CLINICAL PHARMACOLOGY REVIEW

NDA	**206-289**
Submission Date:	**23 October 2013**
Drug Product:	**Atropine Sulfate Ophthalmic Solution USP, 1% w/v (10 mg/mL, as (b) (4) atropine sulfate)**
Trade Name:	**N/A**
Sponsor:	**Akorn, Inc.**
Submission Type:	**505(b)(2) NDA; Priority; Reference:Atropine Sulfate Injection 0.1 mg/mL and 0.05 mg/mL (Atropine Sulfate ANSYR® Plastic Syringe)**
Proposed indications/ dosing regimens:	• **for producing cyclopegia: (b) (4)** • **(b) (4) for pupil dilation: For (b) (4) mydriasis, (b) (4)**
OCP Reviewer:	**Gerlie Gieser, PhD**
Team Leader:	**Philip Colangelo, PharmD, PhD**

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I. Executive Summary

Background

Atropine is an anticholinergic agent that is capable of blocking muscarinic receptors on the iris sphincter muscle and the ciliary muscle controlling lens curvature, resulting in pupil dilation (mydriasis) and temporary paralysis of accommodation (cycloplegia). Although extracts containing atropine had been used since ancient times for pupil dilation, the isolation and accurate characterization of the anticholinergic effects of atropine in its pure form did not occur until the 1800's.

The NDA sponsor has been marketing 1% atropine sulfate ophthalmic solution under "grandfathered" status since 19 June 1995. In accordance with the recommendations in the *FDA Guidance for Marketed Unapproved Drugs*, the sponsor filed a literature based 505(b)(2) NDA. Injectable atropine sulfate products

ATROPEN® (intramuscular) and ANSYR® (intravenous) were approved by FDA in 1973 and 2001, respectively, for non-ophthalmic indications (i.e., for the treatment of pesticide, nerve toxin, and/or muscarinic mushroom poisoning).

The NDA sponsor is seeking approval of the proposed 1% atropine sulfate ophthalmic solution for various indications. To date, the FDA Medical reviewer (Dr. Wiley Chambers) is recommending approval of 1% atropine sulfate ophthalmic solution for producing mydriasis, for producing cycloplegia, as well as for treatment of amblyopia also known as "lazy eye" (based on effect of mydriasis and cycloplegia on the visual acuity of the "good" eye). (b) (4)

A. Recommendations

From a Clinical Pharmacology perspective, this 505(b)(2) NDA for 1% atropine sulfate ophthalmic solution is acceptable provided that satisfactory agreement is reached between the sponsor and the FDA regarding the language in the package insert.

Based on the review of available clinical pharmacokinetic (PK) and pharmacodynamic (PD) literature data, as well as efficacy/safety data from published clinical trials for 1% atropine sulfate ophthalmic solutions, the Clinical Pharmacology reviewer recommends the approval of the proposed 1% atropine sulfate ophthalmic solution for producing mydriasis and/or cycloplegia in adult patients and pediatric patients. See Part III of this NDA review for the detailed labeling recommendations.

B. Post-Marketing Commitments/Requirements

None.

C. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The NDA sponsor did not conduct clinical pharmacology studies or clinical efficacy and safety trials (nor nonclinical studies) specific for the proposed 1% atropine sulfate ophthalmic solution. However, the available literature is adequate to characterize the systemic pharmacokinetics and the pharmacodynamics of topical ocular atropine, and to support the recommended dosing regimens of the proposed 1% atropine sulfate ophthalmic solution for producing mydriasis and cycloplegia.

Systemic Pharmacokinetics (PK) and Systemic Pharmacodynamics (PD):

The Clinical Pharmacokinetics package of this NDA consisted of 5 literature studies but only the publications from the two studies [Kaila, et al (1999); Lahdes, et al (1988)] that evaluated the PK of topical ocular atropine were reviewed. Note that per the sponsor, the average drop size or volume of the proposed to-be-marketed 1% atropine sulfate ophthalmic solution is 37 microliters.

In the open-label, randomized, crossover PK and PD study conducted by Kaila et al (1999), six healthy subjects (24 to 29 years old) received single 0.3 mg doses of atropine sulfate administered as bolus intravenous injection and 0.3 mg administered as 30 microliters of 1% atropine sulfate solution instilled into the study eye, with a 2-week washout period between treatments. The mean ± SD bioavailability of topically applied atropine (measured as l-hyoscyamine, the pharmacologically active isomer) was 63.5 ± 28.6% (range 19 to 95%) of the intravenously administered dose. The mean ± SD peak plasma concentration (Cmax) of l-hyoscyamine for the ophthalmic solution was 288 ± 73 pg/mL, with a mean time-to-maximum concentration (Tmax) of 28 minutes (range: 3 to 60 minutes) post-instillation. The terminal elimination half-life of l-hyoscamine was not dependent on the route of administration (2.97 ± 1.22 hours for intravenous and 2.45 ± 0.76 hours for topical ocular). No statistically significant differences in systolic and diastolic blood pressure or heart rate between treatments were reported.

In the randomized, placebo-controlled PK and PD study conducted by Lahdes, et al (1988), the systemic exposure to l-hyoscyamine, and the anti-cholinergic effects of atropine were investigated in eight ocular surgery patients 56 to 66 years of age, following a single topical ocular 0.4 mg atropine dose (given as 40 microliters of 1% atropine sulfate ophthalmic solution). The mean ± SD Cmax of l-hyoscyamine in these patients was 860 ± 402 pg/mL, achieved within 8 minutes of eyedrop instillation. There were no

statistically significant increases in the blood pressure, heart rate, and saliva secretion in patients treated with topical ocular atropine sulfate, compared to the 8 patients who received the placebo eye drop.

In the Kaila (1999) study, the plasma elimination half-life of atropine following topical ocular administration and following intravenous administration of atropine sulfate in healthy adult subjects 24 to 29 years old was similar to that following intravenous administration of atropine sulfate in healthy adults 16 to 58 years and children > 2 years. The US Package Insert of ATROPEN® (intramuscular atropine sulfate) states: Following intravenous administration, the mean ± SD elimination half-life ($t_{1/2}$) of atropine was reported to be longer in pediatric subjects under 2 years (6.9 ± 3.3 hours) and in geriatric patients 65-75 years (10.0 ± 7.3 hours), compared to in children over 2 years (2.5 ± 1.2 hours) and in adults 16-58 years (3.0 ± 0.9 hours).

Ocular Pharmacodynamics (PD):
With 1% atropine sulfate ophthalmic solution, full mydriasis is achievable with 1 drop; multiple eyedrops are needed to achieve full cycloplegia. Full recovery from these effects could take up to 18 days.

Mydriasis
Based on the study conducted Wolf and Hodge (1946) in healthy subjects 16 to 37 years old, 1 drop of 1% atropine sulfate ophthalmic solution into the eye produced a maximum pupil diameter of 8.3 mm (2.5-fold greater than normal size) within 40 minutes of eye drop instillation. Recovery started at 6 hours after instillation of the eye drop, and it took up to 12 days for the pupil diameter to fully return to its normal size.

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

Systemic Exposure-Safety Considerations and Dosage Recommendations:
(Note that this review focused on the published clinical trials considered adequate by the FDA Medical reviewer.)

A single drop (~ 40 microliters) of 1% atropine sulfate ophthalmic solution into an eye contains 0.4 mg of atropine sulfate. Assuming a mean absolute bioavailability (F_{ocul}) of 65% and a maximum individual subject F_{ocul} of 95%, the total systemic atropine exposures (i.e., AUC) each time 1 drop of the proposed to-be-marketed eyedrops is instilled into both eyes is not expected to be higher than that achieved in adults and children ≥ 4 years old after receiving one intramuscular ATROPEN® dose (1 to 2 mg) as antidote for mild poisoning. Additionally, based on the Lahdes, et al (1999) study, the mean plasma atropine (as l-hyoscyamine) Cmax in ocular surgery patients 56 to 66 years old who received a single topical ocular 0.4 mg dose of 1% atropine sulfate ophthalmic solution is 10% of the mean plasma Cmax following a single intramuscular 2 mg dose of ATROPEN®.

Pediatric patients ≥ 4 years old
Pediatric patients ≥ 4 years old should receive the adult dosages of 1% atropine sulfate ophthalmic solution. In the randomized, double-blind clinical trial conducted by Ebri, et al (2007) in 70 Nigerian children 4 to 15 years old with dark irides, 1 drop of 1% atropine sulfate ophthalmic solution instilled into each eye three times daily for 3 days produced mydriasis (pupil diameter ≥ 6 mm) and cycloplegia (RA of 0 to 0.5 D) in 100% of the children. No systemic side effects were reported.

Pediatric patients < 4 years old
There appears to be literature supporting the efficacy and safety of 1% atropine sulfate ophthalmic solution in children 5 months to < 4 years old (Stolovitch et al., 1992). Assuming 65% mean systemic bioavailability, the systemic atropine exposures in children <5 months following the instillation of 1 drop of 1% atropine sulfate ophthalmic solution in each eye would be higher than that resulting from one intramuscular dose of ATROPEN® in the same pediatric age group with mild symptoms of poisoning (0.5 mg versus 0.25 mg). Following intravenous administration, the plasma elimination half-life of atropine is reported to be longer in pediatric subjects < 2 years than in young adults (7 hours versus 3 hours). Per Dr. Chambers, there is adequate evidence that 1% atropine sulfate at the recommended dosage is safe in pediatric patients < 4 years old.

Elderly and/or ocular surgery patients
No adjustment in the topical ocular dosage of 1% atropine sulfate ophthalmic solution is needed in elderly and/or ocular surgery patients. That the dose-normalized mean plasma Cmax of l-hyoscyamine was approximately 2-fold higher and the Tmax was shorter (8 minutes versus 28 minutes) in the Lahdes, et al (1988) study than in the Kaila, et al (1999) study could be due in part to the impact of advanced age and/or the compromised corneal barrier (as a result of ocular surgery) on the rate and extent of systemic absorption of topical ocular atropine. The administration of a single 0.4 mg dose of atropine sulfate (given as 40 microliters of 1% atropine sulfate solution) resulted in apparently higher plasma atropine exposures in older ocular surgery patients (vs a "historical" control of healthy subjects) but did not result in statistically significant increases in atropine-associated anticholinergic effects (i.e., blood pressure, heart rate, and saliva secretion), as compared to those patients who received the placebo eye drop. Following intravenous administration, the plasma elimination half-life of atropine is longer in elderly subjects than in younger adults (10 hours versus 3 hours). As there is very limited PK and PD data for elderly patients (65 years and older) receiving topical ocular atropine, and some of the indications of the proposed to-be-marketed ophthalmic product would require the instillation of more than 1 drop, elderly and/or ocular surgery patients may need to be monitored for the anticholinergic effects of atropine while on therapy with 1% atropine sulfate ophthalmic solution.

Patients with renal or hepatic impairment
No adjustment in the topical ocular dosage of 1% atropine sulfate ophthalmic solution is needed in patients with renal or hepatic impairment. As renal and hepatic elimination contribute to atropine disposition to a significant extent, patients with renal and/or hepatic impairment may need to be monitored for the anticholinergic effects of atropine while on therapy with 1% atropine sulfate ophthalmic solution.

Patients with dark irides
No adjustment in the topical ocular dosage of 1% atropine sulfate ophthalmic solution is needed for patients with dark irides. In the Ebri, et al (2007) trial, 1 drop of 1% atropine sulfate ophthalmic solution administered three times daily for 3 days into each eye was fully effective in producing cycloplegia (as well as mydriasis) in children with dark irides, with no reported systemic adverse effects. In the double-blind, placebo-controlled study conducted by Barbee and Smith (1957), 30 healthy Caucasian and African-American subjects 16 to 60 years old grouped according to degree of iris pigmentation received 3 drops of 1% atropine sulfate ophthalmic solution in the study eye. After 40 minutes, the mean pupil diameter was > 6 mm in all three race/iris color groups. All subjects with dark or brown irides experienced moderate to marked decrease in accommodation to near vision (i.e., change in rating greater than 3 on Snellen card) 10 minutes after receiving the eyedrops.

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II. Question Based Review

A. General Attributes of the Drug

1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Atropine is a pre-1932 or "grandfathered" drug. The sponsor had been marketing 1% atropine sulfate ophthalmic solution since June 19, 1995. In accordance with the recommendations in the *FDA Guidance for Marketed Unapproved Drugs*, the sponsor filed a literature based 505(b)(2) NDA. Atropine sulfate products for parenteral (i.e., intravenous/intramuscular) administration including ANSYR® and ATROPEN® are currently FDA approved and marketed for non-ophthalmic indications (e.g., for the treatment of pesticide, nerve toxin, and/or muscarinic mushroom poisoning). Oral products consisting of low doses of atropine sulfate in combination with diphenoxalate or difenoxin are approved /marketed in the USA as adjunctive for the management of nonspecific diarrhea whereas the marketing of aerosolized atropine sulfate and certain other atropine injections have been discontinued.

The NDA sponsor did not conduct clinical pharmacology studies or clinical efficacy and safety trials (nor nonclinical studies) specific for the proposed 1% atropine sulfate ophthalmic solution.

2. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Atropine sulfate is a colorless (b) (4) or (b) (4) that is very soluble in water and glacial acetic acid, and is freely soluble in ethanol and glycerol.

Atropine sulfate ophthalmic solution is an isotonic, sterile, clear, colorless solution which contains 10 mg/mL of atropine sulfate (b) (4) and the following excipients: benzalkonium chloride (preservative), edetate disodium (b) (4) hypromellose (b) (4) and a sodium phosphate (b) (4). The pH of the solution is adjusted to (b) (4) using hydrochloric acid and/or sodium hydroxide. The ophthalmic solution has a viscosity of 16 to 24 cps, and an osmolality of 260 to 320 mOsm/kg. The actual drop size is 37 microliters.

The sponsor intends to market 1% atropine sulfate ophthalmic solution in 3 sizes, 2 mL fill in 6 mL bottle, 5 mL fill in 6 mL bottle, and 15 mL fill in 15 mL bottle. Based on two-year long-term and accelerated stability tests conducted for the solutions in the proposed container/closure systems, the proposed expiration dating period for the ophthalmic solution is (b) (4) months.

3. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Atropine (sulfate) inhibits the anticholinergic effect of acetylcholine. When applied via the topical ocular route, atropine blocks the responses of the sphincter muscle of the iris and the accommodative muscle of the ciliary body to cholinergic stimulation, thereby producing pupillary dilation (mydriasis) and paralysis of accommodation (cycloplegia).

The proposed indications for 1% atropine sulfate ophthalmic solution are: (1) (b) (4) mydriasis, and (2) for pupillary dilation (b) (4) for penalization of the healthy eye in amblyopia).

4. What are the proposed dosage(s) and route(s) of administration?

(b) (4)

B. General Clinical Pharmacology

1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor submitted five literature studies to support the clinical pharmacology package of the proposed 1% atropine sulfate ophthalmic solution. Table 1 summarizes the study details and the results of the two published randomized, open-label studies that determined the systemic exposures to atropine (as l-hyoscyamine) and the anticholinergic effects of atropine following a single topical ocular administration of a 1% atropine sulfate ophthalmic solution (Oftan Atropin® 10 mg/ml eyedrops, Star Pharmaceuticals, Tampere, Finland). Specifically, the study conducted by Kaila, et al (1999) was a crossover study that investigated the absolute bioavailability and the pharmacodynamic (anticholinergic) effects of topical ocular atropine 0.3 mg (i.e., 30 mcL of 1% ophthalmic solution) in 6 healthy subjects (24-29 years old) who also received the same dose of intravenous atropine sulfate after a 2-week washout period. The study conducted by Lahdes, et al (1988) is a placebo-controlled study that investigated the systemic exposures to l-hyoscyamine and the pharmacodynamic (anticholinergic) effects in 8 ocular surgery patients (56-66 years old) who received 0.4 mg atropine (i.e., 40 mcL of 1% atropine sulfate ophthalmic solution) at least 12 hours after their last atropine sulfate dose. The reviewer notes that the actual drop volume of the proposed 1% atropine sulfate ophthalmic solution is 37 mcL.

Table 2A and 2B summarize the design of published clinical trials selected by the FDA Medical Reviewer to support the recommendation to approve 1% atropine sulfate ophthalmic solution with the following indications: for producing mydriasis (pupil dilation), for producing cycloplegia (paralysis of accommodation), and for treatment of amblyopia. Note that the Clinical Pharmacology reviewer's labeling recommendations for dosage and administration, and pharmacodynamics were based mainly on the information from these particular trials.

Table 1. Summary of literature studies that evaluated topical ocular atropine pharmacokinetics in humans

Author (Reference)	Design	Population	Dose/Duration	Assay Method	Results
Kaila T, et al. [11]	Open-label; randomized, crossover	5 females, 1 male, healthy subjects: 24-29 years	Ophthalmic: 0.3 mg atropine sulfate Intravenous: 0.3 mg atropine sulfate	Radioreceptor assay for L-hyoscyamine; detection limit of 20 pg/mL.	Mean bioavailability of ophthalmic solution was 63.5% (19-95%). C_{maxoph} = 288.3 pg/mL; T_{maxoph} = 27.6 min. Terminal half-life was similar for both routes of administration. No detectable effects on heart rate or blood pressure after either route of administration.
Lahdes K, et al. [12]	Open-label; randomized, placebo-controlled	Atropine group: 7 males, 1 female; 55-66 years Placebo group: 3 males, 5 females; 38-74 years. All were scheduled for ophthalmic surgery	40 µl of 1% atropine ophthalmic solution (mean dose of 5.7µg/kg); single application to one eye. Placebo (balanced salt solution for ophthalmic use)	Radioreceptor assay for l-hyoscyamine; detection limit of 50 pg/mL	C_{max} = 860 pg/mL was reached 8 minutes after administration. There was no observable effect on heart rate in either group.

Table 2A. Summary of the literature studies selected by the FDA Medical reviewer to support recommendation of 1% atropine sulfate ophthalmic solution for producing mydriasis (pupil dilation)*

Literature Study Author/Year	Study Design	Study Population (age/gender/race, healthy or patients, iris color)	Dosing Regimen of 1% atropine sulfate ophthalmic solution	Efficacy Results (Atropine group only)	Safety Results (include systemic and ocular AEs for Atropine group only)
Ebri et al (2007)	Randomized, parallel group	Nigerian children 4-15 years old with dark irides presenting with eye complaints; 37 males + 33 females	1% atropine (n= 79 subjects) (1 drop in each eye TID x 3 days)	100% (70/70) had pupil dilation, with final pupil diameter ≥ 6mm	-No systemic side effects were reported. -Prolonged blurry vision (100%) -Only 7% (5/70) subjects in the atropine group reported side effects (all mild).
Wolf & Hodge (1946)	Open label, non-randomized	Subjects/patients (16-37 years old)	1% atropine 15 eyes of 13subjects (1 drop)	Maximum pupil diameter=8.3 mm; Tmax = 40 min;Maximal dilation ratio=2.44; time to onset of recovery=6 hours; Residual accommodation at day 5= 0.60	(Note: 11 subjects also received eyedrop other than atropine in the fellow eye)
Chia, Chua et al (2012);	Randomized, double-blind (Study ATOM2)	Children with myopia 6-12 years old; 90-92% Chinese; 51-53% males	0.5% atropine (161 subjects) 0.1% atropine (155 subjects) 0.01% atropine (84 subjects) -manufactured by Ashwood Labs, China (Nightly to both eyes for 2 years)	After 2 weeks of nightly atropine, mesopic pupil diameter increased to 5.2, 7.2 and 7.8 mm, in the 0.01%, 0.1%, and 0.5% groups, respectively; photopic pupil diameter increased to 5.8, 7.4, and 7.9 mm, respectively. The baseline values were: 3.9, 3.9, 4.0 mm (mesopic); 4.7, 4.6, 4.6 mm (photopic).	Allergic conjunctivitis and dermatitis were not observed in 0.01% group but were found in 16 cases in the 0.1% and 0.5% groups
Marron (1940)	Open-label, non-randomized	Students and faculty members with or without vision complaints, 15-40 years old	1% Atropine (214 eyes of 107 subjects) (1 drop TID x 3 days, then 1 drop on the morning of the ocular exam)	Average full dilation=7.9 mm; Tmax=40 min; duration of full dilation=8 hours; time when normal pupil diameter appears=12 days	Systemic and ocular AEs not mentioned in the paper
Barbee and Smith (1957)	Double-blind, placebo-controlled	Healthy subjects 16-60 years (10 Caucasians/blue eyes + 10 Caucasians/brown eyes + 10 African-Americans/dark eyes)	1% Atropine (3 drops in the study eye)	After 40 minutes, mean pupil diameter > 6 mm, and mean change in pupil diameter approximately 3 mm in all 3 eye groups.	No significant increase in intraocular pressure; conjunctival hyperemia and tearing in some subjects

*modified from the FDA Medical reviewer's summary table
-gray shaded rows are randomized studies
TID – three times daily

Table 2B. Summary of the literature studies selected by the FDA Medical reviewer to support recommendation of 1% atropine sulfate ophthalmic solution for producing cycloplegia (paralysis of accommodation)*

Literature Study Author/Year	Study Design	Study Population (include age, gender, healthy or patients, iris color)	Dosing Regimen of 1% atropine sulfate ophthalmic solution (include Brand name, if available)	Efficacy Results (Atropine group only)	Safety Results (include systemic and ocular AEs for Atropine group only)
Ebri et al (2007)	Randomized, parallel group	Nigerian children 4-15 years old, with dark irides presenting with eye complaints	1% atropine (n=79) (1 drop TID x 3 days)	100% (70/70) had RA 0-0.5 D	-No systemic side effects were reported. -Prolonged blurry vision (100%) -Only 7% (5/70) subjects in the atropine group reported side effects (all mild).
Wolf & Hodge (1946)	Open label Non-randomized	Subjects/patients (16-37 years old)	1% atropine 15 eyes of 13subjects (1 drop)	Average maximum RA =0.21 of baseline; time to onset of recovery=1 day; average RA on Day 5=0.60 of baseline	(Note: 11 subjects also received eyedrop other than atropine in the fellow eye)
Chia, Chua et al (2012);	Randomized, double-blind (Study ATOM2)	Children with myopia 6-12 years old; 90-92% Chinese; 51-53% males	0.5% atropine (161 subjects) 0.1% atropine (155 subjects) 0.01% atropine (84 subjects) -manufactured by Ashwood Labs, China (Nightly to both eyes for 2 years)	After 2 weeks of nightly atropine, the A decreased to 11.3, 3.8, and 2.2 D in the 0.01%, 0.1% and 0.5% groups, respectively. The baseline values were: 16.2, 16.7, 15.8, respectively	Allergic conjunctivitis and dermatitis were not observed in 0.01% group but were found in 16 cases in the 0.1% and 0.5% groups
Kawamoto & Hayasaka (1997)	Fixed-sequence, crossover study; atropine 2-4 months after cyclopentolate	Japanese children (32 boys, 19 girls) 3 to 15 years old with brown eyes and who complained of eye abnormalities	0.5% (<6yrs old; n=50 eyes) or 1% Atropine (n=52 eyes) (BID x 7 days)	Mean refraction (spherical equivalent) <6yrs +3.55 D (+ 0.66 difference from cyclopentolate reading) >7yrs +2.60 D (+0.77 difference from cyclopentolate reading)	No serious systemic side effects were reported
Stolovitch et al (1992)	Cross-over study comparing 4 drops versus 8 drops of atropine	Hospitalized children with hyperopia 4.8 months to 11 years (median age: 3.3 years); 50% males	1% atropine (72 eyes of 36 subjects) Stage 1: 1 drop on both eyes TID on day 1 plus 1 drop on the morning of the ocular exam (day 2), Stage 2: 1 drop on the evening of day 2, 1 drop BID on day 3, plus 1 drop on the morning of the 2nd ocular exam	Mean hypermetropic refraction (?) Rt eye: +2.91 D after 4 drops, +2.93 D after 8 drops Lt eye: +3.28 D after 4 drops, +3.29 D after 8 drops	Five children developed flushing and 8 complained of photophobia
Barbee and Smith (1957)	Double-blind, placebo-controlled	Healthy subjects 16-60 years (10 Caucasians/blue eyes + 10 Caucasians/brown eyes + 10 African-Americans/dark eyes)	1% Atropine (3 drops in the study eye)	In all 3 eye types, almost complete and uniform cycloplegia or decrease in accommodation to near vision (measured as change ≥ 3 in Snellen rating) Only 73% of subjects experienced moderate to marked decrease in A to near vision.	No significant increase in intraocular pressure; conjunctival hyperemia and tearing in some subjects

*modified from the FDA Medical reviewer's summary table; gray shaded rows are randomized studies
A: accommodation; D: diopters; RA: residual accommodation; TID: three times daily

2. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

Mydriasis (pupil dilation)
In the randomized, parallel group clinical trial conducted by Ebri, et al (2007), treatments were assessed for mydriatic activity based on the proportion of patients with pupil diameter equal to or greater than 6 mm.

Cycloplegia (b) (4)
Cycloplegia is paralysis of the ciliary muscle of the eye, resulting in loss of accommodation. (b) (4) In the randomized, parallel group clinical trial conducted by Ebri, et al (2007), treatments were assessed for cycloplegic activity based on the proportion of patients with residual accommodation equal to or less than 0.5 Diopters.

Treatment of Amblyopia
Amblyopia is an eye disorder characterized by impaired vision in the "lazy" or the "bad" eye due to failed or poor transmission of visual stimulation through the optic nerve to the brain; patching of the "sound" or the "good" eye is the standard-of care treatment for this disorder. In the randomized, blinded, active-controlled clinical trial conducted by the Pediatric Eye Disease Group (2008), 1% atropine was evaluated (vs. eye patching) for potential to improve visual acuity of the "bad" eye, secondary to cycloplegic effects on and thus blurring of vision of the "good" eye in children 7 to 12 years old.

3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, in the PK studies that measured the systemic exposures to atropine following topical ocular instillation of 1% atropine sulfate in healthy subjects (Kaila et al., 1999), and in ocular surgery patients (Lahdes, et al., 1988), l-hyoscyamine (the biologically active enantiomer of atropine) was quantified in plasma samples. Measurement of plasma l-hyoscyamine concentrations was achieved using radioreceptor binding assays with LLOQ of ≤ 50 pg/mL and which were specific for the biologically active isomer.

Refer also to Section II.F. Analytical Section.

4. Exposure-response

a) What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

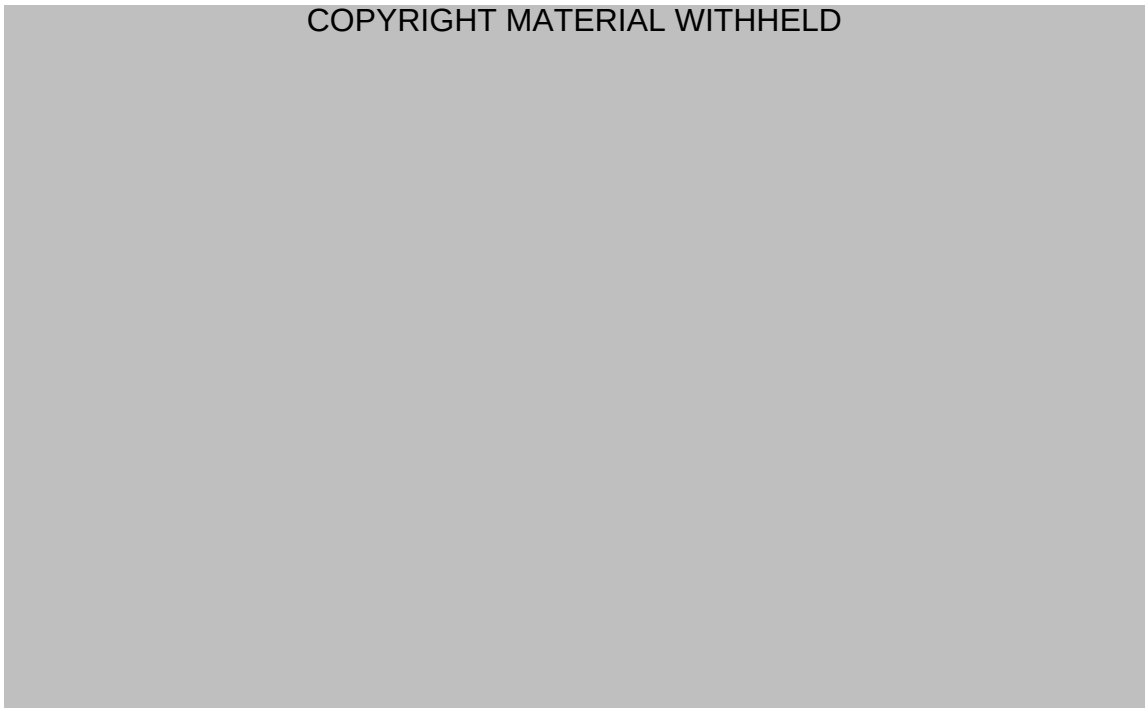
Dose-efficacy relationship.
In the randomized double blinded, parallel group (ATOM2) study conducted by Chia, et al (2012), nightly treatments with lower strengths (i.e., 0.01%, 0.1%, 0.5%), of atropine sulfate ophthalmic solution produced sub-clinically significant (albeit in a dose-related manner) mydriasis (pupil dilation) and cycloplegia (paralysis of accommodation) than reported by other studies with 1% atropine sulfate ophthalmic solution. Specifically, pupil size in the groups treated with atropine sulfate solutions 0.01 - 0.5% increased by only 1 to 3 mm, and accommodation was reduced to only 11.3 - 2.2 D whereas Ebri, et al (2007) reported 100% of patients treated with 1% atropine sulfate achieving a pupil diameter of at least 6 mm, and an accommodation reduced to at least 0.5 D, following a dosage of 1 drop three times daily for 3 days. According to the FDA Medical reviewer, 1% atropine sulfate will be approved for the treatment of amblyopia on the basis of its proven cycloplegic effect which results in the blurring of the vision of the "good" eye.

Systemic Concentration-efficacy relationship.
Since the site of drug application is also the site of action (the eye), plasma atropine (l-hyoscyamine) concentrations are not expected to be directly correlated with the degree of the mydriasis (pupil dilation) and cycloplegia (paralysis of accommodation) in patients receiving 1% atropine sulfate.

Pharmacodynamics
The literature studies conducted by Wolf and Hodge (1946), and Marron (1940) characterized the time course profiles of the mydriatic and cycloplegic effects of atropine sulfate 1% ophthalmic solution.

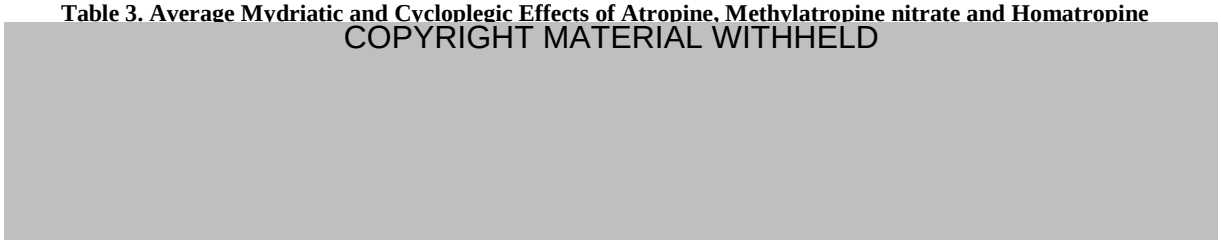
Wolf and Hodge (1946) investigated the mydriatic (pupil dilation) and cycloplegic (loss of accommodation) effects of atropine after the instillation of a single drop of atropine sulfate 1% ophthalmic solution to 16 eyes of subjects 16 – 37 years old. Pupil diameter and accommodation were measured for 14 days or until values approached baseline values (whichever was shorter). Figure 2 shows the effect of 1 drop of atropine sulfate 1% on the range of accommodation and the pupil diameter of 16 eyes. *Mydriasis.* The maximum pupil diameter achieved with 1 drop of 1% atropine sulfate was 8.3 mm; the time to achieve full pupil dilation (mydriasis) was 40 minutes. The pupil diameter starts to go below 6 mm by day 4 and was back to normal size by day 12. *Cyclopegia.* The maximum residual accommodation ratio (D_t/D_0) was 0.21 of baseline, achieved at 5 hours following 1 drop of 1% atropine sulfate. The reported time to onset of recovery from cycloplegia was 1 day, and by the fifth day, the residual accommodation was reported to be still 0.60 of baseline (Table 3).

Figure 2. Time of accommodation and pupil size as a function of time following instillation of 1 drop of atropine sulfate 1%



Adapted from: Wolf and Hodge (1946)

Table 3. Average Mydriatic and Cycloplegic Effects of Atropine, Methylatropine nitrate and Homatropine

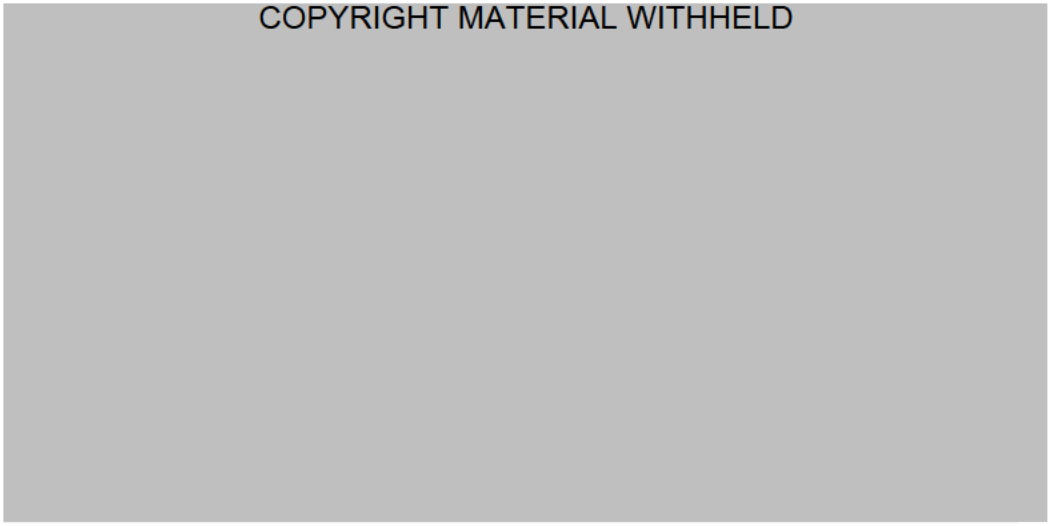


Adapted from: Wolf and Hodge (1946)

Marron (1940) investigated the mydriatic and cycloplegic effect of atropine sulfate 1% solution in subjects 15 to 40 years old after receiving a total of 10 drops (n=216 eyes) or 16 drops (n=26 eyes) of the ophthalmic solution. Atropine sulfate 1% was administered as1 drop three times daily (i.e., at 8 AM, 12 nn and 4 pm) for 3 days or 5 days, and on the morning of the 4th or 6th day. Measurements of the rate of accommodation and pupil diameter were made daily for two weeks. Figure 3 shows the effect of 10 drops of atropine sulfate 1% on the range of accommodation and the pupil diameter of 214 eyes.

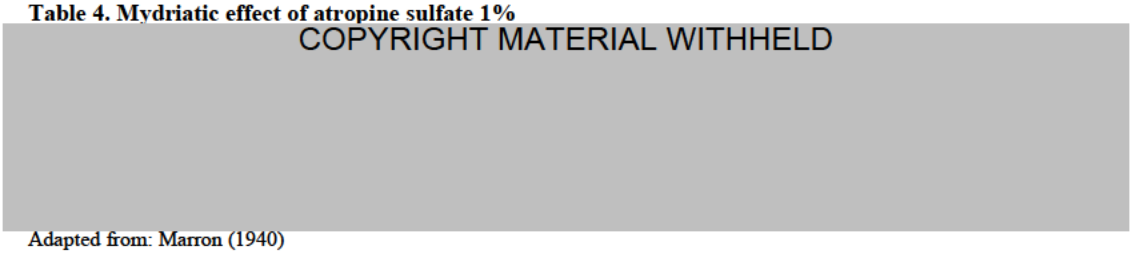
Mydriasis. The time to achieve full mydriasis (pupil dilation) was 40 minutes after the instillation of the 1st drop of atropine sulfate 1% solution (Table 4). The reported average maximum mydriatic effect and the duration of this effect were approximately 8 mm, and 8 hours, respectively. The pupil diameter decreased to below 6 mm starting at 5 days after the last atropine eyedrop instillation, and returned to normal size 12 to 13 days post-last dose. There was no significant difference in the mydriatic effects of 10 drops versus 16 drops of atropine sulfate 1% in these subjects. The magnitude of mydriatic effect did not increase further after the instillation of the 1st of 10 drops. The reported mydriatic effects (i.e., the maximum pupil diameter, the time to achieve full mydriasis, and the time for the pupil diameter to drop below 6 mm post-eyedop instillation) of single dose atropine sulfate in this study are similar to that observed in the later study conducted by Wolf and Hodge (1946).

Figure 3. Time course of range of accommodation and pupil diameter following atropine sulfate 1% administered as 1 drop thrice daily (approximately 4 hours apart) for 3 days and on the morning of the 4th day



Adapted from: Marron (1940)

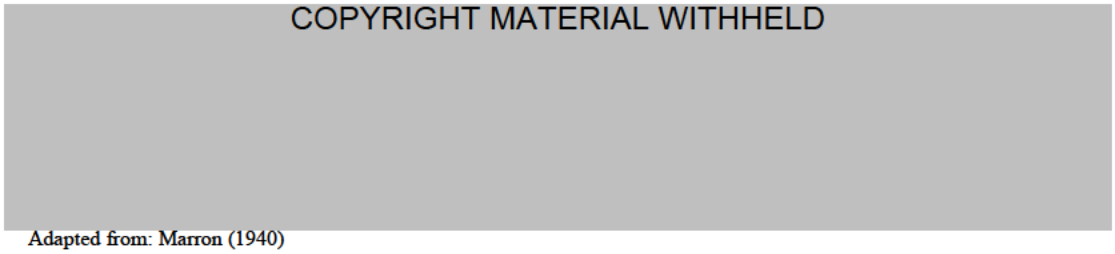
Table 4. Mydriatic effect of atropine sulfate 1%



Adapted from: Marron (1940)

Cycloplegia. When atropine sulfate 1% ophthalmic solution was administered into the eye 1 drop three times daily, the full cycloplegic effect, (i.e., residual accommodation, [D_t/D_0] eyeballed by the reviewer to be 0.18) was achieved after 4 drops, per the author. After 10 drops, the reported range of accommodation at the time of refraction was 1.9 D, and the duration of maximum cycloplegia was 8-24 hours (Table 5). A residual accommodation of less than 2.0 D is regarded as having adequate cycloplegia [Rosenfield and Logan (eds), 2009]; Gettes and Belmont (1961) consider a residual accommodation < 2.5 D at the time ocular examination as the threshold for adequate and effective cycloplegia. Per Marron, by the 3rd day after the last drop, the average patient was able to read newsprint, and the range of accommodation returned to normal 18 days after the instillation of the last drop of atropine sulfate 1%. There was no significant difference in the cycloplegic effects of 10 drops versus 16 drops of atropine sulfate 1% in these subjects. The reported cycloplegic effects (i.e., the maximum pupil diameter, the time to achieve full mydriasis, and the time for the pupil diameter to drop below 6 mm post-eyedrop instillation) of single dose atropine sulfate in this study are similar to that observed in the later study conducted by Wolf and Hodge (1946).

Table 5. Cycloplegic Effect of atropine sulfate 1%



Adapted from: Marron (1940)

b) What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

Note that formal exposure-response relationships were not explored because plasma exposure data from the submitted literature were only available for one strength (i.e., 1%) of atropine sulfate ophthalmic solution, and there were study population differences that could possibly confound interpretation of the exploratory analysis findings. Overall, the findings of the studies that investigated the plasma PK and the PD (i.e., anticholinergic effects) of atropine in either healthy young adults or older ocular surgery patients do not suggest that there is a systemic safety concern following topical ocular administration of 1% atropine sulfate ophthalmic solution, as explained below.

1. Since the mean peak systemic exposure (Cmax) and the mean total systemic exposure (AUC) to atropine (as l-hyoscyamine) are approximately 90% and 35% lower, respectively, following topical ocular instillation of a single 0.3 mg dose of 1% atropine sulfate ophthalmic solution than following administration of the same atropine dose via intravenous (i.v.) injection in healthy subjects (Kaila et al 1999), it was not surprising that this same group of investigators earlier reported no statistically significant increase in the anticholinergic effects of atropine (i.e., blood pressure, heart rate and salivation) in ocular surgery patients who received a single topical ocular 0.4 mg dose of atropine sulfate solution, as compared to those patients who received the placebo eyedrops (Lahdes, et al. 1988. Per the NDA sponsor, the actual drop size is 37 mcL; the systemic exposure findings of the study conducted in older ocular surgery patients is a good representation of what systemic exposures would generally be expected with the to-be-marketed 1% atropine sulfate ophthalmic solution.

2. Additionally, although the dose-normalized mean Cmax of atropine (as l-hyoscyamine) is approximately 2-fold higher and the time to achieve this Cmax is approximately 70% shorter in older ocular surgery patients (age range: 56-66 years; Lahdes et al, 1988) than in healthy young adult subjects (age range: 24-29 years; Kaila et al, 1999), these mean atropine Cmax values (≤ 860 pg/mL) achieved following topical ocular administration of the same brand of 1% atropine sulfate solution (obtained by the same investigator group in studies conducted approximately 11 years apart) are substantially (by at least 90%) lower than that achievable with clinical doses of intramuscularly administered atropine sulfate (ATROPEN®) in adults; 2 mg to 4 mg is required per episode of nerve agent or insecticide poisoning, depending on severity of symptoms. Per the ATROPEN® USPI, the approximate Cmax of atropine following 1.67 mg atropine given intramuscularly to adults by the 2 mg ATROPEN® delivery system was 9,600 ± 1,500 (mean ± SEM) pg/mL, with a mean Tmax of 3 minutes.

c) Does this drug prolong the QT or QTc interval?

The ATROPEN® USPI lists "prolonged QT interval" as one of the adverse reactions reported in published literature for atropine.

d) Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

In general, the proposed dosing regimens of 1% atropine sulfate ophthalmic solution for producing mydriasis and for producing cycloplegia were consistent with known pharmacodynamic (pupil dilation and paralysis of accommodation effect) profiles as reported in the literature, and were supported by the findings of published clinical efficacy studies. See Section IV of this NDA review for recommended edits to the Dosage and Administration, and the Pharmacodynamics sections of the proposed US Package Insert.

3. What are the PK characteristics of the drug and its major metabolite?

Table 6 summarizes the design and the atropine PK parameters of the sponsor's submitted PK studies using 1% atropine sulfate ophthalmic solution.

1. *Kaila et al., (1999).* In a randomized, crossover trial involving 6 healthy young adult subjects (24-29 years old), the absolute bioavailability of atropine was determined following single dose topical instillation of 0.3 mg atropine sulfate administered as 30 mcL of 1% atropine sulfate ophthalmic solution (Oftan-Atropin®, Star Pharmaceuticals Co., Tampere, Finland) relative to the same dose of intravenously administered atropine sulfate. Plasma l-hyoscyamine (the biologically active enantiomer of atropine) was quantified using a radioreceptor binding assay with a lower limit of detection of 2 pg/mL l-hyoscyamine. The mean bioavailability of atropine (as l-hyoscyamine) following topical ocular administration was 64% of that folowing bolus intravenous administration, with large inter-individual differences in absolute bioavailability ranging from 19% to 95% (Figure 4). The mean (range) plasma l-hyoscyamine Cmax was 289 pg/mL (166-355 pg/mL), and was reached at a median (range) Tmax of 19 minutes (3-60 minutes). The mean terminal elimination half-lives of l-hyoscyamine were similar between topically and intravenously administered atropine sulfate (2.45 versus 2.97 hours, respectively).

2. *Lahdes, et al., (1988).* In a randomized, placebo-controlled, parallel group study, 16 hospitalized subjects (56-66 years old) who were on a regular regimen of atropine ophthalmic solution, and who were scheduled for eye surgery, received either a single topical ocular 0.4 mg dose of atropine sulfate (administered as 40 mcL of the 1% ophthalmic solution into the operated eye; Oftan-Atropin®, Star Pharmaceuticals Co., Tampere, Finland) or placebo eye drop. Serum L-hyoscyamine levels were determined over a 90 minute period following dose administration using a radio receptor binding assay (RRA). Peak concentrations of l-hyoscamine of 860 ± 402 pg/mL were reached in 8 minutes (Figure 5).

Table 6. Pharmacokinetic parameters of atropine (measured as l-hyoscyamine) following topical ocular administration of 1% atropine sulfate ophthalmic solution

Ref.	Study Objective	Study Design	Treatment (Dose/Dosage Form/Route)	Subjects (No.(M/F), Type, Age (Mean, Range))	Pharmacokinetic Parameters (Mean ± SD) for l-hyoscyamine)					
					Cmax (pg/mL)	Tmax (min)	$AUC_{(0-t)}$ (h.ng/mL)	$AUC_{(0-inf)}$ (h.ng/mL)	t½ (h)	CL (mL/min/kg)
Kaila et al. (1999)	Determine absolute bioavailability of topical ocular atropine	Open label, randomized, crossover, with 2-week washout period	0.3 mg, single dose, IV solution	6 (1M/5F), Healthy, 24-29 y	NA	NA	NA	1.79 ± 0.64	2 97 ± 1.22	2.3E-5 ± 6.5E-6
			0.3 mg, single dose, ophthalmic solution		288.3 ± 72.91	27.67 ± 26.85	NA	1.02 ± 0.33	2.45 ± 0.76	4E-5 ± 3.1E-5
Lahdes, et al. (1988)	Determine pharmacokinetics of ophthalmic administration	Open label, randomized, parallel, vs. placebo	0.4 mg, ophthalmic solution	8 (7M/1F), ocular surgery patients, 56-66 y	860 ± 402	8	0.72 ± 0.40 [a]	NA	NA	NA

[a] converted to h*ng/mL from $AUC_{(0-90min)}$ of 43.25 ± 24.1 min*ng/mL

Figure 4. Plasma atropine kinetics in six healthy subjects 24 to 29 years old after intravenous (open circles) and ocular (closed squares) application of 0.3 mg atropine. Plasma 1-hyoscyamine concentrations are given in the logarithmic scale as pg/ml units. (Reference: Kaila et al., 1999)

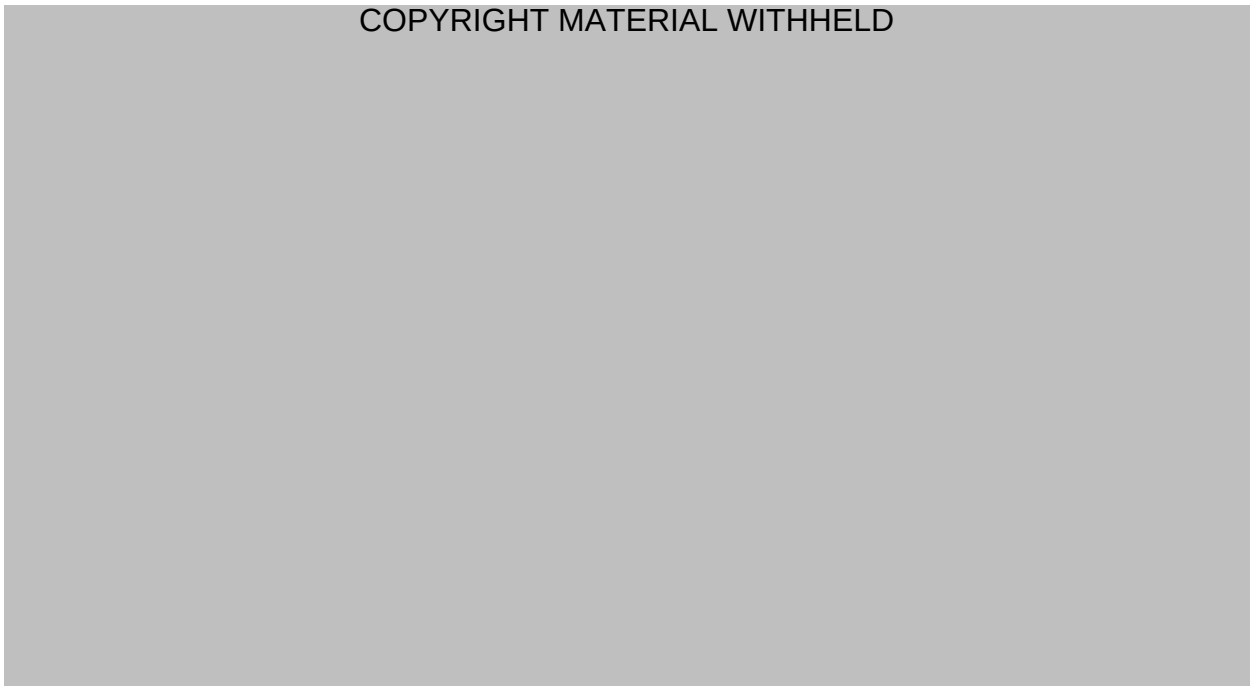
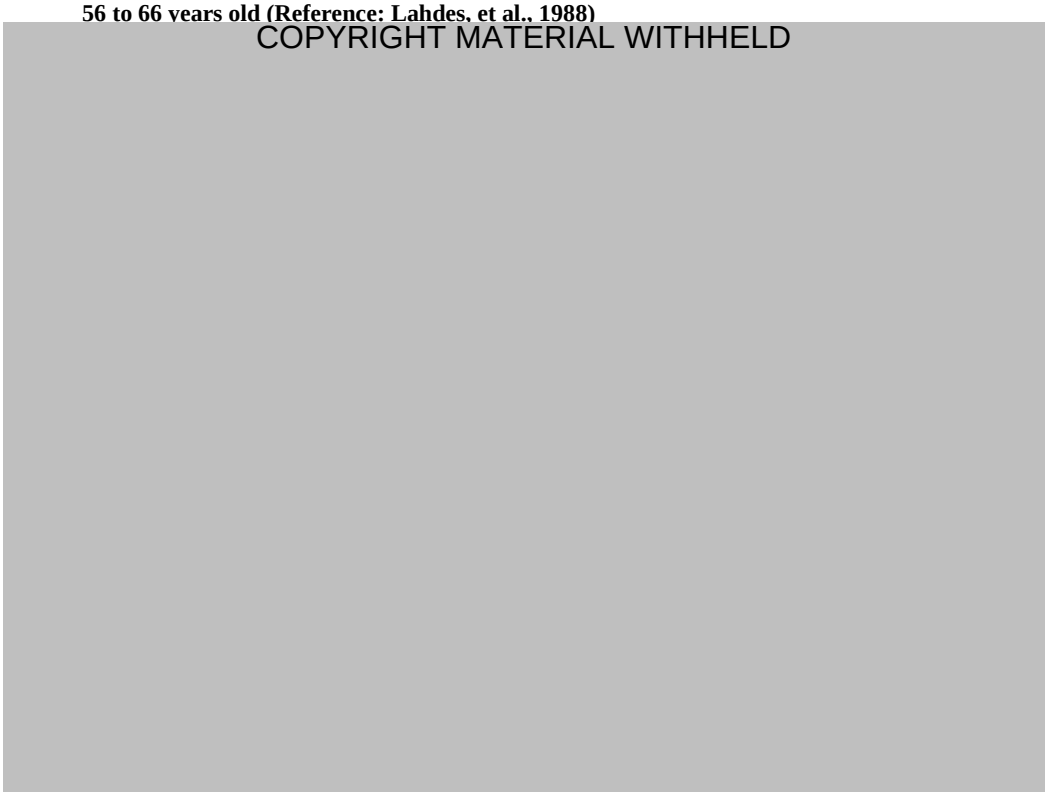


Figure 5. Plasma atropine (as l-hyoscyamine) concentration-time profiles in ocular surgery patients 56 to 66 years old (Reference: Lahdes, et al., 1988)



a) What are the single dose and multiple dose PK parameters?

See Table 6 above for the single dose PK parameter data of 1% atropine sulfate ophthalmic solution. Literature PK data are not available following multiple dose administration of the eye drops.

b) How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The systemic PK of atropine (as l-hyoscyamine) is not expected to be significantly different between healthy subjects and otherwise healthy patients with vision problems. For information regarding the plasma atropine exposures in healthy young adults and in atropine-treatment experienced older ocular surgery patients who received single topical ocular dosing with 1% atropine sulfate ophthalmic solution, (as investigated in separate PK studies), see Section II.3 of this NDA review.

c) What are the characteristics of drug absorption?

The absolute bioavailability of atropine following topical ocular administration of 1% atropine sulfate ophthalmic solution in healthy adult subjects is 65% (average; range 19 to 95%) of that following administration of the same dose of intravenous atropine sulfate.

d) What are the characteristics of drug distribution?

For 1% atropine sulfate ophthalmic solution, the site of drug administration is the site of action (the eye), and there is limited to no data for the distribution characteristics following ophthalmic administration of atropine sulfate.

e) Does the mass balance study suggest renal or hepatic as the major route of elimination?

A Mass Balance study was not conducted specifically for 1% atropine sulfate ophthalmic solution. Atropine reaching systemic circulation is expected to be excreted mainly by renal and hepatic means. Both the intravenous atropine (ANSYR®) and the intramuscular atropine (ATROPEN®) US package inserts state: *Much of the drug is destroyed by enzymatic hydrolysis, particularly in the liver; from 13 to 50% is excreted unchanged in the urine.*

f) What are the characteristics of drug metabolism?

The intravenous atropine (ANSYR®) USPI states: *The major metabolites of atropine are noratropine, atropine-n-oxide, tropine, and tropic acid.*

g) What are the characteristics of drug excretion?

Following topical ocular instillation of a single drop of 1% atropine sulfate ophthalmic solution in healthy young adult subjects (24 to 29 years old), the plasma elimination half-life of atropine (as l-hyoscyamine) was 2.45 hours, similar to when the same subjects were given a single intravenous injection of the same dose of atropine sulfate (2.97 hours). The plasma elimination half-life of atropine in healthy young adults is the same, regardless of the route of administration.

h) Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

There are limited dose-concentration data available in the literature specific for 1% atropine ophthalmic solution.

Note that based on these PK data following intramuscular administration of atropine sulfate, the USPI of intravenous atropine (ANSYR®) states: The pharmacokinetics of atropine is nonlinear after intravenous [sic] administration of 0.5 to 4 mg.

i) How do the PK parameters change with time following chronic dosing?

Only single dose plasma atropine PK data are available for topical ocular administration of atropine sulfate.

j) What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Following topical ocular administration of a single dose of atropine in healthy young adult subjects, the inter-subject coefficient of variation (CV) was 35% for plasma atropine AUC and 25% for Cmax. In older ocular surgery patients who received a single dose of 1% atropine sulfate ophthalmic solution, the inter subject CV was 47% for plasma atropine Cmax and 55% for truncated AUC.

C. Intrinsic Factors

1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

Efficacy and Atropine Dose

Eye color. In three groups of 16-60 year old healthy adults (Caucasians with blue eyes, Caucasians with brown eyes, and African-Americans with dark eyes; n=10 each), 3 drops of 1% atropine sulfate ophthalmic solution produced adequate mydriasis (final pupil diameter > 6 mm), and almost complete and uniform cycloplegia (reduced accommodation as measured by a change of at least 3 in Snellen rating; Barbee and Smith, 1957).

Efficacy and Plasma Atropine Concentration

Because the eye is both the site of drug administration and the site of action, plasma atropine concentrations are not influential in the efficacy of 1% atropine sulfate ophthalmic solution for mydriasis, cycloplegia, and treatment of amblyopia.

Safety and Plasma Atropine Concentration

Advanced age and/or ocular surgery (as well as ongoing therapy with atropine eyedrops and other study design differences) may have contributed to the numerically higher mean dose-normalized plasma Cmax of atropine (as l-hyoscyamine) in patients (56-66 years old; Lahdes, et al., 1988), as compared to healthy young subjects (24-29 years old; Kaila et al., 1999) following topical ocular application of a single drop of 1% atropine sulfate solution. However, this cross-study difference in systemic exposure to atropine following use of 1% atropine sulfate eyedrops is not considered a systemic safety concern for the reasons stated below:

(i) The numerically higher mean dose-normalized plasma atropine Cmax in older ocular surgery patients (versus a “historical” control of healthy young adults) is not considered a systemic safety concern for the proposed ophthalmic product of the applicant, given the observation in the study that there was no statistically significant increase in the pharmacodynamic/anticholinergic effects in atropine sulfate treated patients (who received a single topical ocular atropine dose of 0.4 mg) versus placebo-treated patients (see also Section II.4.b).

(ii) The mean peak plasma atropine concentrations achieved in adult patients treated with a single topical ocular 0.4 mg dose of atropine is approximately 90% lower than that following a single 1.6 mg intramuscular injection of atropine sulfate (ATROPEN® 2mg) used for the treatment of

insecticide or nerve agent poisoning. Note that the actual atropine dose delivered per drop (37 mcL volume) of the proposed 1% atropine sulfate ophthalmic solution is 0.37 mg.

(iii) In the randomized PK and PD study conducted by Kaila et al (1999), the mean absolute bioavailability (based on AUC comparison) of topical ocular atropine sulfate was 65% of that following intravenous atropine sulfate; the mean atropine Cmax following topical ocular dosing with 1% atropine sulfate was approximately 90% lower than following intravenous injection of the same atropine dose (0.3 mg).

For producing mydriasis, the recommended dosage of the proposed eyedrops is 1 drop; for producing cycloplegia, (b) (4).
In a typical adult patient, the peak and the total plasma atropine exposures (Cmax, AUC) of patients including older ocular surgery patients each time they are treated with an eyedrop of 1% atropine sulfate ophthalmic solution would be substantially lower than following the initial intramuscular or intravenous injection of atropine sulfate when used as antidote for various types of poisoning. Thus, the overall systemic safety of 1% atropine ophthalmic solution is not expected to be worse than that following treatment with parenteral atropine.

2. Based upon what is known about exposure-response relationships and their variability, and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

Based on the review of the PK and PD endpoints of the literature studies selected by the FDA Medical reviewer, the Clinical Pharmacology reviewer recommends the following dosing regimens of 1% atropine sulfate ophthalmic solution for adults and children ≥ 4 years old: 1 drop (for producing mydriasis); (b) (4) Note that 1 drop (actual drop volume ~ 40 mcL) of 1% atropine sulfate ophthalmic solution contains 0.4 mg atropine sulfate. Based on literature data, 65% (on average) and up to 95% (on an individual basis) of the administered topical ocular dose of atropine is absorbed.

a) patients with dark irides

No adjustment in the topical ocular dosage of 1% atropine sulfate ophthalmic solution is needed in patients with dark irides. In 16-60 year old adult subjects, adequate pupil dilation, as well as almost complete and uniform cycloplegia was observed regardless of eye color (Barbee and Smith, 1957). In this study conducted by Barbee and coworkers, ephedrine 3%, and Cyclogyl 1% either failed or were less potent as mydriatics, whereas homatropine 4% was less potent as a cycloplegic (based on response to light) in African-American subjects with dark eyes, as compared to other race/eye color groups. Additionally, the USPI of phenylephrine hydrochloride ophthalmic solution 2.5% and 10% states: "Pupillary dilation following topical administration of phenylephrine hydrochloride ophthalmic solution has been demonstrated in controlled clinical studies in adults and pediatric patients with different levels of iris pigmentation. Darker irides tend to dilate slower than lighter irides."

b) elderly patients

No adjustment in the topical ocular dosage of 1% atropine sulfate ophthalmic solution is needed for elderly patients. In the absence of adequate literature data on elderly patients ≥ 65 years old, and for consistency with the ATROPEN® and the ANSYR® US Package Inserts that also do not recommend dosage adjustments of intramuscular and intravenous atropine in elderly patients, the following precautionary language in the USPI of 1% atropine sulfate ophthalmic solution may need to be recommended: While on therapy with 1% atropine sulfate ophthalmic solution, elderly patients should be monitored for any atropine associated systemic adverse effects including changes in blood pressure and heart rate.

There are very limited literature data on the systemic PK and PD of topical ocular atropine in elderly patients ≥ 65 years old; PK, PD and clinical efficacy and safety data are available for patients ≤ 66 years old. In the randomized, placebo-controlled, PK and PD study conducted by Lahdes et al. (1988), there was

no statistically significant increase in the blood pressure, heart rate, and salivary secretion in the ocular surgery patients (i.e., 6 of 8 were at least 60 years old) who received a single 0.4 mg atropine dose (instilled into the eye as 40 mcL of the 1% atropine sulfate solution), compared to a control group (i.e., 4 of 8 were at least 60 years old) who received the placebo eye drop. Additionally, in a placebo-controlled study conducted by Barbee and Smith (1957), adequate pupil dilation and almost complete cycloplegia was observed in adult subjects ≤ 60 years old after receiving topical ocular atropine (i.e., 3 drops of 1% atropine sulfate solution in the eye).

c) pediatric patients

Pediatric patients ≥ 4 years old

No adjustment in the topical ocular dosage of 1% atropine sulfate ophthalmic solution is needed in pediatric patients ≥ 4 years old, as these children were included in an adequate and well-controlled trial that evaluated a dosage of 1% atropine sulfate ophthalmic solution similar to that recommended by this reviewer. In Nigerian pediatric patients 4 to 15 years old with dark irides and presenting with eye complaints, topical ocular administration of atropine sulfate 1% ophthalmic solution (1 drop three times daily for three days) was effective in producing full cycloplegia; 100% of the children had residual accommodation of 0 – 0.5 D (Ebri et al., 2007), with no reported systemic side effects. (Based on PK data available for intravenously administered atropine sulfate, the plasma elimination half-life of atropine in children >4 years is comparable with that in adults 16-58 years old.) In the Ebri trial, 100% of the children experienced full mydriasis; 100% had a final pupil diameter ≥ 6 mm. Although the authors did not report the pupil diameter in these children after the first eyedrop, the time-course profiles of mydriasis as reported previously by Mannon (1940) suggest that instillation of additional 1% atropine eyedrops does not further increase the depth of maximum mydriasis achieved within 40 minutes of the instillation of the first drop.

Pediatric patients < 4 years old

There are limited data on the efficacy and safety of 1% atropine sulfate ophthalmic solution in pediatric patients < 4 years old. The trial conducted by Stolovitch et al. (1992) included patients 4.8 months and older but it did not have a randomized study design.

The Clinical Pharmacology reviewer notes that ATROPEN® (intramuscular atropine sulfate) is approved for use as an antidote to nerve agent poisoning in children weighing 15 lbs to 40 lbs (generally 6 months to 4 years of age); one intramuscular dose of 0.5 mg is recommended for mild poisoning cases. The absolute bioavailability of intramuscular atropine is 100%. In healthy adult subjects, the mean and the maximum individual absolute biovailability of topical ocular atropine sulfate were 65% and 95%, respectively (Kaila et al., 1999). Thus, assuming a mean 65% absolute bioavailability of 1% atropine sulfate solution, the administration of 1 drop into both eyes of a child < 5 months old could result in a total systemic atropine exposure equivalent to that produced by one-time intramuscular administration of 0.5 mg atropine sulfate (which exceeds the recommended ATROPEN® dose of 0.25 mg for children < 6 months). Based on PK data available for intramuscularly administered atropine sulfate, the plasma elimination half-life of atropine in children <2 years is longer than in older children (6.9 ± 3.3 h versus 2.5 ± 1.2 h), suggesting less efficient atropine elimination in younger children. This concern was discussed with the Medical reviewer (Dr. Wiley Chambers) and he stated that there is adequate evidence from the long history of use of atropine sulfate that 1% atropine sulfate eye drops is safe and effective for the recommended indications in pediatric patients < 4 years old.

Of note, the OVERDOSAGE section of the ATROPEN® USPI states: *In children, medical literature published prior to 1951 reports four deaths, all in patients 10 months to 3 years of age, and all associated with [use of 1%] atropine eye drops or ointment. Total estimated ophthalmic doses were 1.6, 2, 4, and 18 mg given as a single dose (2 mg) or over1-2 days. Review of current published literature since 1950 identified no pediatric deaths associated with atropine.*

d) gender

No adjustment in the topical ocular dosage of 1% atropine sulfate ophthalmic solution is recommended based on gender. There were no literature reports suggesting gender dependence of the efficacy and safety of 1% atropine sulfate ophthalmic solution in producing mydriasis and producing cycloplegia. Of note,

dosage adjustment is not recommended for both intramuscular (IM) or intravenous (IV) atropine based on gender (see ATROPEN® and ANSYR® USPI, respectively).

e) race

No adjustment in the topical ocular dosage of 1% atropine sulfate ophthalmic solution is recommended based on race. There were no literature reports suggesting racial dependence of the efficacy and safety of 1% atropine sulfate ophthalmic solution in producing mydriasis and producing cycloplegia. Of note, dosage adjustments are not recommended for intramuscular (IM) or intravenous (IV) atropine based on race (see ATROPEN® and ANSYR® USPI).

f) renal impairment

No adjustment in the topical ocular dosage of 1% atropine sulfate ophthalmic solution is recommended based on degree of renal impairment. Of note, dosage adjustments are not recommended for intramuscular (IM) or intravenous (IV) atropine based on degree of renal impairment (see ATROPEN® and ANSYR® USPI).

Given that (1) more than one dose of atropine sulfate could be needed depending on the indication, (2) absorbed atropine is eliminated by the renal route to a significant extent, and (3) the magnitude of increase in systemic atropine exposures in patients with varying degrees of renal impairment is not known, the following precautionary language in the USPI of 1% atropine sulfate ophthalmic solution is recommended: While on therapy with 1% atropine sulfate ophthalmic solution, patients with renal impairment may need to be monitored for any atropine associated systemic adverse effects including changes in blood pressure and heart rate.

g) hepatic impairment

No adjustment in the topical ocular dosage of 1% atropine sulfate ophthalmic solution is recommended based on degree of hepatic impairment. Of note, dosage adjustments are not recommended for intramuscular (IM) or intravenous (IV) atropine based on degree of hepatic impairment (see ATROPEN® and ANSYR® USPI).

Given that (1) more than one dose of atropine sulfate could be needed depending on the indication, (2) absorbed atropine is eliminated by the hepatic route to a significant extent, and (3) the magnitude of increase in systemic atropine exposures in patients with varying degrees of hepatic impairment is not known, the following precautionary language in the USPI of 1% atropine sulfate ophthalmic solution is recommended: While on therapy with 1% atropine sulfate ophthalmic solution, patients with hepatic impairment may need to be monitored for any atropine associated systemic adverse effects including changes in blood pressure and heart rate.

h) what pharmacogenetics information is there in the application and is it important or not

No adjustment in the topical ocular dosage of 1% atropine sulfate ophthalmic solution is recommended based on clinical genetic differences. There were no literature reports suggesting genetic dependence of the efficacy and safety of 1% atropine sulfate ophthalmic solution in producing mydriasis and producing cycloplegia.

i) what pregnancy and lactation use information is there in the application?

There is no information regarding the pregnancy and lactation for Atropine Sulfate Ophthalmic Solution 1%.

j) other human factors that are important to understanding the drug's efficacy and safety

Higher systemic atropine exposures from topical atropine products are expected in patients with compromised corneal membranes (e.g., following ocular surgery). Of note, the USPI of the phenylephrine hydrochloride ophthalmic solution states: "A higher systemic absorption [of phenylephrine] is expected …when the corneal barrier function is compromised." See also Section II.C.1.

D. Extrinsic Factors

1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure on response?

None.

2. Based upon what is known about exposure -response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

None.

3. Drug-Drug Interactions

a) is there an in vitro basis to suspect in vivo drug-drug interactions?

None.

b) is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

There are no literature studies to ascertain whether atropine is a substrate of CYP450 enzymes with or without genetic polymorphism.

c) is the drug an inhibitor and/or an inducer of CYP enzymes?

There are no literature studies to ascertain whether atropine modulates the activities of CYP450 enzymes.

d) is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

There are no literature studies to ascertain whether atropine is a substrate and/or modulator of P-glycoprotein (drug efflux) transporters.

e) are there other metabolic/transporter pathways that may be important?

None.

f) does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

None.

g) what other co-medications are likely to be administered to the target patient population?

Topical ocular drugs commonly used in patients with vision or other eye problems include those to treat glaucoma, dry eye syndrome, and ocular inflammation. Elderly patients may be taking concomitant oral drugs including those used to treat hypercholesterolemia, hypertension, and diabetes.

h) are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

None.

i) is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Yes, potential additive/synergistic/antagonistic interaction with cholinergic and anti-cholinergic drugs, resulting in altered heart rate and/or blood pressure is possible. The USPI of phenylephrine ophthalmic solution 2.5% and 10% states: "Do not use with phenylephrine hydrochloride or other pressor agents due to risk of tachycardia." "Systemic absorption of sufficient quantities of phenylephrine may lead to systemic α-adrenergic effects, such as rise in blood pressure which may be accompanied by a reflex atropine-sensitive bradycardia."

j) are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

None.

k) What issues related to dose, dosing regimens or administration are unresolved, and represent significant omissions?

None.

E. General Biopharmaceutics

In the NDA filing review, the FDA Biopharmaceutics reviewer (Dr. Elsbeth Chikhale) states: "Since there is no approved NDA or ANDA for Atropine Sulfate Ophthalmic Solution, 1%, a waiver of the requirement to submit in vivo bioequivalence/bioavailability is not applicable."

The sponsor did not conduct bioavailability, bioequivalence and food-effect studies specific for the proposed to-be-marketed 1% atropine sulfate ophthalmic solution. Included in the 505(b)(2) NDA submission were bioavailability studies of atropine following single topical ocular dosing of 1% atropine sulfate ophthalmic solution in healthy subjects and in patients.

F. Analytical Section

1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The two literature studies (Kaila et al., 1999; Lahdes, et al., 1988) that evaluated systemic exposures to topical ocular atropine measured l-hyoscyamine (the pharmacologically active enantiomer) in plasma of healthy subjects and ocular surgery patients who received a single eye drop of 1% atropine sulfate ophthalmic solution.

2. Which metabolites have been selected for analysis and why?

None.

3. For all moieties measured, is free, bound or total measured?

Free (and pharmacologically active) drug is represented in the plasma concentrations as only the free (or the form that is not bound to albumin and/or alpha acid glycoprotein) drug could bind to the drug receptor and produce the measured assay response.

4. What bioanalytical methods are used to assess concentrations? What are the assay validation parameters?

The LLOQ of the radioreceptor assays used to measure plasma l-hyoscyamine concentrations were ≤ 50 pg/mL. Other PK assay performance characteristics were not described in the publications.

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

B. Individual Study Reviews

The Individual study reviews for the following published studies are available upon request:

- *Kaila et al.* Systemic bioavailability of ocularly applied 1% atropine eyedrops. Acta Ophthalmol. Scand. 1999: 77: 193–196
- *Lahdes, Kaila, et al.* Systemic absorption of topically applied ocular atropine. Clin Pharmacol Ther 1988;44:310-4.

C. Consult Review (including Pharmacometric Reviews)

None

D. Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		**Information**
NDA/BLA Number	**NDA 206-289**	**Brand Name**	**Atropine Sulfate Ophthalmic Solution USP, 1%**
OCP Division (I, II, III, IV, V)	**DCP IV**	**Generic Name**	**atropine sulfate, USP**
Medical Division	**DTOP**	**Drug Class**	**anti-muscarinic agent**
OCP Reviewer	**Gerlie Gieser, PhD**	**Indication(s)**	**1) for use in producing cyclopegia & mydriasis; 2) (b) (4) pupil dilation**
OCP Team Leader	**Philip Colangelo, PharmD, PhD**	**Dosage Form**	**ophthalmic solution 1% (10 mg/mL)**
Pharmacometrics Reviewer		**Dosing Regimen**	
Date of Submission	**22 October 2013**	**Route of Administration**	**Topical ocular**
Estimated Due Date of OCP Review		**Sponsor**	**Akorn, Inc.**
Medical Division Due Date		**Priority Classification**	**Priority**
PDUFA Due Date	**30 April 2013**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				

Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**			Kaila et al.
multiple dose:				
Patients-				
single dose:	**X**			Lahdes et al
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:	**X**			
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability	**X**			Kaila et al
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				Pediatric patients included in trials
Literature References	**X**			
Total Number of Studies	**5 + 24**			5 PK + 6 efficacy (primary) + 4 efficacy/safety (supportive) + 14 safety

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			Metabolism -To rely on approved labeling of ANSYR (atropine sulfate for injection)
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			Absolute BA data in literature studies considered adequate since systemic exposure is not expected to be higher than that achieved with dosing of already approved AS i.v./i.m. injection
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			Based on literature articles
5	Has a rationale for dose selection been submitted?	X			Dosing regimens used in clinical trials
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			Based on literature studies; will also rely on PK data available for AS injection
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to			X	

	assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Peds were included in clinical trials.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ____YES____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

Clinical Pharmacology information request:
Please submit an annotated labeling with electronic links to the literature studies supporting each labeling claim.

Gerlie Gieser, PhD — 10/31/2013
Reviewing Clinical Pharmacologist — Date

Philip Colangelo, PharmD, PhD
Team Leader/Supervisor — Date

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

/s/

GERLIE GIESER
04/02/2014

PHILIP M COLANGELO
04/03/2014