

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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

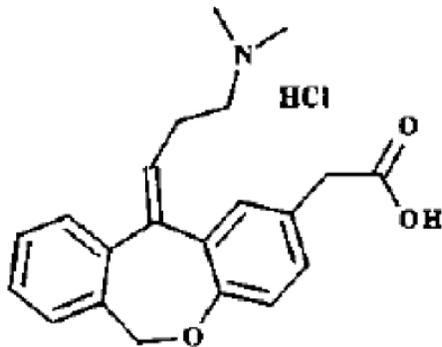
The safety information for this application is primarily derived from Study C-12-028, a 6 week, multicenter, randomized, double-masked, vehicle-controlled, parallel-group study. Subjects at risk for developing allergic conjunctivitis, at least 2 years of age or older with asymptomatic eyes at the time 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 C₂₁H₂₃NO₃•HCl.

The chemical structure is presented below:



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

Composition of Olopatidine Ophthalmic Solution, 0.7% (FID^a (b) (4))

Component	% w/v	Function	Compendial Status
Olopatidine Hydrochloride	0.776 ^B	Active ingredient	USP ^c
Hydroxypropyl-Gamma- Cyclodextrin ^d	(b) (4)	(b) (4)	NOC ^e
Povidone	(b) (4)	(b) (4)	USP
PEG 400	(b) (4)	(b) (4)	NF
Hypromellose	(b) (4)	(b) (4)	USP
Mannitol	(b) (4)	(b) (4)	USP
Boric Acid	(b) (4)	(b) (4)	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)	(b) (4)	USP

^a FID = Formulation Identification Number

^b 0.776% Olopatidine hydrochloride is equivalent to 0.7% Olopatidine free base.

^c Tested by In-house monograph which includes specifications tighter than those in the USP.

^d (b) (4)

^e Non-compendial (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) Impurity @ RRT (b)(4) Impurity @ RRT (b)(4) Any Single Unspecified Impurity ^c Total Impurities	NMT (b)(4)% of active NMT (b)(4)% 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 Clarity Precipitate	Colorless to Light Yellow (B9 to Y3) NMT Ph. Eur. II None
Particulate Matter by HIAC	NMT (b)(4) particles/mL ≥ (b)(4) μm NMT (b)(4) particles/mL ≥ (b)(4) μm NMT (b)(4) particles/mL ≥ (b)(4) 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.

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review:

Olopatadine is a H1 receptor antagonist, an inhibitor of pro-inflammatory mediator release from human conjunctival mast cells, and an inhibitor of histamine stimulated cytokine production by human conjunctival epithelial cells. Most of the nonclinical studies to determine the pharmacologic properties of olopatadine were previously submitted under NDA 20-688 and 21-545.

The applicant conducted pharmacology, ocular distribution and up to a 3- month ocular toxicity study to support the new formulation. Olopatadine exhibited significantly greater anti-allergy efficacy in vivo when administered topically in a 0.7% solution as compared with olopatadine, 0.2%. In pigmented rabbits, no adverse or toxic effects were attributed to olopatadine, 0.77% when administered up to four times daily for 3 months. The NOAEL, 0.7% QID, represents a ~4-fold ocular safety margin over the proposed clinical dose of 0.7%, QD. The formulation used also qualifies the excipients hydroxypropyl- γ -cyclodextrin and povidone K29/32 to (b) (4)%, respectively, for topical ophthalmic solutions.

Pharmacology/Toxicology recommends s approval.

5. Clinical Pharmacology

From the original Clinical Pharmacology Review:

The applicant conducted PK Study C-11-036 to determine the plasma exposures to olopatadine 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 olopatadine (parent drug) concentrations were higher with topically applied PAZEO (olopatadine hydrochloride ophthalmic solution) 0.7% administered as 1 drop per eye once daily for 7 days, compared to that reported for 0.15% olopatadine 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 olopatadine was observed following repeated topical ocular administration of the proposed product.

The mean steady state plasma olopatadine C_{max} and AUC₀₋₁₂ 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 (olopatadine hydrochloride 0.6%) Nasal Spray given 2 sprays per nostril twice daily for 14 days. The N-oxide metabolite of olopatadine (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 olopatadine (M1) were below the LLOQ (0.05 ng/mL) of the PK assay.

Clinical Pharmacology recommends approval.

6. Sterility Assurance

The drug product will be (b) (4) filled into 4 ml LDPE dropper bottles. The HPMC solution will be (b) (4)

The container closure system for olopatadine hydrochloride ophthalmic solution, 0.7% consists of a 4 mL low density polypropylene (LDPE) oval bottle with a LDPE dispensing plug and a polypropylene closure. Bottles will be filled with either 0.5 mL or 2.5 mL of drug product. The oval bottle and dispensing plug (b) (4) The closure will be (b) (4)

Product Quality Microbiology recommends approval.

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review:

All submitted studies were adequate and well controlled studies. The cross-over study (C-10-127) provided information on the “acceptability” of the product but was not designed to demonstrate efficacy. The two conjunctival antigen challenge (CAC) studies (C-10-126 and C-12-053) provided data to support the initial efficacy of the drug product and the duration of its action. The six week safety study (C-12-028) provided safety information in subjects who may use the product in the future.

The efficacy studies, C-10-126 and C-12-053, were multicenter, randomized, double-masked, vehicle controlled, parallel-group studies and used the CAC model. The CAC design has been used to support the majority of drug products approved for the treatment of ocular itching. The study design includes a study visit in which patients with an allergic history are conjunctively challenged in both eyes with progressively higher doses of antigen until they demonstrate a $\geq 2+$ itching and redness reaction. These patients return for a second visit in which the dose which elicited a $\geq 2+$ reaction is administered and only patients who demonstrate a reproducible $\geq 2+$ reaction continue in the study. Patients return for a third visit, during which the test drug product is administered to both eyes and after 24 hours, the antigen which reproducibly elicited a $\geq 2+$ reaction is again administered. The patient’s itching reactions are recorded at 3, 5 and 7 minutes after antigen administration, the patient’s redness reactions are recorded 7, 15 and 20 minutes after antigen administration. The patient’s fourth visit is a repeat of the third visit except that the time after test product administration is reduced to 16 hours. The patient’s fifth visit is a repeat of the third visit, except that the time after test product administration is reduced to 27 minutes.

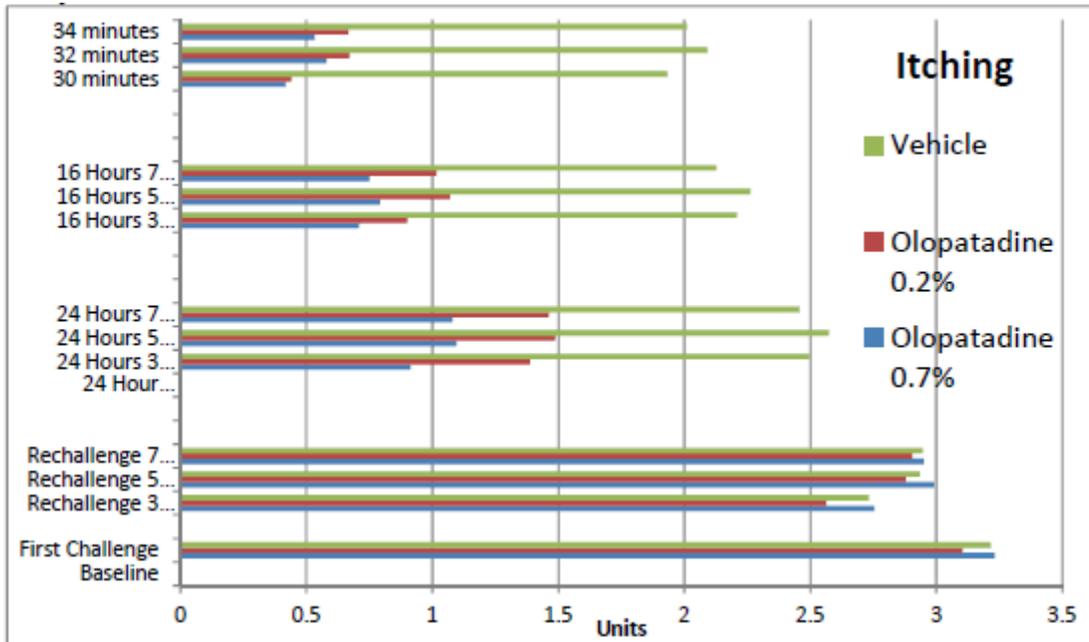
The study designs were similar for both studies with the exception that C-12-053 did not include the 16 hour duration efficacy evaluation visit and had an additional active comparator, PATANOL. Both studies evaluated the same efficacy endpoints (itching and redness) for the onset of action and the 24 hours duration of action. Study C-10-126 included PATADAY (olopatadine hydrochloride ophthalmic solution) 0.2% and Vehicle as comparators; Study C-12-053 included PATADAY, PATANOL (olopatadine hydrochloride ophthalmic solution) 0.1% and Vehicle as comparators. The randomization ratio in C-10-126 was 1:1:1 and in C-12-053, it was 2:2:2:1 (olopatadine hydrochloride ophthalmic solution, 0.7%: PATADAY: PATANOL: Vehicle). In past CAC Studies, differences of approximately 1 unit between test product and vehicle observed in the majority of time points (two out of three in the case of these studies) has been considered clinically significant.

5.1 Tables of Studies/Clinical Trials

Safety and Efficacy Studies in Patients with Allergic Conjunctivitis						
Study Number	Design	Ages	Arms	Number of Subjects	Dosing	Duration
C-10-127 Phase 1 Safety and comfort	Randomized, double masked, crossover, active and vehicle controlled study	18 years of age or older	Olopatadine HCl, 0.7% Vehicle Zaditor	43	1 drop per eye	Single dose
C-11-036 Phase 1 Safety and PK	Randomized, double masked, parallel-group, vehicle controlled study	18 to 65 years of age.	Olopatadine HCl, 0.7% Vehicle	24 12	1 drop per eye once daily	7 days
C-10-126 Phase 3 Efficacy CAC	Randomized, double masked, parallel-group, active and vehicle controlled study	18 years of age or older	Olopatadine HCl, 0.7% Olopatadine, 0.2% Vehicle	66 68 68	1 drop per eye	3 non-consecutive doses over 3 weeks
C-12-053 Phase 3 Efficacy CAC	Randomized, double masked, parallel-group, active and vehicle controlled study	18 years of age or older	Olopatadine HCl, 0.7% Olopatadine HCl, 0.2% Olopatadine HCl, 0.1% Vehicle	98 99 99 49	1 drop per eye	2 non-consecutive doses over 2 weeks
C-12-028 Phase 3 Safety	Randomized, double masked, parallel-group, vehicle controlled study	2 years of age or older	Olopatadine HCl, 0.7% Vehicle	330 169	1 drop per eye once daily	6 weeks

* 4 clinical studies (C-10-126, C-11-036, C-12-028 and C-12-053) used the same, final formulation for Olopatadine HCl Solution, 0.7% (FID (b) (4)), and it's Vehicle (FID (b) (4)). A different initial formulation was used in the first clinical study C-10-127 for Olopatadine HCl Solution, 0.7% (FID (b) (4)), and it's Vehicle (FID (b) (4)). Two studies (C-10-126 and C-12-053) had PATADAY (Olopatadine, 0.2%) as an active comparator and used the same, marketed formulation for PATADAY (FID (b) (4)).

Study C-10-126 - Itching

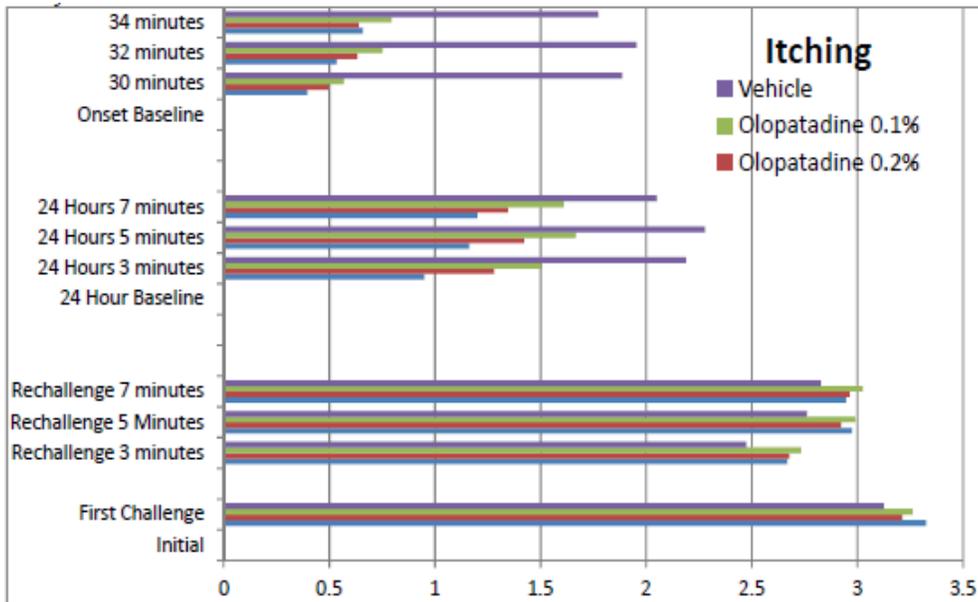


	Olopatadine 0.7% vs Vehicle	Olopatadine 0.7% vs Pataday
24hr duration		
3 min	-1.58*	-0.47†
5 min	-1.48*	-0.39†
7 min	-1.38*	-0.38†
16hr duration		
3 min	-1.50*	-0.19
5 min	-1.47*	-0.28
7 min	-1.38*	-0.27
Onset-of-action		
3 min	-1.52*	-0.03
5 min	-1.51*	-0.10
7 min	-1.48*	-0.14

*p<0.0001, † p<0.05

Efficacy over vehicle for itching has been demonstrated 30 minutes after administration and continues for a duration of at least 24 hours after administration. The effectiveness of Olopatadine 0.7% is relatively similar to Olopatadine 0.2% (Pataday) at the onset of action, but is slightly more evident at 24 hours.

Study C-12-053 - Itching



Endpoint	Comparison	Time	Difference (95% CI)	p-value
Onset of Action CAC	Olopatadine 0.7% vs Vehicle	3Min	-1.53 (-1.76, -1.30)	<.000
		5Min	-1.46 (-1.71, -1.22)	<.000
		7Min	-1.17 (-1.45, -0.90)	<.000
24 Hours CAC	Olopatadine 0.7% vs Vehicle	3Min	-1.29 (-1.60, -0.97)	<.000
		5Min	-1.15 (-1.46, -0.84)	<.000
		7Min	-0.89 (-1.22, -0.57)	<.000
24 Hours CAC	Olopatadine 0.7% vs PATADAY	3Min	-0.31 (-0.57, -0.06)	0.015
		5Min	-0.26 (-0.51, -0.01)	0.045
		7Min	-0.16 (-0.42, 0.11)	0.248
24 Hours CAC	Olopatadine 0.7% vs PATANOL	3Min	-0.52 (-0.78, -0.27)	<.000
		5Min	-0.48 (-0.73, -0.23)	0.000
		7Min	-0.39 (-0.65, -0.12)	0.004

PATADAY = Olopatadine HCl Solution, 0.2%, PATANOL = Olopatadine HCl Solution, 0.1%

For each endpoint, at least 2 of 3 p-values corresponding to the 3 post-CAC comparisons must have been less than 0.05 to declare success for that endpoint.

Efficacy over vehicle for itching has been demonstrated 30 minutes after administration and continues for a duration of at least 24 hours after administration. The effectiveness of Olopatadine 0.7% is relatively similar to Olopatadine 0.2% (Pataday) and Olopatadine 0.1% (Patanol) at the onset of action but is slightly more evident at 24 hours.

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Summary Efficacy Statement

Adequate and well controlled studies support the efficacy of Pazeo (olopatadine hydrochloride ophthalmic solution) 0.7% for the treatment of ocular itching associated with allergic conjunctivitis.

(b) (4)

8. Safety

From the original Medical Officer Review:

The six week safety study (C-12-028) provided safety information in subjects who may use the product in the future. The population was an appropriate population to monitor for the potential to develop an adverse reaction.

Categorization of Adverse Events

Study 12-028	Olopatadine 0.7%		Vehicle	
Adverse Events	N=330		N=169	
Deaths	0		0	
Discontinue due to Adverse Event	0		2	1.2%
Vision blurred	16	4.8%	7	4.1%
Dry eye	11	3.3%	5	3%
Corneal Staining	8	2.4%	7	4.1%
Dysgeusia	8	2.4%	0	
Abnormal sensation in eye	7	2.1%	7	4.1%
Nasopharyngitis	6	1.8%	3	1.8%
Upper respiratory tract infection	6	1.8%	3	1.8%
Conjunctival staining	6	1.8%	1	0.6%
Eye puritus	5	1.5%	2	1.2%
Headache	5	1.5%	3	1.8%
Eye irritation	1	0.3%	5	3%
Ligament sprain	1	0.3%	2	1.2%
Cough	1	0.3%	2	1.2%
Conjunctival hemorrhage	0		2	1.2%
Diarrhea	0		2	1.2%
Gastroenteritis viral	0		2	1.2%

Deaths/Significant Adverse Events

None.

Drug- Specific Safety Explorations

There were no clinically significant changes noted in visual acuity, intraocular pressure, slit lamp or funduscopy in any trial.

Visual Acuity

Study 10-126	Decrease								Increase							
	> 15		10-14		5-9		± 4		5-9		10-14		> 15			
	Letters		Letters		Letters		Letters		Letters		Letters		Letters			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%		
Olopatadine 0.7%	66	0	0		4	6.1	57	86.4	4	6.1	1	1.5	0			
PATADAY ^b	66	0	0		5	7.6	57	86.4	4	6.1	0		0			
Vehicle	68	0	0		7	10.3	59	86.8	2	2.9	0		0			

^b 2 patients had missing baseline or follow-up visual acuity data.

Study 12-053		Olopatadine			PATADAY			PATANOL			Vehicle		
		Total	N	(%)	Total	N	(%)	Total	N	(%)	Total	N	(%)
Increase	≥15 Letters	98	0		99	0		99	0		49	0	
	10-14 Letters		1	(1%)		0			1	(1%)		0	
	5-9 Letters		7	(7%)		1	(1%)		3	(3%)		3	(6%)
No Change	± 4 Letters		79	(81%)		83	(84%)		78	(79%)		41	(84%)
	Decrease	5-9 Letters		10	(10%)		15	(15%)		15	(15%)		5
	10-14 Letters		1	(1%)		0			2	(2%)		0	
	≥15 Letters		0			0			0			0	

Visual Acuity- Baseline to Exit Visit

Study 12-028		Olopatadine 0.7%		Vehicle	
		Total	N (%)	Total	N (%)
Increase	≥15 Letters	326	0	168	2 (1%)
	10-14 Letters		3 (1%)		3 (2%)
	5-9 Letters		19 (6%)		16 (9%)
No Change	± 4 Letters		267 (82%)		129 (77%)
	Decrease	5-9 Letters		31 (9%)	
	10-14 Letters		5 (1%)		3 (2%)
	≥15 Letters		1 (0.3%)		0

4 subjects used the fix and follow method and are not summarized in this table.

IOP

Change from Baseline to Exit Visit in Maximum IOP (mmHg)

IOP- Baseline to Exit Visit		Olopatadine 0.7%			Vehicle		
Study 12-028		Total	N	(%)	Total	N	(%)
Increase	>30 mmHg	301	0		155	0	
	21-30 mmHg		0			0	
	11-20 mmHg		0			0	
	6-10 mmHg		8	(3%)		1	(1%)
No Change	± 5 mmHg		290	(96%)		151	(97%)
Decrease	6-10 mmHg		3	(1%)		3	(2%)
	11-20 mmHg		0			0	
	21-30 mmHg		0			0	
	>30 mmHg		0			0	

mmHg=millimeters of mercury, Baseline=Day 0 Visit, IOP=intraocular pressure

23 subjects in the Olopatadine 0.7% group and 12 subjects in the Vehicle group did not have IOP assessments due to Investigator decisions based upon age.

Safety Summary Statement

The three clinical studies (C-10-126, C-12-053, C-12-028) were used to establish the safety of the drug product. An adequate safety profile has been established

The most commonly reported adverse reactions seen in the six-week trial C-12-028 occurred in 2-5% of patients treated with either PAZEO or vehicle. These events were blurred vision, dry eye, superficial punctate keratitis, dysgeusia and an abnormal sensation in the eye.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

The applicant received a Written Request for pediatric studies with olopatadine hydrochloride ophthalmic solution, 0.7% dated 10/3/2013. In this application, 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 in that age group with allergic conjunctivitis is so small or geographically dispersed.

This application was reviewed by the Pediatric Review Committee on November 12, 2014. The committee agreed that the waiver of children less than two years of age was appropriate.

The Pediatric Exclusivity Board determined on 12/16/14 that exclusivity should be granted for the single moiety.

11. Other Relevant Regulatory Issues

BIOSTATISTICS

Per the original Biostatistics review:

In order to support the approval of this new formulation, the applicant submitted two Phase 3 efficacy studies: Study C-10-126, and Study C- 12-053.

Studies C-10-126 and C-12-053 were similarly designed phase 3 studies. Both were multicenter, randomized, double-masked, active and vehicle controlled, parallel-group studies and used the conjunctival allergen challenge (CAC) model to evaluate the safety and efficacy of Olopatadine 0.7% versus Vehicle or active comparators in the treatment of ocular itching associated with allergic conjunctivitis.

The primary efficacy variable for both studies was patient-evaluated ocular itching severity scores (assessed using a 0-4 scale with 0.5 unit increments: 0 = none, 4 = incapacitating itch). In Study C-10-126, the primary efficacy endpoints were patient-evaluated ocular itching at 3, 5, and 7 minutes post-CAC at both Visits 4B (16-hour duration-of-action) and 5 (onset-of-action). In Study C-12-053, the primary efficacy endpoints were patient-evaluated ocular itching at 3, 5, and 7 minutes post-CAC at both Visit 3B (24-hour duration-of-action) and Visit 4 (onset-of-action).

Based on the efficacy results (Table 1):

- In both Study C-10-126 and Study C-12-053, Olopatadine 0.7% was superior to Vehicle for treating ocular itching associated with allergic conjunctivitis at onset-of-action, and 24-hour duration-of-action.
- In Study C-10-126, at 24-hour duration-of-action, Olopatadine 0.7% was superior to PATADAY for the treatment of ocular itching associated with allergic conjunctivitis. In Study C-12-053, Olopatadine 0.7% was superior to PATADAY for ocular itching associated with allergic conjunctivitis at 24-hour duration-of-action at 2 (3 and 5 minutes) out of 3 post CAC time points. The point estimate for the treatment difference at 7 minutes post-CAC was in favor of Olopatadine 0.7% but did not demonstrate statistical significance.

Table 1: Analysis of Ocular Itching Scores* for Studies C-10-126 and C-12-053 (ITT)

Study	Time Point	Olopatadine, 0.77%	PATADAY (Olopatadine, 0.2%)		PATANOL Dosed Once (Olopatadine, 0.1%)		Vehicle	
		(N = 66)	(N = 68)		(N = 68)		(N = 68)	
		Mean	Mean	Difference (95% CI)	Mean	Difference (95% CI)	Mean	Difference (95% CI)
C-10-126	Onset							
	Average	0.46	0.54	-0.08 (-0.37, 0.21)			1.98	-1.51 (-1.81, -1.23)
	3 mins	0.36	0.39	-0.02 (-0.31, 0.26)			1.90	-1.54 (-1.82, -1.25)
	5 mins	0.53	0.61	-0.08 (-0.39, 0.22)			2.06	-1.53 (-1.84, -1.22)
	7 mins	0.48	0.61	-0.13 (-0.44, 0.17)			1.97	-1.49 (-1.80, -1.18)
	16h							
	Average	0.75	0.96	-0.21 (-0.49, 0.07)			2.20	-1.45 (-1.73, -1.17)
	3 mins	0.70	0.87	-0.17 (-0.44, 0.11)			2.20	-1.50 (-1.77, -1.23)
	5 mins	0.79	1.04	-0.24 (-0.55, 0.07)			2.27	-1.48 (-1.79, -1.16)
	7 mins	0.75	0.98	-0.23 (-0.54, 0.08)			2.13	-1.38 (-1.69, -1.07)
	24h							
	Average	1.04	1.48	-0.44 (-0.72, -0.16)			2.55	-1.51 (-1.79, -1.24)
3 mins	0.93	1.41	-0.48 (-0.76, -0.20)			2.54	-1.61 (-1.88, -1.33)	
5 mins	1.10	1.52	-0.42 (-0.72, -0.12)			2.62	-1.51 (-1.81, -1.21)	
7 mins	1.09	1.50	-0.41 (-0.72, -0.10)			2.50	-1.41 (-1.72, -1.11)	
C-12-053	Onset							
	Average	0.52	0.56	-0.05 (-0.24, 0.14)	0.74	-0.22 (-0.41, -0.03)	1.91	-1.39 (-1.62, -1.16)
	3 mins	0.38	0.47	-0.09 (-0.28, 0.09)	0.59	-0.21 (-0.40, -0.02)	1.91	-1.53 (-1.76, -1.30)
	5 mins	0.53	0.61	-0.08 (-0.29, 0.12)	0.79	-0.26 (-0.47, -0.06)	1.99	-1.46 (-1.71, -1.22)
	7 mins	0.65	0.61	0.04 (-0.18, 0.26)	0.83	-0.18 (-0.41, 0.04)	1.82	-1.17 (-1.45, -0.90)
	24h							
	Average	1.16	1.40	-0.24 (-0.48, -0.00)	1.62	-0.46 (-0.70, -0.23)	2.27	-1.11 (-1.40, -0.82)
	3 mins	1.01	1.33	-0.31 (-0.57, -0.06)	1.53	-0.52 (-0.78, -0.27)	2.30	-1.29 (-1.60, -0.97)
	5 mins	1.22	1.48	-0.26 (-0.51, -0.01)	1.70	-0.48 (-0.73, -0.23)	2.37	-1.15 (-1.46, -0.84)
	7 mins	1.25	1.41	-0.16 (-0.42, 0.11)	1.64	-0.39 (-0.65, -0.12)	2.14	-0.89 (-1.22, -0.57)

* Mean score estimates, treatment differences and corresponding 95% confidence intervals (CIs) were based on analysis of repeated measures using a mixed model with itching scores from each eye (left or right) as the dependent variable and fixed effect terms for investigator, treatment, eye-type (left or right), time, and treatment-by-time interaction.

[†] PATANOL was dosed only once (instead of the approved twice-a-day regimen) at Visit 3A (for 24-hour duration-of-action) and Visit 4 (onset-of-action).

Source: Tables 2.7.3.2-2, 2.7.3.2-3, 2.7.3.2-7, 2.7.3.2-10, and 2.7.3.2-11 of Summary of Clinical Efficacy.

Biometrics recommends approval.

OPDP

The Office of Prescription Drug Products (DPDP) provided a labeling review of the proposed, clean, substantially complete version of the package insert. Edits were incorporated into the labeling document on the SharePoint site

DMEPA

Office of Medication Error Prevention and Risk Management found the proprietary name, Pazeo, acceptable, on 12/10/2014.

DMEPA provided a labeling review of the original carton and container labeling (without preparatory name) on 11/19/2014.

FINANCIAL DISCLOSURE

The applicant has adequately disclosed financial interests/arrangements with clinical investigators. The one reported interest (see Medical Officers review dated 12/14/2014) is not likely to raise questions about the integrity of the data because the studies were multicenter, masked trials and the one investigator with a potential interest was responsible for a small percentage of the overall application.

OSI

An Office of Scientific Investigations (OSI) audit was requested.

The pivotal studies, C-10-126 entitled, “A Multicenter, Randomized, Double-Masked, Vehicle and Active Controlled, Parallel-Group Efficacy and Safety Study of AL-4943A Ophthalmic Solution, 0.77% in Patients with Allergic Conjunctivitis Using the Conjunctival Allergen Challenge (CAC) Model”, and C-12-028 entitled “A Multicenter, Randomized, Double-Masked, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety of AL-4943A Ophthalmic Solution 0.77% Administered Once Daily”, were inspected in support of this application.

Drs. Torkildsen’s and Rand’s clinical sites were selected for inspection because of high subject enrollments and previous inspection histories.

Name of CI, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
Gail Torkildsen, M.D. Andover Eye Associates 138 Haverhill Street Andover, MA 01810	C-10-126/ 3505/ 97	21-24 Oct 2014	NAI
Allison Rand, M.D. Rand Eye Institute 5 Sample Road Deerfield, FL 33064	C-12-028/ 6448/ 40	Nov 2014	Pending, preliminary classification NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

Neither Dr. Torkildsen nor Dr. Rand was issued a Form FDA 483, and these inspections were classified No Action Indicated (NAI). Per OSI, the data generated by these clinical sites appear adequate in support of the respective indication.

12. Labeling

The labeling found in the Appendix (carton and Container labeling and package insert submitted on 1/29/2015) is acceptable.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

NDA 206276 for Pazeo (olopatadine hydrochloride ophthalmic solution) 0.7% is recommended for approval for the treatment of ocular itching associated with allergic conjunctivitis.

Adequate and well controlled studies support the efficacy of Pazeo (olopatadine hydrochloride ophthalmic solution) 0.7% for the treatment of ocular itching associated with allergic conjunctivitis. (b) (4)

The most commonly reported adverse reactions seen in the six-week trial C-12-028 occurred in 2-5% of patients treated with either PAZEO or vehicle. These events were blurred vision, dry eye, superficial punctate keratitis, dysgeusia and an abnormal sensation in the eye.

The benefits of using this drug product outweigh the risks for the above indication.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
01/29/2015

WILEY A CHAMBERS
01/29/2015