Appendix E

VOTE TO PRIOR AUTHORIZE BUTRANS™, PRIMLEV™, XOLOX®, EXALGO™ ER, RYBIX™ ODT, AND SUBOXONE®/SUBUTEX®

OKLAHOMA HEALTH CARE AUTHORITY

NOVEMBER 2010

SUBOXONE®/SUBUTEX® RECOMMENDATIONS

The College of Pharmacy recommends all prescriptions for Suboxone® (buprenorphine/naloxone) tablets and film or Subutex® (buprenorphine), and their generic equivalents if available, require prior authorization.

Criteria for coverage are as follows:

- Prescribed by a licensed physician who qualifies for a waiver under the Drug Addiction Treatment Act (DATA) and has notified the Center for Substance Abuse Treatment of the intention to treat addiction patients and has been assigned a DEA (X) number.
- Diagnosis of opiate abuse/dependence.
- Combination with benzodiazepines, hypnotics, and opioids (including tramadol) will be denied.
- Approval will be for 90 days to allow for concurrent medication monitoring.
- The following limitations will apply:
    - **Suboxone®** 2mg/0.5mg and 8mg/2mg tablets and film: A quantity limit of 90 per 30 days.
    - **Subutex®** 2mg tablets and 8mg tablets will only be approved if the member is pregnant (product may be used for the duration of the pregnancy only), or has a documented serious allergy or adverse reaction to naloxone.

NEW TIER RECOMMENDATIONS

The College of Pharmacy recommends continuation of the Narcotic PBPA Category. In addition, the College of Pharmacy recommends placement of the following products in the current Tier structure:

Butrans™: to be placed in Tier 3 of the long-acting products Tier structure, with a quantity limit of 4 patches every 28 days.

Exalgo™: to be placed in Tier 3 of the long-acting products Tier structure, with a quantity limit of 1 tablet daily for the 8mg, 3 tablets daily for the 12mg, and 4 tablets daily for the 16mg.

Primlev™ and Xolox®: to be placed in Tier 3 of the short-acting products Tier structure, with a quantity limit based on 3,250 mg of acetaminophen daily and a clinical reason why member cannot use currently available similar generic products.

Rybix™ ODT: to be placed in Tier 3 of the short-acting products Tier structure, with a quantity limit of 4 tablets per day and a diagnosis indicating the member has a condition that prevents them from swallowing tablets.

Additionally, the College recommends moving the hydrocodone/APAP products, Xodol® and Zamicet™, from Tier 2 to Tier 3 with additional criteria requiring a clinical reason why the member cannot use currently available similar generic products. The College also recommends that any brand-only formulations of currently available generic narcotic products be placed in Tier 3 with similar criteria.

Narcotic Analgesics			
Tier-1	**Tier-2**	**Tier-3**	**Oncology Only**
All immediate release narcotics not listed in a higher tier	**Long Acting**		
	fentanyl patch (Duragesic®)	oxymorphone (Opana® ER)	
	morphine ER	morphine sulfate (Kadian®)	
		morphine sulfate (Avinza®)	
		oxycodone (OxyContin®)	
		tramadol ER (Ultram ER®, Ryzolt®)	
		morphine and naltrexone (Embeda™)	
		buprenorphine transdermal (Butrans™)	
		hydromorphone (Exalgo™)	
	Short Acting		
	Oxymorphone (Opana®)	tramadol ODT (Rybix™)	fentanyl (Actiq®, Onsolis™, Fentora®)
	Tapentadol (Nucynta™)	oxycodone/APAP (Primlev™, Xolox®)	
		hydrocodone/APAP (Xodol®, Zamicet™)	

Appendix F

Vote to Prior Authorize Vimovo™ (esomeprazole/naproxen)

Oklahoma HealthCare Authority
November 2010

Summary

Vimovo™ (Esomeprazole MG-Naproxen)

- Available in the following strengths: 20mg-375mg, 20mg-500mg.
- Approved by the FDA in April 2010 for the treatment of 1) ankylosing spondylitis, (2) osteoarthritis, (3) rheumatoid arthritis, and to reduce the risk of occurrence of gastric ulcers in patients at risk of developing NSAID-associated gastric ulcer.

Recommendations

The College of Pharmacy recommends to place Vimovo™ (Esomeprazole Mg - Naproxen) in the special PA category of the NSAIDS with the same criteria for the NSAIDS in the Special PA Category:

a. Special indications, such as the diagnosis of gout for indomethacin, OR
b. Previous use of at least two Tier 1 NSAID (from different product lines) AND
c. Reason why a special formulation is needed over a Tier 1 product

NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)		
Tier 1	**Tier 2**	**Special PA**
diclofenac ER (Voltaren® XR) diclofenac potassium (Cataflam®) diclofenac sodium (Voltaren®) etodolac (Lodine®) etodolac ER (Lodine® XL) fenoprofen (Nalfon®) flurbiprofen (Ansaid®) ibuprofen (Motrin®) ketoprofen (Orudis®) ketoprofen ER (Oruvail®) meclofenamate (Meclomen®) meloxicam (Mobic®) nabumetone (Relafen®) naproxen (Naprosyn®) naproxen sodium (Anaprox®) naproxen EC (Naprosyn® EC) oxaprozin (Daypro®) sulindac (Clinoril®) Tolmetin (Tolectin®)	celecoxib (Celebrex®) diclofenac sodium /misoprostol (Arthrotec®)	diclofenac epolamine (Flector®) diclofenac potassium (Zipsor®) diclofenac sodium (Voltaren Gel®) diclofenac potassium (Cambia® pwdr pk) diclofenac sodium (Pennsaid® top drops) indomethacin (Indocin®) mefanamic acid (Ponstel®) naproxen sodium (Naprelan®) piroxicam (Feldene®) naproxen/lansoprasole (Prevacid NapraPac) Vimovo™ (Esomeprazole MG-Naproxen)

Appendix G

FISCAL YEAR 2010 ANNUAL REVIEW OF OCULAR ALLERGY PRODUCTS AND VOTE TO PRIOR AUTHORIZE BEPREVE™ (BEPOTASTINE) AND LASTACAFT™ (ALCAFTADINE)

OKLAHOMA HEALTH CARE AUTHORITY

NOVEMBER 2010

CURRENT PRIOR AUTHORIZATION OF OCULAR ALLERGY MEDICATIONS

- Tier 1 products are covered with no authorization necessary
- Tier 2 authorization requires:
  - FDA approved diagnosis
  - A trial of at least one Tier 1 product of a similar type for a minimum of two weeks in the last 30 days
  - Documentation of clinical need for Tier 2 product over a Tier 1 should be noted on the petition
  - Clinical exceptions granted for products with allergic reaction or contraindication

Tier 1	Tier 2
cromolyn sodium (Crolom®)	nedocromil sodium (Alocril®)
ketotifen fumarate (Alaway®,Zaditor OTC®)	pemirolast potassium (Alamast®)
olopatadine (Patanol®)	emedastine difumarate (Emadine®)
	loteprednol etabonate (Alrex®)
	olopatadine (Pataday®)
	lodoxamide tromethamine (Alomide®)
	epinastine (Elestat®)
	azelastine (Optivar®)

Current Tiers based on Supplemental Rebates

TRENDS IN UTILIZATION

Comparison of Fiscal Years 2009 & 2010

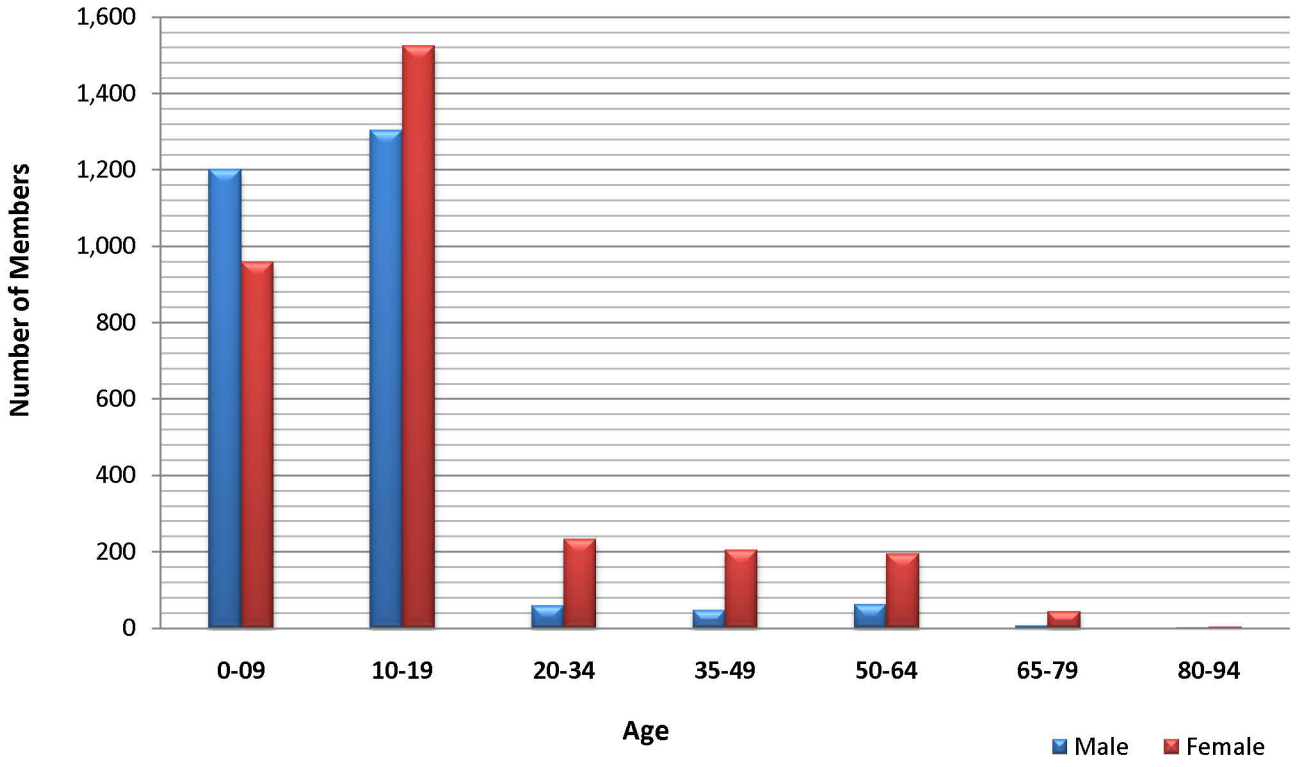
Fiscal Year	Members	Claims	Paid	Paid/Claim	Per-Diem	Units	Days
2009	5,313	7,728	$669,173.07	$86.59	$3.17	35,721	211,208
2010	5,936	8,382	$760,578.28	$90.74	$2.98	43,121	255,110
% change	**+11.7%**	**+8.5%**	**+13.6%**	**+4.8%**	**-6.0%**	**+20.7%**	**+20.8%**
change	**+623**	**+654**	**+$91,405.21**	**+$4.15**	**-$0.19**	**+7,400**	**+43,902**

Utilization Details for Fiscal Year 2010

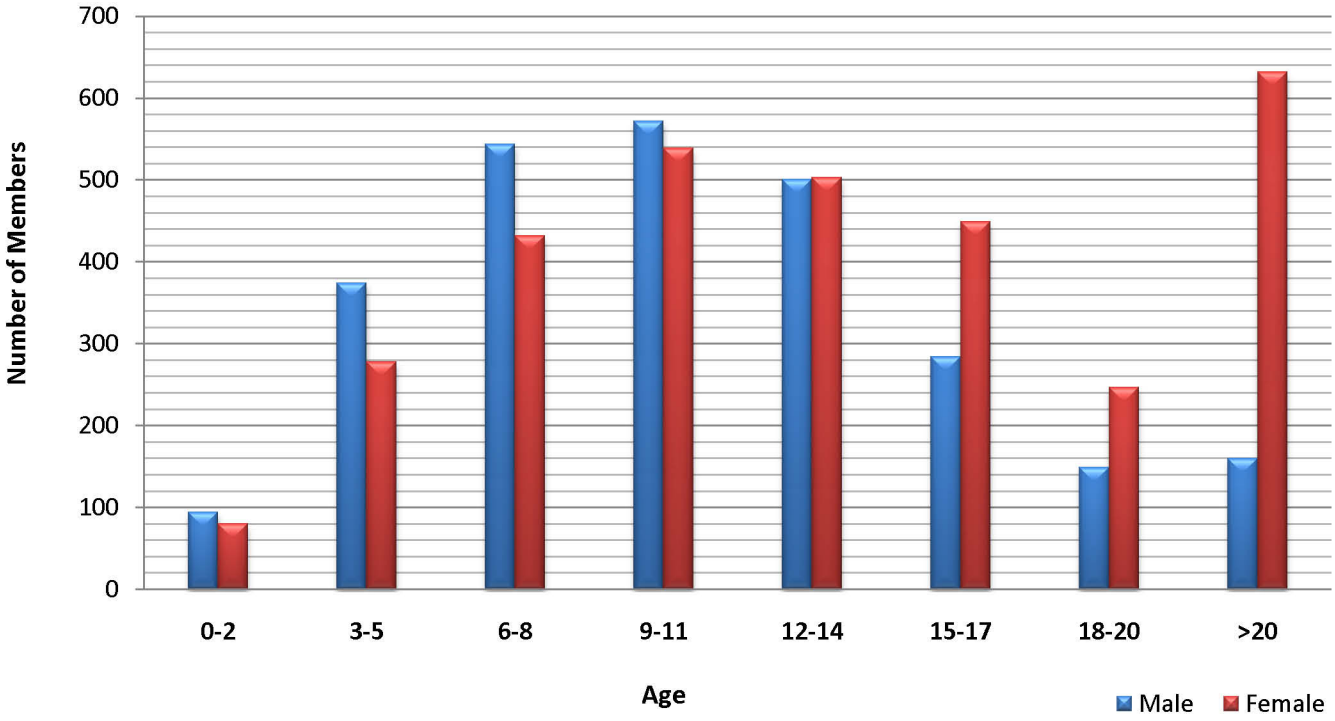
Generic	Brand	Claims	Members	Paid	Claims/ Member	Paid/ Day	% Paid
Olopatadine HCl 0.1%	PATANOL	7,228	5,148	$675,525.12	1.4	$3.08	83.37%
Epinastine HCl 0.05%	ELESTAT	349	223	$33,706.03	1.57	$3.08	4.16%
Azelastine HCl 0.05%	OPTIVAR	257	193	$26,203.14	1.33	$3.19	3.23%
Cromolyn Sodium 4%	CROMOLYN	162	120	$2,805.73	1.35	$0.55	0.35%
Azelastine HCl 0.05%	AZELASTINE	93	74	$8,098.50	1.26	$2.81	1.00%
Olopatadine HCl 0.2%	PATADAY	69	20	$6,403.40	3.45	$3.09	0.79%
Ketotifen Fumarate 0.025%	KETOTIFEN	66	51	$950.50	1.29	$0.48	0.12%
Loteprednol Etabonate 0.2%	ALREX	58	21	$4,967.85	2.76	$3.01	0.61%
Ketotifen Fumarate 0.025%	ZADITOR	47	40	$672.29	1.18	$0.47	0.08%
Ketotifen Fumarate 0.025%	ALAWAY	40	35	$458.88	1.14	$0.37	0.06%
Bepotastine Besilate 1.5%	BEPREVE	7	5	$708.01	1.4	$2.62	0.09%
Ketotifen Fumarate 0.025%	EYE ITCH REL	5	5	$64.58	1	$0.43	0.01%
Ketotifen Fumarate 0.025%	REFRESH EYE	1	1	$14.25	1	$0.48	0.00%
Totals		**8,382**	**5,936***	**$760,578.28**	**1.44**	**$2.98**	**100%**

*Total number of unduplicated members

Demographics of Members Utilizing Ocular Allergy Products in FY2010



Member Demographics for Selected Ages, 0-20

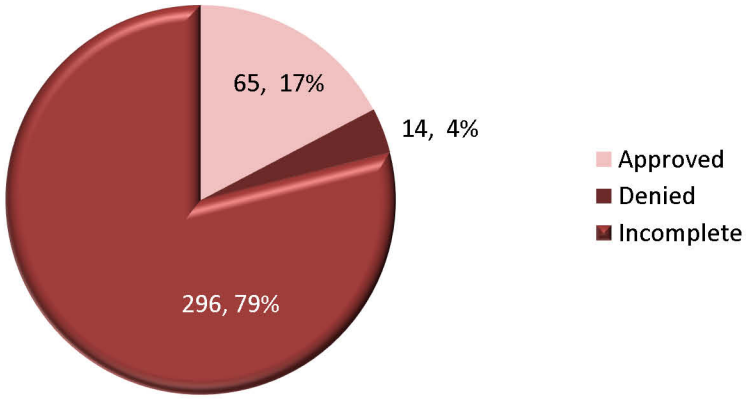


Prescribers of Ocular Allergy Products in FY2010

Specialty	Number of Claims	Total Cost
Optometrist	3,493	$322,610.01
General Pediatrician	1,171	$105,682.46
Family Practitioner	925	$81,101.34
Ophthalmologist	731	$67,847.71
Nurse Practitioner (Other)	588	$52,175.50
Physician Assistant	392	$35,096.68
DDSD-NFM	257	$24,017.51
General Practitioner	211	$18,636.65
Prescriber Only	207	$16,515.29
Allergist	107	$9,827.51
Internist	75	$6,398.72
Otologist, Laryngologist, Rhinologist	63	$5,711.30
Emergency Medicine Practitioner	51	$4,894.61
Others combined*	111	$10,062.99

*includes hand surgeon, anesthesiologist, OB/GYN, psychiatrist, pulmonary disease specialist, gastroenterologist, general dentistry prescriber, personal care (individual), certified registered nurse anesthetist, family nurse practitioner, orthopedic surgeon, pediatric nurse practitioner, general surgeon, urologist, proctologist, podiatrist, radiologist, geriatric practitioner, neurologist, & general internist

Prior Authorizations of Ocular Allergy Products in FY2010



MARKET UPDATE

Bepreve™ (bepotastine 1.5% - approved September 2009) is a topically-active histamine H_1 receptor antagonist that also inhibits the release of histamine from mast cells. It is available as a 1.5% solution in 5mL (AWP - $105.00) and 10ml (AWP - $182.40) bottles. Bepreve™ is indicated for the treatment of ocular itching associated with allergic conjunctivitis and is to be used as one drop in affected eye(s) twice daily. Package insert states that Bepreve™ was more effective than placebo in relieving ocular itching when evaluated in a Conjunctival Antigen Challenge (CAC) study involving 237 patients. The safety of Bepreve™ has been evaluated in 861 patients over 6 weeks in a randomized controlled trial. No studies have been found comparing the efficacy of Bepreve™ against current therapies.

Lastacaft™ (alcaftadine 0.25% - approved July 2010) is a topically active histamine H_1 receptor antagonist that also inhibits the release of histamine from mast cells. It is available as a 0.25% solution in a 3mL volume (dispensed in a 5mL sized dropper bottle). Lastacaft™ is indicated for the prevention of ocular itching in patients with allergic conjunctivitis and is to be used one drop in each eye once daily. Package insert states that Lastacaft™ was more effective than placebo at preventing ocular itching in patients with allergic conjunctivitis who were in a CAC study. The safety of Lastacaft™ has been evaluated in a randomized controlled trial with 909 patients over 6 weeks. No studies have been found comparing the efficacy of Lastacaft™ against current therapies. Lastacaft™ is currently not available on the market yet.

RECOMMENDATIONS

The College of Pharmacy recommends a three tier structure for this category with all medications currently available in generic in Tier 1 and all others in Tier 3. Tier 2 will consist of medications whose manufacturer participates in the supplemental rebate program. In addition the College of Pharmacy recommends addition of Bepreve™ and Lastacaft™ to Tier 3 of the Ocular Allergy PBPA Category. The following prior authorization criteria will apply.

Tier 2 authorization criteria:

1. FDA approved diagnosis
2. A trial of one Tier 1 product for a minimum of two weeks in the last 30 days that did not yield adequate relief of symptoms or resulted in intolerable adverse effects
3. Contraindication to lower tiered medications

Tier 3 authorization criteria:

1. FDA approved diagnosis
2. Recent trials of one Tier 1 product and all available Tier 2 medications for a minimum of two weeks each that did not yield adequate relief of symptoms or resulted in intolerable adverse effects
3. Contraindication to lower tiered medications

Tier 1	Tier 2	Tier 3
cromolyn (Crolom®) ketotifen (Alaway®,Zaditor OTC®)	Supplemental Rebated Tier 3 medications	nedocromil (Alocril®) pemirolast (Alamast®) emedastine (Emadine®) loteprednol (Alrex®) olopatadine (Pataday®) olopatadine (Patanol®) lodoxamide (Alomide®) epinastine (Elestat®) azelastine (Optivar®) bepotastine besilate (Bepreve™) alcalftadine (Lastacaft™)

PRODUCT DETAILS OF BEPREVE™ (BEPOTASTINE BESILATE) OPHTHALMIC SOLUTION

FDA-APPROVED IN U.S. SEPTEMBER 8, 2009

INDICATIONS : Bepreve™ is indicated for the treatment of ocular itching associated with allergic conjunctivitis. It is a topically-active histamine H_1 receptor antagonist and also inhibits the release of histamine from mast cells.

DOSAGE FORMS : Bepreve™ is a 1.5% (15 mg/mL) topical ophthalmic solution that comes in dropper bottles of 2.5mL, 5mL, and 10mL.

ADMINISTRATION: Instill one drop of Bepreve™ into affected eye(s) twice a day for the relief of symptoms associated with allergic conjunctivitis.

CONTRAINDICATIONS: None known

SPECIAL POPULATIONS:

- Pregnancy category C – no adequate, well-controlled studies have been done in pregnant women. Bepreve™ should only be used during pregnancy if the potential benefit outweighs any potential risk. It is not known if Bepreve™ is excreted in human milk.
- Safety in pediatric patients under age 2 has not been established.
- No differences in safety or effectiveness have been observed in elderly patients.

WARNINGS & PRECAUTIONS:

- Care should be taken not to touch the eyelids or surrounding areas with the dropper tip.
- Bepreve™ should not be used to treat contact lens-related irritation. Contact lenses should be removed prior to instillation of Bepreve™ and may be reinserted after 10 minutes. The preservative in Bepreve™, benzalkonium chloride, may be absorbed by soft contact lenses.

ADVERSE REACTIONS:
Common (occurring in approximately 25% of patients): mild taste following instillation.
Less common (occurring in approximately 2-5% of patients): irritation, headache, and nasopharyngitis.

DRUG INTERACTIONS: None known

PATIENT INFORMATION: Patients should be advised that Bepreve™ is for topical ophthalmic use only. The dropper tip should not be touched to any surface as this may cause contamination. Contact lenses should be removed prior to instillation of Bepreve™ and can be reinserted after 10 minutes. Store at 15^{o} to 25^{o} C (59^{o} to 77^{o} F).

PRODUCT DETAILS OF LASTACAFT™ (ALCAFTADINE) OPHTHALMIC SOLUTION

FDA-APPROVED IN U.S. JULY 28, 2010

INDICATIONS : Lastacaft™ is indicated for the prevention of ocular itching associated with allergic conjunctivitis. It is a topically-active histamine H_1 receptor antagonist that also inhibits the release of histamine from mast cells.

DOSAGE FORMS : Lastacaft™ is a 0.25% (2.5 mg/mL) topical ophthalmic solution that comes as 3mL in a 5mL dropper bottle.

ADMINISTRATION : Instill one drop of Lastacaft™ in each eye once daily for the prevention of itching associated with allergic conjunctivitis.

CONTRAINDICATIONS: None known.

SPECIAL POPULATIONS:

- Pregnancy category B – no adequate, well-controlled studies have been done in pregnant women. Lastacaft™ should only be used during pregnancy if it is clearly needed. It is not known whether Lastacaft™ is excreted in human milk.
- Safety and efficacy in pediatric patients under age 2 has not been established.
- No differences in safety or efficacy have been observed in elderly patients.

WARNINGS & PRECAUTIONS:

- Care should be taken not to touch the eyelids or surrounding areas with the dropper tip.
- Lastacaft™ should not be used to treat contact lens-related irritation. Contact lenses should be removed prior to instillation of Lastacaft™ and may be reinserted after 10 minutes. The preservative in Lastacaft™ (benzalkonium chloride) may be absorbed by soft contact lenses.

ADVERSE REACTIONS:

- Most common ocular reactions (occurring in <4% of patients): eye irritation, burning and/or stinging upon instillation, eye redness, and eye pruritus.
- Most common non-ocular reactions (occurring in <3% of patients): nasopharyngitis, headache, and influenza.

DRUG INTERACTIONS: None known.

PATIENT INFORMATION: Patients should be advised that Lastacaft™ is for topical ophthalmic use only. The dropper tip should not be touched to any surface as this may cause contamination. Contact lenses should be removed prior to instillation of Lastacaft™ and can be reinserted after 10 minutes. Store at 15° to 25° C (59° to 77° F).

REFERENCES

Bepreve™ [Full Prescribing Information]. Irvine, CA: ISTA Pharmaceuticals, Inc., 2009.

Lastacaft™ [Full Prescribing Information]. Jacksonville, FL: Vistakon Pharmaceuticals, LLC, 2010.

Appendix H

30-day Notice to Prior Authorize Metozolv ODT® (metoclopramide hydrochloride)

Oklahoma Health Care Authority
November 2010

Manufacturer: Catalent UK Swindon Zydis Limited for Salix Pharmaceuticals, Inc.
Classification: Antiemetic, Dopamine Antagonist
Status: Prescription Only

Metozolv ODT® (metoclopramide hydrochloride) Summary

Metozolv ODT® is the first available orally disintegrating formulation of metoclopramide hydrochloride. Metozolv ODT® is available in 5mg and 10mg ODT tablets that can be placed on the tongue to dissolve without liquids. It is indicated for short-term (4-12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy and for the relief of symptoms in adults with acute and recurrent diabetic gastroparesis.

The recommended dose for gastroesophageal reflux disease (GERD) is 10mg-15mg up to four times daily given at least 30 minutes before eating and at bedtime. For diabetic gastroparesis, the recommended dose is 10mg four times daily at least 30 minutes before eating and at bedtime for two to eight weeks. Therapy with Metozolv ODT® should never exceed 12 weeks in duration to reduce the risk of developing tardive dyskinesia.

Metoclopramide stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions. While its mode of action is unclear, it appears to sensitize tissues to the action of acetylcholine. Metoclopramide increases the tone and amplitude of gastric contractions, relaxes the pyloric sphincter and the duodenal bulb, and increase peristalsis of the duodenum and jejunum resulting in accelerated gastric emptying and intestinal transit. It also increases the resting tone of the lower esophageal sphincter. The antiemetic properties of metoclopramide appear to be a result of its antagonism of central and peripheral dopamine receptors. Metozolv ODT® has similar warnings and precautions to metoclopramide.

Contraindications to the use of Metozolv ODT® include intestinal obstruction, hemorrhage, or perforation; pheochromocytoma; and epilepsy. Metozolv ODT® should not be used in patients receiving other drugs which are likely to cause extrapyramidal reactions, since the frequency and severity of these reactions may be increased. Metozolv ODT® can cause tardive dyskinesia, acute dystonic reactions, drug-induced Parkinsonism, and other extrapyramidal symptoms. The most frequent reported adverse reactions (> 2%) associated with Metozolv ODT® in clinical studies were nausea, vomiting, fatigue, somnolence, and headache.

The cost of therapy with Metozolv ODT® is approximately $139.20 for 30 days of use (#120) while the cost of generic metoclopramide tablets is $12.31 for the same.

Recommendations

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

1. FDA-approved diagnosis of gastroesophageal reflux disease in adults not responding to conventional therapy, or acute and recurrent diabetic gastroparesis in adults.
2. Must provide a clinical reason why the member cannot use the regular formulation of metoclopramide tablets.
3. Therapy will be approved for a period of not more than 12 weeks.

Metozolv ODT® Product Details

Indication

Symptomatic treatment of diabetic gastroparesis; gastroesophageal reflux

Dosage Forms: Orally Disintegrating Tablet

Contraindications

Hypersensitivity to metoclopramide or any component of the formulation; GI obstruction, perforation or hemorrhage; pheochromocytoma; history of seizures or concomitant use of other agents likely to increase extrapyramidal reactions

Pregnancy Risk Factor B

Precautions

Concerns related to adverse effects:

- **Depression**: Mental depression has occurred, symptoms range from mild to severe (suicidal ideation and suicide); use with caution in patients with a history of mental illness.
- **Extrapyramidal symptoms** (EPS): May cause extrapyramidal symptoms, generally manifested as acute dystonic reactions within the initial 24-48 hours of use. Risk of these reactions is increased at higher doses, and in pediatric patients and adults <30 years of age. Pseudoparkinsonism (e.g., bradykinesia, tremor, rigidity) may also occur (usually within first 6 months of therapy) and is generally reversible following discontinuation.
- **Neuroleptic malignant syndrome** (NMS): Use may be associated (rarely) with neuroleptic malignant syndrome (NMS); monitor for mental status changes, fever, muscle rigidity and/or autonomic instability; discontinue use if signs/symptoms appear.
- **Tardive dyskinesia**: **[U.S. Boxed Warning]: May cause tardive dyskinesia, which is often irreversible; duration of treatment and total cumulative dose are associated with an increased risk.** Therapy durations >12 weeks should be avoided (except in rare cases following risk:benefit assessment). Risk appears to be increased in the elderly, women, and diabetics; however, it is not possible to predict which patients will develop tardive dyskinesia. Therapy should be discontinued in any patient if signs/symptoms appear.

Disease-related concerns:

- **Edematous conditions**: Use with caution in patients who are at risk of fluid overload (HF, cirrhosis). May cause transient increase in serum aldosterone; use lowest recommended doses initially and discontinue use if signs/symptoms appear.
- **Hypertension**: Use with caution in patients with hypertension.
- **NADH-cytochrome b5 reductase deficiency**: Patients with NADH-cytochrome b5 reductase deficiency are at increased risk of methemoglobinemia and/or sulfhemoglobinemia.
- **Parkinson's disease**: Use with caution or avoid in patients with Parkinson's disease; may have increased risk of EPS.
- **Renal impairment**: Use with caution in patients with renal impairment; dosage adjustment may be needed.
- **Surgical anastomosis/closure:** Use with caution following surgical anastomosis/closure; promotility agents may theoretically increase pressure in suture lines.

Special populations:

- **Elderly**: Use with caution in the elderly; may have increased risk of tardive dyskinesia, particularly older women.
- **Pediatrics**: EPS are increased in pediatric patients. In neonates, prolonged clearance of metoclopramide may lead to increased serum concentrations. Neonates may also have decreased levels of NADH-cytochrome b5 reductase which increases the risk of methemoglobinemia.

Common Adverse Effects

- Nausea
- Vomiting
- Fatigue
- Dizziness
- Somnolence
- Headache

Less Common Adverse Effects

- Tardive Dyskinesia
- Diarrhea
- Amenorrhea
- Bradycardia
- Acute Dystonia
- Urinary Incontinence
- Visual Disturbances

Drug Interactions

Avoid use with antipsychotics, anti-Parkinson's agents, SSRI's, TCA's, promethazine, droperidol, and tetrabenazine

Patient Information

- Instruct patients to take Metozolv ODT® at least 30 minutes before eating and at bedtime.
- A patient Medication Guide is available for Metozolv ODT® and printed at the end of the prescribing information. Instruct patients, families, and caregivers to read the Medication Guide and assist them in understanding its contents.
- Inform patients or their caregivers of serious potential issues associated with metoclopramideuse such as tardive dyskinesia, extrapyramidal symptoms, and neuroleptic malignant syndrome. Advise patients to inform their physician if symptoms associated with these disorders occur during or after treatment with Metozolv ODT®.
- Inform patients that Metozolv ODT® may cause drowsiness, dizziness, or otherwise impair mental alertness or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle. Sedation may be more pronounced in the elderly or when consuming alcohol.
- Inform patients that the most common adverse reactions in patients treated with Metozolv ODT® or other metoclopramide-containing products

REFERENCES

Metoclopramide *on Lexi-Comp, Inc. 1978-2010 All Rights Reserved.*
Metozolv ODT® Package Insert. Salix Pharmaceuticals. Accessed Online at: http://www.metozolvodt.com/

Appendix I

30 Day Notice to Prior Authorize Special Formulations and Application of Age Restriction of Alzheimer's Medications

Oklahoma HealthCare Authority
November 2010

Background

Alzheimer's disease (AD) is named after Dr. Alois Alzheimer, a German doctor, who first described it in 1906. AD is an irreversible, progressive brain disease most notably characterized by loss of memory and cognition, which is due to a pathological deterioration and death of brain cells. In most people with AD, symptoms first appear after age 60, but damage to the brain begins as many as 10 to 20 years before any obvious signs of memory loss.

The cause of AD is not yet fully understood, but available evidence to date suggests likely causes include genetic, environmental, and lifestyle factors. Some cases of early-onset AD, called familial AD, are caused by gene mutations and can affect people aged 30-60 years old. Emerging research shows certain lifestyle factors, such as a nutritious diet, exercise, social engagement, and mentally stimulating pursuits might help to reduce the risk of cognitive decline and AD. Further research is underway to evaluate associations between cognitive decline and heart disease, high blood pressure, diabetes, and obesity.

Diagnosis

The only definitive way to diagnose AD is with an autopsy as there is no single test that can be used to diagnose AD. Currently, the diagnosis of Alzheimer's is a one of exclusion based on neurological, mental, and cognitive exams, in conjunction with physical exams and laboratory tests to rule out other causes of altered mental status. New imaging technologies such as MRI or CT scans are often a part of the standard medical workup for Alzheimer's disease, but these images are used primarily to detect tumors, evidence of small or large strokes, damage from severe head trauma, or fluid buildup.

Treatment

There is no cure for AD, however there are currently 5 drugs approved by the FDA for the management of AD. These medications are indicated for different severity or stages of the disease, and medications with different mechanisms of action can be used concomitantly. Available medications have not been shown to reverse AD and appear to help patients only for 6 months to a few years by delaying cognitive decline. Treatment should be initiated early in order to enable patients to carry out their daily activities and independent living for a longer period of time which may prolong the time that patients can be managed at home. Other medications such as benzodiazepines, antidepressants, and antipsychotics may help ease the behavioral symptoms associated with AD such as sleeplessness, agitation, wandering, anxiety, anger, and depression, etc. However, these medications have risks associated with their use and the benefits must be weighed against the risks.

The mainstay of current pharmacologic therapy is aimed at increasing levels of chemical messengers in the brain which may increase mental function. The following acetylcholinesterase (AChE) inhibitors increase the concentration of acetylcholine through inhibition of acetylcholinesterase:

- Donepezil **(Aricept®)**
- Galantamine **(Razadyne®, Razadyne ER®, formerly Reminyl®)**
- Rivastigmine **(Exelon®)**
- Tacrine **(Cognex®)**

Memantine **(Namenda®)** helps to regulate glutamate activity in the brain by binding to N-methyl-D-aspartate (NMDA) receptor-operated cation channels. Memantine also blocks the 5-hydroxy-tryptamine-3 receptor and nicotinic acetylcholine receptors.

The following chart shows currently available medications and details pertaining to their use:

Generic Name	Trade Name	FDA Indications	Dosage Forms Available	Dosing Regimen
Memantine	Namenda® Namenda XR®	Treatment of moderate to severe dementia associated with Alzheimer's	Combination package: 5mg (28) and 10mg (21) Oral Solution 2mg/mL IR Tabs: 5 mg, 10 mg XR Tabs: 7mg, 14mg, 21mg, 28mg	IR: 5mg-10mg BID XR: 7mg-28mg QD
Donepezil	Aricept®	Treatment of mild, moderate, or severe dementia associated with Alzheimer's	Tabs: 5mg, 10 mg, 23 mg Orally Disintegrating Tabs: 5mg, 10mg	5mg-23mg QD
Galantamine	Razadyne® Razadyne ER®	Treatment of mild-moderate dementia associated with Alzheimer's	IR Tabs: 4mg, 8mg, 12mg ER Caps: 8 mg, 16mg, 24mg Oral Solution: 4 mg/mL (100 mL)	IR: 4mg-12mg BID ER: 8mg-24mg QD
Rivastigmine	Exelon®	Treatment of mild- moderate dementia associated with Alzheimer's disease or Parkinson's disease	Capsules: 1.5mg, 3mg, 4.5mg, 6mg Oral Solution: 2 mg/mL (120 mL) Transdermal Patch: 4.6 mg/24 hours 9.5 mg/24 hours	1.5mg-6 mg BID Transdermal Patch: 4.6mg-9.5mg QD
Tacrine	Cognex®	Palliative treatment of mild-moderate dementia associated with Alzheimer's	10mg, 20mg, 30mg, and 40 mg Caps	Initial: 10mg QID for at least 4 weeks; If tolerated may increase up to 40mg QID

Utilization of Alzheimer's Medications

Since this is the first drug utilization review of this category, a longer utilization history is included below to reflect the utilization trends that occurred within this category during the timeframe for which Medicare dual-eligible members received their pharmacy benefit through SoonerCare and subsequent changes after Part D took effect in January 2006.

Calendar Year	Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Cost/ Member	Units/ Day
2004	6,098	44,534	$6,323,472.03	$141.99	$4.65	$1,036.97	1.46
2005	6,712	57,558	$8,335,852.93	$144.83	$4.71	$1,241.93	1.47
2006	829	4,200	$584,650.74	$139.20	$4.63	$705.25	1.39
2007	504	3,019	$462,248.18	$153.11	$4.89	$917.16	1.39
2008	535	3,849	$650,285.28	$168.95	$5.41	$1,215.49	1.51
2009	637	4,699	$847,795.65	$180.42	$5.94	$1,330.92	1.57

Comparison of Fiscal Years

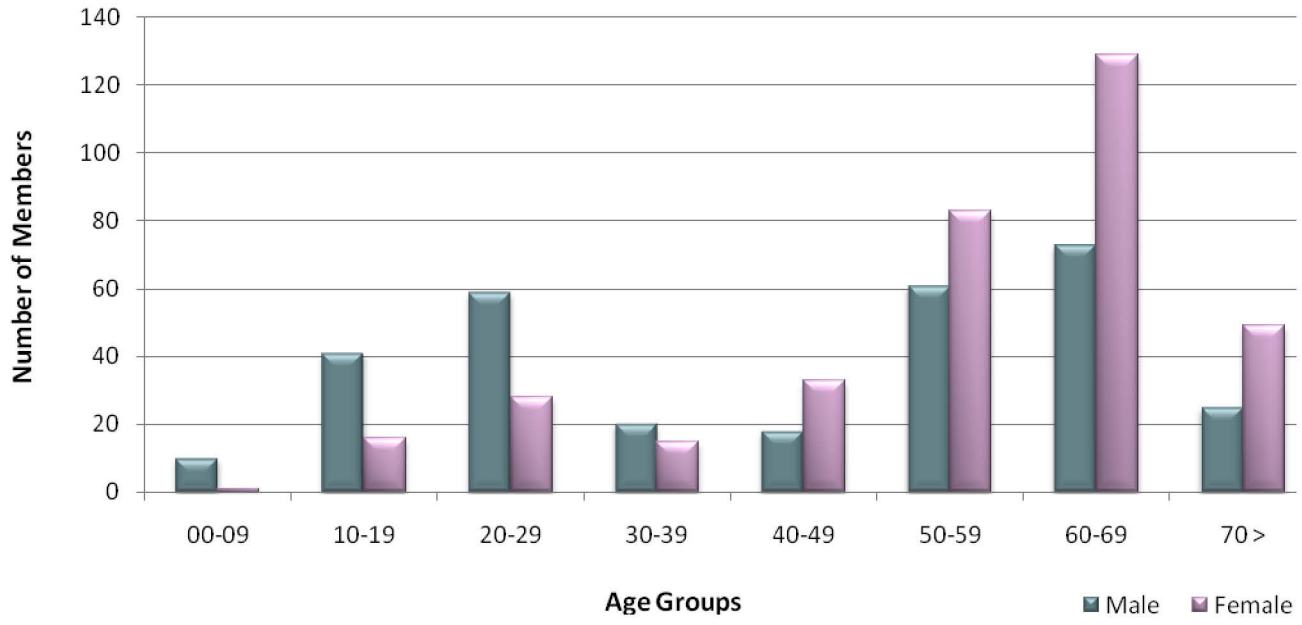
Fiscal Year	Members	Claims	Cost	Cost/Claim	Cost/Day	Units	Days
2009	603	4,251	$742,015.12	$174.55	$5.69	200,741	130,325
2010	662	5,258	$976,397.90	$185.70	$6.13	248,922	159,361
% Change	9.80%	23.70%	31.60%	6.40%	7.70%	24.00%	22.30%
Change	59	1,007	$234,382.78	$11.15	$0.44	48,181	29,036

Utilization Details of Alzheimer's Medications for FY 2010

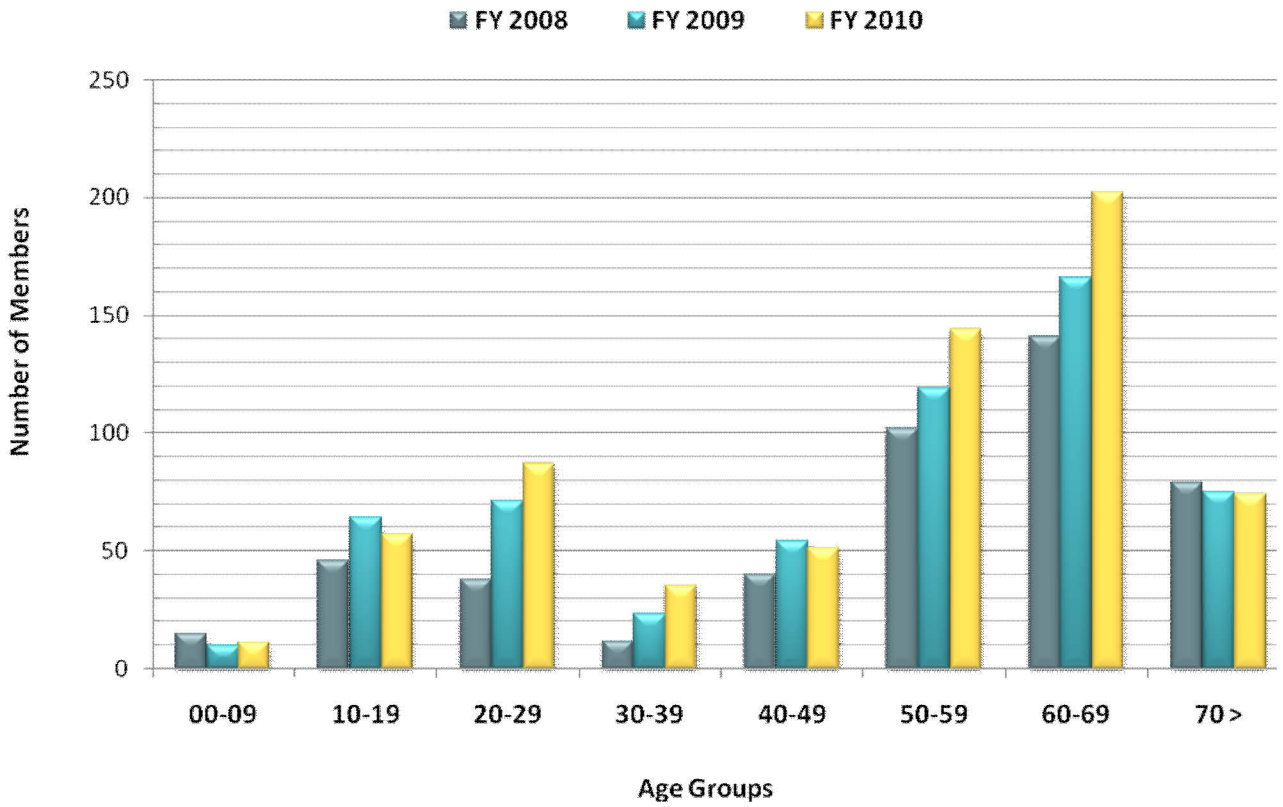
Chemical Name	Brand Name	Claims	Members	Cost	Units/ Day	Claims/ Member	Cost/ Day	% Cost
Memantine	NAMENDA TAB 10MG	2,686	390	$456,686.62	1.98	6.89	$5.71	46.77%
Memantine	NAMENDA TAB 5MG	302	68	$44,470.69	1.83	4.44	$5.18	4.55%
Memantine	NAMENDA TAB 5-10MG	13	13	$1,889.27	1.74	1	$5.16	0.19%
Memantine	NAMENDA SOL 10MG/5ML	1	1	$351.00	12	1	$11.70	0.04%
Donepezil	ARICEPT TAB 10MG	1,453	257	$311,982.87	1	5.65	$6.83	31.95%
Donepezil	ARICEPT TAB 5MG	486	126	$104,410.93	1.02	3.86	$6.90	10.69%
Rivastigmine	EXELON DIS 9.5MG/24	69	17	$13,227.99	1	4.06	$6.39	1.35%
Rivastigmine	EXELON DIS 4.6MG/24	68	17	$14,209.80	1	4	$6.97	1.46%
Rivastigmine	EXELON CAP 3MG	40	5	$9,237.57	2	8	$7.70	0.95%
Rivastigmine	EXELON CAP 1.5MG	29	4	$5,008.02	1.56	7.25	$5.30	0.51%
Rivastigmine	EXELON CAP 4.5MG	11	2	$2,382.61	2	5.5	$7.59	0.24%
Rivastigmine	EXELON CAP 6MG	1	1	$249.97	2	1	$8.33	0.03%
Galantamine	GALANTAMINE TAB 4MG	49	9	$4,320.22	1.58	5.44	$2.96	0.44%
Galantamine	GALANTAMINE TAB 8MG	22	2	$1,928.63	1.45	11	$2.92	0.20%
Galantamine	GALANTAMINE CAP 8MG ER	17	2	$3,446.13	1.35	8.5	$6.76	0.35%
Galantamine	GALANTAMINE CAP 16MG ER	1	1	$170.18	1	1	$5.67	0.02%
Galantamine	GALANTAMINE TAB 12MG	1	1	$112.74	2	1	$3.76	0.01%
Galantamine	RAZADYNE ER CAP 16MG	6	1	$1,146.31	1	6	$6.37	0.12%
Galantamine	RAZADYNE ER CAP 8MG	3	1	$1,166.35	2	3	$12.96	0.12%
	TOTALS	5,258	662*	$976,397.90	1.56	7.94	$6.13	100%

*Total number of unduplicated members

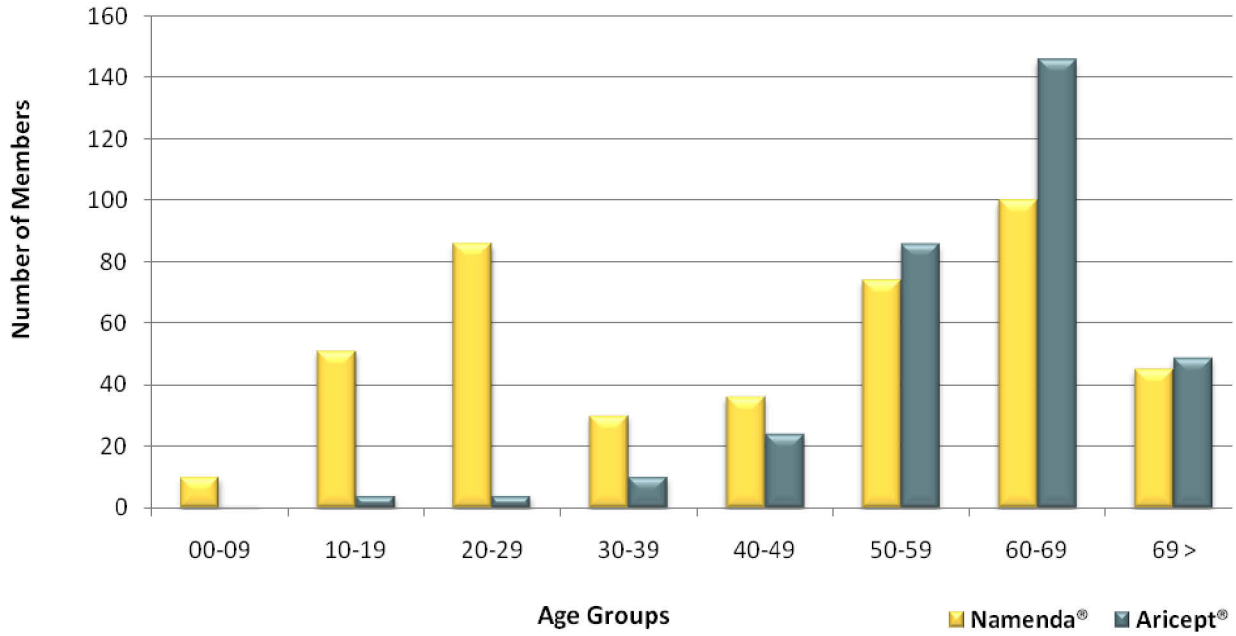
Demographics of Members Utilizing Alzheimer's Medications: FY 2010



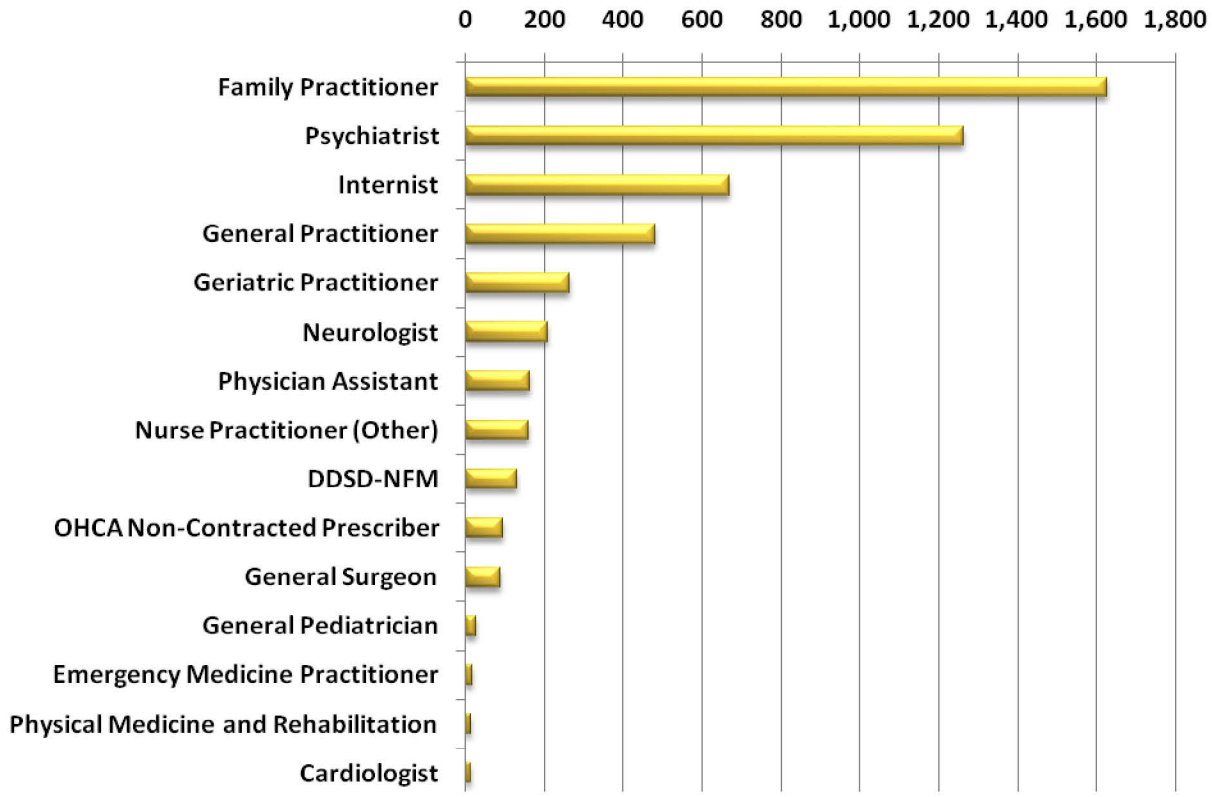
Trends in Demographics of Members Utilizing Alzheimer's Medications



Demographics Overview of Namenda® and Aricept®



Top Prescribers of Alzheimer's Medications by Claims for FY 2010



Discussion and Market Analysis

The utilization data suggests these medications may be used in populations who do not have Alzheimer's disease. The following is a list of the probable off-labeled uses of these medications not related to Alzheimer's disease:

- Impaired Cognition associated with:
  - Down syndrome
  - Multiple sclerosis
  - Vascular dementia
- Phantom limb syndrome
- Opioid analgesic adverse reaction - Sedation
- Progressive supranuclear ophthalmoplegia
- Schizoaffective disorder

Although there are some pilot studies and small trials published on the use of Alzheimer's medications for some of the above conditions[1,2,3,4,5,6,7,8,9,10,11,12] there is a lack of robust clinical data to analyze the efficacy and cost-effectiveness of such use. Of interest is the use of these agents in children with Down Syndrome. Individuals with Down Syndrome exhibit a cholinergic deficiency similar to that found in AD and small studies suggest these agents exert positive gains in language and cognition parameters. However, in 2009, a large randomized controlled clinical trial to assess the efficacy and safety of donepezil in young adults with Down Syndrome showed the donepezil group to have no statistical difference from the placebo group, as was measured by the Severe Impairment Battery test.[13]

Anticipated Patent Expirations

- Donepezil (Aricept®) – November 2010
- Rivastigmine (Exelon® Patch) – August 2012
- Memantine (Namenda®) – April 2015

Namenda XR® (memantine)[14] - Forest Laboratories, Inc. and Merz Pharmaceuticals GmbH announced in June 2010 that Namenda XR® (memantine hydrochloride) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderate to severe dementia of the Alzheimer's type. Namenda XR® is a 28 mg once-daily extended-release formulation of Namenda®.

Aricept® 23mg (donepezil)[15] - Eisai Inc. and Pfizer Inc. announced in July 2010 that the FDA approved a new once-daily, higher-dose, 23mg tablet of Aricept® for the treatment of moderate-to-severe AD. Aricept 23mg tablet offers another dosing option for patients with moderate-to-severe AD, for whom few treatments are available. The approval of Aricept 23mg tablet is based on data from a large head-to-head study of Aricept 23mg tablet versus Aricept 10mg tablet in over 1,400 patients with moderate-to-severe AD. The two primary endpoints measured were improvement in the Severe Impairment Battery (SIB) and the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC+). Aricept 23mg tablet demonstrated a statistically significant improvement in cognition, but did not achieve statistically significant improvement in global function when compared to Aricept® 10mg tablet.

Aricept® (donepezil) Transdermal Patch[16] - Teikoku Pharma USA announced in September of 2010 that the FDA had accepted for review the New Drug Application (NDA) for a new weekly transdermal patch of Aricept®. The Aricept® transdermal patch is expected to provide a potential new treatment option to patients who have trouble swallowing as well as to reduce burden to the cargivers of AD patients.

September 2010 - Researchers at the Gladstone Institute of Neurological Disease uncovered new approaches to reduce toxic proteins in AD and other neurodegenerative diseases.[17] The researchers discovered that regulation of the enzyme SIRT1 may help prevent the formation of a toxic form of the protein tau that kills brain cells in people with Alzheimer's disease. Dr. Gan and her team of researchers have identified a small molecule compound that eliminates toxic p-tau in neurons which may represent a new class of anti-AD drugs.

Conclusion and Recommendations

The anticipated loss of patent protection for Aricept® (donepezil) should significantly decrease costs associated with this class of medications. However, due to new patented special formulations of existing medications, these savings may be offset and costs may increase as utilization is increased due to expected aging of the current population and addition of new members as SoonerCare eligibility is increased. Utilization data also show these agents may be used for other conditions with minimal data to support efficacy, safety, or cost-effectiveness of such use. In conclusion, the College of Pharmacy recommends the following:

1. Prior Authorization of special formulation products including oral solutions, patches, extended release formulations, or other convenience formulations with the following approval criteria:
    a. Member must have a documented reason why the special formulation is clinically necessary over the regular formulation
2. Application of Age Restriction for ages 0-30 with the following approval criteria
    a. FDA approved diagnosis

[1] Tsao JW, Heilman KM. **Donepezil improved memory in multiple sclerosis in a randomized clinical trial**. Neurology. 2005 May 24;64(10):1823

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[3] Mohan M. Carpenter PK. Bennett C. **Donepezil for dementia in people with Down syndrome**. [Review] Cochrane Database of Systematic Reviews. (1):CD007178, 2009.

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[9] Grande LA. O'Donnell BR. Fitzgibbon DR. Terman GW. **Ultra-low dose ketamine and memantine treatment for pain in an opioid-tolerant oncology patient.** Anesthesia & Analgesia. 107(4):1380-3.

[10] Bruera E, Strasser F, Shen L, et al: **The effect of donepezil on sedation and other symptoms in patients receiving opioids for cancer pain: a pilot study.** J Pain Symptom Manage 2003; 26(5):1049-1054.

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[12] Keefe RS. Malhotra AK. Meltzer HY. Kane JM. Buchanan RW. Murthy A. Sovel M. Li C. Goldman R**. Efficacy and safety of donepezil in patients with schizophrenia or schizoaffective disorder: significant placebo/practice effects in a 12-week, randomized, double-blind, placebo-controlled trial.** Neuropsychopharmacology. 33(6):1217-28.

[13] Kishnani PS, Sommer BR, Handen BL, Seltzer B, Capone GT, Spiridigliozzi GA, Heller JH, Richardson S, McRae T. **The efficacy, safety, and tolerability of donepezil for the treatment of young adults with Down syndrome.** Am J Med Genet A., 149A(8):1641-54.

[14] http://www.drugs.com/newdrugs/forest-merz-announce-fda-approval-namenda-xr-moderate-severe-dementia-alzheimer-s-type-2194.html

[15] http://www.news-medical.net/news/20100726/FDA-approves-Aricept-23-mg-tablet-for-Alzheimers-disease.aspx

[16] http://www.drugs.com/news/fda-accepts-aricept-patch-donepezil-transdermal-nda-review-26699.html

[17] http://www.medicalnewstoday.com/articles/202247.php

Appendix J

Drug Utilization Review – Benign Prostate Hyperplasia (BPH)

Oklahoma Health Care Authority
November 2010

Introduction

Symptomatic BPH usually occurs in 10–30% for men around the age of 70.[1] Approximately 37 million men aged >50 years have been affected by BPH.[4] Symptoms typically do not occur before the age of 40 and predominantly occur later in life. Benign prostatic hyperplasia is an enlarged prostate gland which can cause dribbling after urination or the need to urinate more often, most commonly during sleeping hours. The growth of the prostate begins during puberty and continues to grow during most of a male's lifespan. The prostate gland grows larger with age which results in narrowing of the urethra and causes problems in passing urine. Other medical conditions such as infections and tumor growth have been associated with enlarged prostate.

Symptoms

- More frequent urination during the day
- Higher sense of urgency to pass urine
- Diminished urinary flow or leaking
- Burning sensation upon urination
- Disrupted sleep pattern due to nocturnal urination

Diagnosis

- AUA Symptom Index, International Prostate Symptom Score
- Digital Rectal Examination (DRE)
- Prostate-Specific Antigen (PSA) Blood Test
- Rectal Ultrasound and Prostate Biopsy
- Urine Flow Study
- Cystoscopy
- Urinalysis

Treatment and Safety[4]

Medication therapy, minimally invasive therapy (MIT), and surgical intervention are the available treatment options and have been demonstrated to improve symptoms with BPH; however, they are not all equally efficacious. Each therapeutic intervention is associated with potential adverse effects which must be considered depending on severity of illness of the patient. Medical therapy is usually the initial medical intervention selected due to potential adverse effects associated with MIT and surgical procedures. If medical therapy becomes ineffective or intolerable and if disease severity warrants more effective intervention for lower urinary tract symptoms (LUTS) then MIT is the preferred treatment of choice. Patients on MIT with unresolved symptoms may consider surgical intervention which is associated with more

potential adverse effects than MIT. Transurethral resection of the prostate (TURP) is the gold standard surgical intervention.

Alternative Treatments:

- Transurethral microwave heat treatments (TUMT)
- Transurethral needle ablation (TUNA)
- Uro-Lume stent; high risk
- Transurethral resection of the prostate (TURP)
- High-intensity focused ultrasound (HIFU)
- Incision of prostate
- Holmium laser resection/enucleation
- Water-Induced thermotherapy
- Interstitial Laser Coagulation (ILC)

Alternative Treatments Safety Issues:

- Unexpected procedure-related injuries have been associated with the use of transurethral microwave heat treatment devices, so that the safety recommendations published by the United States Food and Drug Administration should be followed when using microwave heat treatment devices.
- Prostatic stents are associated with significant complications, such as encrustation, infection and chronic pain.
- Common risks of transurethral needle ablation include urinary symptoms that can persist for weeks and temporary urinary retention.
- Complications from transurethral resection of the prostate (TURP) include dilutional hyponatremia that occurs when irrigant solution is absorbed into the bloodstream. Other complications that have been reported in more than 5% of patients include, in order of frequency: sexual dysfunction (which may not be attributable to the surgery in all cases), irritative voiding symptoms, bladder neck contracture, need for blood transfusion, urinary tract infections, and hematuria.

Pharmacologic Treatment

Alpha-adrenergic blockers

- Alfuzosin (Uroxatrol®)
- Doxazosin (Cardura®, Cardura XL®)
- Tamsulosin (Flomax®)
- Terazosin (Hytrin®)
- Silodosin (Rapaflo®)

5 Alpha-reductase inhibitors

- Dutasteride (Avodart®)
- Finasteride (Proscar®)

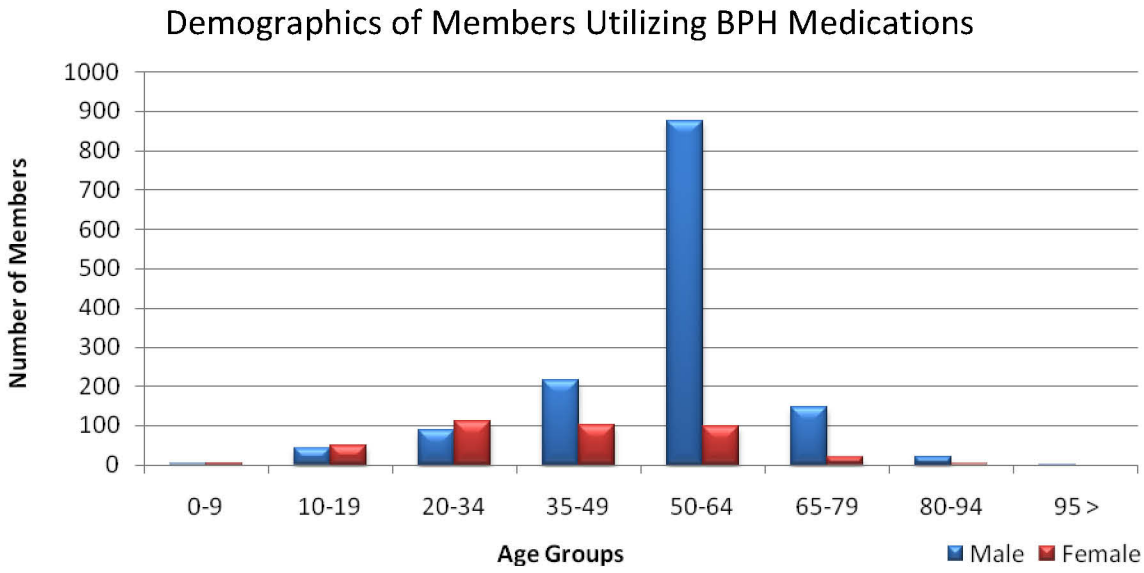
Combination therapy

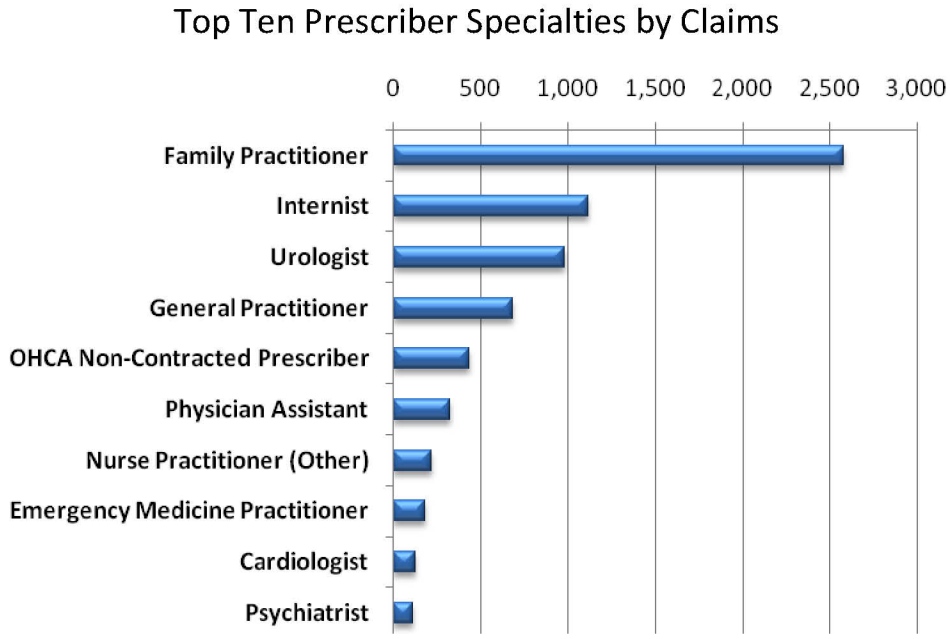
- Dutasteride /Tamsulosin (Jalyn®)

Treatment	Clinical Evidence	Safety
"Watchful Waiting"	Patients with mild symptoms (AUASI ≤7) or moderate-to-severe (AUASI ≥8) who are not bothered my LUTS	
Alpha-adrenergic antagonists (2nd/3rd generation) (Alfuzosin,Doxazosin, Tamsulosin, Terazosin)	Effective for short term therapy BPH/LUTS; Titrate terazosin and doxazosin slowly due to hypotensive effect; tamsulosin and alfuzosin are uroselective; Meta-analysis indicated similar efficacy[5]; faster onset of action;	terazosin and doxazosin: dizziness (15%-26%), asthenia (10%-14%), and postural hypotension (5%-8%); asthenia, dizziness and postural hypertension have been reported in a higher percentage for tamsulosin- (7%-8%-3%) versus alfuzosin- (3%-4%-1%); all have relatively low sexual side effects (3-6%)
5-alpha-reductase inhibitors (Dutasteride, Finasteride)	Effective in long-term reduction in prostate volume, treatment for BPH/LUTS, and reduced need for surgery; finasteride effects type II 5-alpha and dutasteride effects type I-II 5-alpha; slower onset of action; 2 multicenter RCT's revealed similar efficacy compared with alpha blockers[6]	impotence (4%-7%); decreased libido (1%-8%); abnormal ejaculation (2%-4%); and gynecomastia (1%-2%)
alpha-adrenergic antagonist/5-alpha-reductace inhibitor (Dutasteride and Tamsulosin)	Two 1-year RCT's revealed combination therapy not superior to alpha-adrenergic monotherapy but statistically significant symptom improvement over 5-alpha-reductase inhibitor and placebo groups7,8;MTOPS 4-year study revealed doxazosin and finasteride reduced overall risk of clinical progression by 66% versus 39% and 34% for doxazosin and finasteride monotherapy respectively, A higher incidence of erectile dysfunction and dizziness occurred w/ combination therapy[9]	(see above); MTOPS study revealed higher incidence of erectile dysfunction and dizziness with combination therapy
Phytotherapeutic	Serenoa repens (sawpalmetto), Pygeum africanum (African plum), Hypoxis rooperi (South African star grass), Secale cereal (cerniton); 12 month double blind RCT in Europe revealed similar reduction in IPSS scores with saw palmetto versus tamsulosin[10]; Phytotherapeutic agents and other dietary supplements are not currently recommended by the AUA due to integrity of products and validity of clinical trials	
Antiandrogens and gonadotropin-releasing hormone (GnRH) agonists	Effective for BPH/LUTS but resulting androgen deficiency generally makes their use unacceptable to patients	

Utilization of BPH Medications

Fiscal Year	Total Members	Total Claims	Total Cost	Cost per Claim	Per-Diem Cost	Total Units	Total Days
2009	1,493	6,605	$555,965.73	$84.17	$2.26	266,222	245,912
2010	1,778	7,376	$693,377.13	$94.00	$2.56	293,748	271,256
% Change	19.10%	11.70%	24.70%	11.70%	13.30%	10.30%	10.30%
Change	285	771	$137,411.40	$9.83	$0.30	27,526	25,344





Update on Market News

- June 14, 2010 – Jalyn® (Dutasteride 0.5mg/Tamsulosin 0.4mg oral capsules) is the first combination medication approved for treatment of symptoms of BPH. The most common adverse reactions reported in subjects receiving combination therapy were impotence, decreased libido, breast disorders (including breast enlargement and tenderness), ejaculation disorders and dizziness.
- January 2011 – Uroxatrol® (Alfuzosin) patent anticipated to expire.

Cost Comparison Table

Product	Indication	Dosing (max)	30-day Cost
Jalyn® (Dutasteride/Tamsulosin)	BPH	0.5mg/0.4mg daily	$107.40*
Avodart® (Dutasteride)	BPH	0.5mg daily	$107.40*
Flomax® (Tamsulosin)	BPH	0.8mg daily	$247.20*
Uroxatrol® (Alfuzosin)	BPH	10mg daily	$110.40*
Rapaflo® (Silodosin)	BPH	8mg daily	$110.70*
Cardura XL® (Doxazosin)	BPH/Hypertension	8mg daily	$53.70*
Tamsulosin generic	BPH	0.8mg daily	$36.00^
Doxazosin generic	BPH/Hypertension	8mg daily	$6.00^
Terazosin generic	BPH/Hypertension	20mg daily	$6.60^
Finasteride generic	BPH	5mg daily	$22.20^

*EAC cost ^MAC cost

Recommendation

The College of Pharmacy recommends the addition of the BPH class of medications to the Product Based Prior Authorization program. The following Tier 1 drug list has been reviewed and determined to be an acceptable combination for use as initial therapy for the majority of members. The College of Pharmacy recommends this list to the Drug Utilization Review Board based on cost and clinical effectiveness for approval before referral to the Oklahoma Healthcare Authority. The following is the proposed Tier list and approval criteria.

Tier 1	Tier 2
Hytrin® (Terazosin)	Uroxatrol® (Alfuzosin)
Cardura® (Doxazosin)	Rapaflo® (Silodosin)
Flomax® (Tamsulosin)	Cardura XL® (Doxazosin)
Proscar® (Finasteride)	Avodart® (Dutasteride)
	Jalyn® (Dutasteride/Tamsulosin)

Mandatory Generic Plan

Prior Authorization Criteria:

1. FDA approved diagnosis.
2. Recent 4-week trial of at least two Tier-1 medications from different pharmacological classes within the last 90 days
3. Documented adverse effect, drug interaction, or contraindication to all available Tier-1 products.

Utilization Details of BPH Medications

CHEMICAL NAME	BRAND NAME	CLAIMS	UNITS	DAYS	MEMBERS	COST	CLAIMS/ MEMBER	COST/ DAY	%COST
Tamsulosin	FLOMAX CAP 0.4MG	2,810	103,138	95,882	880	$401,406.77	3.19	$4.19	57.89%
Tamsulosin	TAMSULOSIN CAP 0.4MG	1,074	39,926	37,834	569	$143,378.98	1.89	$3.79	20.68%
Doxazosin	DOXAZOSIN TAB 8MG	264	12,540	11,635	75	$2,782.52	3.52	$0.24	0.40%
Doxazosin	DOXAZOSIN TAB 4MG	566	25,888	22,444	153	$5,461.87	3.7	$0.24	0.79%
Doxazosin	DOXAZOSIN TAB 2MG	476	21,730	17,206	137	$4,739.30	3.47	$0.28	0.68%
Doxazosin	DOXAZOSIN TAB 1MG	117	5,337	4,150	43	$962.35	2.72	$0.23	0.14%
Terazosin	TERAZOSIN CAP 10MG	102	4,408	4,108	26	$656.70	3.92	$0.16	0.09%
Terazosin	TERAZOSIN CAP 5MG	205	9,081	8,628	69	$1,474.62	2.97	$0.17	0.21%
Terazosin	TERAZOSIN CAP 2MG	322	14,003	11,383	84	$2,612.04	3.83	$0.23	0.38%
Terazosin	TERAZOSIN CAP 1MG	179	7,229	6,437	58	$1,308.01	3.09	$0.20	0.19%
Dutasteride	AVODART CAP 0.5MG	517	21,686	21,834	141	$76,853.37	3.67	$3.52	11.08%
Finasteride	FINASTERIDE TAB 5MG	491	18,174	18,967	122	$15,633.37	4.02	$0.82	2.25%
Alfuzosin	UROXATRAL TAB 10MG	224	9,373	9,313	67	$32,072.04	3.34	$3.44	4.63%
Silodosin	RAPAFLO CAP 8MG	27	1,115	1,315	10	$3,784.58	2.7	$2.88	0.55%
Silodosin	RAPAFLO CAP 4MG	1	30	30	1	$101.81	1	$3.39	0.01%
Doxazosin	CARDURA XL TAB 4MG	1	90	90	1	$148.80	1	$1.65	0.02%
	Totals	**7,376**	**293,748**	**271,256**	**1,778***	**$693,377.13**	**4.15**	**$2.56**	**100.00**

***Total Number of Unduplicated Members**

References

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8. Kirby R, Roehrborn CG, Boyle P. Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. *Urology.* 2003;61:119-126.
9. McConnell JD, Roehrborn CG, Bautista OM, et al, and the Medical Therapy of Prostatic Symptoms (MTOPS) Research Group. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med.* 2003;349:2387-2398.
10. Debruyne F, Koch G, Boyle P, et. al. [Comparison of a phytotherapeutic agent (Permixon) with an alpha-blocker (Tamsulosin) in the treatment of benign prostatic hyperplasia: a 1-year randomized international study]. [Article in French]. *Prog Urol.* 2002;12:384-392.

Appendix K

U.S. Food and Drug Administration

Drugs

FDA Drug Safety Communication: FDA Recommends Against the Continued Use of Meridia (sibutramine)

Safety Announcement

[10-8-2010] The U.S. Food and Drug Administration (FDA) is recommending against continued prescribing and use of Meridia (sibutramine) because this drug may pose unnecessary cardiovascular risks to patients. FDA has requested that Abbott Laboratories—the manufacturer of Meridia—voluntaril withdraw this drug product from the United States market. Abbott has agreed to voluntarily stop marketing of Meridia in the United States.

Meridia was FDA-approved in November 1997 for weight loss and maintenance of weight loss in patients with a body mass index (BMI) greater than or equal to 30 (≥30) kg/m^2 or for patients with a BMI ≥27 kg/m^2 who have other cardiovascular risk factors. BMI is a measure of body fat in adults that i based on height and weight. Patients with a BMI ≥30 kg/m^2 are considered obese.

FDA's recommendation is based on new data from the Sibutramine Cardiovascular Outcomes (SCOUT) trial, which demonstrated a 16% increase in ris of major adverse cardiovascular events (a composite of non-fatal heart attack, non-fatal stroke, resuscitation after cardiac arrest and cardiovascular death) in patients treated with Meridia compared to patients taking a placebo (see Data Summary below). At the end of the trial (60 months), patients in the Meridia group lost a small amount of body weight compared to patients in the placebo group. FDA has concluded that the risk for an adverse cardiovascular event from Meridia in the population studied outweighed any benefit from the modest weight loss observed with the drug.

In November 2009, and January 2010, FDA announced it was reviewing clinical trial data about a potentially serious effect on the heart from the use o Meridia. The links to these communications are listed below:

- Early Communication about an Ongoing Safety Review of Meridia (sibutramine hydrochloride)[1]
- Follow-Up to the November 2009 Early Communication about an Ongoing Safety Review of Sibutramine, Marketed as Meridia[2]

Additional Information for Patients

If you currently take Meridia, you should:

- Stop taking Meridia and talk to your healthcare professional about alternative weight loss and weight loss management programs.
- Talk to your healthcare professional if you have any concerns about Meridia.
- Contact your healthcare professional right away if you experience pain in the chest, heart palpitations, abnormal heart rate or rhythm, or other symptoms including dizziness and lightheadedness.
- Dispose of unused Meridia in your household trash by following the recommendations outlined in the Federal Drug Disposal Guidelines:[3]
  - Take your Meridia out of its original container and mix it with an undesirable substance, such as used coffee grounds or kitty litter. The medication will be less appealing to children and pets, and unrecognizable to people who may intentionally go through your trash.
  - Put the medication in a sealable bag, empty can, or other container to prevent it from breaking out of a garbage bag.
- Report any side effects with Meridia to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

Additional Information for Healthcare Professionals

FDA recommends that healthcare professionals:

- Stop prescribing and dispensing Meridia to patients.
- Contact patients currently taking Meridia and ask them to stop taking the medication.
- Inform patients of the risks associated with Meridia.
- Discuss alternative weight loss strategies other than Meridia with your patients.
- Be aware of the possible risk of major adverse cardiovascular events with patients taking Meridia and assess patients for these events if they present with any signs or symptoms of cardiovascular disease.
- Report any side effects with Meridia to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

Data Summary

The SCOUT trial was a randomized, double-blind, placebo-controlled multicenter trial conducted between January 2003 and March 2009 in Europe, Latin America, and Australia. The study population consisted of approximately 10,000 men and women aged ≥55 with a BMI between 27 kg/m^2 and 4 kg/m^2, or between 25 kg/m^2 and 27 kg/m^2 with an increased waist circumference. Patients were also required to have a history of cardiovascular disease (coronary artery disease, stroke, occlusive peripheral arterial disease) and/or type 2 diabetes mellitus with at least one other cardiovascular risk factor (hypertension, dyslipidemia, current smoking, or diabetic nephropathy). All patients underwent a 6-week lead-in period on Meridia 10 mg. Eligible patients were then randomized to either placebo or Meridia 10 mg daily. Titration to Meridia 15 mg daily was allowed for individuals with inadequate weight loss on 10 mg daily. The mean duration of exposure to Meridia and placebo was approximately 3.5 years.

There was a 16% increase in the relative risk of the primary outcome event (a composite of non-fatal myocardial infarction, non-fatal stroke, resuscitation after cardiac arrest, and cardiovascular death) in the Meridia group compared to the placebo group [Hazard Ratio (HR)=1.16; 95% CI, 1.03-1.31; p=0.02]. There was no between-treatment difference in cardiovascular death (HR=0.99; 95% CI, 0.82-1.19; p=0.90) or all-cause mortalit (HR=1.04; 95% CI, 0.91-1.20; p=0.54). The primary outcome was driven by non-fatal myocardial infarction and non-fatal stroke (HR=1.28; 95% CI, 1.04-1.57; p=0.02; HR=1.36; 95% CI, 1.04-1.77; p=0.03, respectively).

The difference in mean percent change in body weight at Month 60 (end of the trial) between the Meridia and placebo groups was approximately 2.5%

Subgroup analyses were also conducted on three defined cardiovascular risk groups composed of individuals with: (1) type 2 diabetes mellitus only; (2) a history of cardiovascular disease only; (3) a history of cardiovascular disease and type 2 diabetes mellitus. FDA's analysis demonstrated that the logrank test interaction p-value for the cardiovascular risk subgroup analysis was 0.56, indicating that the magnitudes of risk for major adverse cardia events in the three subgroups were not statistically significantly different.

Data from the SCOUT trial was discussed at the Endocrinologic and Metabolic Drugs Advisory Committee Meeting, held on September 15, 2010 (for complete safety reviews and background information discussed at this meeting see: September 15, 2010 AC meeting[4]).

Related Information

- Abbott Laboratories agrees to withdraw its obesity drug Meridia[5]
  FDA News Release (10/8/2010)
- Questions and Answers: FDA Recommends Against the Continued Use of Meridia (sibutramine)[6]
  10/8/2010
- Memorandum: Recommendation on a regulatory decision for Meridia, 10/4/2010 (PDF - 174KB)[7]
- Meridia (sibutramine hydrochloride) Information[8]

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Links on this page:

1. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm191650.htm
2. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm198206.htm
3. http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm226353.htm
4. http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm19111.htm
5. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm228812.htm
6. http://www.fda.gov/Drugs/DrugSafety/ucm228747.htm
7. http://www.fda.gov/downloads/Drugs/DrugSafety/UCM228795.pdf
8. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm191652.htm
9. http://www.fda.govhttps://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm
10. http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf

U.S. Food and Drug Administration

Drugs

FDA Drug Safety Communication: Safety update for osteoporosis drugs, bisphosphonates, and atypical fractures

Safety Announcement

[10-13-2010] The U.S. Food and Drug Administration (FDA) is updating the public regarding information previously communicated describing the risl of atypical fractures of the thigh, known as subtrochanteric and diaphyseal femur fractures, in patients who take bisphosphonates for osteoporosis. This information will be added to the *Warnings and Precautions* section of the labels of all bisphosphonate drugs approved for the prevention or treatment of osteoporosis.

Bisphosphonates are a class of medicines that can be effective at preventing or slowing the loss of bone mass (osteoporosis) in postmenopausal women, thus reducing the risk of common osteoporotic bone fracture. Osteoporotic fractures can result in pain, hospitalization, and surgery.

Atypical subtrochanteric femur fractures are fractures in the bone just below the hip joint. Diaphyseal femur fractures occur in the long part of the thigh bone. These fractures are very uncommon and appear to account for less than 1% of all hip and femur fractures overall. Although it is not clear i bisphosphonates are the cause, these unusual femur fractures have been predominantly reported in patients taking bisphosphonates.

The bisphosphonates affected by this notice are only those approved to treat osteoporosis, including Fosamax, Fosamax Plus D, Actonel, Actonel with Calcium, Boniva, Atelvia, and Reclast[1] (and their generic products).

This notice does not affect bisphosphonate drugs that only are used to treat Paget's disease or high blood calcium levels due to cancer (i.e., Didronel, Zometa, Skelid, and their generic products).

Although the optimal duration of bisphosphonate use for osteoporosis is unknown, these atypical fractures may be related to long-term term bisphosphonate use. FDA will require a new Limitations of Use statement in the *Indications and Usage* section of the labels for these drugs. This statement will describe the uncertainty of the optimal duration of use of bisphosphonates for the treatment and/or prevention of osteoporosis.

A Medication Guide will also be required to be given to patients when they pick up their bisphosphonate prescription. This Medication Guide will describe the symptoms of atypical femur fracture and recommend that patients notify their healthcare professional if they develop symptoms.

These actions are part of an ongoing safety review of bisphosphonate use and the occurrence of atypical subtrochanteric and diaphyseal femur fractures, as previously announced in a Drug Safety Communication on March 10, 2010[2].

Additional Information for Patients

If you currently take a bisphosphonate, you should:

- Continue to take your medication unless you are told to stop by your healthcare professional.
- Talk to your healthcare professional if you develop new hip or thigh pain (commonly described as dull or aching pain), or have any concerns with your medications.
- Report any side effects with your bisphosphonate medication to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

Additional Information for Healthcare Professionals

FDA recommends that healthcare professionals should:

- Be aware of the possible risk of atypical subtrochanteric and diaphyseal femur fractures in patients taking bisphosphonates.
- Continue to follow the recommendations in the drug label when prescribing bisphosphonates.
- Discuss the known benefits and potential risks of using bisphosphonates with patients.
- Evaluate any patient who presents with new thigh or groin pain to rule out a femoral fracture.
- Discontinue potent antiresorptive medications (including bisphosphonates) in patients who have evidence of a femoral shaft fracture.
- Consider periodic reevaluation of the need for continued bisphosphonate therapy, particularly in patients who have been treated for over 5 years.
- Report any adverse events with the use of bisphosphonates to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

Any information provided to MedWatch should be as detailed as possible and include information concerning fracture location/configuration, magnitude of trauma, fracture details (complete or incomplete, bilateral, or comminuted), presence and duration of prodromal thigh or groin pain, duration of bisphosphonate use, relevant medical history, and concomitant use of other medications.

Data Summary

FDA has reviewed all available data, including data summarized in the American Society for Bone and Mineral Research (ASBMR) Task Force report regarding bisphosphonates and atypical subtrochanteric and diaphyseal femur fractures[1], released on September 14, 2010. These atypical femur fractures can occur anywhere in the femoral shaft, from just below the lesser trochanter to above the supracondylar flare, and are transverse or short oblique in orientation without evidence of comminution. The fractures can be complete (involving both cortices) or incomplete (involving the lateral cortex only), and may be bilateral. Many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. The exact incidence of atypical femoral fractures is unknown but appears to account for less than one percent of hip and femoral fractures overall. Therefore, atypical fractures are very uncommon. Although atypical femoral fractures have been predominantly reported in patients taking bisphosphonates, they have also been reported in patients who have not taken bisphosphonates.

The optimal duration of bisphosphonate treatment for osteoporosis is unknown. Bisphosphonate medications approved for the prevention and/or treatment of osteoporosis have clinical trial data supporting fracture reduction efficacy through at least 3 years of treatment and, in some cases, through 5 years. The FDA is continuing its evaluation of data supporting the safety and effectiveness of long term use (greater than 3 to 5 years) of bisphosphonates for the treatment and prevention of osteoporosis and will provide additional guidance at the completion of our review.

In summary, FDA is continuing its ongoing safety review of bisphosphonate use and the occurrence of atypical femur fractures. As of this notice, the FDA is notifying patients and healthcare professionals of new *Warnings and Precautions* information that is being added regarding this risk to the labels of all bisphosphonate products approved for the prevention or treatment of osteoporosis. A new Limitations of Use statement will describe the uncertainty of the optimal duration of use of bisphosphonates for the treatment and/or prevention of osteoporosis. In addition, the FDA will require that a Medication Guide be included with all bisphosphonate medications approved for osteoporosis indications to better inform patients of the risk for atypical femur fracture.

References:

1. Shane E, Burr D, Ebeling PR, et al. Atypical subtrochanteric and diaphyseal femoral fractures: Report of a task force of the American Society fo Bone and Mineral Research [published online ahead of print]. *Journal of Bone and Mineral Research*. 2010; http://onlinelibrary.wiley.com/doi/10.1002/jbmr.253/pdf[3]. Accessed September 17, 2010.

Related Information

- Bisphosphonates (marketed as Actonel, Actonel+Ca, Aredia, Boniva, Didronel, Fosamax, Fosamax+D, Reclast, Skelid, and Zometa) Information[4]
- FDA Drug Safety Communication: Ongoing safety review of oral bisphosphonates and atypical subtrochanteric femur fractures[5]
- Possible Fracture Risk With Osteoporosis Drugs[6]
- FDA: Possible increased risk of thigh bone fracture with bisphosphonates[7]
- Risk Evaluation and Mitigation Strategies (REMS) Letters to Sponsor/Applicants Requesting Labeling Changes[8]

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2. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203891.htm
3. http://onlinelibrary.wiley.com/doi/10.1002/jbmr.253/pdf
4. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm101551.htm
5. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203891.htm
6. http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm229127.htm
7. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm229171.htm
8. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm148710.htm
9. http://www.fda.govhttps://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm
10. http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf

U.S. Food and Drug Administration

News & Events

FDA NEWS RELEASE

For Immediate Release: Oct. 12, 2010
Media Inquiries: Shelly Burgess, 301-796-4651, shelly.burgess@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves injectable drug to treat opioid-dependent patients

The U.S. Food and Drug Administration today approved Vivitrol to treat and prevent relapse after patients with opioid dependence have undergone detoxification treatment.

Vivitrol is an extended-release formulation of naltrexone administered by intramuscular injection once a month. Naltrexone works to block opioid receptors in the brain. It blocks the effects of drugs like morphine, heroin, and other opioids. It was approved to treat alcohol dependence in 2006.

"Addiction is a serious problem in this country, and can have devastating effects on individuals who are drug-dependent, and on their family members and society," said Janet Woodcock, M.D., director of FDA's Center for Drug Evaluation and Research. "This drug approval represents a significant advancement in addiction treatment."

The safety and efficacy of Vivitrol were studied for six months, comparing Vivitrol treatment to placebo treatment in patients who had completed detoxification and who were no longer physically dependent on opioids. Patients treated with Vivitrol were more likely to stay in treatment and to refrain from using illicit drugs. Thirty-six percent of the Vivitrol-treated patients were able to stay in treatment for the full six months without using drugs, compared with 23 percent in the placebo group.

Patients must not have any opioids in their system when they start taking Vivitrol; otherwise, they may experience withdrawal symptoms from the opioids. Also, patients may be more sensitive to opioids while taking Vivitrol at the time their next scheduled dose is due. If they miss a dose or after treatment with Vivitrol has ended, patients can accidentally overdose if they restart opioid use.

Side effects experienced by those using Vivitrol included nausea, tiredness, headache, dizziness, vomiting, decreased appetite, painful joints, and muscle cramps. Other serious side effects included reactions at the site of the injection, which can be severe and may require surgical intervention, liver damage, allergic reactions such as hives, rashes, swelling of the face, pneumonia, depressed mood, suicide, suicidal thoughts, and suicidal behavior.

Vivitrol should be administered only by a physician as an intramuscular injection, using special administration needles that are provided with the product. Vivitrol should not be injected using any other needle. The recommended dosing regimen is once a month.

Consumers and health care professionals are encouraged to report adverse events to the FDA's MedWatch program at 800-FDA-1088 or online at www.fda.gov/medwatch/how.htm[1].

Vivitrol is manufactured by Alkermes, Inc.

For more information:

- Drugs@FDA[2]

#

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1. http://www.fda.gov/medwatch/how.htm
2. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
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4. http://www.fda.gov/AboutFDA/ContactFDA/StayInformed/RSSFeeds/PressReleases/rss.xml
5. http://www.fda.gov/AboutFDA/ContactFDA/StayInformed/RSSFeeds/ucm144575.htm

U.S. Food and Drug Administration

Drugs

FDA reminder to avoid concomitant use of Plavix (clopidogrel) and omeprazole

Please note this is not a Drug Safety Communication, rather just a reminder of our recommendations from the previous DSC. It is posted on the Plavix Information[1] page.

The U.S. Food and Drug Administration (FDA) is reminding the public that it **continues to warn against the concomitant use of Plavix (clopidogrel) and omeprazole** because the co-administration can result in significant reductions in clopidogrel's active metabolite levels and antiplatelet activity. This information was added to the drug label of Plavix in November 2009, and has been the source of continued discussion in the medical literature.[1]

Patients at risk of heart attacks or strokes, who are given Plavix to prevent blood clots, will not get the full anti-clotting effect if they also take omeprazole. Omeprazole is found in prescription products (Prilosec, Zegerid, and generic products) and over-the-counter products (Prilosec OTC, Zegerid OTC, and generic products).

FDA wishes to emphasize additional facts that may be a source of confusion among healthcare professionals:

- With regard to the proton pump inhibitor (PPI) drug class, this recommendation **applies only to omeprazole** and not to all PPIs. Not all PPIs have the same inhibitory effect on the enzyme (CYP 2C19) that is crucial for conversion of Plavix into its active form.
- Pantoprazole (Protonix) may be an alternative PPI for consideration. It is a weak inhibitor of CYP2C19 and has less effect on the pharmacological activity of Plavix than omeprazole.

For more information, see FDA's previous Drug Safety Communication on the Plavix-omeprazole interaction[2].

[1]Bhatt, DL, Cryer, BL, Contant, CF, et al. Clopidogrel with or without Omeprazole in Coronary Artery Disease; NEJM, 2010; epub ahead of print.

Related Information

- FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug[3]
- Information on Clopidogrel Bisulfate (marketed as Plavix)[4]

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3. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203888.htm
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U.S. Food and Drug Administration

Safety

Fentanyl Transdermal System: Recall - Potential for Active Ingredient to Release Faster Than Specified

[Posted 10/22/2010]

AUDIENCE: Pharmacist, Anesthesia

ISSUE: FDA notified healthcare professionals and patients that laboratory testing identified a patch that released its active ingredient faster than the approved specification. An accelerated release of Fentanyl can lead to adverse events for at-risk patients, including excessive sedation, respiratory depression, hypoventilation (slow breathing), and apnea (temporary suspension of breathing).

BACKGROUND: Fentanyl Transdermal System is indicated for the management of persistent, moderate to severe chronic pain that requires continuous, around-the-clock opioid administration for an extended period of time and cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate release opioids. The product is manufactured for Actavis by Corium International in the United States.

RECOMMENDATION: Wholesalers and retailers are being asked to return the product they have on hand or in stock. See the Press Release for recalled product lots. The Control/Lot number appears on the bottom of the product box and on the black and white side of each individual patch packaging, in the lower left corner.

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

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

[10/21/2010 - Press Release[3] - Actavis Inc.]

Links on this page:

1. http://www.fda.gov/MedWatch/report.htm
2. http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm
3. http://www.fda.gov/Safety/Recalls/ucm230498.htm

U.S. Food and Drug Administration

Safety

Invirase (saquinavir): Label Change - Risk of Abnormal Heart Rhythm

[Posted 10/21/2010]

AUDIENCE: Cardiology, Infectious Disease

ISSUE: FDA notified healthcare professionals of new risk information added to the Warnings and Precautions, Contraindications, and Clinical Pharmacology sections of the antiviral drug Invirase (saquinavir), describing a potential change in the electrical activity of the heart when Invirase is used with another antiviral medication, Norvir (ritonavir). Changes in the electrical activity of the heart may lead to abnormal heart rhythms, known as prolonged QT or PR intervals. A prolonged QT interval can lead to a serious abnormal rhythm called torsades de pointes, which can be fatal. A prolonged PR interval can lead to a serious abnormal rhythm called complete heart block. Torsades de pointes and complete heart block have been reported in patients taking Invirase with Norvir.

BACKGROUND: The medications Invirase and Norvir are given together to treat HIV infection. Norvir must be given at a low dose with Invirase in order to increase the level of Invirase in the body. In February 2010, FDA announced it was reviewing clinical trial data about a potentially serious effect on the heart from the use of Invirase in combination with Norvir.This new information was derived from a clinical study designed to study a drug's impact on the electrical activity of the heart.

RECOMMENDATION: Patients at particular risk are those with underlying heart conditions or those who have existing heart rate or rhythm problems. An electrocardiogram should be performed prior to initiation of treatment. Physicians consider whether ongoing EKG monitoring is appropriate for patients and when it should be done. The Data Summary in the Drug Safety Communication provides more details.

FDA will require that a Medication Guide be given to patients when picking up a prescription for Invirase. The Medication Guide will include information on the risk of abnormal heart rhythms.

[10/21/2010 - Drug Safety Communication[1] - FDA]

Previous MedWatch Alert:

[02/23/2010 - Invirase (saquinavir): Ongoing safety review of clinical trial data[2]]

Links on this page:

1. http://www.fda.gov/Drugs/DrugSafety/ucm230096.htm
2. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm201563.htm

U.S. Food and Drug Administration

News & Events

FDA NEWS RELEASE

For Immediate Release: Oct. 19, 2010
Media Inquiries: Sandy Walsh, 301-796-4669; sandy.walsh@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves Pradaxa to prevent stroke in people with atrial fibrillation

The U.S. Food and Drug Administration today approved Pradaxa capsules (dabigatran etexilate) for the prevention of stroke and blood clots in patients with abnormal heart rhythm (atrial fibrillation).

Atrial fibrillation, which affects more than 2 million Americans, involves very fast and uncoordinated contractions of the heart's two upper heart chambers (atria) and is one of the most common types of abnormal heart rhythm.

"People with atrial fibrillation are at a higher risk of developing blood clots, which can cause a disabling stroke if the clots travel to the brain," said Norman Stockbridge, M.D., Ph.D., director of the Division of Cardiovascular and Renal Products in the FDA's Center for Drug Evaluation and Research.

Pradaxa is an anticoagulant that acts by inhibiting thrombin, an enzyme in the blood that is involved in blood clotting. The safety and efficacy of Pradaxa were studied in a clinical trial comparing Pradaxa with the anticoagulant warfarin. In the trial, patients taking Pradaxa had fewer strokes than those who took warfarin.

"Unlike warfarin, which requires patients to undergo periodic monitoring with blood tests, such monitoring is not necessary for Pradaxa," Stockbridge says.

As with other approved anti-clotting drugs, bleeding, including life-threatening and fatal bleeding, was among the most common adverse reactions reported by patients treated with Pradaxa. Gastrointestinal symptoms, including an uncomfortable feeling in the stomach (dyspepsia), stomach pain, nausea, heartburn, and bloating also were reported.

Pradaxa was approved with a Medication Guide that informs patients of the risk of serious bleeding. The guide will be distributed each time a patient fills a prescription for the medication.

Pradaxa, manufactured by Boehringer Ingelheim Pharmaceuticals Inc. of Ridgefield, Conn., will be available in 75 milligram and 150 milligram capsules.

For more information:

National Heart, Lung, and Blood Institute – What is Atrial Fibrillation?[1]

Approved Drugs: Questions and Answers [2]

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U.S. Food and Drug Administration

Drugs

FDA Drug Safety Communication: Update to Ongoing Safety Review of GnRH Agonists and Notification to Manufacturers of GnRH Agonists to Add New Safety Information to Labeling Regarding Increased Risk of Diabetes and Certain Cardiovascular Diseases

Safety Announcement

[10-20-2010] The U.S. Food and Drug Administration (FDA) has notified the manufacturers of the Gonadotropin-Releasing Hormone (GnRH) agonists of the need to add new safety information to the *Warnings and Precautions* section of the drug labels. This new information warns about increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) in men receiving these medications for the treatment of prostate cancer. FDA's notification to manufacturers of GnRH agonists to add this safety information is based on the Agency's review of several published studies[1-7], described in the Agency's Ongoing Safety Review of GnRH Agonists and possible increased risk of diabetes and certain cardiovascular diseases[1], issued in May 2010.

GnRH agonists are approved to treat the symptoms (palliative treatment) of advanced prostate cancer. The benefits of GnRH agonist use for earlier stages of prostate cancer that have not spread (non-metastatic prostate cancer) have not been established.

Although the risk for diabetes and cardiovascular diseases appears to be low in men receiving GnRH agonists for prostate cancer, it is important for healthcare professionals to evaluate patients for risk factors for these diseases. Healthcare professionals should always carefully weigh the benefits and risks of using GnRH agonists before determining appropriate treatment for prostate cancer.

Patients who are receiving treatment with GnRH agonists should undergo periodic monitoring of blood glucose and/or glycosylated hemoglobin (HbA1c). Increased blood glucose levels may represent development of diabetes or worsening of blood glucose control in patients with diabetes. Healthcare professionals should also monitor patients for signs and symptoms suggestive of development of cardiovascular disease and manage according to current clinical practice.

Additional Information for Patients

- GnRH agonists are sold as the brand names – Lupron, Zoladex, Trelstar, Viadur, and Eligard.
- Before receiving GnRH agonists, tell your healthcare professional if you have diabetes, heart disease, a previous heart attack or stroke, or any cardiovascular risk factors like high blood pressure, high cholesterol, or cigarette smoking.
- If you have any concerns about receiving these medicines, talk to your healthcare professional.
- Report any side effects from the use of GnRH agonists to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page.

Additional Information for Healthcare Professionals

- Most of the studies reviewed by FDA reported small, but statistically significant increased risks of diabetes and/or cardiovascular events in patients receiving GnRH agonists.
- Carefully weigh the known benefits and risks of GnRH agonists when determining appropriate treatment for prostate cancer.
- Monitor blood glucose and/or glycosylated hemoglobin periodically in patients receiving GnRH agonists.
- Monitor patients for signs and symptoms suggestive of development of cardiovascular disease.
- Ensure that cardiovascular risk factors such as cigarette smoking, high blood pressure, high cholesterol, high blood sugar, and being overweight are managed according to current clinical practice.
- Report adverse events involving GnRH agonists to the FDA MedWatch program using the information in the "Contact Us" box at the bottom of this page.

Data Summary

FDA's decision to notify sponsors that new safety information be added regarding increased risk of diabetes and certain cardiovascular diseases to the *Warnings and Precautions* section of the drug labels for GnRH agonists is based on the Agency's review of several published studies[1-7] and a Science Advisory[8] described in the Agency's May 2010 Ongoing Safety Review of GnRH Agonists and possible increased risk of diabetes and certain cardiovascular diseases[2].

References

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2. Keating NL, O'Malley JO, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of Veterans with prostate cancer. *J Natl Cancer Inst*. 2010;102:39-46.
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8. Levine GN, D'Amico AV, Berger P, Clark PE, Eckel RH, Keating NL, et al on behalf of the American Heart Association Council on Clinical Cardiology and Council on Epidemiology and Prevention, the American Cancer Society, and the American Urological Association. Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology. *Circulation*. 2010;121:833-840.

Related Information

- FDA Drug Safety Communication: Ongoing Safety Review of GnRH Agonists and possible increased risk of diabetes and certain cardiovascular diseases[3]

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U.S. Food and Drug Administration

News & Events

FDA NEWS RELEASE

For Immediate Release: Oct. 15, 2010
Media Inquiries: Sandy Walsh, 301-796-4669; sandy.walsh@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves Botox to treat chronic migraine

The U.S. Food and Drug Administration today approved Botox injection (onabotulinumtoxinA) to prevent headaches in adult patients with chronic migraine. Chronic migraine is defined as having a history of migraine and experiencing a headache on most days of the month.

"Chronic migraine is one of the most disabling forms of headache," said Russell Katz, M.D., director of the Division of Neurology Products in the FDA's Center for Drug Evaluation and Research. "Patients with chronic migraine experience a headache more than 14 days of the month. This condition can greatly affect family, work, and social life, so it is important to have a variety of effective treatment options available."

Migraine headaches are described as an intense pulsing or throbbing pain in one area of the head. The headaches are often accompanied by nausea, vomiting, and sensitivity to light and sound. Migraine is three times more common in women than in men. Migraine usually begins with intermittent headache attacks 14 days or fewer each month (episodic migraine), but some patients go on to develop the more disabling chronic migraine.

To treat chronic migraines, Botox is given approximately every 12 weeks as multiple injections around the head and neck to try to dull future headach symptoms. Botox has not been shown to work for the treatment of migraine headaches that occur 14 days or less per month, or for other forms of headache. It is important that patients discuss with their physician whether Botox is appropriate for them.

The most common adverse reactions reported by patients being treated for chronic migraine were neck pain and headache.

OnabotulinumtoxinA, marketed as Botox and Botox Cosmetic, has a boxed warning that says the effects of the botulinum toxin may spread from the area of injection to other areas of the body, causing symptoms similar to those of botulism. Those symptoms include swallowing and breathing difficulties that can be life-threatening. There has not been a confirmed serious case of spread of toxin effect when Botox has been used at the recommended dose to treat chronic migraine, severe underarm sweating, blepharospasm, or strabismus, or when Botox Cosmetic has been used at th recommended dose to improve frown lines.

Botox is manufactured by Allergan Inc. of Irvine, Calif.

For more information:

National Institute of Neurological Disorders and Stroke: Hope Through Research[1]

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