CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208151Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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, and (b) (4)
Applicant	Alcon Research, Ltd.
Associated IND	115869
OCP Review Team	Abhay Joshi, Ph.D.
OCP Final Signatory	Philip Colangelo, Pharm. D., Ph.D.

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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) 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 median (range) time to maximum plasma concentration (Tmax) was* (b) (4) *minutes (range 3 to 60 minutes)* (b) (4) *and the mean (± SD) peak plasma concentration* (b) (4) *(Cmax) of l-hyoscyamine was 228 ± 73 pg/mL. The mean (± SD) plasma half-life was reported* (b) (4) *to be 2.* (b) (4) *5 ± 0.* (b) (4) *8 hours.* (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)

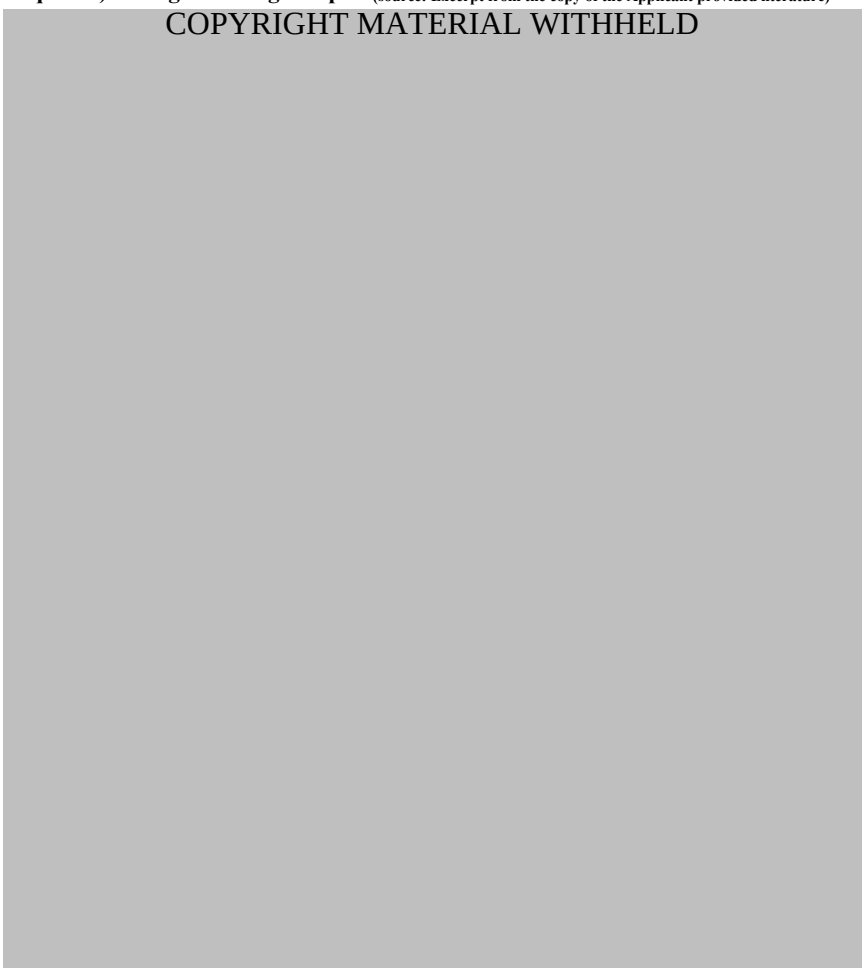

Table 1: Pharmacokinetic Parameters of l-hyoscyamine After Intravenous and Ocular Application of 0.3 mg atropine (source: Excerpt from the copy of the Applicant provided literature)

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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*

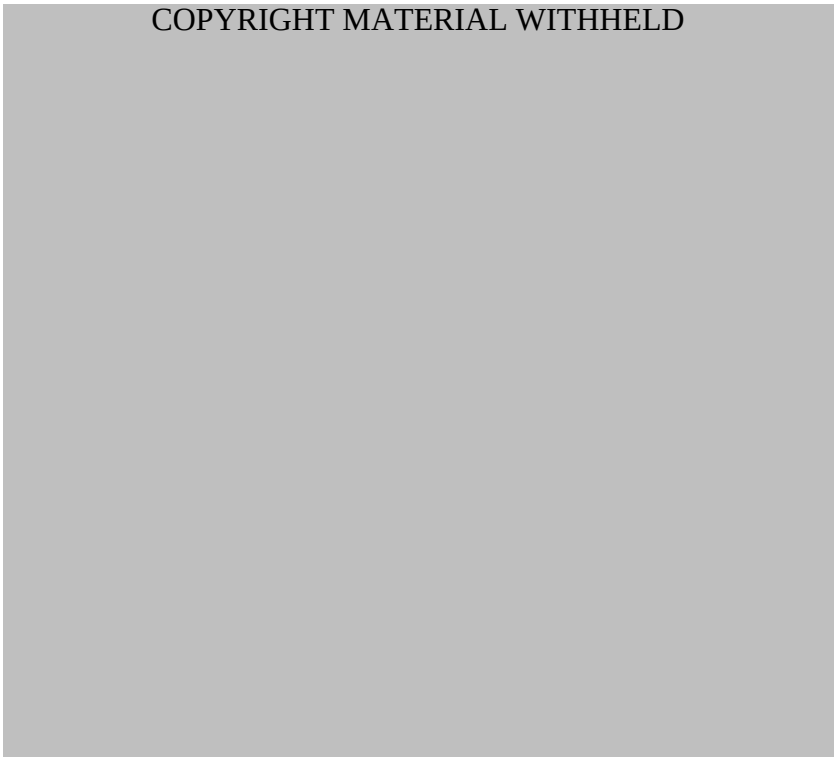
Study Design:

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)



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/s/

ABHAY JOSHI
11/08/2016

PHILIP M COLANGELO
11/09/2016

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	208151	**SDN**	1
Applicant	Alcon Research, Ltd.	**Submission Date**	02/12/2016
Generic Name	Atropine sulfate monohydrate	**Brand Name**	ISOPTO® ATROPINE 1%
Drug Class	Anti-muscarinic agent		
Indication	1) To produce mydriasis and/or cycloplegia 2) To treat amblyopia (b) (4)		
Dosage Regimen	(b) (4)		
Dosage Form	Ophthalmic solution	**Route of Administration**	Topical ophthalmic
OCP Division	DCP-IV	**OND Division**	DTOP

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Abhay Joshi, Ph.D.	Philip Colangelo, Pharm. D., Ph.D.
Pharmacometrics		
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	4/12/2016	**74-Day Letter Date**	4/26/2016
Review Due Date	11/7/2016	**PDUFA Goal Date**	12/12/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☐ Yes ☑ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		
☐ Distribution		

☑ Drug-Drug Interaction		1	Literature data only– See Notes below
In Vivo Studies			
Biopharmaceutics			
☑ Absolute Bioavailability		1	Literature data only– See Notes below
☑ Relative Bioavailability		1	Literature data only– See Notes below
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	10	Literature data only– See Notes below
	☐ Multiple Dose		
Patients	☑ Single Dose	1	Literature data only– See Notes below
	☐ Multiple Dose		
☑ Mass Balance Study		1	Literature data only– See Notes below
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☑ Geriatrics		1	Literature data only– See Notes below
☑ Pediatrics		1	Literature data only– See Notes below
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☑ Healthy Subjects		2	Literature data only– See Notes below
☐ Patients			
☐ QT			
Pharmacometrics			
☐ Population Pharmacokinetics			
☐ Exposure-Efficacy			
☐ Exposure-Safety			

Total Number of Studies	**In Vitro**	1	**In Vivo**	11
Total Number of Studies to be Reviewed		1		2

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	In vivo bioavailability waiver request submitted
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☐Yes ☐No ☑N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐Yes ☐No ☑N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☐Yes ☐No ☑N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☐Yes ☐No ☑N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☐Yes ☐No ☑N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. 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)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Notes:

This NDA is a literature-based 505(b)(2) application. The sponsor has submitted a list of published literature with the complete manuscripts that are relevant to the clinical pharmacokinetics and clinical pharmacology of atropine. The submitted literature(s) is summarized in Table 1. Note however, that only the submitted literature articles dealing with the topical ocular administration of atropine sulfate will be reviewed; the articles dealing with systemic administration will not be reviewed.

Table 1: Listing of the Submitted Literature(s) of Atropine*

Number	Study Objectives	Study Population	Dosing Regimen	Single Dose/ Multiple Dose	Reference
1	To investigate the pharmacological basis of systemic effects of atropine eyedrops	6 (healthy volunteers)	0.3 mg atropine, IV and topical ocular administration	Single Dose	Kaila 1999
2	To evaluate the systemic exposure and pharmacodynamic effects of atropine following single ocular topical	16 (patients undergoing ocular surgery)	0.4 mg of atropine (Oftan-Atropine 1% ophthalmic solution)	Single Dose	Lahdes 1988
3	To evaluate the suitability of radioreceptor assay and radioimmunoassay of atropine for use in pharmacokinetic studies	8 (healthy female volunteers undergoing gynecological surgery)	Single dose of atropine 0.02 mg/kg, IV	Single Dose	Aaltonen 1984
4	To assess atropine pharmacokinetics in normal volunteers given therapeutic doses	6 (healthy volunteers)	Single 1mg atropine, IV	Single Dose	Adams 1982
5	To evaluate the pharmacokinetics of atropine in healthy volunteers	3 (healthy volunteers)	1.4 and 2.2 mg of atropine base, IV	Single Dose	Gundert-Remy 1980
6	To assess the pharmacodynamics and pharmacokinetic effects of intramuscular atropine	6 (healthy male volunteers)	0.01 mg/kg, 0.02 mg/kg atropine or placebo, IV	Single Dose	Kentala 1990
7	To evaluate the pharmacokinetics and pharmacodynamics of atropine in healthy volunteers	3 (healthy male volunteers)	1.35 and 2.15 mg atropine, IV	Single Dose	Hinderling 1985a Hinderling 1985b
8	To evaluate the metabolism of 14C- tropine labeled atropine to man	4 (healthy male volunteers)	2 mg atropine, IM	Single Dose	Kalser 1970
9	To evaluate the pharmacokinetics of atropine by age	52 (13 children, 29 adult patients, 10 elderly patients)	0.02 mg/kg, IV and IM	Single Dose	Virtanen 1982
10	To determine the placental transfer and pharmacokinetics of atropine in the mother	44 (healthy parturients undergoing caesarean section)	0.01 mg/kg, IV and IM	Single Dose	Kanto 1981
11	To determine the kinetics of atropine in maternal venous blood and the placental transfer	45 (healthy parturients)	12.5 µg/kg, IV	Single Dose	Onnen 1979

IV: *Intravenous administration,* ***IM:*** *Intramuscular administration*

*** Adapted and modified from the Sponsor provided report:* ***2.7.2 Summary of Clinical Pharmacology Studies***

Filing Memo

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/s/

ABHAY JOSHI
05/16/2016

PHILIP M COLANGELO
05/16/2016