

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208151Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Renata Albrecht, MD
Subject	Division Director Summary Review
NDA/BLA #	NDA 208151
Supplement #	N/A
Related IND	pIND 115869
Applicant Name	Alcon Research, Ltd.
Application Type	505(b)(2)
Date of Submission	2/12/2016
PDUFA Goal Date	12/12/2016 (standard)
Proprietary Name / Established (USAN) Name	ISOPTO Atropine atropine sulfate ophthalmic solution
Dosage Forms / Strength	solution /eye drops 1%
Preservative	benzalkonium chloride, 0.01% (b)(4)
Route of Administration	Topical
Therapeutic Class	Muscarinic antagonist
Indication(s)	Cycloplegia Mydriasis Amblyopia (b)(4)
Dosage Regimen	(b)(4)
How Supplied	In plastic dropper bottle with red cap in the following sizes: 5mL fill in 8cc bottle; 15mL fill in 15cc bottle
Action/Recommended	<i>Approval of Cycloplegia, Mydriasis, Amblyopia</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Wiley Chambers, William Boyd 9/13/2016
CDTL Review	William Boyd, Wiley Chambers 11/29/2016
Statistical Review	Abel Eshete, Yan Wang 11/8/2016
Pharmacology Toxicology Review	Aaron Ruhland, Lori Kotch 11/7/2016
CMC Review	Haripada Sanker, Milton Sloan, Maotang Zhou, Denise Miller, Vidya Pai, Om Anand, Erin Andrews, Chunchun Zhang, Paul Perdue 10/12/2016, 11/10/2016
Clinical Pharmacology Review	Abhay Joshi, Philip Colangelo 11/9/2016
OPDP/DPDP	Carrie Newcomer 11/7/2016
OSI/DGCPC	N/A
Proprietary Name	Michelle Rutledge, Yelena Maslov, Lubna Merchant 6/1/2016
Conditionally acceptable letter	Todd Bridges 6/2/2016
OSE/DMEPA	Michelle Rutledge, Yelena Maslov 6/8/2016
OSE/DDRE	N/A
OSE/DRISK	N/A
Project Manager	Michael Puglisi

OND=Office of New Drugs
 CDTL=Cross-Discipline Team Leader
 OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance
 OPDP/DPDP=Office of Prescription Drug Promotion/Division of Prescription Drug Promotion
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DDRE= Division of Drug Risk Evaluation
 DRISK=Division of Risk Management

Signatory Authority Review Template

1. Introduction

Alcon Research, Ltd. submitted NDA 208151 for ISOPTO Atropine (atropine sulfate ophthalmic solution) 1%. This is a 505(b)(2) application that relies on clinical and non-clinical information published in the literature.

Atropine has been used and marketed for many decades, and has been the subject of approved NDAs for atropine as the only active ingredient or atropine in combination with other products. Alcon notes a topical ophthalmic formulation of atropine sulfate ophthalmic solution 1% is approved under NDA 206289 (Akorn).

All the reviews and facility inspections have been completed and the review team recommends approval of the application. The CDTL review provides an overall summary of the application, and further details are provided in the primary reviews for this NDA. Labeling has been finalized.

2. Background

Mydriasis is dilation of the pupil; in medicine various drugs are used to dilate the pupil by inhibiting contraction of the circular pupillary sphincter muscle normally stimulated by acetylcholine. This inhibition allows the countering radial pupillary dilator muscle to contract which results in dilation of the pupil, permitting examination of the retina and other deep structures of the eye. Dilation can also be achieved by stimulating the dilator muscles with different products.¹ Some mydriatic agents are used to dilate the pupil before surgery (e.g., cataract surgery). Some of these drugs can also be used to achieve cycloplegia (paralyze the ciliary muscle which controls accommodation while viewing objects) in order to determine the true refractive error of the eye and for the relief of ciliary spasm in the treatment of uveitis. Cycloplegics have also been used in patients with amblyopia to paralyze the ciliary muscles of the healthy eye causing blurred vision and therefore forcing the child to use the “lazy eye,” with the goal of making it stronger. Patching the healthy eye is an alternative treatment strategy for amblyopia. Various studies have also evaluated atropine in the (b) (4) using various concentrations of atropine ((b) (4) % to 1%).

¹ There are two main groups of dilating drops

1. Parasympathetic antagonists (parasympatholytics): act by paralyzing the iris sphincter muscle. This category of medicines will both make the pupil larger and paralyze the muscle involved in focusing of the lens (accommodation). As a result, they will cause the eye to be blurry especially for up close (reading, near play):

◦Tropicamide, ◦Cyclopentolate, ◦Homatropine, ◦Atropine

2. Sympathetic agonists (sympathomimetics): act by stimulating the iris dilator muscle: Phenylephrine.

<http://pgcfa.org/kb/entry/166/>

There are several products available that can achieve mydriasis and cycloplegia. Currently FDA approved products have a treatment-duration ranging from about 4 hours, up to multiple days for atropine 1%.

Drug Substance	Duration (normal individual)	Action	Subject of an approved application
Phenylephrine	~ 4 hours	Mydriasis	Yes
Tropicamide	~ 4 hours	Mydriasis & Cycloplegia	Yes
Cyclopentolate	~ 12 hours	Mydriasis & Cycloplegia	Yes
Scopolamine	~ 72 hours	Mydriasis & Cycloplegia	No
Homatropine	~ 48 hours	Mydriasis & Cycloplegia	No
Atropine	~ 12 days	Mydriasis & Cycloplegia, treatment of Amblyopia	Yes

Source: Clinical Review

Atropine is a naturally occurring tropane alkaloid extracted from deadly nightshade (*Atropa belladonna*), Jimson weed (*Datura stramonium*), mandrake (*Mandragora officinarum*) and other plants of the family Solanaceae. It is a secondary metabolite of these plants and serves as a drug with a wide variety of effects.² The species name "belladonna" ("beautiful woman" in Italian) comes from the original use of deadly nightshade to dilate the pupils of the eyes for cosmetic effect. Both atropine and the genus name for deadly nightshade derive from Atropos, one of the three Fates in Greek mythology.³ Atropine is a competitive antagonist for the muscarinic acetylcholine receptors.⁴ It is classified as an anticholinergic drug (parasympatholytic). Atropine dilates the pupils, increases heart rate, and reduces salivation and other secretions.

Ophthalmic use:⁵

Topical atropine is used as a cycloplegic, to temporarily paralyze the accommodation reflex, and as a mydriatic, to dilate the pupils. Atropine degrades slowly, typically wearing off in 7 to 14 days, so it is generally used as a therapeutic mydriatic, whereas tropicamide (a shorter-acting cholinergic antagonist) and phenylephrine (an α -adrenergic agonist) are more commonly used as an aid to ophthalmic examination.

History⁶

Atropine extracts from the Egyptian henbane were used by Cleopatra in the last century B.C. to dilate her pupils. In the Renaissance, women used the juice of the berries of *Atropa belladonna* to enlarge the pupils of their eyes, for cosmetic reasons. This practice resumed briefly in the late nineteenth- and early twentieth-century in Paris.

The mydriatic effects of atropine were studied among others by the German chemist Friedlieb Ferdinand Runge (1795–1867). In 1831, the German pharmacist Heinrich F. G. Mein (1799-

² Atropine <http://en.wikipedia.org/wiki/Atropine>

³ Forbes Thomas R. Why is it called "beautiful lady" A note on belladonna. *Bull N Y Acad Med* 1977; 53:403-6.

⁴ Rang, Dale, Ritter and More: Pharmacology, p. 139. Elsevier 2003.

⁵ Atropine <http://en.wikipedia.org/wiki/Atropine>

⁶ Atropine <http://en.wikipedia.org/wiki/Atropine>

1864) succeeded in preparing atropine in pure crystalline form. The substance was first synthesized by German chemist Richard Willstätter in 1901.

Alcon writes: atropine sulfate has been commercially available as an ophthalmic solution from several manufacturers in the United States for over 30 years. No formal product development program including pivotal safety and efficacy clinical trials to support its human use has been initiated or completed by the Applicant or by any other manufacturers of the drug.

Alcon's original proposed indications for ISOPTO® Atropine (atropine sulfate ophthalmic solution) 1% are: mydriasis and/or cycloplegia (b) (4)
Atropine can also be used for penalization of the healthy eye in the treatment of amblyopia (b) (4)

Alcon writes: The Applicant acknowledges the commercial availability of Atropine Sulfate Ophthalmic Solution, USP 1% (Akorn, Inc.; NDA 206289). Notwithstanding this approval, the 505(b)(2) regulatory pathway is warranted for this current application, which supports different indications and dosing.

Alcon relies on published scientific literature to support non-clinical safety and toxicology labeling, clinical pharmacology, and safety and efficacy of their NDA 208151, and does not rely on a reference listed drug, as noted on Form 356h. Alcon met with the Agency to discuss their 505(b)(2) submission under preIND 115869 on February 11, 2013.

3. CMC/Device

For details, see the CMC and Quality Microbiology reviews. A brief summary is provided below.

Alcon notes that ISOPTO® Atropine, 1% is manufactured under the principles of Good Manufacturing Practice. The active ingredient conforms to the monograph for Atropine Sulfate, USP. The drug substance information is cross-referenced to Type II DMF # (b) (4) which was found adequate as documented in the review dated 11/10/2016.

OPQ notes that ISOPTO® atropine (atropine sulfate ophthalmic solution) 1% is a sterile, clear, colorless to (b) (4) ophthalmic solution preserved with benzalkonium chloride (BAK) in a multidose low density polyethylene (LDPE) round bottles with 2 presentations, 5 mL fill in a 8 mL round bottle, and 15 mL fill in a 15 mL round bottle, both with LDPE (b) (4) and red polypropylene (PP) closure.

All excipients used in the formulation are adequately qualified. No novel excipients are used in the formulation. There is no overage of the active in the formulation. The drug product specification includes tests for appearance, identification, assay, impurity, BAK, pH, osmolality, viscosity, particulate matter, and sterility. The proposed specification is acceptable.

All analytical methods are either USP or modified USP methods and are described in reasonable detail and adequately validated. Additionally, all microbiology related issues concerning the drug product have been satisfactorily resolved. The drug product meets the requirements of the USP monograph.

Twenty four months of stability data for six registration batches at long term condition (25°C/40%RH) and 5°C are provided. Six months of accelerated stability data for both container closure configurations is submitted in the NDA.

A drop size study was conducted to simulate patient use of ISOPTO®. The data indicate an average drop size of 41.0 µl with a standard deviation of 2.5 µl.

Atropine sulfate ophthalmic solution contains atropine 1% at a pH of 3.5 to 6. Each mL of atropine sulfate (1%) is equivalent to (contains) 8.3 mg of atropine. The preservative is benzalkonium chloride (b)(4)%, inactive ingredients include hypromellose, boric acid, sodium hydroxide and/or hydrochloric acid (to adjust pH) and purified water.

The drug product container (b)(4) are presterilized by (b)(4) while the polypropylene (PP) closures are also pre-sterilized by (b)(4). Since the applicant has been using the same process for the manufacture of the proposed drug product on commercial scales for over 30 years, this is considered as a mature and low-risk process from the OPQ perspective. The drug product is a sterile, buffered, preserved, aqueous ophthalmic solution. The process involves sterile (b)(4)

There are no trends observed on all the test parameters when the drug products were stored at long term storage condition (2-25°C). These results support the following: Expiration Date & Storage Conditions: 24 months with the storage statement of: Store at 2-25°C (36-77°F).

The applicant submitted literature publication containing bioavailability data and the OPQ Biopharmaceutics reviewer determined the bridge between the formulation used in the publications with the PK information and the proposed drug product is adequate. Even though the applicant submitted a biowaiver request under 21 CFR 320.22(e), the CFR 320.21 requirement for submission of bioavailability and/or bioequivalence data has been met by the provided literature information and therefore a biowaiver request is not needed. From the Biopharmaceutics perspective there is an adequate bridge between some of the formulations used in the articles submitted to support PK, safety and efficacy and the proposed drug product. (OPQ review pages 90-93).

The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities.

Comment:

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product. Manufacturing site inspections are acceptable. There are no outstanding CMC issues to preclude approval.

4. Nonclinical Pharmacology/Toxicology

For details, see the Pharmacology/Toxicology Review. A brief summary it provided below.

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. No listed drugs were referenced.

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 resulted in decreased weight gain and death at doses much higher than those expected following topical ophthalmic exposure.

The systemic administration of atropine was associated with decreased male fertility. The anticholinergic antimuscarinic effects of atropine may interfere with the rhythmic release of pituitary gonadotropins and result in decreased estrogen.

Drug specification limits have been lowered and/or qualified clinically based on the marketed product.

Labeling will reflect that: There are no adequate and well-controlled studies of atropine sulfate in pregnant women. Animal development and reproduction studies have not been conducted with atropine. Since it is not known whether topically administered atropine sulfate can cause fetal harm, ISOPTO Atropine should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

Because there is no information on the presence of atropine in human milk, the health benefits of breastfeeding versus any potential adverse effect on the infant should be considered when ISOPTO Atropine 1% is administered to a nursing woman.

Atropine sulfate was negative in the Salmonella/microsome mutagenicity test. Studies to evaluate carcinogenicity and impairment of fertility have not been conducted.

Comment:

I concur with the conclusions reached by the pharmacology/toxicology reviewers to recommend approval and the proposed labeling revisions which have been incorporated in labeling. There are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

For details, see the Clinical Pharmacology Review. A brief summary it provided below.

Per Alcon, atropine consists of two enantiomers, l-hyoscyamine and d-hyoscyamine. Only the l-enantiomer is biologically active. It binds with high affinity to muscarinic acetylcholine receptors, and is responsible for the therapeutic effects of the drug. Atropine is a potent compound and is known to antagonize human muscarinic cholinergic actions at plasma concentrations less than 100 pg/mL (Section 2.5.3).

To support this 505(b)(2) NDA, the Applicant is relying on the scientific literature. The pharmacokinetic parameters of atropine (measured as l-hyoscyamine) following topical ocular administration of 1% atropine sulfate ophthalmic solution, summarized from two publications, are shown in the following table.

Study /Reference	Dosing Regimen	Subjects count (M/F), Type, Age Range	Pharmacokinetic Parameters ^{Mean ± SD} _{Range} for l-hyoscyamine				
			C _{max} (pg/mL)	T _{max} (min)	AUC (h*ng/mL)	t _{1/2} (h)	F%
Kaila 1999	Single IV dose - 0.3 mg	6 (1M/5F), Healthy, 24-29 y	NA	NA	$\frac{1.79 \pm 0.64}{1.15 - 3}$	$\frac{2.97 \pm 1.22}{1.3 - 4.3}$	NA
	Topical ophthalmic - 0.3 mg		$\frac{288 \pm 73}{166 - 355}$	$\frac{28 \pm 27}{3 - 60}$	$\frac{1.02 \pm 0.33}{0.36 - 1.25}$	$\frac{2.45 \pm 0.76}{1.5 - 3.6}$	$\frac{63.5 \pm 28.6}{19 - 95}$
Lahdes 1988	Topical ophthalmic - 0.4 mg	8 (7M/1F), ocular surgery patients, 56-66 y	$\frac{860 \pm 402}{NA}$	NA	$\frac{0.72 \pm 0.4}{0.04 - 1.29}$	NA	NA

Mydriasis

Based on the study conducted Wolf and Hodge (1946)⁷ in healthy subjects 16 to 37 years old, 1 drop of 1% atropine sulfate ophthalmic solution into the eye produced a maximum pupil diameter of 8.3 mm within 40 minutes of eye drop instillation. Recovery started at 6 hours after instillation of the eye drop, and it took up to 12 days for the pupil diameter to fully return to its normal size.

Cycloplegia

Based on the study conducted by Marron (1940)⁸ in subjects 15 to 40 years old, 1 drop of 1% atropine sulfate ophthalmic solution instilled in the eye three times daily for 3 days with an additional 1 drop on the morning of the day of the ocular examination produced a residual accommodation (RA) of 1.9 D (17% of baseline); maximum effect was observed after the 4th of 10 drops. The average patient was able to read newsprint by the third day after the last instillation, and it took up to 18 days for the range of accommodation to fully return to normal. (In this study, the maximum extent of pupil dilation or mydriasis was achieved after the first drop and did not increase further with the instillation of additional eyedrops.)

The ocular pharmacodynamics (PD) from two publications indicate that with 1% atropine sulfate ophthalmic solution, full mydriasis is achievable with 1 drop; multiple eyedrops are needed to achieve full cycloplegia. Full recovery from these effects could take up to 18 days.

⁷ Wolf AV, Hodge HC. Effects of atropine sulfate, methylatropine nitrate (metropine) and homatropine hydrobromide on adult human eyes. *Arch Ophthal* 1946; 36: 293-301.

⁸ Marron J. Cycloplegia and mydriasis by use of atropine, scopolamine, and homatropine-paradrine. *Arch Ophthalmol* 1940; 23: 340-50.

Labeling will reflect that: Atropine is a muscarinic antagonist; it 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 onset of action after administration of atropine sulfate ophthalmic solution is usually within minutes with maximal effect being reached in hours. The effect can last for multiple days. Further details about times for individual indications will be included in the Clinical Studies section.

In a study of healthy subjects, after topical ocular administration of 30 μ L of atropine sulfate ophthalmic solution, 1%, the mean (\pm SD) systemic bioavailability of l-hyoscyamine was reported to be approximately $64 \pm 29\%$ (range 19% to 95%) as compared to intravenous administration of atropine sulfate. The mean (\pm SD) time to maximum plasma concentration (Tmax) was approximately 28 ± 27 minutes (range 3 to 60 minutes), and the mean (\pm SD) peak plasma concentration (Cmax) of l-hyoscyamine was 288 ± 73 pg/mL. The mean (\pm SD) plasma half-life was reported to be approximately 2.5 ± 0.8 hours.

In a separate study of patients undergoing ocular surgery, after topical ocular administration of 40 μ L of atropine sulfate ophthalmic solution, 1%, the mean (\pm SD) plasma Cmax of l-hyoscyamine was 860 ± 402 pg/mL.

Comment:

I concur with the conclusions reached by the clinical pharmacology reviewers to recommend approval. Labeling revisions to this section have been completed. There are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

For details, see the Clinical and Statistical reviews. A brief summary is provided below.

The applicant identified numerous publications based on their literature search and selected 15 publications to support efficacy of atropine for their 505(b)(2) application. The medical officer performed a literature search, read the abstracts, and identified additional articles for detailed review. The articles supporting this application were published between 1940 and 2014 and evaluate atropine sulfate ophthalmic solutions (including the 1% concentration) in the proposed indications. The studies included subjects from 2 months to 92 years in age, of various races and eye color. Three of the publications identified the Alcon product as being used for the study; the majority of publications do not specify the source of the product. Given that Alcon is one of several companies that has marketed the product for decades, it is likely that some of the other studies used Alcon product.

A list of the publications reviewed is provided below for reference, and a summary of individual publications for the indications of (a) mydriasis and cycloplegia, (b) (b) (4) (c) amblyopia is included in the subsections for these proposed indications.

#	First Author	Title	Journal	Year	Source of Drug Product
Studies submitted by Alcon in support of the indications for Mydriasis and Cycloplegia					
1	Celebi	The comparison of cyclopentolate and atropine in patients with refractive accommodative esotropia by means of retinoscopy, autorefractometry and biometric lens thickness	Acta Ophthalmologica Scandinavica 77:426-429	1999	Not identified
2	Ebri A	Cost-effectiveness of cycloplegia agents: results of a randomized controlled trial in nigerian children	Invest Ophthalmol Vis Sci 48(3):1025-1031	2007	Not identified
3	Liu	Evaluation of cycloplegic effect of cyclopentolate and atropine	Chin J Exp Ophthalmol 30(4): 353-356	2012	Shenyang Xingqi Pharmaceutical Co., Ltd.
4	Caruba	Preoperative mydriasis obtained by ophthalmic insert versus eye drops	J Fr Ophthalmol; 29(7): 789-795.	2006	
5	McCormick	Pupil dilation using a pledget sponge: a randomized controlled trial	Clinical and Experimental Ophthalmology 34:545-549.	2006	Not identified
6	Barbee RF	A comparative study of mydriatic and cycloplegic agents	Am J Ophthalmol ;44(5 Pt 1):617-22	1957	Not identified

(b) (4)

Studies submitted by Alcon to support the indications of Amblyopia

11	Pediatric Eye Disease Investigator Group	Patching vs atropine to treat amblyopia in children aged 7 to 12 years: a randomized trial	Arch Ophthalmol 126(12):1634-1642	2008	Not identified
12	Repka MX	Treatment of severe amblyopia with weekend atropine: results from 2 randomized clinical trials	J AAPOS 13:258-263	2009	Not identified

#	First Author	Title	Journal	Year	Source of Drug Product
13	Foley-Nolan	Atropine penalisation versus occlusion as the primary treatment for amblyopia	Br J Ophthalmology 81:54-57.	1997	Not identified
14	Pediatric Eye Disease Investigator Group	Randomized trial of treatment of amblyopia in children aged 7 to 17 years	Arch Ophthalmol 123:437-447.	2005	Not identified
15	Tejedor	Comparative efficacy of penalization methods in moderate to mild amblyopia	Am J Ophthalmol 145:562-569.	2008	Colircusi Atropina 1%; AlconCusi, Barcelona, Spain
Additional references submitted by Alcon for review					
16	Marron J	Cycloplegia and mydriasis by use of atropine, scopolamine and homatropine-paredrine	Arch Ophthalmol 23:340-350	1940	Not identified
17	Wolf AV	Effects of atropine sulfate, methylatropine nitrate (metropine) and homatropine hydrobromide on adult human eyes	Arch Ophthalmol. 36(3):293-301	1946	Not identified
18	Kawamoto K	Cycloplegic refractions in japanese children: a comparison of atropine and cyclopentolate	Ophthalmologica 211:57-60	1997	Not identified
19	Stolovitch C	Atropine cycloplegia : how many instillations does one need?	J Pediatr Ophthalmol Strabismus 29:175-176	1992	Not identified
(b) (4)					
21	Arnold RW	Duration and effect of single dose atropine: paralysis of accommodation in penalization treatment of functional amblyopia	Binocular Vision & Strabismus Quarterly; 19(2):81-86.	2004	Alcon
(b) (4)					
23	Salazar M	Iris pigmentation and atropine mydriasis	J Pharm Exp Therapeutics 197(1):79-88	1975	Supported in part by Alcon

Adapted from the Medical Officer Review NDA 208151, with additional references

(a) Mydriasis and Cycloplegia

The applicant identified six selected studies in support of the indications of mydriasis and cycloplegia, and the reviewer identified additional ones:

Celebi 1999: The cycloplegic effect of cyclopentolate 1% was compared to atropine 1% in 32 pediatric patients with refractive accommodative esotropia. Both cyclopentolate and atropine produced a definite cycloplegia ($p < 0.001$), but the difference between the cycloplegic effect of cyclopentolate and atropine was statistically insignificant ($p > 0.05$).

Ebri 2007: The study enrolled 233 children ages 4 to 15 years who were randomized to cyclopentolate 1%, cyclopentolate 1% plus 0.5% tropicamide and 1% atropine. An optometrist measured the residual accommodation (primary outcome), dilated pupil size, pupil response to

light, and self-reported side effects (secondary outcomes). The atropine group had significantly lower mean residual accommodation than the other two groups. Atropine and the combined regimen produced better results for negative response to light and dilated pupil size than cyclopentolate.

TABLE 2. Effectiveness of the Cycloplegic Agents: Residual Accommodation, Pupillary Dilatation, Pupillary Response and Side Effects

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Data are the number of subjects with the percentage of the total group in parentheses.

* All side effects were mild. Prolonged blurry near vision was not included, as only children in the atropine group were reviewed 3 days after the initial examination.

Liu 2012: Cyclopentolate 1% and atropine 1% were compared in 80 children (160 eyes) ages 4-9 years and achieved **mydriasis** and **cycloplegia**. None reported serious reactions; some had flushed face or red eyes. The authors concluded cyclopentolate may be preferable in children with myopia and atropine is preferable in children with hyperopia. They discuss that as a conventional cycloplegic agent, atropine shows a strongest cycloplegic effect, but it would take a longer time to take effect, and adverse reactions such as face flushing, dry mouth, and tachycardia are seen. In contrast, cyclopentolate takes a short time to take effect, it may paralyze ciliary muscle 45 min after its application, and its cycloplegic effect may disappear about 24h after its application. Results of multiple studies suggest that the cycloplegic effect correlates to iris color.

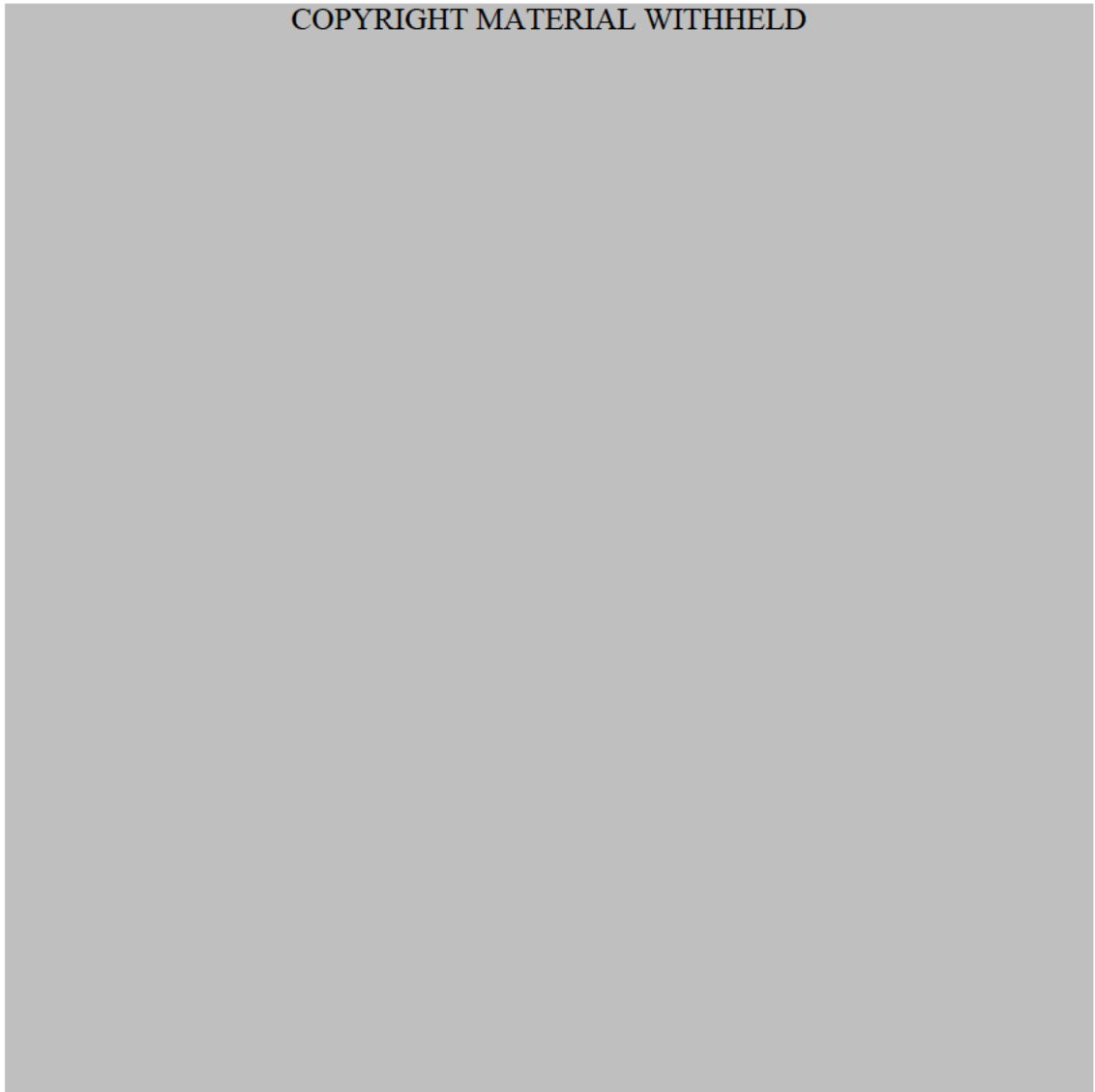
Caruba 2006: Topical administration of atropine 1% in 51 preoperative patients, including other topical or insert products, resulted in **mydriasis** >5mm in 96% of insert and 85% of topical drop group. More detailed results are provided in the table below.

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McCormick 2006: Fifty-six patients were randomized to tropicamide 1%, phenylephrine 2.5% and atropine 1% drops, or pledget cellulose sponge soaked with these 3 **mydriatics** before cataract surgery. The mean pupil diameter in the control group was 7.23 (6.91–7.94) 95% confidence intervals [CI]) and 7.44 (6.96–7.92) 95% CI in the pledget group.

Barbee 1957: A total of 300 normal men and women ranging from 16 to 60 years of age were tested with one of 10 agents, including atropine 1% and placebo, to measure the effect on pupil size and cycloplegia. As seen the effect of **mydriasis** and **cycloplegia** were highly significant and achieved at 40 minutes in Caucasian and African American subjects (columns third from right in figures from the publication).

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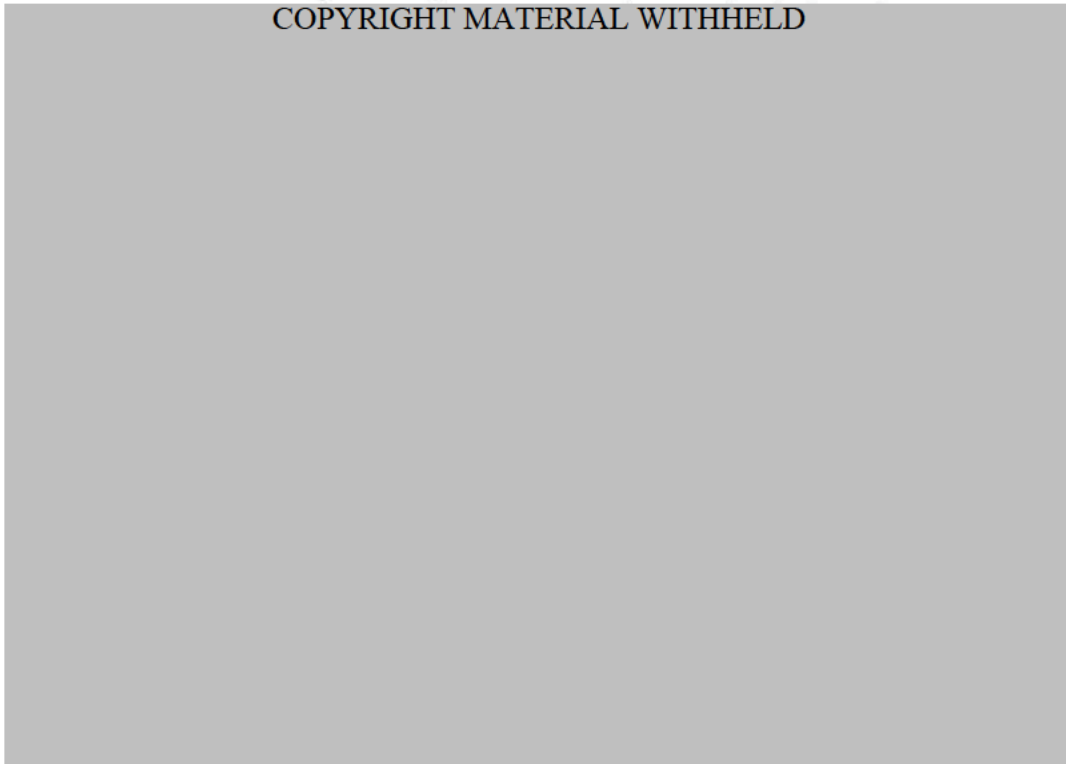


The following additional references were derived from the Medical Officer Reviews:

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

Administration of atropine 1% resulted in clinically significant mydriasis within 40 minutes and clinically significant cycloplegia for at least 8 hours as shown in the tables below

TABLE 1.—Comparison of the Results of the Cycloplegic Effect
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Wolf 1946 Atropine 1% 15 eyes, Methylatropine 1% 23 eyes, Homatropine 1% 7 eyes

	Initial Pupil	Time to Max Mydriasis	Time to Max Cycloplegia	Maximum Pupillary Diameter	Residual
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 1 day.

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.

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**.

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

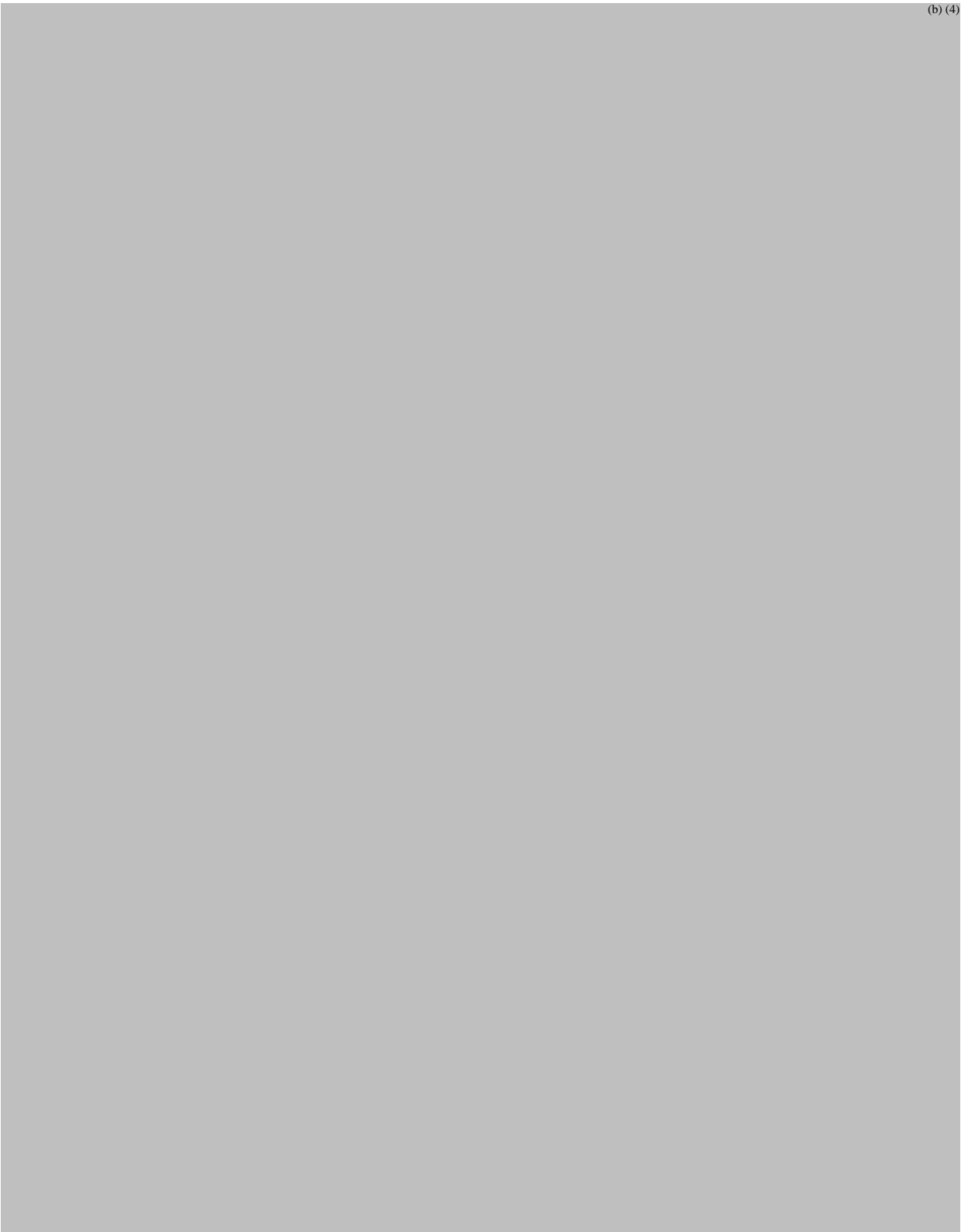
Diopters of Hypermetropia found after Four or Eight Instillations of Atropine

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.

Summary: Overall, these studies demonstrate that atropine sulfate 1% is effective in achieving **mydriasis** of sufficient diameter and **cycloplegia** of sufficient duration. Four of the publications (Barbee, 1957; Ebri, 2007; Marron, 1940; Wolf, 1946) provided results to support indications for cycloplegia and mydriasis. In these studies, 229 children and adults were given atropine 1% and showed that mean dilation due to atropine treatment ranged from 6.5 to 8.3 mm, with the majority of subjects having values above 6 mm.

Both clinical and statistical reviewers concluded that the mydriasis effect and the cycloplegia effect of atropine 1% was consistent across a broad subject population with the majority of subjects showing dilation of 6 mm or more and minimal accommodation from light stimulation. These effects were generally comparable or better than what was observed for a variety of controls.



(c) Amblyopia

The applicant identified five selected studies in support of the indication of amblyopia; the reviewer identified one additional article:

PEDIG 2008:

A total of 193 children (7-12 years old) were randomized to patching or atropine eye drops 1%, for 2 hours on weekends for the treatment of moderate **amblyopia** (visual acuity, 20/40-20/100). 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. This difference met the pre specified definition for equivalence (confidence interval ≤ 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%).

Repka 2009:

In a multicenter clinical trial, 419 children with **amblyopia** (visual acuity, 20/40 to 20/100) were randomly assigned to patching (minimum of 6 h/d) or atropine sulfate eyedrops, 1% (1 drop daily), for 6 months. Treatment after 6 months was at the discretion of the investigator. Two years after enrollment, an unselected subgroup of 188 children were enrolled into long-term follow-up. The Outcome was visual acuity at 15 years of age with the electronic Early Treatment Diabetic Retinopathy Study test in amblyopic and fellow eyes. At 15 years of age, most children treated for moderate amblyopia when younger than 7 years have good visual acuity, although mild residual amblyopia is common. The outcome was not significantly different with atropine or patching.

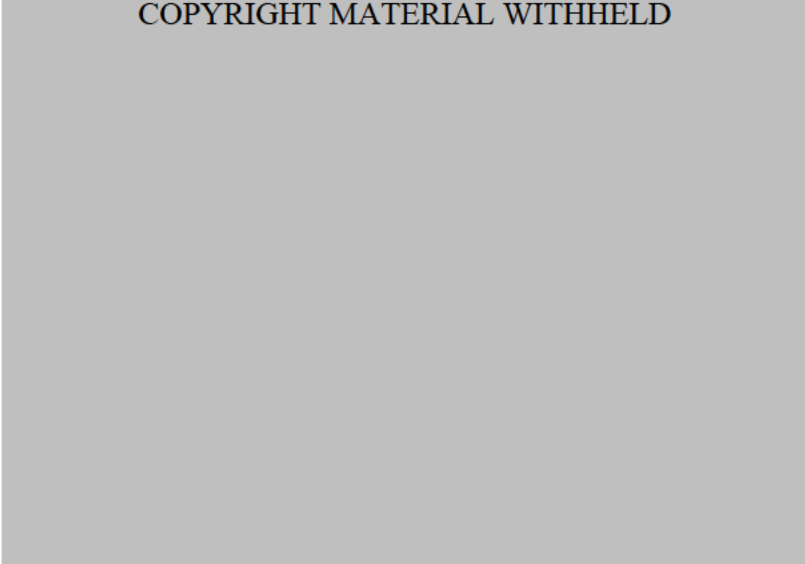
Foley-Nolan 1997:

Thirty six patients were randomized to atropine 1% or patching. In this study atropine was shown to be as effective as patching in the treatment of **amblyopia**. Patient acceptance of atropine was superior and compliance higher (94% vs 55%).

PEDIG 2005:

At 49 clinical sites, 507 patients with **amblyopia** and visual acuity ranging from 20/40 to 20/400 were randomized to either 2-6 hours per day of prescribed patching (plus atropine sulfate for children aged 7 to 12 years) or an optical correction only group. Patients whose amblyopic eye acuity improved 10 or more letters (~2 lines) by 24 weeks were considered responders. The results in the 7- to 12-year-olds (n=404) showed 53% of the treatment group were responders compared with 25% of the optical correction group (P<.001). In the 13- to 17-year-olds (n = 103), the responder rates were 25% and 23%, respectively, overall but 47% and 20%, respectively, among patients not previously treated with patching and/or atropine for amblyopia (adjusted p = .03). Most patients, including responders, were left with a residual visual acuity deficit.

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Tejedor 2008:

Thirty-two children (2 to 10 years of age) with **amblyopia** were randomized to atropine 1% or lenses. Average improvement in visual acuity of the amblyopic eye was larger in the atropine than in the optical penalization group (3.4 and 1.8 logMAR lines, respectively), as well as average improvement in interocular difference of visual acuity (2.8 and 1.3 logMAR lines, respectively).

Summary: Atropine 1% was effective in improving the visual acuity in the amblyopic eye.

The Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products⁹ discusses the use of published literature to support NDA approval.

When published trials are the sole basis for approval, features that make the published data informative include:

- a. Multiple studies conducted by different investigators where each of the studies clearly has an adequate design and where the findings across studies are consistent.
- b. A high level of detail in the published reports, including clear and adequate descriptions of statistical plans, analytic methods (prospectively determined), and study endpoints, and a full accounting of all enrolled patients.
- c. Clearly appropriate endpoints that can be objectively assessed and are not dependent on investigator judgment (e.g., overall mortality, blood pressure, or microbial eradication). Such endpoints are more readily interpreted than more subjective endpoints such as cause-specific mortality or relief of symptoms.
- d. Robust results achieved by protocol-specified analyses that yield a consistent conclusion of efficacy and do not require selected post hoc analyses such as covariate adjustment, subsetting, or reduced data sets (e.g., analysis of only responders or compliant patients, or of an "eligible" or "evaluable" subset).
- e. Conduct of studies by groups with properly documented operating procedures and a history of implementing such procedures effectively.

The above guidance further notes that there have been approvals based primarily or exclusively on published reports. Examples cited include the initial approval of secretin for evaluation of pancreatic function and recent approvals of bleomycin and talc for malignant pleural effusion and doxycycline for malaria.

Therefore, based on the available regulations and guidances, there is sufficient published literature regarding the mechanism of action, the clinical pharmacology and the safety and efficacy of atropine sulfate ophthalmic solution 1% to support approval of the indications for mydriasis, cycloplegia and treatment of amblyopia.

Comment:

I concur there is sufficient data to support indications for mydriasis, cycloplegia and for the treatment of amblyopia, by penalizing the normal eye.

8. Safety

For further details, the Clinical Reviews should be consulted. A brief summary is provided below.

As noted above, atropine has been known for centuries and used for many years; as a result, there is extensive information on adverse reactions associated with atropine. These reactions include elevated blood pressure, ventricular fibrillation, supraventricular or ventricular tachycardia, dizziness, nausea, blurred vision, loss of balance, dilated pupils, photophobia, glare, dry mouth, drowsiness, and potentially extreme confusion, dissociative hallucinations and excitation especially amongst the elderly. These latter effects are because atropine is able

⁹ <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm078749.pdf>

to cross the blood–brain barrier. Because of the hallucinogenic properties, some have used the drug recreationally, though this is potentially dangerous and often unpleasant.¹⁰

Atropine is incapacitating at doses of 10 to 20 mg per person. In overdoses, atropine is poisonous. Its LD50 is estimated to be 453 mg per person (per oral). The antidote to atropine is physostigmine or pilocarpine. One eyedrop of atropine contains 0.4 mg atropine sulfate, and the bioavailability of topically administered ophthalmic solution is about 63%. Therefore the resulting systemic exposure following topical atropine is much lower than following the doses associated with incapacitation and LD50 doses noted above.

The adverse effects of atropine may be summarized by the saying: “as hot as a hare, blind as a bat, dry as a bone, red as a beetroot, and mad as a hatter”. Patients are ‘blind’ owing to the induced cycloplegia, “dry” and “hot” due to the inhibition of the sweat and salivary glands (one of the first signs of atropine poisoning is a dry mouth), “red” because of peripheral vasodilation (produced in an attempt to lose heat and to overcome the lack of function of the sweat glands) and ‘mad’ owing to effects on the central nervous system (CNS).

The clinical reviewer notes that: 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. For example, RM Ingram reported on refractions of 1648 children aged 11 to 13 months in which atropine 1% was used for cycloplegia.

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 amblyopia (b) (4) used daily administrations for periods of months (amblyopia) (b) (4)

Alcon notes that the safety profile of topical ocular atropine sulfate (atropine) has been demonstrated in over two decades of pharmacovigilance data. Literature reports of topical ocular atropine administered (b) (4) adverse event findings in a vulnerable population exposed to drug for an extended period of time, although studies in adult and elderly populations are generally of shorter duration.

The following table is provided in Section 2.7.4. of the NDA to support safety, and is intended to show that long-term administration is tolerated. However, the current product is 1% concentration, (b) (4), thus the most relevant studies are of 1% atropine. The most common adverse reactions reported in the selected articles include: eye irritation, pain, blurred vision, dilated pupils, photophobia, glare, allergic conjunctivitis, allergic blepharitis/dermatitis, facial flushing. These are consistent with information reported in other publications as well as textbooks.

¹⁰ <http://en.wikipedia.org/wiki/Atropine>

Table 2.7.4.1-1 Description of Safety Studies with Atropine

Study Design	Safety Evaluation in the Study	No. of Subjects	Dosing Regimen	Reference
(b) (4)				
Multicenter, randomized	To assess the safety of atropine in the treatment of amblyopia	180	Weekend 1% atropine use	Pediatric Eye Disease Investigator Group 2009
(b) (4)				

Eye pain and stinging occurs upon instillation of atropine sulfate 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.
- Decreased tearing due to inhibition of the lacrimal gland.
- Dryness of the skin, mouth and throat due to decreased secretion from the mucous membranes.
- Flushed skin of face and neck is an expected pharmacologic anticholinergic reaction.
- 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.

- Individuals with Down syndrome, spastic paralysis, or brain damage are particularly susceptible to central nervous system disturbances, cardiopulmonary, and gastrointestinal toxicity from systemic absorption of atropine.
- Tachycardia. Low dose atropine will initially cause a slowing of the heart rate, but increased dosing can lead to tachycardia.

The use of atropine with monoamine oxidase inhibitors can potentially precipitate a hypertensive crisis; therefore this use is generally not recommended.

In the event of over dosage with atropine sulfate ophthalmic solution, 1%, supportive care may include a short acting barbiturate or diazepam; artificial respiration with oxygen, cooling measures to help to reduce fever. The fatal adult dose of atropine is not known.

Post-marketing data have been summarized by Alcon in 2.7.4.6. This includes cumulative postmarketing adverse event cases reported for ISOPTO Atropine (atropine sulfate ophthalmic solution) 1% from the time of product launch through 31 December 2015, during which time (b) (4) units were sold. The majority of reported adverse events associated with atropine were for general disorders and administration site conditions (26%) and eye disorders (24%) which were assessed predominantly as non-serious. The most common adverse events (serious or non-serious) were reported for the eye, the cardiac system, nervous system, and medication errors, with occasional reports of gastrointestinal effects and respiratory events. These reports are consistent with the reported adverse reactions in the published literature.

Comment:

I concur with the conclusions and recommendations for approval of the application by the clinical reviewers. The labeling has been revised and includes safety information for atropine available from the published literature.

9. Advisory Committee Meeting

Atropine has been marketed in ophthalmic and systemic formulations for years. Alcon has marketed their product for 30 years. The application did not identify scientific issues for presentation and discussion at the Advisory Committee meeting.

10. Pediatrics

The published studies included pediatric patients. Labeling states that due to the potential for systemic absorption of atropine, the use of Atropine Sulfate Ophthalmic Solution, USP 1% in children under the age of 3 months is not recommended and the use in children between 3 months and under 3 years of age should be limited to no more than one drop per eye. (b) (4)

The application was presented at the Pediatric Review Committee meeting July 13, 2016, and the committee agreed to the approval of a fully assessed product but excluding use in infants less than 3 months of age because of the concern of adverse reactions due to systemic absorption in that age group.

11. Other Relevant Regulatory Issues

Office of Scientific Investigation (OSI) Audits

The clinical trials to support this application are from the published literature; there was no source documentation for these trials.

Financial Disclosure

No financial information was provided as the studies supporting this application were provided from the scientific literature.

Other Regulatory Issues

This is a 505(b)(2) application and the 505(b)(2) committee has cleared this application for approval.

12. Labeling

- The proprietary name ISOPTO Atropine, was found acceptable by DMEPA, and a provisionally acceptable letter was sent on 6/2/2016.
- Physician labeling (PLR) has been finalized and input from the reviewers and consultants was discussed and incorporated as warranted, and differences in labeling recommendations are addressed in the CDTL review.
- The Established Pharmaceutical Class is muscarinic antagonist.
- Carton and immediate container labels have been finalized after input from reviewers and consultants was discussed and changes incorporated as warranted, differences summarized in the CDTL review.
- Patient labeling/Medication guide – these are not proposed for the current product.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

NDA 208151, ISOPTO Atropine will be approved for the indications of mydriasis, cycloplegia and treatment of amblyopia by penalizing the healthy eye. All disciplines recommend approval and manufacturing facilities are Acceptable. Labeling has been finalized.

- Risk Benefit Assessment

Mydriasis (dilation of the pupil) and cycloplegia (temporary paralysis of the accommodation reflex) are induced medically for various diagnostic and treatment reasons in the area of ophthalmology. Amblyopia is a condition where one eye inadequately processes visual signal transmission to the brain, and the brain ignores or ‘turns off’ the signal from the ‘lazy eye.’

There are several products available that can achieve mydriasis and cycloplegia, including atropine sulfate ophthalmic solution USP 1%. Because atropine degrades slowly, typically wearing off in 7 to 14 days, it is generally used as a therapeutic mydriatic, whereas tropicamide (a shorter-acting cholinergic antagonist) or phenylephrine (an α -adrenergic agonist) is used as an aid to ophthalmic examination. Atropine induces mydriasis by blocking

contraction of the circular pupillary sphincter muscle, which is normally stimulated by acetylcholine release, thereby allowing the radial pupillary dilator muscle to contract and dilate the pupil. Atropine induces cycloplegia by paralyzing the ciliary muscles, whose action inhibits accommodation to allow accurate refraction in children, helps to relieve pain associated with iridocyclitis, and treats ciliary block glaucoma.

Atropine is a naturally occurring tropane alkaloid extracted from deadly nightshade (*Atropa belladonna*), Jimson weed (*Datura stramonium*), mandrake (*Mandragora officinarum*) and other plants of the family Solanaceae. These plants have been known since antiquity. The current 505(b)(2) submission is supported by published non-clinical and clinical studies. The primary reviewers examined the publications submitted and selected representative publications for review; their findings are documented in their reviews.

The efficacy of atropine is summarized in the clinical and statistical reviews, and shows that topical administration of atropine sulfate ophthalmic solution, 1% results in maximal mydriasis in minutes and maximal cycloplegia is usually achieved in hours and full recovery takes multiple days. There are some differences in the specific duration of these events in different publications and indications. In patients with amblyopia, clinical results showed that the treatment effect of atropine was not significantly different from patching of the healthy eye.

Because of atropine's long history, adverse reactions associated with various doses, including overdoses are known. There are reports of pediatric deaths before the 1950s when young children received total doses ranging from 1.6 to 4 mg. Therefore dosing is not recommended in infants below 3 months and children 3 months to 3 years should receive only a single eyedrop.

The pharmacologic and toxic effect of atropine is related to doses; therefore the dosing regimen is limited to older children (who receive one drop) and to older patients who may receive two doses per day. There is no need to adjust these doses based on race, gender, age, iris color, renal or hepatic impairment.

Overall, the benefit outweighs the risks of atropine when used as labeled and the labeling provides sufficient information for the safe and effective use of the product.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
None
- Recommendation for other Postmarketing Requirements and Commitments
None

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/s/

RENATA ALBRECHT
12/01/2016