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APPLICATION NUMBER:

208151Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW of NDA 208-151

Application Type	Original NDA
Application Number(s)	208-151
Priority or Standard	Standard Review
Submit Date(s)	2/12/2016
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Division / Office	Division of Transplant and Ophthalmology Products, Office of Antimicrobial Products
Reviewer Name(s)	Wiley A. Chambers, MD
Review Completion Date	September 13, 2016
Established Name	Atropine ophthalmic solution
Therapeutic Class	Anticholinergic
Applicant	Alcon Research, Ltd 6201 South Freeway Fort Worth, TX 76134-2099
Proposed Indication(s)	Cycloplegia Pupillary dilation Amblyopia (b) (4)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 208-151, atropine ophthalmic solution, 1%, an anticholinergic is recommended to be approved for use in creating pupillary dilation (mydriasis), cycloplegia, and for penalization of the healthy eye in the treatment of amblyopia. (b) (4)

1.2 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 in the setting of an ophthalmic examination or in the treatment ocular inflammation, 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.

1.3 Recommendations for Post marketing Risk Evaluation and Mitigation Strategies

Routine monitoring is recommended.

1.4 Recommendations for Post marketing Requirements and Commitments

There are no recommended post marketing requirements.

2 Introduction and Regulatory Background

2.1 Product Information

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

2.2 Tables of Currently Available Treatments for Proposed Indications

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	~14 days	Mydriasis, Cycloplegia, and in the treatment of amblyopia	Yes

- 2.3 Availability of Proposed Active Ingredient in the United States
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.

2.4 Important Safety Issues with Consideration to Related Drugs

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.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

There is no evidence that the submitted studies were not conducted in accordance with acceptable clinical ethical standards.

3.2 Compliance with Good Clinical Practices

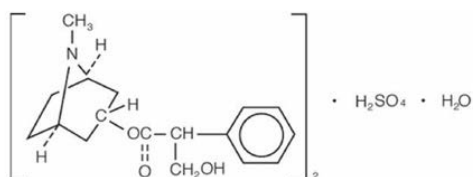
The clinical studies included in this application appeared to conform to Good Clinical Practices.

3.3 Financial Disclosures

The clinical studies included in this application were conducted in Europe and the US prior to any requirements for financial disclosures.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls



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.

Drug Product Specifications

Parameter	Target	Range
Atropine sulfate monohydrate	(b) (4) mg/mL	(b) (4) %
Benzalkonium chloride	(b) (4) mg/mL	(b) (4) %
(b) (4)		NMT (b) (4) %
Impurity @ RRT (b) (4)		NMT (b) (4) %
Any Single Unspecified Impurity*		NMT (b) (4) %
Total Impurities		NMT (b) (4) %
pH		3.5 to 6.0
Viscosity		(b) (4) cps
Osmolality		260 to 330 mOsm/Kg
Product Appearance		Colorless to (b) (4) NMT Ph Eur II
Sterility	Sterile	Sterile
Particulate Matter	NMT (b) (4) 10µm NMT (b) (4) 25µm NMT (b) (4) 50µm	NMT (b) (4) 10µm NMT (b) (4) 25µm NMT (b) (4) 50µm

* Report any impurity $\geq$ (b) (4) % of active except drug substance synthetic/process impurities

Reviewer's Comments: *Acceptable.*

Primary Packaging Materials and Components

Component	Component Material	(b) (4) Suppliers
Round bottle	Low Density Polyethylene	(b) (4)
(b) (4)	Low Density Polyethylene	
Closure	Polypropylene	
Label	Paper (b) (4)	Not applicable

^a Letters of Authorization to reference the DMFs listed are provided.

^b Low Density Polyethylene

^c Polypropylene

Reviewer's Comments: *Acceptable.*

4.2 Clinical Microbiology

Not applicable for this application.

4.3 Nonclinical Pharmacology/Toxicology

Nonclinical studies to investigate the pharmacologic effect of the drug substance are published. These studies were conducted well after the drug product was in common use.

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. Interference with the cholinergic system can affect reproduction. Since it is not known whether topically administered atropine sulfate can cause fetal harm or affect reproduction capacity, Atropine sulfate ophthalmic solution, (1%) should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

Traces of atropine have been found in human milk after following administration of atropine solution for injection. Because some systemic absorption occurs from following topical administration, caution should be exercised when atropine sulfate ophthalmic solution, 1% is administered to a nursing woman.

Studies to evaluate carcinogenicity and impairment of fertility have not been conducted.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The drug product causes local and systemic anticholinergic effects.

4.4.2 Pharmacodynamics

Lahdes K *et al.* Systemic absorption of topically applied ocular atropine. *Clin Pharmacol Ther* 1988; 44:310-4.

Atropine plasma levels, blood pressure, heart rate, and salivary secretion were monitored after ocular application. Eight patients received 40 µL, 1% atropine in the lower cul-de-sac of one eye in connection with ocular surgery. Atropine plasma levels were determined for 90 minutes by radioreceptor assay. A peak plasma atropine concentration of 860 ± 402 pg/mL was reached within 8 minutes in all patients. The ocular absorption of atropine was at least as rapid as that reported for intramuscular administration. Ocular atropine did not affect patient's blood pressure or heart rate when compared with those of the placebo group. Thirty minutes after administration of atropine eye drops, the salivary secretion in the experimental group was reduced, but was statistically insignificant from the placebo group.

4.4.3 Pharmacokinetics

Kaila T *et al.* Systemic bioavailability of ocularly applied 1% atropine eye drops. *Acta Ophthalmol. Scand.* 1999; 77: 193–196

Randomized, crossover study. 0.3 mg atropine either intravenously or ocularly to six healthy volunteers. The plasma concentrations of the biologically active atropine enantiomer, 1-hyoscyamine, were determined using a muscarinic cholinergic binding assay.

The mean area under the curve from zero to infinity ($AUC_{0-\infty}$) for 1-hyoscyamine was 1.862 ± 0.580 µg/L·hr after intravenous, and 1.092 ± 0.381 µg/L·hr after ocular administration (mean $\pm$ sd, n=6), respectively. The mean bioavailability was $63.5 \pm 28.6\%$ (min 19%, max 95%). Large inter-individual differences characterized the absorption and elimination phases of 1-hyoscyamine kinetics. The terminal half-life ($t_{1/2\beta}$) of 1-hyoscyamine in plasma was not affected by the route of drug administration.

Age affects the elimination of atropine from the systemic circulation. In young children, less than 2 years of age, a larger volume of distribution is responsible for prolonged elimination and in the elderly, greater than 65 years of age, clearance is decreased. Age has no effect on the serum protein binding of atropine. [Virtanen *et al.* *Acta Anaesth. Scand.* 1982;26:297-300.]

5 Sources of Clinical Data

5.1 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
(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
(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
(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 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
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 197(1):79-88	1975	Supported in part by Alcon
(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 Ophthalmologica 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

#	First Author	Title	Journal	Year	Source of Drug Product
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 Chonic 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
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

#	First Author	Title	Journal	Year	Source of Drug Product
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, Methlatropine 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

5.2 Review Strategy and Linkage (Bridge) to Proposed Product

In addition to the applicant's references (listed as articles 1-20 in the table above), a literature search was conducted 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 were reviewed in detail. Representative clinical studies were identified and are listed in section 5.3. 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.

5.3 Discussion of Representative Individual Studies/Clinical Trials

Publications were reviewed for 4 indications.

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)

6 Review of Efficacy

6.1 Mydriasis and Cycloplegia

Barbee 1957 Double-blind, placebo controlled

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Reviewer's Comments: *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)

Reviewer's Comments: *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%)

Reviewer's Comments: *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)

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

Reviewer's Comments: *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, Methyldropine 1% 23 eyes, Homatropine 1% 7 eyes

	Initial	Time to Max		Maximum	Residual
	Pupil	Mydriasis	Cycloplegia	Pupillary Diameter	Accommodation
Atropine	3.4	40 min	5 hr	8.3	0.21
Methyldropine	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
Methyldropine	6 hours	6 hours
Homatropine	6 hours	1 hour

Reviewer's Comments: *Clinically significant pupil dilation occurred within 40 minutes and lasted for at least 6 hours. Clinically significant cycloplegia occurred within 5 hours lasting for at least one day.*

Riddell WJB 1946 A Clinical Trial of a Synthetic Mydriatic

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

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

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

Reviewer's Comments: *Clinically significant pupil dilation occurred for a duration of at least 4 days.*

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

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

Reviewer's Comments: *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 $+3.89 \pm 2.45$ D) and cyclopentolate refraction (mean $+3.58 \pm 2.30$ D).

Reviewer's Comments: *Atropine provided clinically important cycloplegia.*

Hiatt RL 1983 Comparison of Atropine and Tropicamide in Esotropia

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

Reviewer's Comments: *Atropine provided clinically important cycloplegia.*

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

Diopeters 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

Reviewer's Comments: *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 >2.5years) and compared with the results after 3 days of receiving 1 atropine eye drops 3 times daily. In 86.5% the spherical equivalents differ not more than 1.0 diopter ($p = 0.05$); the correlation was 0.99. Astigmatic corrections were in agreement in 95.5%, the axis of cylinders in 93.0%; the correlations were 0.95 and 0.97. The residual accommodation 90 minutes after 2 drops of atropine was not more than 1 diopter in all children. The additional cycloplegic effect of the three-day-atropinization was only 0.5 diopters.

Reviewer's Comments: *This article supports the conclusion that 3 days of atropinization is not usually necessary.*

6.2 Treatment of Amblyopia

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

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

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

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

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

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

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.

Reviewer's Comments: *This study demonstrates a clinically significant improvement in visual acuity achieved by atropine penalization of the eye with better visual function.*

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Reviewer's Summary Efficacy Conclusion:

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)

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

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

7.1.2 Categorization of Adverse Events

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

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Due to the long history and frequent use of atropine solution, there has been adequate exposure for safety evaluation.

7.2.2 Explorations for Dose Response

Atropine eye drops in concentrations from 0.1% through 1% have been demonstrated to produce clinically significant pupillary dilation and cycloplegia.

7.2.3 Special Animal and/or In Vitro Testing

None

7.3 Major Safety Results

7.3.1 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 including a patent ductus arteriosus in two patients.

7.3.2 Nonfatal Serious Adverse Events

See section 7.3.4.

7.3.3 Dropouts and/or Discontinuations

The majority of reported use involves a single course over a couple of days or a single administration of atropine. In most cases, there was not opportunity to discontinue or dropout once therapy had been administered.

7.3.4 Significant Adverse Events

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.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Light sensitivity is usually the most commonly reported adverse reaction. The most frequently reported systemic events are usually dry mouth, irritability and headaches.

7.4.2 Laboratory Findings

Abnormal clinical laboratory data was not reported in the published study reports. Atropine is not known to cause changes in laboratory findings.

7.4.3 Vital Signs

Atropine is well known in low doses to slow the heart rate, but continued or larger doses will cause tachycardia.

7.4.4 Electrocardiograms (ECGs)

No ECG was reported in the studies performed.

7.4.5 Special Safety Studies/Clinical Trials

No special studies were conducted.

7.4.6 Immunogenicity

Atropine is not believed to cause immunogenicity.

7.5 Other Safety Explorations

Drug-Drug Interactions

The use of atropine and monoamine oxidase inhibitor (MAOI) is generally not recommended because of the potential to precipitate hypertensive crisis.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Atropine sulfate has not demonstrated any genotoxic potential and has not been shown to be carcinogenic.

7.6.2 Human Reproduction and Pregnancy Data

Animal reproduction studies with topical ophthalmic atropine solution have not been conducted. Systemic inhibition of the cholinergic system can interfere with reproductive systems.

7.6.3 Pediatrics and Assessment of Effects on Growth

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.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The signs and symptoms of atropine poisoning or overdose have been well described and are often described by phrases such as: “hot as a hare, red as a beet, dry as a bone, blind as a bat and mad as a hatter.” Severe cases of intoxication can result in ataxia, insomnia, drowsiness, convulsions, high fever and coma. [North RV, Kelly ME. Uses and adverse effects of Atropine. *Ophthalmol Physiol Opt.* 1987; 7(2):109-114.]

7.7 Summary of Safety

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.

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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/

WILEY A CHAMBERS
09/13/2016

WILLIAM M BOYD
09/13/2016

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 208151

Applicant: Alcon Research
Ltd.

Stamp Date: 2/12/2016

Drug Name: Atropine 1%
(atropine sulfate ophthalmic
solution)

NDA Type: Original NDA 505(b)(2)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).				eCTD
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm)	X			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(2)
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?				Literature
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?				No
14.	Describe the scientific bridge (e.g., BA/BE studies)				Same active ingredient used in clinical literature
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: Study Title:		X		

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Sample Size: Treatment Arms: Location in submission:				
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:	X	X		Yes for the mydriasis, cycloplegia, and amblyopia indications. (b) (4)
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
21.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dosage (or dosage range) believed to be efficacious?			X	
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
25.	Has the applicant submitted the coding dictionary ² used for			X	

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	mapping investigator verbatim terms to preferred terms?				
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm)?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?		X		
37.	Are all datasets to support the critical safety analyses available and complete?			X	
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and	X			

as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	adverse dropouts)?				
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?		X		

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Wiley A. Chambers, MD
Reviewing Medical Officer

April 4, 2016
Date

William Boyd, MD
Clinical Team Leader

April 4, 2016
Date

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

/s/

WILEY A CHAMBERS
04/04/2016

WILLIAM M BOYD
04/04/2016