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APPLICATION NUMBER:

213581Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	213581
Link to EDR	View submission in docuBridge
Submission Date	May 26, 2021
Submission Type	Standard
Brand Name	Atropine Sulfate Ophthalmic Solution, USP 1%
Generic Name	Atropine sulfate monohydrate
Dosage Form and Strength	Sterile ophthalmic solution, 1%
Route of Administration	Topical ophthalmic
Proposed Indication	Mydriasis, cycloplegia, and penalization of the healthy eye in the treatment of amblyopia
Applicant	Paragon BioTeck, Inc.
Associated IND	139379
OCP Review Team	Selim Fakhruddin, Ph.D. (primary) Ping Ji, Ph.D. (secondary)
OCP Final Signatory	Ping Ji, Ph.D.

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1 EXECUTIVE SUMMARY

Paragon Bioteck, Inc. ('the Applicant' for NDA213581) is seeking approval of Atropine Sulfate Ophthalmic Solution, USP 1%, as ophthalmic drops to produce mydriasis and/or cycloplegia, as well as for penalization of the healthy eye in the treatment of amblyopia. Atropine Sulfate Ophthalmic Solution, USP 1%, is an aseptically prepared, sterile, preservative-free ophthalmic solution that contains 1% atropine sulfate monohydrate. The proposed dosing regimen is to instill one drop in the eye(s) and may be repeated up to twice daily as needed.

This NDA is a literature-based 505(b)(2) application, and the Applicant has not conducted any supportive clinical safety and efficacy studies, nor any pharmacokinetic (PK) or other clinical pharmacology studies. To support this NDA, the Applicant is relying on the pharmacological, pharmacokinetic, and toxicological information of atropine from the scientific literature. Specifically, the supportive clinical pharmacology/PK information in this NDA included two literature studies, (1) Kaila 1999[1] and (2) Lahdes 1988[2] to evaluate the systemic exposure to atropine following the administration of 1% atropine sulfate ophthalmic solution. In addition, the Applicant has requested a waiver of evidence of in vivo bioavailability (BA) or bioequivalence (BE) studies for Atropine Sulfate Ophthalmic Solution, USP 1%, on the basis of compatibility with public health due to its long history of clinical safety and effectiveness.

1.1 Recommendations

The Clinical Pharmacology information provided by the Applicant in this submission is acceptable, and the Clinical Pharmacology review team recommends approval of NDA 213581 for Atropine Sulfate Ophthalmic Solution, USP 1%.

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 AND BIOPHARMACEUTICS ASSESSMENT

2.1 Pharmacology and clinical pharmacokinetics

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

The Applicant did not conduct any clinical pharmacology studies in support of the proposed drug product. However, the Applicant has provided two clinical studies that 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. Table 1 lists a summary of the two randomized, open-label studies that determined the systemic exposures resulting from a single topical ocular administration of a 1% atropine sulfate solution. Table 2 summarizes the PK parameter estimates from those studies. Detailed information on these studies is provided in Section 4.

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: Pharmacology and PK of atropine (measured as l-hyoscyamine) following topical ocular administration of 1% atropine sulfate ophthalmic solution from literature, Kaila 1999[1] and Lahdes 1988[2].

Mechanism of action	Atropine consists of two enantiomers, l-hyoscyamine and d-hyoscyamine. Only the l-enantiomer is biologically active which binds with high affinity to muscarinic acetylcholine receptors and is responsible for the therapeutic effects of the drug. Atropine is a potent compound and is known to antagonize human muscarinic cholinoceptor actions at plasma concentrations less than 100 pg/mL.
Cmax	After ocular administration of a single dose of 0.3 mg atropine sulfate to healthy subjects, mean Cmax (±SD) is 288 ± 73 pg/mL, and range is 166 – 355 pg/mL. After ocular administration of a single dose of 0.4 mg atropine sulfate to patients undergoing ocular surgery, mean Cmax (±SD) is 860 ± 402 pg/mL.
AUC0-inf	After ocular administration of a single dose of 0.3 mg atropine sulfate to healthy subjects, mean AUC0-inf (±SD) is 1.02 ± 0.33 h*ng/mL, and range is 0.36 – 1.25 h*ng/mL. After ocular administration of a single dose of 0.4 mg atropine sulfate to patients undergoing ocular surgery, mean AUC0-90 (±SD) is 0.72 ± 0.4 h*ng/mL, and range is 0.40 – 1.29 h*ng/mL.
Bioavailability	In healthy subjects, the mean bioavailability of topically applied atropine was 63.5 ± 29% (range 19 to 95%) with large inter-individual differences. Mean maximum observed plasma concentration for the ophthalmic solution was 288 ± 73 pg/mL.
Tmax	Maximum concentration was reached in 28 ± 27 min after administration.
Metabolism	Atropine is destroyed by enzymatic hydrolysis, particularly in the liver; from 13 to 50% is excreted unchanged in the urine. Traces are found in

	various secretions, including milk. The major metabolites of atropine are noratropine, atropin-n-oxide, tropine, and tropic acid.
Excretion	From 13 to 50% is excreted unchanged in the urine.
Half-life	After topical ocular administration: 2.45 ± 0.76 hours; After intravenous administration: 2.97 ± 1.22 hours.

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 (e.g., 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 (b) (4)

(b) (4)

It is noteworthy that for two previously approved NDA applications, e.g., NDA 206289 and NDA208151 for 1% atropine ophthalmic solution, the pertinent Clinical Pharmacology information was derived from the same literature as for this application. Refer to the clinical pharmacology review for these two NDAs.

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 (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**. Since the Applicant did not perform PK studies for their own product, the PK data in the proposed label is based on the literature data from previous studies and is similar to the approved labels for Atropine Sulfate Ophthalmic Solution, USP 1% (NDA 206289, NDA 208151)

12.3 Pharmacokinetics

In a study of healthy subjects, after topical ocular administration of 30 µL of 1% atropine sulfate, the mean (± SD) systemic bioavailability of l-hyoscyamine was reported to be approximately 64 ± 29% (range 19% to 95%), as compared to intravenous administration of atropine sulfate. The median (range) time to maximum plasma concentration (Tmax) was 19 minutes (range 3 to 60 minutes), and the mean (± SD) peak plasma concentration (Cmax) of l-hyoscyamine was 228 ± 73 pg/mL. The mean (± SD) plasma half-life was reported to be 2.5 ± 0. 8 hours.
In a separate study of patients undergoing ocular surgery, after topical ocular administration of 40 µL of 1% atropine sulfate, the mean (± SD) plasma Cmax of l-hyoscyamine was 860 ± 402 pg/mL, which was observed within 8 minutes following administration.

3 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Parenteral (intravenous/intramuscular) atropine sulfate product such as AtroPen® and Atropine Sulfate Injection (Ansyr®) are currently FDA-approved 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.

Thus far, 2 products containing atropine sulfate 1% ophthalmic solution for topical ocular administration have been approved through 505(b)(2) pathway with the same indications as proposed in this application (NDA 206289 and NDA208151). It is noteworthy that the pertinent supportive Clinical Pharmacology/PK information for these two NDAs was derived from two literature studies, (1) Kaila 1999[1] and (2) Lahdes 1988[2] that evaluated the systemic exposure to atropine following the administration of 1% atropine sulfate ophthalmic solution. The Applicant for this current NDA 213581is also relying on the same two literature studies for Clinical Pharmacology/PK information for the proposed labeling.

Both of these ophthalmic formulations contain benzalkonium chloride as a preservative. In contrast, the proposed ophthalmic formulation under the current application doesn't contain BAK. The Applicant has requested a waiver of evidence of in vivo bioavailability for Atropine 1%, on the basis of compatibility with public health due to its long history of clinical safety and effectiveness. The Biopharmaceutics review team considered that the requested waiver of BA/BE studies is based on good cause option set forth in 21 C.F.R 320.22(e) (via email).

Under IND 139379, the pre-IND meeting took place on July 13, 2018. The Agency agreed during the meeting that a 505(b)(2) application was an acceptable pathway for a new drug application in which the applicant did not have a right to reference studies conducted in support of the drug product. The Agency acknowledged that studies using atropine prior to the 1950s were preservative free and referencing these studies would be supportive of their product. The

Applicant submitted 3 literature studies published prior to 1950 (Marron 1940[3], Wolf and Hodge 1946[4] , Riddell 1946[5]), which demonstrated efficacy of atropine sulfate 1% ophthalmic solution in producing mydriasis and cycloplegia. Refer to clinical review for details on these 3 literature studies.

3.2 Clinical Pharmacology Review Questions

3.2.1 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.

3.2.2 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.

3.2.3 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.

4 APPENDICES

Atropine is an alkaloid containing a racemic mixture of d- and l-hyoscyamine of which the latter is biologically active because of its high affinity to muscarinic acetylcholine receptors. 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 evaluate the safety.
Relevant clinical pharmacology information on l-hyoscyamine was mainly derived from two published studies in the literature, e.g., Kaila et al. 1999[1] and Lahdes et al. 1988[2]. These studies evaluated the extent of systemic exposure to l-hyoscyamine from topical ocular administration of 1% atropine sulfate. Overall, it is observed that the systemic bioavailability of l-hyoscyamine

[3] Marron J (1940). Cycloplegia and mydriasis by use of atropine, scopolamine and homatropine-paredrine. Arch Ophthalmol., vol. 23(2), pp 340-350.
[4] Wolf AV and Hodge HC (1946). Effects of atropine sulfate, methylatropine nitrate (metropine) and homatropine hydrobromide on adul human eyes. Arch Ophthalmol., vol. 36(3), pp 293-301.
[5] Riddell WJB (1946). A clinical trial of a synthetic mydriatic (dimethylaminoethyl Benzilate Ethochloride). Br J Ophthalmol., vol. 30, pp 1-7.

from the ocular site is considerable with large interindividual variability. Hence, l-hyoscyamine was detectable in the systemic circulation with no associated anticholinergic side effects as evident in both studies. Both of the studies are summarized below.

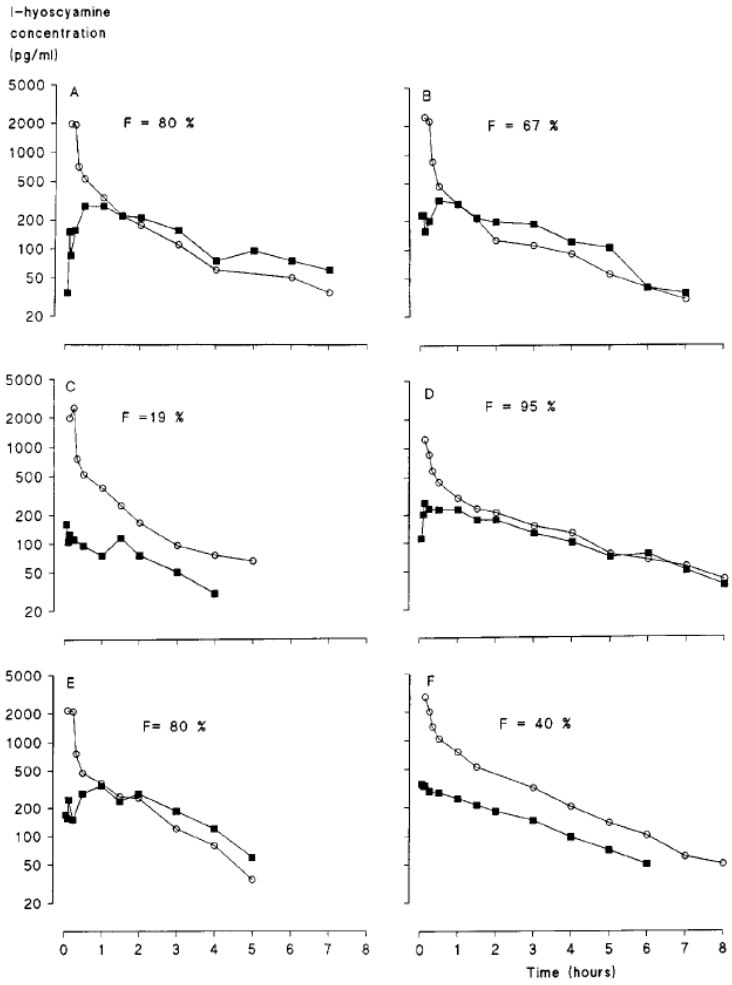
4.1 Literature Reference 1: Kaila et al., (1999)

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 2). 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, e.g., 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: Applicant provided literature, Kaila 1999[1]

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, e.g., 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.

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

Title: *Systemic Absorption of Topically Applied Ocular Atropine*

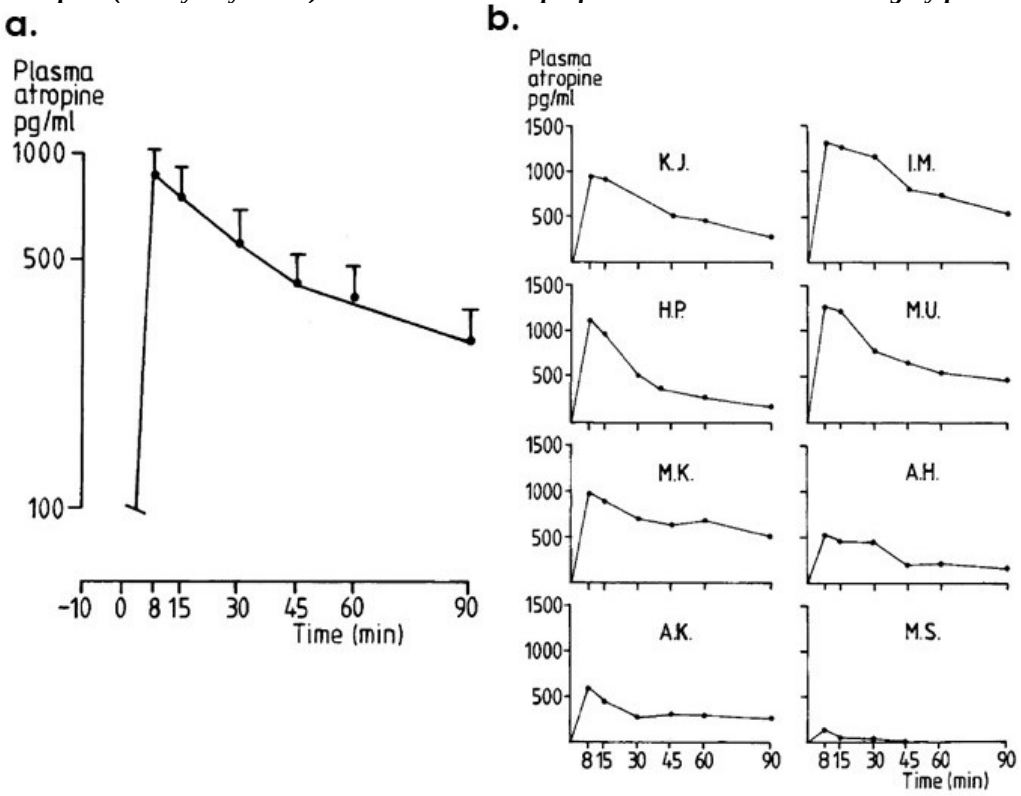
Study Design:
This study was conducted in 16 hospitalized patients who regularly received ocular atropine. After randomization, half of the patients received a drop of 40 µl of 1% atropine ophthalmic solution instilled unilaterally to the lower cul-de-sac of the eye. The remaining eight patients received 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 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 e.g., 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 and were observed in the first collected sample, e.g., at 8 minutes (Figure 2). 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 not allow a valid estimation of elimination half-lives; however, the authors are citing the reported l-hyoscyamine elimination half-lives that range 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: a) Plasma atropine (as l-hyoscyamine) concentrations in eight patients (mean ± SE). b) Plasma atropine (as l-hyoscyamine) concentration-time profiles in individual ocular surgery patients 56 to 66 years old.



Source: Applicant provided literature, Lahdes 1988[2]

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