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

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

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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.

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