Drug Utilization Review Board

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

Wednesday
January 8, 2014
6:00 p.m.

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

MEMORANDUM

TO: Drug Utilization Review Board Members

FROM: Chris Le, Pharm.D.

SUBJECT: **Packet Contents for Board Meeting – January 8, 2014**

DATE: January 2, 2014

NOTE: The DUR Board will meet at 6:00 p.m. The meeting will be held in the Ponca Room at the Oklahoma Health Care Authority Offices in Shepherd Mall. (North Entrance)

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

Call to Order

Public Comment Forum

Independent Review of the SoonerCare Pharmacy Benefit and Management

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

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

Action Item – Vote to Prior Authorize Breo™ Ellipta™ (Fluticasone Furoate and Vilanterol Inhalation Powder) – See Appendix C

30 Day Notice to Prior Authorize Procysbi™ (Cysteamine Bitartrate) – See Appendix D

30 Day Notice to Prior Authorize Ravicti® (Glycerol Phenylbutyrate) – See Appendix E

30 Day Notice to Prior Authorize Sirturo™ (Bedaquiline Fumarate) – See Appendix F

30 Day Notice to Prior Authorize Tobi® (Tobramycin Solution), Tobi® Podhaler™ (Tobramycin Powder), and Pulmozyme® (Dornase Alfa) – See Appendix G

FDA and DEA Updates – See Appendix H

Future Business

Adjournment

Oklahoma Health Care Authority
Drug Utilization Review Board
(DUR Board)
Meeting – January 8, 2014 @ 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 Shawna Kittridge, RPH, MHS:

3. **Independent Review of the SoonerCare Pharmacy Benefit and Management**

Items to be presented by Dr. Muchmore, Chairman:

4. **Action Item – Approval of DUR Board Meeting Minutes – See Appendix A.**
   A. December 11, 2013 DUR Minutes – Vote
   B. December 11, 2013 DUR Recommendation Memorandum

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

5. **Update on DUR / Medication Coverage Authorization Unit – See Appendix B.**
   A. Medication Coverage Activity for December 2013
   B. Pharmacy Help Desk Activity for December 2013

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

6. **Action Item – Vote to Prior Authorize Breo™ Ellipta™ (Fluticasone Furoate and Vilanterol Inhalation Powder) – See Appendix C.**
   A. COP Recommendations

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

7. **30 Day Notice to Prior Authorize Procysbi™ (Cysteamine Bitartrate) – See Appendix D.**
   A. Introduction
   B. Medication Summary
   C. COP Recommendations
   D. Product Details

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

8. **30 Day Notice to Prior Authorize Ravicti® (Glycerol Phenylbutyrate) – See Appendix E.**
   A. Introduction
   B. Medication Summary
   C. COP Recommendations

D. Product Details

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

9. 30 Day Notice to Prior Authorize Sirturo™ (Bedaquiline Fumarate) – See Appendix F.

A. Introduction
B. Medication Summary
C. COP Recommendations
D. Product Details

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

8. 30 Day Notice to Prior Authorize Tobi® (Tobramycin Solution), Tobi® Podhaler™ (Tobramycin Powder), and Pulmozyme® (Dornase Alfa) – Appendix G.

A. Introduction
B. Utilization Review
C. Utilization Details
D. COP Recommendations

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

9. FDA and DEA Updates – See Appendix H.

10. Future Business

A. Annual Reviews
B. New Product Reviews

11. Adjournment

“Independent Review of the SoonerCare Pharmacy Benefit and Management”

Presenters:
Shawna Kittridge, RPh, MHS
Principal
Mercer Government Human Services Consulting - Pharmacy Sector Lead

Barb Mart, RPh
Senior Consultant
Mercer Government Human Services Consulting

Appendix A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES OF MEETING OF DECEMBER 11, 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	
Michyla Adams, Pharm.D.; Clinical Pharmacist	x	
Karen Egesdal, D.Ph.; SMAC-ProDUR Coordinator/OHCA Liaison	x	
Bethany Holderread, Pharm. D.; Clinical Coordinator	x	
Shellie Keast, Ph.D.; Assistant Professor	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
Ashley Teel, Pharm.D.; Clinical Pharmacist	x	
Jo'Nel Weber, Pharm.D.; Clinical Pharmacist		x
Graduate Students: Tim Pham	x	

	PRESENT	ABSENT
Marlene Asmussen, R.N.; Population Care Management Director		x
Nico Gomez, Chief Executive Officer	x	
Chris Le, Pharm.D.; Clinical Pharmacist Consultant	x	
Sylvia Lopez, M.D., FAAP; Chief Medical Officer	x	
Ed Long, Chief Communications Officer		x
Jennie Melendez, Marketing Coordinator		x
Nancy Nesser, Pharm.D., J.D.; Pharmacy Director	x	
Rebecca Pasternik-Ikard, Deputy State Medicaid Director	x	
Jill Ratterman, D.Ph.; Pharmacy Specialist	x	
Garth Splinter, M.D., M.B.A.; Medicaid Director	x	
Kerri Wade, Pharmacy Operations Manager	x	

OTHERS PRESENT:		
Mark DeClerk, Lilly	Clint Degner, Novartis	Deitra Macy, PDI
Don Kempin, Novo Nordisk	John Brynson, Impax	Nate Myers, Sunovion
Charlene Kaiser, Amgen	Russ Wilson, J&J	Jim Chapman, Abbvie
Brian Maves, Pfizer	Roger Grotzinger, BMS	Eric Gardner, Vertex
Jim Fowler, Astra Zeneca	Warren Tayes , Merck	Nicole DeFreese, Lilly

PRESENT FOR PUBLIC COMMENT:	
	None

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**

No speakers for comment

ACTION: NONE REQUIRED

AGENDA ITEM NO. 3: **APPROVAL OF DUR BOARD MINUTES**

3A: NOVEMBER 13, 2013 DUR MINUTES

3B: NOVEMBER 13, 2013 DUR RECOMMENDATION MEMORANDUM

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 4: **ANNOUNCEMENT REGARDING DUR BOARD MEETING TIME AND LOCATION**

Presented by Dr. Nesser

ACTION: NONE REQUIRED

AGENDA ITEM NO. 5: **UPDATE ON MEDICATION COVERAGE AUTHORIZATION UNIT, RETRODUR AND VOTE TO PRIOR AUTHORIZE KETOCONAZOLE ORAL TABLETS**

5A: MEDICATION COVERAGE ACTIVITY: NOVEMBER 2013

5B: PHARMACY HELP DESK ACTIVITY: NOVEMBER 2013

5C: RETROSPECTIVE DRUG UTILIZATION REVIEW REPORT FOR JULY, AUGUST, AND SEPTEMBER

5D: VOTE TO PRIOR AUTHORIZE KETOCONAZOLE ORAL TABLETS

Materials included in agenda packet; presented by Dr. Holderread

Dr. Winegardener moved to approve; seconded by Dr. Harrell

ACTION: MOTION CARRIED

AGENDA ITEM NO. 6: **VOTE TO UPDATE THE ANTIHYPERTENSIVE PRODUCT BASED PRIOR AUTHORIZATION CATEGORY AND PRIOR AUTHORIZE EPANED™**

6A: COP RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Holderread

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 7: **VOTE TO PRIOR AUTHORIZE ZETONNA®**

7A: COP RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Teel
Dr. Harrell moved to approve; seconded by Dr. Kuhls
ACTION: MOTION CARRIED

AGENDA ITEM NO. 8: **VOTE TO PRIOR AUTHORIZE RESCULA® AND SIMBRINZA™**

8A: COP RECOMMENDATIONS

Materials included in agenda packet; presented Dr. Adams
Dr. Winegardener moved to approve; seconded by Dr. Bell
ACTION: MOTION CARRIED

AGENDA ITEM NO. 9: **VOTE TO PRIOR AUTHORIZE SKLICE®**

9A: COP RECOMMENDATIONS

Materials included in agenda packet; presented Dr. Adams
Dr. Kuhls moved to approve; seconded by Dr. Preslar
ACTION: MOTION CARRIED

AGENDA ITEM NO. 10: **FISCAL YEAR 2013 ANNUAL REVIEW OF ADVAIR®, SYMBICORT®, DULERA®, AND 30 DAY NOTICE TO PRIOR AUTHORIZE BREO™ ELLIPTA™**

10A: CURRENT PRIOR AUTHORIZATION CRITERIA
10B: PRIOR AUTHORIZATION REVIEW
10C: MARKET NEWS AND UPDATES
10D: PRODUCT SUMMARY
10E: COP RECOMMENDATIONS
10F: UTILIZATION DETAILS
10G: PRODUCT DETAILS

Materials included in agenda packet; presented Dr. Nawaz
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
12A: ANNUAL REVIEWS
12B: NEW PRODUCT REVIEWS
ACTION: NONE REQUIRED

AGENDA ITEM NO. 13: **ADJOURNMENT FOR EXECUTIVE SESSION**

The meeting was adjourned at 6:33 pm

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

Memorandum

Date: December 12, 2013

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

From: Bethany Holderread, Pharm.D.
Clinical Pharmacist
Pharmacy Management Consultants

Subject: DUR Board Recommendations from Meeting of December 11, 2013

Recommendation 1: Retrospective Drug Utilization Review Report: Duplication of Narcotic Therapy and Vote to Prior Authorize Ketoconazole Oral Tablets

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends prior authorization of ketoconazole oral tablets with the following criteria:

Consideration for approval requires the following:

1. FDA approved indication of systemic fungal infections with one of the following:
    a. blastomycosis
    b. coccidioidomycosis
    c. histoplasmosis
    d. chromomycosis
    e. paracoccidioidomycosis; and
2. Member is 3 years old or older; and
3. Member does not have underlying hepatic disease; and
4. Trials with other effective oral antifungal therapies, including fluconazole, itraconazole, and voriconazole, have failed to resolve infection; or

5. Other effective oral antifungal therapies are not tolerated or potential benefits outweigh the potential risks; and
6. Hepatic function tests must be done at baseline and weekly during treatment.
7. A clinical exception may apply for members with a diagnosis of Cushing's disease when other modalities are not available.

Recommendation 2: Vote to Update the Antihypertensive Product Based Prior Authorization Category and Prior Authorize Epaned™ (Enalapril Powder for Oral Solution)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the following:

1. Move Verelan® PM (verapamil ER) into Tier-2 of the CCB category.
2. Move Dynacirc® (isradipine) into Tier-2 of the CCB category.
3. Move Avapro® (irbesartan) and Avalide® (irbesartan/HCTZ) into Tier-1 of the ARB category.
4. Move Aceon® (perindopril erbumine) into Tier-2 of the ACEI category.
5. Prior authorize Monopril-HCT® (fosinopril/HCTZ) with the following criteria:
    a. Consideration for approval requires a patient specific, clinically significant reason why the member cannot use the individual components.
6. Prior authorize Cardizem® CD (diltiazem CD) 360mg capsules with the following criteria:
    a. Consideration for approval requires a patient specific, clinically significant reason why the member cannot use two 180mg Cardizem CD (diltiazem CD) capsules.
7. Place duration and quantity limits on the use of nimodipine oral capsules and Nymalize™ (nimodipine oral solution) as follows:
    a. A quantity limit of 252 capsules for 21 days will apply for Nimodipine oral capsules.
    b. A quantity limit of 2,838 mL for 21 days will apply for Nymalize™ oral solution.
8. Place an age restriction on the use of Epaned™ (enalapril powder for oral solution) for members aged 7 years or older with the following criteria:
    a. Consideration for approval requires a patient specific, clinically significant reason why the member cannot swallow the oral tablet formulation even when crushed.

Recommendation 3: Vote to Prior Authorize Zetonna® (Ciclesonide Nasal Aerosol)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the addition of Zetonna® (ciclesonide) to Tier 3 of the Nasal Allergy Product Based Prior Authorization category. The existing criteria for this category will apply.

1. The following criteria are required for approval of a Tier 2 product:
    a. Documented adverse effect or contraindication to all preferred Tier 1 products.
    b. Failure with all Tier 1 medications defined as no beneficial response after at least three weeks of use at the maximum recommended dose.
2. The following criteria are required for approval of a Tier 3 product:
    a. All Tier 2 criteria must be met.
    b. Failure with all available Tier 2 products defined as no beneficial response after at least three weeks of use at the maximum recommended dose.
3. No grandfathering of Tier 2 or Tier 3 products will be allowed for this category.
4. For members 2 to 4 years of age, the age appropriate lower-tiered generic products must be used prior to the use of higher tiered products.
5. Approvals will be for the duration of three months, except for members with chronic diseases such as asthma or COPD, in which case authorizations will be for the duration of one year.

Nasal Allergy Products		
Tier 1	***Tier 2***	***Tier 3***
fluticasone(Flonase®)	**beclomethasone** (Beconase® AQ)	**ciclesonide** (Omnaris®)
flunisolide (Nasalide®, Nasarel™)	**olapatadine** (Patanase®)	**budesonide** (Rhinocort® AQ)
triamcinolone (Nasacort® AQ)		**fluticasone** (Veramyst™)
		mometasone (Nasonex®)
		beclomethasone (QNasl®)
		azelastine (Astepro®)
		azelastine (Astelin®)
		azelastine/fluticasone (Dymista™)
		Ciclesonide (Zetonna®)

Tier structure based on supplemental rebate participation.

Recommendation 4: Vote to Prior Authorize Rescula® (Unoprostone) and Simbrinza™ (Brinzolamide/Brimonidine)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the addition of Simbrinza™ and Rescula® to Tier 2 of the Glaucoma Medications Product Based Prior Authorization category. The existing criteria for this category will apply. As recommended by the DUR Board, the College of Pharmacy will implement an educational initiative consisting of a targeted mailing to prescribers of glaucoma medications and postcards to members with a diagnosis of glaucoma to increase the appropriate utilization of medications and annual eye exams in the Oklahoma SoonerCare population.

Glaucoma Medications	
Tier 1	**Tier 2**
Beta-Blockers	
betaxolol (Betoptic® 0.5%)	betaxolol (Betoptic-S®)
carteolol 1% soln (Ocupress®)	brimonidine/timolol (Combigan®)
dorzolamide/timolol (Cosopt®)	timolol maleate (Timoptic Ocudose®)
levobunolol (Betagan®)	
metipranolol (OptiPranolol®)	
timolol maleate (Betimol®, Istalol®, Timoptic®, Timoptic-XE®)	
Prostaglandin Analogs	
travoprost (Travatan®, Travatan-Z®)	bimatoprost (Lumigan®)
latanoprost (Xalatan®)	tafluprost (Zioptan™)
	unoprostone (Rescula®)
Alpha-2 Adrenergic Agonists	
brimonidine 0.2%	brimonidine (Alphagan-P® 0.1%, 0.15%)
	apraclonidine (Iopidine®)
	brimonidine/timolol (Combigan®)
	brinzolamide/brimonidine (Simbrinza™)
Carbonic Anhydrase Inhibitors	
dorzolamide/timolol (Cosopt®)	brinzolamide (Azopt®)
dorzolamide (Trusopt®)	**brinzolamide/brimonidine (Simbrinza™)**
acetazolamide (Diamox®)*	
methazolamide (Neptazane®)*	
**Indicates Oral Products Only*	
Cholinergic Agonists/Cholinesterase Inhibitors	
pilocarpine (Isopto Carpine®, Pilopine HS®)	carbachol (Miostat®)
	echothiophate iodide (Phospholine Iodide®)

Tier structure based on supplemental rebate participation.

Recommendation 5: Vote to Prior Authorize Sklice™ (Ivermectin)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the addition of Sklice® to Tier 3 of the Pediculicides Product Based Prior Authorization category. The existing criteria for this category will apply, and a quantity limit of 117 grams (4 ounces) every 30 days will also apply. In addition, the College of Pharmacy recommends an educational initiative targeting prescribers to remind them that SoonerCare covers OTC products with a prescription. The educational mailing will include a letter, a sample prescription, and a list of covered OTC products.

Approval Criteria:

- **Consideration for approval of a Tier 2 medication** requires a trial with one Tier 1 medication with inadequate response or adverse effect.
- **Consideration for approval of a Tier 3 medication** requires trials with all available Tier 2 medication(s) with inadequate response or adverse effect.
- Clinical exception applies if there is known resistance to OTC permethrin and pyrethrin.

TIER 1	TIER 2	TIER 3
Covered OTC & Rx Permethrin Products Generics with SMAC Pricing	Benzyl Alcohol (Ulesfia™) lotion Spinosad (Natroba™) suspension	Lindane lotion & shampoo Malathion (Ovide®) lotion **Ivermectin (Sklice®) lotion**

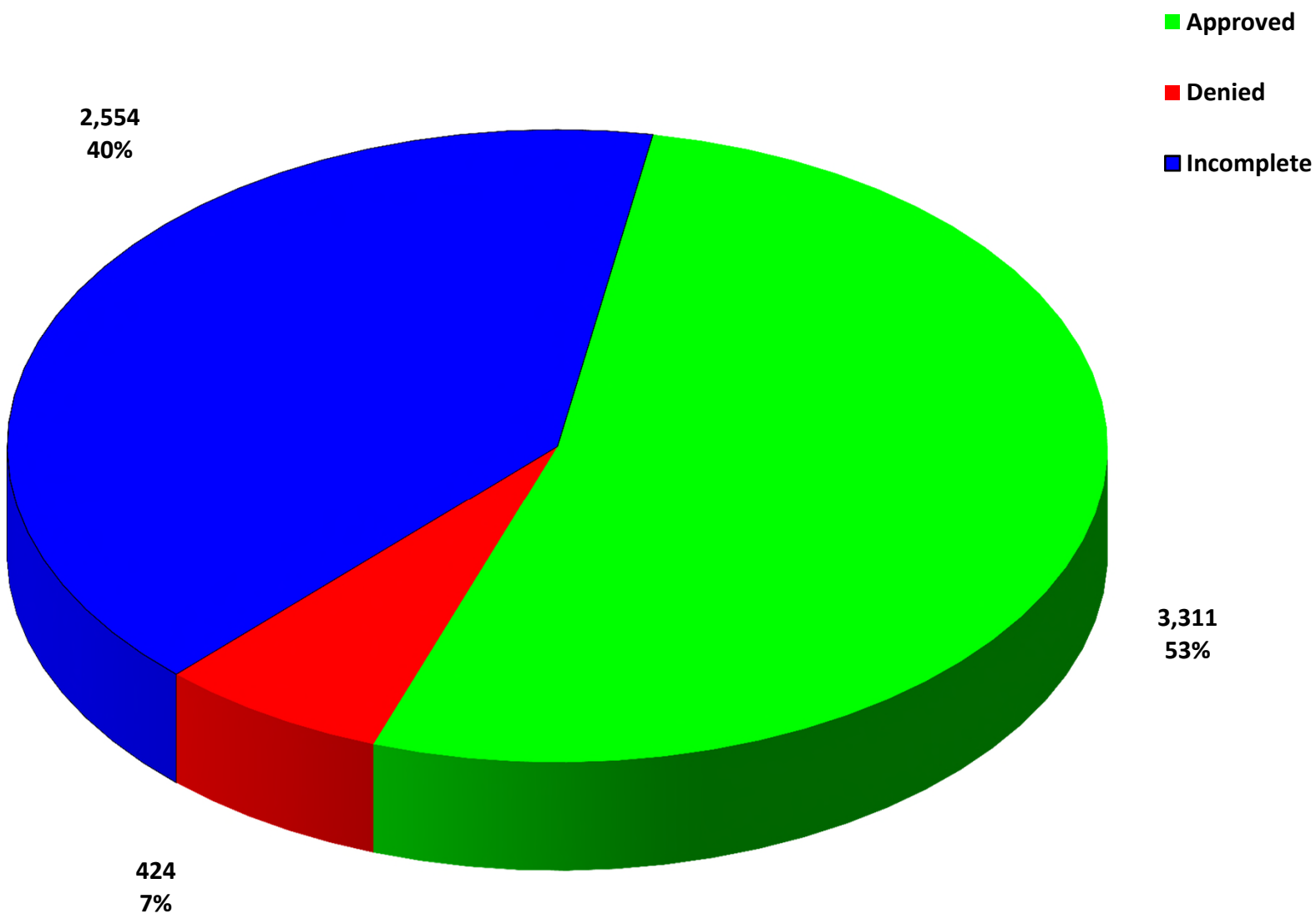
Tier structure based on supplemental rebate participation.

Recommendation 6: Annual Review of Advair® (Fluticasone Propionate/Salmeterol, Symbicort® (Budesonide/Formoterol), Dulera® (Mometasone/Formoterol) and 30 Day Notice to Prior Authorize Breo™ Ellipta™ (Fluticasone Furoate/Vilanterol Inhalation Powder)

NO ACTION REQUIRED.

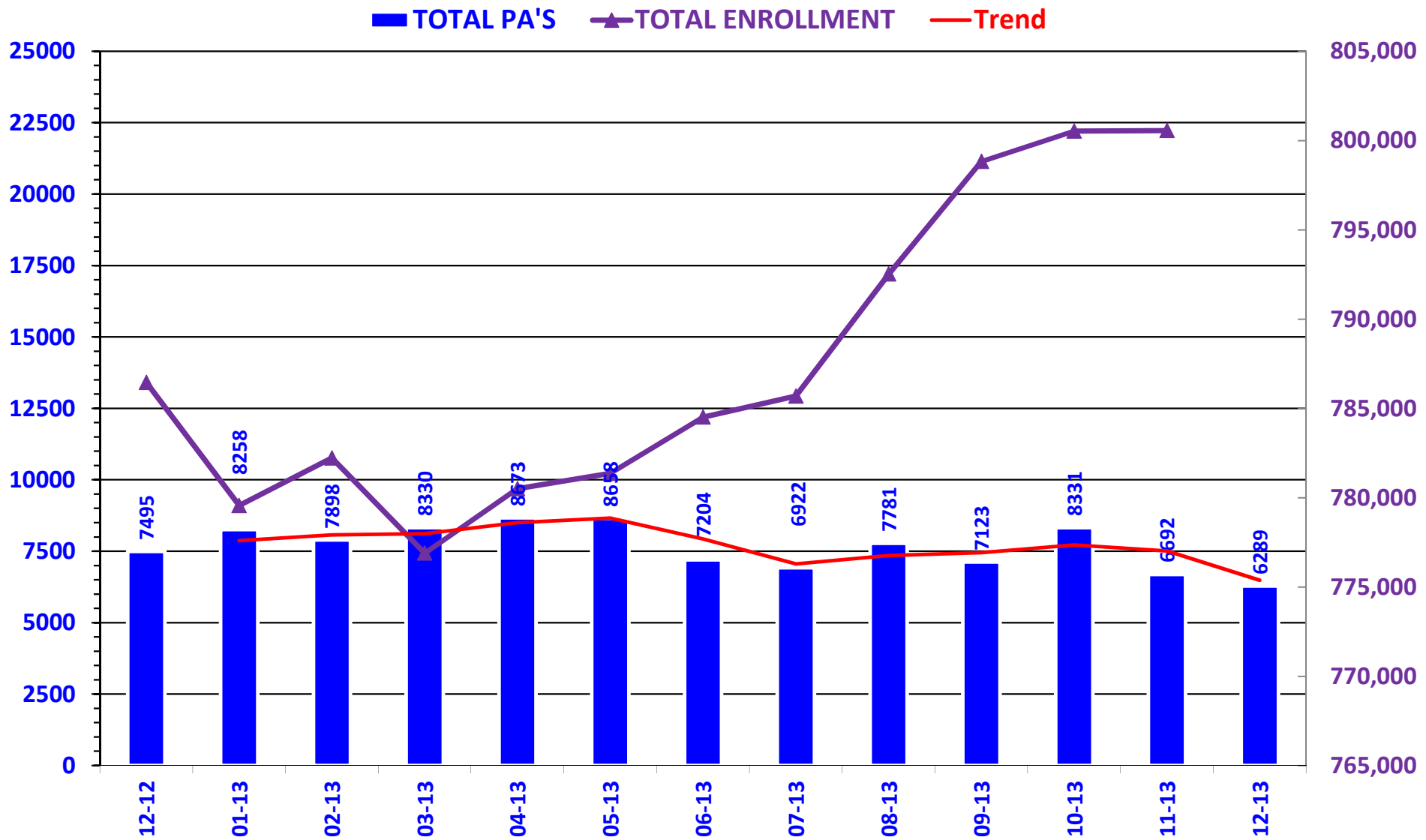
Appendix B

PRIOR AUTHORIZATION ACTIVITY REPORT: DECEMBER



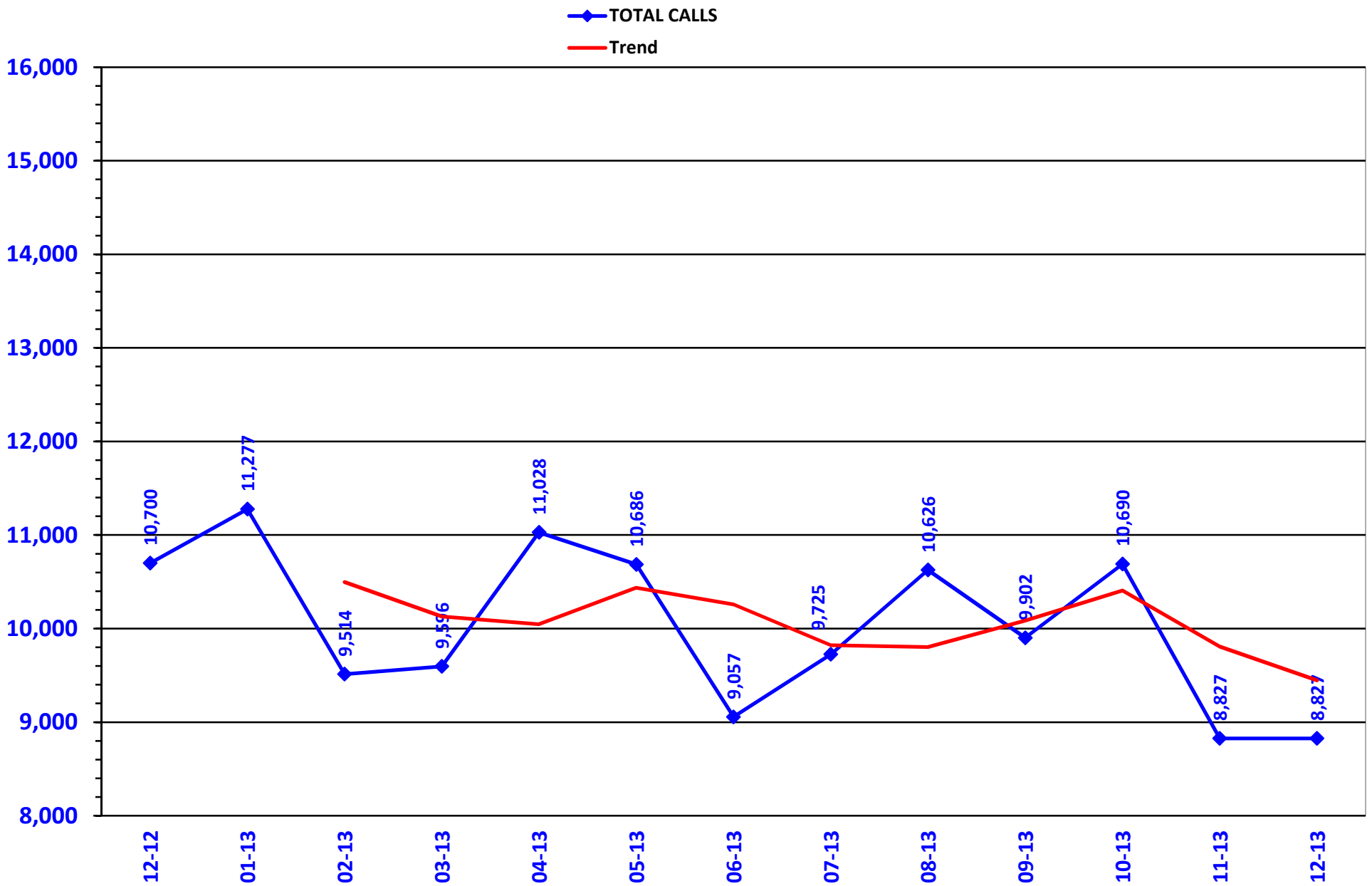
PA totals include approved/denied/incomplete/overrides

PRIOR AUTHORIZATION REPORT: DECEMBER 2012 – DECEMBER 2013



PA totals include approved/denied/incomplete/overrides

CALL VOLUME MONTHLY REPORT:
DECEMBER 2012 - DECEMBER 2013



Prior Authorization Activity

12/1/2013 Through 12/31/2013

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort/Dulera	348	156	5	187	351
Analgesic, Narcotic	364	191	14	159	245
Angiotensin Receptor Antagonist	47	12	3	32	219
Antiasthma	225	134	6	85	308
Antibiotic	21	3	5	13	10
Anticoagulant	58	37	2	19	258
Anticonvulsant	82	49	0	33	306
Antidepressant	183	48	13	122	349
Antidiabetic	106	51	4	51	348
Antihistamine	79	55	4	20	333
Antihyperlipidemic	15	4	1	10	359
Antimigraine	48	15	2	31	359
Antiplatelet	21	15	0	6	338
Antiulcers	233	53	36	144	152
Anxiolytic	65	52	0	13	262
Atypical Antipsychotics	371	243	1	127	343
Biologics	46	31	0	15	334
Bladder Control	61	6	11	44	301
Botox	12	11	1	0	358
Calcium Channel Blockers	11	6	0	5	254
Cardiovascular	37	18	3	16	267
Chronic Obstructive Pulmonary Disease	15	2	2	11	95
Dermatological	123	28	41	54	92
Endocrine & Metabolic Drugs	51	42	1	8	128
Erythropoietin Stimulating Agents	19	11	0	8	96
Fibromyalgia	123	28	15	80	311
Gastrointestinal Agents	112	37	11	64	185
Glaucoma	14	3	1	10	360
Growth Hormones	51	38	5	8	155
HFA Rescue Inhalers	63	18	6	39	324
Insomnia	47	11	7	29	164
Multiple Sclerosis	26	13	0	13	279
Muscle Relaxant	82	27	30	25	60
Nasal Allergy	89	9	30	50	184
Neurological Agents	56	39	4	13	317
Nsaids	149	23	10	116	314
Ocular Allergy	24	6	3	15	167
Ophthalmic Anti-infectives	34	3	1	30	6
Osteoporosis	22	6	0	16	360
Other*	122	41	12	69	239
Otic Antibiotic	19	7	0	12	14
Pediculicide	95	38	4	53	17
Prenatal Vitamins	10	0	0	10	0
Smoking Cess.	13	4	0	9	79
Statins	68	21	3	44	346
Stimulant	508	343	14	151	326
Suboxone/Subutex	172	135	2	35	79
Synagis	210	127	23	60	87
Testosterone	79	18	6	55	353
Topical Antifungal	42	1	5	36	85
Topical Corticosteroids	104	2	14	88	224
Vitamin	48	18	20	10	341
Pharmacotherapy	79	68	1	10	118
Emergency PAs	0	0	0	0	
Total	**5,102**	**2,357**	**382**	**2,363**	

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

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Overrides					
Brand	28	17	1	10	267
Cumulative Early Refill	4	4	0	0	180
Dosage Change	309	287	0	22	6
High Dose	1	1	0	0	177
Ingredient Duplication	8	8	0	0	4
Lost/Broken Rx	87	80	3	4	4
NDC vs Age	2	2	0	0	181
Nursing Home Issue	79	75	1	3	5
Other	37	32	1	4	15
Quantity vs. Days Supply	545	392	18	135	262
Stolen	15	9	5	1	4
Temporary Unlock	44	38	3	3	39
Third Brand Request	32	13	10	9	38
Overrides Total	**1,187**	**954**	**42**	**191**	
Total Regular PAs + Overrides	**6,289**	**3,311**	**424**	**2,554**	

Denial Reasons	
Unable to verify required trials.	2,175
Does not meet established criteria.	430
Lack required information to process request.	367

Other PA Activity	
Duplicate Requests	358
Letters	2,863
No Process	10
Changes to existing PAs	463
Partials	775

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

Appendix C

Vote to Prior Authorize Breo™ Ellipta™ (Fluticasone Furoate/Vilanterol Inhalation Powder)

Oklahoma Health Care Authority
January 2013

Recommendations

The College of Pharmacy recommends prior authorization of Breo™ Ellipta™ (fluticasone furoate/vilanterol inhalation powder) with the following criteria:

1. FDA approved diagnosis of COPD or chronic bronchitis and/or emphysema associated with COPD; and
2. Trials of Advair® and Symbicort®, at FDA approved COPD doses, consisting of at least 30 days each within the last 90 days that did not adequately control COPD symptoms.

Appendix D

30 Day Notice to Prior Authorize Procysbi™ (Cysteamine Bitartrate)

Oklahoma Health Care Authority
January 2014

Manufacturer	Raptor Pharmaceuticals Inc.
Classification	Renal-Urologic Agent
Status	Prescription Only

Introduction[1, 2, 3, 4]

Cystinosis is a rare genetic condition in which the amino acid cystine accumulates in the body as a consequence of a deficiency of the lysosomal membrane transporter protein cystinosin. Reduced removal of the amino acid cystine from lysosomes leads to crystals that can build up and damage cells.

There are three types of cystinosis: nephropathic cystinosis, intermediate cystinosis, and ocular cystinosis. All three are caused by mutations in the cystinosin protein and inherited in an autosomal recessive pattern. The most severe and common type is infantile nephropathic cystinosis. Symptoms develop at 6-12 months of age and include Fanconi's syndrome, rickets, impaired growth, polyuria, and polydipsia. The buildup of cystine results in kidney damage and subsequent loss of sugar, proteins and salts through the urine. In the absence of treatment in early childhood nephropathic cystinosis may lead to end stage renal disease. Infantile nephropathic cystinosis is typically diagnosed by 1 year of age; intermediate nephropathic cystinosis manifests more commonly in early adolescence and is generally diagnosed by 12 years of age. Cystinosis has an estimated prevalence of 500 patients in the United States, and about 3,000 patients worldwide.[3]

Currently, the FDA approved drugs used to treat nephropathic cystinosis include Cystagon® (cysteamine bitartrate), an immediate-release capsule, and Procysbi™ (cysteamine bitartrate), a delayed-release capsule. While Cystagon® is taken every six hours, Procysbi™ is a long-acting formulation that is taken every 12 hours. Cystagon® was FDA approved in 1994, and is available only as a brand formulation. Unlike Procysbi™, Cystagon® has been studied in children under 6 years of age and does not have a minimum age of use. Cysteamine is the standard treatment for cystinosis. The dose is titrated to reduce the leukocyte cystine concentration to below 1.0 nmol half-cystine/mg protein. Oral cysteamine therapy has proven effective in mitigating the effects of the disease by delaying renal failure, enhancing growth, preventing hypothyroidism, and preventing late complications. Cysteamine is not a cure for cystinosis, and long-term treatment is required.

Medication Summary[5]

- **Indications:** Procysbi™ (cysteamine bitartrate) is a cystine-depleting agent indicated for the management of nephropathic cystinosis in adults and children ages 6 years and older. Procysbi™ was FDA approved in April 2013 and is the only delayed-release product approved by the FDA to treat nephropathic cystinosis.

- **Dosing:** The recommended dose is 1.3gram/m^2/day by mouth divided twice daily. The dose should be titrated to maintain a plasma cysteamine concentration >0.1mg/L, or a white blood cell (WBC) cystine level <1 nmol half-cystine/mg protein. WBC cystine levels should be monitored monthly for three months, then quarterly for one year, then twice yearly.

- **Mechanism of Action:** Procysbi™ controls cystine levels by participating within lysosomes in a thiol-disulfide interchange reaction converting cystine into cysteine and cysteine-cysteamine mixed disulfide which can exit the lysosome preventing accumulation within the cell.

- **Efficacy:** The efficacy of Procysbi™ was evaluated in a phase 3 multicenter, randomized, crossover trial comparing immediate-release cysteamine bitartrate vs. Procysbi™ in 43 patients with nephropathic cystinosis. The trial demonstrated that at steady-state, Procysbi™ administered every 12 hours was non-inferior to immediate-release cysteamine bitartrate administered every 6 hours with respect to the depletion of WBC cystine levels. Forty patients completing the trial are continuing treatment with Procysbi™ in an ongoing, open-label extension trial. An interim analysis was performed after all patients had been treated with Procysbi™ for at least 12 months. The analysis indicated that patients who switched from immediate-release cysteamine to Procysbi™ maintained a WBC level <1 nmol half-cystine/mg protein for up to 19 months at a total daily dose equal to their total daily dose of immediate-release cysteamine at entry.

- **Utilization:** There has been no utilization of Procysbi™ in the SoonerCare population since its approval in April 2013. In fiscal year 2013, Cystagon® has been used by one member with a verified diagnosis of cystinosis.

- **Cost:**

Procysbi™ or Cystagon® Dosage Form	EAC Per Tablet or Capsule	EAC Per Day	EAC for 30 days of Therapy
Procysbi™ 25mg and 75mg Delayed-Release Capsules	$65.74	$1,314.80	$39,444.00
Cystagon® 50mg and 150mg Capsules	$0.33 and $1.13	$11.30	$339.00

EAC= estimated acquisition cost

Daily dosing based on a patient with a body surface area of 1.14m^2 (average BSA for a 10 year old).

Recommendations

The College of Pharmacy recommends the prior authorization of Procysbi™ (cysteamine bitartrate) with the following criteria:

1. An FDA approved diagnosis of nephropathic cystinosis; and
2. A patient specific, clinically significant reason why member cannot use the short-acting formulation Cystagon® (cysteamine bitartrate).

PRODUCT DETAILS OF PROCYSBI™ (CYSTEAMINE BITARATE)[5]

INDICATIONS AND USE:

- Procysbi™ (cysteamine bitartrate) is indicated for the treatment of nephropathic cystinosis in adults and children 6 years and older.

DOSAGE FORMS:

- Procysbi™ is available as 25mg and 75mg delayed-release capsules.

ADMISTRATION:

- Procysbi™ therapy should be initiated promptly once the diagnosis is confirmed (i.e., increased WBC cystine concentration).
- Cysteamine-naïve patients should be started on 1⁄6 to 1⁄4 of the maintenance dose of Procysbi™. The dose should be raised gradually over 4 to 6 weeks to help reduce the risk of side-effects.
- The recommended Procysbi™ maintenance dose is 1.3 gram/m^2/day, in two divided doses given every 12 hours.
- The dose can be titrated up to 1.95 grams/m^2/day to maintain a plasma cysteamine concentration >0.1mg/L, or WBC cystine level <1 nmol half-cystine/mg protein. WBC cystine levels should be monitored monthly for three months, then quarterly for one year, then twice yearly.
- Procysbi™ should be taken at least 2 hours after and at least 30 minutes before eating.
- Procysbi™ should be swallowed whole. Patients should not crush or chew capsules or capsule contents.
- For patients who have difficulty swallowing capsules, Procysbi™ can be opened and sprinkled on applesauce or orange juice. Procysbi™ can be given via feeding tube by opening capsule and mixing intact granules into applesauce.

CONTRAINDICATIONS:

- The use of Procysbi™ is contraindicated in patients who are hypersensitive to penicillamine.

SPECIAL POPULATIONS:

- Procysbi™ is classified as pregnancy category C. There are no adequate and well-controlled studies in pregnant women. Procysbi™ was teratogenic and fetotoxic in rats at doses less than the recommended human maintenance dose. Procysbi™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- It is not known whether Procysbi™ is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from Procysbi™, nursing is not recommended.
- The risks and benefits of treatment with Procysbi™ in children under 6 years old are not yet established.

WARNINGS AND PRECAUTIONS:

- Skin and bone lesions that resemble clinical findings for Ehlers-Danlos syndrome have been reported in patients treated with high doses of Procysbi™. Monitor patients for development of skin or bone lesions and interrupt Procysbi™ dosing if patients develop these lesions.
- Severe skin rashes such as toxic epidermal necrolysis have been reported in patients receiving Procysbi™. If severe skin rashes develop, discontinue use of any cysteamine product permanently.
- Gastrointestinal ulceration and bleeding have been reported in patients receiving Procysbi™.
- Central nervous system symptoms such as seizures, lethargy, somnolence, depression, and encephalopathy have been associated with Procysbi™. Interrupt or adjust the dose as necessary.
- Procysbi™ has been associated with reversible leukopenia and elevated alkaline phosphatase levels. Therefore, blood counts and alkaline phosphatase levels should be monitored.
- Benign intracranial hypertension has been reported in patients receiving Procysbi™ treatment. Physicians should monitor patients for signs and symptoms including headache, tinnitus, dizziness, nausea, diplopia, blurry vision, loss of vision, pain behind the eye or pain with eye movement.

ADVERSE REACTIONS:

- The most commonly reported adverse reactions during clinical trials (occurring in at least 5% of patients treated with Procysbi™) were vomiting, abdominal pain/discomfort, headaches, nausea, diarrhea, anorexia/decreased appetite, breath odor, fatigue, dizziness, skin odor, and rash.

DRUG INTERACTIONS:

- Procysbi™ can be administered with electrolyte (except bicarbonate) and mineral replacements necessary for management of Fanconi Syndrome as well as vitamin D and thyroid hormone.
- An in-vitro study indicates Procysbi™ is not an inhibitor of CYP enzymes. The potential for cysteamine to affect the pharmacokinetics of other drugs via these enzymes is low.

PATIENT COUNSELING INFORMATION:

1. Take Procysbi™ at least 2 hours after and at least 30 minutes before eating. It is permissible to eat 1⁄2 cup of food within 1 hour before and 1 hour after taking Procysbi™, but it must be taken consistently in relation to food from one day to another.
2. Take Procysbi™ consistently and do not miss doses. Take a missed dose as soon as possible. If it is within 4 hours of the next dose, skip the missed dose and take the next regularly scheduled dose. Do not double the dose.
3. It is important to keep all laboratory appointments while taking Procysbi™.
4. Procysbi™ may cause seizures, lethargy, somnolence, depression, and encephalopathy that may require interrupting or decreasing the dose of Procysbi™.

5. Procysbi™ may cause ulcers and bleeding. Contact your physician immediately if you experience stomach pain, nausea, vomiting, loss of appetite, or are vomiting blood.
6. Contact your physician immediately if you experience a skin rash or skin changes.
7. Contact your physician immediately if you experience headache, tinnitus, dizziness, nausea, double vision, blurry vision, loss of vision, or eye pain.
8. Procysbi™ may cause abnormalities of the skin, bones, and joints.

[1] Cystinosis. National Institute of Health. Available online at: http://ghr.nlm.nih.gov/condition=cystinosis. Last revised 05/2013. Last accessed 12/16/2013.
[2] Infantile Nephropathic Cystinosis Standards of Care. Cystinosis Research Network. Available online at: https://cystinosis.org/images/family-support/resources/CRN_Standards_12pgloRes.pdf. Last revised 06/2012. Last accessed 12/16/13.
[3] FDA approves Procysbi™ for rare genetic condition. U.S. Food and Drug Administration. Available online at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm350091.htm. Last revised 05/2013. Last accessed 12/16/2013.
[4] Brodin-Sartorius A, Tete MJ, Niaudet P et al. Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults. *Kidney International.* 2012; 81: 179-189.
[5] Procysbi™ Product Information. Raptor Pharmaceuticals Inc. Available online at: http://www.procysbi.com/docs/Procysbi-Full-Prescribing-Information.pdf. Last revised 04/2013. Last accessed 12/16/2013.

Appendix E

30 Day Notice to Prior Authorize Ravicti®
(Glycerol Phenylbutyrate)

Oklahoma Health Care Authority
January 2014

Manufacturer	Hyperion Therapeutics, Inc.
Classification	Hyperammonemia agent
Status	Prescription Only

Introduction[1,2,3,4,5]

The urea cycle is a process that takes place primarily in the liver in which nitrogen waste (ammonia, NH_3) is removed from the body. After consumption, proteins are broken down into amino acids. Ammonia is produced from leftover amino acids and must be eliminated. The liver produces several enzymes that convert ammonia into urea, which is excreted in the urine. If this process is disturbed, ammonia levels begin to rise. Urea cycle disorders (UCDs) are inherited deficiencies of enzymes or transporters necessary for the synthesis of urea from ammonia. Absence of these enzymes or transporters results in the accumulation of toxic levels of ammonia in the blood, with possible complications of confusion and eventually disorientation, swelling of the brain, brain damage, coma, and death.

As a group, UCDs occur in 1 in 35,000 newborns in the United States. Ornithine transcarbamylase (OTC) deficiency is the most common of these disorders, with males more often affected than females.[6] UCDs are often diagnosed when the child is still an infant. Signs may include abnormal amino acids in blood and urine, abnormal level of orotic acid in blood or urine, or high blood ammonia level. Within the first week after birth, the baby may develop symptoms of confusion, decreased food intake, disliking protein-containing foods, increased sleepiness, difficulty waking, nausea, and vomiting. Neonatal onset UCDs are caused by severe enzyme deficiencies or complete absence of enzyme function. Individuals with childhood or adult onset disease have partial enzyme deficiencies. The percentage of enzyme function, and therefore ability to rid the body of ammonia varies widely between individuals with partial enzyme deficiencies.

The treatment of UCDs consists of dietary protein management to limit ammonia production in conjunction with medications and/or supplements which provide alternative pathways for the removal of ammonia from the bloodstream. Dietary protein must be carefully monitored and some restriction is necessary; too much dietary protein causes excessive ammonia production. However, if protein intake is too restrictive or insufficient calories are provided, lean muscle mass will be broken down(catabolism) to obtain the amino acids or energy required, and this catabolism creates excessive ammonia. The correct nutritional balance for each individual in each stage of growth is critical in avoiding hyperammonemic crises. Treatment of UCDs may include supplementation with special amino acid formulas developed specifically for UCDs, which can be prescribed to provide approximately 50% of the daily dietary protein allowance.

Special low-protein infant and toddler formulas are also available. Sodium phenylbutyrate (Buphenyl®) is the primary medication used to treat UCDs. Sodium benzoate is also used in some patients, solely or in conjunction with Buphenyl®; both are "ammonia scavengers", providing alternative pathways for removal of ammonia from the bloodstream and helping to prevent hyperammonemia. These medications are administered three to four times per day in order to ensure continual removal of toxic ammonia from the bloodstream. Buphenyl® contains 125mg sodium per gram of sodium phenylbutyrate, which at a maximum dose of 20g per day, results in 2500mg of sodium per day. Buphenyl® is available as an oral powder and oral tablets; sodium benzoate is available as a powder for oral solution that requires compounding. When optimal management fails, or in the case of neonatal onset carbamyl phosphate synthetase (CPS) and ornithine transcarbamylase (OTC) deficiency, liver transplant becomes a treatment option.

Medication Summary[7,8,9,10]

Indications: Ravicti® (glycerol phenylbutyrate) was approved by the FDA in February 2013 for use as a nitrogen-binding agent for chronic management of adult and pediatric patients ≥ 2 years of age with urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. Ravicti® must be used with dietary protein restriction and, in some cases, dietary supplements. Ravicti® is not indicated for the treatment of acute hyperammonemia in patients with UCDs because more rapidly acting interventions are essential to reduce plasma ammonia levels.

Dosing: Ravicti® is available as a 1.1 g/mL glycerol phenylbutyrate oral solution (which delivers 1.02 g/mL of phenylbutyrate). Ravicti® should be given in 3 equally divided doses, each rounded up to the nearest 0.5 mL, and should be taken with food. The maximum total daily dosage is 17.5 mL (19 g). In determining the starting dose of Ravicti® in phenylbutyrate-naïve patients, the prescriber should consider the patient's residual urea synthetic capacity, dietary protein restrictions, and diet adherence.

Mechanism of Action: Ravicti® is an "ammonia scavenger", providing an alternative pathway for removal of ammonia from the bloodstream and helping to prevent hyperammonemia.

Efficacy: The efficacy of Ravicti® was evaluated in adult patients with UCDs in a randomized, double-blind, active-controlled, crossover, noninferiority study, comparing Ravicti® to sodium phenylbutyrate by evaluating venous ammonia levels in patients with UCDs who had been on sodium phenylbutyrate prior to enrollment. The primary endpoint was the 24-hour area under the curve (AUC) for venous ammonia on days 14 and 28 when the drugs were expected to be at steady state. Patients were randomized to receive either sodium phenylbutyrate for 2 weeks then Ravicti® for 2 weeks, or Ravicti® for 2 weeks then sodium phenylbutyrate for 2 weeks. Both medications were administered TID with meals, and patients adhered to a low-protein diet and received amino acid supplementation throughout the study. Ravicti® was noninferior to sodium phenylbutyrate with respect to the 24-hour AUC for ammonia. The efficacy of

Ravicti® was also evaluated in pediatric patients 2 to 17 years of age in two fixed-sequence, open-label, sodium phenylbutyrate to Ravicti® crossover studies. The 24-hour AUC for blood ammonia were similar between treatments.

Cost: The estimated acquisition cost of Ravicti® is $99.00/mL. At maximum dose (17.5 mL per day), a one month supply would cost $51,975.00, resulting in an annual cost of $623,700.00. The following table is a cost comparison of Ravicti® and Buphenyl®, the primary medication used to treat UCDs.

Medication name	Maximum Dose	EAC*	Cost/month	Cost/year
Ravicti® oral solution	17.5 mL	$99.00	$51,975.00	$623,700.00
Buphenyl® 500mg tablets	20 g (40 tablets)	$10.97	$13,164.00	$157,968.00
Buphenyl® oral powder	20 g	$21.95	$13,170.00	$158,040.00

*EAC= Estimated Acquisition Cost per milliliter, gram, or tablet

Recommendations

The College of Pharmacy recommends prior authorization of Ravicti® (glycerol phenylbutyrate) with the following criteria:

Ravicti® Approval Criteria:

1. FDA approved diagnosis of urea cycle disorder (UCD); and
2. Active management with protein restricted diet; and
3. A patient specific, clinically significant reason why member cannot use sodium phenylbutyrate (Buphenyl®).

PRODUCT DETAILS OF RAVICTI® (GLYCEROL PHENYLBUTYRATE)[8,9]

INDICATIONS AND USE: Ravicti® (glycerol phenylbutyrate) is indicated for use as a nitrogen-binding agent for chronic management of adult and pediatric patients ≥ 2 years of age with UCDs who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. Ravicti® must be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements).

DOSAGE FORMS: 1.1 g/mL glycerol phenylbutyrate oral solution

ADMINISTRATION:

- Ravicti® should be prescribed by a physician experienced in the management of UCDs.
- Ravicti® should be administered in three equally divided doses, each rounded up to the nearest 0.5 mL, directly into the mouth via oral syringe or dosing cup, and should be taken with food.
    - Ravicti® can be administered directly into a nasogastric tube or gastrostomy tube using an oral syringe, followed by flushing with 30 mL of water and allowing the flush to drain. Flush a second time with an additional 30 mL of water to clear the tube.
- The maximum total daily dosage of Ravicti® is 17.5 mL (19 g).
- Patients switching from sodium phenylbutyrate to Ravicti® should receive the dosage of Ravicti® that contains the same amount of phenylbutyrate. The conversion is as follows: total daily dosage of Ravicti® (mL) = total daily dosage of sodium phenylbutyrate (g) x 0.86.
- The recommended dosage range for phenylbutyrate-naïve patients, based upon body surface area, is 4.5 to 11.2 mL/m²/day (5 to 12.4 g/m²/day).
    - For patients with some residual enzyme activity who are not adequately controlled with protein restriction, the recommended starting dosage is 4.5 mL/m²/day.
    - In determining the starting dose of Ravicti® in treatment-naïve patients, the patient's residual urea synthetic capacity, dietary protein requirements, and diet adherence should be considered.

CONTRAINDICATIONS:

- Patients less than 2 months of age. Children < 2 months of age may have immature pancreatic exocrine function, which could impair hydrolysis of Ravicti®, leading to impaired absorption of phenylbutyrate and hyperammonemia.
- Known hypersensitivity to phenylbutyrate. Signs of hypersensitivity include wheezing, dyspnea, coughing, hypotension, flushing, nausea, and rash.

SPECIAL POPULATIONS:

- **Pregnancy:** There are no adequate or well-controlled studies with Ravicti® in pregnant women. A voluntary patient registry will include evaluation of pregnancy outcomes in patients with UCDs. Ravicti® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (Category C)
- **Nursing Mothers:** It is not known whether Ravicti® or metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions from Ravicti® in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into consideration the importance of the drug to the health of the mother.
- **Pediatrics:** The safety and efficacy of Ravicti® in pediatric patients 2 months to < 2 years of age have not been established. Ravicti® is contraindicated in patients < 2 months of age.

- **Geriatrics:** Clinical studies of Ravicti® did not include sufficient numbers of subjects ≥ 65 years of age to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
- **Renal Impairment:** The efficacy and safety of Ravicti® in patients with renal impairment are unknown. Monitor ammonia levels closely when starting patients with impaired renal function on Ravicti®.
- **Hepatic Impairment:** No studies have been conducted in UCD patients with hepatic impairment. Because conversion of phenylacetic acid (PAA) to phenylacetylglutamine (PAGN) occurs in the liver, patients with hepatic impairment may have reduced conversion capability and higher plasma PAA and PAA to PAGN ratio. Therefore, dosage for patients with moderate to severe hepatic impairment should be started at the lower end of the recommended dosing range and should be kept on the lowest dose necessary to control their ammonia levels.

WARNINGS AND PRECAUTIONS:

- **Neurotoxicity:** The major metabolite of Ravicti®, PAA, is associated with neurotoxicity. Signs and symptoms of PAA neurotoxicity, including somnolence, fatigue, lightheadedness, headache, dysgeusia, hypoacusis, disorientation, impaired memory, and exacerbation of preexisting neuropathy, were observed at plasma PAA concentrations ≥ 500 µg/mL in a study of cancer patients who were administered IV PAA. In this study, the adverse effects were reversible. In healthy subjects, after administration of 4 mL and 6 mL Ravicti® three times daily for 3 days, a dose-dependent increase in all-grade nervous system adverse reactions was observed, even at exposure levels of PAA < 100 µg/mL. If symptoms of vomiting, nausea, headache, somnolence, confusion, or sleepiness are present in the absence of high ammonia or other concomitant illnesses, reduce the Ravicti® dosage.
- **Reduced Phenylbutyrate Absorption in Pancreatic Insufficiency or Intestinal Malabsorption:** Exocrine pancreatic enzymes hydrolyze Ravicti® in the small intestine, separating the active moiety, phenylbutyrate, from glycerol. This process allows phenylbutyrate to be absorbed into the circulation. Low or absent pancreatic enzymes or intestinal disease resulting in fat malabsorption may result in reduced or absent digestion of Ravicti® and/or absorption of phenylbutyrate and reduced control of plasma ammonia. Monitor ammonia levels closely in patients with pancreatic insufficiency or intestinal malabsorption.

ADVERSE REACTIONS:

- Adverse reactions occurring in open-label, long-term studies with Ravicti® include:
    - Occurring in ≥ 10% of adult patients: nausea, vomiting, diarrhea, decreased appetite, hyperammonemia, dizziness, headache, and fatigue.
    - Occurring in ≥ 10% of pediatric patients: upper abdominal pain, rash, nausea, vomiting, diarrhea, decreased appetite, hyperammonemia, and headache.

DRUG INTERACTIONS:

- **Corticosteroids:** The use of corticosteroids may cause the breakdown of body protein and increase plasma ammonia levels.
- **Valproic Acid and Haloperidol:** Hyperammonemia may be induced by valproic acid or by haloperidol.

- **Probenecid:** Probenecid may inhibit the renal excretion of metabolites of Ravicti®, including PAGN and PAA.

PATIENT COUNSELING INFORMATION:

- Ravicti® is an oral solution that is indicated for chronic management of urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. Ravicti® must be used with dietary protein restriction and, in some cases, dietary supplements.
- Before using Ravicti®, talk to your doctor or healthcare provider if you are pregnant or plan to become pregnant, or are breastfeeding.
- Talk to your doctor or healthcare provider if you are allergic to phenylbutyrate or any components of Ravicti®.
- Talk to your doctor or healthcare provider about other medications you are currently taking.
- Common adverse reactions of Ravicti® include diarrhea, gas, and headache.
- Adverse reactions of Ravicti® are sometimes the same as symptoms of high blood ammonia levels. Headache, feeling tired, lightheadedness, confusion, abnormal taste, hearing loss, and impaired memory are possible serious adverse reactions of Ravicti®, associated with neurological toxicity. If you experience these symptoms, call your doctor right away.
- Use Ravicti® exactly as prescribed by your doctor.
- There is a voluntary registry for UCD patients which will assess long-term outcomes in patients with UCDs, including growth and neurocognitive outcomes and the outcome of pregnancy for women with UCDs who become pregnant. For more information regarding this voluntary registry program, visit www.ucdregistry.com or call 1-855-823-2595.

---

[1] Hereditary Urea Cycle Abnormality. Medline Plus. Available online at: http://www.nlm.nih.gov/medlineplus/ency/article/000372.htm. Last revised 2/2/12. Last accessed 12/17/13.

[2] Urea Cycle Disorders. National Urea Cycle Disorders Foundation. Available online at: http://www.nucdf.org/ucd.htm. Last revised 2/1/13. Last accessed 12/17/13.

[3] Urea Cycle Disorders Treatment Guidelines. Rare Clinical Diseases Research Network. Available online at: http://rarediseasesnetwork.epi.usf.edu/ucdc/physicians/guidelines-main.htm. Last revised 2005. Last accessed 12/17/13.

[4] Buphenyl® Package Insert. Med Library.org. Available online at: http://medlibrary.org/lib/rx/meds/buphenyl-1/. Last revised 6/11/13. Last accessed 12/17/13.

[5] Buphenyl® Full Prescribing Information. Hyperion Therapeutics, Inc. Available online at: http://www.hyperiontx.com/sites/default/files/BUPHENYL_Prescribing_Information.pdf. Last revised 4/2009. Last accessed 12/17/13.

[6] Summar ML, Koelker S, Freedenberg D, et al. The Incidence of Urea Cycle Disorders. *Molecular Genetics and Metabolism.* 2013; 110: 179-180.

[7] Ravicti® Drug Information. Micromedex 2.0. Available online at: http://www.micromedexsolutions.com/micromedex2/librarian/PFDefaultActionId/evidencexpert.DoIntegratedSearch. Last revised 2/19/13. Last accessed 12/17/13.

[8] Ravicti® Package Insert. Med Library.org. Available online at: http://medlibrary.org/lib/rx/meds/ravicti/. Last revised 2/8/13. Last accessed 12/17/13.

[9] Ravicti® Full Prescribing Information. Hyperion Therapeutics, Inc. Available online at: http://www.ravicti.com/hcp/files/RAVICTI_Prescribing_Information.pdf. Last revised 2/2013. Last accessed 12/17/13.

[10] Ravicti® FDA Approval History. Drugs@FDA: Orange Book. Available online at: http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=203284&TABLE1=OB_Rx. Last revised 12/16/13. Last accessed 12/17/13.

Appendix F

30 Day Notice to Prior Authorize Sirturo™ (Bedaquiline)

Oklahoma Health Care Authority
January 2014

Manufacturer	Kemwell Pvt. Ltd. For Janssen Therapeutics, LP
Classification	Anti-Infective Agent
Status	Prescription Only

Introduction[1,2,3,4]

Multidrug-resistant tuberculosis (MDR-TB) is caused by *Mycobacterium tuberculosis* that is resistant to at least isoniazid and rifampin, two first-line TB drugs. MDR-TB develops when TB that is susceptible to first-line medications is not treated sufficiently because of substandard treatment regimens or non-adherence with treatment.

The World Health Organization (WHO) estimates that there were about 450,000 new MDR-TB cases in the world in 2012.[2] The Center for Disease Control and Prevention (CDC) estimated a total of 69 TB culture-positive cases in the state of Oklahoma in 2012; three of those cases were found to be resistant to isoniazid, while none were found to be MDR.[3]

MDR-TB must be treated with an appropriate drug regimen to prevent further transmission. The medications for treatment of MDR-TB are limited, and adverse drug reactions commonly result in discontinuation of therapy. Compared to drug-susceptible TB the treatment of MDR-TB is extensive. Treatment of drug-susceptible TB is typically limited to a regimen of 4 drugs for a duration of 6 months. In contrast, MDR-TB requires 18–24 months of treatment with five or six medications that tend to be less effective, more toxic, and more costly than a standard first-line regimen. Current guidelines from the CDC for treatment of MDR-TB recommend a regimen consisting of a fluoroquinolone, pyrazinamide, ethambutol, an injectable agent, and an alternative agent for MDR-TB. Alternative agents include ethionamide, clarithromycin, linezolid, and amoxicillin/clavulanate.

Medication Summary[5,6]

- **Indications:** Sirturo™ (bedaquiline fumarate) is a diarylquinoline antimycobacterial agent indicated as part of combination therapy in adults with pulmonary MDR-TB. The CDC recommends Sirturo™ should only be used with clinical expert consultation and administered by direct observation to adults aged 18 years and older when an effective treatment regimen cannot otherwise be provided. Sirturo™ was FDA approved in December 2012 under the provisions of the accelerated approval regulations for “serious or life-threatening illnesses.”

- **Dosing:** The recommended dose is 400mg by mouth once daily for two weeks followed by 200mg three times weekly for 22 weeks.

- **Mechanism of Action:** Sirturo™ is the first medication approved for pulmonary MDR-TB with a novel mechanism of action in over 40 years. Sirturo™ inhibits mycobacterial adenosine 5'triphosphate synthase, an enzyme that is essential for the generation of energy in *Mycobacterium tuberculosis.*

- **Efficacy:** The efficacy of Sirturo™ was evaluated in a placebo-controlled, double-blind, randomized trial conducted in newly diagnosed patients with multi-drug resistant pulmonary *Mycobacterium tuberculosis*. Patients received treatment with a combination of 5 antimycobacterial agents in addition to Sirturo™ or placebo. Sirturo™ was administered as 400 mg once daily for the first 2 weeks and as 200 mg 3 times per week for the following 22 weeks. The Sirturo™ treatment group had a decreased time to culture conversion and improved culture conversion rates compared to the placebo treatment group at Week 24. Median time to culture conversion was 83 days for the Sirturo™ treatment group compared to 125 days for the placebo group.

- **Safety:** The use of Sirturo™ has a black box warning for an increased risk of death. An increased risk of death was seen in the Sirturo™ treatment group compared to the placebo treatment group in one placebo-controlled trial. No clear cause of death related to Sirturo™ toxicity was identified. The black box warning also conveys risk of QT prolongation with Sirturo™ therapy. Concomitant use with drugs that prolong the QT interval may cause additive QT prolongation.

- **Utilization:** There has been no utilization of Sirturo™ in the SoonerCare population since its approval in December 2012.

- **Cost:**

Antimycobacterial Agent	Cost Per Tablet or Capsule	Cost Per Day	Cost for Complete Course of Therapy
Sirturo™ 100mg tablets	$168.51*	$674.04	$31,679.88 (24 Weeks)
Pyrazinamide 500mg tablets	2.09^{\alpha}$	$6.27	$1,404.48 (32 Weeks$^{\infty}$)
Ethambutol 400mg tablets	1.20^{\alpha}$	$3.60	$806.40 (32 Weeks$^{\infty}$)

*EAC = Estimated acquisition cost for brand medications

$^{\alpha}$SMAC = state maximum allowable cost for generic medications.

∞32 weeks of therapy based on WHO guidelines for intensive phase treatment of MDR-TB.

Recommendations

The College of Pharmacy recommends the prior authorization of Sirturo™ (bedaquiline fumarate) with the following criteria:

1. An FDA approved diagnosis of pulmonary multi-drug resistant tuberculosis (MDR-TB); and
2. Member must be 18 years of age or older; and
3. An alternative, effective treatment regimen cannot otherwise be provided; and
4. Medical supervision by an infectious disease specialist; and
5. Sirturo™ must be used in combination with at least three other drugs to which the patient's MDR-TB isolate has been shown to be susceptible; and
6. Sirturo™ must be administered under direct observation; and
7. Baseline ECG should be obtained and repeated 2, 12, and 24 weeks after starting treatment; and
8. Liver enzymes should be obtained at baseline and monitored monthly.
9. Sirturo™ will not be approved for the treatment of latent, extra-pulmonary or drug-sensitive tuberculosis. MDR-TB must be confirmed by sensitivity cultures indicating resistance to at least isoniazid and rifampin.
10. A quantity limit of 88 tablets per 30 days will apply.
11. Approvals will be for the duration of 24 weeks.

PRODUCT DETAILS OF SIRTURO™ (BEDAQUILINE FUMARATE)[5]

INDICATIONS AND USE: Sirturo™ (bedaquiline fumarate) is indicated as a part of combination therapy for the treatment of MDR-TB in adults. Sirturo™ should be reserved for when an effective treatment regimen cannot otherwise be provided; it is not indicated for the treatment of latent, extra-pulmonary or drug-sensitive tuberculosis.

DOSAGE FORMS: Sirturo™ is available as 100mg tablets.

ADMISTRATION: The recommended dose of Sirturo™ is 400mg by mouth once daily for 2 weeks followed by 200mg three times per week for 22 weeks. Sirturo™ should be taken with food and the tablets should be swallowed whole with water.

CONTRAINDICATIONS: None

SPECIAL POPULATIONS:

- Sirturo™ is classified as pregnancy category B. There are no adequate and well-controlled studies in pregnant women. Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the fetus due to Sirturo™. Sirturo™ should be used during pregnancy only if clearly needed.
- It is not known whether Sirturo™ is excreted in human breast milk.
- The safety and effectiveness of Sirturo™ in children less than 18 years of age have not been established.
- Clinical studies of Sirturo™ did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients.
- No dosage adjustment is required in patients with mild to moderate renal impairment or in patients with mild to moderate hepatic impairment.
- Use with caution in patients with severe renal or hepatic impairment and only when the benefits outweigh the risks.

WARNINGS AND PRECAUTIONS:

Black Box Warning: An increased risk of death was seen in the Sirturo™ treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%) in one placebo-controlled trial. Only use Sirturo™ when an effective treatment regimen cannot otherwise be provided. QT prolongation can occur with Sirturo™. Concomitant use with drugs that prolong the QT interval may cause additive QT prolongation.

- Sirturo™ prolongs the QT interval. An ECG should be obtained before initiation of treatment, and at least 2, 12, and 24 weeks after starting treatment with Sirturo™. Serum potassium, calcium, and magnesium should be obtained at baseline and corrected if abnormal.

- Hepatic-related adverse drug reactions have been reported with use of Sirturo™. Monitor liver-related laboratory tests (ALT, AST, alkaline phosphatase and bilirubin) baseline, monthly while on treatment, and as needed.
- Non-adherence to the treatment regimen could result in failure or resistance.

ADVERSE REACTIONS: The most commonly reported adverse reactions during clinical trials (occurring in at least 10% of patients treated with Sirturo™) were nausea, arthralgia, and headache.

DRUG INTERACTIONS:

- Sirturo™ exposure may be reduced during co-administration with inducers of CYP3A4 such as rifampin.
- Sirturo™ exposure may be increased during co-administration with inhibitors of CYP3A4 such as ketoconazole.
- Clinical data in HIV/MDR-TB co-infected patients and the combined use of antiretroviral agents with Sirturo™ are not available.
- Additive or synergistic QT prolongation was observed when Sirturo™ was co-administered with other drugs that prolong the QT interval.

PATIENT COUNSELING INFORMATION:

1. Sirturo™ is an antibiotic prescription medicine used to treat resistant tuberculosis of the lungs in people with limited treatment options.
2. It is important to complete the full course of treatment with Sirturo™ and your other TB medicines.
3. Take Sirturo™ by mouth with food. Swallow the tablets whole with water.
4. Do not skip Sirturo™ doses. If you miss your dose during week 1 or 2 do not take a double dose to make up for the missed dose. If you miss your dose after the first two weeks of treatment take the missed dose as soon as possible.
5. You should not drink alcohol while taking Sirturo™.
6. Sirturo™ can cause serious heart rhythm changes. Tell your healthcare provider right away if you have a change in your heartbeat or if you faint.
7. Sirturo™ can cause liver problems. Call your healthcare provider right away if you have unexplained symptoms such as nausea or vomiting, stomach pain, unusual tiredness, loss of appetite, light colored bowel movements, dark colored urine, or yellowing of your skin or eyes.

[1] Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate (Sirturo™) for the Treatment of Multidrug-Resistant Tuberculosis. Centers for Disease Control and Prevention. Available online at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6209a1.htm. Last revised 10/2013. Last accessed 12/16/2013.

[2] Multidrug-resistant tuberculosis (MDR-TB): October 2013 Update. World Health Organization. Available online at: http://www.who.int/tb/challenges/mdr/mdr_tb_factsheet.pdf. Last revised 10/2013. Last accessed 12/16/2013.

[3] CDC TB Fact Sheets: Trends in Tuberculosis-United States. Centers for Disease Control and Prevention. Available online at: http://www.cdc.gov/tb/publications/factsheets/statistics/TBTrends.htm. Last revised 09/2013. Last accessed 12/16/2013

[4] FDA approves Sirturo™. U.S. Food and Drug Administration. Available online at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333695.htm. Last revised 01/2013. Last accessed 12/16/2013.

[5] Sirturo™ Product Information. Janssen Products, LP. Available online at: http://wwwsirturo.com/sites/default/files/pdf/sirturo-pi.pdf. Last revised 10/2013. Last accessed 12/16/2013.

[6] Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. World Health Organization. Available online at: http://www.who.int/tb/challenges/mdr/programmatic_guidelines_for_mdrtb/en/. Last revised 2011. Last accessed 12/16/13.

Appendix G

30 Day Notice to Prior Authorize Tobi® (Tobramycin Solution), Tobi® Podhaler™ (Tobramycin Powder), and Pulmozyme® (Dornase Alfa)

Oklahoma Health Care Authority
January 2013

Introduction

Cystic fibrosis affects approximately 30,000 people in the United States, with approximately 1,000 new cases diagnosed each year.[1] There were approximately 250 SoonerCare members with a reported diagnosis of cystic fibrosis during calendar year 2013. Cystic fibrosis is caused by a congenital defect of the cystic fibrosis transmembrane conductance regulator gene which results in a complex of symptoms. Respiratory symptoms caused by pathological production of thick viscous mucus often lead to respiratory complications which may result in life threatening lung infections. Inhaled medications are commonly used in cystic fibrosis patients to improve respiratory function and to decrease risk of respiratory tract infections. These include the following:

1. Pulmozyme® (dornase alfa) – cleaves and depolymerizes extracellular DNA which allows endogenous enzymes to break down proteins and decrease viscosity of purulent mucus.
2. Tobi® (tobramycin) – treatment and prevention of respiratory tract infections associated with *Pseudomonas aeruginosa*.
3. Inhaled bronchodilators – typically administered as nebulized albuterol solution before chest therapy to increase respiratory function.
4. Hypertonic saline inhalation – used to increase hydration of airway surfaces, which improves lung function, reduces risk of pulmonary exacerbations, and is not associated with worsening bacterial infections.

Utilization of Tobi® (Tobramycin) Products and Pulmozyme® (Dornase Alfa)

Periodically, the utilization of Tobi® products and Pulmozyme® has been evaluated internally to ensure appropriate and cost-effective use of these products. The recent utilization review of these products, coupled with the loss of patent protection for Tobi® and the FDA approval of Tobi® Podhaler™ during fiscal year 2013, yields opportunities for cost savings as presented below.

Tobi®, Tobi® Podhaler™ and Pulmozyme® Utilization Trends

Timeframe	Members*	Claims	Cost	Cost/Claim	Cost/Day	Units	Days
Oct 2011-Sept 2012	244	1467	$4,749,749.27	$3,237.73	$112.08	210,994	42,377
Oct 2012-Sept 2013	229	1281	$4,773,836.24	$3,726.65	$129.18	178,819	36,956
% Change	-6.55%	-14.52%	0.50%	13.12%	13.23%	-17.99%	-14.67%
Change	-15	-186	$24,086.97	$488.92	$17.09	-32,175	-5,421

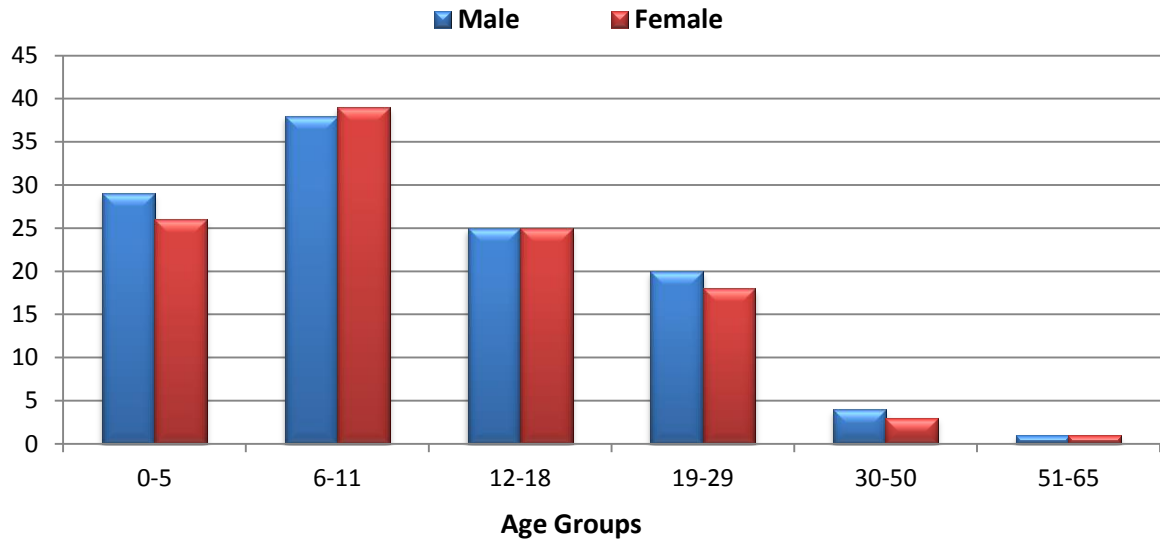
*Total number of unduplicated members.

Utilization Details (October 1, 2012 – September 30, 2013)

Chemical Name	Brand Name	Claims	Members	Cost	Units/ Day	Claims/ Member	Cost/ Claim
Dornase Alfa	PULMOZYME® SOL 1MG/ML	889	168	$2,358,689.18	2.88	5.29	$2,653.19
Tobramycin	TOBI® NEB 300/5ML	348	131	$2,104,119.91	9.93	2.66	$6,046.32
Tobramycin	TOBI® PODHALR™ CAP 28MG [β]	44	28	$311,027.15	8	1.57	$7,068.80
	Totals	**1,281**	**229***	**$4,773,836.24**	**4.84**	**5.59**	**$3,726.65**

*Total number of unduplicated members.
[β] Marketed in March of 2013.

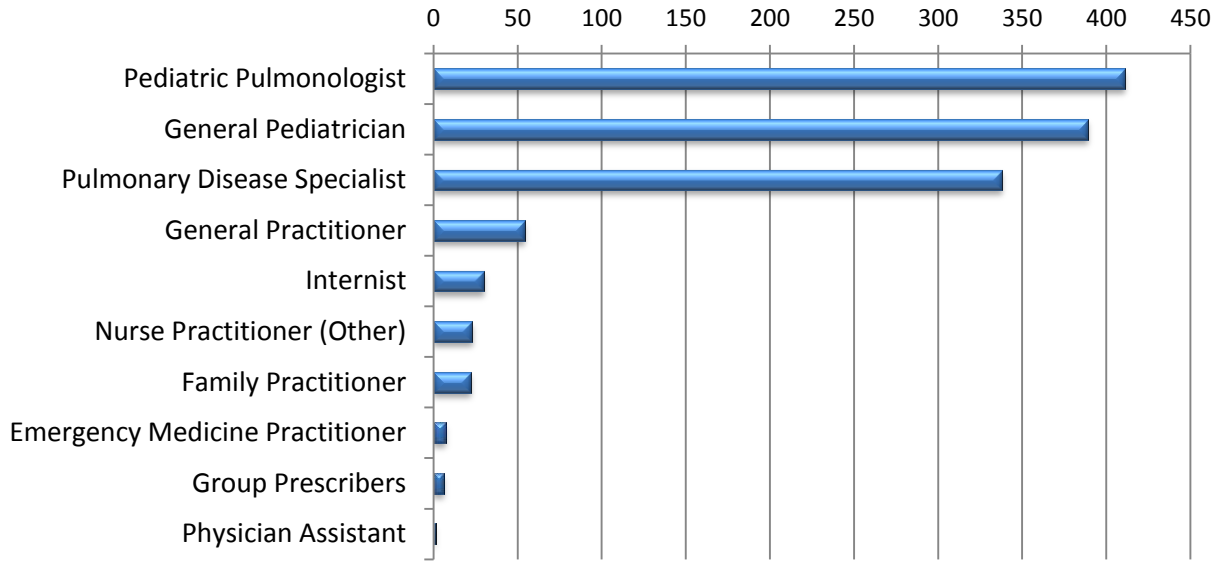
Demographics (October 1, 2012 – September 30, 2013)



There were a total of 136 members who utilized a Tobi® inhalation product during the evaluated timeframe. Of these, 47 members (35%) did not have a reported diagnosis of cystic fibrosis within the previous 24 months of medical claims history. Most of these members had severe concomitant diagnoses such as cerebral palsy, quadriplegia, and/or chronic respiratory disease. The majority of these members also had a diagnosis of pneumonia, although only 12 members had a specific diagnosis code of pneumonia due to *pseudomonas*. The off-labeled use of Tobi® in this group of members during the evaluated timeframe resulted in a total cost of approximately $725,000.

There were a total of 168 members who utilized Pulmozyme® during the same timeframe. Of these, 17 members (10%) did not have a reported diagnosis of cystic fibrosis within the previous 24 months of medical claims history. Concomitant diagnoses in this group of members include pneumonia, asthma, acute and chronic bronchitis, cerebral palsy, acute and chronic respiratory failure, pulmonary collapse, muscular dystrophy, and/or dependence on respirator. The off-labeled use of Pulmozyme® in this group of members during the evaluated timeframe resulted in a total cost of approximately $250,000.

Prescriber Specialties by Total Claims
(October 1, 2012 – September 30, 2013)



Efficacy of Tobi® (Tobramycin) Products and Pulmozyme® (Dornase Alfa)

Tobi® is an antibacterial aminoglycoside indicated for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*. Tobi® has been shown to[2]:

- Decrease amount of *Pseudomonas aeruginosa* in sputum
- Improve pulmonary function (increased FEV_1 % predicted between 7% to 11%)
- Decrease hospitalization days (~3 days)
- Decreased need for IV anti-pseudomonal antibiotic use

Tobi® oral inhalation solution, approved in 1997, is available as 300mg/5ml single dose ampules. Tobi® requires 20–30 minutes to nebulize and is inhaled twice daily for cycles of 28 days of treatment, followed by 28 days of no treatment. Tobi® Podhaler™ is available as 28mg capsules of tobramycin powder for oral inhalation. It is to be administered as 4 capsules inhaled via a specialized inhaler twice daily. Tobi® Podhaler™ does not require refrigeration and only requires 2-7 minutes for administration.

Over the past decade, the use of Tobi® for pneumonia associated with *Pseudomonas aeruginosa* in patients without cystic fibrosis has been evaluated. However, these studies have been small and have not shown inhaled tobramycin to be clearly beneficial over other treatment options. One trial showed pathogens were eradicated from sputum significantly more frequently in patients who received endotracheal tobramycin compared to placebo, but no significant differences were shown in clinical outcomes between the two groups.[3] Another smaller study consisting of only 10 patients showed aerosolized tobramycin in the treatment of ventilator-associated pneumonia was safe and effective, but the study was unable to determine

if it would lead to better clinical or cost effective outcomes when compared to other treatment options available, such as systemic antibiotics.[4]

Pulmozyme®, approved in 1993, is a genetically engineered recombinant human DNase, an enzyme which selectively cleaves DNA. Pulmozyme® liquefies bronchial mucus by cleaving extracellular DNA, which is present in very high concentrations in airway secretions of CF patients. It is administered once daily and requires 6–10 minutes to be administered as nebulized therapy.

Pulmozyme® has also been evaluated in patients without CF. One retrospective study evaluated the clinical and radiologic changes in pediatric patients who received Pulmozyme® for persistent atelectasis not attributed to cardiovascular causes who were unresponsive to treatment with inhaled bronchodilators and physiotherapy. Of the patients analyzed, 17 of 25 patients experienced clinical improvement, 5 remained unchanged, and 3 experienced temporary clinical deterioration.[5] Another trial showed that use of Pulmozyme® in critically ill patients with lung atelectasis resulted in no statistical difference when compared with hypertonic saline or normal saline.[6] A pilot study for use of Pulmozyme® in non-intubated adult asthmatics refractory to bronchodilators resulted in no clinical improvement when compared with placebo.[7]

Recommendations

The College of Pharmacy recommends the following:

1. Reserve use of Tobi® and Pulmozyme® for members who have a diagnosis of cystic fibrosis. These medications will not require a prior authorization and claims will pay at the point of sale if member has a reported diagnosis of CF within the past 24 months of claims history. If the member does not have a reported diagnosis, a manual prior authorization will be required for coverage consideration.
2. Prior authorize Tobi® Podhaler™ with the following criteria:
    a. A diagnosis of cystic fibrosis; and
    b. A patient specific, clinically significant reason why member cannot use the Tobi® oral inhalation solution.
3. Restrict use of Tobi® products to 28 days of therapy per every 56 days to ensure cycles of 28 days on therapy followed by 28 days off therapy. Use outside of this recommended regimen may be considered for coverage via a manual petition.

[1] Cystic Fibrosis Foundation. About Cystic Fibrosis: What You Need to Know. Available at http://www.cff.org/AboutCF/. Last accessed 12/19/2013.

[2] Tobi Product Information. Novartis Pharmaceuticals. Available online at: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=94f9e516-6bf6-4e30-8dde-8833c25c2560. Last accessed 12/26/2013. Last revised 11/2013.

[3] Brown, R. B., J. A. Kruse, G. W. Counts, J. A. Russell, N. V. Christou, M. L. Sands, and the Endotracheal Tobramycin Study Group. 1990. Double-blind study of endotracheal tobramycin in the treatment of gram-negative bacterial pneumonia. Antimicrob. Agents Chemother. 34:269-*272*

[4] Ali Hallal, Stephen M. Cohn, Nicholas Namias, Fahim Habib, Gio Baracco, Ronald J. Manning, Bruce Crookes, and Carl I. Schulman. Surgical Infections. February 2007, 8(1): 73-82. doi:10.1089/sur.2006.051

[5] Tom Hendriks, Matthijs de Hoog, Maarten H Lequin, Annick S Devos, and Peter JFM Merkus. DNase and atelectasis in non-cystic fibrosis pediatric patients. Crit Care. 2005; 9(4): R351–R356.

[6] Youness HA, Mathews K, Elya MK, Kinasewitz GT, Keddissi JI. Dornase alpha compared to hypertonic saline for lung atelectasis in critically ill patients. J Aerosol Med Pulm Drug Deliv. 2012 Dec;25(6):342-8. doi: 10.1089/jamp.2011.0954. Epub 2012 Mar 13

[7] Silverman RA, Foley F, Dalipi R, Kline M, Lesser M. The use of rhDNAse in severely ill, non-intubated adult asthmatics refractory to bronchodilators: a pilot study. Respir Med. 2012 Aug;106(8):1096-102. doi: 10.1016/j.rmed.2012.04.002. Epub 2012 May 12.

Appendix H

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

FDA NEWS RELEASE

For Immediate Release: Dec. 6, 2013

FDA approves Sovaldi for chronic hepatitis C

Drug is third with breakthrough therapy designation to receive FDA approval

The U.S. Food and Drug Administration today approved Sovaldi (sofosbuvir) to treat chronic hepatitis C virus (HCV) infection. Sovaldi is the first drug that has demonstrated safety and efficacy to treat certain types of HCV infection without the need for co-administration of interferon.

Sovaldi is the second drug approved by the FDA in the past two weeks to treat chronic HCV infection. On November 22, the FDA approved Olysio (simeprevir).

Hepatitis C is a viral disease that causes inflammation of the liver that can lead to diminished liver function or liver failure. Most people infected with HCV have no symptoms of the disease until liver damage becomes apparent, which may take several years. Some people with chronic HCV infection develop scarring and poor liver function (cirrhosis) over many years, which can lead to complications such as bleeding, jaundice (yellowish eyes or skin), fluid accumulation in the abdomen, infections or liver cancer. According to the Centers for Disease Control and Prevention, about 3.2 million Americans are infected with HCV.

Sovaldi is a nucleotide analog inhibitor that blocks a specific protein needed by the hepatitis C virus to replicate. Sovaldi is to be used as a component of a combination antiviral treatment regimen for chronic HCV infection. There are several different types of HCV infection. Depending on the type of HCV infection a patient has, the treatment regimen could include Sovaldi and ribavirin or Sovaldi, ribavirin and peginterferon-alfa. Ribavirin and peginterferon-alfa are two drugs also used to treat HCV infection.

Sovaldi's effectiveness was evaluated in six clinical trials consisting of 1,947 participants who had not previously received treatment for their disease (treatment-naive) or had not responded to previous treatment (treatment-experienced), including participants co-infected with HCV and HIV. The trials were designed to measure whether the hepatitis C virus was no longer detected in the blood at least 12 weeks after finishing treatment (sustained virologic response), suggesting a participant's HCV infection has been cured.

Results from all clinical trials showed a treatment regimen containing Sovaldi was effective in treating multiple types of the hepatitis C virus. Additionally, Sovaldi demonstrated efficacy in participants who could not tolerate or take an interferon-based treatment regimen and in participants with liver cancer awaiting liver transplantation, addressing unmet medical needs in these populations.

The most common side effects reported in clinical study participants treated with Sovaldi and ribavirin were fatigue and headache. In participants treated with Sovaldi, ribavirin and peginterferon-alfa, the most common side effects reported were fatigue, headache, nausea, insomnia and anemia.

Sovaldi is the third drug with breakthrough therapy designation to receive FDA approval. The FDA can designate a drug as a breakthrough therapy at the request of the sponsor if preliminary clinical evidence indicates the drug may demonstrate a substantial improvement over available therapies for patients with serious or life-threatening diseases. Sovaldi was reviewed under the FDA's priority review program, which provides for an expedited review of drugs that treat serious conditions and, if approved, would provide significant improvement in safety or effectiveness.

Sovaldi is marketed by Gilead, based in Foster City, Calif. Olysio is marketed by Raritan, N.J.-based Janssen Pharmaceuticals.

FDA NEWS RELEASE

For Immediate Release: Dec. 11, 2013

FDA approves first generic versions of antidepressant drug Cymbalta

The U.S. Food and Drug Administration today approved the first generic versions of Cymbalta (duloxetine delayed-release capsules), a prescription medicine used to treat depression and other conditions.

Aurobindo Pharma Ltd., Dr. Reddy's Laboratories Ltd., Lupin Ltd., Sun Pharma Global FZE, Teva Pharmaceuticals USA, and Torrent Pharmaceuticals Ltd. have received FDA approval to market duloxetine in various strengths.

Depression is characterized by symptoms that interfere with a person's ability to work, sleep, study, eat, and enjoy once-pleasurable activities. Episodes of depression often recur throughout a person's lifetime. Signs and symptoms of depression include: depressed mood, loss of interest in usual activities, significant change in weight or appetite, insomnia or excessive sleeping (hypersomnia), restlessness/pacing (psychomotor agitation), increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and suicide attempts or thoughts of suicide.

Duloxetine and other antidepressant drugs have a boxed warning describing the increased risk of suicidal thinking and behavior during initial treatment in children, adolescents, and young adults ages 18 to 24. The warning also says data do not show this increased risk in those older than 24 years and that patients ages 65 and older who take antidepressants have a decreased risk of suicidal thinking and behavior.

The warning says depression and other serious psychiatric disorders themselves are the most important causes of suicide and that close monitoring of patients starting these medications is necessary. Duloxetine must be dispensed with a patient medication guide that describes important information about the drug's uses and risks.

Common adverse reactions reported by people taking Cymbalta include nausea, dry mouth, drowsiness, fatigue, decreased appetite, increased sweating, and dizziness.

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

Information about the availability of generic duloxetine can be obtained from the manufacturers.

FDA NEWS RELEASE

For Immediate Release: Dec. 6, 2013

FDA approves first drug treatment for Peyronie's disease

The U.S. Food and Drug Administration today approved a new use for Xiaflex (collagenase clostridium histolyticum) as the first FDA-approved medicine to treat men with bothersome curvature of the penis, a condition known as Peyronie's disease.

Xiaflex is the first FDA-approved non-surgical treatment option for men with this condition, who have a plaque (lump) in the penis that results in a curvature deformity of at least 30 degrees upon erection. Peyronie's disease is caused by scar tissue that develops under the skin of the penis. This scar tissue causes an abnormal bend during erection and can cause problems such as bothersome symptoms during intercourse.

Xiaflex is a biologic medicine (made from the protein product of a living organism, collagenase clostridial histolyticum). Xiaflex was first approved by the FDA in 2010 for the treatment of Dupuytren's contracture, a progressive hand disease that can affect a person's ability to straighten and properly use their fingers. Xiaflex is believed to work for Peyronie's disease by breaking down the buildup of collagen (a structural protein in connective tissue) that causes the curvature deformity.

A treatment course for Peyronie's disease consists of a maximum of four treatment cycles. Each treatment cycle consists of two Xiaflex injection procedures (in which Xiaflex is injected directly into the

collagen-containing structure of the penis) and one penile modeling procedure performed by the health care professional.
The safety and effectiveness of Xiaflex for the treatment of Peyronie's disease were established in two randomized double-blind, placebo-controlled studies in 832 men with Peyronie's disease with penile curvature deformity of at least 30 degrees. Participants were given up to four treatment cycles of Xiaflex or placebo and were then followed 52 weeks. Xiaflex treatment significantly reduced penile curvature deformity and related bothersome effects compared with placebo.
When prescribed for the treatment of Peyronie's disease, Xiaflex is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) because of the risks of serious adverse reactions, including penile fracture (rupture of one of the penile bodies within the penile shaft, also known as corporal rupture) and other serious penile injury. Xiaflex for the treatment of Peyronie's disease should be administered by a health care professional who is experienced in the treatment of male urological diseases. The REMS requires participating health care professionals to be certified within the program by enrolling and completing training in the administration of Xiaflex treatment for Peyronie's disease. The REMS also requires health care facilities to be certified within the program and ensure that Xiaflex is dispensed only for use by certified health care professionals.
The most common adverse reactions associated with use of Xiaflex for Peyronie's disease include penile hematoma, penile swelling and penile pain.
Consumers and health care professionals are encouraged to report adverse reactions from the use of Xiaflex to the FDA's MedWatch Adverse Event Reporting program at www.fda.gov/MedWatch or by calling 1-800-FDA-1088.
Xiaflex is marketed by Auxilium Pharmaceuticals, Inc., based in Chesterbrook, Pa.

Safety Announcements

FDA Drug Safety Communication: FDA requires multiple new safety measures for leukemia drug Iclusig; company expected to resume marketing

[12-20-2013] The U.S. Food and Drug Administration (FDA) is requiring several new safety measures for the leukemia drug Iclusig (ponatinib) to address the risk of life-threatening blood clots and severe narrowing of blood vessels. Once these new safety measures are in place, the manufacturer of Iclusig is expected to resume marketing to appropriate patients. Health care professionals should review these additional safety measures and carefully consider them when evaluating the risks and benefits of Iclusig for each patient.
The required safety measures involve label changes to narrow the indication, provide additional warnings and precautions about the risk of blood clots and severe narrowing of blood vessels, revise recommendations about dosage and administration of Iclusig, and update the patient Medication Guide. We are also requiring a risk evaluation and mitigation strategy (REMS). In addition, the manufacturer of Iclusig, ARIAD Pharmaceuticals, must conduct postmarket investigations to further characterize the drug's safety and dosing.
On October 31, 2013, FDA requested and ARIAD agreed to voluntarily suspend marketing of Iclusig. FDA's request resulted from FDA's investigation, which revealed a steady increase in the number of serious vascular occlusion events identified through continued safety monitoring of the drug. This observation represented a significant change in the safety profile of Iclusig as the proportion of patients on the drug experiencing vascular occlusion events such as blood clots and severe narrowing of blood vessels was significantly greater than the proportion reported at the time of its approval in December 2012.
During the marketing suspension, Iclusig treatment has been available through single patient or emergency investigational new drug applications (INDs). Patients should continue to receive Iclusig under their authorized IND until marketing of Iclusig is resumed. FDA is working closely with ARIAD on the new safety measures and anticipates these will be in place by the end of January 2014. Once that process is complete, patients being treated under these INDs can be transitioned back to receiving the marketed Iclusig product.
In more detail, the new safety measures for Iclusig include the following:

- The indications for use are limited to:

    - Treatment of adult patients with T315I-positive chronic myeloid leukemia (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).
    - Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.
- The *Warnings and Precautions* in the label are revised to describe the vascular occlusion events. This includes a description of the observed arterial and venous thrombosis and occlusions that have occurred in at least 27% — more than one in every four — of patients treated with Iclusig.
- The *Dosage and Administration* recommendations are revised to state that the optimal dose of Iclusig has not been identified. The recommended starting dose remains 45 mg administered orally once daily with or without food; however, additional information is included regarding dose decreases and discontinuations.
- The patient Medication Guide is revised to include additional safety information consistent with the safety information in the revised drug label.
- The Iclusig REMS will inform prescribers about the approved indications for use and the serious risk of vascular occlusion and thromboembolism associated with the drug. The REMS includes the following:
    - REMS letter to healthcare professionals who are known or likely to prescribe Iclusig
    - REMS letter for professional societies to be distributed to their members
    - REMS fact sheet for health care professionals
    - Public statement to be published quarterly for one year in several professional journals
    - Information to be prominently displayed at scientific meetings
    - Iclusig REMS Web site to provide access to all REMS materials for the duration of the REMS
- ARIAD's postmarket investigations will further evaluate dose selection, drug exposure, treatment response, and toxicity of Iclusig therapy.

We urge health care professionals and patients to report side effects involving Iclusig to the FDA MedWatch program.

Safety Announcements

FDA Drug Safety Communication: FDA warns of rare risk of long-lasting erections in males taking methylphenidate ADHD medications and has approved label changes

[12-17-2013] The U.S. Food and Drug Administration (FDA) is warning that methylphenidate products, one type of stimulant drug used to treat attention deficit hyperactivity disorder (ADHD), may in rare instances cause prolonged and sometimes painful erections known as priapism. FDA continues to monitor the safety of drugs after they are approved, and, based on a recent review of methylphenidate products, we have updated the drug labels and patient Medication Guides to include information about the rare but serious risk of priapism. Patients who take methylphenidate and develop erections lasting longer than four hours should seek immediate medical treatment to prevent long-term problems with the penis. If not treated right away, priapism can lead to permanent damage to the penis.

Priapism can occur in males of any age and happens when blood in the penis becomes trapped, leading to an abnormally long-lasting and sometimes painful erection. Younger males, especially those who have not yet reached puberty, may not recognize the problem or may be embarrassed to tell anyone if it occurs. All male patients and their caregivers should be taught the signs and symptoms of priapism and the importance of seeking immediate medical treatment if it occurs.

Methylphenidate products are among the medicines that can be used to treat ADHD. One of the most common childhood brain disorders, ADHD can continue through adolescence and adulthood and causes symptoms such as difficulty staying focused and paying attention, difficulty controlling behavior, and hyperactivity. Medications such as methylphenidate used to treat ADHD benefit patients with the disorder by increasing focus, reducing impulsivity, and improving overall social functioning. Therefore, patients who have been prescribed a methylphenidate product should not stop taking it without first talking to their health care professionals.

In our review, the median age of patients taking a methylphenidate product who experienced priapism was 12.5 years (range 8 to 33 years). In a few patients, priapism occurred after an increase in the dosage of methylphenidate, but priapism has also occurred under other conditions, such as during short periods of time when the drug was stopped temporarily, when there was a longer than typical time between doses, or after stopping the drug permanently. Two patients required surgical intervention; one required shunt placement, and the other had to have needle aspiration of the corpus cavernosum.
The risk of priapism may cause some health care professionals to consider switching patients to the non-stimulant drug Strattera (atomoxetine), another drug used to treat ADHD; however, atomoxetine has also been associated with priapism in young children, teenagers, and adults. Priapism appears to be more common in patients taking atomoxetine than in patients taking methylphenidate products. Health care professionals should be cautious when considering changing patients from methylphenidate to atomoxetine.
Amphetamine products are also used to treat ADHD, and we have received reports of priapism in four patients taking an amphetamine product. However, whether the amphetamine products caused the priapism is uncertain, because all of these patients had been taking other medications that are thought to cause priapism. Therefore, we cannot conclude that the use of amphetamine products can result in priapism.

Current Drug Shortages Index (as of December 23, 2013):

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

Acetylcysteine Inhalation Solution UPDATED 12/17/2013
Amikacin Injection
Aminocaproic Acid Injection (initial posting 3/8/2013)
Aminophylline (initial posting 12/10/2012)
Ammonium Chloride Injection (initial posting 3/8/2013)
Amytal Sodium Injection (initial posting date 1/31/2013)
Atracurium Besylate (initial posting 2/27/2012)
Atropine Sulfate Injection
Barium Sulfate for Suspension (initial posting 10/12/2012)
Bismuth Subsalicylate; Metronidazole; Tetracycline Hydrochloride (Helidac) (initial posting 3/8/2012)
Bumetanide Injection (initial posting 6/21/2012)
Bupivacaine Hydrochloride (Marcaine, Sensorcaine) Injection UPDATED 12/17/2013
Buprenorphine Hydrochloride (Buprenex) Injection
Caffeine and Ergotamine Tartrate (Cafergot) Tablets (initial posting 3/8/2012)
Caffeine Anhydrous (125mg/mL); Sodium Benzoate (125mg/mL) Injection
Calcium Chloride Injection (initial posting 12/13/2012)
Calcium Gluconate Injection (initial posting 1/10/2013) UPDATED 12/17/2013
Chromic Chloride Injection
Cidofovir Injection (initial posting 2/15/2013)
Citric Acid; Gluconolactone; Magnesium Carbonate (Renacidin) Solution for Irrigation (initial posting 6/30/2012)
Clindamycin phosphate (Cleocin) (initial posting 10/2/2013) UPDATED 12/17/2013
Copper Injection (initial posting 4/25/2013)
Cyanocobalamin Injection (initial posting 1/25/2013) UPDATED 12/17/2013
Daunorubicin Hydrochloride Solution for Injection
Denileukin Diftitox (Ontak) (initial posting 9/22/2012)
Desmopressin Acetate (DDAVP) Injection (initial posting 5/7/2013)
Dexamethasone Sodium Phosphate Injection (initial posting 1/15/2013) UPDATED 12/17/2013
Dextrose Injection (initial posting 5/23/2012)
Dipyridamole Injection (initial posting 7/24/2012)

Dobutamine Hydrochloride Injection (initial posting 4/26/2013)
Doxorubicin (Adriamycin) Lyophilized Powder (initial posting 12/2/2011)
Epinephrine Injection (initial posting 4/27/2012)
Epinephrine 1mg/mL (Preservative Free) (initial posting 6/21/2012)
Ethiodol (Ethiodized Oil) Ampules
Etomidate (Amidate) Injection (initial posting 2/9/2012)
Fentanyl Citrate (Sublimaze) Injection
Fluphenazine Decanoate Injection 4/25/2013 UPDATED 12/17/2013
Fluphenazine Hydrochloride Injection
Furosemide Injection (initial posting 6/20/2012) UPDATED 12/17/2013
Heparin Sodium Injection (initial posting 7/5/2012) UPDATED 12/17/2013
Hydromorphone Hydrochloride (Dilaudid) Injection (initial posting 3/7/2012)
Hydromorphone Hydrochloride Tablets (initial posting 2/19/2013)
Intravenous Fat Emulsion
Isoniazid; Rifampin (Rifamate) Capsules 3/15/2013
Ketorolac Tromethamine Injection UPDATED 12/17/2013
Leucovorin Calcium Lyophilized Powder for Injection
Leuprolide Acetate Injection
Levothyroxine Sodium (Levoxyl) Tablets (initial posting date - 3/15/2013)
Lidocaine Hydrochloride (Xylocaine) Injection (initial posting date - 2/22/2012) UPDATED 12/17/2013
Liotrix (Thyrolar) Tablets
Lomustine Capsules (initial posting date - 5/9/2013)
Lorazepam (Ativan) Injection
Magnesium Sulfate Injection UPDATED 12/17/2013
Mannitol (Osmitrol, Resectisol) Injection (initial posting date - 12/21/2011) UPDATED 12/17/2013
Mecasermin [rDNA origin] (Increlex) Injection (initial posting date - 4/26/2013)
Methazolamide (Glauctabs, Neptazane) Tablets
Methyldopate Hydrochloride Injection
Methylin Chewable Tablets (initial posting date - 2 /19/2013)
Methylphenidate Hydrochloride ER Tablets (initial posting date - 2/19/2013)
Methylphenidate Hydrochloride Tablets (initial posting date - 2/19/2013) UPDATED 12/19/2013
Metoclopramide (Reglan) Injection
Morphine Sulfate Injection
Morphine Sulfate (Astramorph PF, Duramorph, Infumorph) Injection (Preservative Free)
UPDATED 12/17/2013
Multi-Vitamin Infusion (Adult and Pediatric)
Nalbuphine Hydrochloride (Nubain) Injection (initial posting 5/15/2012)
Neostigmine Methylsulfate Injection (initial posting 1/14/2013) UPDATED 12/17/2013
Nitroglycerin in 5% Dextrose Injection (initial posting 12/20/2013) New!!
Ondansetron (Zofran) 2mg/mL Injection UPDATED 12/18/2013
Pancuronium Bromide Injection
Papaverine Hydrochloride Injection (initial posting 12/17/2012)
Pegvisomant (Somavert) Injection (initial posting 10/21/2013)
Phosphate (Glycophos) Injection (initial posting 5/29/2013) UPDATED 12/18/2013
Pilocarpine HCL Opthalmic Gel 4% (Pilopine HS) (initial posting 6/1/2012)
Potassium Acetate Injection, USP 2mEq/mL
Potassium Chloride Injection (initial posting 5/15/2012) UPDATED 12/18/2013
Potassium Phosphate Injection UPDATED 12/18/2013
Procainamide HCL Injection
Prochlorperazine Injection (initial posting 1/30/2012)
Promethazine Injection (initial posting 2/10/2012)

Reserpine Tablets (initial posting 4/17/2013)
Rifampin for Injection (initial posting 3/22/2013)
Secretin Synthetic Human (ChiRhoStim) Injection (ChiRhoStim) (initial posting 6/15/2012)
Selenium Injection
Sincalide (Kinevac) Lyophilized Powder for Injection (initial posting 6/21/2013)
Sodium Chloride 0.9% (5.8mL and 20mL) (initial posting 5/4/2012)
Sodium Chloride 23.4% UPDATED 12/18/2013
Sodium Phosphate Injection
Succinylcholine (Anectine, Quelicin) Injection (initial posting 8/17/2012)
Sufentanil Citrate (Sufenta) Injection
Sulfamethoxazole 80mg/ml;Trimethoprim 16mg/ml (SMX/TMP) (Bactrim) Injection
Telavancin (Vibativ) Injection
Tetracycline Capsules
Thiotepa (Thioplex) for Injection
Ticarcillin Disodium/Clavulanic Potassium (Timentin) Injection (initial posting 8/16/2012)
Tiopronin (Thiola)
Tobramycin Solution for Injection UPDATED 12/18/2013
Trace Elements (initial posting 1/24/2013) UPDATED 12/18/2013
Tromethamine (Tham) Injection (initial posting 5/2/2012)
Verapamil Hydrochloride Injection, USP (initial posting 4/17/2013)
Vitamin A Palmitate (Aquasol A)
Zinc Injection (initial posting 2/15/2012)