CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206276Orig1s000

MEDICAL REVIEW(S)

Clinical Investigator Financial Disclosure NDA 206276
Review Template

Application Number: 206276

Submission Date(s): July 30, 2014

Applicant: Alcon Laboratories

Product: Olopatadine hydrochloride 0.7%

Reviewer: Wiley A. Chambers, MD

Date of Review: December 14, 2014

Covered Clinical Study (Name and/or Number): C-10-126

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 3		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Covered Clinical Study (Name and/or Number): C-12-053

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 6		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Covered Clinical Study (Name and/or Number): C-12-028

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 15		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The applicant has adequately disclosed financial interests/arrangements with clinical investigators. The one reported interest 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. The applicant reports that they took the following steps to minimize potential bias:

- The studies were double-masked in which patients were randomized sequentially at each investigational center to receive 1 of 2 (in C-12-028), 3 (in C-10-126) or 4 (in C-12-053) masked study drugs.

- For each study, a list of sequential subject numbers was generated by a member of the Alcon SAS programming group not involved in the conduct of the study or had any contact with study subjects or investigators. Each subject number was associated with a treatment according to a random process. Only once all study data was verified, validated and the database locked, individual subject data were unmasked.

- As a double-masked study, the patients, the Investigators, the investigational center staff, the Sponsor, and the clinical monitors were not aware of the treatment assigned to the individual study patients.

- All study drugs were identical in appearance and supplied in masked bottles with identical packaging and labeling.

- To minimize any potential Investigator bias, designated study site staff personnel administered the first dose of study medication in the subject's eyes during Visit 1 in C-12-028 and at all dosing visits for studies C-10-126 (Visits 3A, 4A and 5) and C-12-053 (Visits 3A and 4).

- All efficacy and safety variables were assessed by masked observers.

- The treatment code was not broken at any time during any of the studies by either the investigator or the Sponsor.

- Frequent on-site monitoring was performed during the conduct of the studies to ensure compliance with protocol guidelines.

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/s/

WILEY A CHAMBERS
12/14/2014

Clinical Review of NDA 206276

Application Type	NDA
Application Number(s)	206276
Priority or Standard	Priority
Submit Date(s)	July 30, 2014
Received Date(s)	July 30, 2014
PDUFA Goal Date	January 30, 2015
Review Division	Division of Transplant and Ophthalmology Products
Reviewer Name	Wiley A. Chambers, MD
Review Completion Date	September 15, 2014
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.

Template Version: March 6, 2009

Table of Contents

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 (b) (4) preservative.

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	(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
(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)	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 ≥ (b) (4) 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

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	[redacted] (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] [redacted] (b) (4) adjusted based on assay results

No significant interaction was noted between olopatadine (10 μM) 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 ΔQTc. 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.	*In vitro*	*In vitro*
	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		*In vitro*, 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 service 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/m^2 basis, the ratio is approximately 19.5 (6 mg/m^2 divided by 0.308 mg/m^2).

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

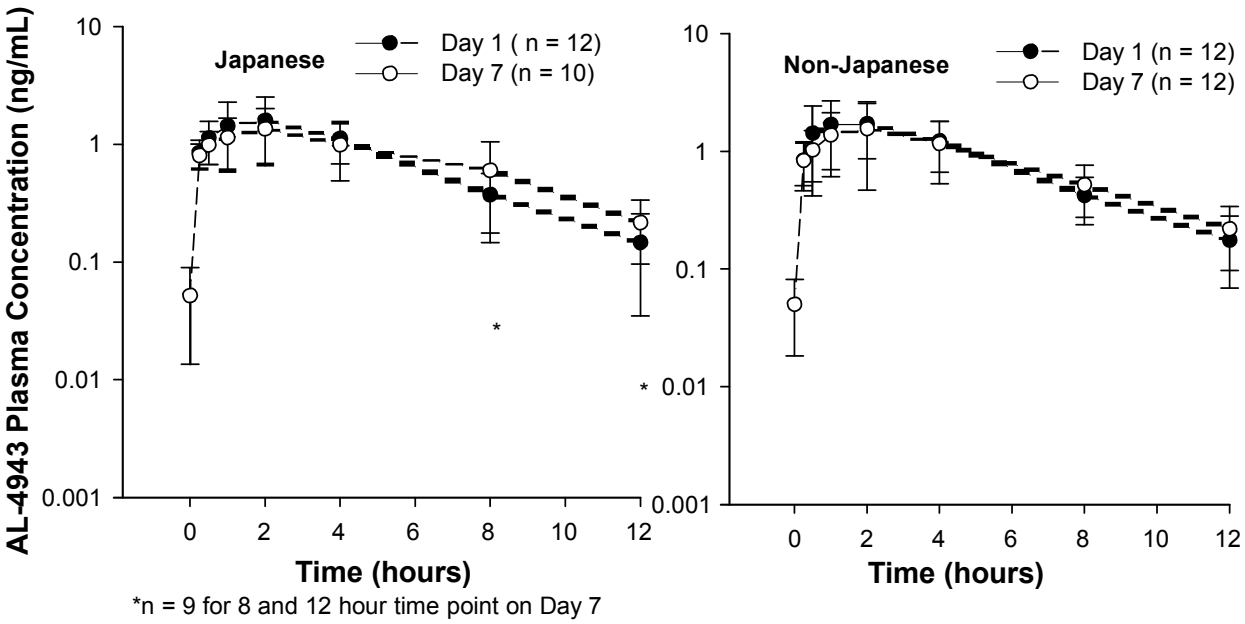
A Randomized, Double-Masked, Vehicle-Controlled, Multiple-Dose Safety and Pharmacokinetic Study of AL-4943A Ophthalmic Solution, 0.77% Following Topical Ocular Administration in Healthy Normal Subjects

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
Cmax (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)
Tmax (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)
AUC0-12 (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)
t1/2 (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)

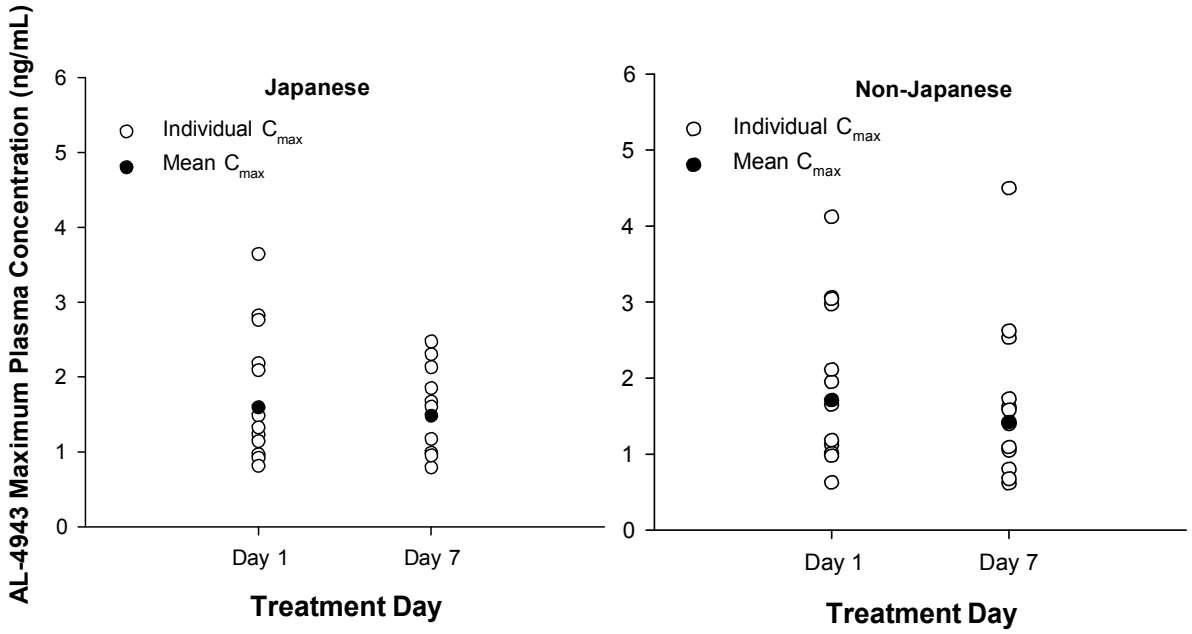
a: Cmax and AUC0-12 expressed as geometric mean and range (min to max);
b: Tmax expressed as median and range (min to max)
c: t1/2 expressed as arithmetic mean with n = 7 for Japanese subjects
Source: Table 14.2.1.-13 and Table 14.2.1-14

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



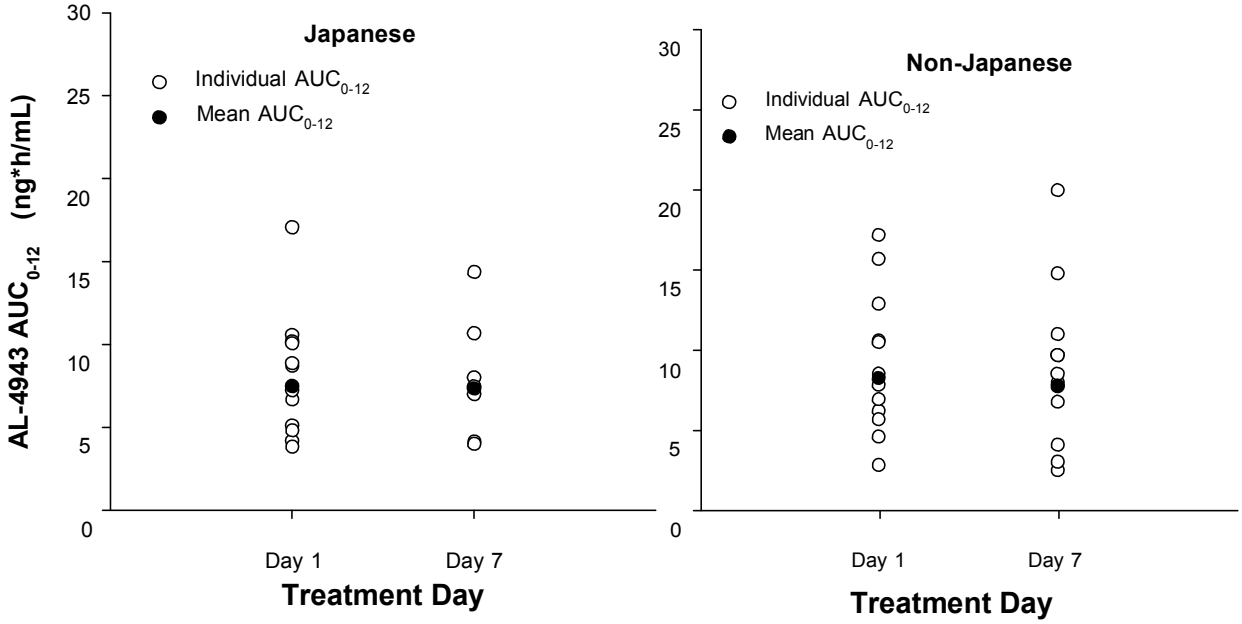
*n = 9 for 8 and 12 hour time point on Day 7

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 AUC_{0-12} 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 m^2. 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 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)).

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 ≥2+ itching and redness reaction. These patients return for a second visit in which the dose which elicited a ≥2+ reaction is administered and only patients who demonstrate a reproducible ≥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 ≥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 to27 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 (Oloptadine 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.

	Study Visits							Early Exit Visit
Procedure/ Assessment	**Visit 1** Day -21 (± 2 days)	**Visit 2** Day -14 (± 3 days)	**Visit 3A** Day 0	**Visit 3B** Day 1	**Visit 4A** Day 14 (± 2 days)	**Visit 4B** Day after Visit 4A	**Visit 5** 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 (+/- 1min) 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		18	19	18
5476	Bergmann, Mark MD Eye Care Associates of Greater Cincinnati, Inc. 2859 Boudinot Ave., Suite 301 Cincinnati, OH 45238		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		20	22	22	10
3733	Rice, Robert MD 5430 Fredericksburg Rd San Antonio, TX 78229 (210) 340-1212		15	15	15	8

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

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		27	13
1806	Sall, Kenneth MD Sall Research Medical Center 11423 187th Street, Suite 200 Artesa, CA 90701		27	13
1159	Jerkins, Gary MD Nashville Vision Associates 4306 Harding Rd. Suite 202 Nashville, TN 37205		24	13
2600	Wirta, David MD 520 Superior Ave. Suite 235 Newport Beach, CA 92663		24	13
3349	Cottingham, Andrew Jr. MD Texas Quest Medical Research 15900 La Cantera Parkway, Suite 19205 San Antonio, TX 78256		23	11
6339	Swanic, Matthew MD Eye Care Associates of Nevada 501 Rose Street, Suite 150 Las Vegas, NV 89106		23	11
4798	Abrams, Marc MD PhD Abrams Eye Center 2322 East 22nd Street Cleveland, OH 44115		22	12

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		22	12
3112	Kwapiszeski, Bradley MD Heart of America Eye Care, PA 8901 West 74th Street, Suite 281 Shawnee Mission, KS 66204		20	10
6390	Restivo, Vincent MD Hill Country Eye Center 12171 West Parmer Lane, Ste 201 Cedar Park, TX 78613		20	10
4311	Tekwani, Navin MD Tekwani Vision Center, Inc. 9911 Kennerly Rd. Suite A St. Louis, MO 63128		20	10
6264	Endl, Michael II MD Fichte, Endl & Elmer Eyecare 2825 Niagara Falls Blvd. Suite 130 Amherst, NY 14228		17	9
6710	Desai, Neel MD The Eye Institute of West Florida 148 13th Street Southwest Largo, FL 33770		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	

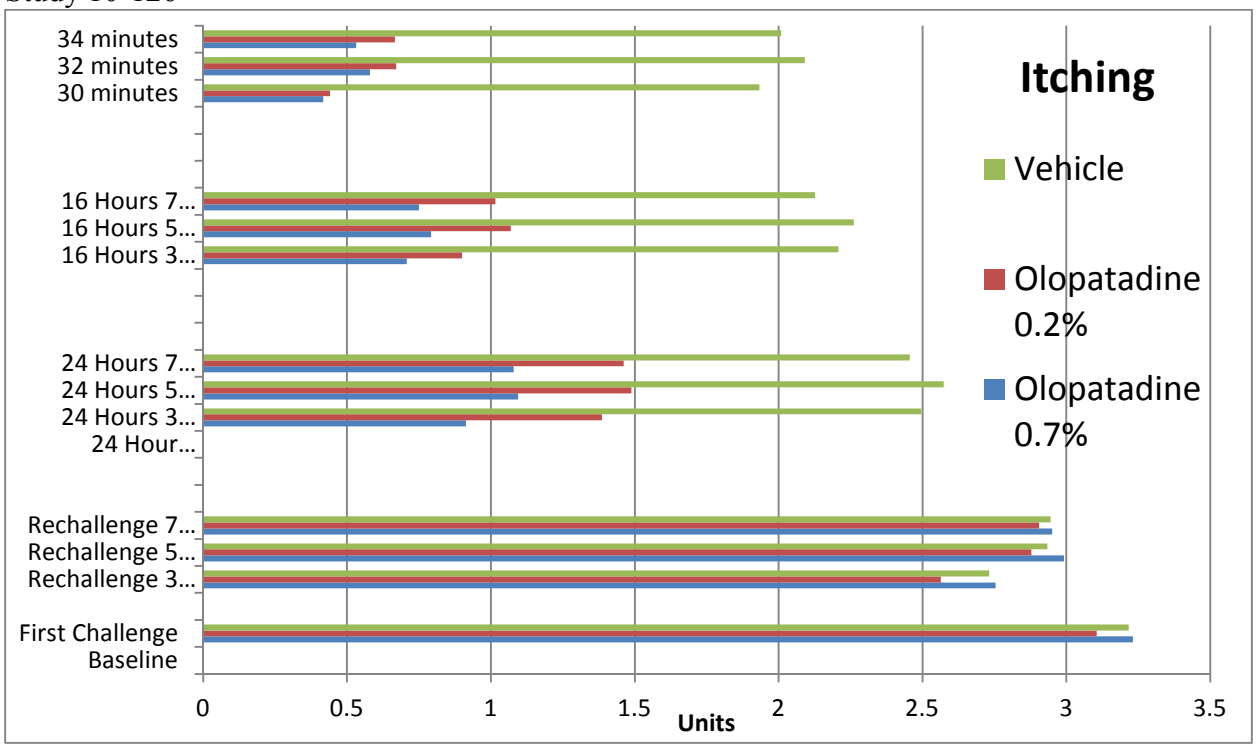
[a] Subject 2117 (discontinued=other) was randomized to Olopatadine 0.7% in error and is not included in the safety population.

Study 12-053	Olopatadine 0.7%	PATADAY	PATANOL	Vehicle	Overall
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

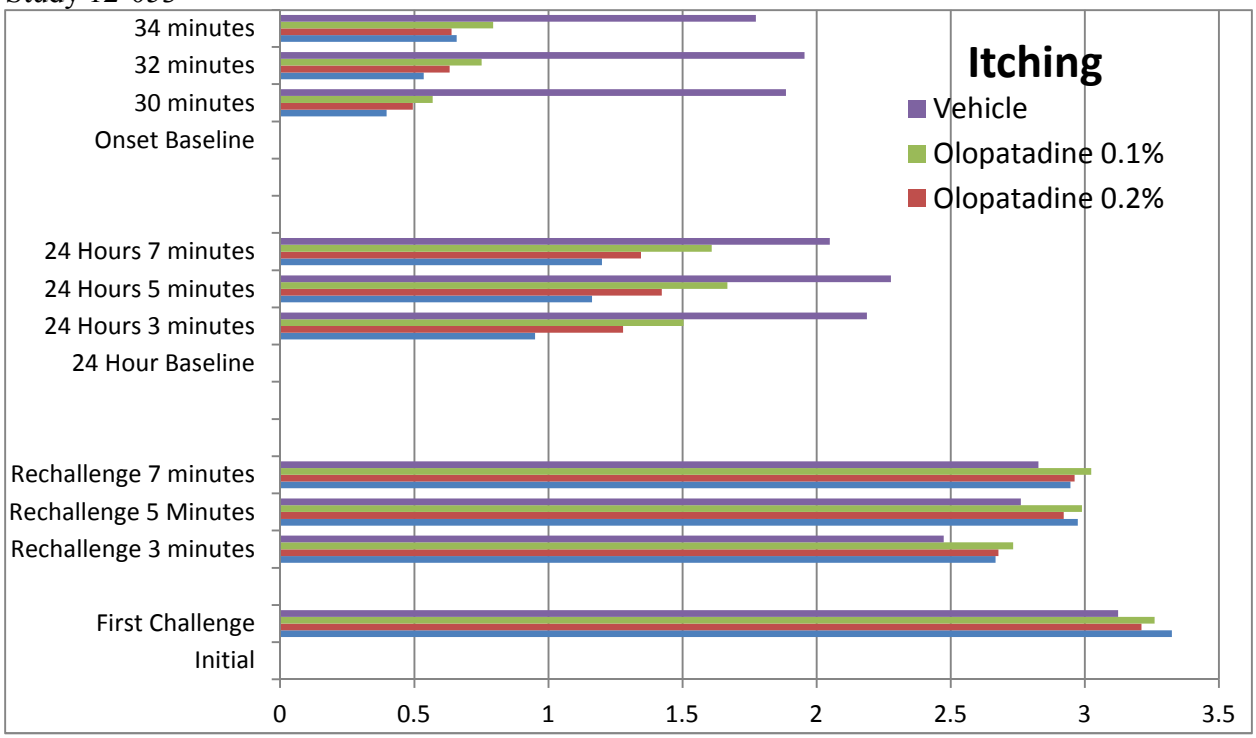


	Olopatadine 0.7% vs Vehicle	Olopatadine 0.7% vs Pataday
24hr duration		
3 min	-1.58*	-0.47†
5 min	-1.48*	-0.39†
7 min	-1.38*	-0.38†
16hr duration		
3 min	-1.50*	-0.19
5 min	-1.47*	-0.28
7 min	-1.38*	-0.27
Onset-of-action		
3 min	-1.52*	-0.03
5 min	-1.51*	-0.10
7 min	-1.48*	-0.14

*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
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.*

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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 Letters		10-14 Letters		5-9 Letters		± 4 Letters		5-9 Letters		10-14 Letters		> 15 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.

		Olopatadine			**PATADAY**			**PATANOL**			**Vehicle**		
Study 12-053		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%)
	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 (b) (6). Patient delivered a healthy baby girl on (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 (b) (6). Patient delivered a healthy baby on (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

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/s/

WILEY A CHAMBERS
09/15/2014

WILLIAM M BOYD
09/15/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 206276 **Applicant: Alcon** **Stamp Date: July 30, 2014**

Drug Name: Olopatadine

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?				
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?				
15.	Describe the scientific bridge (e.g., BA/BE studies)				
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	X			
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 Indication: Itching Pivotal Study #2 Indication: Itching				
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?				
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	adverse dropouts (and serious adverse events if requested by the Division)?				
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Wiley A. Chambers, MD	8/15/14
Reviewing Medical Officer	Date
William Boyd, MD	8/15/14
Clinical Team Leader	Date

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