CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208151Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 29, 2016
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	208151
Applicant	Alcon Research, Ltd 6201 South Freeway Fort Worth, TX 76134-2099
Date of Submission	February 12, 2016
PDUFA Goal Date	December 12, 2016
Proprietary Name / Established (USAN) names	Isopto Atropine (atropine sulfate ophthalmic solution) 1%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	1. Cycloplegia 2. Pupillary dilation 3. Amblyopia (b) (4)
Recommended:	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 in the antimuscarinic subclass of anti-cholinergic agents. 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 cholinoceptor 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 an approved new drug applications. Akorn's atropine ophthalmic solution, 1% is the only approved atropine ophthalmic solution.

Other dosage forms of atropine are marketed in the United States. Some of these products have approved new drug applications and others do not.

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.

Table of Currently Available Treatments for Proposed Indications

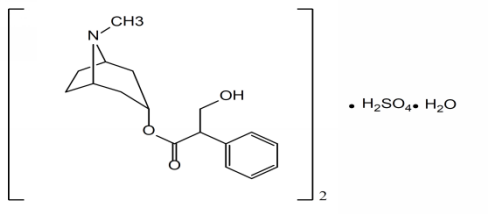
Drug Substance	Duration (normal individual)	Action	Subject of an approved ophthalmic application
Phenylephrine	~ 4 hours	Mydriasis	Yes
Tropicamide	~ 4 hours	Mydriasis & Cycloplegia	Yes
Cyclopentolate	~ 12 hours	Mydriasis & Cycloplegia	Yes
Scopolamine	~ 72 hours	Mydriasis & Cycloplegia	No
Homatropine	~ 48 hours	Mydriasis & Cycloplegia	No
Atropine	~14 days	Mydriasis, Cycloplegia, and in the treatment of amblyopia	Yes

The Applicant requested a "Pre-IND" meeting with the Division of Transplant and Ophthalmology Products. The meeting took place on February 11, 2013, during which the Agency agreed that a 505(b)(2) application was an acceptable pathway for a new drug application in which the applicant did not have a right to reference studies conducted in support of the drug product.

There are numerous literature articles supporting the clinical use of atropine ophthalmic solution. Many of the articles identify a specific brand name product (the current applicant's unapproved, marketed product). None of the literature articles necessary to support approval specifically identify the listed drug that is a pharmaceutical equivalent to the proposed product (NDA 206289). There is no listed drug relied upon.

3. CMC

Structural Formula:



Formulation:

Ingredient	Function	W/V
Atropine sulfate monohydrate	Active	1.0*
Hypromellose	(b) (4)	
Benzalkonium Chloride	Preservative	0.01
Boric Acid	(b) (4)	
Sodium hydroxide	pH adjuster	To adjust pH (b) (4)
Hydrochloric acid	pH adjuster	To adjust pH (b) (4)
Purified Water	(b) (4)	

*Quantity equivalent to 8.3 mg/mL of Atropine.

Source: 3.2.P.1 Description and Composition of the Drug Product

Drug Product Specifications

Test	Specification
Atropine Sulfate Identity[a] (HPLC)	Positive
Atropine Sulfate Identity[a] (TLC)	Positive
Atropine Sulfate Assay (HPLC)	(b) (4) % of label
Atropine Sulfate Impurities:[b] (b) (4) Impurity @ RRT (b) (4) Any Single Unspecified Impurity [c] Total Impurities	 NMT (b) (4) % of Active NMT (b) (4) % of Active NMT (b) (4) % of Active NMT (b) (4) % of Active
Benzalkonium Chloride Identity [a]	Positive
Benzalkonium Chloride Assay	(b) (4) % of label
pH	3.5-6.0
Osmolality	260-330 mOsm/kg
Appearance of Solution: Color Clarity Precipitate	 Colorless to (b) (4) NMT Ph. Eur. II None
Viscosity	(b) (4) cps
Particulate Matter by HIAC	NMT (b) (4) particles/mL ≥ 10µm NMT (b) particle/mL ≥ 25µm NMT (b) particles/mL ≥ 50µm
Sterility [d]	Meets USP Requirements

[a]Release Test only
[b]Report any impurity ≥ (b) (4) % of active
[c]Report any impurity ≥ except drug substance synthetic/process impurities
[d]Sterility testing will not be routinely conducted on production lots except at release. However, if tested, samples will comply with USP requirements

NMT = Not more than

Source: 3.2.P.5.1 Specifications

Primary Packaging Materials and Components (Drug Product)

The package system is comprised of a [redacted] low density polyethylene (LDPE) round bottle with a [redacted] and a red polypropylene (PP) closure. The primary packaging component materials information is summarized in the table below. The bottle [redacted] components will be sterilized by [redacted], and the closure will be [redacted] sterilized. Tamper evidence is provided [redacted] around the neck and closure area of the bottle.

Table 3.2.P.7–1.

Component	Component Material	[redacted] Suppliers	Material DMF[a]
Round bottle	Low Density Polyethylene	[redacted]	[redacted]
[redacted]	Low Density Polyethylene		
Closure	Polypropylene		
Label	Paper [redacted]	Not Applicable	Not applicable

[a] Letters of Authorization to reference the DMFs listed are provided.
[b] Low Density Polyethylene
[c] Polypropylene

Source: 3.2.P.7 Container Closure System

Facilities

From the Product Quality reviews finalized 10/12/2016 and 11/10/2016:

Atropine Sulfate Ophthalmic Solution, 1%, is a sterile, preserved, multi-dose aqueous ophthalmic solution. Two presentations are proposed - 5 mL in 8 mL round LDPE bottle and 15 mL in 15 mL round LDPE bottle, with 15 mm flat tip LDPE [redacted] and 15 mm PP red [redacted] closure. The product has been manufactured and was marketed by the applicant for over 30 years. The review of facilities supporting the submission has been completed and at this time, there appear to be no significant risks to drug product quality based on evaluation of compliance and inspectional history. No preapproval inspections were deemed necessary to support the submission. All the facilities are determined acceptable to support approval of NDA-208151 at this time.

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment
(b) (4)							

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment
Alcon Research Ltd.	1610287	SLQ	Drug Product Manufacturing and Testing				
(b) (4)							N/A
							N/A

NDA 208151 is recommended for approval from the Product Quality perspective.

4. Nonclinical Pharmacology/Toxicology

From the Pharmacology/Toxicology Review finalized 11/7/2016:

The subject of this New Drug Application is Isopto Atropine (atropine sulfate ophthalmic solution) 1%. The proposed indications are for use in producing cycloplegia and mydriasis and treating amblyopia (b) (4). 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 Applicant relies only on published data. 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 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 study in mice reported that exposure to atropine on Day 8 or Day 9 of gestation was associated with an increase in skeletal anomalies, including one occurrence of axial skeletal fusion, and one occurrence of a soft tissue anomaly, exencephaly. The authors of the paper, however, concluded that atropine was not teratogenic. Given the low incidence of each anomaly and inadequate study design, a definitive conclusion regarding teratogenicity cannot be reached. As such, the labeling should state that the potential for fetal harm remains unknown and atropine should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

NDA 208151 is recommended for approval from a Pharmacology/Toxicology perspective.

5. Clinical Pharmacology/Biopharmaceutics

From the Clinical Pharmacology Review finalized 11/9/2016:

This NDA is a literature-based 505(b)(2) application, and the Applicant has not conducted any supportive clinical safety and efficacy studies, nor any pharmacokinetic (PK) or other clinical pharmacology studies. To support this NDA, the Applicant is relying on the pharmacological, pharmacokinetic, and toxicological information of atropine from the scientific literature.

The Clinical Pharmacology information provided by the Applicant in this submission is acceptable, and the Clinical Pharmacology review team recommends that NDA 208151 for Isopto Atropine 1% ophthalmic drops be approved for pupillary dilation and/or cycloplegia, and for penalization of the healthy eye in the treatment of amblyopia.

The Clinical Pharmacology recommendation is based on the following:

1) Information from two literature studies, (1) Kaila, et al (1999) and (2) Lahdes, et al (1988) that evaluated the systemic exposure to the pharmacologically active enantiomer of atropine, l-hyoscyamine, following the administration of 1% atropine sulfate ophthalmic solution.

2) Established safety of 1% atropine ophthalmic solution in children greater than 3 months of age and in adults, which is supported by adequate and well controlled studies in the literature (Medical Review by Dr. Chambers, 09/13/2016).

6. Sterility Assurance

From the Product Quality reviews finalized 10/12/2016 and 11/10/2016:

NDA micro review 208135.doc, 25 January 2016 reviewed [redacted] (b) (4) the filling equipment, [redacted] (b) (4) sterilization of equipment, container closure component [redacted] (b) (4), and container closure component [redacted] (b) (4) sterilization.

There are no outstanding issues, the application is recommended for approval from a quality microbiology perspective.

7. Clinical/Statistical- Efficacy

From the Medical Officer Review finalized 9/13/2016:

Table 1 - Tables of Studies/Clinical Trials

#	First Author	Title	Journal	Year	Source of Drug Product
1	Barbee RF	A comparative study of mydriatic and cycloplegic agents	Am J Ophthalmol ;44(5 Pt 1):617-22	1957	Not identified
2	Caruba	Preoperative mydriasis obtained by ophthalmic insert versus eye drops	J Fr Ophthalmol; 29(7): 789-795.	2006	
3	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
[redacted] (b) (4)					
6	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
[redacted] (b) (4)					
8	Fan DSP	Comparative study on the Safety and Efficacy of different cycloplegics agents in children with darkly pigmented irides	Clinical and Experimental Ophthalmology 32:462-467	2004	CibaVision
9	Foley-Nolan	Atropine penalisation versus occlusion as the primary treatment for amblyopia	Br J Ophthalmology 81:54-57.	1997	Not identified
10	Kaila T	Systemic bioavailability of ocular applied 1% atropine eyedrops	Acta Ophthalmol Scand 77:193-196	1999	Star Pharmaceuticals Tampere, Finland
[redacted] (b) (4)					
12	Liu	Evaluation of Cycloplegic Effect of Cyclopentolate and Atropine	Chin J Exp Ophthalmol 30(4): 353-356	2012	Shenyang Xingqi Pharmaceutical Co., Ltd.
13	McCormick	Pupil dilation using a pledget sponge: a randomized controlled trial	Clinical and Experimental Ophthalmology 34:545-549.	2006	Not identified
14	Miranda	Residual Accommodation	Arch Ophthal 87:515-517	1972	
15	Pediatric Eye Disease Investigator	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

#	First Author	Title	Journal	Year	Source of Drug Product
	Group				
16	Repka MX	Treatment of severe amblyopia with weekend atropine: Results from 2 randomized clinical trials	J AAPOS 13:258-263	2009	Not identified
17	Salazar M	Iris Pigmentation and Atropine Mydriasis	J Pharm Exp Therapeutics	1975	Supported in part by
					(b) (4)
19	Tejedor	Comparative Efficacy of Penalization Methods in Moderate to Mild Amblyopia	Am J Ophthalmol 145:562-569.	2008	Colircusi Atropina 1%; AlconCusi, Barcelona, Spain
					(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
22	Auffarth G	Cycloplegic refraction in children: Single-dose-atropinization versus three day atropinization	Documenta Ophthmologica 80:353-362	1992	Not identified
23	Bartlett, JD	Administration of and Adverse Reactions to Cycloplegic Agents	Am J Optometry 55(4): 227-233	1978	Not identified
24	Bothman L	Homatropine and Atropine Cycloplegia: A comparative study	Arch Ophthalmology 7:389-398	1932	Not identified
25	Boudet J	Dose-response effects of atropine in human volunteers	Fundam Clin Pharmacol. 5:635-640	1991	Not identified
26	Choo	The studies on the Residual Accommodation of Koreans	Yonsei Medical Journal 4:73-76.	1963	Not identified
27	Cowan EC	Clinical Evaluation of a New Mydriatic - Mydrilate	Brit J Ophthalmol 46:730-736.	1962	Not identified
28	Cristini G	The Vascular Action of Pilocarpine, Eserine, Adrealine and Atropine and their influence in Primary Chronic Glaucoma	Brit J Ophthalmol 33:228-242	1949	Not identified
29	Emiru VP	Response to mydriatics in the African	Brit J Ophthalmol 55:538-543	1971	Not identified
30	Farhood QK	Cycloplegic Refraction in Children with Cyclopentolate vs Atropine	J Clin Exp Ophthalmol 3(7):239-244	2012	Not identified
31	Fraser H	Oxyphenonium Bromide as a Mydriatic	Brit J Ophthalmol 40:751-753	1956	Not identified
32	Gettes BC	Evaluation of Five New Cycloplegic Drugs	Arch Ophthalmol 49:24-27	1953	Not identified
33	Gettes BC	Three new cycloplegics drugs	Arch Ophthalmol 51:467-472.	1954	Not identified
34	Hartgraves H	The Synergistic Action of Atropine and Epinephrine on the Intrinsic Muscles of the Eye	Arch Ophthalmol. 5(2):212-218	1931	Not identified
35	Hiatt RL	Comparison of Atropine and Tropicamide in Esotropia	Annals Ophthalmol 15 (4): 341-343	1983	Not identified
36	Hiraoka T	Influences of Cycloplegia with Topical Atropine on Ocular Higher-Order Aberrations	Ophthalmol 120:8-13	2013	Not identified
37	Hoefnagel D	Toxic Effects of Atropine and Homatropine Eyedrops in Children	New Eng J Med 264:168-171	1961	Not identified
38	Ingram RM	Refraction of 1-year-old children after atropine cycloplegia	Brit J Ophthalmol 63:343-347	1979	Not identified
39	Ingram RM	Refraction of 1-year-old children after cycloplegia with 1% cyclopentolate: comparison with findings after atropinization	Brit J Ophthalmol 63:348-352	1979	Not identified
40	Jackson E	Cycloplegia for Diagnosis	Arch Ophthalmol 11(1):133-140	1934	Not identified
41	Janes RG	The Penetration of C^{14}-Labeled Atropine into the Eye	Arch Ophthalmol 62(1):69-74	1959	Not identified
42	Kawamoto K	Cycloplegic Refractions in Japanese Children: A Comparison of Atropine and Cyclopentolate	Ophthalmologica 211:57-60	1997	Not identified
43	Khurana AK	Status of cyclopentolate as a Cycloplegic in Children: A comparison with Atropine and Homatropine	Acta Ophthalmologica 66:721-724	1988	Not identified
44	Lahdes K	Systemic absorption of topically applied ocular atropine	Clin Pharmacol 44:310-314	1988	Star Pharmaceuticals, Tampere, Finland
45	Lowe RF	Angle-Closure, Pupil Dilatation and Pupil Block	Brit J Ophthalmol 50:385-389	1966	Not identified

#	First Author	Title	Journal	Year	Source of Drug Product
46	Mann I	A new synthetic mydriatics	Br J Ophthalmol 30(1): 8–11	1946	Not identified
47	Marron J	Cycloplegia and Mydriasis by use of Atropine, Scopolamine and Homatropine-Paredrine	Arch Ophthalmol 23:340-350	1940	Not identified
48	Narvaez J	Pupil dilation using a standard cataract surgery regimen alone or with atropine 1.0% pretreatment	J Cataract Refract Surg 36:563-567	2010	Not identified
49	North RV	A Review of the Uses and Adverse Effects of Topical Administration of Atropine	Ophthalmol Physiol Opt 7(2):109-114	1987	Not identified
50	Noske W	Cycloplegic refraction using atropine minidrops	Strabismus 1(1):17-23	1993	Not identified
51	Obianwu HO	The relationship between the Mydriatic Action and the Colour of the Iris	Brit J Ophthalmol 49:264-270	1965	Not identified
52	Pendse GS	Refraction in Relation to Age and Sex	Arch Ophthalmol 52(3):404-412	1954	Not identified
53	Riddell WJB	A Clinical Trial of a Synthetic Mydriatic	Brit J Ophthalmol 30:1-7	1946	Not identified
					(b) (4)
55	Rosenbaum AL	Cycloplegic Refraction in Esotropic Children	Ophthalmol 88:1031-1034	1981	Not identified
56	Rosenfield M	A Comparison of the effects of Cycloplegics on Accommodation Ability for Distance Vision and the Apparent Near Point	Ophthalmol Physiol Opt 6(3):317-320	1986	Not identified
57	Shah BM	Comparing homatropine and atropine in pediatric cycloplegics refractions	J AAPOS 15:245-250	2011	Not identified
					(b) (4)
59	Smith SA	Factors determining the Potency of Mydriatic Drugs in Man	Br J Clin Pharm 3:503-507	1976	Support from Smith & Nephew
60	Soares R	Determination of Atropine Enantiomers in Ophthalmic Solutions by Liquid Chromatography using a Chiral AGP Column	J AOAC Int. 92(6):1663-72.	2009	Not identified
61	Stolovitch C	Atropine Cycloplegia: How Many Instillations Does One Need?	J Pediatr Ophthalmol Strabismus 29:175-176	1992	Not identified
62	Thorne FH	Cycloplegics	Arch. of Ophthalmol 22:274–287	1939	Not identified
63	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
64	Zetterstrom C	A cross-over study of the cycloplegics effects of a single topical application of cyclopentolate-phenylephrine and routine atropinization for 3.5 days	Acta Ophthalmologica 63:525-529	1985	Not identified

The applicant's originally submitted references are listed as studies/trials 1-20 in the comprehensive table above.

The Medical Officer also conducted an independent literature search using the terms "Atropine" and "Eye." Abstracts were screened for adequate and well controlled studies. Published clinical trial results were reviewed. References of articles were reviewed for potential additional articles. Sixty-four articles in the preceding table (see above) were reviewed in detail.

Representative clinical studies were identified and are listed in the following table. 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. The drug product has been

demonstrated to penetrate the cornea directly to the site of action (iris and ciliary body). The exact formulation for many of the referenced studies relied on to support the safety or efficacy is unknown, although as noted in the table, some were the product which is the subject of this application and were supplied by Alcon. Because Alcon marketed this product for many years, it is likely that some of the references which do not specify the source of the Atropine were also Alcon's product. It is also likely that several of the individual products were made by multiple different manufacturers over the span of 150 years and the formulations are not exactly the same.

Table 2 - Representative Individual Studies/Clinical Trials

Study	Indication	Design	Arms (# of subjects)
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 their own control /comparison to baseline	Atropine 1% (36)
Pediatric Eye Disease Group 2008	Amblyopia	Randomized Parallel groups Blinded assessment	Atropine 1% (95) Patching (98)

(b) (4)

Mydriasis and Cycloplegia Indications

Barbee 1957 Double-blind, placebo controlled

The parasympatholytic agents, scopolamine, atropine and homatropine all induced significant mydriasis of essentially equal degrees in all three iris color 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%, and cyclopentolate 1%. 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 size increases with atropine were clinically significant but were less than the triple combination of phenylephrine 2.5%, tropicamide 1%, and cyclopentolate 1%.

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

Atropine:	Duration of Maximum Cycloplegia	8-24 hours
(10 drops)	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	Duration of Maximum Cycloplegia	40 minutes
(10 drops)	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	Duration of Maximum Cycloplegia	50 minutes
Paredrine	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 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	Recovery Time Cycloplegia
Atropine	6 hours	1 day
Methylatropine	6 hours	6 hours
Homatropine	6 hours	1 hour

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 was produced for 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.

Mean Refraction	50 eyes Children younger than 6 years	52 eyes 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, i.e. relevant, 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, i.e. relevant, 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% atropine children >2.5 years) 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 Indication

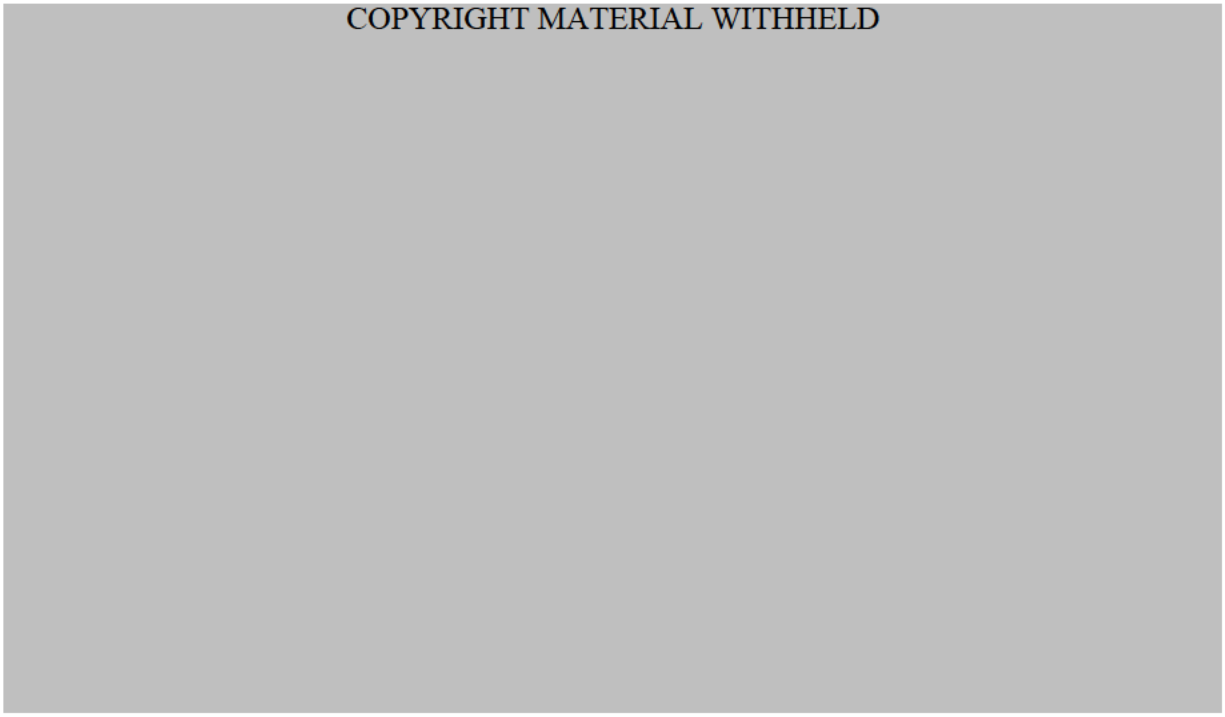
Pediatric Eye Disease Group 2008 Randomized Parallel groups masked assessment Atropine 1% vs Patching

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 ≤ 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%).



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

Conclusions: 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 atropine penalization of the eye with better visual function.

(b) (4)

4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Efficacy Summary Statement

There are multiple adequate and well controlled studies which demonstrate the efficacy of atropine solution 1% in producing clinically significant mydriasis and cycloplegia. These studies, along with the 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.

(b) (4)

8. Safety

From the Medical Officer Review finalized 9/13/2016:

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 regiments of administration. Studies of the treatment (b) (4) 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 in the antimuscarinic subclass of anticholinergics. 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 mucus 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 pediatric information is provided in this NDA for atropine sulfate ophthalmic solution.

Evidence is suggestive of a reduction in the growth of the eye following chronic use of atropine; however, there is limited information beyond two to three years of use. The effect does appear to be dose dependent.

Due to the high systemic exposure following use, the limited need for cycloplegia in children under 3 months, the limited need for amblyopia treatment by pharmacologic penalization in children under 3 months and the availability of alternative drug products for pupillary dilation, atropine 1% solution is not recommended for use in children under the age of 3 months. Use in children under 30 months of age should be limited to no more than a single drop per day.

This application was presented at PeRC on July 13, 2016. Proposed Indications: (1) For mydriasis, (2) cycloplegia, (3) penalization of the healthy eye in treatment of amblyopia, and [redacted] (b) (4)

The Division stated that [redacted] (b) (4) The Division clarified that this is a marketed unapproved drug.

PeRC agreed to the approval of a fully assessed product but not labeled for less than 3 months of age because of the concern of adverse events with systemic absorption in infants < 3 months of age.

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 11/8/2016:

The statistical reviewer has reviewed the relevant publications identified by both the applicant and Medical Officer and did not identify any major statistical issues. The Medical Officer concluded that there is sufficient statistical evidence in the publications to support the proposed indications of mydriasis and cycloplegia and treatment of amblyopia. However, because the statistical reviewer was not able to determine whether the atropine evaluated in the

publications is similar to the to-be-marketed product, the final determination for the approval of the product is deferred to the clinical review team.

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.

Regarding Prescribing Information:

> Revise the proposed proprietary name to Isopto Atropine (b) (4)
> DMEPA notes Alcon submitted an amendment to the proprietary name request as, Isopto Atropine, on May 11, 2016.

Reviewer Comments: *This item has been addressed in the final draft labeling.*

Regarding Container label and Carton labeling:

1. Move the strength percentage of 1% to appear immediately after the established name. (b) (4)

Reviewer Comments: *We do not recommend repositioning the prominent percentage notation on the carton/container labeling. There is a safety issue involved with the use of different concentrations of atropine ophthalmic solutions in approved, unapproved, and compounded products. A single drop of atropine 1% can dilate an eye for up to 14 days; the adverse event safety profiles are different for these different concentrations.*

The applicant has revised their final carton/container labeling to read: Isopto Atropine (atropine sulfate ophthalmic solution) 1%. Although not the Division's preference, this revision of the carton/container labeling is acceptable.

2. We recommend you add the route of administration such as, "For ophthalmic use" to the principal display panel, to assist with the correct use of this product.

Reviewer Comments: *The recommendation is noted but is redundant. The established name of this product contains "ophthalmic solution" and the Usage instructions describe using the product in the eye(s).*

3. Ensure that the font size of established name is to at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2) to increase readability of this important information on the principal display panel (PDP)1.

Reviewer Comments: *The established name should be a font size that is at least half as large of that of the proprietary name and a prominence commensurate with the proprietary name, as stated in 21 CFR 201.10(g)(2).*

4. Consider decreasing prominence of the company name and graphic (tear drop with horizontal lines) so that it does not compete with the most important information on the labels and labels such as proprietary name, established name and strength. As currently presented, the company name and graphic are as prominent as the proprietary name.

Reviewer Comments: *Provided the established name is corrected for prominence, we have no objection to the size or prominence of the company name and graphic.*

In a letter dated 6/2/2016, DMEPA found the proposed proprietary name, Isopto Atropine, conditionally acceptable.

OPDP
The Office of Prescription Drug Promotion (OPDP) provided a labeling review of the original package insert.

Comment [NC1]: OPDP Comment: We note that superficial keratitis is listed in Section 6.1 as a "commonly occurring adverse reaction". OPDP defers to DTOP if "superficial keratitis" should also be included here.

Reviewer Comments: *This item has been addressed in the final draft labeling.*

Comment [NC2]: OPDP Comment: Recommend including incidence rates of AEs if available from the literature references/studies used in support of this application.

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

Comment [NC3]: OPDP Comment: We recommend including this AE information [superficial keratitis] in the Highlights section of the PI. Defer to DTOP.

Reviewer Comments: Reviewer Comments: *Although common, superficial keratitis is not as clinically relevant as the listed reactions in the Highlights.*

Comment [NC4]: OPDP Comment: This term [rapid] is vague and we recommend quantifying it, if possible.

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

Comment [NC5]: OPDP Comment: We note that Section 14 states, "The maximum effect for mydriasis is achieved in about 30–40 minutes after administration" and "The maximum effect for cycloplegia is achieved within 60–180 minutes after administration," We recommend consistency and defer to DTOP.

Reviewer Comments: *This item has been addressed in the final draft labeling.*

Comment [NC6]: OPDP Comment: We note that Section 14 states, "The maximum effect for mydriasis is achieved in about 30–40 minutes after administration, with recovery after approximately 7– 10 days. The maximum effect for cycloplegia is achieved within 60–180 minutes after administration, with recovery after approximately 7– 12 days." We recommend consistency and defer to DTOP.

Reviewer Comments: *This item has been addressed in the final draft labeling.*

Comment [NC7]: OPDP Comment: We note that Section 12.2 states, "with maximal effect (b) (4) hours." We defer to DTOP.

Reviewer Comments: *This item has been addressed in the final draft labeling.*

Comment [NC8]: OPDP Comment: We note that Section 12.2 states, "The effect can last (b) (4) " We defer to DTOP.

Reviewer Comments: *This item has been addressed in the final draft labeling.*

Comment [NC9]: We note that Section 12.2 states, "with maximal effect (b) (4) hours." We defer to DTOP.

Reviewer Comments: *This item has been addressed in the final draft labeling.*

Comment [NC10]: OPDP Comment: We note that Section 12.2 states, "The effect can last (b) (4)." We defer to DTOP.

Reviewer Comments: *This item has been addressed in the final draft labeling.*

Comment [NC11]: OPDP Comment: (b) (4) in Section 6.1 as an AE? We note that "Blurred Vision" is listed in Section 5.1 and in Section 6.1 as a common AE. We defer to DTOP if this should be listed here as well.

Reviewer Comments: *This item has been addressed in the final draft labeling.*

12. Labeling

The package insert and carton and container labeling submitted 11/29/2016 are acceptable with minor editorial revisions involving capitalization.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 208151, Isopto Atropine (atropine sulfate ophthalmic solution) 1%, is recommended to be approved for use in creating pupillary dilation, cycloplegia, and in the treatment of amblyopia. Isopto Atropine (atropine sulfate ophthalmic solution) 1% is (b) (4)

The package insert and carton and container labeling submitted 11/29/2016 are acceptable with minor editorial revisions involving capitalization.

All manufacturing 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 208151, Isopto Atropine (atropine sulfate ophthalmic solution) 1%, is recommended to be approved for use in creating pupillary dilation, cycloplegia, and in the treatment of amblyopia. Isopto Atropine (atropine sulfate ophthalmic solution) 1% is (b) (4)

The package insert and carton and container labeling submitted 11/29/2016 are acceptable with minor editorial revisions involving capitalization. . See Appendix of this review.

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

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
11/30/2016

WILEY A CHAMBERS
11/30/2016