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APPLICATION NUMBER:

206276Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 29, 2015
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA#	206276
Applicant	Alcon Research Ltd
Date of Submissions	July 30, 2014
PDUFA Goal Date	January 30, 2016
Proprietary Name / Established (USAN) names	Pazeo (olopatadine hydrochloride ophthalmic solution) 0.7%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Treatment of ocular itching associated with allergic conjunctivitis
Recommended:	Recommended for Approval

1. Introduction

Olopatadine is a sterile, multi-dose ophthalmic solution containing olopatadine for topical administration to the eyes. Olopatadine is a relatively selective histamine H1 antagonist and it inhibits the release of histamine from the mast cells. The active ingredient in the formulation, Olopatadine, is the same as in the US approved products, PATADAY 0.2% (NDA 21-545) and PATANOL Ophthalmic Solution, 0.1% (NDA 20-688).

This is a 505(b)(1) application.

2. Background

Clinical studies were conducted by Alcon under IND 60,991. Two Pre-NDA meetings were held between Alcon and the Agency. One meeting was held on July 30, 2012, and the second was held on August 26, 2013.

Alcon Research, Ltd. (Alcon) developed PATANOL (olopatadine hydrochloride ophthalmic solution), 0.1% for the treatment of allergic conjunctivitis (NDA 20-688). PATADAY (olopatadine hydrochloride ophthalmic solution), 0.2% was subsequently developed to provide a once daily treatment regimen for itching associated with allergic conjunctivitis (NDA 21-545). PATANASE (olopatadine 0.6%) was developed for the treatment of nasal allergy symptoms (NDA 21-861). The currently proposed product (olopatadine hydrochloride ophthalmic solution, 0.7%) was intended by Alcon to increase the duration of efficacy over the existing marketed products (PATANOL and PATADAY).

Formulation Comparison between PATANOL, PATADAY, and Olopatadine HCl Solution, 0.7%

Component	Concentration (% w/v)		
	Olopatadine HCl Solution, 0.7%	PATADAY	PATANOL
Olopatadine Hydrochloride	0.776 [a]	0.222 [b]	0.111 [c]
Benzalkonium Chloride	(b) (4)		
Hydroxypropyl-γ-cyclodextrin			
Edetate Disodium			
Povidone K29/32			
PEG 400			
Hydroxypropyl Methylcellulose (2910)			
Sodium Chloride			
Mannitol			
Boric Acid			
Dibasic Sodium Phosphate, Anhydrous			
Sodium Hydroxide and Hydrochloric Acid			
Purified Water			

[a] Equivalent to 0.7% Olopatadine free base
[b] Equivalent to 0.2% Olopatadine free base
[c] Equivalent to 0.1% Olopatadine free base
[d] (b) (4) adjusted based on assay results

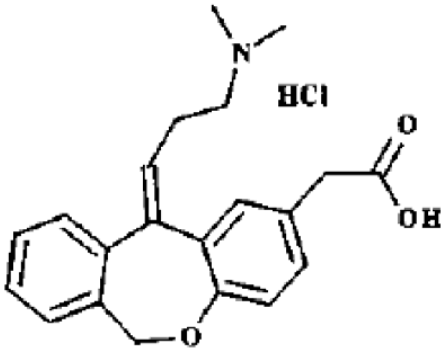
The safety information for this application is primarily derived from Study C-12-028, a 6 week, multicenter, randomized, double-masked, vehicle-controlled, parallel-group study. Subjects at risk for developing allergic conjunctivitis, at least 2 years of age or older with asymptomatic eyes at the time of study entry were randomized in a 2:1 ratio to, Olopatadine HCl Solution, 0.7% or vehicle respectively. Subjects younger than 6 years of age were randomized from 1 randomization schedule; subjects 6 years of age or older were randomized from another randomization schedule.

The applicant has requested a partial waiver of the Pediatric Assessment requirements. The waiver would be for children less than two years of age because necessary studies are impossible or highly impractical, e.g., because the number of patients with allergic conjunctivitis in that age group is so small or geographically dispersed.

3. Product Quality

Olopatadine hydrochloride is a white, crystalline, water-soluble powder with a molecular weight of 373.88 and a molecular formula of $C_{21}H_{23}NO_3$•HCl.

The chemical structure is presented below:



Chemical Name: 11-[(Z)-3(Dimethylamino) propylidene]-6-11dihydrodibenz[b,e] oxepin-2-acetic acid, hydrochloride

Composition of Olopatadine Ophthalmic Solution, 0.7% (FID[a] (b) (4))

Component	% w/v	Function	Compendial Status
Olopatadine Hydrochloride	0.776[B]	Active ingredient	USP[c]
Hydroxypropyl-Gamma- Cyclodextrin[d]	(b) (4)		NOC[e]
Povidone			USP
PEG 400			NF
Hypromellose			USP
Mannitol			USP
Boric Acid			NF
Benzalkonium Chloride	0.015[f]	Preservative	NF
Sodium Hydroxide and/or Hydrochloric Acid	(b) (4) pH 7.2	pH adjust	NF
Purified Water	(b) (4)		USP

[a] FID = Formulation Identification Number
[b] 0.776% Olopatadine hydrochloride is equivalent to 0.7% Olopatadine free base.
[c] Tested by In-house monograph which includes specifications tighter than those in the USP.
[d] (b) (4)
[e] Non-compendial
[f] (b) (4)

Mannitol is described in the USP as (b) (4). Additional information was requested from the applicant to support this claim. On October 17, 2014, Alcon stated that although mannitol itself is not a (b) (4) boric acid (b) (4) solution. (b) (4)

Proposed Specifications for Olopatadine Ophthalmic Solution, 0.7%

Test	Specification
Olopatadine Identity (HPLC)[a]	Positive
Olopatadine Identity (TLC)[a]	Positive
Olopatadine Assay (HPLC)	(b) (4)% Label
Olopatadine Impurities (HPLC)[b]:	
(b) (4)	NMT (b) (4)% of active
	NMT % of active
	NMT % of active
Impurity @ RRT (b) (4)	NMT % of active
Impurity @ RRT	NMT % of active
Any Single Unspecified Impurity[c]	NMT % of active
Total Impurities	NMT % of active
Benzalkonium Chloride Identity (HPLC)[a]	Positive
Benzalkonium Chloride Assay (HPLC)	(b) (4)% Label
pH (Potentiometric)	(b) (4)
Osmolality (Freezing Point Depression)	(b) (4)mOsm/kg
Viscosity, Liquid (b) (4)	(b) (4)mPa.s
Appearance (Visual):	
Color	Colorless to Light Yellow (B9 to Y3)
Clarity	NMT Ph. Eur. II
Precipitate	None
Particulate Matter by HIAC	NMT (b) (4) particles/mL ≥ (b) (4)µm
	NMT particles/mL ≥ µm
	NMT particles/mL ≥ µm
Bacterial Endotoxins[a]	< (b) (4)EU/mL
Sterility[d]	Meets USP Requirements

[a] Release test only.
[b] Report any impurity ≥ (b) (4)% of active except drug substance synthetic impurities.
[c] Includes (b) (4) and others
[d] Sterility testing will not be routinely conducted on production lots except at release. However, if tested, samples will comply with USP Requirements.
NMT = Not more than

INSPECTIONS:

The Office of Compliance has given an acceptable recommendation for both the drug substance manufacturing facility (b) (4) and the drug product manufacturing facility (Alcon Research, LTD., Fort Worth, Texas and Alcon- Covreour nv, Puurs, Belgium).

Product Quality recommends approval.

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