

Clinical Review of NDA 206276

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Review Division	Division of Transplant and Ophthalmology Products
Reviewer Name	Wiley A. Chambers, MD
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Established Name	Olopatadine Hydrochloride Ophthalmic Solution 0. 7%
(Proposed) Trade Name	Pazeo
Therapeutic Class	Relatively selective histamine H1 antagonist and an inhibitor of the release of histamine from the mast cells
Applicant	Alcon Research Ltd
Dosing Regimen	One drop in each affected eye once a day
Indication(s)	Treatment of ocular itching associated with allergic conjunctivitis.

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 206276, Olopatadine hydrochloride ophthalmic solution, 0.7% is recommended to be approved for the treatment of ocular itching with the labeling attached to this review.

1.2 Risk Benefit Assessment

Olopatadine hydrochloride ophthalmic solution, 0.7% has demonstrated efficacy in the treatment of ocular itching with minimal safety risks. The benefits are considered to outweigh the risks.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Routine postmarketing surveillance is recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended postmarketing commitments or requirements.

2 Introduction and Regulatory Background

2.1 Product Information

Olopatadine is a sterile, multi-dose ophthalmic solution containing olopatadine for topical administration to the eyes. The formulation includes povidone, polyethylene glycol 400, hydroxypropyl methylcellulose hydroxypropyl-gamma-cyclodextrin, boric acid, mannitol, and benzalkonium chloride as preservative. (b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Lastacaft	Alcaftadine	Ocular itching
Optivar	Azelastine Hydrochloride	Ocular itching
Bepreve	Bepotastine	Ocular itching
Elestat	Epinastine Hydrochloride	Ocular itching
Alocril	Nedocromil sodium	Ocular itching
Pataday	Olopatadine hydrochloride	Ocular itching
Alamast	Pemirolast potassium	Ocular itching
Acular	Ketorolac tromethamine	Ocular itching
Emadine	Emedastine difumarate	Allergic conjunctivitis
Alrex	Loteprednol etabonate	Allergic conjunctivitis
Patanol	Olopatadine hydrochloride	Allergic conjunctivitis

2.3 Availability of Proposed Active Ingredient in the United States

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).

2.4 Important Safety Issues With Consideration to Related Drugs -None.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Clinical studies were conducted 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.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

There is no evidence that the submitted studies were not conducted in accordance with acceptable clinical ethical standards.

3.2 Compliance with Good Clinical Practices

The clinical studies included in this application appear to be in compliance with Good Clinical Practices. Several of the investigators have been inspected in the past by the Agency.

Protocol C-10-126:

Torkildsen:	97 Subjects; (b) (6) INDs;	VAI 2009; NAI 2006
Macejko:	55 subjects (b) (6) INDs;	VAI 2009
Bergmann:	50 subjects; (b) (6) INDs;	NAI 2009

Protocol C-12-053:

McLaurin:	100 subjects; (b) (6) INDs;	NAI 2012
Torkildsen:	74 subjects	VAI 2009; NAI 2006
Rice:	53 subjects; (b) (6) INDs;	No inspections

Protocol C-12-028

Meier:	40 subjects; (b) (6) INDs;	NAI 09
Rand:	40 subjects; IND;	No inspections
Sall:	40 subjects; (b) (6) INDs;	VAI 13; VAI 10; VAI 10; NAI 03; NAI 99; NAI 97

3.3 Financial Disclosures- See separate review of Financial Disclosure.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Olopatadine HCl Ophthalmic Solution, 0.7% is supplied in a low density polyethylene (LDPE) white oval bottle with (b) (4) dispensing plug and (b) (4) closure. The product has a 2.5 mL fill trade size and a 0.5 mL fill sample size. The filled containers are labeled and the 0.5 mL sample size is placed in a (b) (4).

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			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

(b) (4)

Reviewer's Comments: *The functions listed in the table above have been provided by the applicant. I do not agree with the characterization of mannitol (b) (4). I believe it is better characterized as (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

Reviewer's Comments: *Acceptable, although the Bacterial Endotoxin specification is not necessary.*

4.2 Clinical Microbiology

Not applicable for this application.

4.3 Preclinical Pharmacology/Toxicology

Alcon Research, Ltd. (Alcon) developed PATANOL® (olopatadine hydrochloride ophthalmic solution), 0.1% for the treatment of allergic conjunctivitis (NDA 20-688). PATADAY™ (Olopatadine 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 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

No significant interaction was noted between olopatadine (10 μ M) and α -adrenergic, muscarinic cholinergic, dopamine. Neuropharmacological studies indicate that olopatadine at oral doses as high as 300 mg/kg, did not inhibit motor coordination, phenylbenzoquinone induced writhing, reserpine induced blepharoptosis or physostigmine induced lethality, nor did it exhibit any anticonvulsant activity.

The effects of olopatadine (3-100 mg/kg) on the circulatory system (i.e., electrocardiogram (ECG), heart rate and blood pressure) were investigated following oral administration in conscious dogs. Over the dose range 3-30 mg/kg, oral administration of olopatadine did not affect Δ QTc. No significant effects on blood pressure were observed at olopatadine oral doses as high as 100 mg/kg. No significant change in heart rate

or prolongation of the QT interval was observed when olopatadine administered by oral route (30 mg/kg) was used in combination with the CYP3A4 inhibiting drug itraconazole administered orally (100 mg/kg).

To support the development of Olopatadine HCl Solution, 0.7%, a nonclinical ocular tissue distribution study was conducted to characterize the ocular distribution and systemic pharmacokinetics of olopatadine following single bilateral topical ocular instillation of 0.2% PATADAY or Olopatadine HCl Solution, 0.7% (Clinical Formulation) to male New Zealand White (NZW) rabbits a). Plasma and ocular tissues (aqueous humor, choroid, cornea, bulbar conjunctiva, iris-ciliary body (ICB), whole lens and retina) were collected in a sparse fashion up to 24 hours post-dose to measure AL-4943 using a validated LC tandem mass spectrometry (LC/MS/MS) method. Olopatadine was absorbed into the eye and reached maximal levels within 30 minutes to 2 hours for most ocular tissues and plasma except lens (Tmax: 4.0 hours to 8.0 hours). Tissues associated with the site of dosing, i.e., conjunctiva and cornea had the highest concentrations of olopatadine in both PATADAY (609 ng/g and 720 ng/g) and Olopatadine HCl Solution, 0.7% (3000 ng/g and 2230 ng/g) treatment group, respectively. The mean Cmax estimates in aqueous humor, choroid, ICB and lens increased with increasing concentrations of olopatadine.

A two-week topical ocular study of two prototype 0.7% olopatadine ophthalmic formulations was conducted in pigmented rabbits (NZW x New Zealand Red (NZR): F1-Cross rabbits). Additionally, a 3-month repeated topical ocular dose study using pigmented rabbits was conducted with the 0.7% olopatadine ophthalmic solution formulation proposed for marketing in order to qualify the use of the excipients by the ocular route of administration. These studies were conducted in accordance to GLP regulation. Five non-GLP local tolerance studies using either NZW or pigmented rabbits were conducted with various prototype formulations of 0.7% olopatadine ophthalmic solutions to evaluate the topical irritation potential as well as the ocular toxicity potential of the higher concentration formulation.

Species Study design	Daily dose (mg/day or mg/kg) (Sex)	N	Systemic exposure		
			Analyte	Cmax [ng/mL]	AUC(0-4hr) [ng·h/mL]
Rabbit 2 week topical ocular	0.7% HD Olopatadine with SBCD (2.95 mg/day) ^a (M/F)	4	AL-24956	0.215	0.629
			AL-38189	0.108	0.0876
			AL-4943	12.7	34.0
	0.7% HD Olopatadine with HPBCD (2.75 mg/day) ^b (M/F)	4	AL-24956	0.241	0.681
			AL-38189	0.0999	0.0730
			AL-4943	15.2	39.2
Rabbit 3 month topical ocular	High Dose Olopatadine Ophthalmic Solution, 0.7%	4	AL-24956	0.200	0.546
			AL-38189	0.135	0.0598
			AL-4943	15.1	37.4

AL-4943 (Olopatadine) and its Metabolites, AL-24956 (M1) and AL-38189 (M3)

^a Based on an average drop size of 52.6 µL ^b Based on an average drop size of 49.1 µL

Olopatadine Nonclinical Studies Submitted to Previous Olopatadine Applications

Type of Study	Duration of Dosing	Route of Admin	Species
Single Dose	Single dose	Oral, IV, Topical Ocular	Mouse, Rat, Rabbit, Dog
Repeat Dose	4-, 13-, 52-week	Oral	Rat, Dog
	4-week, 1-, 3-, 6-mon	Topical Ocular	Rabbit, Monkey
Genotoxicity	Ames, Chrom. Ab.	<i>In vitro</i>	<i>In vitro</i>
	Micronucleus	Oral	Mouse
Carcinogenicity	78-, 104-week	Oral/Diet	Mouse, Rat
Reproductive and Developmental	Seg I	Oral	Rat
	Seg II	Oral	Rat, Rabbit
	Seg III	Oral	Rat
Local Tolerance	1 day	Topical Ocular	Rabbit
Sensitization	Intradermal injection / topical challenges		Guinea Pig
Antigenicity	Oral/IP, Oral/IM		Mouse, Guinea Pig
Impurities	1 day	Topical Ocular	Rabbit
Degradation Products	Ames, Mouse Lymphoma, SHE cell, Micronucleus, 28-day SC, 26-week SC, 1-month Topical Ocular, 1-day Oral		<i>In vitro</i> , Mouse, Rabbit

Reviewer's Comments:

Oral doses of 1 mg/kg/day of olopatadine in rats have resulted in plasma C_{MAX} levels ranging from 208-339 ng/mL and plasma AUC of 431-1437 ng.hr/mL. The C_{MAX} and AUC levels have been shown to be dose proportional for oral doses between 1mg/kg and 25 mg/kg. Plasma levels for doses above 25 mg/kg have not been reported in the application and do not appear to have been measured.

The C_{MAX} levels noted above, following oral dosing of 1 mg/kg/day in rats, are 145-230 times the C_{MAX} level seen in humans following a topical ophthalmic dose to humans. A 1 mg/kg oral olopatadine dose in rats resulted in an AUC level that was 50-160 times the level seen following a human ophthalmic dose. Subjects in the human study averaged 70.6 kg and had an average body surface 1.8 meter squared. If calculated on a mg/kg basis, with a drop size of 0.04 mL, the ratio is approximately 125 (1 mg/kg/day divided by 0.008mg/kg/day). If calculated on a mg/m² basis, the ratio is approximately 19.5 (6 mg/m² divided by 0.308 mg/m²).

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Olopatadine is a relatively selective histamine H1 antagonist and it inhibits the release of histamine from the mast cells.

4.4.2 Pharmacodynamics – *Not directly measured in humans*

4.4.3 Pharmacokinetics

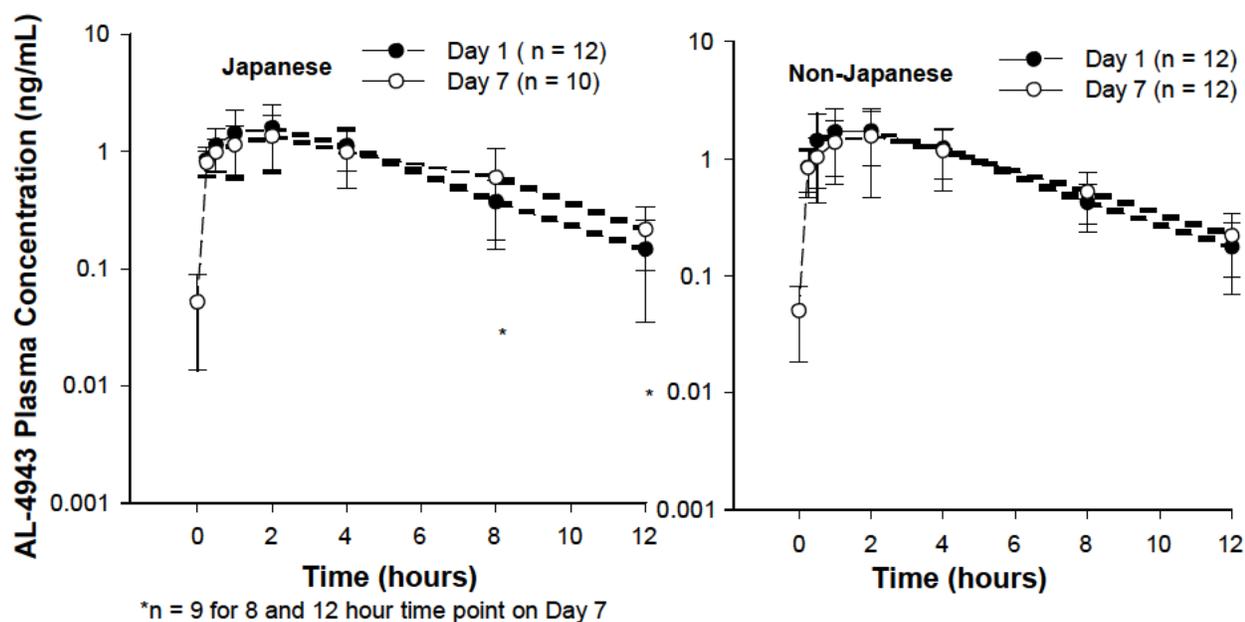
A Randomized, Double-Masked, Vehicle-Controlled, Multiple-Dose Safety and Pharmacokinetic Study of AL-4943A Ophthalmic Solution, 0.77% Following Topical Ocular Administration in Healthy Normal Subjects

Olopatadine 0.7% Pharmacokinetics on Day 1 and Day 7

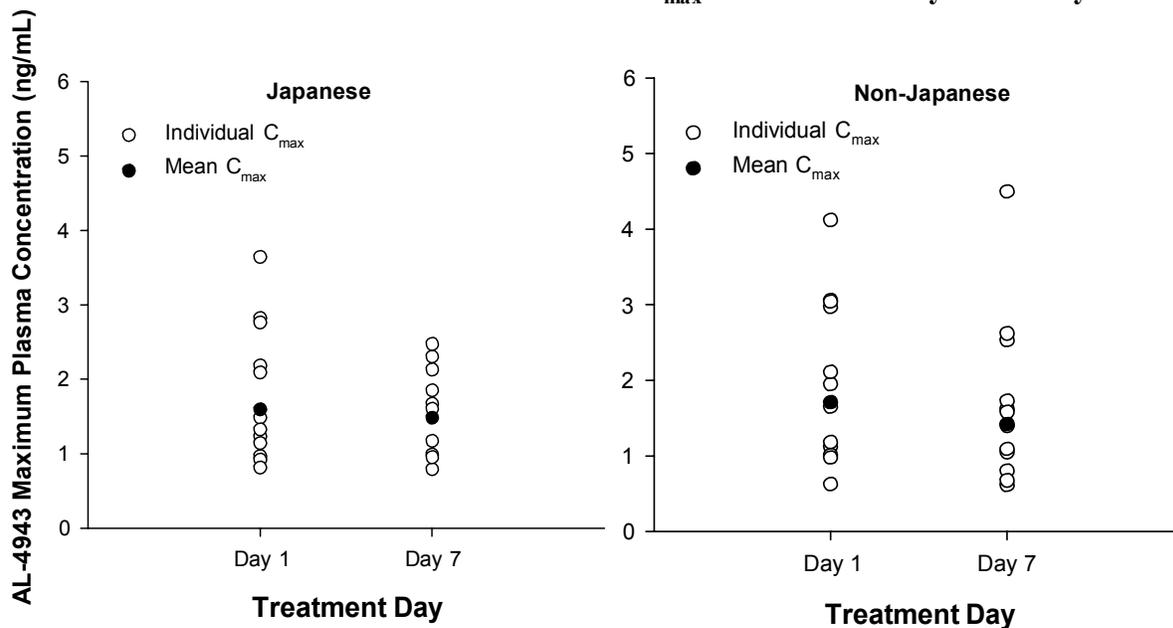
PK Parameters	Single Dose (Day 1)		Multiple Dose (Day 7)	
	Japanese	Non-Japanese	Japanese	Non-Japanese
N	12	12	10	12
C _{max} (ng/mL) ^a	1.59 (0.810-3.64)	1.71 (0.624-4.12)	1.48 (0.787-2.47)	1.42 (0.613-4.50)
T _{max} (hr) ^b	2.00 (0.50-4.02)	2.00 (0.25-4.00)	2.00 (0.50-8.00)	1.50 (0.25-4.00)
AUC ₀₋₁₂ (ng*hr/mL) ^a	8.62 (4.96-18.2)	9.48 (4.05-18.4)	8.48 (5.13-15.5)	8.95 (3.72-21.2)
t _{1/2} (hr)	2.79 (2.13-5.78)	3.01 (2.05-5.35)	3.03 ^c (2.13-3.59)	3.61 (2.28-7.77)

a: C_{max} and AUC₀₋₁₂ expressed as geometric mean and range (min to max);
 b: T_{max} expressed as median and range (min to max)
 c: t_{1/2} expressed as arithmetic mean with n = 7 for Japanese subjects
 Source: Table 14.2.1.-13 and Table 14.2.1-14

Mean (SD) AL-4943 Plasma Concentration Versus Time Profiles on Day 1 and Day 7

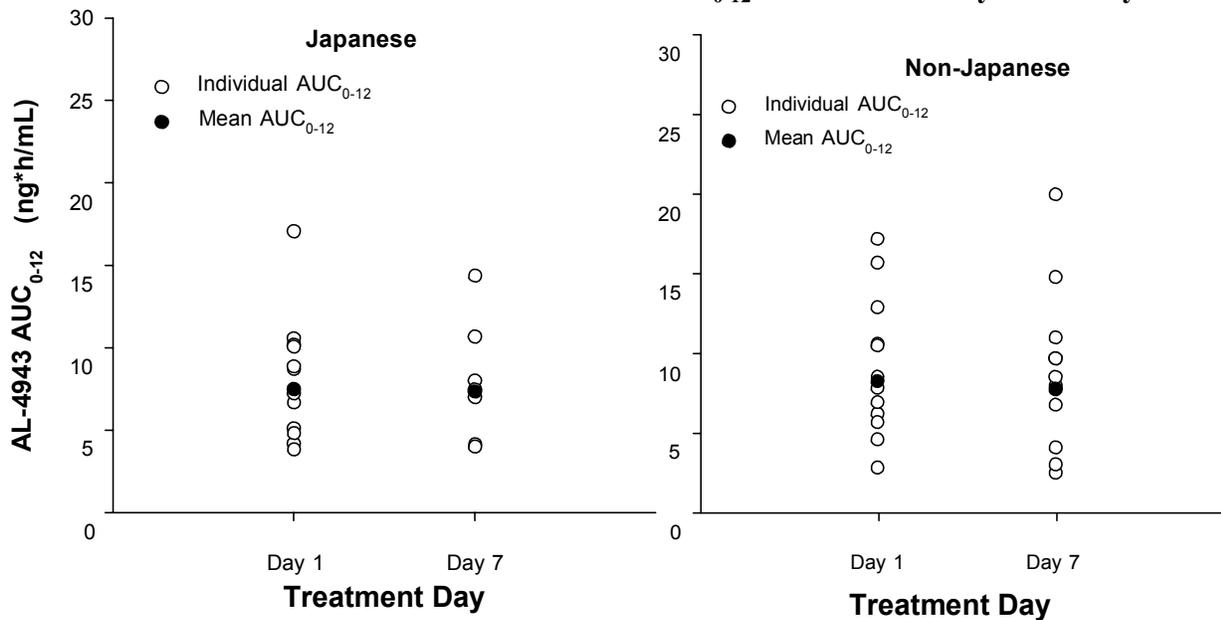


Individual and Geometric Mean AL-4943 C_{max} Estimates on Day 1 and Day 7



Source = Tables 14.2.1.-13 and 14.2.1.-14 and 16.2.6.-9

Individual and Geometric Mean AL-4943 AUC₀₋₁₂ Estimates on Day 1 and Day 7



Source = Tables 14.2.1.-13 and 14.2.1.-14 and 16.2.6.-9

In this study the average body surface area was 1.82 m². The average weight was 70.6 kg.

5 Sources of Clinical Data

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 its 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 its 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)).

5.2 Review Strategy

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

5.3 Discussion of Individual Studies/Clinical Trials

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 is shown on the table below and 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 HCl Solution, 0.7%: PATADAY: PATANOL: Vehicle).

In past CAC Studies, differences of 0.9-1 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.

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. Safety variables and assessments included best-corrected visual acuity, slit-lamp, intraocular pressure (IOP), dilated fundus evaluations, pulse, blood pressure, and adverse events.

Clinical Review of NDA 206276
Wiley A. Chambers, MD
Olopatadine hydrochloride ophthalmic solution, 0.7%

	Study Visits							Early Exit Visit
	Visit 1	Visit 2	Visit 3A	Visit 3B	Visit 4A	Visit 4B	Visit 5	
Procedure/ Assessment	Day - 21 (± 2 days)	Day - 14 (± 3 days)	Day 0	Day 1	Day 14 (± 2 days)	Day after Visit 4A	Day 21 (+ 3 days)	
Informed Consent	X							
Demographics	X							
Medical/Medication History	X							
Allergic Skin Test ¹	X							
Medical/Medication History Update		X	X	X	X	X	X	X
Urine Pregnancy Test ²	X						X	X
Inclusion/Exclusion	X	X	X					
BCVA ³	X	X	X	X	X	X	X	X
Slit-Lamp Examination ³	X	X	X	X	X	X	X	X
IOP Assessment ⁴	X						X	X
DFE ⁴	X						X	X
Screening Conjunctival Allergen Challenge (CAC)	X	X						
Ocular Allergic Signs and Symptoms Assessments	X	X	X	X ⁵	X	X ⁵	X ⁵	
Randomization			X					
Administer Treatment(s)			X		X		X	
Ocular Discomfort Assessment			X					
Adverse Events (Both Volunteered and Elicited)	X	X	X	X	X	X	X	X
Treatment Efficacy CAC				X ⁶		X ⁷	X ⁸	
Exit							X	X

¹ If one has not been done within 24 months prior to Visit 1

² Females of childbearing potential only

³ Prior to CAC and/or treatment instillation at all visits; also after all post-CAC assessments at Visit 5/Exit

⁴ After all post-CAC assessments

⁵ Pre-CAC and 3, 5, 7, 15 and 20 minutes post-CAC (window of +/- 1 min. for each time point)

⁶ 24 hours (+ 1hr) after treatment instillation

⁷ 16 hours (+ 1hr) after treatment instillation

⁸ 27 minutes (+/- 1 min) after treatment instillation

Number of patients for each Investigator:

Efficacy Study 10-126

Study 10-126 Investigator Number	Principal Investigator	Subinvestigators	Olopatadine 0.7%	PATADAY	Vehicle
3505	Torkildsen, Gail MD Andover Eye Associates 138 Haverhill Street Andover, MA 01810	(b) (6)	32	32	33
5126	Macejko, Thomas, MD Eye Care Associates of Greater Cincinnati, Inc. 563 Wessel Drive Fairfield, OH 45014	(b) (6)	18	19	18
5476	Bergmann, Mark MD Eye Care Associates of Greater Cincinnati, Inc. 2859 Boudinot Ave., Suite 301 Cincinnati, OH 45238	(b) (6)	16	17	17

Efficacy Study 12-053

Study 12-053 Investigator Number	Principal Investigator	Subinvestigators	Olopatadine 0.7%	PATADAY	Patanol	Vehicle
4011	McLaurin, Eugene MD 6060 Primacy Pkwy Suite 200 Memphis, TN 38119 (901) 761-4620	(b) (6)	28	29	28	15
3505	Torkildsen, Gail MD 138 Haverhill St Andover, MA 01810 (978) 684-7516	(b) (6)	20	22	22	10
3733	Rice, Robert MD 5430 Fredericksburg Rd San Antonio, TX 78229 (210) 340-1212	(b) (6)	15	15	15	8

Clinical Review of NDA 206276
 Wiley A. Chambers, MD
 Olopatadine hydrochloride ophthalmic solution, 0.7%

Study 12-053 Investigator Number	Principal Investigator	Subinvestigators	Olopatadine 0.7%	PATADAY	Patanol	Vehicle
		(b) (6)				
3133	Ackerman, Stacey MD 1703 S. Broad Street Suite 103 Philadelphia, PA 19148 (215) 339-8100		14	13	13	6
3807	Silverstein, Steven MD 40 Blue Ridge Blvd #1000 Kansas City, MO 64133 (816) 358-3600		12	12	12	6
3920	Dao, Jung MD 3815 E. Bell Road Phoenix, AZ 85032 (602) 258-4321		9	8	9	4

Clinical Review of NDA 206276
Wiley A. Chambers, MD
Olopatadine hydrochloride ophthalmic solution, 0.7%

Study 12-053 Investigator Number	Principal Investigator	Subinvestigators	Olopatadine 0.7%	PATADAY	Patanol	Vehicle
		(b) (6)				

Safety Study 12-028

Study 12-028 Investigator Number	Principal Investigator	Subinvestigators	Olopatadine 0.7%	Vehicle
4755	Meier, Edward MD Eye Care Associates of Greater Cincinnati, Inc. 6394 Thornberry Ct Mason, OH 45040	(b) (6)	27	13
6448	Rand, Allison MD Rand Eye Institute 5 Sample Rd. Deerfield, FL 33064	(b) (6)	27	13
1806	Sall, Kenneth MD Sall Research Medical Center 11423 187th Street, Suite 200 Artesa, CA 90701	(b) (6)	27	13
1159	Jerkins, Gary MD Nashville Vision Associates 4306 Harding Rd. Suite 202 Nashville, TN 37205	(b) (6)	24	13
2600	Wirta, David MD 520 Superior Ave. Suite 235 Newport Beach, CA 92663	(b) (6)	24	13
3349	Cottingham, Andrew Jr. MD Texas Quest Medical Research 15900 La Cantera Parkway, Suite 19205 San Antonio, TX 78256	(b) (6)	23	11
6339	Swanic, Matthew MD Eye Care Associates of Nevada 501 Rose Street, Suite 150 Las Vegas, NV 89106	(b) (6)	23	11
4798	Abrams, Marc MD PhD Abrams Eye Center 2322 East 22nd Street Cleveland, OH 44115	(b) (6)	22	12

Clinical Review of NDA 206276
Wiley A. Chambers, MD
Olopatadine hydrochloride ophthalmic solution, 0.7%

Study 12-028 Investigator Number	Principal Investigator	Subinvestigators	Olopatadine 0.7%	Vehicle
1927	DuBiner, Harvey MD Eye Care Centers Management 1000 Corporate Center Drive, Suites 100 and 120 Morrow, GA 30260	(b) (6)	22	12
6326	Smyth-Medina, Robert MD North Valley Eye Medical Group, Inc. 11550 Indian Hills Rd. Suite 341 Mission Hills, CA 91345	(b) (6)	22	12
3112	Kwapiszewski, Bradley MD Heart of America Eye Care, PA 8901 West 74th Street, Suite 281 Shawnee Mission, KS 66204	(b) (6)	20	10
6390	Restivo, Vincent MD Hill Country Eye Center 12171 West Parmer Lane, Ste 201 Cedar Park, TX 78613	(b) (6)	20	10
4311	Tekwani, Navin MD Tekwani Vision Center, Inc. 9911 Kennerly Rd. Suite A St. Louis, MO 63128	(b) (6)	20	10
6264	Endl, Michael II MD Fichte, Endl & Elmer Eyecare 2825 Niagara Falls Blvd. Suite 130 Amherst, NY 14228	(b) (6)	17	9
6710	Desai, Neel MD The Eye Institute of West Florida 148 13th Street Southwest Largo, FL 33770	(b) (6)	12	7

6 Review of Efficacy

6.1 Indication - Ocular Itching

6.1.1 Methods

Standard conjunctival antigen challenge studies evaluated the potential prevention of itching and redness.

6.1.2 Demographics – All trials

		CAC #1 (C-10-126)	CAC #2 (C-12-053)	Safety (C-12-028)	Comfort (C-10-127)
Age*	Mean (years)	41.1	40.7	32.1	41.4
	Std Dev	13.5	12.8	16.6	14.7
	N	202	345	499	43
	Min (years)	18	18	2	18
	Max (years)	77	75	74	65
	2 -11 years, n (%)	0	0	68 (13.6)	0
	12- 17 years, n (%)	0	0	7 (1.4)	0
	18 - 64 years, n (%)	196 (97.0)	333 (96.5)	413 (82.8)	41 (95.3)
≥ 65 years, n (%)	6 (3.0)	12 (3.5)	11 (2.2)	2 (4.7)	
Gender	Male	78 (38.6)	141 (40.9)	174 (34.9)	22 (51.2)
	Female	124 (61.4)	204 (59.1)	325 (65.1)	21 (48.8)
Ethnicity	Hispanic or Latino	17 (8.4)	59 (17.1)	131 (26.3)	0
	Not Hispanic or Latino	185 (91.6)	285 (82.6)	368 (73.7)	43 (100.0)
Race	White	161 (79.7)	263 (76.2)	429 (86.0)	42 (97.7)
	Black or African American	33 (16.3)	62 (18.0)	37 (7.4)	1 (2.3)
	Asian	3 (1.5)	7 (2.0)	16 (3.2)	0
	Native Hawaiian or Other Pacific Islander	0	0	3 (0.6)	0
	American Indian or Alaska Native	3 (1.5)	5 (1.4)	1 (0.2)	0
	Multi-racial	0 (0.0)	3 (0.9)	7 (1.4)	0
	Other	2 (1.0)	5 (1.4)	6 (1.2)	0

Reviewer's Comments: *The population studied is considered representative of the US population.*

Demographic Statistics by Treatment

Study 10-126	Olopatadine 0.7%	Olopatadine 0.2%	Vehicle
Average Age	41	41	42
White	50	54	57
Black or African American	14	11	8
Other Race	2	3	3
Brown Iris	39	36	32
Blue Iris	15	16	23
Green Iris	3	6	7
Hazel Iris	9	9	6
Grey Iris	0	1	0
Male	23	26	29
Female	43	42	39

Reviewer's Comments: *The groups were reasonably well balanced.*

Study 12-053	Olopatadine 0.7%	Pataday	Patanol	Vehicle
Average Age	39	42	41	42
White	81	70	77	35
Black or African American	13	26	14	9
Other	4	3	8	5
Male	37	44	43	17
Female	61	55	56	32

Reviewer's Comments: *The groups were reasonably well balanced. Iris color should have been collected during the study.*

Study 12-028	Olopatadine 0.7% (N=330)	Vehicle (N=169)
<6 years old	38 (11.5)	18 (10.7)
6-17 years old	13 (3.9)	6 (3.6)
≥18 years old	279 (84.5)	145 (85.8)
Mean Age (SD)	32.4 (17.1)	31.5 (15.7)
Median Age	31.0	31.0
(Min, Max) Age	(2, 74)	(2, 71)
Male	116 (35.2)	58 (34.3)
Female	214 (64.8)	111 (65.7)
Hispanic or Latino	87 (26.4)	44 (26.0)
Not Hispanic or Latino	243 (73.6)	125 (74.0)
White	289 (87.6)	140 (82.8)
Black or African American	20 (6.1)	17 (10.1)
Asian	12 (3.6)	4 (2.4)
Native Hawaiian or Other Pacific Islander	2 (0.6)	1 (0.6)
American Indian or Alaska Native	0 (0.0)	1 (0.6)
Multi-racial	4 (1.2)	3 (1.8)
Other race	3 (0.9)	3 (1.8)
Brown Iris Color	169 (51%)	93 (55%)
Hazel Iris Color	45 (17%)	29 (17%)
Green Iris Color	26 (8%)	18 (11%)
Blue Iris Color	86 (26%)	29 (17%)
Grey Iris Color	4 (1%)	0

Reviewer's Comments: *The groups were reasonably well balanced.*

6.1.3 Subject Disposition

Study 10-126	Olopatadine		
	0.7%	PATADAY	Vehicle
Patient Status	N	n	n
Randomized	66	68	68
Treated	66	68	68
Completed	63	63	60
Total Discontinued	3	5	8

Adverse event*	2	0	1
Lost to Follow-Up	1	0	2
Patient's Decision Unrelated to an Adverse Event	0	0	1
Other**	0	5	4

*One patient on vehicle discontinued due an ear infection. Two patients on Olopatadine 0.7% discontinued due to episodes of viral gastroenteritis.

**Two patients on Pataday discontinued because of pregnancy. One patient on Pataday should have been excluded based on entry criteria. Four patients on vehicle and two patients on Pataday had scheduling conflicts.

	Overall	Olopatadine 0.7%	Vehicle
Study 12-028	n	n (%)	n (%)
Enrolled	518		
Screen Failure	18		
Randomized ^a		331 (100%)	169 (100%)
Completed Study		329 (99%)	166 (98%)
Discontinued		2 (1%)	3 (2%)
Adverse Event		0	2 (1%)
Death		0	0
Lost to Follow-up		0	1 (1%)
Non-compliance with Study Drug		0	0
Physician Decision		0	0
Pregnancy		1 (0.3%)	0
Protocol Violation		0	0
Study Terminated by Sponsor		0	0
Withdrawal by Subject		0	0
Other		1 (0.3%)	0

^a Subject 2117 (discontinued=other) was randomized to Olopatadine 0.7% in error and is not included in the safety population.

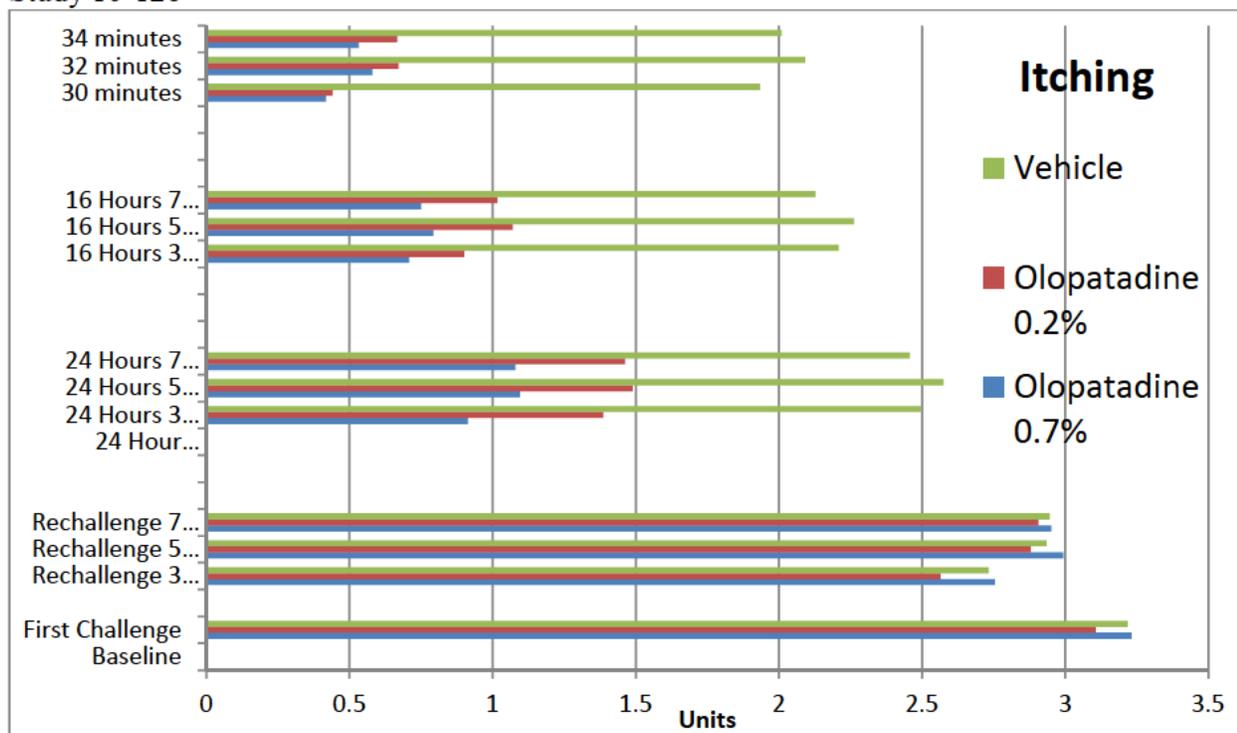
Study 12-053	Olopatadine				Overall
	0.7%	PATADAY	PATANOL	Vehicle	
Enrolled					902
Discontinued Before Randomization					557
Screen Failure					390
Adverse Event					12
Lost to Follow-up					26
Protocol Violation					2
Withdrawal by Patient					85
Other					42
Randomized	98 (100%)	99 (100%)	99 (100%)	49 (100%)	
Completed Study	93 (95)	94 (95)	90 (91%)	48 (98)	
Discontinued	5 (5%)	5 (5%)	9 (9%)	1 (2%)	
Screen Failure	0	0	0	0	
Adverse Event*	2 (2%)	0	0	0	
Death	0	0	0	0	
Lost to Follow-up	0	0	2 (2%)	0	
Non-compliance with Study Drug	0	0	0	0	
Physician Decision	0	0	0	0	
Pregnancy	0	0	0	0	
Progressive Disease	1 (1%)	4 (4%)	3 (3%)	0	
Protocol Violation	1 (1%)	1 (1%)	1 (1%)	0	
Study Terminated by Sponsor	0	0	0	0	
Withdrawal by Patient	1 (1%)	0	3 (3%)	1 (2%)	
Other	0	0	0	0	

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

*Influenza infection was responsible for each patient discontinuing.

6.1.4 Analysis of Primary Endpoint - Itching

Study 10-126

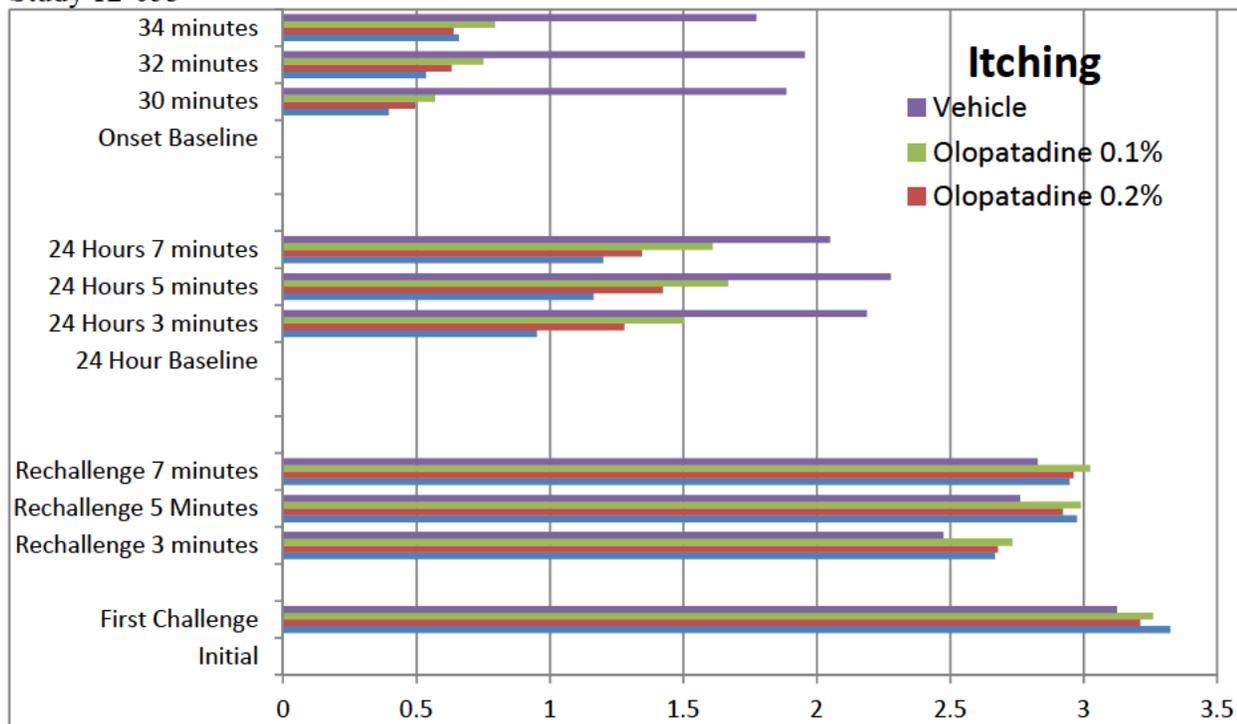


	Olopatadine 0.7% vs Vehicle	Olopatadine 0.7% vs Pataday
24hr duration		
3 min	-1.58*	-0.47†
5 min	-1.48*	-0.39†
7 min	-1.38*	-0.38†
16hr duration		
3 min	-1.50*	-0.19
5 min	-1.47*	-0.28
7 min	-1.38*	-0.27
Onset-of-action		
3 min	-1.52*	-0.03
5 min	-1.51*	-0.10
7 min	-1.48*	-0.14

*p<0.0001, † p<0.05

Reviewer's Comments: Efficacy over vehicle for itching has been demonstrated 30 minutes after administration and continued 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 slightly more evident at 24 hours.

Study 12-053



Endpoint Comparison Time Difference (95% CI) p-value

Endpoint	Comparison	Time	Difference (95% CI)	p-value
Onset of Action CAC	Olopatadine 0.7% vs Vehicle	3Min	-1.53 (-1.76, -1.30)	<.0001
		5Min	-1.46 (-1.71, -1.22)	<.0001
		7Min	-1.17 (-1.45, -0.90)	<.0001
24 Hours CAC	Olopatadine 0.7% vs Vehicle	3Min	-1.29 (-1.60, -0.97)	<.0001
		5Min	-1.15 (-1.46, -0.84)	<.0001
		7Min	-0.89 (-1.22, -0.57)	<.0001
24 Hours CAC	Olopatadine 0.7% vs PATADAY	3Min	-0.31 (-0.57, -0.06)	0.0156
		5Min	-0.26 (-0.51, -0.01)	0.0456
		7Min	-0.16 (-0.42, 0.11)	0.2481
24 Hours CAC	Olopatadine 0.7% vs PATANOL	3Min	-0.52 (-0.78, -0.27)	<.0001
		5Min	-0.48 (-0.73, -0.23)	0.0002
		7Min	-0.39 (-0.65, -0.12)	0.0043

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.

Reviewer's Comments: *Efficacy over vehicle for itching has been demonstrated 30 minutes after administration and continued 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 slightly more evident at 24 hours.*

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study 12-028 was a 6 week, multicenter, randomized, double-masked, vehicle-controlled, parallel-group study evaluating the safety of Olopatadine HCl Solution, 0.7% compared to Vehicle when administered once daily in both eyes for 6 weeks. Subjects were randomized 2:1, Olopatadine HCl Solution, 0.7%:Vehicle. Subjects younger than 6 years of age were randomized from one randomization schedule; subjects 6 years of age or older were randomized from another randomization schedule. All randomized subjects received 1 drop of either Olopatadine HCl Solution, 0.7% or Vehicle in both eyes for 6 weeks. Subjects were contacted by telephone 1 week after the last dose of study medication to assess changes in concomitant medications and report adverse events. Safety variables and assessments included best-corrected visual acuity, slit-lamp, intraocular pressure (IOP), dilated fundus evaluations, pulse, blood pressure, and adverse events. At the Baseline Visit (Day 0) and at each subsequent office visit (Week 1, Week 3, Week 6), best-corrected visual acuity was measured and slit-lamp evaluations were performed for the eyelids, conjunctiva, cornea, iris/anterior chamber, and lens. At the Baseline Visit (Day 0) and at the last office visit (Week 6), IOP was measured, a dilated fundus examination (DFE) of the vitreous, retina/macula/choroid, and optic nerve was performed, and vital signs (pulse and blood pressure) were taken. At each office visit and during telephone contacts at Weeks 2, 4, and 5, adverse events and dosing compliance were recorded and concomitant medications updated. The Exit Visit occurred via telephone contact at Week 7. Adverse events were recorded and concomitant medications updated.

Schedule of Safety-Related Parameter Measurements

Study Activity	Visit 1 Baseline	Visit 2 Week 1	TC Week 2	Visit 3 Week 3	TC Week 4	TC Week 5	Visit 4 Week 6	TC/Exit Visit Week 7
Day Number	Day 0	Day 7 ±3 Days	Day 14 ±3 Days	Day 21 ±3 Days	Day 28 ±3 Days	Day 35 ±3 Days	Day 42 ±3 Days	Day 49 ±3 Days
Visual acuity	X	X		X			X	
Ocular signs	X	X		X			X	
Intraocular pressure	X						X	
Fundus examination	X						X	
Vital signs	X						X	

TC = telephone contact

7.1.2 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%

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence - N/A

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety study includes a six week duration of use which is typical of an allergy season. The subjects were individuals at risk for developing allergic conjunctivitis. The population was an appropriate population to monitor for the potential to develop an adverse reaction.

7.3 Major Safety Results

- 7.3.1 Deaths -None
- 7.3.2 Nonfatal Serious Adverse Events -None
- 7.3.3 Dropouts and/or Discontinuations -None related to study medication.
- 7.3.4 Significant Adverse Events -None.

7.4 Supportive Safety Results

- 7.4.1 Common Adverse Events -see Table in 7.1.2.
- 7.4.2 Laboratory Findings -No significant finding.
- 7.4.3 Vital Signs -No significant findings.
- 7.4.4 Electrocardiograms (ECGs) -Not performed.
- 7.4.5 Special Safety Studies/Clinical Trials

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	%	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	

There were no clinically significant changes noted in Visual Acuity, Intraocular Pressure, Slit Lamp or Funduscopy in either trial.

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%)		15	(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.

Reviewer's Comments: *There was no significant difference between groups in visual acuity.*

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.

Reviewer's Comments: *There was no significant difference between groups in intraocular pressure.*

Slit Lamp, Fundus Exam and Vital Signs

Reviewer's Comments: *There were no significant findings on the slit lamp and fundus exam. There were no significant differences in vital signs between the groups.*

7.5 Other Safety Explorations - None

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity -*No human studies have been conducted.*

7.6.2 Human Reproduction and Pregnancy Data

Subject 2036 in Study 10-126 became Pregnant during the study. The subject entered the study on February 3, 2012, with a negative pregnancy test. The subject was using a spermicide with a barrier as a method of contraception. The subject was first exposed to Olopatadine 0.2% on February 23, 2012. Pregnancy was confirmed on [REDACTED] (b) (6). Patient delivered a healthy baby girl on [REDACTED] (b) (6). The newborn did not have any congenital anomalies.

Subject 1879 in Study 12-028 became Pregnant during the study. The subject entered the study on November 16, 2012, with a negative pregnancy test. The subject was using a spermicide with a barrier as a method of contraception. The subject was first exposed to Olopatadine 0.7% on November 16, 2012. Pregnancy was confirmed on [REDACTED] (b) (6). Patient delivered a healthy baby on [REDACTED] (b) (6). The newborn did not have any congenital anomalies.

7.6.3 Pediatrics and Assessment of Effects on Growth

Pediatric patients were evaluated in the safety study, Protocol 12-028. The distribution of pediatric patients by age is listed below:

Ages	Vehicle	Olopatadine 0.7%
1	0	0
2	1	9
3	9	5
4	3	9
5	5	15
6	1	1
7	1	2
8	0	0
9	0	2
10	1	1
11	0	3
12	1	1
13	0	1
14	0	0
15	1	2
16	1	0
17	0	0
18	2	12
19	4	6
20	4	8

Reviewer's Comments: *No significant safety issues were identified in the pediatric patients who were evaluated. Data from this trial suggests that Olopatadine can be used in children, two years of age and older.*

Request for Waiver of a Pediatric Assessment in Children less than 2 years of age:

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 is so small or geographically dispersed.

Reviewer's Comments: *Recommend granting waiver request for children less than two years of age.*

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound – *None.*

8 Post-marketing Experience

Products Containing Olopatadine

Trade Name	Presentation	Registered Region	First Approval
PATANOL (US)/ OPATANOL (EU)	Topical ocular solution (0.1% olopatadine) BID (two times per day) dosing	Globally (128 countries)	1996 (NDA 20-688)
PATADAY	Topical ocular solution (0.2% olopatadine) QD (once a day) dosing	US, Japan, South America, India (Total of 41 countries)	2001 (NDA 21-545)
PATANASE	Nasal spray (0.6% olopatadine)	US	2004 (NDA 21-861)
Allelock	Oral tablet (5 mg olopatadine)	Japan	2001

Reviewer's Comments: *Reported adverse events have been consistent with the events observed in the clinical trials of Olopatadine 0.7% and the clinical trials for the 0.1% and 0.2% concentrations.*

9. Labeling -*Recommended changes have been incorporated in the labeling that follows:*

4 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/

WILEY A CHAMBERS
09/15/2014

WILLIAM M BOYD
09/15/2014