# CLINICAL REVIEW of NDA 208-151

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| Application Type | Original NDA |
| Application Number(s) | 208-151 |
| Priority or Standard | Standard Review |
| Submit Date(s) | 2/12/2016 |
| Received Date(s) | 2/12/2016 |
| | |
| 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<br>6201 South Freeway<br>Fort Worth, TX 76134-2099 |
| | |
| Proposed Indication(s) | Cycloplegia<br>Pupillary dilation<br>Amblyopia<br>(b) (4) |

Template Version: March 6, 2009

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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** (b) (4)

| 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 |
| (b) (4) | | | No |
| | | | 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

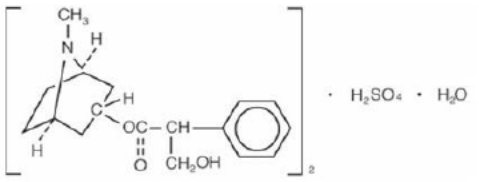
The clinical studies included in this application appeared to conform to Good Clinical Practices.

### 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 |
| Purified Water | (b) (4) | |

*Quantity equivalent to 8.3 mg/mL of Atropine.

**Drug Product Specifications**

(b) (4)

**Reviewer's Comments:** *Acceptable.*

**Primary Packaging Materials and Components**

| Component | Component Material | (b) (4) Suppliers |
|---|---|---|
| Round bottle | Low Density Polyethylene | (b) (4) |
| Dispensing plug | 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 cholinoceptor binding assay.

The mean area under the curve from zero to infinitum ($AUC_{0-\infty}$) 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 ± sd, n=6), respectively. The mean bioavailability was 63.5±28.6% (min 19%, max 95%). Large inter-individual differences characterized the absorption and elimination phases of 1-hyoscyamine kinetics. The terminal half-life (t½ß) 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 | Preolperative 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 | (b) (4) | | | | |
| 5 | | | | | |
| 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 | (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 |
| 11 | (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 |
| 18 | (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 |
| 20 | (b) (4) | | | | |
| 21 | Arnold RW | Duration and Effect of Single Dose Atropine: Paralysis of Accommodation in Penalization Treatment of Functional Amblyopia | Binocular Vision & Strabismus Quarterly; 19(2):81-86. | 2004 | Alcon |
| 22 | Auffarth G | Cycloplegic refraction in children: Single-dose-atropinization versus three day atropinization | Documenta Ophthmologica 80:353-362 | 1992 | Not identified |
| 23 | Bartlett, JD | Administration of and Adverse Reactions to Cycloplegic Agents | Am J Optometry 55(4): 227-233 | 1978 | Not identified |

| # | 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 |
| 54 | (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 |
| 58 | (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<br><br>Cycloplegia | Non-randomized<br>Double-blind | Atropine 1%<br>Plus 9 other agents<br>Total of 300 patients |
| Chia 2012 | Pupil dilation<br><br>Cycloplegia | Randomized<br>Double-blind | Atropine 0.5% (161)<br>Atropine 0.1% (155)<br>Atropine 0.01% (84) |
| Ebri 2007 | Pupil dilation<br><br>Cycloplegia | Randomized<br>Parallel groups | Atropine 1% (79)<br>Cyclopentolate 1% +Tropicamide 0.5% (78)<br>Cyclopentolate 1% (76) |
| Marron 1940 | Pupil dilation<br><br>Cycloplegia | Non-randomized | Atropine 1% (107)<br>Scopolamine 0.5% (21)<br>Homatropine 5% (25) |
| Wolf 1946 | Pupil dilation<br><br>Cycloplegia | Non-randomized<br>Open label | Atropine 1% 15 eyes (13)<br>Methylatropine 1% 23 eyes(21)<br>Homatropine 1% 7 eyes (7) |
| Kawamoto 1997 | Cycloplegia | Sequential groups | Atropine 0.5% (<6yrs old) or 1% (6 and older)<br>Cyclopentolate 1%<br>Total of 51 children |
| Stolovitch 1992 | Cycloplegia | Subject their own control /comparison to baseline | Atropine 1% (36) |
| Pediatric Eye Disease Group 2008 | Amblyopia | Randomized<br>Parallel groups<br>Blinded assessment | Atropine 1% (95)<br>Patching (98) |
| [redacted] | | | (b) (4) |

## 6 Review of Efficacy

### 6.1 Mydriasis and Cyclоplegia

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

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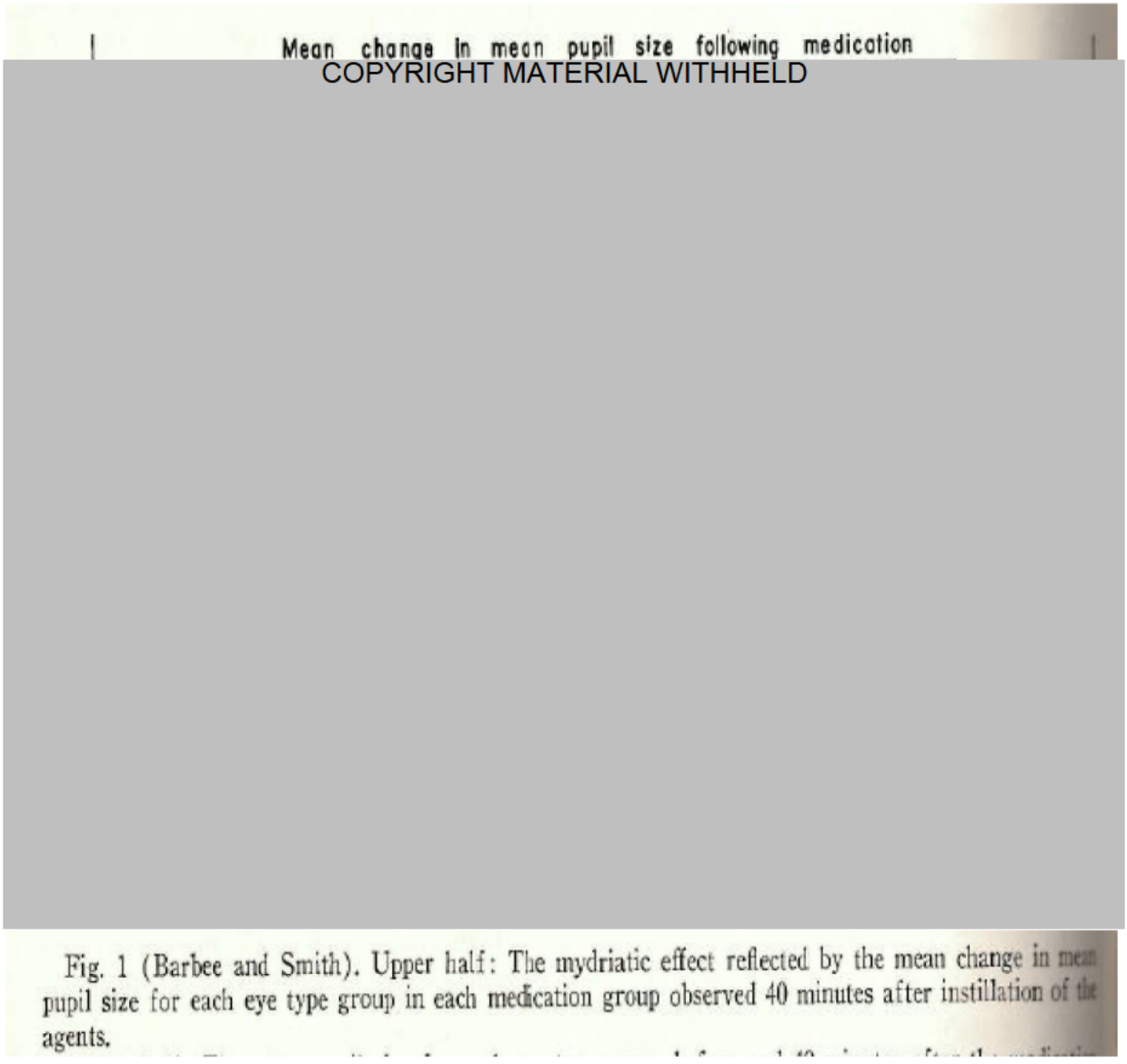



Fig. 1 (Barbee and Smith). Upper half: The mydriatic effect reflected by the mean change in mean pupil size for each eye type group in each medication group observed 40 minutes after instillation of the agents.

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

**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, Methylatropine 1% 23 eyes, Homatropine 1% 7 eyes**

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

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

**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<br>Children younger than 6 years | 52 eyes<br>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 ± 2.45 D) and cyclopentolate refraction (mean +3.58 ± 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.**

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 |

**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

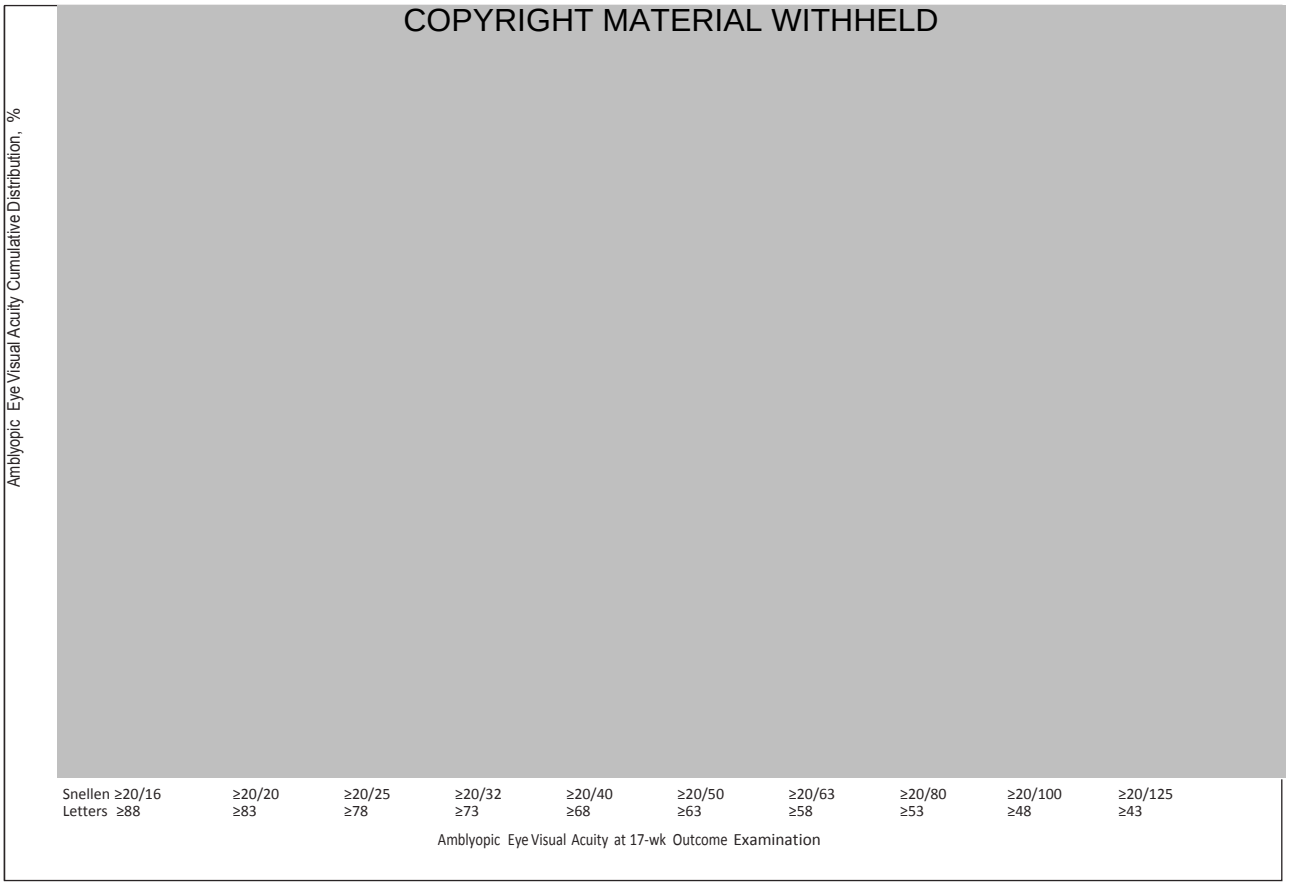
**Pediatric Eye Disease Group 2008 Randomized Parallel groups masked assessment**
**Atropine 1% vs Patching**

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%).




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 regiments of administration. Studies of the treatment of myopia and amblyopia used daily administrations for periods of months (amblyopia) to years (myopia).

### 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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/s/

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WILEY A CHAMBERS
09/13/2016

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09/13/2016