Office of Clinical Pharmacology Review

NDA or BLA Number	208151
Link to EDR	EDR Link
Submission Date	February 12, 2016
Submission Type	Standard
Brand Name	Isopto Atropine 1%
Generic Name	Atropine sulfate monohydrate
Dosage Form and Strength	Sterile ophthalmic solution, 1%
Route of Administration	Topical ophthalmic
Proposed Indication	Mydriasis, Cycloplegia, Amblyopia, [redacted]
Applicant	Alcon Research, Ltd.
Associated IND	115869
OCP Review Team	Abhay Joshi, Ph.D.
OCP Final Signatory	Philip Colangelo, Pharm. D., Ph.D.

Table of Contents

1 EXECUTIVE SUMMARY

NDA 208151 is for ISOPTO Atropine 1%, which is a sterile ophthalmic solution that contains 1% atropine sulfate monohydrate. The Applicant is seeking approval for the use of ISOPTO Atropine 1% ophthalmic drops to produce mydriasis and/or cycloplegia, as well as to treat amblyopia (b) (4) The proposed dosing regimen is to instill (b) (4)

This NDA is a literature-based 505(b)(2) application and the Applicant has not conducted any supportive clinical safety and efficacy studies, nor any pharmacokinetic (PK) or other clinical pharmacology studies. To support this NDA, the Applicant is relying on the pharmacological, pharmacokinetic, and toxicological information of atropine from the scientific literature. In addition, in pursuant to 21 C.F.R. 320.22(e), the Applicant has requested a waiver of evidence of in vivo bioavailability for ISOPTO Atropine 1%, on the basis of compatibility with public health due to its long history of clinical safety and effectiveness.

The Medical Officer recommends ISOPTO Atropine 1%, be approved for use in producing pupillary dilation, cycloplegia, and for penalization of the healthy eye in the treatment of amblyopia; (b) (4) (W. Chambers, MD; Review date: 09/13/2016). In 2013, a separate literature based 505(b)(2) application for NDA 206289 for 1% atropine ophthalmic solution was submitted to the FDA. The Applicant of NDA 206289 was also seeking approval for the same indications that are currently being requested in this application. For NDA 206289, the Medical Officer also recommended that 1% atropine ophthalmic solution be approved for producing pupillary dilation, cycloplegia, and in the treatment of amblyopia; (b) (4) (W. Chambers, MD; Review date: 04/07/2014).

It is noteworthy that the pertinent supportive Clinical Pharmacology/PK information for previous NDA 206289 was derived from two literature studies, (1) Kaila, et al (1999) and (2) Lahdes, et al (1988) that evaluated the systemic exposure to atropine following the administration of 1% atropine sulfate ophthalmic solution. The Applicant for this current NDA 208151is also relying on the same two literature studies for Clinical Pharmacology/PK information for the proposed labeling.

1.1 Recommendations

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

1) Information from two literature studies, (1) Kaila, et al (1999) and (2) Lahdes, et al (1988) that evaluated the systemic exposure to the pharmacologically active enantiomer

of atropine, l-hyoscyamine, following the administration of 1% atropine sulfate ophthalmic solution.

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

The Reviewer's proposed labeling changes/recommendations in Section 2.3 of this Review will be forwarded to the Applicant.

1.2 Post-Marketing Requirements and Commitments

None.

2 SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

The Applicant did not conduct any clinical pharmacology studies in support of the proposed drug product: ISOPTO Atropine 1%. However, the Applicant has provided 11 clinical pharmacology studies published in the scientific literature. From those 11 studies, two clinical studies have evaluated the extent of systemic exposure to atropine from the topical ocular administration of 1% atropine sulfate solution. The following is the summary of the pertinent Clinical Pharmacology information that is derived from those two studies.

2.1 Pharmacology and Clinical Pharmacokinetics

A summary of the two randomized, open-label studies that determined the systemic exposures to l-hyoscyamine resulting from a single topical ocular administration of a 1% atropine sulfate solution are provided in Table 1below. Table 2 (below) summarizes the PK parameter estimates from those studies. Detailed information on these studies is provided in Section 4.

The parameter estimates from Table 2 indicate that the systemic exposure to l-hyoscyamine from the topical ocular administration of 1% atropine solution was low and highly variable between subjects / patients. In addition, no statistically significant increase in the anticholinergic effects of atropine (i.e., blood pressure, heart rate, and salivation) was reported in the 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 eye drops. The 0.4 mg dose of atropine is approximately similar to the dose currently being proposed for this new formulation (1 drop ISOPTO Atropine 1% (b) (4) mg of atropine).

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

Study Design	Study Objectives (No. of Patients)	Dosing Regimen	Reference
Randomized, crossover	To investigate the pharmacological basis of systemic effects of atropine eye drops (n=6)	0.3 mg atropine IV and topical ocular administration	Kaila 1999
Randomized, placebo-controlled study	To evaluate the systemic exposure and pharmacodynamics effects of atropine following single ocular topical (n=16)	0.4 mg of atropine (Oftan-Atropine 1% ophthalmic solution)	Lahdes 1988

Table 2: Pharmacokinetic parameters of atropine (measured as l-hyoscyamine) following topical ocular administration of 1% atropine sulfate ophthalmic solution

Study /Reference	Dosing Regimen	Subjects count (M/F), Type, Age Range	Pharmacokinetic Parameters $\frac{Mean \pm SD}{Range}$ for l-hyoscyamine				
			C_{max} (pg/mL)	T_{max} (min)	AUC (h*ng/mL)	$t_{½}$ (h)	F%
Kaila 1999	Single IV dose - 0.3 mg	6 (1M/5F), Healthy, 24-29 y	*NA*	*NA*	$\frac{1.79 \pm 0.64}{1.15 - 3}$	$\frac{2.97 \pm 1.22}{1.3 - 4.3}$	NA
	Topical ophthalmic – 0.3 mg		$\frac{288 \pm 73}{166 - 355}$	$\frac{28 \pm 27}{3 - 60}$	$\frac{1.02 \pm 0.33}{0.36 - 1.25}$	$\frac{2.45 \pm 0.76}{1.5 - 3.6}$	$\frac{63.5 \pm 28.6}{19 - 95}$
Lahdes 1988	Topical ophthalmic – 0.4 mg	8 (7M/1F),ocular surgery patients, 56-66 y	$\frac{860 \pm 402}{NA}$	NA	$\frac{0.72 \pm 0.4}{0.04 - 1.29}$	NA	NA

As mentioned previously in Section 1, a separate NDA application, i.e., NDA 206289, for 1% atropine ophthalmic solution was approved by the FDA in 2013. For that application, the pertinent Clinical Pharmacology information was derived from the same literature as this application, which was found acceptable to the previous Clinical Pharmacology Reviewer (Gerlie Gieser, Ph.D; Review date: 04/03/2014). Additionally, for this current NDA submission, the efficacy and safety information provided in support of the proposed drug product were deemed acceptable by the Medical Reviewer (W. Chambers, MD; Review date 09/13/2016).

Therefore, collectively, the PK information cited by the Applicant is deemed acceptable by the Clinical Pharmacology review team for this current NDA.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosing is [redacted] (b) (4)

2.2.2 Therapeutic individualization

No new information on therapeutic individualization was submitted in this application.

2.3 Summary of Labeling Recommendations

The Office of Clinical Pharmacology has the following labeling recommendations/edits in **Section 12.3 Pharmacokinetics**.

12.3 Pharmacokinetics

[redacted] (b) (4) *In a study of healthy subjects,* [redacted] (b) (4) *after topical ocular administration of 30 µL of 1% atropine sulfate, the mean (± SD) systemic bioavailability of l-hyoscyamine was reported* [redacted] (b) (4) *to be* [redacted] (b) (4) *approximately 64 ±* [redacted] (b) (4) *29% (range 19% to 95%), as compared to intravenous administration of*

atropine sulfate. (b) (4) -The (b) (4) time to maximum plasma concentration (Tmax) was (b) (4) (range 3 to 60 minutes) (b) (4) and the mean (± SD) peak plasma concentration (b) (4) (Cmax) of l-hyoscyamine was (b) (4) ± 73 pg/mL. The mean (± SD) (b) (4)

In a separate study of patients undergoing ocular surgery, after topical ocular administration of (b) (4) 40 µL of 1% atropine sulfate, (b) (4) -the mean (± SD) plasma Cmax of l-hyoscyamine was 860 ± 402 pg/mL, (b) (4)

(b) (4)

3 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Clinical Pharmacology Questions

3.1.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

No, the provided Clinical Pharmacology information does not provide supportive evidence of effectiveness. The site of drug administration and the site of action is eye, and the systemic exposure to atropine is not expected to relate to the efficacy of 1% atropine sulfate ophthalmic solution for mydriasis, cycloplegia, and treatment of amblyopia.

3.1.2 Is the proposed general dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed general dosing regimen is appropriate for the general patient population for which the indication is being sought.

3.1.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

No. There is no additional information pertinent to the intrinsic factors being submitted with this application that warrants a need for a subpopulation based alternative dosing regimen or management strategy.

It is noteworthy that the Medical Reviewer recommends the following age based dosing regimen (Review W. Chambers, MD; Review date: 09/13/2016)

- In individuals from three (3) months of age or greater 1 drop topically to the cul-de-sac of the conjunctiva, forty minutes prior to the intended maximal dilation time
- In individuals 3 years of age or greater, doses may be repeated up to twice daily as needed

4 APPENDICES

Atropine is an alkaloid that consists two enantiomers, l-hyoscyamine and d-hyoscyamine. L-hyoscyamine has high affinity to muscarinic acetylcholine receptors and is reported to be biologically active; consequently, it is responsible for the therapeutic and anticholinergic side effects of atropine. Therefore, from a Clinical Pharmacology perspective, information on the extent of systemic exposure to l-hyoscyamine resulting from the topical administration of 1% atropine ophthalmic solution is important to gauge the safety.

The pertinent supportive Clinical Pharmacology information was derived from two published studies in the literature, i.e., Kaila, et al (1999) and Lahdes, et al (1988), which evaluated the systemic exposure to l-hyoscyamine from the topical ocular administration of 1% atropine sulfate. Collectively, these results show that the systemic exposure to l-hyoscyamine resulting from the topical administration of 1% atropine ophthalmic solution are detectable and has high intra-individual variability. However, neither of the studies reported any treatment associated anticholinergic side effects. These two studies are summarized below.

Literature Reference 1: Kaila et al., (1999)

Title: *Systemic Bioavailability of Ocularly Applied 1% Atropine Eyedrops*

Study Design:

This was a randomized crossover study conducted in six healthy volunteers. After randomization, the subjects received 0.3 mg atropine either as a bolus intravenous injection of 0.3 ml atropine sulfate solution (Atropine 1 mg/ml inject) or as a drop of 30 µl of 1% atropine sulfate ophthalmic solution instilled unilaterally to the lower cul-de-sac of the eye. A washout period of two weeks was kept between those two treatments. Venous blood samples of 5 ml were taken for l-hyoscyamine analysis at 3, 5, 8, 10, 15, 20, 30 and 50 minutes, and 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours after drug dosing. Plasma l-hyoscyamine concentrations were analyzed with a radioreceptor binding assay (RRA) that measures the drug binding to rat neuronal muscarinic cholinoceptors. The reported detection limit of the radioreceptor binding assay for l-hyoscyamine in plasma was 20 pg/ml. Based on the plasma l-hyoscyamine concentrations, C_{max}, T_{max}, AUC, λ_z, elimination $t_{1/2}$, clearance, and the bioavailability of atropine (F) was calculated following the ocular administration.

Results:

The mean bioavailability of atropine (as l-hyoscyamine) following topical ocular administration was 64% of that following bolus intravenous administration, with large inter-individual differences in bioavailability ranging from 19% to 95% (Figure 1 and Table 1). The mean plasma l-hyoscyamine C_{max} was 289 pg/mL with the range of 166-355 pg/mL, at the median T_{max} of 19 minutes (range= 3 to 60 minutes). The mean terminal elimination half-lives of l-hyoscyamine were similar between topical and intravenous administrations, i.e., 2.45 and 2.97 hours, respectively.

Figure 1: Plasma l-hyoscyamine Concentrations After Intravenous (open circles) and Ocular (closed squares) dosing of 0.3 mg atropine (source: Excerpt from the copy of the Applicant provided literature)

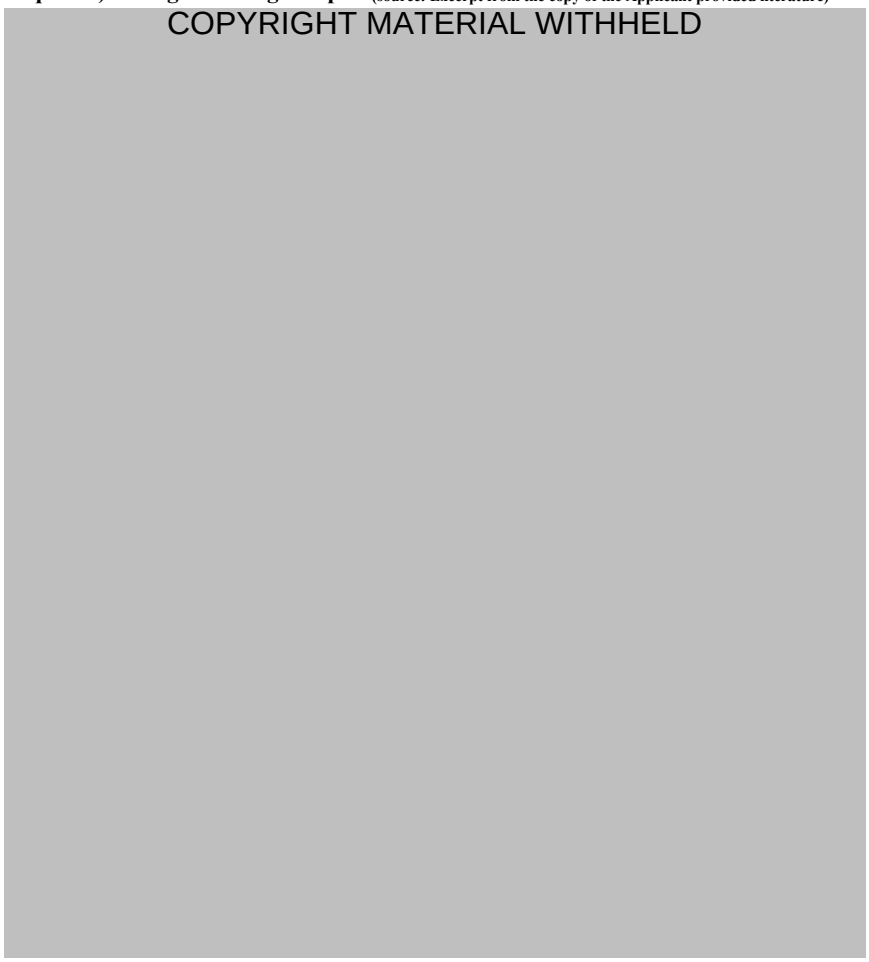


Table 1: Pharmacokinetic Parameters of l-hyoscyamine After Intravenous and Ocular Application of 0.3 mg atropine (source: Excerpt from the copy of the Applicant provided literature)

COPYRIGHT MATERIAL WITHHELD

With regard to the safety assessments, no statistically significant differences were reported in the systolic or diastolic blood pressures and heart rates between the two treatment arms, i.e., intravenous and ocular treatment groups, at different time levels. In addition, no statistically significant differences were reported in the systolic and diastolic blood pressures or heart rates between different time points within the treatment groups.

Literature Reference 2: Lahdes, et al., (1988)

Title: *Systemic Absorption of Topically Applied Ocular Atropine*

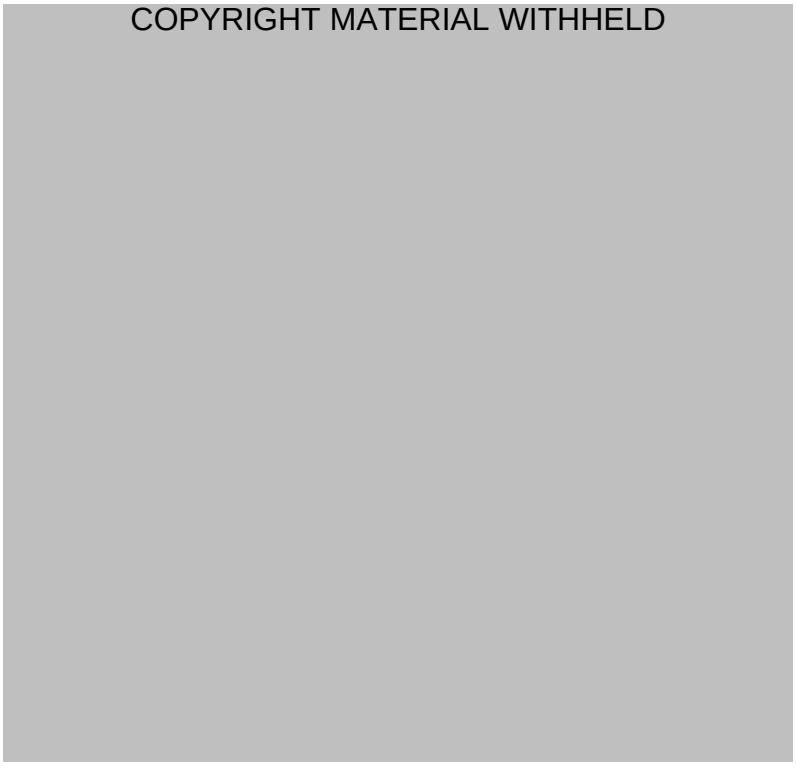
Study Design:

This study was conducted in 16 hospitalized patients who regularly received ocular atropine. After randomization, half of the patients received a drop of 40 µl of 1% atropine ophthalmic solution instilled unilaterally to the lower cul-de-sac of the eye. The remaining eight patients received an identical volume of placebo eye drops. For each arm, the dosing occurred after a washout period of at least 12 hours. Blood samples were collected from the both groups at 8, 15, 30, 45, 60, and 90 minutes. Atropine concentrations in plasma were determined by a modification of the radioreceptor assay that had the limit of sensitivity of 50 pg/ml in plasma. The atropine radioreceptor assay used in this study measured only the active component of atropine i.e., l-hyoscyamine. Based on the plasma l-hyoscyamine concentrations, C_{max}, and $AUC_{(0-90)}$ were calculated.

Results:

Serum l-hyoscyamine levels were determined over a 90 minute period following dose administration using a radio receptor binding assay (RRA). The reported mean C_{max} for l-hyoscamine was 860 pg/mL were observed in the first collected sample, i.e., at 8 minutes (Figure 1). The mean $AUC_{(0-90)}$ was 43245 pg/ml*min (range: 2350 – 77163 pg/ml*min). Since the blood samples were collected for only 90 min, the plasma concentrations from this study did no allowed a valid estimation of elimination half-lives; however, the authors are citing the reported the l-hyoscyamine elimination half-lives that ranges from 1.9 to 4.3 hour. With regard to the safety assessments, no statistically significant differences were reported in the systolic and diastolic blood pressures or heart rates between the atropine and control groups.

Figure 2 Plasma atropine (as l-hyoscyamine) concentration-time profiles in ocular surgery patients 56 to 66 years old(source: Excerpt from the copy of the Applicant provided literature)



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

/s/

ABHAY JOSHI
11/08/2016

PHILIP M COLANGELO
11/09/2016