

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206289Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review for NDA 206289

<b>Date</b>	June 26, 2014
<b>From</b>	William M. Boyd, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA #</b>	206289
<b>Applicant</b>	Akorn, Inc.
<b>Date of Submission</b>	10/22/13
<b>PDUFA Goal Date</b>	4/30/14
<b>Type of Application</b>	505(b)(2)
<b>Name</b>	Atropine Ophthalmic Solution
<b>Dosage forms / Strength</b>	Ophthalmic solution, 1%
<b>Proposed Indication(s)</b>	For use in creating pupillary dilation, cycloplegia, and in the treatment of amblyopia
<b>Recommended:</b>	Recommended for Approval

### 1. Introduction

Atropine ophthalmic solution has been used for pupillary dilation and cycloplegia for over 100 years.

Atropine is a reversible antagonist of muscarine-like actions of acetyl-choline and is therefore classified as an antimuscarinic agent. Atropine is relatively selective for muscarinic receptors. Its potency at nicotinic receptors is much lower, and actions at non-muscarinic receptors are generally undetectable clinically. Atropine does not distinguish among the M1, M2, and M3 subgroups of muscarinic receptors.

The pupillary constrictor muscle depends on muscarinic cholinergic activation. This activation is blocked by topical atropine resulting in unopposed sympathetic dilator activity and mydriasis. Atropine also weakens the contraction of the ciliary muscle, or cycloplegia. Cycloplegia results in loss of the ability to accommodate such that the eye cannot focus for near vision.

### 2. Background

This is a 505(b)(2) application. Atropine ophthalmic solution is currently marketed by the applicant and a number of other manufacturers without approved new drug applications. Other dosage forms of atropine are marketed in the United States. Some with approved new drug applications and others without approved new drug applications.

Pupillary dilation and cycloplegia impair visual function. When these actions are necessary for greater than 72 hours either for diagnostic or therapeutic action, there are no pharmacologic alternatives. When maximal cycloplegia is required, there are no therapeutic alternatives.

### 3. CMC

**Drug Product Formulation:**

Ingredient	Function	mg/mL
Atropine sulfate (b) (4)	Active	10.0 mg*
Hypromellose 2910	(b) (4)	(b) (4)
Benzalkonium Chloride	Preservative	0.1 Mg
Dibasic sodium phosphate (b) (4)	(b) (4)	(b) (4)
Monobasic sodium phosphate (b) (4)	(b) (4)	(b) (4)
Edetate Disodium	(b) (4)	(b) (4)
Sodium hydroxide	pH adjuster	To adjust pH 3.5 to 6.0
Hydrochloric acid	pH adjuster	To adjust pH 3.5 to 6.0
Water for injection	(b) (4)	(b) (4)

\*Quantity equivalent to 10 mg/mL of Atropine Sulfate (b) (4)

**Drug Product Specifications:**

Parameter	Target	Range
(b) (4)		

From the CMC Review finalized 4/4/2014:

The drug substance information is referenced to (b) (4) (b) (4) (b) (4) updated the DMF on November 2013 to update the specification to align with the current USP monograph which became effective August 1, 2013. Batch analysis of all four batches of the drug substance used by Akorn complied with the current drug substance specification. Therefore, DMF (b) (4) is adequate to support NDA 206289.

Atropine Sulfate Ophthalmic solution USP, 1% is a sterile, (b) (4) and preserved aqueous solution formulated for topical application. Each milliliter of Atropine Sulfate Ophthalmic Solution USP, 1% contains atropine sulfate (b) (4) USP, 1% (10 mg/mL) and the following inactives: Hypromellose (b) (4) (2910), Dibasic Sodium Phosphate (b) (4), Monobasic Sodium Phosphate (b) (4), Edetate Disodium, Water for Injection, Hydrochloric Acid and/or Sodium Hydroxide to adjust the pH. Benzalkonium Chloride, 0.01% (0.1 mg/mL) is used as preservative. All excipients are compendial.

Atropine Sulfate Ophthalmic Solution USP, 1%, has acceptable stability for at least 18 months for all three configuration sizes (2 mL in 6 mL bottle, 5 mL in 6 mL bottle and 15 mL in 15 mL bottle) when stored at 25°C ± 2 °C.

On June 26, 2014, an overall acceptable recommendation was issued in EES for NDA 206289. All facilities have been found acceptable.



## 4. Nonclinical Pharmacology/Toxicology

From the Pharmacology/Toxicology Review finalized 4/3/2014:

The applicant filed the NDA as a 505(b)(2) application. All nonclinical pharmacology/toxicology data included in the application are derived from published literature sources. The receptors antagonized by atropine are the peripheral structures that are stimulated or inhibited by muscarine (i.e., exocrine glands and smooth and cardiac muscle). Findings in nonclinical studies reflect this mechanism of action including mydriasis, tachycardia, decreased water intake, water retention and decreased urine volume. Decreased salivation was also observed. Chronic exposure results in decreased weight gain and death at doses much higher than those expected following topical ophthalmic exposure.

Publications submitted by the applicant indicate that atropine sulfate showed no genotoxic potential and was not carcinogenic.

The systemic administration of atropine was associated with decreases in male fertility. Nonclinical data suggest anticholinergic effects on contraction of vas deferens and seminal vesicle during emission resulting in decreased sperm volume and altered composition of the ejaculate. Administration of atropine in female rats resulted in marked vascular congestion, epithelial necrosis and fibrous tissue proliferation of the uterine tissue. Atropine administration was associated with a reduction of uterine parameters like uterine diameter, thickness of myometrium and endometrium and surface epithelial cell height. The results suggest that the anticholinergic effects of atropine may interfere with the rhythmic release of pituitary gonadotropins and result in decreased estrogen.

Teratology studies of atropine were limited. A sub-study in mice in a single publication reported that exposure to atropine on Day 8 or Day 9 of gestation was associated with an increase in skeletal anomalies which included one occurrence of axial skeletal fusion and one occurrence of a soft tissue anomaly, exencephaly. The authors of the paper, however, concluded that atropine alone was not teratogenic. Given the low incidence of each anomaly and inadequate study design, a definitive conclusion regarding teratogenicity cannot be reached.

## 5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review finalized 4/3/2014:

Atropine is an anticholinergic agent that is capable of blocking muscarinic receptors on the iris sphincter muscle and the ciliary muscle controlling lens curvature, resulting in pupil dilation (mydriasis) and temporary paralysis of accommodation (cycloplegia). Although extracts

containing atropine had been used since ancient times for pupil dilation, the isolation and accurate characterization of the anticholinergic effects of atropine in its pure form did not occur until the 1800's.

Based on the review of available clinical pharmacokinetic (PK) and pharmacodynamic (PD) literature data, as well as efficacy/safety data from published clinical trials for 1% atropine sulfate ophthalmic solutions, the Clinical Pharmacology reviewer recommends the approval of the proposed 1% atropine sulfate ophthalmic solution for producing mydriasis and/or cycloplegia in adult patients and pediatric patients.

## 6. Sterility Assurance

From the Product Quality Microbiology Review dated 2/24/14:

(b) (4)  
No product quality microbiology deficiencies were identified based upon the information provided.

## 7. Clinical/Statistical - Efficacy

From the original Medical Officer Review dated 4/7/2014:

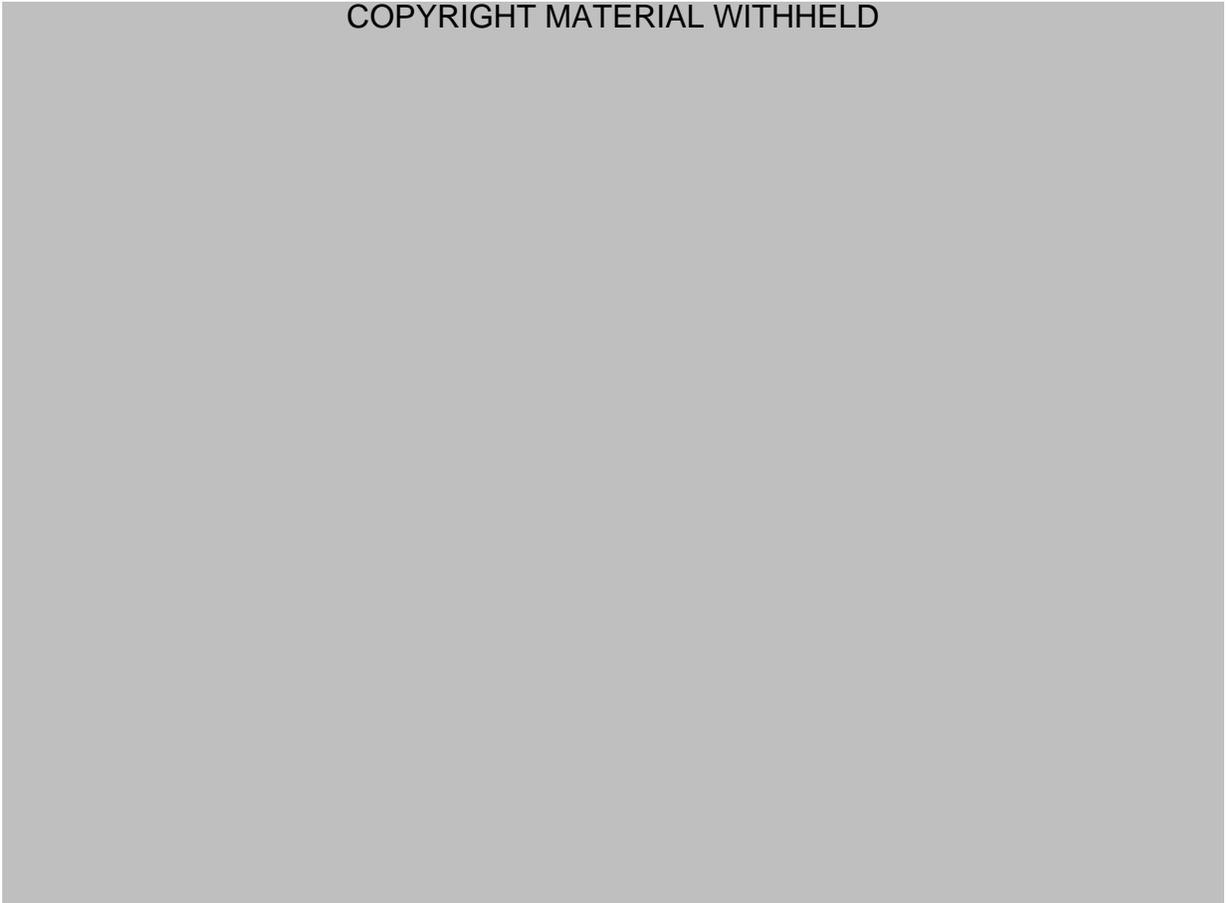
Representative clinical studies were identified. These studies include subjects from two months through 92 years in age, multiple races, ethnicities and eye colors. These studies are all relevant to the proposed product because they are studies conducted with atropine solution 1%. The active ingredient is chemically the same as the proposed product and the product is dosed topically to the cornea, directly adjacent to the site of action (iris and ciliary body). The exact formulation for each of the referenced studies relied on to support the safety or efficacy is unknown. It is likely that the individual products were made by multiple different manufacturers over the span of 150 years and the formulations are not exactly the same.

<b>Study</b>	<b>Indication</b>	<b>Design</b>	<b>Arms (# of subjects)</b>
Barbee 1957	Pupil dilation Cycloplegia	Non-randomized Double-blind	Atropine 1% Plus 9 other agents Total of 300 patients
Chia 2012	Pupil dilation Cycloplegia	Randomized Double-blind	Atropine 0.5% (161) Atropine 0.1% (155) Atropine 0.01% (84)
Ebri 2007	Pupil dilation Cycloplegia	Randomized Parallel groups	Atropine 1% (79) Cyclopentolate 1% +Tropicamide 0.5% 78) Cyclopentolate 1% (76)
Marron 1940	Pupil dilation Cycloplegia	Non-randomized	Atropine 1% (107) Scopolamine 0.5% (21) Homatropine 5% (25)
Wolf 1946	Pupil dilation Cycloplegia	Non-randomized Open label	Atropine 1% 15 eyes (13) Methylatropine 1% 23 eyes(21) Homatropine 1% 7 eyes (7)
Kawamoto 1997	Cycloplegia	Sequential groups	Atropine 0.5% (<6yrs old) or 1% (6 and older) Cyclopentolate 1% Total of 51 children
Stolovitch 1992	Cycloplegia	Subject own control /comparison to baseline	Atropine 1% (36)
Pediatric Eye Disease Group 2008	Amblyopia	Randomized Parallel groups Blinded assessment	Atropine 1% (95) Patching (98)

## **Mydriasis and Cycloplegia Indications**

**Barbee 1957    Double-blind, placebo controlled**

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The parasympatholytic agents, scopolamine, atropine and homatropine all induced significant mydriasis of essentially equal degrees in all three eye types.

**Chia 2012 Randomized, Double-blind, 2 year study; Atropine 0.5% (161 subjects), Atropine 0.1% (155 subjects), Atropine 0.01% (84 subjects)**

Accommodation (D)	0.01%	0.1%	0.5%
Baseline	16.2 (3.4)	16.7 (3.0)	15.8 (3.4)
Year 1	11.7 (4.3)	6.0 (3.4)	3.6 (3.2)
Year 2	11.8 (3.2)	6.8 (3.4)	4.0 (2.6)
Mesopic pupil diameter (mm)			
Baseline	3.9 (0.6)	3.9 (0.6)	4.0 (0.7)
Year 1	5.1 (0.9)	6.7 (1.0)	7.5 (1.1)
Year 2	5.1 (0.9)	6.7 (1.1)	7.5 (1.2)
Photopic pupil diameter (mm)			
Baseline	4.7 (0.7)	4.6 (0.7)	4.6 (0.7)
Year 1	5.6 (0.8)	7.0 (1.0)	7.7 (1.0)
Year 2	5.5 (0.8)	6.9 (1.0)	7.8 (1.1)

This study demonstrates a dose response in both decreasing accommodation and increasing pupil diameters.

**Ebri 2007 Randomized, Parallel, Active control. Atropine 1% (79 eyes), Cyclopentolate 1%+Tropicamide 0.5% (78 eyes), Cyclopentolate 1% (76 eyes)**

	Cyclopentolate	Cyclopentolate 1% Tropicamide 0.5% Combined Regimen	Atropine 1%
Residual accommodation			
0.0-0.5 D	41 (54%)	55 (71%)	70 (100%)
>0.5-1D	24 (32%)	19 (25%)	0
>1.0-1.5D	8 (11%)	2 (3%)	0
>1.5D	3 (4%)	1 (1%)	0
Dilated pupil size			
< 6 mm	36 (47%)	5 (6%)	0
≥ 6 mm	40 (53%)	72 (94%)	70 (100%)
Response to light			
Negative	19 (25%)	51 (66%)	68 (97%)
Positive	57 (75%)	26 (34%)	2 (3%)

The study demonstrates superiority of Atropine 1% over Cyclopentolate in both mydriasis and reduction of accommodation.

**Narvaez J 2010 Pupil dilation using a standard cataract surgery regimen alone or with atropine 1.0% pretreatment**

Prospective, unmasked study, the baseline pupil size in 72 eyes of 54 volunteers (age 21-92) was measured. Pupil size was then measured 30 minutes after instillation of phenylephrine 2.5%, tropicamide 1.0%, and cyclopentolate 1.0%. Several days later, the subjects returned for repeat measurements after pretreating the study eye(s) with atropine 1%, 3 times a day the day previously and once on the morning of repeat dilation and measurements. Pupil size was again measured after administration of the standard regimen.

	Diameter (mm)	
Baseline pupil size	4.1 ± 0.7	CI (3.9-4.3)
Atropine	6.9 ± 1.2	CI (6.9-7.3)
Phenylephrine, tropicamide, and cyclopentolate	7.3 ± 1.2	CI (7.0-7.7)

Pupil increases with atropine were clinically significant, but less than the triple combination of phenylephrine 2.5%, tropicamide 1.0%, and cyclopentolate 1.0%.

**Marron 1940 Atropine 1% (107 eyes), Scopolamine 0.5% (21 eyes), Homatropine 5% (25 eyes)**

Atropine: (10 drops)	Duration of Maximum Cycloplegia	8-24 hours
	Time at Which Patient First Reads	3 days
	Accommodation Normal	18 days
	Full Mydriasis	40 minutes
	Duration of Full Mydriasis	8 hours
	Time when normal diameter appears	12 days
Scopolamine (10 drops)	Duration of Maximum Cycloplegia	40 minutes
	Time at Which Patient First Reads	3 days
	Accommodation Normal	8 days
	Full Mydriasis	20 minutes
	Duration of Full Mydriasis	8 hours
	Time when normal diameter appears	8 days
Homatropine Paredrine	Duration of Maximum Cycloplegia	50 minutes
	Time at Which Patient First Reads	6 hours
	Accommodation Normal	36 hours
	Full Mydriasis	30 minutes
	Duration of Full Mydriasis	95 minutes
	Time when normal diameter appears	48 hours

Administration of atropine 1% resulted in clinically significant mydriasis within 40 minutes and clinically significant cycloplegia for at least 8 hours.

**Wolf 1946 Atropine 1% 15 eyes, Methylatropine 1% 23 eyes, Homatropine 1% 7 eyes**

	Initial		Time to Max		Maximum	Residual
	Pupil	Mydriasis	Cycloplegia	Pupillary Diameter	Accommodation	
Atropine	3.4	40 min	5 hr	8.3	0.21	
Methylatropine	3.3	50 min	5 hr	7.7	0.29	
Homatropine	3.4	40 min	25 min	5.9	0.55	

	Recovery Time	
	Mydriasis	Cycloplegia
Atropine	6 hours	1 day
Methylatropine	6 hours	6 hours
Homatropine	6 hours	1 hour

Clinically significant pupil dilation occurred within 40 minutes and lasted for at least 6 hours.  
 Clinically significant cycloplegia occurred within 5 hours lasting for at least one day.

**Riddell WJB 1946 A Clinical Trial of a Synthetic Mydriatic**

The size of the pupils was estimated by means of the pupillometer fitted to the driving wheel of a Morton ophthalmoscope before the drops were placed in the eyes. In five subjects two drops of E.3 were placed in the right eye and two drops of atropine in the left eye. Readings were taken of the size of the pupils at time intervals up to seven days.

Pupil Size (mm)	Hours												
	0	¼	½	1	2	4	5	6	8	10	15	20	21
E.3	4.2	5	5.9	8.2	7.7	7.5	8	7.5	7.7				5
Atropine 1%	4.2	7	8.2	8.3	7.7	7	9	7	8.3				8

Pupil Size (mm)	Days					
	2	3	4	5	6	7
E.3	4.7	3.8	4	3.7	3.8	4.3
Atropine 1%	7.9	7.3	6.7	5.8	6	5.7

Clinically significant pupil dilation occurred for a duration of at least 4 days.

**Kawamoto 1997 Atropine 0.5% (<6yrs old), 1% (6 and older), Cyclopentolate 1%  
 Total of 102 eyes of 51 children. Sequential treatment separated by 2-4 months.**

C	Mean Refraction	50 eyes	52 eyes
		Children younger than 6 years	Children older than 6 years
Cyclopentolate		+2.89	+1.83
Atropine 1%			+2.60
Atropine 0.5%		+3.55	
Difference		0.66	0.77

The difference in mean refraction represents a difference in accommodation. For each group, treatment with atropine resulted in greater accommodative loss.

**Farhood 2012 Cycloplegic Refraction in Children with Cyclopentolate vs Atropine**

Objective: To evaluate the safety and efficacy of two cycloplegic regimens in hyperopic children. The responses to cycloplegia in different age groups and presence of strabismus were also compared.

Methods: Atropine eye drops 1% bid x 3 days, later followed by cyclopentolate eye drops 1% was evaluated in fifty children aged 3 to 8 years old. Cycloplegic refractions were assessed.

Results: The total refractions were recorded after cycloplegia with atropine 1% or cyclopentolate 1% eye drops. Atropine refraction (mean+3.89 ± 2.45 D) and cyclopentolate refraction (mean +3.58 ± 2.30 D).

Atropine provided clinically important cycloplegia.

**Hiatt RL 1983 Comparison of Atropine and Tropicamide in Esotropia**

Forty-one patients with esodeviation (82 eyes) were subjected first to 1% tropicamide and retinoscopy and then to retinoscopy after the use of 0.5% to 1% atropine sulfate in children from 2 months to 5 years. There were 20 male and 21 female patients. There were 11 black and 30 white patients. In all cases, there was a greater plus spherical equivalent found with atropine than with tropicamide, and it varied from +0.25 D to as much as + 1.75 D, the average being +0.80 D for the 82 eyes. In general, the higher the plus refractive error, the larger the difference found between atropine and tropicamide.

Atropine provided clinically important cycloplegia.

**Stolovitch 1992      Subject own control /comparison to baseline. Atropine 1%  
36 patients, 72 eyes. Ages 4 months to 11 years.**

Diopters of Hypermetropia found after Four or Eight Instillations of Atropine

Eye	No of Instillations	Mean
RE	8	+2.93
RE	4	+2.91
LE	8	+3.29
LE	4	+3.28

This study demonstrates that no additional cycloplegic effect occurs between 4 and 8 doses of atropine.

**Auffarth G 1992      Cycloplegic refraction in children: Single-dose-atropinization versus three  
day atropinization**

Refractive measurements under atropine cycloplegia were tested in 90 strabismic children aged two to seven years. Refraction was determined by an autorefractor 90 minutes after application of two drops of atropine (0.5% atropine children <2.5 years; 1.0% atropine children >2.5years) and compared with the results after 3 days of receiving 1 atropine eye drops 3 times daily. In 86.5% the spherical equivalents differ not more than 1.0 diopter ( $p = 0.05$ ); the correlation was 0.99. Astigmatic corrections were in agreement in 95.5%, the axis of cylinders in 93.0%; the correlations were 0.95 and 0.97. The residual accommodation 90 minutes after 2 drops of atropine was not more than 1 diopter in all children. The additional cycloplegic effect of the three-day-atropinization was only 0.5 diopters.

This article supports the conclusion that 3 days of atropinization is not usually necessary.

## Treatment of Amblyopia

### **Pediatric Eye Disease Group 2008      Randomized Parallel groups masked assessment Atropine 1% vs Patching**

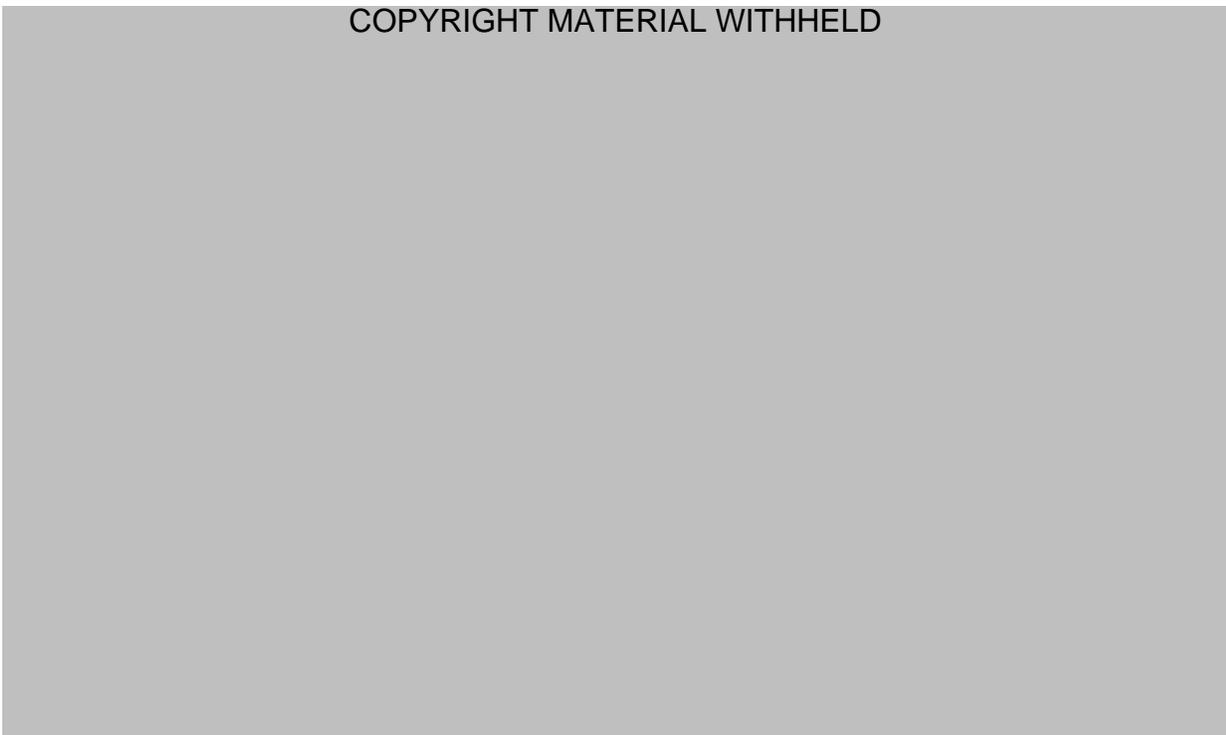
**Objective:** To compare patching with atropine eye drops in the treatment of moderate amblyopia (visual acuity, 20/40-20/100) in children aged 7 to 12 years.

**Methods:** Randomized, multicenter clinical trial, 193 children with amblyopia were assigned to receive weekend atropine or patching of the sound eye 2 hours per day.

**Main Outcome Measure:** Masked assessment of visual acuity in the amblyopic eye using the electronic Early Treatment Diabetic Retinopathy Study testing protocol at 17 weeks.

Results: At 17 weeks, visual acuity had improved from baseline by an average of 7.6 letters in the atropine group and 8.6 letters in the patching group. The mean difference between groups (patching – atropine) adjusted for baseline acuity was 1.2 letters (ends of complementary 1-sided 95% confidence intervals for non-inferiority, -0.7, 3.1 letters). This difference met the pre-specified definition for equivalence (confidence interval  $\leq 5$  letters). Visual acuity in the amblyopic eye was 20/25 or better in 15 participants in the atropine group (17%) and 20 in the patching group (24%; difference, 7%; 95% confidence interval, -3% to 17%).

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Cumulative distribution of visual acuity scores in the amblyopic eye at the 17-week outcome examination, according to treatment group.

Treatment with atropine or patching led to similar degrees of improvement among 7- to 12-year-olds with moderate amblyopia. About 1 in 5 achieved visual acuity of 20/25 or better in the amblyopic eye.

This study demonstrates a clinically significant improvement in visual acuity achieved by penalization of the eye with better visual function.

(b) (4)

### **Efficacy Summary Statement**

Multiple adequate and well controlled studies demonstrate the efficacy of atropine solution 1% in producing clinically significant mydriasis and cycloplegia. These studies, along with the single adequate and well controlled study in the treatment of amblyopia, are also sufficient to support the efficacy in the treatment of amblyopia because the effectiveness of the treatment of amblyopia is a result of visual penalization due to cycloplegia.

The use of atropine solution 1% for the treatment of (b) (4) is not supported in the available literature.

## 8. Safety

From the original Medical Officer Review dated 4/7/2014:

Studies have been conducted to evaluate the effect of atropine on the eyes for over 160 years. Studies range from evaluations of a few patients to studies of over 1500 patients. The published literature includes reviews of the adverse events of topical atropine as well as individual case reports. Mydriasis and cycloplegia studies often used one to three day regimens of administration. Studies of the treatment of (b) (4) and amblyopia used daily administrations for periods of months (amblyopia) (b) (4)

### Adverse Events

Adverse events related to the use of atropine are directly related to its anticholinergic pharmacologic properties. Atropine is an antimuscarinic. It acts directly on smooth and cardiac muscle and on exocrine glands innervated by postganglionic parasympathetic nerves blocking the action of acetylcholine.

Systemic adverse events reported include dryness of skin, mouth, and throat from decreased secretions from mucous membranes; restlessness, irritability or delirium from stimulation of the central nervous system; tachycardia; flushed skin of the face and neck.

Eye pain and stinging occurs upon instillation of atropine ophthalmic solution. Other commonly occurring adverse reactions include blurred vision, photophobia, superficial keratitis and decreased lacrimation. Allergic reactions such as papillary conjunctivitis, contact dermatitis, and lid edema may also occur less commonly.

The following are the most commonly reported and clinically significant reported adverse reactions. With the exception of the allergic reactions, all are a result of the known and expected pharmacologic action:

- Allergic reactions including contact dermatitis usually confined to the lids and conjunctiva characterized by itching, redness, swelling and discharge.
- Photophobia due to the increase in pupil size.
- Decreased tearing due to inhibition of the lacrimal gland.
- Dryness of the skin, mouth and throat due to decreased secretion from the mucous membranes.

- Restlessness, irritability or delirium due to stimulation of the central nervous system. Most are thought to be due to atropine intoxication and often associated with pre-existing mental health issues.
- Tachycardia. Low dose atropine will initially cause a slowing of the heart rate, but increased dosing can lead to tachycardia.
- Flushed skin of face and neck is an expected pharmacologic anticholinergic reaction.

## **Deaths**

Deaths have occurred rarely in young children with significant contributory medical conditions. Five reported cases of death have occurred, all in children under 3 years of age in which the patients also had severe congenital problems include a patent ductus arteriosus in two patients.

## **Safety Summary Statement**

The safety of atropine ophthalmic solution 1% in children greater than 3 months of age and in adults is supported by adequate and well controlled studies in the literature.

## **9. Advisory Committee Meeting**

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

## **10. Pediatrics**

Pediatric studies are complete and the pediatric information is provided in this NDA for Atropine Sulfate Ophthalmic Solution.

Due to the potential for systemic absorption of atropine ophthalmic solution, the use of atropine ophthalmic solution, 1% in children under the age of 3 months is not recommended and the use in children under 3 years of age should be limited to no more than one drop per eye per day.

## 11. Other Relevant Regulatory Issues

Pharmacology/Toxicology, Clinical Pharmacology, Clinical, Product Quality Microbiology and Biostatistics have recommended approval of this new drug application.

### **FINANCIAL DISCLOSURE**

This is a 505(b)(2) new drug application primarily based on literature. In accordance with 21 CFR Part 54, no financial disclosure is appropriate for this application. There are no “covered clinical studies” in this submission.

### **OSI**

An Office of Scientific Investigations (OSI) audit was not requested. This is a 505(b)(2) supplemental application primarily based on literature.

### **BIOSTATISTICS**

Per the Biostatistics consultative review finalized 3/12/2014:

The FDA clinical reviewer selected five publications that described studies demonstrating mydriasis (pupil dilation) and cycloplegia due to atropine treatment and two publications that demonstrated cycloplegia alone (Table 3.1.1).

**Table 3.1.1 Design of studies measuring responses of mydriasis and/or cycloplegia to atropine 1% ophthalmic solution**

Study	Design	Arms (# of subjects)	Atropine Dosing	Responses	Subject Population
<b>Studies that measured cycloplegia and mydriasis</b>					
Barbee 1957	NR, DB Placebo controls	Atropine 1% Plus 7 other agents & 2 placebo controls 30 pts/arm: 10 white, blue-eyed subj 10 white, brown-eyed subj 10 black, brown-eyed subj.	3 drops given in one eye	40' after drops  Dilation measured with a ruler Change in accommodation measured with Snellen rating card	Aged 16-60 yrs No ocular disease Black and white subjects Blue and brown eyed
Chia 2012	R, DB	Atropine 0.5% (161) Atropine 0.1% (155) Atropine 0.01% (84)	1 drop nightly for 2 years	Myopia progression	Aged 6-12 yrs Myopic refraction of > 2D
Ebri 2007	R, P	Atropine 1% (79) Cyclopentolate 1% +Tropicamide 0.5% (78) Cyclopentolate 1% (76)	1 drop 3x daily for 3 consecutive days	Dilation measured with a ruler Residual Accom. measured with retinoscopy (diff. subtracting near from far)	Aged 4-15 yrs Nigerian All brown eyed Presented with eye complaint
Marron 1940	NR groups of subjects for each drug	Atropine 1% (107) Scopolamine 0.5% (21) Homatropine 5% (25)	1 drop 3x daily for 3 consecutive days +1 drop AM of exam	Dilation measured with a pupillometer Accom. measured with a Prince's rule Did not report residual accom.	Aged 15-40 yrs U. of Chicago Students & faculty with eye complaint
Wolf 1946	NR Open label Incomplete Crossover	Atropine 1% 15 eyes (13) Methylatropine 1% 23 eyes (21) Homatropine 1% 7 eyes (7)	1 drop	Dilation measured with a pupillometer Accom. measured with newsprint on a slide. Resid accom measured as a ratio	Aged 16-37 yrs
<b>Studies that measured cycloplegia only</b>					
Kawamoto 1997	Sequential groups Cyclopentolate then Atropine	Atropine 0.5% (<6yrs old) or 1% Cyclopentolate 1% Total of 51 children	2x daily for 7 days	Refraction measured with autorefractometer	Aged 3-15yrs Japanese Most hyperopes (far-sighted)
Stolovitch 1992	Subject own control /comparison to baseline	Atropine 1% (36)	1 drop 3x on one day +1 drop AM of exam & repeated	Refraction measured with retinoscopy	Aged 5mos-11yrs Hyperopic Caucasian children in TelAviv

DB=Double-blind SB=Single-blind P=Parallel groups R=Randomized NR=Non-randomized

Four publications (Barbee, Ebri, Marron and Wolf) provided evidence that atropine 1% is effective at increasing dilation and decreasing accommodation in broad populations. One study (Ebri) provided strong statistical evidence of the effectiveness of atropine 1% compared to cyclopentolate 1% or tropicamide 0.5% plus cyclopentolate 1% for dilation and cycloplegia.

**OPDP**

A review of the substantially complete labeling was completed by the Office of Prescription Drug Promotion (OPDP) on 9/9/2014.

**Comment [CGC1]:** OPDP Comment: Please note that the comments on the full PI should be applied to the Highlights section as well, where applicable.

**Comment [CGC2]:** OPDP Comment: We note that this information is not communicated in the full PI Warnings and Precautions 5.2. We recommend revising for consistency between the Highlights and full PI.

**Comment [CGC3]:** OPDP Comment: We note that the full PI communicates this risk as “eye pain.” For consistency, we recommend utilizing the same language here and in the full PI. Please consider revising as necessary.

**Comment [CGC4]:** OPDP Comment: We note that the full PI also lists, “superficial keratitis” as a common adverse reaction. We recommend including this additional common adverse reaction in the Highlights.

**Reviewer Comments:** *These 4 items have been addressed in the final draft labeling.*

**Comment [CGC5]:** OPDP Comment: We are concerned that this language [ Indication 1.3] may misleadingly suggest that the drug has been found to be effective in treating and/or correcting amblyopia. We note that this drug is used for penalization, which we believe allows the patient to use/ train the amblyopic eye to see; if atropine does not treat/correct the amblyopia eye in any way, we recommend revising. Would it be more appropriate to use the language, (b) (4)

**Reviewer Comments:** *The proposed terminology, penalization of the healthy eye in the treatment of amblyopia, is medically correct. The atropine has no effect on the amblyopic eye; it is the healthy eye that is “penalized” with cycloplegia.*

**Comment [CGC6]:** OPDP Comment: Are there any recommended monitoring procedures for patients that do present with elevated blood pressure? For example, the Phenylephrine HCl Ophthalmic Solution label (NDA 203510) includes, “The post-treatment blood pressure of patients with cardiac and endocrine diseases and any patients who develop symptoms should be carefully monitored.” If applicable to atropine, we recommend including similar language.

**Reviewer Comments:** *By definition, the appropriate monitoring for elevated blood pressure is measurement of blood pressure.*

**Comment [CGC7]:** OPDP Comment: We note that this is a 505(b)(2) application. If possible, we recommend communicating the number of patients exposed to atropine, doses (or ranges if applicable) that patients received, and study design(s) for the studies included.

**Reviewer Comments:** *These suggested edits, while useful, cannot be accurately summarized for this 505(b)(2) application.*

**Comment [CGC8]:** OPDP Comment: If possible, we recommend communicating the incidence or incidence range for the most common adverse reactions associated with atropine ophthalmic solution.

**Reviewer Comments:** *These suggested edits, while useful, cannot be accurately summarized for this 505(b)(2) application.*

**Comment [CGC9]:** OPDP Comment: We note that an atropine label (NDA 01706) does not include a description of “reversible” antagonist under the Mechanism of Action (MOA) header. We would just like to confirm that this is an accurate description of the MOA of atropine.

**Reviewer Comments:** *Yes. It is accurate.*

**Comment [CGC10]:** OPDP Comment: We note that an atropine injection label (NDA 017106) states that the protein binding of atropine is 14 to 22% in plasma. We would just like to confirm that this percentage (about 44%) is correct.

**Reviewer Comments:** *Yes. It is accurate.*

**Comment [CGC11]:** OPDP Comment: If possible, please consider including specific study design information describing these “several controlled clinical studies.” Also, if possible, please consider communicating the total number of patients treated with atropine in these studies as well as the dose or dose range and duration of treatment with atropine in these studies.

**Reviewer Comments:** *These suggested edits, while useful, cannot be accurately summarized for this 505(b)(2) application.*

#### **DMEPA**

The Division of Medication Error Prevention and Analysis (DMEPA) provided a labeling review of the original package insert and original carton and container labeling.

## **12. Labeling**

NDA 206289, Atropine Ophthalmic Solution is recommended to be approved for use in creating pupillary dilation, cycloplegia, and in the treatment of amblyopia. Atropine ophthalmic solution is not recommended to be approved for the (b) (4).

The package insert (submitted 4/30/14) and carton and container labeling (submitted 4/25/14) are acceptable. See Appendix of this review.

### 13. Recommendations/Risk Benefit Assessment

**RECOMMENDED REGULATORY ACTION:**

NDA 206289, Atropine Ophthalmic Solution is recommended to be approved for use in creating pupillary dilation, cycloplegia, and in the treatment of amblyopia. Atropine ophthalmic solution is not recommended to be approved for the [REDACTED] (b) (4).

The package insert (submitted 4/30/14) and carton and container labeling (submitted 4/25/14) are acceptable.

On June 26, 2014, an overall acceptable recommendation was issued in EES for NDA 206289. All facilities have been found acceptable.

**RISK BENEFIT ASSESSMENT:**

Pupillary dilation and cycloplegia impair visual function. When multiday, pupillary dilation is required, and/or pupillary dilation in the setting of ocular inflammation is required, the benefits outweigh the risks associated with the use of atropine. These risks are based on its known action as anticholinergic pharmacologic action in an otherwise normal individual.

When maximal cycloplegia is required, the benefits of the use of atropine outweigh the known and potential risks.

The benefits outweigh the risks when atropine ophthalmic solution is used for ocular penalization as an alternative to ocular penalization by patching in the treatment of amblyopia.

**RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:**

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

### Appendix

NDA 206289, Atropine Ophthalmic Solution is recommended to be approved for use in creating pupillary dilation, cycloplegia, and in the treatment of amblyopia. Atropine ophthalmic solution is not recommended to be approved for the [REDACTED] (b) (4).

The package insert (submitted 4/30/14) and carton and container labeling (submitted 4/25/14) are acceptable.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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WILLIAM M BOYD  
06/27/2014

WILEY A CHAMBERS  
06/27/2014