL cholesterol
84478 Triglycerides

Possible reasons your patient was flagged as unmonitored when monitoring had been performed:

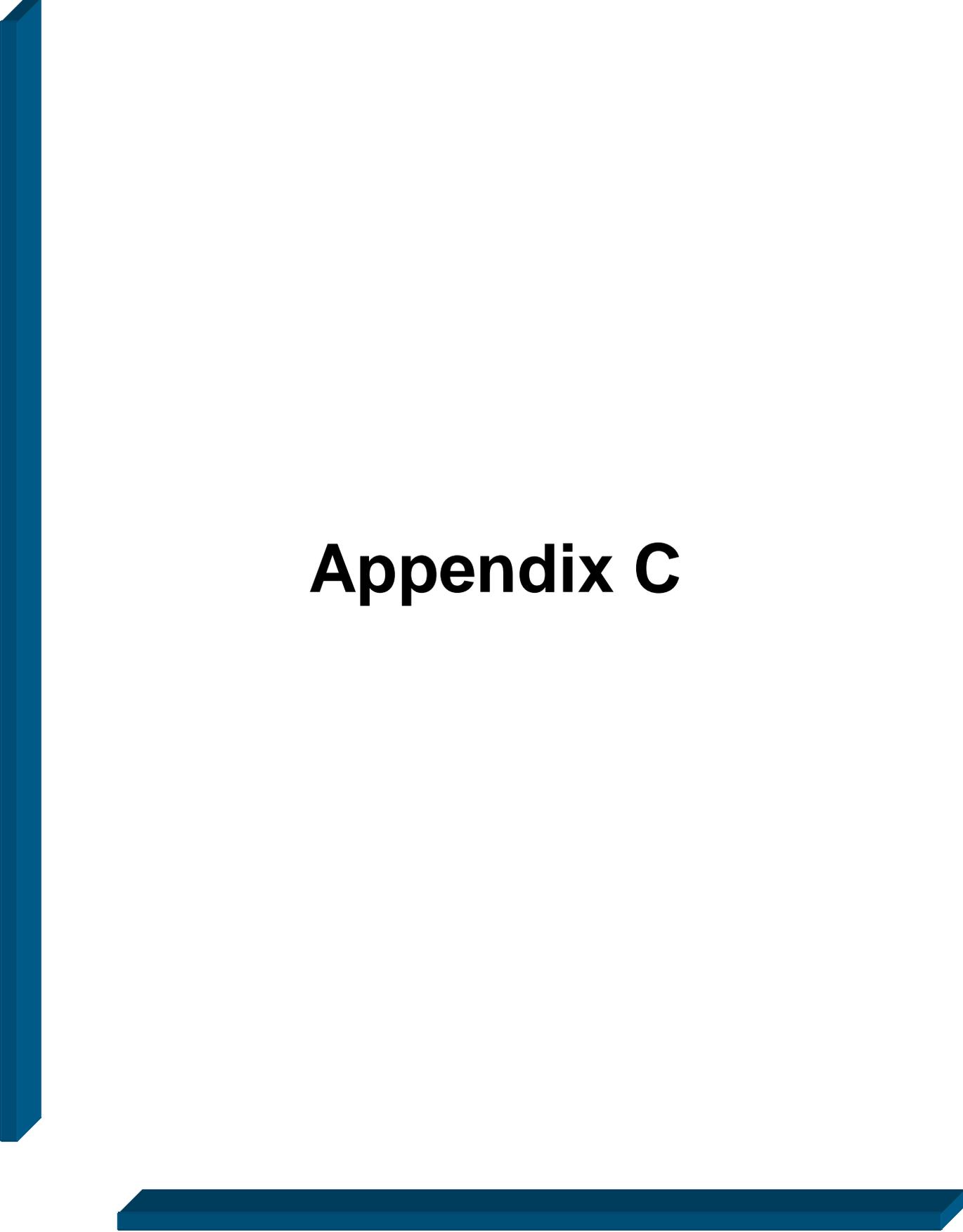
- Billing was processed by a hospital-associated claim.
- CPT code used is not listed above.
- Date of service for the monitoring was outside of the review period.

If you routinely use coding not listed above, please provide this information on the response form so that it can be considered for inclusion in future reviews.

Note: CPT codes, with the exception of 83036 (A1c) and 83704 (lipids) were taken from:

Morrato, E. H., J. W. Newcomer, et al. (2009). "Metabolic screening after the American Diabetes Association's consensus statement on antipsychotic drugs and diabetes." *Diabetes care* **32**(6): 1037-1042.

Morrato, E. H., G. E. Nicol, et al. (2010). "Metabolic screening in children receiving antipsychotic drug treatment." *Archives of pediatrics & adolescent medicine* 164(4): 344-351.



Appendix C

Vote to Prior Authorize Chronic Obstructive Pulmonary Disease Medications

Oklahoma Health Care Authority
March 2013

This category was introduced for possible inclusion in the Product Based Prior Authorization program in December 2012. See the December 2012, January 2013, and February 2013 DUR packet for a more complete discussion of the category. This notice is presented to meet the statutory requirements of 63 O.S. Sec. 5030.5.

Recommendations

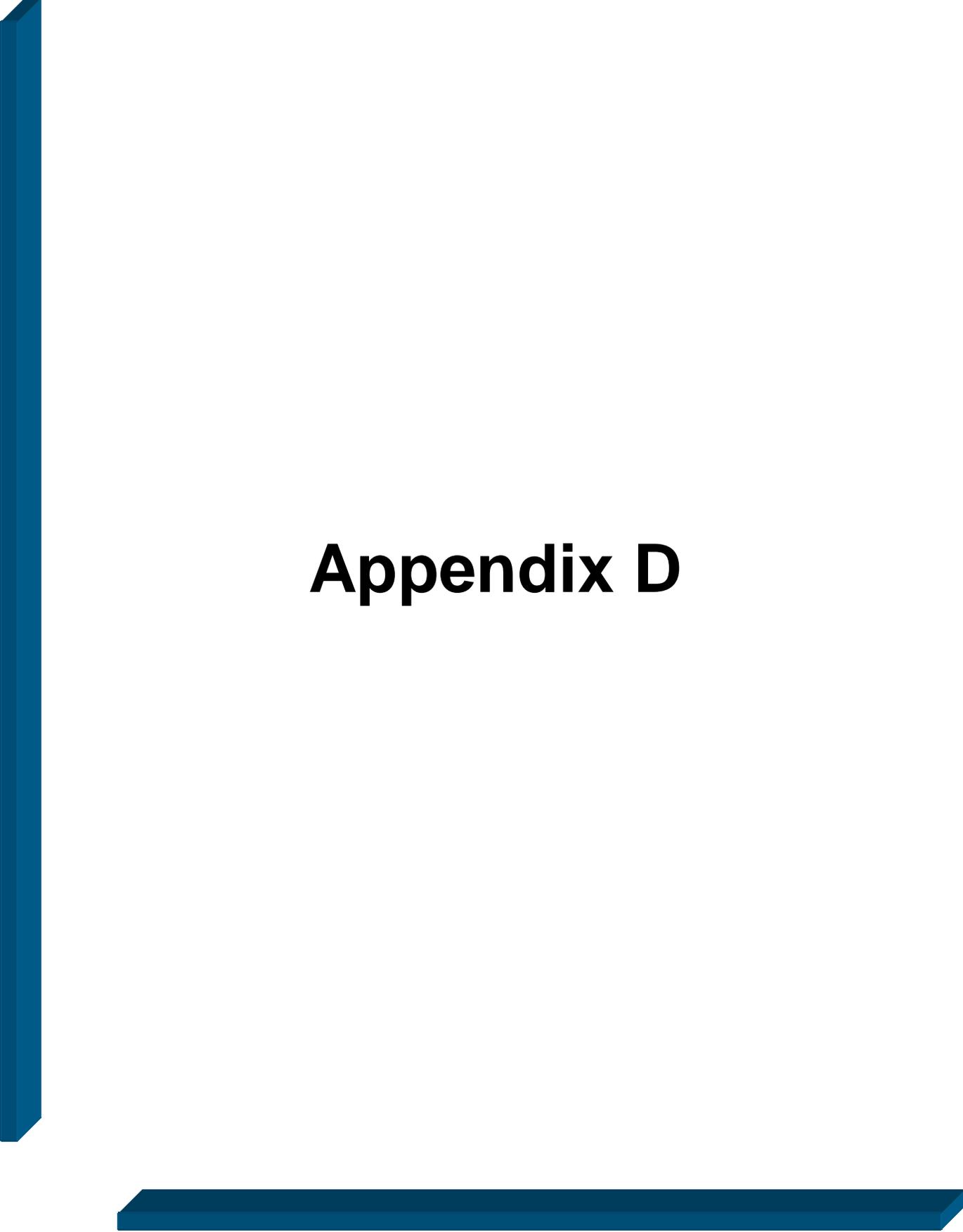
The College of Pharmacy recommends establishing a Product Based Prior Authorization category for long acting bronchodilator medications to ensure appropriate and cost-effective utilization in accordance with current treatment guidelines. The following Tier 1 drug list has been determined to be acceptable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

Vote to Prior Authorize Miscellaneous Corticosteroid Products

Oklahoma Health Care Authority
March 2013

Recommendations

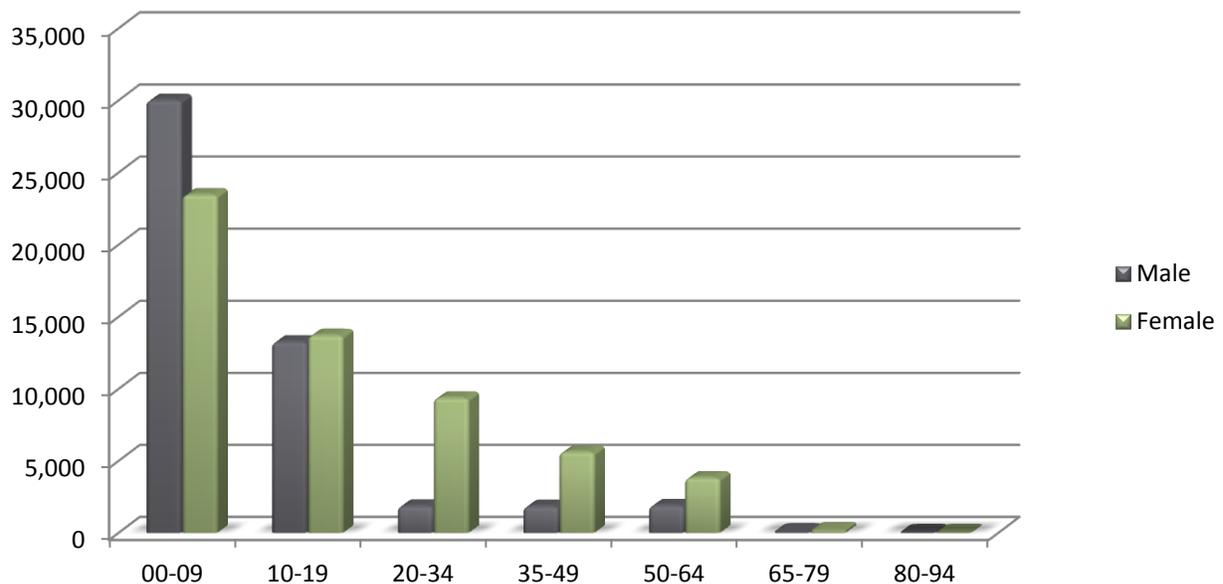
The College of Pharmacy recommends prior authorization of the following products:

- Orapred ODT® (prednisolone sodium phosphate, orally disintegrating tabs)
- Prednisolone sodium phosphate oral solution: 5 mg/5 ml, 20 mg/5 ml (Veripred™), and 25 mg/5ml

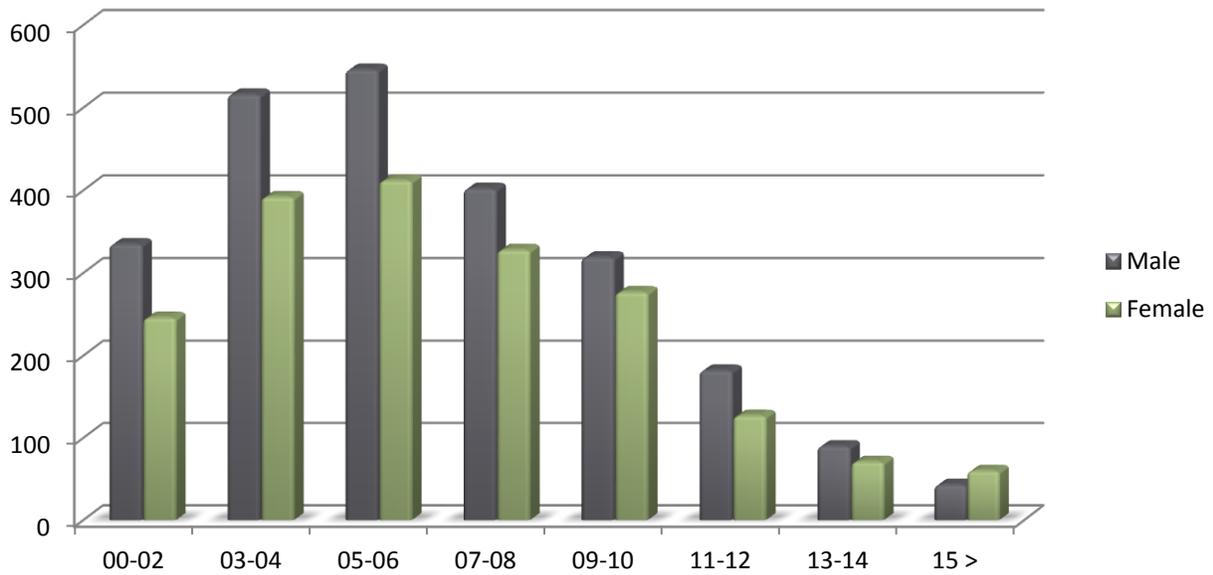
Approval Criteria:

1. Approval requires a patient specific, clinically significant reason why the member cannot use a tablet or an alternative strength liquid formulation.
2. Orapred ODT® will have a quantity limit of 10 tabs per month available without prior authorization for members 10 years or younger.

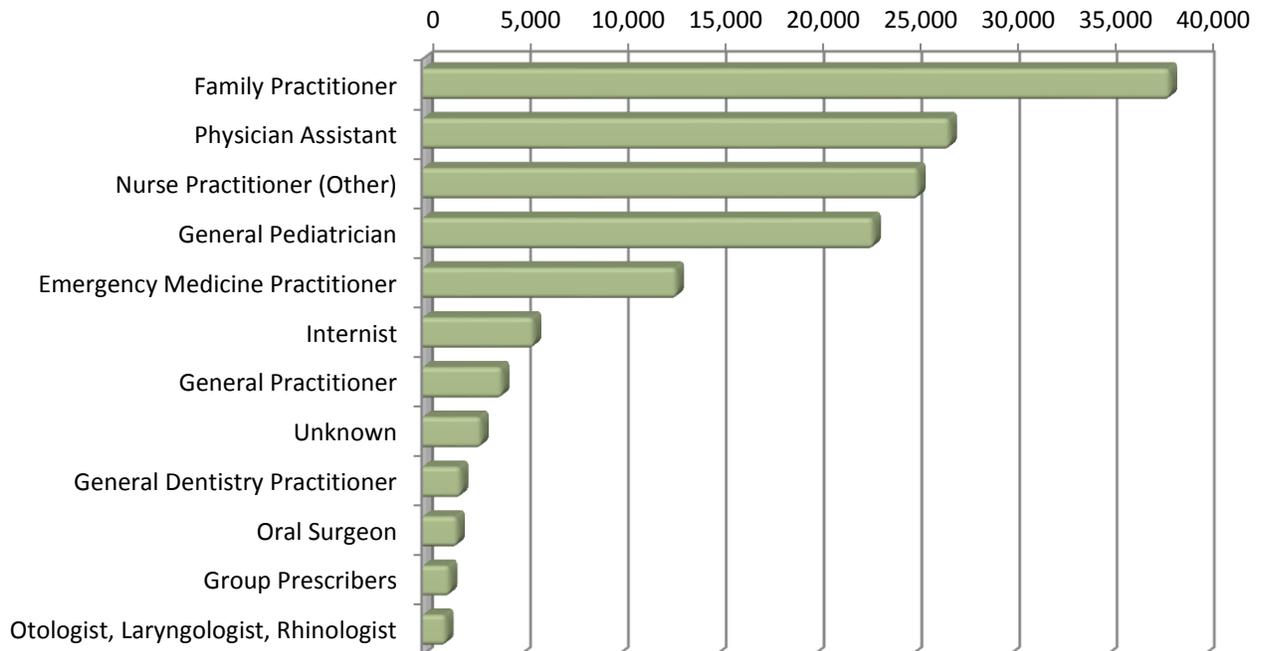
Demographics – Solid and Liquid Dosage Forms



Demographic - Orapred ODT®



Prescriber Specialty by Claims - Solid and Liquid Dosage Forms



Corticosteroid Utilization Details or Oral Solid Products: Fiscal Year 2012

Medication	Claims	Members	Paid	Cost/ mg	Cost/ Day	Units/ Day	Claims/ Member	% Paid
BUDESONIDE CAP 3MG/24HR	133	52	\$130,099.54	\$3.69	\$32.54	2.65	2.56	8.42%
ENTOCORT EC CAP 3MG/24HR	3	3	\$4,022.12	\$6.14	\$45.19	2.7	1	0.26%
CORTISONE AC TAB 25MG	37	7	\$783.92	\$0.01	\$0.57	1.68	5.29	0.05%
DEXAMETHASON TAB 0.5MG	121	70	\$640.06	\$0.26	\$0.24	1.17	1.73	0.04%
DEXAMETHASON TAB 0.75MG	109	83	\$849.47	\$0.27	\$0.50	1.92	1.31	0.06%
DEXAMETHASON TAB 1MG	173	113	\$1,977.57	\$0.20	\$0.91	2.94	1.53	0.13%
DEXAMETHASON TAB 1.5MG	16	11	\$147.03	\$0.12	\$0.76	2.58	1.45	0.01%
ZEMA-PAK PAK 6 DAY	2	2	\$43.74	\$0.12	\$1.62	1.56	1	0.00%
DEXAMETHASON TAB 2MG	168	109	\$2,801.91	\$0.20	\$1.16	1.98	1.54	0.18%
DEXAMETHASON TAB 4MG	1,773	1,314	\$11,937.06	\$0.05	\$0.67	2.23	1.35	0.77%
DEXAMETHASON TAB 6MG	27	26	\$226.47	\$0.07	\$1.80	2.89	1.04	0.01%
HYDROCORT TAB 5MG	768	131	\$18,736.49	\$0.06	\$0.89	2.71	5.86	1.21%
CORTEF TAB 5MG	2	2	\$79.46	\$0.09	\$1.32	3.58	1	0.01%
HYDROCORT TAB 10MG	296	79	\$11,176.37	\$0.05	\$1.27	2.64	3.75	0.72%
CORTEF TAB 10MG	27	4	\$345.45	\$0.07	\$0.44	0.98	6.75	0.02%
HYDROCORT TAB 20MG	361	98	\$4,551.21	\$0.02	\$0.38	1.79	3.68	0.29%
MEDROL TAB 2MG	4	4	\$77.68	\$0.39	\$1.41	8.45	1	0.01%
METHYLPRED TAB 4MG	439	354	\$18,195.92	\$0.30	\$2.64	2.34	1.24	1.18%
METHYLPRED TAB 8MG	5	5	\$180.31	\$0.26	\$4.62	2.49	1	0.01%
METHYLPRED TAB 16MG	90	84	\$3,486.01	\$0.17	\$3.55	1.2	1.07	0.23%
MEDROL TAB 32MG	2	1	\$136.48	\$0.15	\$1.52	0.33	2	0.01%
METHYLPRED TAB 32MG	2	2	\$34.13	\$0.13	\$5.69	1.17	1	0.00%
METHYLPRED PAK 4MG	21,818	19,117	\$572,556.01	\$0.30	\$4.25	3.41	1.14	37.07%
MEDROL PAK 4MG	162	120	\$3,486.76	\$0.37	\$3.52	3.08	1.35	0.23%
MILLIPRED TAB 5MG	135	121	\$1,884.31	\$0.10	\$1.75	2.74	1.12	0.12%
MILLIPRED DP PAK 5MG	894	801	\$22,948.38	\$0.13	\$3.69	3.49	1.12	1.49%
ORAPRED ODT TAB 10MG	879	760	\$69,174.90	\$0.69	\$11.61	1.71	1.16	4.48%
ORAPRED ODT TAB 15MG	3,066	2,591	\$290,339.58	\$0.69	\$15.86	1.49	1.18	18.80%
ORAPRED ODT TAB 30MG	1,416	1,202	\$147,866.03	\$0.49	\$19.38	1.28	1.18	9.57%
PREDNISONE TAB 1MG	343	121	\$4,470.25	\$0.07	\$0.47	3.17	2.83	0.29%
PREDNISONE TAB 2.5MG	114	60	\$731.51	\$0.05	\$0.22	1.81	1.9	0.05%
PREDNISONE TAB 5MG	4,547	3,049	\$19,085.38	<\$0.01	\$0.20	1.94	1.49	1.24%
PREDNISONE TAB 10MG	13,028	10,151	\$63,143.65	<\$0.01	\$0.38	2.17	1.28	4.09%
PREDNISONE TAB 20MG	24,489	19,941	\$109,835.82	<\$0.01	\$0.60	1.89	1.23	7.11%
PREDNISONE TAB 50MG	4,086	3,565	\$20,104.12	<\$0.01	\$0.88	1.04	1.15	1.30%
PREDNISONE PAK 5MG	393	377	\$2,799.92	\$0.03	\$0.83	2.91	1.04	0.18%
PREDNISONE PAK 10MG	566	514	\$5,318.56	\$0.02	\$1.17	3.43	1.1	0.34%
TOTALS	80,498	56,601*	\$1,544,351.14		\$2.08	2.28	1.42	100%

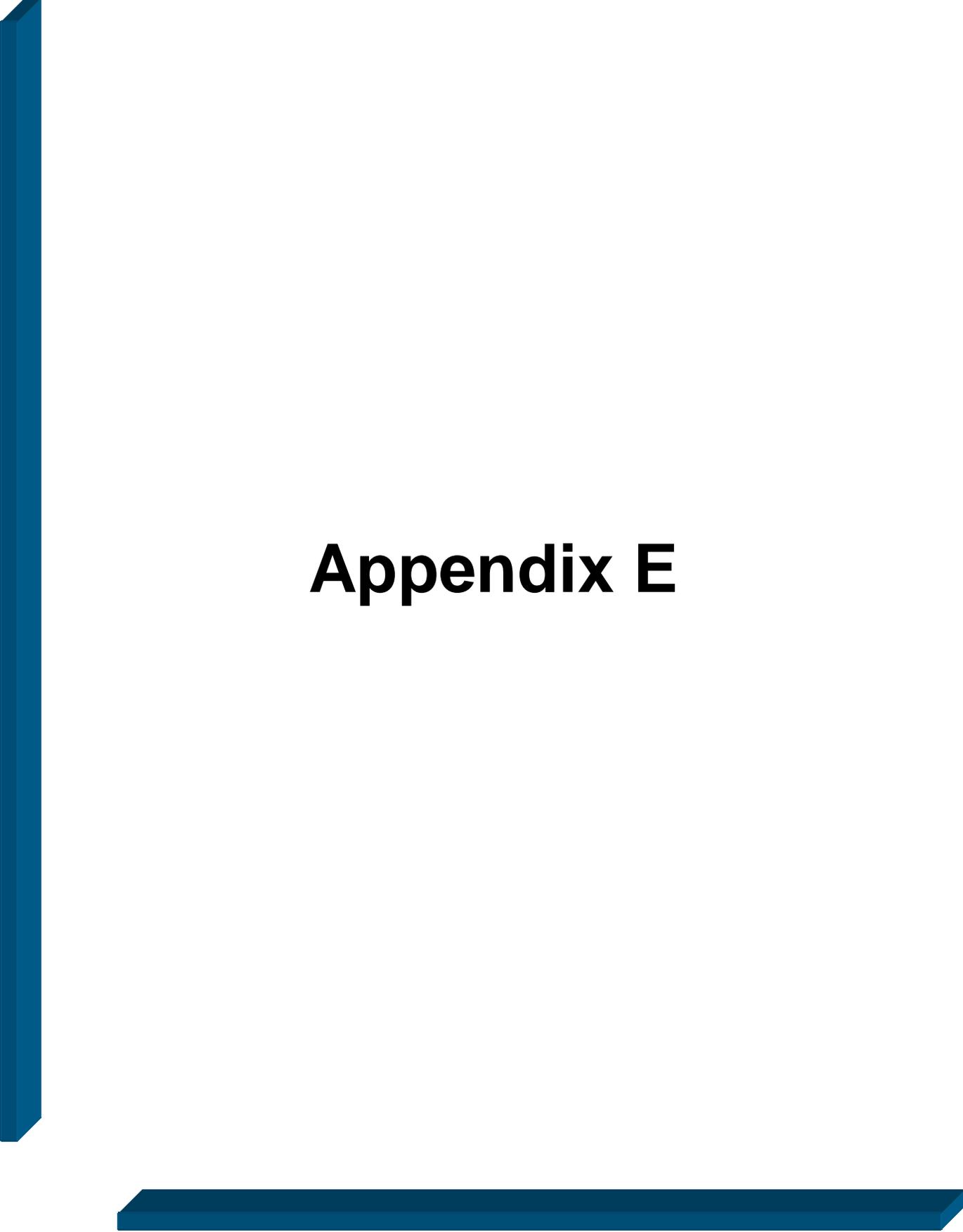
*Total number of unduplicated members

Corticosteroid Utilization Details of Oral Liquid Products: Fiscal Year 2012

Medication	Claims	Members	Paid	Cost/ mg	Cost/ Day	Units/ Day	Claims/ Member	% Paid
DEXAMETHASON CON 1MG/ML	169	139	\$2,913.47	\$0.62	\$2.88	4.11	1.22	0.35%
DEXAMETHASON ELX 0.5/5ML	1,664	1,374	\$32,868.79	\$2.30	\$2.75	24.71	1.21	3.92%
BAYCADRON ELX 0.5/5ML	1	1	\$19.18	\$2.30	\$1.60	15	1	0.00%
DEXAMETHASON SOL 0.5/5ML	557	474	\$5,605.16	\$2.30	\$1.40	13.55	1.18	0.67%
PRED SOD PHO SOL 5MG/5ML	3,078	2,700	\$44,448.44	\$0.23	\$2.42	9.26	1.14	5.31%
PRED SOD PHO SOL 6.7/5ML	635	529	\$8,570.25	\$0.23	\$2.10	8.98	1.2	1.02%
PEDIAPRED SOL 6.7/5ML	3	2	\$76.35	\$0.49	\$7.63	20	1.5	0.01%
MILLIPRED SOL 10MG/5ML	6,610	5,360	\$127,152.85	\$0.17	\$3.38	8.36	1.23	15.18%
PREDNISOLONE SOL 15MG/5ML	33,833	25,772	\$298,842.47	\$0.03	\$1.54	6.9	1.31	35.68%
VERIPRED 20 SOL 20MG/5ML	6,610	5,167	\$173,038.33	\$0.17	\$4.58	5.94	1.27	20.66%
PREDNISOLONE SYP 5MG/5ML	1	1	\$4.17	\$0.13	\$2.08	60	1	0.00%
PREDNISOLONE SYP 15MG/5ML	1	1	\$6.11	\$0.03	\$1.22	5	1	0.00%
PREDNISOLONE SOL 15MG/5ML	19,606	16,290	\$131,718.73	\$0.03	\$1.15	6.9	1.2	15.73%
PREDNISOLONE SYP 15MG/5ML	10	10	\$69.49	\$0.03	\$1.16	13	1	0.01%
PREDNISONE CON 5MG/ML	16	16	\$1,106.82	\$0.25	\$7.09	6.28	1	0.13%
PREDNISONE SOL 5MG/5ML	717	676	\$11,150.68	\$0.18	\$2.33	11.36	1.06	1.35%
TOTALS	73,469	51,699**	\$837,591.29		\$1.96	7.67	1.42	100%

*Total number of unduplicated members

**Prednisolone 25 mg/5 ml was approved in September 2012, no data available, cost/mg = \$0.14



Appendix E

Calendar Year 2012 Annual Review of Diabetes Medication and 30 Day Notice to Prior Authorize Juvisync® (sitagliptin/simvastatin), Bydureon® (exenatide ER), Jentadueto® (linagliptin/metformin), Janumet XR® (sitagliptin/metformin ER), Nesina® (alogliptin), Kazano® (alogliptin/metformin), and Oseni® (alogliptin/pioglitazone)

Oklahoma Health Care Authority, March 2013

Current Prior Authorization Criteria Implemented January 2012

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

Tier 1	Tier 2*	Tier 3	Special PA
<u>Biaguanides</u>	<u>DPP-4 Inhibitors</u>	<u>GLP-1 Agonists</u>	<u>Biaguanides</u>
Metformin (Glucophage®)	Linagliptin (Tradjenta®)	Exenatide (Byetta®)	Metformin solution (Riomet®)
Metformin SR (Glucophage XR®)	Saxagliptin (Onglyza®)		Metformin Long-Acting (Fortamet®, Glumetza®)
Metformin-Glyburide (Glucovance®)	Saxagliptin-Metformin (Kombiglyze®)	<u>Alpha-Glucosidase Inhibitors</u>	
Metformin-Glipizide (Metaglip®)	Sitagliptin (Januvia®)	Miglitol (Glyset®)	<u>Thiazolidinediones</u>
	Sitagliptin-Metformin (Janumet®)		Rosiglitazone (Avandia®)
<u>Sulfonylureas</u>	<u>Glinides</u>		Pioglitazone (Actos®)
Glyburide (Diabeta®)	Repaglinide-Metformin (Prandimet®)		Rosiglitazone-Metformin (Avandamet®)
Glyburide Micronized (Micronase®)	Repaglinide (Prandin®)		Rosiglitazone-Glimepiride (Avandaryl®)
Glipizide (Glucotrol®)	Nateglinide (Starlix®)		Pioglitazone-Metformin (Actoplus Met®, Actoplus Met XR®)
Glipizide SR (Glucotrol XL®)	<u>GLP-1 Agonists</u>		Pioglitazone-Glimepiride (Duetact®)
Glimepiride (Amaryl®)	Liraglutide (Victoza®)		
<u>Miscellaneous</u>	<u>Alpha-Glucosidase Inhibitors</u>		<u>Amylinomimetic</u>
Chlorpropamide	Acarbose (Precose®)		Pramlintide (Symlin®)
Tolbutamide			

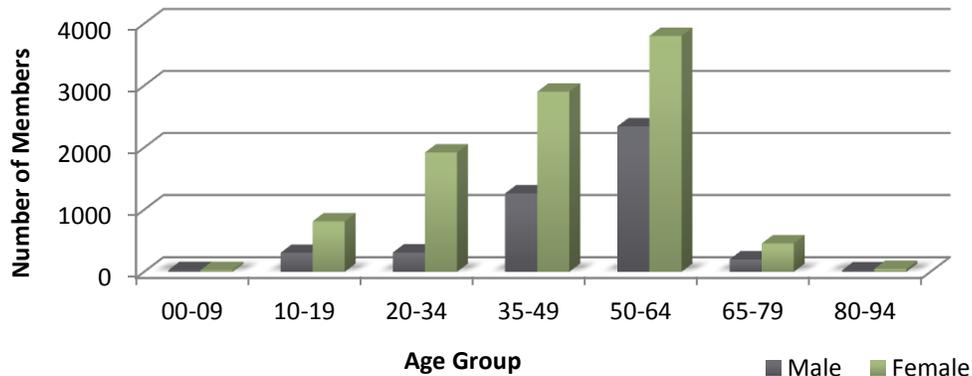
*Supplemental rebate for Tier 3 products or similarly priced generic products only.

Utilization of Diabetes Medications

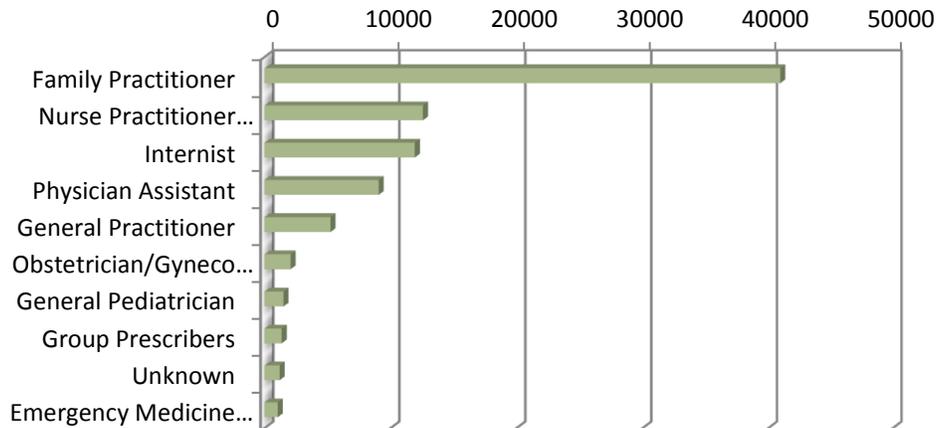
Comparison of Calendar Years (CY)

CY	Members	Claims	Cost	Cost/Claim	Cost/Day	Units	Days
2011	13,896	85,704	\$5,686,802.16	\$66.35	\$1.96	5,282,468	2,897,474
2012	14,428	90,446	\$5,151,869.59	\$56.96	\$1.70	5,620,244	3,024,734
% Change	3.8%	5.5%	-9.4%	-14.2%	-13.3%	6.4%	4.4%
Change	532	4,742	\$534,932.57	\$9.39	\$0.26	337,776	127,260

Demographics of Members Utilizing Diabetes Medications: CY 2012



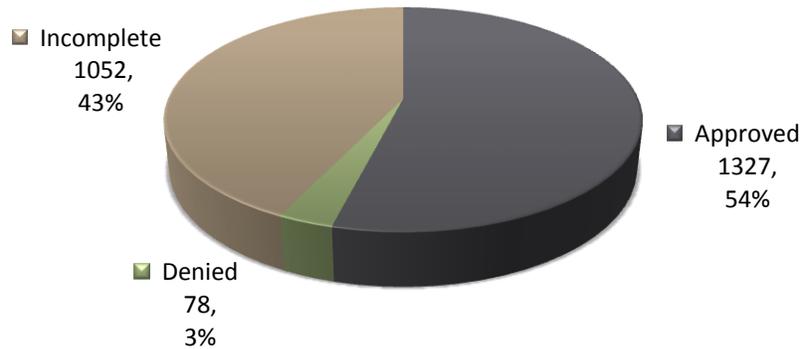
Prescribers of Diabetes Medications by Number of Claims: CY 2012



Prior Authorization of Diabetes Medications

There were a total of 2,457 petitions submitted for this PBPA category during calendar year 2012. Computer edits are in place to detect Tier 1 medications in member's recent claims history and generate automated prior authorizations where possible. The following chart shows the status of the submitted petitions.

Status of Petitions for Diabetes Medications: CY 2012



Market News and Updates

- Fortamet® (metformin) – patent expired October 2011
- Avandia/Avandaryl® (rosiglitazone products) - patent expired March 2012
- Actos® (pioglitazone) – patent expired August 2012
- Juvisync® (sitagliptin/simvastatin) – approved October 2011
- Bydureon® (exenatide) – approved January 2012
- Jentadueto® (linagliptin/metformin) – approved January 2012
- Janumet XR® (sitagliptin/metformin) – approved February 2012
- Nesina® (alogliptin) – approved January 2013
- Kazano® (alogliptin/metformin) – approved January 2013
- Oseni® (alogliptin/pioglitazone) – approved January 2013
- Duetact® (pioglitazone/glimepiride) – generic approved January 2013

Cost Comparisons

Drug Name	EAC/Day	Dosing
Tradjenta®(linagliptin) 5 mg	\$8.51	Once daily
Jentadueto®(linagliptin/metformin) 2.5/1000 mg	\$8.50	Twice daily
Januvia® (sitagliptin) 100 mg	\$8.66	Once daily
Onglyza® (saxagliptin)	\$8.65	Once daily
Kombiglyze® (saxagliptin/metformin) 2.5/1000mg	\$8.64	Up to two daily
Janumet® (sitagliptin/metformin) 50/1000 mg	\$8.66	Twice daily
Janumet XR® (sitagliptin/metformin) 50/1000 mg	\$8.66	Two once daily
Juvisync® (sitagliptin/simvastatin) 100/40 mg	\$8.66	Twice daily
Nesina® (alogliptin) 25 mg	\$8.66	Once daily
Kazano® (alogliptin/metformin) 12.5/1000 mg	\$8.66	Twice daily
Oseni® (alogliptin/pioglitazone) 25/45 mg	\$8.66	Once daily
Victoza (liraglutide) 0.6 mg (2 pack)	\$10.68	Once daily
Byetta (exenatide) 10 mcg (2.4 ml)	\$11.10	Twice daily
Bydureon (exenatide) 2 mg (4 pack)	\$13.17	Once weekly

EAC = estimated acquisition cost

Conclusion and Recommendations

The College of Pharmacy recommends the placement of Jentaduetto® (linagliptin/metformin), Janumet XR® (sitagliptin/metformin ER), Juvisync® (sitagliptin/simvastatin), Nesina® (alogliptin), Kazano® (alogliptin/metformin), and Bydureon® (exenatide ER) into Tier 3 and Oseni® (alogliptin/pioglitazone) into the Special PA category of the Diabetes Medication PBPA category with the following criteria:

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

Tier 1	Tier 2*	Tier 3	Special PA
<u>Biguanides</u> Metformin (Glucophage®) Metformin SR (Glucophage XR®) Metformin-Glyburide (Glucovance®) Metformin-Glipizide (Metaglip®)	<u>DPP-4 Inhibitors</u> Linagliptin (Tradjenta®) Saxagliptin (Onglyza®) Saxagliptin-Metformin (Kombiglyze®) Sitagliptin (Januvia®) Sitagliptin-Metformin (Janumet®)	<u>DPP-4 Inhibitors</u> Sitagliptin-Met ER (Janumet XR®) Sitagliptin-Simvastatin (Juvisync®) Linagliptin-Metformin (Jentaduetto™) Alogliptin (Nesina®) Alogliptin-Metformin (Kazano®)	<u>Biguanides</u> Metformin solution (Riomet®) Metformin Long-Acting (Fortamet®, Glumetza®)
<u>Sulfonylureas</u> Glyburide (Diabeta®) Glyburide Micronized (Micronase®) Glipizide (Glucotrol®) Glipizide SR (Glucotrol XL®) Glimpiride (Amaryl®)	<u>Glinides</u> Repaglinide-Metformin (Prandimet®) Repaglinide (Prandin®) Nateglinide (Starlix®)	<u>GLP-1 Agonists</u> Exenatide (Byetta®) Exenatide Qweek (Bydureon®)	<u>Thiazolidinediones</u> Rosiglitazone (Avandia®) Pioglitazone (Actos®) Rosiglitazone-Metformin (Avandamet®) Rosiglitazone-Glimepiride (Avandaryl®) Pioglitazone-Metformin (Actoplus Met®, Actoplus Met XR®) Pioglitazone-Glimepiride (Duetact®)
<u>Miscellaneous</u> Chlorpropamide Tolbutamide	<u>Alpha-Glucosidase Inhibitors</u> Acarbose (Precose®)	<u>Alpha-Glucosidase Inhibitors</u> Miglitol (Glyset®)	Pioglitazone-Alogliptin (Oseni®) <u>Amylinomimetic</u> Pramlintide (Symlin®)

*Supplemental rebate for Tier 3 products or similarly priced generic products only.

Utilization Details of Diabetes Medications: Calendar Year 2012

Product	Claims	Members	Total Reimbursed	Units/Day	Claims/Member	Cost/Day
Metformin Tab 500 mg	24,564	6,505	\$187,274.27	2.15	3.78	\$0.24
Metformin Tab 1000 mg	19,323	4,336	\$179,465.95	1.95	4.46	\$0.29
Metformin ER Tab 500 mg	4,311	1,234	\$44,805.61	2.26	3.49	\$0.31
Metformin Tab 850 mg	2,044	445	\$21,555.92	2.1	4.59	\$0.33
Metformin ER Tab 750 mg	471	140	\$6,432.72	1.64	3.36	\$0.38
Glumetza Tab 1000 mg	36	5	\$18,106.92	2	7.2	\$17.07
Metformin ER Tab 1000 mg	23	6	\$8,117.82	1.26	3.83	\$10.02
Riomet Solution	8	7	\$856.53	9.62	1.14	\$3.64
Glumetza Tab 500 mg	5	2	\$1,288.32	2.41	2.5	\$8.88
Fortamet Tab 1000 mg	2	1	\$1,236.28	2	2	\$20.60
Metformin Subtotal	50,787		\$469,140.34			
Glipizide Tab 10 MG	3,541	826	\$28,957.47	1.93	4.29	\$0.24
Glipizide Tab 5 mg	3,026	791	\$18,639.98	1.68	3.83	\$0.18
Glipizide ER Tab 10 mg	1,510	350	\$30,473.17	1.56	4.31	\$0.59
Glipizide ER Tab 5 mg	891	247	\$12,276.41	1.35	3.61	\$0.37
Glipizide XL Tab 10 mg	799	198	\$16,462.69	1.43	4.04	\$0.53
Glipizide ER Tab 2.5 MG	343	102	\$4,744.45	1.21	3.36	\$0.37
Glipizide XL Tab 5mg	313	84	\$4,272.80	1.29	3.73	\$0.34
Glipizide-Metformin Tab 5-500 mg	236	41	\$10,426.80	3	5.76	\$1.43
Glipizide XL Tab 2.5mg	76	28	\$1,039.86	1.12	2.71	\$0.35
Glipizide-Metformin Tab 2.5-500 mg	75	17	\$2,928.54	2.39	4.41	\$1.28
Glucotrol XL Tab 2.5 mg	10	6	\$116.00	1	1.67	\$0.39
Glipizide-Metformin Tab 2.5-250 mg	5	1	\$174.76	2	5	\$1.06
Glucotrol Tab 5mg	1	1	\$5.07	0.5	1	\$0.17
Glipizide Subtotal	10,826		\$130,518.00			
Glyburide Tab 5 mg	6,433	1,470	\$122,216.40	2.32	4.38	\$0.58
Glyburide Tab 2.5 mg	1,575	671	\$17,753.41	1.5	2.35	\$0.33
Glyburide-Metformin Tab 5-500 mg	1,357	224	\$21,741.66	3.16	6.06	\$0.52
Glyburide-Metformin Tab 2.5-500 mg	433	81	\$6,211.66	2.48	5.35	\$0.42
Glyburide Tab 1.25 mg	116	37	\$1,134.49	1.25	3.14	\$0.25
Glyburide Micronized Tab 6 mg	100	26	\$1,252.15	2.25	3.85	\$0.38
Glyburide Micronized Tab 3 mg	69	24	\$659.58	1.85	2.88	\$0.26
Glyburide-Metformin Tab 1.25-250 mg	21	5	\$254.76	1.76	4.2	\$0.40
Glyburide Micronized Tab 1.5 mg	5	3	\$44.34	1.14	1.67	\$0.21
Glyburide Subtotal	10,109		\$171,268.45			
Januvia Tab 100 mg	3,907	897	\$1,188,609.56	1.01	4.36	\$7.71
Janumet Tab 50-1000 mg	2,108	385	\$489,980.96	1.96	5.48	\$7.42
Januvia Tab 50 mg	1,068	267	\$335,099.69	1.16	4	\$8.92
Janumet Tab 50-500 mg	670	125	\$159,448.89	1.94	5.36	\$7.38
Januvia Tab 25 mg	172	45	\$50,378.58	1.07	3.82	\$8.22
Janumet XR Tab 100-1000 mg	56	14	\$13,085.78	1	4	\$7.79
Janumet XR Tab 50-1000 mg	44	20	\$7,559.42	1.49	2.2	\$5.79
Janumet XR Tab 50-500 mg	5	1	\$560.95	1	5	\$3.74
Juvisync Tab 100-20 mg	2	2	\$473.72	1	1	\$7.90
Sitagliptin Subtotal	8,032		\$2,245,197.55			
Glimepiride Tab 4 mg	2,144	489	\$20,541.10	1.44	4.38	\$0.26
Glimepiride Tab 2 mg	1,333	344	\$11,231.46	1.3	3.88	\$0.23
Glimepiride Tab 1 mg	397	100	\$2,877.38	1.19	3.97	\$0.19
Glimepiride Subtotal	3,874		\$34,649.94			

Product	Claims	Members	Total Reimbursed	Units/Day	Claims/Member	Cost/Day
Actos Tab 30 mg	887	225	\$327,364.71	0.99	3.94	\$9.34
Actos Tab 45 mg	606	151	\$251,957.80	1	4.01	\$10.19
Actos Tab 15 mg	465	124	\$123,374.75	1.11	3.75	\$6.87
Pioglitazone HCl Tab 30 mg	331	134	\$60,834.41	1	2.47	\$4.59
Pioglitazone Tab 45 mg	198	87	\$42,091.85	0.99	2.28	\$4.90
Pioglitazone Tab 15 mg	165	63	\$23,523.39	1.12	2.62	\$3.46
Actosplus Met Tab 15-850 mg	146	32	\$45,623.37	1.95	4.56	\$9.26
Actosplus Met Tab 15-500 mg	107	24	\$30,551.55	1.81	4.46	\$8.62
Pioglitazone-Metformin Tab 15-850 mg	70	25	\$19,369.65	1.95	2.8	\$8.73
Pioglitazone-Metformin Tab 15-500 mg	40	14	\$10,650.74	1.95	2.86	\$8.45
Actosplus Met XR Tab 15-1000 mg	37	5	\$9,251.00	1.57	7.4	\$8.33
Duetact Tab 4-30 mg	25	5	\$8,229.15	1.04	5	\$10.16
Actosplus Met XR Tab30-1000 mg	12	2	\$5,632.87	1	6	\$10.43
Duetact Tab 2-30 mg	1	1	\$852.26	1	1	\$9.47
Pioglitazone Subtotal	3090		\$959,307.50			
Victoza	1,155	271	\$473,955.84	0.26	4.26	\$13.26
Liraglutide Subtotal	1,155		\$473,955.84			
Onglyza Tab 5 mg	633	134	\$180,711.38	1.03	4.72	\$7.85
Kombiglyze Tab 2.5-1000 mg	121	24	\$25,244.76	1.7	5.04	\$6.42
Kombiglyze Tab 5-1000 mg	107	27	\$34,513.42	1.12	3.96	\$8.61
Onglyza Tab 2.5 mg	98	18	\$22,705.53	1	5.44	\$7.48
Kombiglyze Tab 5-500 mg	8	4	\$2,806.25	1	2	\$7.80
Saxagliptin Subtotal	967		\$265,981.34			
Tradjenta Tab 5 mg	591	143	\$132,192.59	1	4.13	\$7.47
Linagliptin Subtotal	591		\$132,192.59			
Byetta 10 mcg	350	97	\$132,587.78	0.08	3.61	\$10.11
Byetta 5 mcg	136	54	\$46,448.14	0.04	2.52	\$10.34
Bydureon	22	9	\$7,813.67	0.14	2.44	\$12.56
Exenatide Subtotal	508		\$186,849.59			
Nateglinide Tab 120 mg	110	21	\$8,493.15	2.59	5.24	\$2.55
Nateglinide Tab 60mg	65	18	\$5,193.05	2.77	3.61	\$2.58
Starlix Tab 120 mg	1	1	\$102.51	3	1	\$3.42
Nateglinide Subtotal	176		\$13,788.71			
Acarbose Tab 25 mg	88	23	\$3,552.35	3.34	3.83	\$1.35
Acarbose Tab 50 mg	35	9	\$1,761.69	3.34	3.89	\$1.68
Acarbose Tab 100 mg	28	6	\$1,492.11	3	4.67	\$1.77
Acarbose Subtotal	151		\$6,806.15			
Prandin Tab 1 mg	52	11	\$11,154.21	2.19	4.73	\$6.15
Prandin Tab 2 mg	44	8	\$14,726.25	3.63	5.5	\$10.47
Prandin Tab 0.5 mg	18	4	\$2,698.39	1.5	4.5	\$4.50
Prandin Tab 2-500 mg	2	1	\$282.74	2	2	\$4.71
Repaglinide Subtotal	116		\$28,861.59			
Symlin Pen 120	28	3	\$28,479.86	0.36	9.33	\$30.39
Symlin Pen 60	5	2	\$1,780.51	0.1	2.5	\$12.20
Pramlintide Subtotal	33		\$30,260.37			
Tolbutamide Tab 500 mg	12	1	\$1,124.68	4	12	\$3.12
Tolbutamide Subtotal	12		\$1,124.68			
Glyset Tab 50 mg	9	3	\$984.40	2.78	3	\$3.65
Glyset Tab 25 mg	1	1	\$106.05	3	1	\$3.53
Miglitol Subtotal	10		\$1,090.45			

Product	Claims	Members	Total Reimbursed	Units/Day	Claims/Member	Cost/Day
Chlorpropamide Tab 250 mg	3	2	\$76.05	0.9	1.5	\$0.51
Chlorpropamide Tab 100 mg	2	2	\$42.92	2.5	1	\$0.72
Chlorpropamide Subtotal	5		\$118.97			
Tolazamide Tab 250 mg	3	1	\$83.37	1	3	\$0.93
Tolazamide Tab 250 mg	3		\$83.37			
Grand Total	90,446	14,428*	\$5,151,869.59	1.86	6.27	\$1.70

*Total unduplicated number of members

PRODUCT DETAILS OF JENTADUETO® (LINAGLIPTIN/METFORMIN)²

INDICATIONS: Jentadueto® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate.

DOSAGE FORM: 2.5/500mg, 2.5/850mg, and 2.5/1000mg tablets

ADMINISTRATION: twice daily with meals.

CONTRAINDICATIONS: renal impairment, metabolic acidosis, and hypersensitivity.

SPECIAL POPULATIONS:

- **Pregnancy Category B.** There are no adequate and well controlled studies in pregnant women; animal studies revealed no evidence of fetal harm.
- **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.
- **Geriatric Use:** No dose adjustment is needed for age alone.
- **Renal Impairment:** Renal impairment (e.g., serum creatinine ≥ 1.5 mg/dL for men or ≥ 1.4 mg/dL for women, or abnormal creatinine clearance) is contraindicated.
- **Hepatic Impairment:** Impaired hepatic function has been associated with cases of lactic acidosis with metformin therapy therefore Jentadueto® should generally be avoided in patients with clinical or laboratory evidence of hepatic impairment.

WARNINGS & PRECAUTIONS:

- **Hypoglycemia:** A lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with Jentadueto®.
- **Vitamin B₁₂ Levels:** Metformin may lower Vitamin B₁₂ levels. Monitor hematologic parameters annually.
- **Alcohol Intake:** Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake.
- **Hypoxic States:** Cardiovascular collapse (shock) from whatever cause (e.g., acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia) has been associated with lactic acidosis and may also cause prerenal azotemia. Jentadueto® should be promptly discontinued.
- **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with any antidiabetic drug.

ADVERSE REACTIONS: (occurring >2%)

Nasopharyngitis, diarrhea, hypoglycemia, pancreatitis

PRODUCT DETAILS OF JANUMET XR® (SITAGLIPTIN/METFORMIN ER)³

INDICATIONS: Janumet XR® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin extended release is appropriate.

DOSAGE FORM: 50/500mg, 50/1000mg, and 100/1000mg tablets

ADMINISTRATION: once daily with a meal preferably in the evening

CONTRAINDICATIONS: renal impairment, metabolic acidosis, and hypersensitivity.

SPECIAL POPULATIONS:

- **Pregnancy Category B.** There are no adequate and well controlled studies in pregnant women; animal studies revealed no evidence of fetal harm.
- **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.
- **Geriatric Use:** No dose adjustment is needed for age alone.
- **Renal Impairment:** Renal impairment (e.g., serum creatinine ≥ 1.5 mg/dL for men or ≥ 1.4 mg/dL for women, or abnormal creatinine clearance) is contraindicated.
- **Hepatic Impairment:** Impaired hepatic function has been associated with cases of lactic acidosis with metformin therapy therefore Janumet XR® should generally be avoided in patients with clinical or laboratory evidence of hepatic impairment.

WARNINGS & PRECAUTIONS:

- **Hypoglycemia:** A lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with Janumet XR®.
- **Vitamin B₁₂ Levels:** Metformin may lower Vitamin B₁₂ levels. Monitor hematologic parameters annually.
- **Alcohol Intake:** Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake.
- **Pancreatitis:** There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis in patients treated with sitagliptin. Janumet XR® should be promptly discontinued.
- **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with any antidiabetic drug.

ADVERSE REACTIONS: (occurring $\geq 5\%$)

Diarrhea, headache, hypoglycemia, upper respiratory tract infections

PRODUCT DETAILS OF JUVISYNC® (SITAGLIPTIN/SIMVASTATIN)⁴

INDICATIONS: Juvisync® is indicated in patients for whom treatment with both sitagliptin and simvastatin is appropriate. Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Simvastatin is an HMG-CoA reductase inhibitor (statin) indicated as an adjunctive therapy to diet to: Reduce the risk of total mortality, non-fatal myocardial infarction, stroke, need for revascularization, elevated total-C, LDL-C, Apo B, TG and increase HDL-C.

DOSAGE FORM: 100/10mg, 100/20mg, 100/40mg, 50/10mg, 50/20mg, and 50/40mg tablets.

ADMINISTRATION: once a day in the evening.

CONTRAINDICATIONS: Concomitant administration of strong CYP3A4 inhibitors, concomitant administration of gemfibrozil, cyclosporine, or danazol, active liver disease, hypersensitivity, women who are pregnant or may become pregnant, and nursing mothers.

SPECIAL POPULATIONS:

- **Pregnancy Category X.** Contraindicated in women who are or may become pregnant.
- **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.
- **Geriatric Use:** Should be prescribed with caution in the elderly.
- **Renal Impairment:** Not recommended for use in patients with severe renal impairment or ESRD.
- **Hepatic Impairment:** Contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels.

WARNINGS & PRECAUTIONS:

- **Hypoglycemia:** A lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with Juvisync®.
- **Alcohol Intake:** Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake.
- **Pancreatitis:** There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis in patients treated with sitagliptin. Juvisync® should be promptly discontinued.
- **Skeletal Muscle Effects:** Risk increase with higher doses and concomitant use of certain medicines. Patients should be advised to report promptly any unexplained and/or persistent muscle pain, tenderness, or weakness. Juvisync® therapy should be discontinued immediately.

ADVERSE REACTIONS: (occurring ≥5%)

Nasopharyngitis, constipation, nausea, abdominal pain, headache, hypoglycemia, upper respiratory tract infections

PRODUCT DETAILS OF BYDUREON® (EXENATIDE ER)⁵

INDICATIONS: Bydureon® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings.

DOSAGE FORM: 2mg exenatide for extended-release injectable suspension.

ADMINISTRATION: 2 mg by subcutaneous injection once every seven days (weekly), at any time of day and with or without meals.

CONTRAINDICATIONS: Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2, and hypersensitivity.

SPECIAL POPULATIONS:

- **Pregnancy Category C.** There are no adequate and well-controlled studies with use in pregnant women.
- **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.
- **Geriatric Use:** Should be prescribed with caution in the elderly.
- **Renal Impairment:** Not recommended for use in patients with severe renal impairment or ESRD.
- **Hepatic Impairment:** No pharmacokinetic study has been performed in patients with a diagnosis of acute or chronic hepatic impairment.

WARNINGS & PRECAUTIONS:

- **Hypoglycemia:** Increased risk when Bydureon® (exenatide extended-release for injectable suspension) is used in combination with a sulfonylurea.
- **Severe Gastrointestinal Disease:** Not recommended if severe gastrointestinal disease.
- **Pancreatitis:** There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis in patients treated with exenatide. Bydureon® should be promptly discontinued.
- **Thyroid C-cell Tumors:** Counsel patients regarding the risk of medullary thyroid carcinoma and the symptoms of thyroid tumors
- **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with any antidiabetic drug.

ADVERSE REACTIONS: (occurring ≥5%)

Diarrhea, nausea, headache, vomiting, constipation, injection site pruritus, nodule and dyspepsia.

PRODUCT DETAILS OF NESINA® (ALOGLIPTIN)⁶

INDICATIONS: Nesina® is indicated for use as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus as monotherapy or in combination with other antidiabetic medications, including metformin, sulfonylureas, thiazolidinediones, or insulin.

DOSAGE FORM: 6.25mg, 12.5mg, and 25mg tablets

ADMINISTRATION: Once daily with or without food.

CONTRAINDICATIONS: Hypersensitivity

SPECIAL POPULATIONS:

- **Pregnancy Category B.** There are no adequate and well controlled studies in pregnant women; animal studies revealed no evidence of fetal harm.
- **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.
- **Geriatric Use:** Greater sensitivity of some older individuals cannot be ruled out.
- **Renal Impairment:** Dose for moderate renal impairment is 12.5mg once daily and severe renal impairment the dose is 6.25mg.
- **Hepatic Impairment:** No dose adjustments are required.

WARNINGS & PRECAUTIONS:

- **Hypoglycemia:** A lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with Nesina®.
- **Hepatic Effects:** Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. If liver injury is detected, promptly interrupt Nesina® and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart Nesina® if liver injury is confirmed and no alternative etiology can be found.
- **Pancreatitis:** There have been postmarketing reports of acute pancreatitis. Nesina® should be promptly discontinued if pancreatitis is suspected.
- **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with any antidiabetic drug.

ADVERSE REACTIONS: (Occurring in ≥4%)

Nasopharyngitis, headache, and upper respiratory tract infection

PRODUCT DETAILS OF OSENI® (ALOGLIPTIN/PIOGLITAZONE)⁷

INDICATIONS: Oseni® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

DOSAGE FORM: 12.5/15mg, 12.5/30mg, 12.5/45mg, 25/15mg, 25/30mg and 25/45 tablets

ADMINISTRATION: Once daily with or without food.

CONTRAINDICATIONS: Hypersensitivity, established NYHA Class III or IV heart failure.

SPECIAL POPULATIONS:

- **Pregnancy Category B.** There are no adequate and well controlled studies in pregnant women; animal studies revealed no evidence of fetal harm.
- **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.
- **Geriatric Use:** No dose adjustment is necessary based on age.
- **Renal Impairment:** Dose for moderate renal impairment is 12.5/15mg, 12.5/30mg or 12.5/45mg once daily. Oseni® should be avoided in severe renal impairment.
- **Hepatic Impairment:** Use caution when administering Oseni® to patients with liver disease.

WARNINGS & PRECAUTIONS:

- **Hypoglycemia:** A lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with Oseni®.
- **Edema:** Dose-related edema may occur.
- **Fractures:** Increased incidence in female patients. Apply current standards of care for assessing and maintaining bone health
- **Congestive heart failure:** Fluid retention may occur and can exacerbate or lead to congestive heart failure. Combination use with insulin and use in congestive heart failure NYHA Class I and II may increase risk. Monitor patients for signs and symptoms
- **Bladder cancer:** Preclinical and clinical trial data, and results from an observational study suggest an increased risk of bladder cancer in pioglitazone users. The observational data further suggest that the risk increases with duration of use. Do not use in patients with active bladder cancer. Use caution when using in patients with a prior history of bladder cancer
- **Hepatic Effects:** Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. If liver injury is detected, promptly interrupt Oseni® and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart Oseni® if liver injury is confirmed and no alternative etiology can be found.
- **Pancreatitis:** There have been postmarketing reports of acute pancreatitis. Oseni® should be promptly discontinued if pancreatitis is suspected.
- **Macular edema:** There have been postmarketing reports of macular edema. Recommend regular eye exams in all patients with diabetes according to current standards of care with prompt evaluation for acute visual changes.

- **Macrovascular Outcomes:** There have been no clinical studies establishing conclusion evidence of macrovascular risk reduction with any antidiabetic drug.

ADVERSE REACTIONS: (Occurring in $\geq 4\%$)

Nasopharyngitis, back pain, and upper respiratory tract infection

PRODUCT DETAILS OF KAZANO® (ALOGLIPTIN/METFORMIN)⁸

INDICATIONS: Kazano® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

DOSAGE FORM: 12.5/500mg, 12.5/1000mg

ADMINISTRATION: Twice daily with food.

CONTRAINDICATIONS: Hypersensitivity; renal impairment (Serum creatinine ≥ 1.5 mg/dL for men, ≥ 1.4 mg/dL in women); metabolic acidosis, including ketoacidosis.

SPECIAL POPULATIONS:

- **Pregnancy Category B.** There are no adequate and well controlled studies in pregnant women; animal studies revealed no evidence of fetal harm.
- **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.
- **Geriatric Use:** Caution should be used in elderly patients due to the possibility of renal impairment associated with increasing age.
- **Renal Impairment:** Kazano® is contraindicated in patients with renal impairment
- **Hepatic Impairment:** Use caution when administering Kazano® to patients with liver disease. Kazano® contains metformin and use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis.

WARNINGS & PRECAUTIONS:

- **Lactic acidosis:** Rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment and is fatal in approximately 50% of cases. It may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant hypoperfusion and hypoxemia. Patients should be cautioned against excessive alcohol intake while on this drug.
- **Pancreatitis:** There have been postmarketing reports of acute pancreatitis in patients taking alogliptin. Patients should be observed carefully for signs and symptoms of pancreatitis.
- **Hypersensitivity:** There have been postmarketing reports of serious hypersensitivity reactions treated with alogliptin. These reactions include anaphylaxis, angioedema, and severe cutaneous adverse reactions including Stevens-Johnson syndrome. If a serious hypersensitivity reaction is suspected, discontinue Kazano®, assess for other potential causes for the event, and institute alternative treatment for diabetes.
- **Hepatic effects:** There have been postmarketing reports of fatal and non-fatal hepatic failure in patients taking alogliptin, although the reports contain insufficient information necessary to establish the probable cause. Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.

- **Monitoring renal function:** Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment. Therefore, Kazano[®] is contraindicated in patients with renal impairment.
- **Hypoxic states:** Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on Kazano[®] therapy, the drug should be promptly discontinued.
- **Alcohol intake:** Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake while receiving Kazano[®].
- **Vitamin B12 levels:** In one study, a decrease to subnormal levels from previously normal serum Vitamin B12 levels, without clinical manifestation, was observed in approximately 7% of patients. Measurement of hematologic parameters on an annual basis is advised in patients on Kazano[®] and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate Vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B12 levels. In these patients, routine serum Vitamin B12 measurements at two- to three-year intervals may be useful.
- **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Kazano or any other antidiabetic drug.

ADVERSE REACTIONS: (Occurring in $\geq 4\%$) Upper respiratory tract infection, nasopharyngitis, back pain, diarrhea, hypertension, headache, urinary tract infection.

¹AACE/ACE Diabetes Algorithm. Available at www.aace.com/pub.

²Jentadueto[®] Prescribing Information. Boehringer Ingelheim Pharmaceuticals, Inc. Accessed online at: <http://bidocs.boehringeringelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/PIs/Jentadueto/Jentadueto.pdf> Last revised January 2012.

³Janumet XR[®] Prescribing Information. Merck Sharp & Dohme Corp. Accessed online at: http://www.merck.com/product/usa/pi_circulars/j/janumet_xr/janumet_xr_pi.pdf Last revised April 2012.

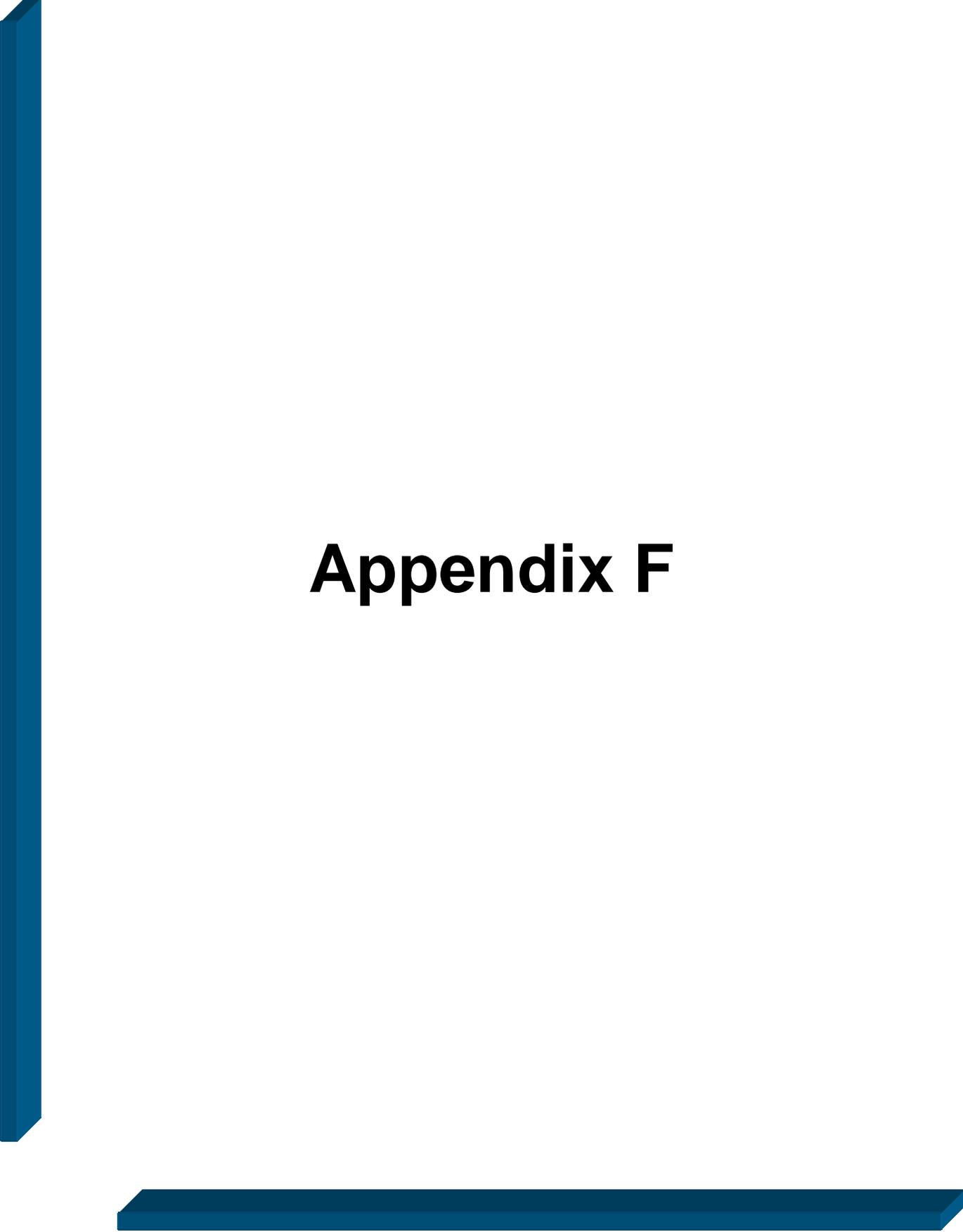
⁴Juvisync[®] Prescribing Information. Merck Sharp & Dohme Corp. Accessed online at: http://www.merck.com/product/usa/pi_circulars/j/juvisync/juvisync_pi.pdf Last revised October 2012

⁵Bydureon[®] Prescribing Information. Amylin Pharmaceuticals, Inc. Accessed online at: http://documents.bydureon.com/Bydureon_PI.pdf Last revised January 2012

⁶Nesina[®] Prescribing Information. Takeda Pharmaceuticals America, Inc. Accessed online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022271s000lbl.pdf Last revised January 2013.

⁷Oseni[®] Prescribing Information. Takeda Pharmaceuticals America, Inc. Accessed online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022426s000lbl.pdf Last revised January 2013.

⁸Kazano[®] Prescribing Information. Takeda Pharmaceuticals America, Inc. Accessed online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203414s000lbl.pdf Last revised January 2013.



Appendix F

FY 2012 Annual Review of Anticoagulants and Platelet Aggregation Inhibitors and 30-Day Notice to Prior Authorize Eliquis® (Apixaban)

**Oklahoma Health Care Authority
March 2013**

Current Prior Authorization Criteria

Effient® (Prasugrel) Approval Criteria:

1. The first 90 days of therapy do not require prior authorization.
2. Approved diagnostic criteria: Unstable Angina/Non-ST-Segment Elevated Myocardial Infarction and ST-Segment Elevated MI patients who are to be managed with percutaneous coronary intervention (PCI), primary or delayed (stent placement)
3. Length of approval: 1 year
4. Effient® (prasugrel) will not be approved for members with the following situations:
 - a. Coronary Artery Bypass Graft surgery
 - b. Members with a history of Transient Ischemic Attack or stroke
5. Members greater than 75 years of age will generally not be approved without supporting information.
6. After the end of 15 months, prescribers should provide supporting information for the continuation of this product.

Plavix® 300 mg (Clopidogrel) Approval Criteria:

1. FDA approved diagnosis of non-ST-segment elevated acute coronary syndrome or ST segment elevated acute myocardial infarction.
2. Approval will be for only one dose of 300mg.

Brilinta® (Ticagrelor) Approval Criteria:

1. The first 90 days of therapy do not require prior authorization.
2. Approved diagnostic criteria: Acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction) with or without percutaneous coronary intervention (PCI).
3. Length of approval: 1 year

Pradaxa® (Dabigatran) Approval Criteria:

1. FDA approved indication of nonvalvular atrial fibrillation. (Special consideration will be given for a diagnosis of DVT when warfarin is not a viable option.)

Xarelto® (Rivaroxaban) Approval Criteria:

1. 10 mg tablets: the first 35 days will not require prior authorization to allow for use for DVT prophylaxis only.
2. 15 mg and 20 mg: a diagnosis of nonvalvular atrial fibrillation will be required.

Utilization of Anticoagulants and Platelet Aggregation Inhibitors

Comparison of Fiscal Years for Anticoagulants: Pradaxa® & Xarelto®

Fiscal Year	Members	Claims	Cost	Cost/Claim	Perdiem	Units	Days
2011	80	215	\$45,556.64	\$211.89	\$6.99	12,814	6,517
2012	234	747	\$164,588.10	\$220.33	\$7.73	37,945	21,298
% Change	192.50%	247.40%	261.30%	4.00%	10.60%	196.10%	226.80%
Change	154	532	\$119,031.46	\$8.44	\$0.74	25,131	14,781

Comparison of Fiscal Years for Platelet Aggregation Inhibitors: Effient®, Plavix®, & Brilinta®

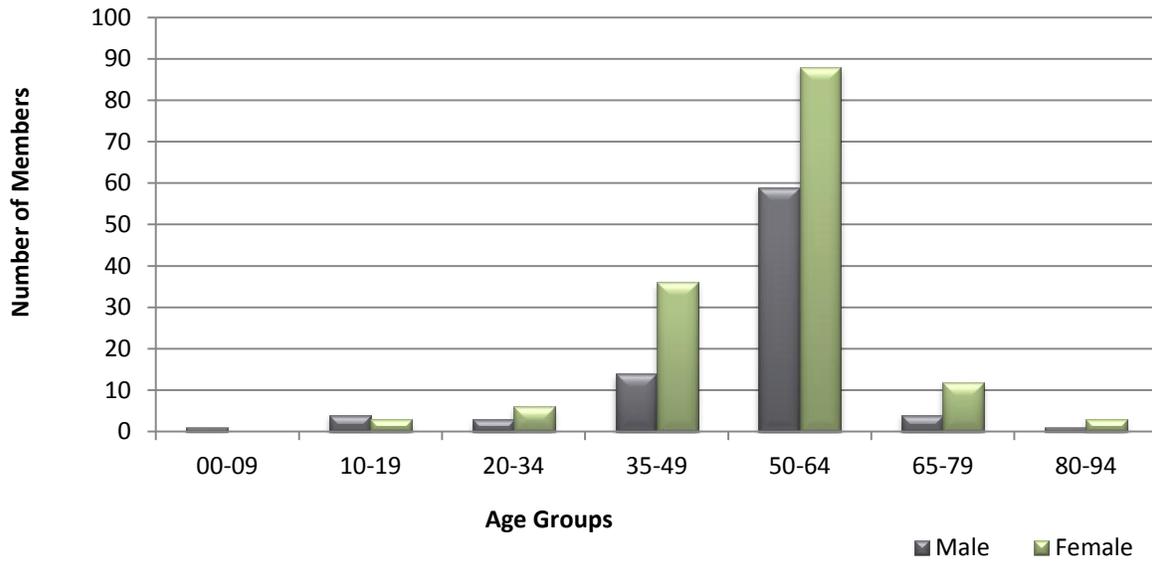
Fiscal Year	Members	Claims	Cost	Cost/Claim	Perdiem	Units	Days
2011	2,700	11,662	\$2,546,872.12	\$218.39	\$5.87	433,998	434,002
2012	2,723	12,612	\$2,841,457.57	\$225.30	\$6.00	474,585	473,807
% Change	0.90%	8.10%	11.60%	3.20%	2.20%	9.40%	9.20%
Change	23	950	\$294,585.45	\$6.91	\$0.13	40,587	39,805

Utilization Details

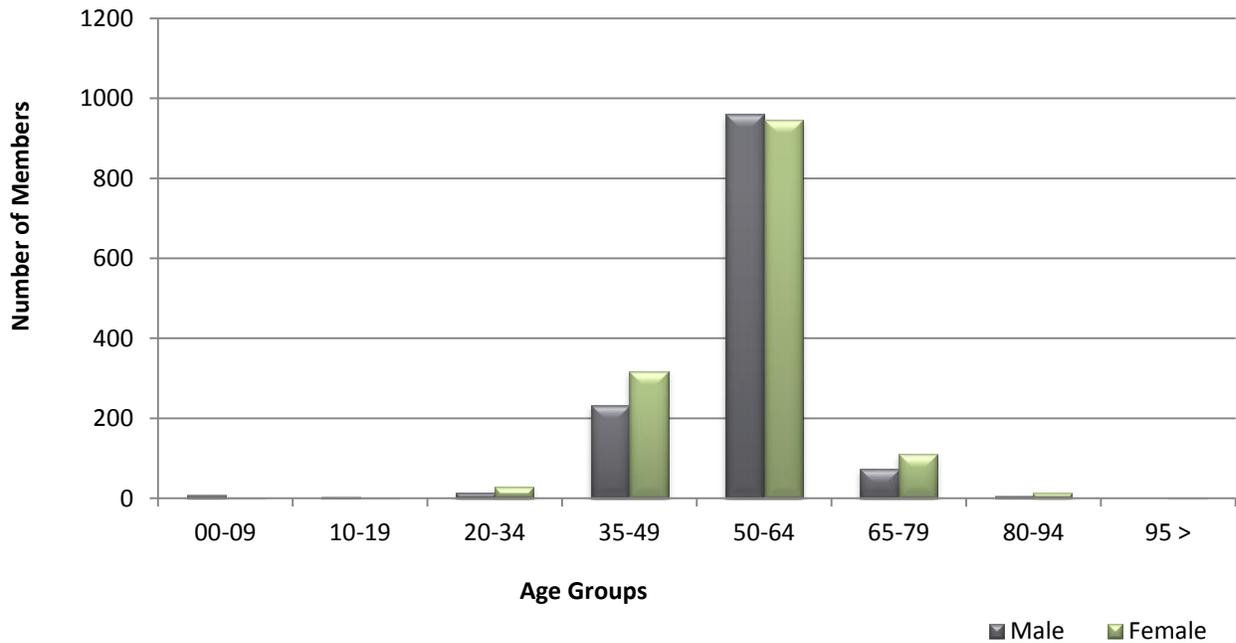
CHEMICAL NAME	BRAND NAME	CLAIMS	MEMBERS	COST	COST/ DAY	%COST
Clopidogrel	PLAVIX TAB 75MG	10,766	2,444	\$2,638,349.63	\$6.51	87.77%
Clopidogrel	CLOPIDOGREL TAB 75MG	1,036	953	\$18,135.92	\$0.45	0.60%
	SUBTOTAL	11,802	3,397	\$2,656,485.55	\$5.96	88.37%
Prasugrel	EFFIENT TAB 10MG	794	208	\$181,334.02	\$6.56	6.03%
Prasugrel	EFFIENT TAB 5MG	6	3	\$1,206.70	\$6.70	0.04%
	SUBTOTAL	800	211	\$182,540.72	\$6.56	6.07%
Ticagrelor	BRILINTA TAB 90MG	10	5	\$2,431.30	\$8.10	0.08%
	SUBTOTAL	10	5	\$2,431.30	\$8.10	0.08%
Dabigatran	PRADAXA CAP 150MG	555	109	\$128,184.09	\$7.50	4.26%
Dabigatran	PRADAXA CAP 75MG	2	2	\$588.39	\$7.35	0.02%
	SUBTOTAL	557	111	\$128,772.48	\$7.49	4.28%
Rivaroxaban	XARELTO TAB 10MG	143	111	\$24,868.65	\$9.12	0.83%
Rivaroxaban	XARELTO TAB 20MG	41	15	\$9,458.77	\$7.69	0.31%
Rivaroxaban	XARELTO TAB 15MG	6	4	\$1,488.20	\$8.70	0.05%
	SUBTOTAL	190	130	\$35,815.62	\$8.67	1.19%
	TOTAL	13,359	2,950*	\$3,006,045.67	\$6.07	100.00%

*Total number of unduplicated members

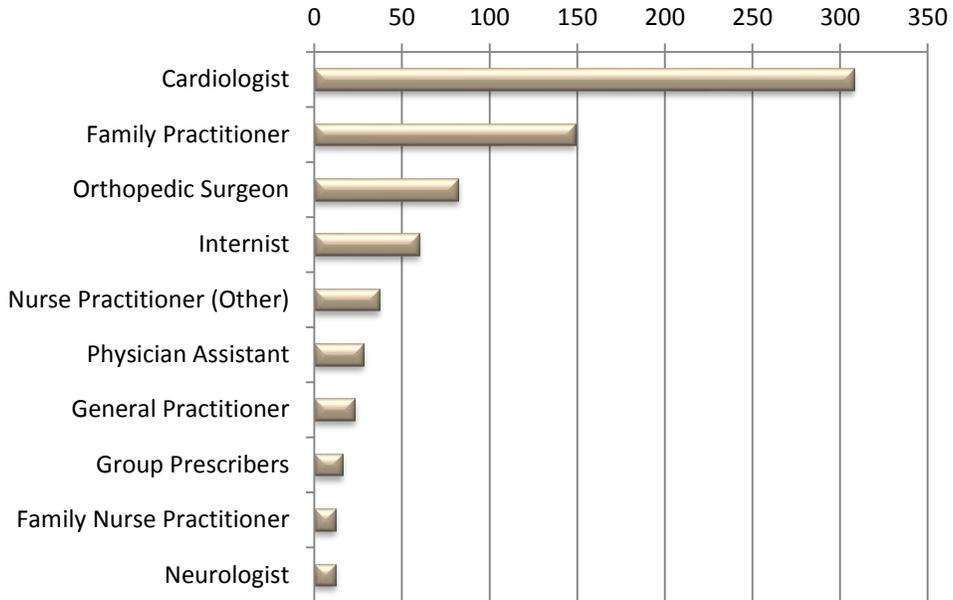
FY 2012 Demographics of Members Utilizing Anticoagulants: Pradaxa® & Xarelto®



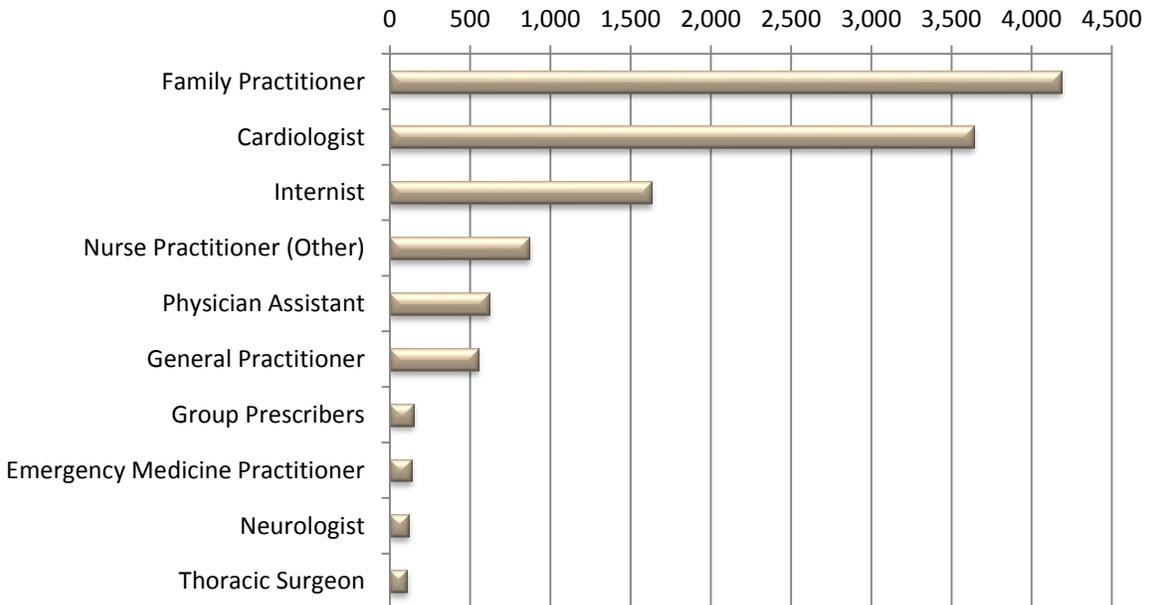
FY 2012 Demographics of Members Utilizing Platelet Aggregation Inhibitors: Effient®, Plavix®, & Brilinta®



**FY 2012 Top Prescribers of Anticoagulants by Number of Claims:
Pradaxa® & Xarelto®**



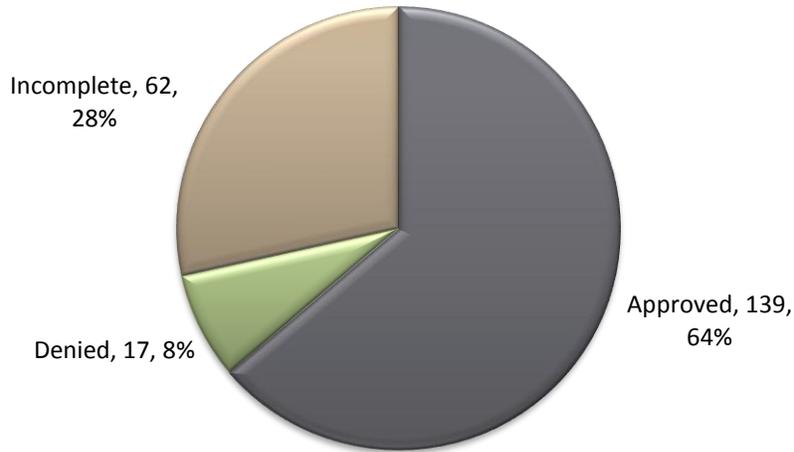
**FY 2012 Top Prescribers of Platelet Aggregation Inhibitors by Number of Claims:
Effient®, Plavix®, & Brilinta®**



Prior Authorization of Anticoagulants and Platelet Aggregation Inhibitors

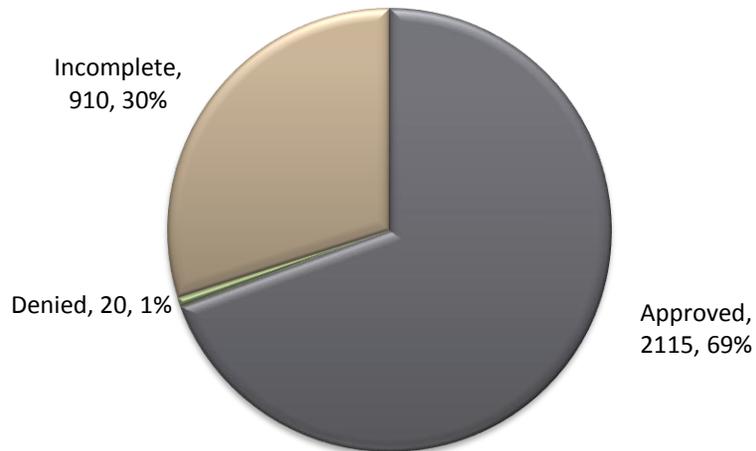
There were a total of 218 petitions submitted for Pradaxa® and Xarelto® during fiscal year 2012. The following chart shows the status of the submitted petitions.

Status of Petitions for Anticoagulants: Pradaxa® & Xarelto®



There were a total of 3,045 petitions submitted for Effient®, Plavix®, and Brilinta® during fiscal year 2012. The following chart shows the status of the submitted petitions.

Status of Petitions for Platelet Aggregation Inhibitors: Effient®, Plavix®, & Brilinta®



Market News and Update

- **Anticipated Patent Expirations:**¹
 - Effient® (prasugrel)-April 2017
 - Pradaxa® (dabigatran)-February 2018
 - Brilinta® (ticagrelor)-July 2018
 - Xarelto® (rivaroxaban)-December 2020

- **10/2010** The U.S. Food and Drug Administration (FDA) reiterated to the public that it continues to caution against the concomitant use of Plavix® (clopidogrel) and Prilosec® (omeprazole) because the co-administration can result in significant reductions in active metabolite levels and antiplatelet activity of Plavix® (clopidogrel). A black box warning has been added to the prescribing information regarding this issue.²

- **05/2012** Plavix® (clopidogrel) became widely available as a generic product
 - SMAC \$0.23 per tablet

- **11/2012.** The FDA evaluated new information about the risk of serious bleeding associated with use of the anticoagulants Pradaxa® (dabigatran) and warfarin. Their evaluation determined that bleeding rates associated with new use of Pradaxa® (dabigatran) do not appear to be greater than bleeding rates associated with new use of warfarin. FDA is continuing the ongoing safety review of this issue.³

- **11/2012** The FDA expanded the approved use of Xarelto® (rivaroxaban) to include treating deep vein thrombosis (DVT) or pulmonary embolism (PE), and to reduce the risk of recurrent DVT and PE.⁴
 - New dosing: 15mg by mouth twice daily with food for 21 days followed by 20mg by mouth once daily with food

- **12/2012** The FDA informed the public Pradaxa® (dabigatran) should not be used to prevent stroke or blood clots in patients with mechanical heart valves. A clinical trial in Europe (the RE-ALIGN trial) was recently terminated because Pradaxa® (dabigatran) users with mechanical heart valves were more likely to experience strokes, heart attacks, and blood clots than were users of the anticoagulant warfarin. There was also more bleeding after valve surgery in the Pradaxa® (dabigatran) users.⁵

- **12/2012** FDA approves Eliquis® (apixaban) to reduce the risk of stroke, blood clots in patients with non-valvular atrial fibrillation.⁶

Eliquis® (apixaban) Summary⁷

- **Indications:** Eliquis® (apixaban) is a factor Xa inhibitor indicated for reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. The safety and efficacy of Eliquis® (apixaban) has not been studied in patients with prosthetic heart valves. Therefore, use of Eliquis® (apixaban) is not recommended in these patients.
- **Dosing:** Eliquis® (apixaban) is available as 2.5 and 5 mg tablets. The recommended dose for most patients is 5 mg by mouth twice daily. The 2.5 mg twice daily dose is recommended for patients with at least 2 of the following characteristics:
 - age >80 years
 - body weight ≤60 kg
 - serum creatinine ≥1.5 mg/dL

The 2.5 mg dose is also recommended in patients when co-administered with potent dual inhibitors of CYP3A4 and P-glycoprotein. The transition from warfarin to Eliquis® (apixaban) consists of discontinuing warfarin and starting Eliquis® (apixaban) when the INR is below 2. Tablets may be taken without regard to food.

- **Efficacy:** The ARISTOTLE trial compared the efficacy of Eliquis® (apixaban) with warfarin for stroke prevention in patients with atrial fibrillation. The randomized, multinational, double-blind trial evaluated participants with a diagnosis of atrial fibrillation and at least one additional risk factor for stroke. The trial was designed to test for noninferiority to warfarin with a primary outcome of ischemic or hemorrhagic stroke, or systemic embolism. Eliquis® (apixaban) was found to have a statistically significant lower risk (1.27% for Eliquis® (apixaban) vs. 1.60% for warfarin) of overall stroke or systemic embolism (HR 0.79; 95% CI (0.66-0.95) P<0.01). Additionally Eliquis® (apixaban) had fewer major bleeding events (2.13% for Eliquis® (apixaban) vs. 3.09% for warfarin); HR 0.69; 95% CI (0.60-0.80) p<0.001), and resulted in lower mortality from any cause (3.52% for Eliquis® (apixaban) vs. 3.94% for warfarin; HR 0.89; 95% CI (0.80-0.998) P<0.047).⁸
- **Cost:** Eliquis® (apixaban) comes in the following strengths:

Eliquis® (apixaban) Strength	EAC Per Tablet	EAC Per Day
2.5mg	\$4.41	\$8.82
5mg	\$4.41	\$8.82

EAC= estimated acquisition cost

Conclusions and Recommendations:

The College of Pharmacy recommends the following:

Prior Authorization of Eliquis® (apixaban) with the following Criteria:

1. FDA approved diagnosis of nonvalvular atrial fibrillation.

Updating the Prior Authorization Criteria for Xarelto® (rivaroxaban):

1. FDA approved diagnosis of one of the following: non valvular atrial fibrillation, **deep vein thrombosis (DVT), pulmonary embolism (PE), or to reduce the risk of recurrent DVT and PE.**
2. 10 mg: the first 35 days will not require prior authorization to allow for use for postsurgical DVT prophylaxis only.
3. 15 mg and 20 mg: a diagnosis of nonvalvular atrial fibrillation, **deep vein thrombosis (DVT), pulmonary embolism (PE), or prophylaxis of recurrent DVT or PE** will be required.

PRODUCT DETAILS OF ELIQUIS® (APIXABAN)⁷

INDICATIONS: Eliquis® (apixaban) is a factor Xa inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

DOSAGE FORMS: 2.5 mg and 5 mg tablets.

ADMINISTRATION:

- The recommended dose is 5 mg orally twice daily.
- In patients with at least 2 of the following characteristics: age \geq 80 years, body weight \leq 60 kg, or serum creatinine \geq 1.5 mg/dL, the recommended dose is 2.5 mg twice daily.
- Eliquis® (apixaban) can be taken with or without food.

CONTRAINDICATIONS:

- Active pathological bleeding
- Severe hypersensitivity to Eliquis® (apixaban)

SPECIAL POPULATIONS:

- **Pregnancy:** There are no adequate and well-controlled studies with Eliquis® (apixaban) in pregnant women. Eliquis® (apixaban) should be used during pregnancy only if the potential benefit justifies the potential risk.
- **Nursing Mothers:** It is not known whether Eliquis® (apixaban) is excreted in human milk. Women should be instructed either to discontinue breastfeeding or to discontinue Eliquis® (apixaban) therapy, taking into account the importance of the drug to the mother.
- **Pediatrics:** Safety and effectiveness in pediatric patients has not been established.
- **Geriatrics:** Of the total subjects in clinical studies of Eliquis® (apixaban), >69% were 65 and older, and >31% were 75 and older. The effects of Eliquis® (apixaban) on the risk of stroke and major bleeding compared to warfarin were maintained in geriatric subjects. Use of 2.5mg twice daily is recommended in patients 80 years or older with a serum creatinine 1.5mg/dL or higher or if patient has a body weight 60 kg or less.
- **Hepatic Impairment:** No dose adjustment is required in patients with mild hepatic impairment. Dosing recommendations are not provided in patients with moderate hepatic impairment due to limited clinical experience with Eliquis® (apixaban) in these patients. Eliquis® (apixaban) is not recommended in patients with severe hepatic impairment.
- **Renal Impairment:** Use of 2.5mg twice daily is recommended in patients with a serum creatinine 1.5mg/dL or higher if patient is 80 years or older or has a body weight 60 kg or less. No data available in patients with creatinine clearance <15 ml/min or on dialysis.

WARNINGS AND PRECAUTIONS:

- Black box warning: Increased risk of stroke with discontinuation of Eliquis® (apixaban).

- Eliquis® (apixaban) increases the risk of bleeding and can cause serious, potentially fatal, bleeding.

ADVERSE REACTIONS: Most common serious adverse reactions reported were related to bleeding.

DRUG INTERACTIONS:

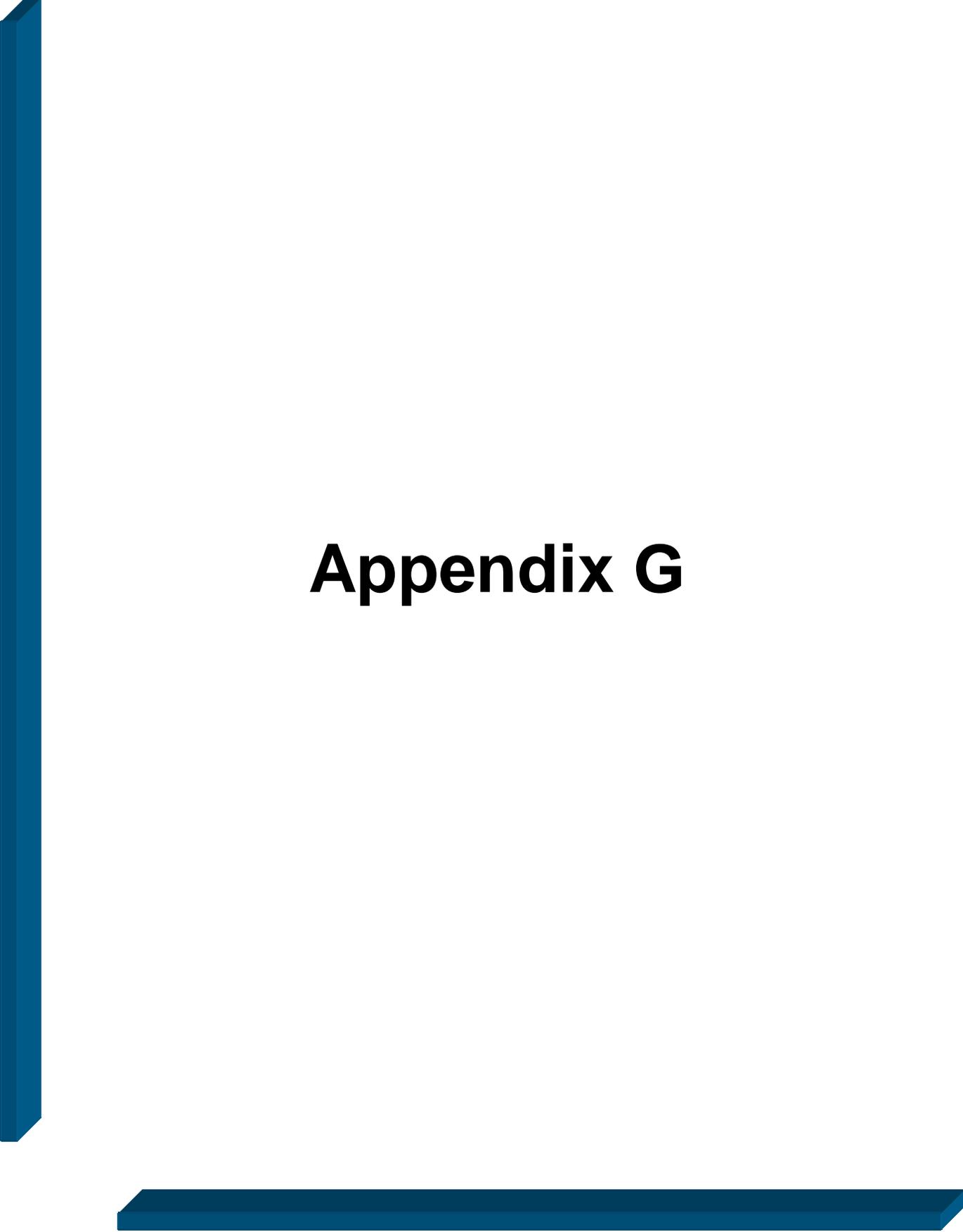
- Eliquis® (apixaban) is a substrate of both CYP3A4 and P-glycoprotein.
- Inhibitors of CYP3A4 and P-glycoprotein increase exposure to Eliquis® (apixaban) and increase the risk of bleeding (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin)
- Concomitant use of strong dual inhibitors of CYP3A4 and P-glycoprotein increase blood levels of Eliquis® (apixaban). Reduce Eliquis® (apixaban) dose to 2.5 mg or avoid simultaneous use.
- Inducers of CYP3A4 and P-glycoprotein decrease exposure to Eliquis® (apixaban) and increase the risk of stroke. (e.g., rifampin, carbamazepine, phenytoin, St. John's wort)
- Concomitant use of strong dual inducers of CYP3A4 and P-glycoprotein reduce blood levels of Eliquis® (apixaban). Concomitant use should be avoided.

PATIENT COUNSELING INFORMATION:

- You should not discontinue Eliquis® (apixaban) without talking to your physician first. Stopping Eliquis® (apixaban) increases your risk of having a stroke.
- It may take longer than usual for bleeding to stop, and you may bruise or bleed more easily when treated with Eliquis® (apixaban). Report any unusual bleeding to your physician and seek immediate medical attention if you develop unusual or severe bleeding.
- You should tell your physician and dentist you are taking Eliquis® (apixaban), and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDS), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- Take Eliquis® (apixaban) by mouth twice daily with or without food.

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Appendix G

30 Day Notice to Prior Authorize Kuvan® (Sapropterin)

Oklahoma Health Care Authority
March 2013

Introduction

Phenylketonuria (PKU) is a rare genetic metabolic disorder in which the phenylalanine hydroxylase (PAH) gene is defective, resulting in the body's inability to metabolize phenylalanine, an amino acid found in all foods containing protein. In classic PKU, the most severe form of the disorder, the body's ability to metabolize phenylalanine is minimal, resulting in severe brain damage and other serious medical problems. Some mutations allow the enzyme to work a little better than it does in classic PKU, which results in smaller risk of brain damage.

In the United States, PKU occurs in 1 in 10,000 to 15,000 newborns. The following is a brief timeline of interesting highlights that have occurred in the past 100 years¹.

- **1934:** Dr. Asbjorn Folling discovered PKU by noticing a strange odor in the urine of severely mentally challenged patients. Folling thought the disease was most likely inherited, and was the first to suggest using diet to manage it.
- **1951:** The first supplement, in the form of a phenylalanine-free protein drink, was developed by Horst Bickel.
- **1958:** Robert Guthrie developed a fast, simple, and inexpensive test for PKU requiring a sample of only one drop of blood.
- **1966:** PKU newborn screening was implemented in hospitals across the country using the Guthrie test.

The mainstay of treatment is dietary restriction of phenylalanine². Infants are given a special formula without phenylalanine. Older children and adults have to avoid protein-rich foods such as meat, fish, eggs, cheese, beans, nuts, etc. They must also avoid artificial sweeteners with aspartame, which contains phenylalanine. Non-restricted foods include vegetables, fruits, some grains (like low-protein cereals, breads and pasta) and other low-phenylalanine foods.

PKU meal plans are different for each baby and can vary over time as the baby matures. People with PKU must follow the restricted diet through their whole life. Monitoring of phenylalanine levels is performed as often as once a week or more often for the first year of life. After that, testing may be done once or twice a month and when the diet is changed to meet the nutritional needs.

Kuvan® Medication Summary³

Kuvan® (sapropterin) was approved by the FDA in 2007 to reduce blood phenylalanine levels in patients with hyperphenylalaninemia due to tetrahydrobiopterin (BH4) responsive

phenylketonuria. Kuvan® is a biologically active synthetic form of tetrahydrobiopterin (BH4) that reduces blood phenylalanine levels by activating residual PAH enzymes and improving the normal oxidative metabolism of phenylalanine.

Kuvan® is to be used in conjunction with a phenylalanine-restricted diet and patients on Kuvan® still require blood phenylalanine monitoring to ensure levels are adequately controlled. Use of Kuvan® does not eliminate the need for ongoing dietary management and not all patients with PKU respond to treatment with Kuvan®. In clinical trials, approximately 20% to 56% of PKU patients responded to treatment with Kuvan®. Response to treatment cannot be pre-determined by laboratory testing (e.g., genetic testing), and can only be determined by a trial of Kuvan®.

Kuvan® is available as 100mg oral tablets. The recommended starting dose of Kuvan® is 10 mg/kg/day taken once daily, which is typically 7 tablets for the average adult. Kuvan® should be taken orally with food to increase the absorption. Kuvan® tablets should be dissolved in 4 to 8 oz. (120-240 mL) of water or apple juice and taken within 15 minutes. Kuvan® is a pregnancy category C medication. The most common side effects reported when using Kuvan® are headache, diarrhea, abdominal pain, upper respiratory tract infection, throat pain, vomiting, and nausea. Kuvan® should be used with caution when co-administered with levodopa, medications known to inhibit folate metabolism (methotrexate), or nitrates.

The estimated acquisition cost of Kuvan® is \$33.42 per tablet. Depending on the weight of the individual, monthly cost of therapy could range from \$3,000 to \$7000. The following table shows the utilization details for calendar year 2012.

MEDICATION	CLAIMS	MEMBERS	UNITS	DAYS	COST	UNITS/ DAY	CLAIMS/ MEMBER	COST/ DAY
KUVAN TAB 100MG	179	20	40,770	5,370	\$1,228,344.29	7.59	8.95	\$228.74

Recommendations

The College of Pharmacy recommends prior authorization of Kuvan® with the following criteria:

Kuvan® Approval Criteria:

1. FDA approved diagnosis of phenylketonuria.
2. Active management with phenylalanine restricted diet.
3. Initial approval will be for 30 days in duration. After which time, prescriber must verify that the member responded to treatment as defined by laboratory documentation of ≥30% decrease in blood phenylalanine levels.
4. Subsequent approvals will be for the duration of a year.

PRODUCT DETAILS OF KUVAN® (SAPROPTERIN)

INDICATIONS: Kuvan® is indicated to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH4) responsive phenylketonuria (PKU). Kuvan® is to be used in conjunction with a phenylalanine restricted diet.

DOSAGE FORMS: Kuvan® tablets are unscored, uncoated, immediate-release tablets for oral use. Each tablet contains 100 mg of sapropterin dihydrochloride. Tablets are round, off-white to light yellow, mottled, and debossed with "177".

ADMINISTRATION:

- The recommended starting dose of Kuvan® is 10 mg/kg/day taken once daily.
- Doses of Kuvan® may be adjusted in the range of 5 to 20 mg/kg taken once daily. Blood Phe levels must be monitored regularly.
- Kuvan® should be taken orally with food to increase the absorption.
- Kuvan® tablets should be dissolved in 4 to 8 oz. (120-240 mL) of water or apple juice and taken within 15 minutes.

CONTRAINDICATIONS: none listed

SPECIAL POPULATIONS:

Pregnancy: Pregnancy Category C. This drug should be used during pregnancy only if clearly needed. There are no adequate and well-controlled studies in pregnant women. Women who are exposed to Kuvan® during pregnancy are encouraged to enroll in the Kuvan® patient registry.

Nursing Mothers: Kuvan® is excreted in the milk of intravenously, but not orally treated lactating rats. It is not known whether sapropterin is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from sapropterin and because of the potential for tumorigenicity shown for sapropterin in the rat carcinogenicity study, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Geriatrics: Clinical studies of Kuvan® in patients with PKU did not include patients aged 65 years and older. It is not known whether these patients respond differently than younger patients.

Hepatic or Renal Impairment: Patients with renal impairment have not been evaluated in clinical trials. Patients who have renal impairment should be carefully monitored when receiving Kuvan®. Patients with liver impairment have not been evaluated in clinical trials with Kuvan®. Patients who have liver impairment should be carefully monitored when receiving Kuvan® because hepatic damage has been associated with impaired Phe metabolism.

WARNINGS AND PRECAUTIONS:

Monitor Blood Phe Levels During Treatment: Prolonged exposure to elevated blood Phe levels can injure the brain and reduce brain function. To ensure adequate blood Phe control, blood Phe levels must still be carefully monitored even though patients are receiving Kuvan® which can reduce blood Phe levels.

Treat All Patients With a Phe-restricted Diet: The initiation of Kuvan® therapy does not eliminate the need for ongoing dietary management. Not all patients with PKU respond to treatment with Kuvan®. In clinical trials, approximately 20% to 56% of PKU patients responded to treatment with Kuvan®. Response to treatment cannot be pre-determined by laboratory testing (e.g., genetic testing), and can only be determined by a therapeutic trial of Kuvan®

ADVERSE REACTIONS: The most common side effects reported when using Kuvan® are:

- Headache
- Diarrhea
- Abdominal pain
- Upper respiratory tract infection
- Throat pain
- Vomiting
- Nausea

DRUG INTERACTIONS:

Use With Caution When Co-administering Kuvan® and Levodopa. Caution should be used with the administration of Kuvan® to patients who are receiving levodopa. In a 10-year post-marketing safety surveillance program for a non-PKU indication using another formulation of the same active ingredient (sapropterin), 3 patients with underlying neurologic disorders experienced convulsions, exacerbation of convulsions, over-stimulation, or irritability during co-administration of levodopa and sapropterin.

Use With Caution When Co-administering Kuvan® and Medications Known to Inhibit Folate Metabolism. Drugs known to affect folate metabolism (e.g., methotrexate) and their derivatives should be used with caution while taking Kuvan® because these drugs can decrease BH4 levels by inhibiting the enzyme dihydropteridine reductase (DHPR).

Use With Caution When Co-administering Kuvan® and Drugs Known to Affect Nitric Oxide-Mediated Vasorelaxation. Caution should be used with the administration of Kuvan® to patients who are receiving drugs that affect nitric oxide mediated vasorelaxation (e.g., PDE-5 inhibitors such as sildenafil, vardenafil, or tadalafil), because both sapropterin dihydrochloride and PDE-5 inhibitors may induce vasorelaxation. The additive effect of sapropterin and PDE-5 inhibitor co-administration could lead to a reduction in blood pressure; however, the combined use of these medications has not been evaluated in humans. In animal studies, orally administered Kuvan® in combination with a PDE-5 inhibitor had no effect on blood pressure.

PATIENT COUNSELING INFORMATION:

What should I tell my doctor before taking Kuvan®?

Before you start taking Kuvan®, let your doctor know about all of your medical conditions, prescription and nonprescription medications you are currently taking including if you:

- Have a fever
- Are pregnant or planning to become pregnant
- Are breast feeding
- Have liver problems
- Are allergic to Kuvan® or any other medications
- Have poor nutrition or are anorexic

- Are taking levodopa
- Are taking drugs that inhibit folate metabolism (e.g., methotrexate) because these drugs could affect how Kuvan® works in your body
- Are taking medicines for erectile dysfunction like Viagra® (sildenafil), Levitra® (vardenafil), or Cialis® (tadalafil)

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines and herbal and dietary supplements. Kuvan® and many other medicines may interact with each other. Your doctor needs to know what medicines you take so he or she can decide if Kuvan® is right for you.

Know the medicines you take. Keep a list of your medicines with you to show your doctor. Do not take other medicines while taking Kuvan® without first talking to your doctor.

How should I take Kuvan®?

- Kuvan® tablets are taken at one time each day. Take Kuvan® exactly as your doctor has told you.
- Take Kuvan® once a day with food and preferably at the same time each day.
- Kuvan® Tablets should be dissolved in 4 to 8 ounces (1/2 to 1 cup) of water or apple juice.
- To dissolve the tablets, mix them in water or apple juice, and drink within 15 minutes.
 - It may take a few minutes for the tablets to dissolve. To make the tablets dissolve faster, you can stir or crush them.
 - The tablets may not dissolve completely. You may see small pieces floating on top of the water or apple juice. This is normal and safe for you to swallow.
 - If after drinking your medicine you still see pieces of the tablets, you should add more water or apple juice to make sure that you take all of your medicine.
- If you forget to take your dose of Kuvan®, take it as soon as you remember that day. If you miss a day, do not double your dose the next day, just skip the missed dose.
- The recommended starting dose of Kuvan® is 10 mg/kg taken once a day. Your doctor will tell you the dose you should take and when to take it.
- Your doctor can change your dose depending on how you respond to treatment.

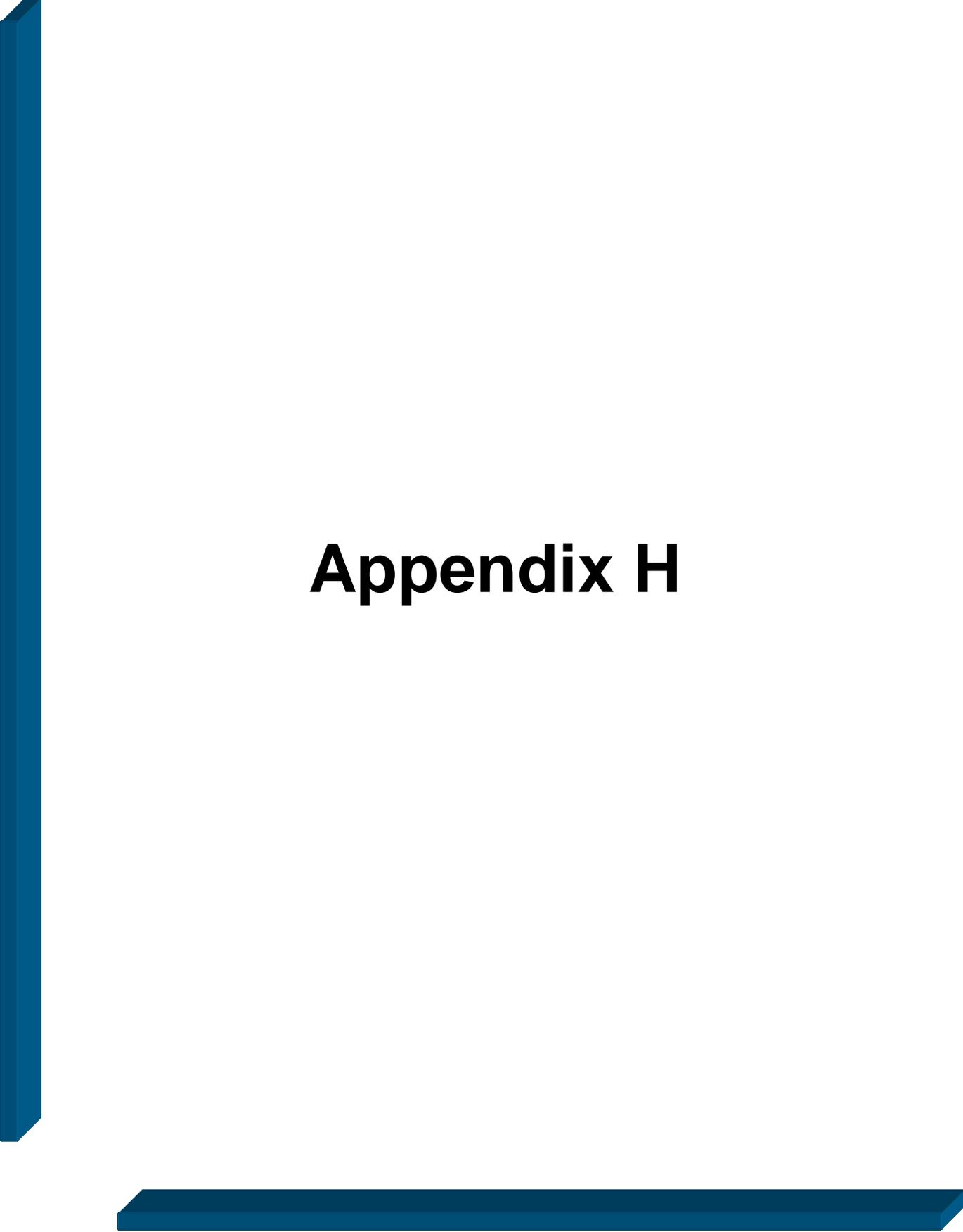
How should I store Kuvan®?

- Store in a cool, dry place between 68°F and 77°F (20°–25°C).
- Do not leave Kuvan® in hot or humid places, such as your car or bathroom cabinet.
- Keep Kuvan® in its original bottle with the cap closed tightly and do not remove the desiccant.
- The color of the tablets may change over time to light yellow. This is normal and you can take these tablets.

¹ <http://www.pku.com/What-is-PKU/history-of-phenylketonuria.php>

² http://www.marchofdimes.com/baby/birthdefects_pku.html

³ Kuvan® Prescribing Information. BioMarin Pharmaceutical, Inc. Available online at: <http://www.kuvan.com/hcp/kuvan-full-prescribing-information.html#q17-6>. Last revised 2010; Last accessed 2/18/2013.



Appendix H

30 Day Notice to Prior Authorize Gattex® (Teduglutide)

Oklahoma Health Care Authority
March 2013

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

Introduction and Product Summary^{1,2,3,4}

Short Bowel Syndrome is a condition in which nutrients are not adequately absorbed because a large portion of the small intestine has been surgically removed, or is absent due to a congenital abnormality. Treatment includes a high-calorie diet, either orally or via parental nutrition. Medications such as proton pump inhibitors may be used for symptomatic management of acid hypersecretion and bile salt-binding agents, such as cholestyramine may be used to bind the unabsorbed bile salts in the colon to decrease fluid and electrolyte losses. Subcutaneous octreotide (25-100mcg 3 times a day) may be used to decrease small bowel transit, which increases absorption. Other anti-motility agents may also be used such as loperamide or diphenoxylate. Zorbtive® (somatropin), a recombinant human growth hormone product, is indicated for the treatment of short bowel syndrome in adults⁵. Intestinal mucosa contains receptors for growth hormone and the administration of growth hormone has been shown to enhance the transmucosal transport of water, electrolytes, and nutrients. NutreStore®, a glutamine powder for oral solution, is indicated to be taken with Zorbtive® therapy. Other possible treatments include vitamins and minerals, oral or injected, to supplement the diet.

For patients undergoing surgical resection of the bowel, parenteral nutrition may be necessary in the post-surgical time period; however, oral food intake is encouraged when possible to stimulate the remaining bowels to function better and to help bowel adaptation. Bowel adaptation is variable, but typically requires a year or more. Gradually, most patients are able to resume and increase oral food intake. The process of weaning the patient off parenteral nutrition can begin once oral calorie intake exceeds 1000 kcal/d. Despite bowel adaptation and nutritional therapy, some patients must be maintained on long-term parenteral nutrition. These patients usually are those with less than 60 cm of small bowel remaining, loss of the ileum and ileocecal valve, and loss of the colon.

Gattex® (teduglutide) was approved by the FDA in December 2012 for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support. Gattex® is an analog of human glucagon-like peptide-2 (GLP-2), a naturally occurring peptide secreted in the distal intestine. When Gattex® binds to intestinal GLP-2 receptors multiple mediators, including insulin-like growth factor-1 (IGF-1), nitric oxide, and keratinocyte growth factor are released. GLP-2 is known to increase intestinal absorption by increasing blood flow in the intestine and liver, and inhibiting gastric acid secretion.

Gattex® (teduglutide) is available as a lyophilized powder, which must be reconstituted and administered as a subcutaneous injection within 3 hours after reconstitution. The recommended dose is 0.05 mg/kg once daily on alternating sites between 1 of the 4 quadrants of the abdomen, or into alternating thighs or alternating arms. It is available in 5mg single use vials.

Efficacy²

Study I

- 24 week placebo control trial consisting of 86 patients with SBS who were dependent on parenteral nutrition/intravenous (PN/IV) support for at least 12 months and required PN at least 3 times per week.
- Gattex, 0.05 mg/kg/day, was administered subcutaneously once daily for 24 weeks.
- Primary efficacy endpoint was defined as a 20% reduction in PN volume from baseline to 20 and 24 weeks.
- 63% (27/43) of Gattex[®] treated patients versus 30% (13/43) of placebo-treated subjects were considered responders (p=0.002).
- At Week 24, the mean reduction in weekly PN/I.V. volume was 4.4 Liters for Gattex[®] treated patients (from pre-treatment baseline of 12.9 Liters) versus 2.3 Liters for placebo-treated patients (from pre-treatment baseline of 13.2 Liters/week) (p<0.001).
- Twenty-one subjects on Gattex[®] (53.8%) versus 9 on placebo (23.1%) achieved at least a one-day reduction in PN/I.V. support.

Study II

- Ongoing two-year open-label extension of Study 1 with 88 patients who received Gattex 0.05 mg/kg/day, 76 of whom had been in Study I. The remainder had been optimized and stabilized but not randomized in Study I because of closed enrollment.
- The primary endpoint were the responders from Study 1 with sustained response after one year, or a 20% or greater reduction of parenteral support after an additional 28 weeks of continuous Gattex treatment.
- A 20% or greater reduction of parenteral support was achieved in 72% (31/43) of patients after an additional 28 weeks of continuous Gattex[®] treatment. The mean reduction of weekly PN/I.V. volume was 5.2 L/week after one year of continuous GATTEX treatment.
- Six patients in Study 2 were weaned off their PN/I.V. support while on Gattex[®]. Patients were maintained on Gattex[®] even if no longer requiring PN/I.V. support. These 6 patients had required PN/I.V. support for 3 to 18 years, and prior to Gattex[®] had required between 4 L/week and 13 L/week of PN/I.V. support.

Study III

- 24 week trial of 84 patients with SBS who were dependent on parenteral nutrition/intravenous (PN/IV) support for at least 12 months and required PN at least 3 times per week.
- Gattex 0.05 mg/kg/day or Gattex 0.10 mg/kg/day or placebo was administered once daily
- The primary efficacy endpoint was also defined as a 20% decrease in PN/IV fluid from baseline.
- Response was defined as at least 20% reduction in PN/I.V. fluid from baseline to weeks 20 and 24.
- 46% of subjects on Gattex[®] 0.05 mg/kg/day responded versus 6% on placebo.
- Patients on Gattex[®] at both dose levels experienced a 2.5 L/week reduction in parenteral support requirements versus 0.9 L/week for placebo at 24 weeks. Two patients in the Gattex[®] 0.05 mg/kg/day dose group were weaned off parenteral support by Week 24.

Study IV

- 28 month blinded extension of Study 3, with 65 patients from study 3.
- Primary endpoint was sustained response on Gattex[®] after one year of treatment.

- Of responders in Study 3 who entered Study 4, 75% sustained response on Gattex® after one year of treatment. In the Gattex® 0.05 mg/kg/day dose group, a 20% or greater reduction of parenteral support was achieved in 68% (17/25) of patients.
- The mean reduction of weekly PN/I.V. volume was 4.9 L/week (52% reduction from baseline) after one year of continuous Gattex® treatment.
- The patients who had been completely weaned off PN/I.V. support in Study 3 remained off parenteral support through Study 4. During Study 4, an additional patient from Study 3 was weaned off parenteral support.

Safety and Precautions²

The most commonly reported ($\geq 10\%$) adverse reactions in patients treated with Gattex® across all clinical studies (n = 566) were:

- Abdominal pain (30.0%)
- Injection site reactions (22.4%)
- Nausea (18.2%)
- Headaches (15.9%)
- Abdominal distension (13.8%)
- Upper respiratory tract infection (11.8%)

The following adverse reactions of special interest occurred during clinical trials with Gattex®. For more information, please see the product information section included at the end of this report.

- Colorectal polyps
- Small bowel neoplasia
- Acceleration of neoplastic growth
- Intestinal obstruction
- Gallbladder and biliary tract disease
- Pancreatic disease
- Fluid overload
- Increased absorption of concomitant oral medication

Administration of Gattex® may trigger the development of antibodies. Anti-Gattex® antibodies appear to have no impact on short term (up to 1.5 years) efficacy and safety although the long-term impact is unknown.

Cost Comparison

The following is a comparison of costs associated with therapies for short bowel syndrome.

Therapy	EAC per unit	EAC Per diem	EAC per 30 days	EAC per year
Gattex® Kit	\$853.00	\$853.00	\$25,605	\$307,258.00
Zorbitive™	\$879.00	\$879.00	\$24,600 (4-wk therapy)	N/A
NutreStore® packets	\$3.38	\$21.00	\$630.00	\$2,272 (16-wk therapy)
Octreotide 100 mcg/mL	\$8.34*	\$25.02*	\$750.60*	\$9,007.20*
Cholestyramine 4g pkts	\$0.16*	\$0.64*	\$19.20*	\$230.00*
Diphenoxylate/atropine tabs	\$0.24*	\$1.92*	\$57.60*	\$691.20
Pantoprazole 40 mg	\$0.21*	\$0.21*	\$6.30*	\$77.00*

EAC = Estimated acquisition cost for brand name medications. *SMAC = State maximum allowable cost for generic medications. Prices based on 4 meals a day where applicable.

Recommendations

The College of Pharmacy recommends medical prior authorization of this medication.

Criteria for Approval for Gattex® (Teduglutide):

1. Member must have diagnosis of severe Short Bowel Syndrome, and
2. Require parental nutrition at least 3 times per week, every week, for the past 12 months, with
3. Documentation of the following:
 - a. Prior use of supportive therapies such anti-motility agents, proton pump inhibitors, bile acid sequestrants, and octreotide.
 - b. Colonoscopy within the previous 6 months, with removal of polyps if present.
 - c. Gastro-intestinal malignancy has been ruled out.
4. Approval will be for the duration of 3 months, after which time, prescriber must verify benefit of medication by documented reduction of at least 20% in parenteral support.
5. Subsequent approvals will be for the duration of a year.

PRODUCT DETAILS OF GATTEX® (TEDUGLUTIDE) FDA-APPROVED 2012

INDICATIONS: Gattex® (teduglutide [rDNA origin] for injection) is a glucagon-like peptide-2 (GLP-2) analog indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support

DOSAGE FORMS: Gattex® for injection:

- Each single-use glass vial containing 5 mg of teduglutide as a white, lyophilized powder for reconstitution with 0.5 mL sterile water for injection provided in a prefilled syringe

ADMINISTRATION:

- Reconstitution with the 0.5 mL sterile water for injection provided in the prefilled syringe results in a 10 mg/mL solution. A maximum of 0.38 mL of reconstituted solution which contains 3.8 mg teduglutide can then be withdrawn from the vial
- Administer by subcutaneous injection; alternate sites between 1 of the 4 quadrants of the abdomen, or into alternating thighs or alternating arms
- Recommended once daily dose of Gattex® is 0.05 mg/kg

CONTRAINDICATIONS: None listed.

SPECIAL POPULATIONS:

- **Pregnancy:** Pregnancy Category B. Reproduction studies with teduglutide have been performed in pregnant rats at subcutaneous doses up to 50 mg/kg/day (about 1000 times the recommended daily dose 0.05 mg/kg/day). These studies did not reveal any evidence of impaired fertility or harm to the fetus due to teduglutide. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, teduglutide should be used during pregnancy only if clearly needed.
- **Nursing Mothers:** It is not known whether teduglutide is excreted in human milk. Teduglutide is excreted in the milk of lactating rats, and the highest concentration in the milk was 2.9% of the plasma concentration following a single subcutaneous injection of 25 mg/kg. Because of the potential for serious adverse reactions to nursing infants from teduglutide, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
- **Pediatrics:** Safety and efficacy in pediatric patients have not been established.
- **Geriatrics:** No dose adjustment is necessary in patients above the age of 65 years. Of the 566 subjects treated with teduglutide, 43 subjects were 65 years or older, whereas 6 subjects were 75 years of age or older. In the SBS studies, no overall differences in safety or efficacy 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.
- **Hepatic Impairment:** Gattex® has not been formally studied in subjects with severe hepatic impairment. No dosage adjustment is necessary for patients with mild and moderate hepatic impairment based on a study conducted in Child-Pugh grade B subjects.
- **Renal Impairment:** Reduce the dose of Gattex® by 50% in patients with moderate and severe renal impairment (CrCl < 50 mL/min) and end-stage renal disease (ESRD).

WARNINGS AND PRECAUTIONS:

- **Colorectal polyps:** Identified during the clinical trials. Colonoscopy of the entire colon with removal of polyps should be done within 6 months prior to starting treatment with Gattex[®]. A follow-up colonoscopy is recommended at the end of 1 year of Gattex[®]. In case of diagnosis of colorectal cancer, Gattex therapy should be discontinued.
- **Small bowel neoplasia:** Based on benign tumor findings in the rat carcinogenicity study, patients should be monitored clinically for small bowel neoplasia. If a benign neoplasm is found, it should be removed. In case of small bowel cancer, Gattex[®] therapy should be discontinued.
- **Acceleration of neoplastic growth:** Based on the pharmacologic activity and findings in animals, Gattex[®] has the potential to cause hyperplastic changes including neoplasia. In patients at increased risk for malignancy, the clinical decision to use Gattex[®] should be considered only if the benefits outweigh the risks. In patients with active gastrointestinal malignancy (GI tract, hepatobiliary, pancreatic), Gattex[®] therapy should be discontinued. In patients with active non-gastrointestinal malignancy, the clinical decision to continue Gattex[®] should be made based on risk-benefit considerations.
- **Intestinal obstruction:** Intestinal obstruction has been reported in clinical trials. In patients who develop intestinal or stomal obstruction, Gattex[®] should be temporarily discontinued while the patient is clinically managed. Gattex[®] may be restarted when the obstructive presentation resolves, if clinically indicated.
- **Gallbladder and biliary tract disease:** Cholecystitis, cholangitis, and cholelithiasis, have been reported in clinical studies. For identification of the onset or worsening of gallbladder/biliary disease, patients should undergo laboratory assessment of bilirubin and alkaline phosphatase within 6 months prior to starting Gattex[®], and at least every 6 months while on Gattex[®]; or more frequently if needed. If clinically meaningful changes are seen, further evaluation including imaging of the gallbladder and/or biliary tract is recommended; and the need for continued Gattex[®] treatment should be reassessed.
- **Pancreatic disease:** Pancreatitis has been reported in clinical studies. For identification of onset or worsening of pancreatic disease, patients should undergo laboratory assessment of lipase and amylase within 6 months prior to starting Gattex[®], and at least every 6 months while on Gattex[®]; or more frequently if needed. If clinically meaningful changes are seen, further evaluation such as imaging of the pancreas is recommended; and the need for continued Gattex[®] treatment should be reassessed.
- **Fluid overload:** Fluid overload and congestive heart failure have been observed in clinical trials, which were felt to be related to enhanced fluid absorption associated with Gattex[®]. If fluid overload occurs, parenteral support should be adjusted and Gattex[®] treatment should be reassessed, especially in patients with underlying cardiovascular disease. If significant cardiac deterioration develops while on Gattex[®], the need for continued Gattex[®] treatment should be reassessed.
- **Increased absorption of concomitant oral medication:** Altered mental status in association with Gattex[®] has been observed in patients on benzodiazepines in clinical trials. Patients on concomitant oral drugs (e.g., benzodiazepines, phenothiazines) requiring titration or with a narrow therapeutic index may require dose adjustment while on Gattex[®].

ADVERSE REACTIONS: common adverse reactions reported are:

- Incidence > 20% include: abdominal pain, upper respiratory tract infection, nausea
- Incidence > 10% include: abdominal distension, vomiting, fluid overload
- Incidence >5% include: flatulence, hypersensitivity, appetite disorders, sleep disturbances, cough, skin hemorrhage
- Subjects with stoma: GI Stoma complication = 41.9%

DRUG INTERACTIONS:

- **Potential for Increased Absorption of Oral Medications:** Based upon the pharmacodynamic effect of Gattex[®], there is a potential for increased absorption of concomitant oral medications, which should be considered if these drugs require titration or have a narrow therapeutic index.

- **Concomitant Drug Therapy:** Clinical interaction studies were not performed. No inhibition or induction of the cytochrome P450 enzyme system has been observed based on *in vitro* studies although the relevance of *in vitro* studies to an *in vivo* setting is unknown.

HEALTHCARE PROVIDER AND COUNSELING INFORMATION:

- Store Gattex® powder at room temperature up to 77°F (25°C).
- Do not freeze Gattex®.
- Use the Gattex® powder by the expiration date on the “Use By” sticker on the kit.
- Gattex® should not be administered intravenously or intramuscularly.
- The drug should be used for subcutaneous injection within 3 hours after reconstitution.
- Subcutaneous administration has been associated with injection site reactions, but if patient experience a severe reaction including severe rash, the patient should contact their physician.
- Patients may experience abdominal pain and swelling of their stoma especially when starting therapy with Gattex®, if they experience symptoms of intestinal obstruction, they should contact their physician.
- Patients should be advised to read the Medication Guide as they are starting Gattex® therapy and to re-read it each time their prescription is renewed.

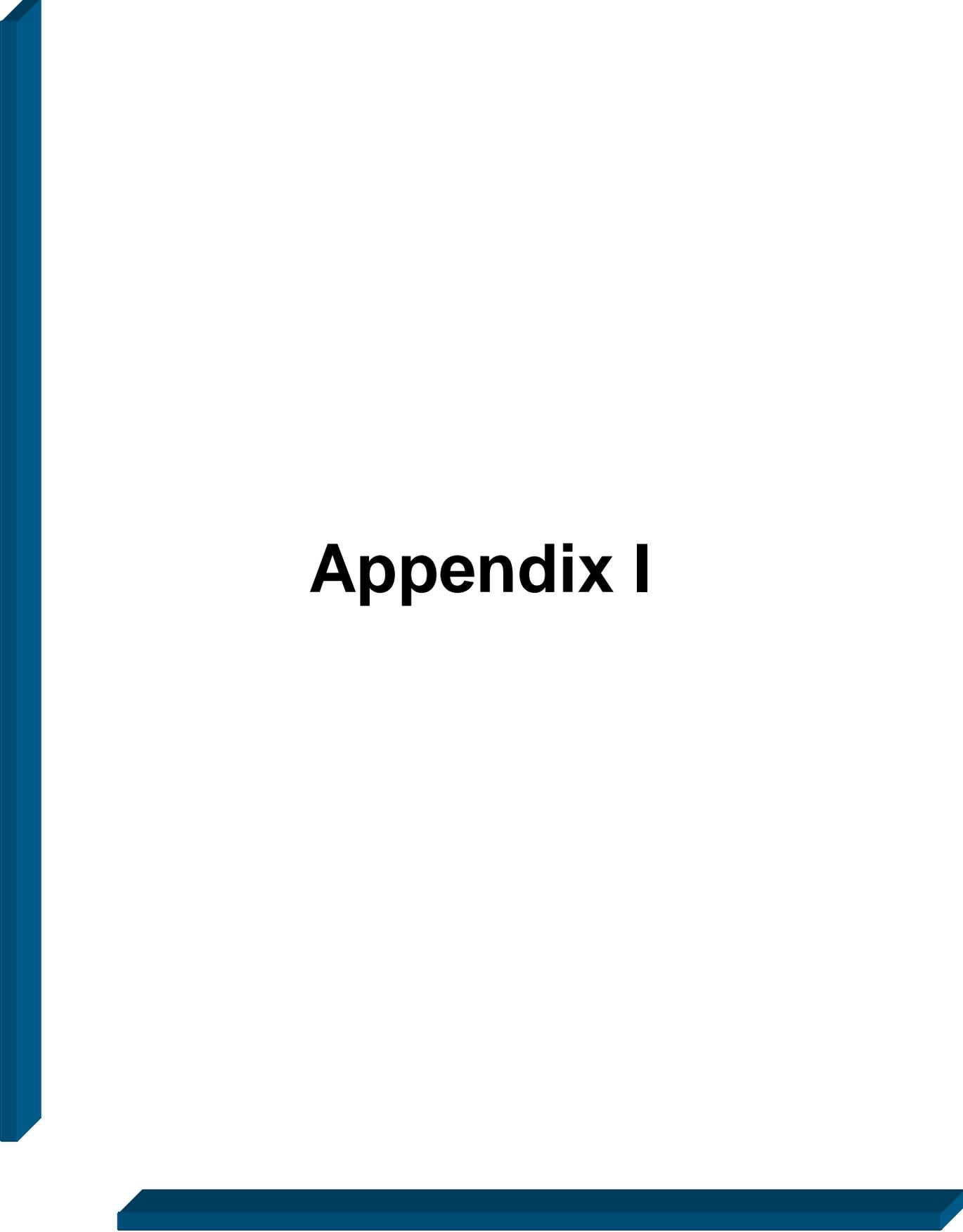
¹ Burt Cagir, MD, FACS; Chief Editor: John Geibel, MD, DSc, MA . Short Bowel Syndrome. Medscape Reference. Available online at: <http://emedicine.medscape.com/article/193391-overview>. Last accessed 2/27/2013.

² Semrad CE. Approach to the patient with diarrhea and malabsorption. In: Goldman L, Schafer AI, eds. *Cecil Medicine*. 24th ed. Philadelphia, PA: Saunders Elsevier; 2011: chap 142. February 2011.

³ Gattex® Prescribing Information. NPS Pharmaceuticals, Inc. Available online at: <http://gattex.com/Content/files/PI-IFU.pdf>. Last revised December 2012; Last accessed 2/18/13.

⁴ Vandera Nehra. Short Bowel and Dumping Syndromes: Long Term Control. Medscape Education. Available online at: http://www.medscape.org/viewarticle/439683_4. Last accessed 3/4/2013

⁵ Daily Med Current Medication Information. Available online at: <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=63165>. Last accessed 3/4/2013.



Appendix I

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

FDA NEWS RELEASE

For Immediate Release: Jan. 29, 2013

FDA approves new orphan drug Kynamro to treat inherited cholesterol disorder

The U.S. Food and Drug Administration today approved Kynamro (mipomersen sodium) injection as an addition to lipid-lowering medications and diet to treat patients with a rare type of high cholesterol called homozygous familial hypercholesterolemia (HoFH). The addition of Kynamro helps to reduce low-density lipoprotein-cholesterol (LDL-C), apolipoprotein B, total cholesterol, and non-high density lipoprotein-cholesterol (non HDL-C).

HoFH, an inherited condition that affects about one out of every one million people in the United States, occurs when the body is unable to remove LDL-C, often called "bad" cholesterol, from the blood causing abnormally high levels of circulating LDL-C. For those with HoFH, heart attacks and death often occur before age 30. Kynamro is an orphan drug approval, meaning it was developed to treat a disorder affecting fewer than 200,000 people. In December 2012, the FDA approved Juxtapid (lomitapide) to reduce LDL-C, total cholesterol, apolipoprotein B, and non HDL-C in patients with HoFH.

The safety and effectiveness of Kynamro were evaluated in a clinical trial of 51 patients with HoFH. On average, levels of LDL-C fell by about 25 percent during the first 26 weeks in those receiving the drug. Kynamro carries a Boxed Warning on the serious risk of liver toxicity because it is associated with liver enzyme abnormalities and accumulation of fat in the liver, which could lead to progressive liver disease with chronic use.

The FDA approved Kynamro with a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use, including prescriber and pharmacy certification, and documentation of safe-use conditions, which requires a prescription authorization form for each new prescription.

The most common adverse reactions in the clinical trial included injection site reactions, flu-like symptoms, nausea, headache and elevations in liver enzymes (serum transaminases).

The FDA is requiring four postmarketing studies for Kynamro: the development of a sensitive assay that binds double-stranded (ds) DNA; a study to assess for the presence of antibodies to ds-DNA in patients treated with Kynamro; a long-term registry of patients with HoFH to determine the long-term safety of Kynamro; and an enhanced pharmacovigilance program to monitor reports of malignancy, immune-mediated reactions, and hepatic abnormalities in patients treated with Kynamro.

Kynamro is manufactured by Cambridge, Mass.-based Genzyme Corp.

FDA NEWS RELEASE

For Immediate Release: Feb. 4, 2013

FDA approval of generic version of cancer drug Doxil is expected to help resolve shortage

The U.S. Food and Drug Administration today approved the first generic version of the cancer drug Doxil (doxorubicin hydrochloride liposome injection).

Doxorubicin hydrochloride liposome injection is currently on the FDA's drug shortage list. For products on the shortage list, the FDA's Office of Generic Drugs is using a priority review system to expedite the review of generic applications to help alleviate shortages.

Generic drugs approved by the FDA have the same high quality and strength as brand-name drugs. The generic manufacturing and packaging sites must pass the same quality standards as those of brand-name drugs.

The generic is made by Sun Pharma Global FZE (Sun). Doxorubicin hydrochloride liposome injection is administered intravenously by a health care professional. Sun's generic will be available in 20 milligram and 50 milligram vials.

In February 2012, to address the shortage of doxorubicin hydrochloride liposome injection, the FDA announced it would exercise enforcement discretion for temporary controlled importation of Lipodox (doxorubicin hydrochloride liposome injection), an alternative to Doxil produced by Sun and its authorized distributor, Caraco Pharmaceutical Laboratories Ltd. that is not approved in the United States. Enforcement discretion was also used to release one lot of Janssen's Doxil made under an unapproved manufacturing process.

For the present time, FDA intends to continue exercising enforcement discretion for importation of Lipodox, and limited supplies of Doxil are available. Once supplies of Sun's generic doxorubicin hydrochloride liposome injection are sufficient to meet projected demand, FDA expects to stop exercising enforcement discretion for any unapproved doxorubicin HCl liposomal product.

FDA NEWS RELEASE

For Immediate Release: Feb. 8, 2013

FDA approves Pomalyst for advanced multiple myeloma

The U.S. Food and Drug Administration today approved Pomalyst (pomalidomide) to treat patients with multiple myeloma whose disease progressed after being treated with other cancer drugs.

Multiple myeloma is a form of blood cancer that primarily affects older adults and arises from plasma cells in the bone marrow. According to the National Cancer Institute, approximately 21,700 Americans are diagnosed with multiple myeloma and 10,710 die yearly from the disease.

Pomalyst is a pill that modulates the body's immune system to destroy cancerous cells and inhibit their growth. It is intended for patients who have received at least two prior therapies, including lenalidomide and bortezomib, and whose disease did not respond to treatment and progressed within 60 days of the last treatment (relapsed and refractory).

In July 2012, FDA approved Kyprolis (carfilzomib) to treat multiple myeloma. Similar to Kyprolis, Pomalyst 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 also granted orphan product designation because it is intended to treat a rare disease or condition.

Pomalyst's safety and effectiveness was evaluated in a clinical trial of 221 patients with relapsed or refractory multiple myeloma. The trial was designed to measure the number of patients whose cancer completely or partially disappeared after treatment (objective response rate, or ORR). Patients were randomly assigned to receive Pomalyst alone or Pomalyst with low-dose dexamethasone, a corticosteroid.

Results showed 7.4 percent of patients treated with Pomalyst alone achieved ORR. The median duration of response has not yet been reached in these patients. In patients treated with Pomalyst plus low-dose dexamethasone, 29.2 percent achieved ORR with a 7.4-month median duration of response.

Pomalyst carries a Boxed Warning alerting patients and health care professionals that the drug should not be used in pregnant women because it can cause severe life-threatening birth defects, and that the drug can cause blood clots.

Because of Pomalyst's embryo-fetal risk, it is available only through the Pomalyst Risk Evaluation and Mitigation Strategy (REMS) Program. Prescribers must be certified with the Pomalyst REMS Program by enrolling and complying with the REMS requirements. Patients must sign a Patient-Physician agreement form and comply with the REMS requirements. In particular, female patients who are not pregnant but can become pregnant must comply with the pregnancy testing and contraception requirements, and males must comply with contraception requirements. Pharmacies must be certified with the Pomalyst REMS Program, must only

dispense to patients who are authorized to receive the drug and must comply with REMS requirements. Both lenalidomide and thalidomide have similar REMS.

Common side effects include a decrease in infection-fighting white blood cells (neutropenia), fatigue and weakness, low red blood cell count (anemia), constipation, diarrhea, low levels of platelets in the blood (thrombocytopenia), upper respiratory tract infections, back pain and fever.

Pomalyst, lenalidomide and thalidomide are marketed by Celgene, based in Summit, N.J. Kyprolis is marketed by South San Francisco, Calif.-based Onyx Pharmaceuticals.

FDA NEWS RELEASE

For Immediate Release: Feb. 26, 2013

FDA approves Ospheña for postmenopausal women experiencing pain during sex

The U.S. Food and Drug Administration today approved Ospheña (ospemifene) to treat women experiencing moderate to severe dyspareunia (pain during sexual intercourse), a symptom of vulvar and vaginal atrophy due to menopause.

Dyspareunia is a condition associated with declining levels of estrogen hormones during menopause. Less estrogen can make vaginal tissues thinner, drier and more fragile, resulting in pain during sexual intercourse. Ospheña, a pill taken with food once daily, acts like estrogen on vaginal tissues to make them thicker and less fragile, resulting in a reduction in the amount of pain women experience with sexual intercourse.

Ospheña's safety and effectiveness were established in three clinical studies of 1,889 postmenopausal women with symptoms of vulvar and vaginal atrophy. Women were randomly assigned to receive Ospheña or a placebo. After 12 weeks of treatment, results from the first two trials showed a statistically significant improvement of dyspareunia in Ospheña-treated women compared with women receiving placebo. Results from the third study support Ospheña's long-term safety in treating dyspareunia.

Ospheña is being approved with a boxed warning alerting women and health care professionals that the drug, which acts like estrogen on vaginal tissues, has shown it can stimulate the lining of the uterus (endometrium) and cause it to thicken. In fertile women, this thickening of the endometrium occurs monthly before menstruation. Postmenopausal women no longer experience menstruation, and a stimulated endometrium is not normal. Women should see their health care professional if they experience any unusual bleeding as it may be a sign of endometrial cancer or a condition that can lead to it. Ospheña should be prescribed for the shortest duration consistent with treatment goals and risks for the individual woman.

The boxed warning also states the incidence rates of thrombotic and hemorrhagic strokes (0.72 and 1.45 per thousand women, respectively) and the incidence rate of deep vein thrombosis (1.45 per thousand women). These rates are considered to represent low risks in contrast to the increased risks of stroke and deep vein thrombosis seen with estrogen-alone therapy.

Common side effects reported during clinical trials included hot flush/flushes, vaginal discharge, muscle spasms, genital discharge and excessive sweating.

Ospheña is marketed by Florham Park, N.J.-based Shionogi, Inc.

FDA NEWS RELEASE

For Immediate Release: Feb. 25, 2013

FDA approves Stivarga for advanced gastrointestinal stromal tumors

The U.S. Food and Drug Administration today expanded the approved use of Stivarga (regorafenib) to treat patients with advanced gastrointestinal stromal tumors (GIST) that cannot be surgically removed and no longer respond to other FDA-approved treatments for this disease.

GIST is a tumor in which cancerous cells form in the tissues of the gastrointestinal tract, part of the body's digestive system. According to the National Cancer Institute, an estimated 3,300 to 6,000 new cases of GIST occur yearly in the United States, most often in older adults.

Stivarga, a multi-kinase inhibitor, blocks several enzymes that promote cancer growth. With this new approval, Stivarga is intended to be used in patients whose GIST cancer cannot be removed by surgery or has spread to other parts of the body (metastatic) and is no longer responding to Gleevec (imatinib) and Sutent (sunitinib), two other FDA-approved drugs to treat GIST.

Stivarga was reviewed under the FDA's priority review program, which provides 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. The drug was also granted orphan product designation because it is intended to treat a rare disease.

The safety and effectiveness of Stivarga for this use were evaluated in a clinical study of 199 patients with GIST that could not be surgically removed and progressed after treatment with Gleevec or Sutent. Patients were randomly assigned to receive either Stivarga or a placebo. All patients also received optimal supportive care, which includes treatments to help manage side effects and symptoms of cancer.

Patients in the study took Stivarga or placebo until either the cancer progressed or the side effects became unacceptable. Results showed patients who took Stivarga had a delay in tumor growth (progression-free survival) that was, on average, 3.9 months later than patients who were given placebo. Patients who received the placebo were given the opportunity to switch to Stivarga when their cancer progressed.

The most common side effects reported in patients treated with Stivarga were weakness and fatigue, hand-foot syndrome (also called palmar-plantar erythrodysesthesia), diarrhea, loss of appetite, high blood pressure, mouth sores, infection, changes in voice volume or quality, pain, weight loss, stomach pain, rash, fever and nausea.

Serious side effects, which occurred in less than one percent of patients, were liver damage, severe bleeding, blistering and peeling of skin, very high blood pressures requiring emergency treatment, heart attacks and perforations (holes) in the intestines.

Stivarga was approved in September 2012 to treat colorectal cancer. It is marketed by Bayer HealthCare Pharmaceuticals, based in Wayne, N.J. Gleevec is marketed by East Hanover, N.J.-based Novartis, and Sutent is marketed by New York City-based Pfizer.

FDA NEWS RELEASE

For Immediate Release: Feb. 22, 2013

FDA approves new treatment for late-stage breast cancer

The U.S. Food and Drug Administration today approved Kadcyla (ado-trastuzumab emtansine), a new therapy for patients with HER2-positive, late-stage (metastatic) breast cancer.

HER2 is a protein involved in normal cell growth. It is found in increased amounts on some types of cancer cells (HER2-positive), including some breast cancers. In these HER2-positive breast cancers, the increased amount of the HER2 protein contributes to cancer cell growth and survival.

Kadcyla is intended for patients who were previously treated with trastuzumab, another anti-HER2 therapy, and taxanes, a class of chemotherapy drugs commonly used for the treatment of breast cancer.

Referred to as T-DM1 during clinical research, Kadcyla was reviewed under the FDA's priority review program, which provides for an expedited six-month review of drugs that may provide safe and effective therapy when no satisfactory alternative therapy exists, or offer significant improvement compared to marketed products. Other FDA-approved drugs used to treat HER2-positive breast cancer include trastuzumab (1998), lapatinib (2007) and pertuzumab (2012).

The safety and effectiveness of Kadcyla were evaluated in a clinical study of 991 patients randomly assigned to receive Kadcyla or lapatinib plus capecitabine, another chemotherapy drug. Patients received treatment until

either the cancer progressed or the side effects became intolerable. The study was designed to measure progression-free survival, the length of time patients lived without the cancer progressing, and overall survival, the length of time patients lived before death.

Results showed that patients treated with Kadcylla had a median progression-free survival of 9.6 months compared to 6.4 months in patients treated with lapatinib plus capecitabine. The median overall survival was 30.9 months in the Kadcylla group and 25.1 months in the lapatinib plus capecitabine group.

Kadcylla is being approved with a Boxed Warning alerting patients and health care professionals that the drug can cause liver toxicity, heart toxicity and death. The drug can also cause severe life-threatening birth defects, and pregnancy status should be verified prior to starting Kadcylla treatment.

The most common side effects reported in patients treated with Kadcylla were nausea, fatigue, pain in the muscles or joints, low levels of platelets in the blood (thrombocytopenia), increased levels of liver enzymes, headache, and constipation.

Breast cancer is the second leading cause of cancer-related death among women. An estimated 232,340 women will be diagnosed with breast cancer, and 39,620 will die from the disease in 2013, according to the National Cancer Institute. Almost 20 percent of breast cancers have increased amounts of the HER2 protein. Kadcylla, trastuzumab and pertuzumab are marketed by South San Francisco, Calif.-based Genentech, a member of the Roche Group. Lapatinib is marketed by GlaxoSmithKline, based in Research Triangle Park, N.C.

Safety Announcements

FDA Drug Safety Communication: Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy

[2-20-2013] The U.S. Food and Drug Administration (FDA) is updating the public about new actions being taken to address a known safety concern with codeine use in certain children after tonsillectomy and/or adenoidectomy (surgery to remove the tonsils and/or adenoids). Deaths have occurred post-operatively in children with obstructive sleep apnea who received codeine for pain relief following a tonsillectomy and/or adenoidectomy. Codeine is converted to morphine by the liver. These children had evidence of being ultra-rapid metabolizers of codeine, which is an inherited (genetic) ability that causes the liver to convert codeine into life-threatening or fatal amounts of morphine in the body.

A new Boxed Warning, FDA's strongest warning, will be added to the drug label of codeine-containing products about the risk of codeine in post-operative pain management in children following tonsillectomy and/or adenoidectomy. A Contraindication, which is a formal means for FDA to make a strong recommendation against use of a drug in certain patients, will be added to restrict codeine from being used in this setting. The Warnings/Precautions, Pediatric Use, and Patient Counseling Information sections of the drug label will also be updated.

In August 2012, FDA announced it was reviewing the safety of codeine due to cases of deaths and serious adverse events in children who took the drug after a tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine. FDA conducted a comprehensive safety review to identify additional cases of overdose or death in children taking codeine and to determine if these adverse events occurred in any other treatment settings. Many of the cases of serious adverse events or death occurred in children with obstructive sleep apnea who received codeine after a tonsillectomy and/or adenoidectomy (see Data Summary). Since these children already had underlying breathing problems, they may have been particularly sensitive to the breathing difficulties that can result when codeine is converted in the body to high levels of morphine. However, this contraindication applies to all children undergoing tonsillectomy and/or adenoidectomy because it is not easy to determine which children might be ultra-rapid metabolizers of codeine.

Health care professionals should prescribe an alternate analgesic for post-operative pain control in children who are undergoing tonsillectomy and/or adenoidectomy. Codeine should not be used for pain in children following these procedures.

For management of other types of pain in children, codeine should only be used if the benefits are anticipated to outweigh the risks.

Parents and caregivers who observe unusual sleepiness, confusion, or difficult or noisy breathing in their child should stop giving codeine and seek medical attention immediately, as these are signs of overdose.

Safety Announcements

For Immediate Release: Feb. 24, 2013

FDA alerts health care providers of recall of anemia drug Omontys

The U.S. Food and Drug Administration is alerting health care providers and patients of a voluntary nationwide recall of all lots of Omontys Injection by Affymax, Inc., of Palo Alto, Calif., and Takeda Pharmaceuticals Company Limited, of Deerfield, Ill. The recall is due to reports of anaphylaxis, a serious and life-threatening allergic reaction. Omontys is used to treat anemia in adult dialysis patients.

Until further notice, health care providers should stop using Omontys and return the product to Takeda Pharmaceuticals.

According to the companies, serious and fatal hypersensitivity reactions have been reported in some patients receiving their first dose of Omontys, given by intravenous injection. The reactions have occurred within 30 minutes following the dose. There have been no reports of reactions following subsequent dosing, or in patients who have completed their dialysis session.

The FDA has been notified by Affymax of 19 reports of anaphylaxis from dialysis centers in the United States. Three of the anaphylaxis cases resulted in death. Other patients required prompt medical intervention and in some cases hospitalization. Some of the reports included patients who were able to be resuscitated by doctors. However, anaphylaxis is life-threatening and resuscitation efforts are not always successful. Affymax and Takeda are investigating these adverse reactions. Customers may call 1-855-466-6689 for additional information.

The FDA asks health care professionals and consumers to report any adverse reactions to the FDA's MedWatch program:

- i Complete and submit the report online at www.fda.gov/medwatch/report.htm
- i Download and complete the form, then submit it via fax at 1-800-FDA-0178

Anemia is common in adult patients who have chronic kidney disease (CKD) and who are on dialysis. Omontys, approved by the FDA in March 2012, is an erythropoiesis-stimulating agent (ESA) that aids in the formation of red blood cells. Additional ESA products are available to treat anemia, including Procrit, Epogen, and Aranesp.

Safety Announcements

FDA Drug Safety Communication: FDA suspends pediatric clinical trials of Sensipar (cinacalcet hydrochloride) after report of death

[2-26-2013] The U.S. Food and Drug Administration (FDA) has stopped all pediatric clinical trials of Sensipar (cinacalcet hydrochloride) after the recent death of a 14-year-old patient in a trial. FDA continues to gather information on the circumstances surrounding the patient's death. Sensipar is a medication used to decrease the release of parathyroid hormone (PTH) from the parathyroid gland. Sensipar lowers high PTH levels leading to lower calcium levels in the blood; when calcium levels are too low it can result in health problems. FDA has approved Sensipar for use in adults but not in children (less than 18 years of age), and the clinical trials were underway to determine if the drug is effective and can be used safely in children.

Posting this information does not mean that FDA has concluded whether or not Sensipar had a role in the patient's death. This communication is intended to inform health care professionals that we are evaluating the information and will communicate our final conclusions and recommendations when our review is complete. At this time, we remind health care professionals of the following:

- i Sensipar lowers calcium levels in the blood. Patients should be monitored for the development of low serum calcium levels (hypocalcemia).
- i The potential signs of low serum calcium levels include muscular problems such as muscle cramping, tetany, convulsions, paresthesias, and myalgias.
- i If serum calcium levels decrease below the normal range, appropriate steps should be taken to increase calcium levels, such as by providing supplemental calcium, initiating or increasing the dose of a calcium-based phosphate binder, initiating or increasing the dose of vitamin D sterols, or temporarily withholding treatment with Sensipar.
- i Serum calcium levels should be measured within 1 week after initiation or dose adjustment of Sensipar. Once a maintenance dose has been established, serum calcium should be measured monthly.
- i The most frequently reported side effects in adult clinical trials of Sensipar were nausea, vomiting, and diarrhea.

FDA has not approved Sensipar for use in children. Sensipar is a calcium-sensing receptor agonist indicated in adults for:

- i Secondary hyperparathyroidism in patients with chronic kidney disease on dialysis
- i Hypercalcemia in patients with parathyroid cancer
- i Severe hypercalcemia in patients with primary hyperparathyroidism who are unable to undergo parathyroidectomy

We urge both health care professionals and patients to report adverse events involving Sensipar to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Current Drug Shortages Index (as of February 28, 2013):

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

[Acetylcysteine Inhalation Solution](#) **UPDATED** 2/21/2013

[Acyclovir Sodium Injection](#) (initial posting 11/13/2012)

[Alfentanil \(Alfenta\) Injection](#) (initial posting 1/23/2012)

[Alteplase \(Cathflo Activase\)](#) (initial posting 1/27/2012) **New!!**

[Amikacin Injection](#) **UPDATED** 3/4/2013

[Amino Acid Products](#) (initial posting 2/14/2012) **UPDATED** 2/28/2013

[Aminophylline](#) (initial posting 12/10/2012)

[Ammonium Chloride Injection](#)

[Amytal Sodium Injection](#) (initial posting date 1/31/2013)

[Argatroban Injection](#) (initial posting date 2/11/2013)

[Atracurium besylate](#) (initial posting 2/27/2012) **UPDATED** 2/28/2013

[Atropine Sulfate Injection](#) **UPDATED** 2/21/2013

[Bacteriostatic 0.9% Sodium Chloride](#) (initial posting 9/10/2012)

[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)

[Bupivacaine Hydrochloride \(Marcaine, Sensorcaine\) Injection](#) **UPDATED** 2/21/2013

[Buprenorphine hydrochloride \(Buprenex\) 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) **UPDATED** 2/25/2013

[Calcium Gluconate Injection](#) (initial posting 1/10/2013) **UPDATED** 2/25/2013

[Cetorelix Acetate for Injection \(Cetrotide\)](#) (initial posting 9/20/2012)

[Chromic Chloride Injection](#) **UPDATED** 2/21/2013

[Cidofovir Injection](#) (initial posting 2/15/2013)

[Citric Acid; Gluconolactone; Magnesium Carbonate Solution \(Renacidin\); Irrigation](#) (initial posting 6/30/2012)

[Cyanocobalamin Injection](#)

[Daunorubicin Hydrochloride Solution for Injection](#)

[Denileukin diftitox \(Ontak\) injection](#) (initial posting 9/22/2012)

[Desmopressin Injection \(DDAVP\)](#)

[Dexamethasone Sodium Phosphate Injection](#) (initial posting 1/15/2013) **UPDATED** 2/26/2013

[Dexrazoxane \(Zinecard\) Injection](#)

[Dextrose Injection](#) (initial posting 5/23/2012) **UPDATED** 2/21/2013

[Diazepam Injection](#)

[Dipyridamole Injection](#) (initial posting 7/24/2012)

[Doxorubicin \(adriamycin\) lyophilized powder](#) (initial posting 12/2/2011)

[Doxorubicin Liposomal Injection](#)

[Doxycycline Hyclate](#) (initial posting 1/18/2013)

[Edetate Calcium Disodium \(Calcium Disodium Versenate\) Injection](#) (initial posting 10/12/2012)

[Epinephrine Injection](#) (initial posting 4/27/2012) **UPDATED** 2/21/2013

[Epinephrine 1mg/mL \(Preservative Free\)](#) (initial posting 6/21/2012) **UPDATED** 2/21/2013

[Ethiodol \(ETHIODIZED OIL\) ampules](#)

[Etomidate \(Amidate\) Injection](#) (initial posting 2/9/2012) **UPDATED** 2/21/2013

[Fentanyl Citrate \(Sublimaze\) Injection](#) **UPDATED** 2/21/2013

[Fluticasone Propionate and Salmeterol \(Advair HFA\) Inhalation Powder](#) (initial posting date) - 10/17/2012)

[Fosphenytoin Sodium \(Cerebyx\) Injection](#) (initial posting 3/30/2012)

[Fospropofol disodium \(Lusedra\) Injection](#) (initial posting 6/18/2012)

[Furosemide Injection](#) (initial posting 6/20/2012) **UPDATED** 2/21/2013

[Gallium Nitrate Injection \(Ganite\)](#) (initial posting 4/4/2012)

[Heparin Sodium Premixes](#) (initial posting 7/5/2012) **UPDATED** 2/21/2013

[Hydromorphone Hydrochloride \(Dilaudid\) Injection](#) (initial posting 3/7/2012) **UPDATED** 2/21/2013

[Hydromorphone Hydrochloride Tablets](#) (initial posting 2/19/2013) **New!!**

[Ibandronate sodium \(Boniva\) injection](#) (initial posting 6/6/2012)

[Intravenous Fat Emulsion](#)

[Isoniazid Tablets](#) **UPDATED** 3/4/2013

[Ketorolac Tromethamine Injection](#)

[Leucovorin Calcium Lyophilized Powder for Injection](#) **UPDATED** 3/4/2013

[Leuprolide Acetate Injection](#)

[Lidocaine HCl, 4% Topical Solution](#) (initial posting date - 2/12/2013)

[Lidocaine \(Xylocaine\) Hydrochloride Injection](#) (initial posting date - 2/22/2012) **UPDATED** 2/21/2013

[Liotrix \(Thyrolar\) Tablets](#)

[Lorazepam \(Ativan\) Injection](#) **UPDATED** 2/21/2013

[Magnesium Sulfate Injection](#) **UPDATED** 2/21/2013

[Mannitol Injection \(Osmitrol, Resectisol\) Injection](#) (initial posting date - 12/21/2011) **UPDATED** 2/21/2013

[Methazolamide \(Glauctabs, Neptazane\) Tablets](#)

[Methoxsalen \(Oxsoralen\) 1% topical lotion](#)

[Methyldopate HCL Injection](#)

[Methylphenidate Hydrochloride Tablets](#) (initial posting date - 2/19/2013) **New!!**

[Methylphenidate Hydrochloride ER Tablets](#) (initial posting date - 2/19/2013) **New!!**

[Methylin Chewable Tablets](#) (initial posting date - 2/19/2013) **New!!**

[Metoclopramide \(Reglan\) Injection](#)

[Midazolam HCL \(Versed\) Injection](#) **UPDATED** 2/21/2013

[Morphine Sulfate Injection](#) **UPDATED** 2/21/2013

[Morphine Sulfate \(Astramorph PF, Duramorph, Infumorph\) Injection \(Preservative Free\)](#) **UPDATED** 2/21/2013

[Multi-Vitamin Infusion \(Adult and pediatric\)](#) **UPDATED** 2/21/2013

[Nalbuphine HCl \(Nubain\) Injection](#) (initial posting 5/15/2012) **UPDATED** 2/21/2013

[Naloxone \(Narcan\) Injection](#) (initial posting 2/22/2012) **UPDATED** 2/21/2013

[Neostigmine Methylsulfate Injection](#) (initial posting 1/14/2013)

[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** 3/4/2013

[Ondansetron Injection 32 mg/50 mL premixed bags](#)

[Oseltamivir Phosphate \(Tamiflu\) for Oral Suspension \(6mg/mL 60 mL\)](#) (Initial posting 1/10/2013)

[Pancuronium Bromide Injection](#)

[Papaverine Hydrochloride Injection](#) (initial posting 12/17/2012)

[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)

[Phentolamine Mesylate \(Regitine\) Injection](#)

[Pilocarpine HCL Ophthalmic Gel 4% \(Pilopine HS\)](#) (initial posting 6/1/2012)

[Potassium Acetate Injection, USP 2 mEq/mL](#) **UPDATED** 2/21/2013

[Potassium Chloride Injection 2 mEq/mL](#) (initial posting 5/15/2012) **UPDATED** 2/21/2013

[Potassium Phosphate Injection](#)

[Procainamide HCL Injection](#) **UPDATED** 2/21/2013

[Prochlorperazine Injection](#) (initial posting 1/30/2012)

[Promethazine Injection](#) (initial posting 2/10/2012)

[Propofol \(Diprivan\) Injection](#) (initial posting 4/5/2012) **UPDATED** 3/4/2013

[Secretin Synthetic Human \(ChiRhoStim\) Injection \(ChiRhoStim\)](#) (initial posting 6/15/2012)

[Selenium Injection](#) **UPDATED** 2/25/2013

[Sodium Acetate Injection](#) (initial posting 3/20/2012) **UPDATED** 2/21/2013

[Sodium benzoate and Sodium phenylacetate \(Ammonul\) Injection](#)

[Sodium Bicarbonate Injection](#) (initial posting 4/4/2012) **UPDATED** 2/21/2013

[Sodium Chloride 0.9% \(5.8mL and 20mL\)](#) (initial posting 5/4/2012)

[Sodium Chloride 23.4%](#)

[Sodium Phosphate Injection](#)

[Succinylcholine \(Anectine, Quelicin\) Injection](#) (initial posting 8/17/2012) **UPDATED** 2/21/2013

[Sufentanil Citrate \(Sufenta\) Injection](#)

[Sulfamethoxazole 80mg/trimethoprim 160mg/ml injection \(SMX/TMP\) Bactrim\)](#)

[Technetium Tc99m Bicisate for Injection \(Neurolite\)¹⁰⁹](#) (initial posting 5/4/2012)

[Technetium Tc99m Sestamibi Kit for Injection¹¹⁰](#) (initial posting 2/14/2012)

[Telavancin \(Vibativ\) Injection](#)

[Tetracycline Capsules](#)

[Thiotepa \(Thioplex\) for Injection](#)

[Ticarillin disodium/Clavulanic Potassium Injection \(Timentin\)](#) (initial posting 8/16/12)

[Ticlopidine \(Ticlid\) Tablets](#)

[Tobramycin Solution for Injection](#)

[Trace Elements](#) (initial posting 1/24/2013)

[Tromethamine \(Tham\) Injection](#) (initial posting 5/2/2012)

[Vinblastine Sulfate Injection](#) (initial posting 1/31/2012)

[Vitamin A Palmitate \(Aquasol A\) Injection](#)

[Zinc Injection](#) (initial posting 2/15/2012)

