CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213581Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader and Division Director Review of NDA 213581

Review Completion Date	See DARRTS Stamp Date
From	William M. Boyd, M.D., Wiley Chambers, M.D.
Subject	Cross-Discipline Team Leader and Division Director Review
NDA #	213581
Applicant	Paragon BioTeck, Inc
Date of Submission	May 26, 2021
PDUFA Goal Date	March 26, 2022
Proprietary Name	N/A
Established or Proper Name	Atropine Sulfate Ophthalmic Solution, USP 1%
Dosage Form(s)	Topical ophthalmic solution
Recommended Indication/Population	Indicated for: • Mydriasis • Cycloplegia • Penalization of the healthy eye in the treatment of amblyopia
Dosing Regimen(s)	One drop topically to the cul-de-sac of the conjunctiva in one or both eyes as indicated, forty minutes prior to the intended maximal dilation time
Regulatory Action	Approval

Reviewers/Consultants	**Names of Discipline Reviewers**
OND RPM	Dheera Semidey
CDTL	William Boyd
Division Director	Wiley Chambers
Clinical Team Leader	Jennifer Harris
Clinical Reviewer	Shilpa Rose
Pharmacology Toxicology Reviewer	Erin Ruhland
Statistical Reviewer	Abel Eshete
Clinical Pharmacology Reviewer	Selim Fakhruddin,
OND Labeling Reviewer	Derek Alberding
OPQ Drug Substance Reviewer	Jing Li
OPQ Drug Product Reviewer	Anne Marie Russell
OPQ Manufacturing/Facilities Reviewer	Upasana Sahu
OPQ Microbiology Reviewer	Karthik Krishnan
OPQ Biopharmaceutics	Parnali Chatterjee
OPQ RPM	Kelly Ballard
OPQ Technical Lead	Chunchun Zhang
OPDP Reviewer	Carrie Newcomer
DMEPA Reviewer	Nasim Roosta,
DMEPA Team Lead	Valerie Vaughan

CDTL=Cross-Discipline Team Leader
DMEPA=Division of Medication Error Prevention and Analysis
OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion

1. Summary

Atropine is a naturally occurring tropane alkaloid extracted from deadly nightshade (Atropa belladonna), Jimson weed (Datura stramonium), mandrake (Mandragora officinarum) and other plants of the family Solanaceae. It is a secondary metabolite of these plants and has a wide variety of pharmacological effects that have been known about and utilized for hundreds of years. Atropine is a competitive antagonist for the muscarinic acetylcholine receptors. It is classified as an anticholinergic agent since it antagonizes the muscarinic-like actions of acetylcholine and other choline esters.

Atropine is used clinically for a range of purposes including as a temporary blockade of severe or life-threatening muscarinic effects, e.g., as an antisialagogue, an antivagal agent, an antidote for organophosphorus, carbamate, or muscarinic mushroom poisoning, and to treat symptomatic bradycardia. It is also used in combination with diphenoxylate hydrochloride in the management of diarrhea and in the eye as a mydriatic and/or cycloplegic and for the treatment of amblyopia.

This is a 505(b)(2) application which relies on the literature. As required by regulation, it lists two pharmaceutical equivalents as reference listed drugs (RLDs) NDA 206289 Atropine and NDA 208151 Isopto atropine.

The data from the literature contained in the submission and described in this review, establishes the efficacy of Atropine Sulfate Ophthalmic Solution USP, 1% for the indications of cycloplegia, mydriasis, and penalization of the healthy eye in the treatment of amblyopia.

2. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The data contained in this submission establishes the efficacy of Atropine Sulfate Ophthalmic Solution, USP 1% by demonstrating that it is effective in the dilation of the pupil, cycloplegia, and penalization of the good eye in the treatment of amblyopia. 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Multiday pupillary dilation and maximal cycloplegia is commonly by required by clinicians for diagnostic or therapeutic action. Pupillary dilation and cycloplegia for greater than 72 hours is needed in the setting of an ophthalmic examination or in the treatment of ocular inflammation. • Multiday pupillary dilation and maximal cycloplegia are used for penalization of the healthy eye in the treatment of amblyopia.	Atropine acts as a competitive antagonist of the parasympathetic (and sympathetic) acetylcholine muscarinic receptors. Topical atropine on the eye induces mydriasis by inhibiting contraction of the circular pupillary sphincter muscle normally stimulated by acetylcholine. This inhibition allows the countering radial pupillary dilator muscle to contract which results in dilation of the pupil. Additionally, atropine induces cycloplegia by paralysis of the ciliary muscle which controls accommodation while viewing objects. Long-term blurriness of the healthy eye allows for penalization and treatment of amblyopia. Preservative free formulation provides an alternate atropine formulation.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Tropicamide ophthalmic solution available in 0.5% and 1%, and Phenylephrine ophthalmic solution, available in 2.5% and 10% are the most commonly used, marketed topical agents used for short term mydriasis (pupil dilation) • Cyclopentolate available at 0.5%, 1% and 2%, Scopolamine 0.25%, and Homatropine 5% are the most commonly used, marketed topical agents used for the long-term mydriasis (pupil dilation) and cycloplegia (paralysis of the ciliary muscle of the eye). • Atropine ophthalmic sulfate 1% solutions are approved with preservatives. • Patching of the healthy eye is the current treatment to penalize the healthy eye and treat amblyopia.	This product, if approved, would provide an alternative, preservative free delivery of atropine sulfate 1% for diagnostic procedures and therapeutics in conditions where long term pupil dilation and cycloplegia is desired.
Benefit	• Mydriasis (dilation of the pupil) can be achieved pharmacologically by inhibiting the contraction of the circular pupillary sphincter muscle normally stimulated by acetylcholine. This inhibition allows the countering radially pupillary dilator muscle to contract resulting in dilation of the pupil, permitting examination of the retina and other deep structures of the eye. Some mydriatic agents can also be used to achieve cycloplegia (paralysis of the ciliary muscle which controls accommodation while viewing objects) which allows determination of the true refractive error of the eye and can be used for the relief of ciliary spasm in the treatment of uveitis. • Cycloplegics have also been used in patients with amblyopia as a pharmacological alternative to the use of an eye patch to paralyze the ciliary muscles of the healthy eye causing blurred	Atropine Sulfate Ophthalmic Solution, USP 1% was effective in dilation of the pupil, cycloplegia, and penalization for the treatment of amblyopia.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	vision and therefore forcing the child to use the "lazy eye," with the goal of making it stronger.	
Risk and Risk Management	• The treatment emergent adverse events for the atropine 1% preservative free were similar to those observed in the literature.	The literature reviewed for this application demonstrates the safety and efficacy for this product.

3. Background

Mydriasis (dilation of the pupil) can be achieved pharmacologically by inhibiting the contraction of the circular pupillary sphincter muscle normally stimulated by acetylcholine. This inhibition allows the countering radially pupillary dilator muscle to contract resulting in dilation of the pupil, permitting examination of the retina and other deep structures of the eye. Some mydriatic agents can also be used to achieve cycloplegia (paralysis of the ciliary muscle which controls accommodation while viewing objects) which allows determination of the true refractive error of the eye and can be used for the relief of ciliary spasm in the treatment of uveitis.

Cycloplegics have also been used in patients with amblyopia as a pharmacological alternative to the use of an eye patch to paralyze the ciliary muscles of the healthy eye causing blurred vision and therefore forcing the child to use the "lazy eye," with the goal of making it stronger.

Under IND 139379, the pre-IND meeting took place on July 13, 2018. The Agency agreed during the meeting 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. A second meeting took place on January 4, 2021, during which the Agency confirmed that the withdrawal of the Unapproved Drug Initiative (UDI) guidance documents would not affect the successful filing of the NDA via the intended regulatory pathway for Atropine Sulfate Ophthalmic Solution, USP 1%, as previously agreed with the Division of Ophthalmology.

The product has been marketed as an unapproved drug product in the United States.

Topical Pharmaceutical Ophthalmic Solutions Used for Pupil Dilation

PRODUCT	DURATION	ACTION	APPROVED	NOTES
Phenylephrine	~3 to 8 hours	Mydriasis	Yes	2.5% and 10% solutions
Tropicamide	~6-7 hours	Mydriasis & Cycloplegia	Yes	0.5% and 1% solutions
Cyclopentolate	~12 hours	Mydriasis & Cycloplegia	Yes	1% solution
Scopolamine	~72 hours	Mydriasis & Cycloplegia	No	
Homatropine	~48 hours	Mydriasis & Cycloplegia	No	
Atropine	~12 days	Mydriasis & Cycloplegia, and Treatment of Amblyopia	Yes	Available in ointment and solution.

4. Product Quality

OPQ completed their original integrated review of the original application on 2/24/2022.

Atropine Sulfate Ophthalmic Solution USP, 1% is a sterile, aqueous solution which does not contain an antimicrobial preservative. The drug product is aseptically prepared using [redacted] technology and delivered into a 0.4 mL, unit dose, LDPE vial. The drug product is formulated for topical, ocular application. In the formulation, [redacted].

The drug product is regulated as a drug device combination product per the Genus decision. The 356h form was updated to indicate this classification on 2/14/2022. CDRH confirmed that no CDRH GMP/QS consult is necessary for this product.

4.1. Drug Product Composition

Composition

Component	Formulation Quantity (% w/v)	Batch Quantity (mg/mL)	Function
Atropine Sulfate	1%	10[a]	Active ingredient
Boric acid	[redacted]		
Hydroxypropyl methylcellulose [redacted]			
Hydrochloric acid, [redacted]	As needed	As needed	pH Adjustment
Sodium hydroxide [redacted]	As needed	As needed	pH Adjustment
Water for Injection (WFI)	[redacted]		

Source: Module 2.3.P.1 Description and Composition of the Drug Product

4.2. Product Specifications

Release and Shelf-Life Specifications

Test	Procedure	Release	Shelf Life
Description	Visual	Clear colorless solution. Essentially Free of Visible Particles	Colorless to slightly yellow solution. Essentially Free of Visible Particles
ID-A Retention Time	[redacted]	RT of the major peak of the sample solution corresponds to that of the standard solution	Not tested
ID-B UV		Meets requirements	Not tested
Atropine Sulfate Assay		93.0 to 107.0%	93.0 to 107.0%
Tropic acid [redacted] Impurity		NMT [redacted]%	NMT [redacted]%
[redacted]		NMT [redacted]%	NMT [redacted]%
Apoatropine [redacted]		NMT [redacted]%	NMT [redacted]%
Any individual unspecified impurity		NMT [redacted]%	NMT [redacted]%
Total impurities		NMT 7.0%	NMT 7.0%
pH	USP <791>	[redacted] to [redacted]	[redacted] to [redacted]
Osmolality	USP <785>	[redacted] to [redacted] mOsm kg	[redacted] to [redacted] mOsm kg
Particulate Matter	USP <789>	≥ [redacted] µm: NMT [redacted] particles/mL ≥ [redacted] µm: NMT [redacted] particles/mL ≥ [redacted] µm: NMT [redacted] particles/mL	[redacted] µm: NMT [redacted] particles/mL [redacted] µm: NMT [redacted] particles/mL [redacted] µm: NMT [redacted] particles/mL

Test	Procedure	Release	Shelf Life
Minimum Fill Volume	USP <755>	The average content of 10 containers is not less than the labeled amount (0.4 mL), and the net content of any single container is not less than (b) (4)% of the labeled amount	Not tested
Content Uniformity	USP <905>	Compliant with <905>	Compliant with <905>
Sterility	USP <71>	Meets the requirements	Meets the requirements
Viscosity	USP <912>	< (b) (4) cps	< (b) (4) cps

UV=Ultraviolet, RRT=Relative Retention Time, USP=United States Pharmacopeia

Source: Module 3.2.P.5.1 Specification(s)

4.3. Microbiology

The applicant has provided adequate sterility assurance. No approvability issues were identified from a sterility assurance or microbiology product quality perspective.

4.4. Establishment Information

The Office of Pharmaceutical Manufacturing Assessment (OPMA) has issued an overall acceptable recommendation for all the facilities on Feb 23, 2022.

Manufacturer	Contact Information (Name of Contact, Address, Telephone and Email)	US Drug Registration No. (FEI), MF No., DUNS No, DMF No.	Manufacturing Steps/Type of Testing	Ready for Inspection (Y/N)
Drug Substance				
(b) (4)				

Status: Approved, based on previous history

(b) (4)

Status: Approved, based on previous history

Manufacturer	Contact Information (Name of Contact, Address, Telephone and Email)	US Drug Registration No. (FEI), MF No., DUNS No, DMF No.	Manufacturing Steps/Type of Testing	Ready for Inspection (Y/N)
Drug Product				
Unither Manufacturing, LLC. (Unither)	Office: 775 Jefferson Rd. Site: 331 Clay Road, Rochester NY 14623 USA Contact Person: Renee Wagner Email address: Renee.Wager@unither-pharma.com	FEI Number: 1314625 DUNS Number: 079176615	Drug product manufacturer Release testing Stability testing Primary and secondary packaging	Yes

Profile: SLQ
Status: PAI completed. Final PAI outcome: VAI
Facility: Approved based on PAI

4.5. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps

There are no post-marketing commitments or requirements recommended.

4.6. OPQ Recommendation

NDA 213581 is recommended for approval from Product Quality perspective.

5. Nonclinical Pharmacology/Toxicology

From the original Nonclinical Pharmacology/Toxicology Review dated 3/2/2022:

The Applicant filed the NDA as a 505(b)(2) application. All nonclinical pharmacology/toxicology data

included in the application are derived from published literature sources.

The receptors antagonized by atropine are the peripheral structures that are stimulated or inhibited by muscarine (i.e., exocrine glands and smooth and cardiac muscle). Findings in nonclinical studies reflect this mechanism of action including mydriasis, tachycardia, decreased water intake, decreased salivation, water retention and decreased urine volume. Chronic systemic 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 proliferation of the uterine tissue. Atropine administration was associated with a reduction of uterine parameters like uterine diameter, thickness of myometrium and endometrium and surface epithelial cell height. The results suggest that the anticholinergic effects of atropine may interfere with the rhythmic release of pituitary gonadotropins and result in decreased estrogen.

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

The application is approvable from a Pharmacology/Toxicology perspective.

6. Clinical Pharmacology

The onset of action after administration of Atropine Sulfate Ophthalmic Solution USP, 1% generally occurs in minutes with maximal effect seen in hours and the effect lasts multiple days.

From the original Clinical Pharmacology Review dated 2/17/2022:

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. Specifically, the supportive clinical

pharmacology/PK information in this NDA included two literature studies, ([1]) Kaila 1999 and ([2]) Lahdes 1988 to evaluate the systemic exposure to atropine following the administration of 1% atropine sulfate ophthalmic solution. In addition, the Applicant has requested a waiver of evidence of in vivo bioavailability (BA) or bioequivalence (BE) studies for Atropine Sulfate Ophthalmic Solution, USP 1%, on the basis of compatibility with public health due to its long history of clinical safety and effectiveness.

The Clinical Pharmacology review team recommends approval of NDA 213581 for Atropine Sulfate Ophthalmic Solution, USP 1%.

7. Clinical Efficacy

From the original Medical Officer Review dated 3/2/2022:

7.1. Table 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
4	Chia A	Atropine for the Treatment of Childhood Myopia: Safety and Efficacy of 0.5%, 0.1% and 1% Doses (Atropine for the Treatment of Myopia 2)	Ophthalmology 119:347-354.	2012	Ashwood Labs, Macau, China
5	Chua WH	Atropine for the Treatment of Childhood Myopia	Ophthalmology 113:2285-2291	2006	Alcon
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
7	Fan DSP	Topical Atropine in Retarding Myopic Progression and Axial Length Growth in Children with Moderate to Severe Myopia: A Pilot Study	Jpn J Ophthalmol 51:27-33	2007	Alcon
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
11	Li	Atropine Slows Myopia Progression More in Asian than White Children by Meta-analysis	Optomety and Visual Science	2014	Not identified
12	Liu	Evaluation of Cycloplegic Effect of Cyclopentolate and Atropine	Chin J Exp Ophthalmol 30(4): 353-356	2012	Shenyang Xingqi Pharmaceutical Co., Ltd.

[1] Kaila T, Korte JM, Saari KM (1999). Systemic bioavailability of ocularly applied 1% atropine eyedrops. Acta Ophthalmol Scand., vol. 77, pp 193-196.
[2] Lahdes K, Kaila T, Huupponen R, Salminen L, and Iisalo E (1998). Systemic absorption of topically applied ocular atropine. Clin. Pharmacol. Ther., vol. 44(3), pp 310-314.

#	First Author	Title	Journal	Year	Source of Drug Product
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 Ophthalmol 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
18	Shih YF	An intervention trial on efficacy of atropine and multi-focal glasses in controlling myopic progression	Acta Ophthalmol Scand 79:233-236	2001	Not identified
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
20	Tong L	Atropine for the Treatment of Childhood Myopia: Effect on Myopia Progression after Cessation of Atropine	Ophthalmol 116:572-579	2009	Alcon (Puurs, Belgium)
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, Adrenaline 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

#	First Author	Title	Journal	Year	Source of Drug Product
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
53	Riddell WJB	A Clinical Trial of a Synthetic Mydriatic	Brit J Ophthalmol 30:1-7	1946	Not identified
54	Romano PE	Management of Progressive School Myopia with Topical Atropine Eyedrops and Photochromic Bifocal Spectacles	Binocular Vision and Strabismus Quarterly 15(3) 257-260	2000	Not identified
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
58	Shih YF	Effects of Different Concentrations of Atropine on Controlling Myopia in Myopic Children	J Ocular Pharm 15(1):85-90	1999	Not identified
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

7.2. Review Strategy

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. The formulations were not all the same.

7.3. Mydriasis and Cycloplegia

Auffarth 1992
Refractive measurements under atropine cycloplegia were tested in 90 strabismus children aged two to seven years. Refraction was determined by an autorefractor 90 minutes after application of two drops of atropine (0.5% children <2.5 years; 1.0% atropine children >2.5 years) and compared with the results after 3 days of receiving 1 atropine eye drop 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.

Barbee 1957
Double-blind, placebo controlled.

Barbee and colleagues studied the mydriatic and cycloplegic effect of a number of parasympatholytic and sympathomimetic eye drops including atropine 1% compared to 2 different placebos (normal saline and boric acid 4%). Thirty subjects (30 eyes) were tested for each active agent or placebo. IOP was measured 2 minutes after installation of a topical ocular anesthetic (pontocaine 0.5%) followed by evaluations for pupil size (mydriasis) and reaction to light 1957 and accommodation (cycloplegia) 20 minutes later. Mydriasis was measured with a ruler on the bridge of the nose and cycloplegia with a Snellen Rating Card.

Three drops of an agent were instilled into one eye of a subject with the other eye acting as a control. The results showed that atropine 1% demonstrated significant mydriasis when compared to the sympathomimetic agents and placebo and highly significant (almost complete) cycloplegia. There was no significant increase in IOP with any of the agents tested. The most common adverse events were blurred vision and burning. Conjunctival hyperemia and tearing was observed in 6 of the 30 atropine subjects. The parasympatholytic agents, scopolamine, atropine and homatropine all induced significant mydriasis of essentially equal degrees in all three iris color types. Scopolamine and atropine uniformly produced the greatest cycloplegia in all three eye type groups.

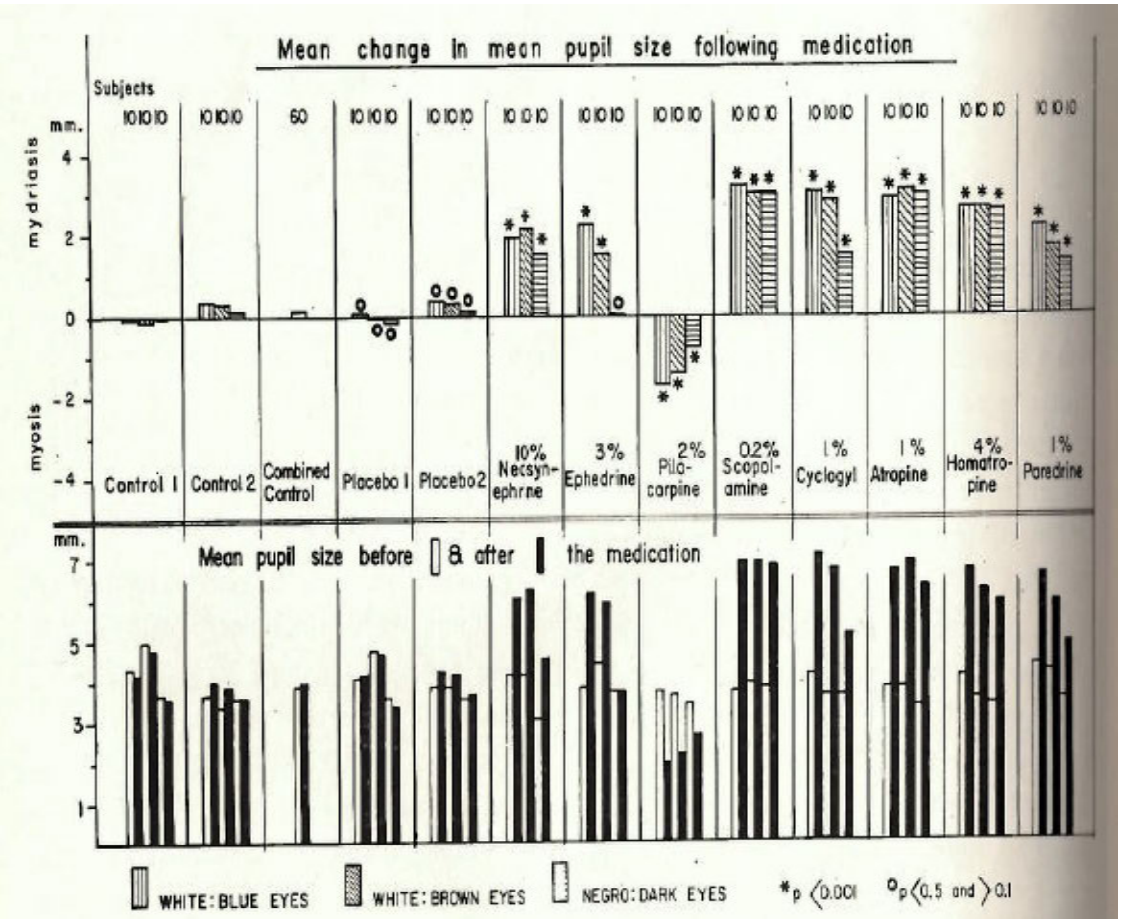

Fig. 1 (Barbee and Smith). Upper half: The mydriatic effect reflected by the mean change in mean pupil size for each eye type group in each medication group observed 40 minutes after instillation of the agents.

Celebi 1999

This study compared the cycloplegic effect of cyclopentolate HCl 1% and atropine sulfate 1% in patients with refractive accommodative esotropia by means of retinoscopy, autorefractometer and measurement of lens thickness by biometry.

Thirty-two children ages 5 to 10 years with a deviation of under 10 prism diopters underwent retinoscopic, autorefractometric and biometric evaluations at first in dry and then wet conditions with cyclopentolate HCl 1% and then atropine sulfate 1% one week apart. Cyclopentolate 1% and atropine 1% produced similar and sufficient cycloplegia in children with refractive accommodative esotropia.

No safety findings were reported in this study.

Chia 2012 Randomized, Double-blind, 2 year study; Atropine 0.5% (161 subjects), Atropine 0.1% (155 subjects), Atropine 1% (84 subjects)

Accommodation (D)	1%	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.

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

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

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

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 increases with atropine were clinically significant but were less than the triple combination of phenylephrine 2.5%, tropicamide 1%, and cyclopentolate 1%.

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

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

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

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

7.4. Penalization of the Healthy Eye in the 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%).

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 literature article describes a randomized, multicenter clinical trial. This trial demonstrates a clinically significant improvement in visual acuity achieved by atropine penalization of the eye with better visual function.

Foley-Nolan et al. 1997 Atropine penalization versus occlusion as the primary treatment for amblyopia

Aims/background: Pharmacological penalization of non-amblyopic eyes is an infrequently used alternative to occlusion for treating amblyopia. The authors compared the efficacy of atropine penalization and that of occlusion as a primary treatment for amblyopia.

Methods: Thirty six newly diagnosed patients with amblyopia were allocated to two groups for treatment. Eighteen patients in each group were treated either with atropine penalization (group A) or occlusion therapy (group P).

Results: There was a statistically significant improvement in visual acuity in both groups treated. In group A improvement of the geometric mean visual acuity of the amblyopic eye was from 6/50 to 6/11 ($p < 0.001$). In group P improvement of the geometric mean visual acuity was from 6/60 to 6/19 ($p < 0.001$). In group A non-compliance with treatment was only 6% (2/18). Non-compliance in group P was 45% (8/18) at some stages of the treatment. Neither group produced an incidence of occlusion amblyopia.

Conclusions: In this study atropine penalization has been shown to be as effective as occlusion therapy in the treatment of amblyopia. Patient acceptance of atropine penalization was superior to that for occlusion therapy as was shown by the compliance rate. Atropine treatment was also advantageous in that compliance could be readily checked by inspection.

This literature article describes a randomized, single center clinical trial. This trial demonstrates a clinically significant improvement in visual acuity achieved by atropine penalization of the eye with better visual function.

Li et al. 2019 Conventional occlusion versus pharmacologic penalization for amblyopia

Li T, Qureshi R, Taylor K. Conventional occlusion versus pharmacologic penalization for amblyopia. Cochrane Database of Systematic Reviews 2019, Issue 8. Art. No.: CD006460.
DOI: 10.1002/14651858.CD006460.pub3.

Background: Amblyopia is defined as impaired visual acuity in one or both eyes without demonstrable abnormality of the visual pathway and is not immediately resolved by wearing glasses.

Objectives: In performing this systematic review, we aimed to synthesize the best available evidence regarding the effectiveness and safety of conventional occlusion therapy compared to atropine penalization in treating amblyopia.

Search methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) (2018, Issue 8); Ovid MEDLINE; Ovid Embase; LILACS BIREME; ClinicalTrials.gov; ISRCTN; and the WHO ICTRP on 7 September 2018.

Selection criteria: We included randomized/quasi-randomized controlled trials comparing conventional occlusion to atropine penalization for amblyopia.

Data collection and analysis: Two review authors independently screened abstracts and full-text articles, abstracted data, and assessed risk of bias.

Main results: We included seven trials (five randomized controlled trials and two quasi-randomized controlled trials) conducted in six countries (China, India, Iran, Ireland, Spain, and the United States) with a total of 1177 amblyopic eyes. Three of these seven trials were from the original 2009 version of the review. We assessed two trials as having a low risk of bias across all domains, and the remaining five trials as having unclear or high risk of bias for some domains. As different occlusion modalities, atropine penalization regimens, and populations were used across the included trials, we did not conduct any meta-analysis due to clinical and statistical heterogeneity. Evidence from six trials (two at low risk of bias) suggests that atropine penalization is as effective as conventional occlusion in improving visual acuity. Similar improvement in visual acuity was reported at all time points at which it was assessed, ranging from five weeks (improvement of 1 line) to 10 years (improvement of greater than 3 lines). At six months, although most participants (363/522) come from a trial rated as at low risk of bias with a precise estimate (mean difference (MD) 0.03, 95% confidence interval (CI) 0.00 to 0.06), two other trials rated as at high risk of bias produced inconsistent estimates and wide confidence intervals (MD -0.02, 95% CI -0.11 to 0.07 and MD -0.14, 95% CI -0.23 to -0.05; moderate-certainty evidence). At 24 months, additional improvement was found in both groups, but there continued to be no meaningful difference between those receiving occlusion and those receiving atropine therapies (moderate-certainty evidence). We did not find any difference in ocular alignment, stereo acuity, or sound eye visual acuity between occlusion and atropine penalization groups (moderate-certainty evidence). Both treatments were well tolerated. Atropine was associated with better adherence (moderate-certainty evidence) and quality of life (moderate-certainty evidence), but also a higher reported risk of adverse events in terms of mild reduction in the visual acuity of the sound eye not requiring treatment and light sensitivity (high-certainty evidence). Skin, lid, or conjunctival irritation were more common among participants receiving patching than those receiving atropine (high-certainty evidence). Atropine penalization costs less than conventional occlusion.

Authors' conclusions: Both conventional occlusion and atropine penalization produce visual acuity improvement in the amblyopic eye. Atropine penalization appears to be as effective as conventional occlusion, although the magnitude of improvement differed among the trials we analyzed.

This literature summary describes adequate and well controlled studies in different regions of the world supporting the safety and effectiveness of atropine penalization in the treatment of amblyopia.

Riddell WJB 1946 A Clinical Trial of a Synthetic Mydriatic

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

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

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

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

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

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 cycloplegia.

Hiatt RL 1983 Comparison of Atropine and Tropicamide in Esotropia

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

Atropine provided clinically important cycloplegia.

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

Diopters of Hypermetropia found after Four or Eight Instillations of Atropine

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

Atropine provided clinically important cycloplegia.

7.5. Preservative Free Atropine

Few of the publications presented as representative studies for safety and efficacy identify the source of the atropine product which limits the ability to make a direct comparison between the safety and efficacy of preserved and non-preserved formulations. However, any studies using atropine prior to the 1950's would be preservative free and hence supportive of the safety and efficacy of the proposed drug product. Additionally, those studies where the product was "not identified" or could not be determined that a preservative free product was administered are supportive information for the proposed drug product.

7.6. Efficacy Summary Statement

The data from the literature contained in the submission and described in this review, establishes the efficacy of Atropine Sulfate Ophthalmic Solution USP, 1% for the indications of cycloplegia, mydriasis, and penalization of the healthy eye in the treatment of amblyopia.

8. Safety

From the original Medical Officer Review dated 3/2/2022:

8.1. Safety Database

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.

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.

8.2. 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.

8.3. 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.

8.4. Safety Summary Statement

The safety of Atropine Sulfate Ophthalmic Solution USP, 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

The application did not raise any new efficacy or safety issues. There were no issues that were thought to benefit from a discussion at an advisory committee meeting. An Advisory Committee Meeting was not held for the NDA.

10. Pediatrics

This application did not trigger PREA, i.e., no new indication, new dosage form, a new dosing regimen, a new route of administration, or new active ingredient.

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 (b) (4) of age should be limited to no more than a single drop per day.

11. Biostatistics

Other applications for Atropine Sulfate Ophthalmic Solution USP, 1% have received approval by the FDA for the same indications based on the same published literature. A full statistical review would be redundant; Clinical agrees that no formal statistical review is needed for this application.

12. Financial Disclosure

Not applicable. This is a literature supported NDA.

13. Study Integrity

An Office of Scientific Investigations (OSI) audit was not requested. This is a literature supported NDA.

14. DMEPA

DMEPA participated in labeling discussions and finalized a labeling review of the submitted labeling on 11/19/2021.

The applicant did not submit a request for review of a proposed proprietary name.

15. OPDP

The Office of Prescription Drug Promotion (OPDP) participated in labeling discussions and completed a review of the product labeling dated 2/23/2022.

16. Patient Experience Data

Patient Experience Data Relevant to this Application

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		Section 7
		☒	Patient reported outcome (PRO)	
		☒	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	Section

		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

17. Labeling

NDA 213581 Atropine Sulfate Ophthalmic Solution, USP 1% labeling submitted to the Agency on 3/14/2022 and attached to the end of this review is acceptable.

18. Regulatory Action

NDA 213581 Atropine Sulfate Ophthalmic Solution, USP 1% will be approved for 1) Cycloplegia 2) Mydriasis, and 3) the Penalization of the healthy eye in the treatment of amblyopia.

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

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM M BOYD
03/15/2022 03:03:04 PM

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