CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206276Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 206276	**Reviewer:** Banu Sizanli Zolnik, Ph.D.	
Division:	Division of Transplant and Ophthalmic Products		
Applicant:	Alcon Research LTD	**Biopharmaceutics Team Leader (Acting):** Elsbeth Chikhale, Ph.D.	
Trade Name:	Pazeo	**Acting Biopharmaceutics Supervisor:** Paul Seo, Ph.D.	
Generic Name:	Olopatadine Hydrochloride	**Date Assigned:**	August 1, 2014
Indication	Treatment of ocular itching associated with allergic conjunctivitis	**Date of Review:**	December 23, 2014
Dosage Form/ Strength	0.7% Ophthalmic Solution	**Route of Administration**	Ophthalmic

SUBMISSIONS REVIEWED IN THIS DOCUMENT		
Submission Dates	**Date of informal/Formal Consult**	**Primary Review due in DARRTS**
Original submission Dated July 30, 2014	NA	01/03/2017
Type of Submission:	Original 505 (b)(2) Application	
Review Key Points:	▪ The evaluation of the biowaiver request	

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

Submission:
NDA 206276 for Olopatadine Ophthalmic solution, 0.7% (0.776% olopatadine hydrochloride is equivalent to 0.7% free base) is a 505 (b)(2) submission. Olopatadine is an antihistamine and mast cell stabilizer and the proposed indication is the treatment of ocular itching associated with allergic conjunctivitis. The listed drug product is Patanol®, NDA 20-688.

The approved olopatadine HCl products are listed below:

- Patanol® (olopatadine HCl) ophthalmic solution eq. 0.1% base was approved by FDA under NDA 20-688 on December 18, 1996, for the treatment of the signs and symptoms of allergic conjunctivitis.
- Pataday® (olopatadine HCl) ophthalmic solution eq. 0.2% base was approved by FDA under NDA 21-545 on December 22, 2004, for the treatment of ocular itching associated with allergic conjunctivitis.
- Patanases® is a nasal spray olopatadine HCL formulation indicated for the relief of the symptoms of seasonal allergic rhinitis. This product was approved under NDA 21-861on April 15, 2008.

The current proposed product was developed with the intention ~~of~~ to increase the duration of efficacy compared to the marketed products Patanol® and Pataday®.
The Applicant conducted two clinical safety and efficacy studies (C-10-126 and C-12-053) in support of approval of the proposed product. The Applicant also conducted clinical pharmacology study C-11-036, a Phase 1 pharmacokinetic study following single and multiple dose topical ocular administration of olopatadine HCL ophthalmic solution 0.77% in Japanese 24 healthy subjects. Phase 1 PK study is evaluated by Office of Pharmacology reviewer Dr. Gerlie Geiser. Dr. Gieser's review (dated 10/16/2014) states "*In healthy subjects topical ocular dosing of 1 drop of Pazeo once daily for 7 days into both eyes resulted in mean ± SD (range) steady state plasma olopatadine C_{max} and AUC_{0-12} of 1.6 ± 0.9 ng (0.6 to 4.5 ng/mL) and 9.7± 4.4 ng*h/mL (3.7 to 21.2 ng*h/mL), respectively. The olopatadine C_{max} and AUC $_{0-12}$ after the first dose were similar to those measured on day 7 suggesting that there was no systemic accumulation of olopatadine after repeated topical ocular dosing with Pazeo®*".

Review:
The Biopharmaceutics review is focused on the evaluation of the overall information/data supporting the approvability of the biowaiver request.

Per 21 CFR 320.22 (b)(1), the Applicant is requesting a waiver from the requirements for submission of in vivo bioavailability or bioequivalence data on the basis that the proposed product is an ophthalmic product applied topically in the eye and is intended only for local therapeutic effect. However, the Applicant conducted a PK study (which was reviewed by Dr. Gerlie Gieser) in healthy subjects. Therefore, a biowaiver request is not applicable.

RECOMMENDATION:
The ONDQA-Biopharmaceutics team has reviewed NDA 206276 submitted on July 30, 2014. From the Biopharmaceutics perspective, NDA 206276 Pazeo (olopatadine hydrochloride) ophthalmic solution 0.7% is recommended for **APPROVAL.**

Banu Sizanli Zolnik, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Banu S. Zolnik -S
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Banu S. Zolnik -S, 0.9.2342.19200300.100.1.1=1300438310
Date: 2014.12.23 16:08:30 -05'00'

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Team Leader (Acting)
Office of New Drug Quality Assessment

Elsbeth G. Chikhale -S
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Date: 2014.12.23 18:56:51 -05'00'

cc: P. Seo

RISK ASSESSMENT TABLE

From Initial Quality Assessment			Review Assessment		
Product attribute / CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation Approach	Risk Evaluation [Acceptable/ Unacceptable]	Lifecycle Considerations/ Comments**
Solution	NA	L	NA	NA	NA

* Risk ranking applies to product attribute/CQA (L, M, H)

CLINICAL PHARMACOLOGY REVIEW

NDA:	**206-276 (N-000)**
Submission Date:	**30 July 2014**
Drug Product:	**olapatadine hydrochloride ophthalmic solution, 0.7%**
Trade Name:	**PAZEO®**
Proposed indication:	**for treatment of ocular itching associated with allergic conjunctivitis**
Sponsor:	**Alcon Research, Ltd**
Submission Type:	**505(b)(1) NDA**
OCP Reviewer:	**Gerlie Gieser, Ph.D.**
Team Leader:	**Philip M. Colangelo, Pharm.D., Ph.D.**

I. Executive Summary:

Alcon is seeking approval of PAZEO® (olapatadine hydrochloride, 0.7%) ophthalmic solution for the treatment of ocular itching associated with allergic conjunctivitis; the proposed dosage is 1 drop into each eye once daily. The sponsor reported that in two adequate well-controlled Phase 3 Conjunctival Allergen Challenge (CAC) trials, PAZEO® (0.7%) demonstrated superiority to vehicle and the active comparator(s) PATADAY® (olapatadine hydrochloride 0.2%; Alcon) and PATANOL® (olapatadine hydrochloride 0.1%; Alcon) when 1 drop per eye of the treatments were administered to adult allergic conjunctivitis patients at 2 to 3 non-consecutive days over 2 to 3 weeks (i.e., on days 0, 14, 21). Additionally, the safety and tolerability of PAZEO® (given as 1 drop per eye once daily for 6 weeks) was demonstrated in healthy subjects 2 years and older (Study C-12-028). The sponsor's subgroup analyses of safety data generated in Study C-12-028 did not reveal any clinically significant differences in the types and the rates of adverse events with respect to age, gender, race, concomitant disease, concomitant medications, and iris color. In Study C-12-028, dysgeusia (taste perversion) was the only unique common adverse event reported for PAZEO® 0.7%, although the rate (2.4%) was not higher than that reported for PATADAY® 0.2% (i.e., 5% or less, in the US package insert).

Summary of Clinical Pharmacology Findings

The sponsor conducted PK Study C-11-036 to determine the plasma exposures to olapatadine and its two (N-oxide and mono-desmethyl) metabolites following single and repeated topical ocular administration of the proposed commercial ophthalmic solution in 24 healthy adult subjects; 19 subjects had a complete set of PK profiles on Days 1 and 7. The plasma olapatadine (parent drug) concentrations were higher with topically applied PAZEO® (olapatadine hydrochloride 0.7%) ophthalmic solution administered as 1 drop per eye once daily for 7 days, compared to that reported for 0.15% olapatadine ophthalmic solution administered as 1 drop per eye twice daily for 2 weeks (see the PATADAY® and PATANOL® US package inserts), although no apparent accumulation of olapatadine was observed following repeated topical ocular administration of the proposed product. The mean steady state plasma olapatadine Cmax and AUC_{0-12} measured with PAZEO® in this PK study were lower (by 90% to 93%, and by 85% to 88%, respectively) than that reported in adult healthy subjects and seasonal allergic rhinitis patients following administration of PATANASE® (olapatadine hydrochloride 0.6%; Alcon) Nasal Spray given 2 sprays per nostril twice daily for 14 days. The N-oxide metabolite of olapatadine (M3) was detected in less than 10% of the total plasma samples in approximately half of the study participants; the maximum plasma concentration was 0.174 ng/mL measured during the first 4 hours post-dosing. Plasma concentrations of desmethyl olapatadine (M1) were below the LLOQ (0.05 ng/mL) of the PK assay.

Recommendations

From a Clinical Pharmacology perspective, this NDA of olapatadine hydrochloride 0.7% ophthalmic solution is recommended for approval. See Section III of this document for the reviewer's recommended edits to the sponsor's proposed language in Section 12.3 of the proposed package insert.

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Gerlie Gieser, Ph.D.
Office Clinical Pharmacology
Division of Clinical Pharmacology 4

RD/FT signed by Philip M. Colangelo, Pharm.D., Ph.D. (TL) _____

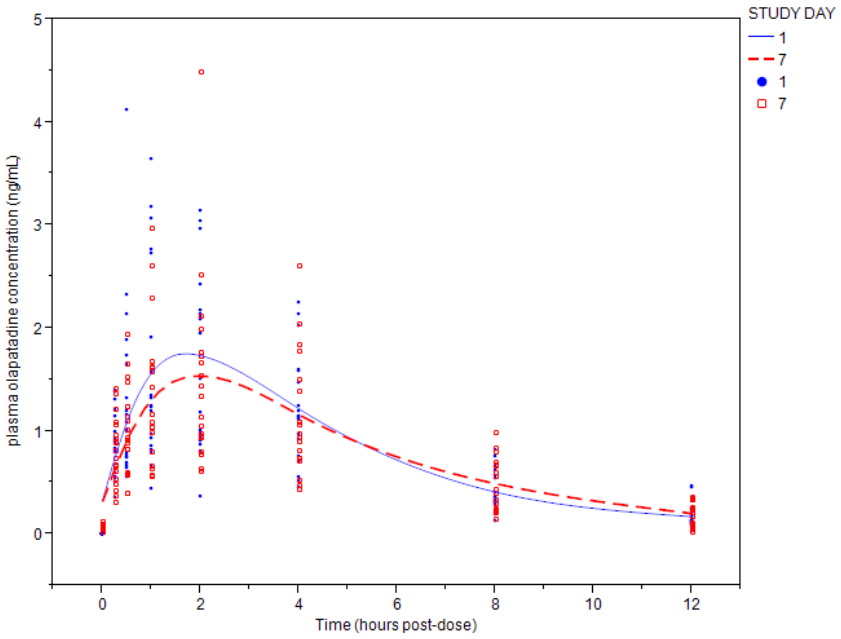
II. Question-Based Review:

A. General Clinical Pharmacology

1. What are the PK parameters of the drug and its metabolites after single and multiple dosing?

The PK of olapatadine and its n-oxide and mono-desmethyl metabolites following single and repeated topical ocular dosing of PAZEO® (1 drop once daily for 7 days) were investigated in 24 healthy adult subjects (24 to 62 years old, weighing 54 to 99 kg). The time course of plasma olapatadine concentrations for 19 subjects with a complete set of PK parameters for the two PK profiling days (Days 1 and 7) are depicted in Figure 1; the corresponding PK parameters are summarized in Table 1. The mean olapatadine Cmax, and AUC_{0-12} were similar on day 1 and day 7, suggesting the lack of systemic accumulation after repeated topical ocular dosing with PAZEO®. The olapatadine Cmax and AUC were not significantly influenced by gender, race, age and bodyweight.

Figure 1. Plasma olapatadine concentration-time profiles following 1 day and 7 days of topical ocular dosing with PAZEO® administered as 1 drop per eye once daily to healthy adult subjects (Study C-11-036)



*analysis includes 19 subjects with complete set of PK profiles on Days 1 and 7

Table 1. Pharmacokinetic Parameters of Olopatadine after Single and Multiple Once Daily Dosing of PAZEO® in Healthy Adult Subjects (Study C-11-036); [Mean ± SD; Median (range)]

Olapatadine PK parameter	**Day 1** (n=19)	**Day 7** (n=19)
T_{max} (hours)	1.65 ± 1.07; 2 (0.25 - 4.02)	1.86 ± 1.1; 2 (0.25 - 4)
C_{max} (ng/mL)	1.9 ± 1; 1.7 (0.6 - 4.1)	1.6 ± 0.9; 1.6 (0.6 - 4.5)
AUC_{0-12} (ng*h/mL)	10 ± 4.3; 9.1 (4.1 - 18.4)	9.7 ± 4.4; 9.1 (3.7 - 21.2)
$t_{1/2}$ (hours)	3.01 ± 1.07; 2.56 (2.05 - 5.78)	3.4 ± 1.2; 3.3 (2.13 - 7.77)

*analysis includes 19 subjects with complete set of PK profiles on Days 1 and 7

Compared to two approved olapatadine ophthalmic solutions marketed by Alcon Research, Ltd, i.e., PATADAY® 0.2% (given 1 drop per eye once daily) and PATANOL® 0.1% (given 1 drop per eye twice daily), the plasma olapatadine (parent drug) concentrations following topical ocular use of PAZEO® at the proposed dosage were higher in the healthy adult subjects who participated in the PK study. The package inserts of PATADAY® and PATANOL® states: "Following topical ocular administration of olopatadine 0.15% ophthalmic solution in man, olopatadine was shown to have a low systemic exposure. Two studies in normal volunteers (totaling 24 subjects) dosed bilaterally with olopatadine 0.15% ophthalmic solution once every 12 hours for 2 weeks demonstrated plasma concentrations to be generally below the quantitation limit of the assay (< 0.5 ng/mL). Samples in which olopatadine was quantifiable were typically found within 2 hours of dosing and ranged from 0.5 to 1.3 ng/mL."

Compared to PATANASE® (olapatadine 0.66%) Nasal Spray when given as 2 sprays per nostril twice daily, the measured mean steady state Cmax and AUC_{0-12} were lower (by 90% to 93%, and by 85% to 88%, respectively) in the healthy subjects of the PK study following topical ocular use of PAZEO® at the proposed dosage. The reviewer notes that even if adjusting the observed mean olapatadine Cmax and AUC_{0-12} for the low absolute recoveries (<40%) of the simultaneous PK assay (see Section B.3 of this NDA review), the exposures to olapatadine (and its metabolites) would still be significantly lower than that previously reported for PATANASE®. The PATANASE US package insert describes the systemic exposures to olapatadine in healthy subjects and patients, as follows:

"Absorption: *Healthy Subjects:* Olopatadine was absorbed with individual peak plasma concentrations observed between 30 minutes and 1 hour after twice daily intranasal administration of PATANASE Nasal Spray. The mean (± SD) steady-state peak plasma concentration (Cmax) of olopatadine was 16.0 ± 8.99 ng/mL. Systemic exposure as indexed by area under the curve (AUC_{0-12}) averaged 66.0 ± 26.8 ng·h/mL. The average absolute bioavailability of intranasal olopatadine is 57%. The mean accumulation ratio following multiple intranasal administration of PATANASE Nasal Spray was about 1.3.
Seasonal Allergic Rhinitis (SAR) Patients: Systemic exposure of olopatadine in SAR patients after twice daily intranasal administration of PATANASE Nasal Spray was comparable to that observed in healthy subjects. Olopatadine was absorbed with peak plasma concentrations observed between 15 minutes and 2 hours. The mean steady-state Cmax was 23.3 ± 6.2 ng/mL and AUC_{0-12} averaged 78.0 ± 13.9 ng·h/mL."

Table 2. Mean ± SD (range) Pharmacokinetic Parameters of Olopatadine after Multiple QD or BID Intranasal Doses

Study	Dose/Regimen (N)	Cmax (ng/mL)	Tmax (h)	AUC_{0-12} (ng*h/mL)	$t_{1/2}$ (h)
Study C-02-10 SAR patients	0.4%/BID x 14 days (N=14)	15.9 ± 6.4 (3.65-29.0)	1.00 ± 0.55 (0.25-2.00)	57.3 ± 24.5 (10.4-114)	8.3 ± 4.9 (2.1-21.3)
	0.6%/BID x 14 days (N=13)	23.3 ± 6.2 (14.4-35.3)	0.97 ± 0.52 (0.08 - 1.50)	78.0 ± 13.9 (54.4- 103)	10.4 ± 5.1 (4.0-21.8)
Study C-00-58 Healthy Subjects	0.1%/QD x 3 days (N=12)	4.36 ± 2.27 (0.41 -7.92)	1.23 ± 0.59 (0.50 -2.00)	13.92± 5.90 (1.40 -20.67)	6.3 ± 4.1 (1.96 - 13.5)
	0.1%/BID x 3 days (N=12)	3.42 ± 1.31 (0.97 — 5.05)	1.06 ± 0.42 (0.50 - 1.50)	12.03 ± 3.66 (4.80 - 16.54)	8.3 ± 3.5 (3.06 - 13.3)
	0.2%/BID x 3 days (N=12)	8.48 ± 3.12 (2.77- 15.0)	1.25 ± 0.38 (0.75-2.00)	28.33 ± 9.88 (11.09- 14.03)	15.0 ± 9.6 (3.16-29.9)

Source Clinical Pharmacology review of PATANASE® (olapatadine 0.6% intranasal spray) NDA
SAR (Seasonal Allergic Rhinitis); BID (twice daily); QD (once daily)

That the average elimination half-life of olapatadine (3.5 hours) on Day 1 and at steady state following topical ocular administration of PAZEO® is shorter than that reported for intranasally administered olapatadine and orally administered olapatadine (8 to 12 hours) could be explained by the possible

dependence of the systemic elimination of this drug on the circulating concentrations. Based on the Clinical Pharmacology review of the PATANASE® NDA, there appears to have been a trend of longer mean elimination half-life with higher cumulative doses of olapatadine nasal spray (see $t_{1/2}$, Cmax, and AUC_{0-12} of olapatadine of healthy subjects in Table 2).

The reviewer confirms that desmethyl olapatadine (M1) was not detected in any of the plasma samples collected in PK Study C-11-036. On the other hand, N-oxide olapatadine (M3) was detected in 8.9% (27/304) of the plasma samples (from 58% or 11 of the 19 subjects with a complete set of olapatadine PK parameters on Day 1 and Day 7). In those with detectable levels, the maximum steady state M3 concentration was 0.174 ng/mL, measured during the first 4 hours post-dose. When considering all plasma samples collected in the PK study, i.e., even those obtained from subjects who did not have a complete set of olapatadine PK parameters on Day 1 and Day 7, similar proportions of plasma samples (8.6%) and patients with detectable M3 levels (58%; 14/24) were observed. The reviewer notes that the sponsor reported that only 6 of the 24 subjects had "observable" n-oxide olapatadine in their plasma on day 1, and only 1 subject on day 7.

B. Analytical Section

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

The samples were processed using a protein-precipitation extraction technique, followed by a validated HPLC/MS/MS assay to measure the concentrations of olapatadine, n-oxide olapatadine and mon-desmethyl olapatadine in the plasma samples of healthy subjects who participated in PK Study C-11-036. AL-25287 was used as the internal standard.

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

Two minor active metabolites (N-oxide and mono-desmethyl olapatadine) were measured in the plasma samples obtained during the conduct of PK Study C-11-036, as these were the same two metabolites that were measured in the plasma samples of PK studies conducted by Alcon during the development of PATADAY®, PATANOL® ophthalmic solutions, and PATANASE® Nasal Spray.

3. What are the performance characteristics of the PK assay?

The PK assay used to quantify olapatadine and its n-oxide and mono-desmethyl metabolites was at least 10-fold more sensitive than the assay that was used previously by Alcon for the PK study as described in the PATADAY®0.2% and PATANOL®0.1% ophthalmic solution US package inserts, but was the same as that used for the PK measurements as described in the PATANASE® Nasal Spray US package insert. For all three analytes, the LLOQ of the most current PK assay was 0.05 ng/mL, and the ULOQ was 50 ng/mL. Table 3 summarizes the validation parameters for the PK assay. Compared to the assay used for PATANASE®, low absolute recoveries were noted for olapatadine, M1 and M3 (88%, 92%, 56% versus 39%, 39%, 35%), however the absolute recovery was also low for the internal standard (33.9%). Furthermore, the precision of the analyte and internal standard recovery replicates at each QC concentration were <15%, suggesting that the extraction process is of acceptable reproducibility. [The 2013 draft FDA Guidance on Bioanalytical Method Validation states that the recovery of the analyte need not be 100%, but the extent of recovery of an analyte and of the internal standard should be consistent, precise, and reproducible.] The bioanalytical report stated that all reported data were from analytical runs that met all applicable

validation acceptance criteria, and that the validation data demonstrate the adequacy of the PK assay for routine use in the measurement of plasma concentrations of olapatadine and its metabolites.

Table 3. Original Validation Parameters for Olapatadine and its N-oxide and Mono-desmethyl Metabolites in Human K2EDTA Plasma by HPLC/MS/MS/MS

Validation Parameter	olapatadine	M1 (N-desmethyl)	M3 (N-oxide)
LLOQ	0.05 ng/mL	0.05 ng/mL	0.05 ng/mL
ULOQ	50 ng/mL	50 ng/mL	50 ng/mL
Accuracy (%CV)			
Inter-day	-3.10 to 2.40	-2.30 to 2.00	-3.56 to 3.00
Intra-day	-3.40 to 2.00	-2.33 to 2.00	-5.50 to 5.40
Precision (%CV)			
Inter-day	1.62 to 5.75	1.56 to 7.52	2.53 to 9.18
Intra-day	1.22 to 8.84	1.85 to 17.15	1.83 to 8.69
Recovery of Analyte (%)			
Absolute	38.9	38.8	34.7
Relative	83.1	81.6	83.6
Recovery of IS (%)			
Absolute	(b) (4)		
Relative			
Reproducibility of Matrix Effects			
Accuracy (% Bias)	0.67	-8.67	-6.67 to 6.67
Precision (%CV)	8.21	6.33	6.10 to 9.29
Specificity against endogenous interferences	10 Lots of Blank Matrix: No significant interferences (> (b) (4) % of the mean LLOQ response or > (b) (4) % of the mean internal standard response) were found at the retention times of the analytes of interest.		
Hemolysis Interference	No samples had (b) (4) % hemolysis.		
Injection carry-over	None was detected at > (b) (4) % of the LLOQ response for all analytes of interest		
Stability			
Freeze-Thaw Cycles	5		
Short-Term, RT	(b) (4) hours		
Reinjection (Autosampler), RT	hours		
Sample Processing, RT (after extraction prior to reconstitution)	(b) (4) hour		
Post-Preparative, RT			
Long-Term Matrix,-70°C	(b) (4) hours		
Long-Term Matrix,-20°C	372 days		
	372 days		

RT (room temperature); IS (Internal Standard)

III. Detailed Labeling Recommendations

Below are the reviewer's recommended labeling edits (added text = underscore; deleted text = strikethrough).

12.3 Pharmacokinetics

In healthy subjects, (b) (4) -topical ocular dosing of 1 drop of (b) (4) PAZEO® once daily for 7 days into both eyes (b) (4) resulted in mean ± SD (range) steady state plasma olapatadine C_{max} and AUC_{0-12} (b) (4) of 1.6 ± 0.9 ng/mL (0.6 to 4.5 ng/mL) and 9.7 ± 4.4 ng*h/mL (3.7 to 21.2 ng*h/mL), respectively. The olapatadine C_{max} and AUC_{0-12} after the first dose were similar to those measured on day 7 in these subjects, suggesting that there was no systemic accumulation of olapatadine after repeated topical ocular dosing with PAZEO®. (b) (4) The median (range) time to achieve peak olapatadine concentrations (T_{max}) was

2.0 hours (0.25 to 4 hours)- (b) (4) The mean ± SD (range) elimination half-life of (b) (4) olapatadine was 3.4 ± 1.2 hours (2 to 8 hours). N-oxide olapatadine (M3) was detected during the first 4 hours after bilateral topical ocular dosing of PAZEO® in approximately half of the subjects and in less than 10% of the total plasma samples collected, at concentrations not exceeding 0.121 ng/mL on day 1 and 0.174 ng/mL on day 7. (b) (4) None of the plasma samples from these subjects had mono-desmethyl olapatadine (M1) concentrations that (b) (4) were above the lower limit of quantitation (0.05 ng/mL) of the PK assay, (b) (4).

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/s/

GERLIE GIESER
10/16/2014

PHILIP M COLANGELO
10/16/2014

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	NDA 206-276	Brand Name	TRADENAME®
OCP Division (I, II, III, IV, V)	DCP4	Generic Name	olapatadine hydrochloride
Medical Division	DTOP	Drug Class	H_1 receptor antagonist; mast cell stabilizer
OCP Reviewer	Gerlie Gieser, PhD	Indication(s)	For treatment of ocular itching associated with allergic conjunctivitis (patients 2 years and older)
OCP Team Leader	Philip Colangelo, PharmD, PhD	Dosage Form	ophthalmic solution (0.77%)
Pharmacometrics Reviewer	-	Dosing Regimen	one drop in each affected eye once daily
Date of Submission	30 July 2014	Route of Administration	topical ocular
Estimated Due Date of OCP Review	03 January 2015	Sponsor	Alcon Research, Ltd
Medical Division Due Date	TBD	Priority Classification	Priority
PDUFA Due Date	30 January 2015		

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:				
multiple dose:	X			adults (Japanese/non-Japanese)
Patients-				
single dose:				
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 -				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
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	**X**			**peds ≥ 2 years included in safety trial**
Literature References				
Total Number of Studies	**6**			**1 PK study (HVs) + 4 clinical trials**

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	Not a NME. Sponsor attempted to quantify metabolites in the completed PK study. For reference, additional ADME info available for API after topical ocular, intranasal, and oral administration (PATADAY®, PATANASE® USPIs)
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			Systemic PK in HVs after repeated topical ocular admin.
4	Did the sponsor submit data to allow the	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

	evaluation of the validity of the analytical assay?				
5	Has a rationale for dose selection been submitted?	X			Dosing regimen evaluated in pivotal 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			
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			Active comparators in two Ph3 trials contain lower strengths (0.2% and 0.1%) of the API
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	Systemic exposure not relevant to efficacy; relative BA of topical ocular vs oral/intranasal to be considered for systemic safety assessment
14	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?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	X			
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	X			
17	Is there adequate information on the	X			

	pharmacokinetics and exposure-response in the clinical pharmacology section of the label?				
	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.
NONE

Gerlie Gieser, PhD — 03 September 2014
Reviewing Clinical Pharmacologist — Date

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

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

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/s/

GERLIE GIESER
09/11/2014

PHILIP M COLANGELO
09/11/2014