CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206276Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	206276
Supporting document/s:	SDN014 (eCTD013)
Applicant's letter date:	1/22/2015
CDER stamp date:	1/22/2015
Product:	Olopatadine hydrochloride ophthalmic solution, 0.77%
Indication:	Treatment of signs and symptoms of allergic conjunctivitis
Applicant:	Alcon Research Ltd 6201 South Freeway MS TC 45 Fort Worth, TX 76134
Review Division:	Division of Transplant and Ophthalmology Products
Reviewer:	Aaron M Ruhland, PhD
Supervisor/Team Leader:	Lori Kotch, PhD, DABT
Division Director:	Renata Albrecht, MD
Project Manager:	Lois Almoza

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1 Executive Summary

1.1 Introduction

The subject of this NDA is olopatadine hydrochloride ophthalmic solution, 0.77% administered as a once daily topical ocular drop for the treatment of ocular itching associated with allergic conjunctivitis. A nonclinical review of the approvability of the NDA application has been conducted (dated 12-31-2014). This review represents reconsideration of Section 8 of the labeling following a counterproposal by the applicant. Specifically, the applicant contends that labeling language in Section 8 describing increased embryolethality and cleft palate in rats following oral administration of 60 mg/kg olopatadine during gestation falls within or near historical control values. The applicant submitted historical control data from nonclinical embryo-fetal studies to support these arguments .

1.2 Brief Discussion of Nonclinical Findings

- The applicant's argument that increased embryolethality following daily oral olopatadine doses of 60 mg/kg in pregnant rats falls within the historical control range is supported by the data submitted. The FDA proposed labeling has been amended in support of these findings.
- The applicant's argument that (b) (4) . The FDA proposed labeling has not been amended in support of these findings.
- It was suggested in internal discussion that (b) (4) be deleted from the labeling to reduce potential confusion when comparing this multiple to that of the 1 mg/kg/day based on comparison of exposure (i.e. 45 – 150 fold).
- The human exposure (AUC_{0-12}) to Pazeo following the recommended dosing regimen reported in Section 12.3 of the labeling was changed based upon the Clinical Pharmacology reviewer's calculations (changed from (b) (4) to 9.7 ng·hr/mL). The human AUC reported in Section 8 and resultant safety margin calculations have been revised to reflect this change.
- During ongoing revision, the applicant suggested the addition of the following statement to Section 8.3:
    - "An oral dose of 1 mg/kg olopatadine in rats resulted in a range of systemic plasma area under the curve (AUC) levels that were 45 to 150 times higher than the observed human exposure [9.7 ng·hr/mL] following administration of the recommended human ophthalmic dose."

1.3. Labeling

1.3.1 Former FDA proposed labeling (see letter dated 12-31-2014)

8.1 Pregnancy

Risk Summary
There are no adequate or well-controlled studies with PAZEO in pregnant women. Olopatadine caused maternal toxicity and embryofetal toxicity in rats at levels 1080 to 14,400 times the maximum recommended human ophthalmic dose (MRHOD)). There was no toxicity in rat offspring at (b) (4) times MRHOD. Olopatadine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data
In a rabbit embryofetal study, rabbits treated orally at 400 mg/kg/day during organogenesis showed a decrease in live fetuses. This dose is 14,400 times the MRHOD, on a mg/m^2 basis.

An oral dose of 600 mg/kg/day olopatadine (10,800 times the MRHOD) was shown to be maternally toxic in rats, producing death and reduced maternal body weight gain. When administered to rats throughout organogenesis, olopatadine produced (b) (4) cleft palate at 60 mg/kg/day (1080 times the MRHOD), and reduced fetal weight in rats at 600 mg/kg/day. When administered to rats during late gestation and throughout the lactation period, olopatadine produced decreased neonatal survival at 60 mg/kg/day and reduced body weight gain in offspring at 4 mg/kg/day (b) (4). A dose of 2 mg/kg/day olopatadine produced no toxicity in rat offspring. An oral dose of 1 mg/kg olopatadine in rats resulted in a range of systemic plasma area under the curve (AUC) levels that were (b) (4) times higher than the observed human exposure (b) (4) following administration of the recommended human ophthalmic dose.

8.3 Nursing Mothers
Olopatadine has been identified in the milk of nursing rats following oral administration. Oral administration of olopatadine doses at or above 4 mg/kg/day throughout the lactation period produced decreased body weight gain in rat offspring; a dose of 2 mg/kg/day olopatadine produced no toxicity. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in the human breast milk. Nevertheless, caution should be exercised when PAZEO is administered to a nursing mother.

1.3.2. Applicant's proposed amended labeling (SDN014; 1-22-2015)

Blue double-underlined text represents applicant's proposed additions to the labeling; Red strikethrough text represents applicant's proposed deletions from the labeling:

8.1 Pregnancy

Risk Summary
There are no adequate or well-controlled studies with PAZEO in pregnant women. Olopatadine caused maternal toxicity and embryofetal toxicity in rats at levels 10, (b) (4) 0 to 14,400 times the maximum recommended human ophthalmic dose (MRHOD)). There was no toxicity in rat offspring at (b) (4) times MRHOD. Olopatadine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data
In a rabbit embryofetal study, rabbits treated orally at 400 mg/kg/day during organogenesis showed a decrease in live fetuses. This dose is 14,400 times the MRHOD, on a mg/m^2 basis.

An oral dose of 600 mg/kg/day olopatadine (10,800 times the MRHOD) was shown to be maternally toxic in rats, producing death and reduced maternal body weight gain. When administered to rats throughout organogenesis, olopatadine produced decreased embryofetal viability and (b) (4) reduced fetal weight in rats at 600 mg/kg/day. When administered to rats during late gestation and throughout the lactation period, olopatadine produced decreased neonatal survival at 60 mg/kg/day and reduced body weight gain in offspring at 4 mg/kg/day (b) (4). A dose of 2 mg/kg/day olopatadine produced no toxicity in rat offspring. An oral dose of 1 mg/kg olopatadine in rats resulted in a range of systemic plasma area under the curve (AUC) levels that were (b) (4) times higher than the observed human exposure (b) (4) following administration of the recommended human ophthalmic dose.

8.3 Nursing Mothers
Olopatadine has been identified in the milk of nursing rats following oral administration. Oral administration of olopatadine doses at or above 4 mg/kg/day throughout the lactation period produced decreased body weight gain in rat offspring; a dose of 2 mg/kg/day olopatadine produced no toxicity. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in the human breast milk. Nevertheless, caution should be exercised when PAZEO is administered to a nursing mother.

1.3.3 Data submitted by applicant to support proposed labeling changes

Morita, H., *et al*., 1987; "Spontaneous malformations in laboratory animals: Frequency of external, internal and skeletal malformations in rats, rabbits, and mice", *Cong Anom*, 27: 147 – 206.

Embryolethality

Following review of data from Study A-89-52, an embryo-fetal toxicity study in rats submitted to support the NDA, it was concluded that the (b) (4) dose caused

increased embryo-fetal lethality with significantly higher death in the olopatadine treated group compared to control (7.2% vs 2.9%, respectively):

Dose (mg/kg/day)	Control	60	200	600	Oxatomide
# of dams	24	24	22	22	24
Implantations	314	340	308	324	354
Alive (% of implantations)	97	92.8*	93.5*	92.8	81.6**
Early death (% of implantations)	2.9	7.2*	6.3*	7.2	15.1**
Late death (% of implantations)	0	0	0.3	0	3.3**
B.W. (m, f)	3.1, 2.9	3.1, 2.9	3.0, 2.8	2.8**, 2.6**	2.8**, 2.6**

Historical data submitted by the applicant (Morita, *et al.*) were reviewed. The data in Wistar rats were derived from two common strains: JCL and SLC. In JCL:Wistar rats, mean (range) fetal mortality among 1327 dams was 6% (2.5 – 15.8%). In SLC:Wistar rats, fetal mortality among 1232 dams was 4.5% (2.5 – 22.5%). While embryolethality in the olopatadine treated rats was significant higher than controls, the results fall within the published historic range. (b) (4) The data support this argument.

Cleft Palate

In Study A-89-52, cleft palate was reported in 2 fetuses (2 litters) treated with olopatadine (both instances occurred in the 60 mg/kg treated group). Across all olopatadine treated groups, this represents an incidence of 2/905 (0.22%) among all treated fetuses or 2/68 (2.9%) among all treated litters. These data were compared to the historical data submitted by the applicant (Morita, *et al.*).

In JCL:Wistar rats, a total of 2 instances of cleft palate were reported among 18,205 fetuses analyzed (0.011%). If an average litter size of 10 fetuses is assumed, this represents an incidence of 2/1820 litters (0.11%). Therefore, the incidence of 0.22% of fetuses or 2.9% of litters reported for the olopatadine treated groups represents an increase of 20-fold and 26-fold over the historical rate among fetuses and litters, respectively.

In SLC:Wistar rats, one (1) instance of cleft palate was reported among 10,713 fetuses analyzed (0.0093%). If an average litter size of 10 fetuses is assumed, this represents an incidence of 1/1071 litters (0.093%). Therefore, the incidence of 0.22% of fetuses or 2.9% of litters reported for the olopatadine treated groups represents an increase of 24-fold and 31-fold, respectively, over the historical rate.

Therefore, it is concluded that olopatadine treatment was associated with an increase in the incidence of cleft palate compared to the concurrent controls in the study and

historical control data submitted by the applicant. The labeling will remain unchanged to reflect these data.

1.3.4 Revised FDA labeling

8.1 Pregnancy

Risk Summary
There are no adequate or well-controlled studies with PAZEO in pregnant women. Olopatadine caused maternal toxicity and embryofetal toxicity in rats at levels 1080 to 14,400 times the maximum recommended human ophthalmic dose (MRHOD). There was no toxicity in rat offspring at (b) (4) 45 to (b) (4) 150 times MRHOD. Olopatadine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data
In a rabbit embryofetal study, rabbits treated orally at 400 mg/kg/day during organogenesis showed a decrease in live fetuses. This dose is 14,400 times the MRHOD, on a mg/m^2 basis.

An oral dose of 600 mg/kg/day olopatadine (10,800 times the MRHOD) was shown to be maternally toxic in rats, producing death and reduced maternal body weight gain. When administered to rats throughout organogenesis, olopatadine produced (b) (4) cleft palate at 60 mg/kg/day (1080 times the MRHOD)~~,~~ and decreased embryofetal viability and reduced fetal weight in rats at 600 mg/kg/day. When administered to rats during late gestation and throughout the lactation period, olopatadine produced decreased neonatal survival at 60 mg/kg/day and reduced body weight gain in offspring at 4 mg/kg/day (b) (4). A dose of 2 mg/kg/day olopatadine produced no toxicity in rat offspring. An oral dose of 1 mg/kg olopatadine in rats resulted in a range of systemic plasma area under the curve (AUC) levels that were (b) (4) 45 to (b) (4) 150 times higher than the observed human exposure [(b) (4) 9.7 ng·hr/mL] following administration of the recommended human ophthalmic dose.

8.3 Nursing Mothers
Olopatadine has been identified in the milk of nursing rats following oral administration. Oral administration of olopatadine doses at or above 4 mg/kg/day throughout the lactation period produced decreased body weight gain in rat offspring; a dose of 2 mg/kg/day olopatadine produced no toxicity. An oral dose of 1 mg/kg olopatadine in rats resulted in a range of systemic plasma area under the curve (AUC) levels that were 45 to 150 times higher than the observed human exposure [9.7 ng·hr/mL] following administration of the recommended human ophthalmic dose. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in the human breast milk. Nevertheless, caution should be exercised when PAZEO is administered to a nursing mother.

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/s/

AARON M RUHLAND
01/28/2015

LORI E KOTCH
01/28/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	206276
Supporting document/s:	N001
Applicant's letter date:	7/30/2014
CDER stamp date:	7/30/2014
Product:	Olopatadine hydrochloride ophthalmic solution, 0.77%
Indication:	Treatment of signs and symptoms of allergic conjunctivitis
Applicant:	Alcon Research Ltd 6201 South Freeway MS TC 45 Fort Worth, TX 76134
Review Division:	Division of Transplant and Ophthalmology Products
Reviewer:	Aaron M Ruhland, PhD
Supervisor/Team Leader:	Lori Kotch, PhD, DABT
Division Director:	Renata Albrecht, MD
Project Manager:	Lois Almoza

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Reference ID: 3681271

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1 Executive Summary

1.1 Introduction

The subject of this NDA is olopatadine hydrochloride ophthalmic solution, 0.77% administered as a once daily topical ocular drop for the treatment of ocular itching associated with allergic conjunctivitis. Olopatadine hydrochloride ophthalmic solution is currently approved as a topical ocular formulation in Patanol® (0.1%, BID) and Pataday® (0.2%, QD). The applicant conducted pharmacology, comparative ocular distribution/pharmacokinetic and ocular toxicity studies of olopatadine hydrochloride ophthalmic solution, 0.77**%** to support the new formulation and higher concentration of olopatadine hydrochloride compared to the previously approved formulations.

1.2 Brief Discussion of Nonclinical Findings

- A dose dependent increase in conjunctival and intraocular distribution was reported for olopatadine, 0.77% compared to Pataday®
- In a 90-day repeat-dose ocular toxicity study, no toxicity, ocular or systemic, was attributed to olopatadine, 0.77% administered bilaterally. This dose correlates with an approximate 4-fold margin over the proposed clinical dose.

1.3 Recommendations

1.3.1 Approvability

- P/T recommends approval

1.3.2 Labeling

1.3.2.1 Applicant's version of labeling

Blue double-underlined text represents additions to the Pataday® labeling; red strikethrough text represents deletions from the Pataday® labeling:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy (b) (4)

(b) (4)

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

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(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number: 113806-05-6

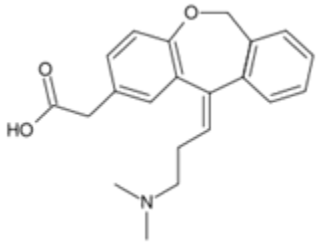
Generic Name: Olopatadine hydrochloride ophthalmic solution, 0.77%

Code Name: Pazeo

Chemical Name: {(11*Z*)-11-[3-(dimethylamino)propylidene]-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl}acetic acid

Molecular Formula/Molecular Weight: $C_{21}H_{23}NO_3$ / 337.4 g/mol

Structure or Biochemical Description:



Pharmacologic Class: Histamine-1 receptor inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

- DMF [redacted] (b) (4)
- NDA 20-688: Patanol®, olopatadine hydrochloride ophthalmic solution, 0.1%
  - Approved: 12-18-1996
- IND 44,216: Patanol®
- NDA 21-545: Pataday®, olopatadine hydrochloride ophthalmic solution, 0.2%
  - Approved: 12-22-2004
- IND 60,991, Pataday®

2.3 Drug Formulation

Component	% w/v	Function
Olopatadine hydrochloride	0.776	Active ingredient
Hydroxypropyl-gamma cyclodextrin	[redacted] (b) (4)	
Povidone		
Polyethylene glycol		
Hypromellose		
Mannitol		
Boric Acid		
Benzalkonium chloride	0.015	Preservative
Sodium hydroxide and/or hydrochloric acid	qs to pH 7.2	pH adjustment
Purified water	[redacted] (b) (4)	

Formulation comparison of Pazeo® with Patanol® and Pataday®:

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Component	Pazeo® (olopatadine HCl Solution, 0.77%)	Pataday®	Patanol®
Olopatadine HCl	0.776	0.222	0.111
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			

2.4 Comments on Novel Excipients

All excipients are qualified for topical ophthalmic administration except hydroxypropyl-γ-cyclodextrin and povidone K29/32 (b) (4). The applicant conducted a 3-month ocular toxicology study with the to-be-marketed formulation which qualifies the excipients at the proposed levels for topical ophthalmic administration.

2.5 Proposed Clinical Population and Dosing Regimen

The recommended dose is one drop in each affected eye once a day. In the nonclinical sections of the labeling, the applicant bases calculated safety margins on a 0.035 mL drop size. The daily dose per eye is 270 µg/eye/day (540 µg/day total daily dose if administered bilaterally).

3 Studies Submitted

3.1 Studies Reviewed

Pharmacology

- Report TDOC-0016656: Preclinical pharmacology of high-dose (0.7%) olopatadine (AL-4943A) in an *in vivo* model of ocular allergy

Pharmacokinetics

- Report TDOC-0015572: Single dose ocular distribution comparison study between 0.2% Pataday® versus 0.77% high dose olopatadine (final formulation) in NZW male rabbits
- Report TDOC-0013348: Toxicokinetics of AL-4943, AL-24956 (M1) and AL-38189 (M3) in toxicology study N-10-166: AL-4943 (high dose olopatadine): two-week topical ocular irritation and systemic toxicity study in pigmented rabbits
- Report TDOC-0015752: Toxicokinetics of AL-4943 in toxicology study N-11-110: AL-4943AQ (high dose olopatadine): three-month QID topical ocular irritation and systemic toxicity study in pigmented rabbits

Toxicology

- Single dose toxicity
  - Report TDOC-0001715: Seventy two-hour ocular evaluation of olopatadine HCl nasal spray following single-dose administration in New Zealand White rabbits
- Repeat dose toxicity
  - Report TDOC-0013437: AL-4943A (high dose olopatadine): two-week topical ocular irritation and systemic toxicity study in pigmented rabbits
  - Report TDOC-0015211: AL-4943A (high dose olopatadine): three-month QID topical ocular irritation and systemic toxicity study in pigmented rabbits

3.2 Studies Not Reviewed

Pharmacology

- Report 019:39900:0895: Effect of olopatadine on contralateral eye responses in a model of histamine-induced vascular permeability

Safety Pharmacology

- Report 1156: Effects of (b) (4) on the sleep-wakefulness cycle of cats
- Report 137:30:0700: Effects of olopatadine hydrochloride on cloned hERG channels
- Report 89-121(Y): Pharmacological properties of (b) (4) 4679- effects on the central and peripheral nervous systems

Pharmacokinetics

- Report TDOC-0009658: Validation of an HPLC tandem mass spectrometry (HPLC/MS/MS) method for the determination of olopatadine (AL-4943), M1,M2 and M3 in human plasma (K_2EDTA) at tandem labs

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- Report TDOC-0015730: Olopatadine (AL-4943), M1 (AL-24956) and M3 (AL-38189) human K2EDTA plasma concentrations for Alcon Study C-11-036

Repeat dose toxicity

- Systemic administration
  - Report A-90-92: Toxicological study of (b) (4) a 52-week chronic oral toxicity study of (b) (4) in dogs
    -
  - Report A-90-82: 52-week chronic oral toxicity study of (b) (4) in rats

- Ocular administration
  - Report 102:38520:0895: Six month chronic topical ocular irritation and systemic toxicity evaluation of AL-4943A ophthalmic solution in primates
  - Report 030:38520:0395: Six-month topical ocular irritation and systemic toxicity evaluation of AL-4943A ophthalmic solution in rabbits

Genotoxicity

- Report A-88-147: Toxicological study of (b) (4) chromosomal aberration test of (b) (4) on CHL cells *in vitro*
- Report A-88-93: Toxicological study of (b) (4) bacterial reverse mutation assay of (b) (4)
- Report A-90-17: Micronucleus test of (b) (4) administered orally to mice

Carcinogenicity

- Report 92/KKY009/1065: Oncogenicity study by dietary administration to CD-1 mice for 78 weeks
- Report 93/KKY008/0386: (b) (4) Oncogenicity study by dietary administration to F-344 rats for 104 weeks

Reproductive and developmental toxicity

- Report A-89-26: Toxicological study of (b) (4) Fertility study of (b) (4) in rats
- Report A-89-52: Reproduction study of (b) (4) – Teratogenicity study of (b) (4) in rats
- Report A-89-59: Reproduction study of (b) (4) Teratogenicity study of (b) (4) in rabbits

3.3 Previous Reviews Referenced

- NDA 20-688: Patanol®, olopatadine hydrochloride ophthalmic solution, 0.1%
  - Pharm/Tox review conducted by Asoke Mukherjee, Ph.D. (review dated 7-16-1996)
- NDA 21-545: Pataday®, olopatadine hydrochloride ophthalmic solution, 0.2%
  - Pharm/Tox review conducted by Maria Rivera, Ph.D. (review dated 2-24-03).

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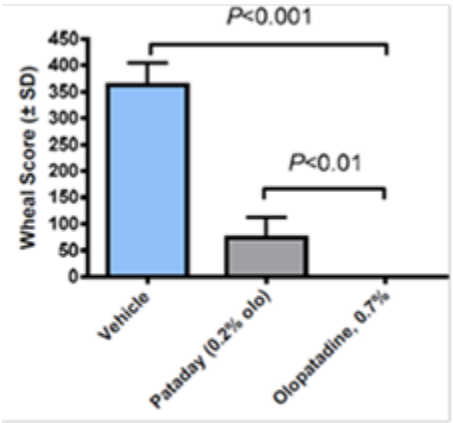
4 Pharmacology

4.1 Primary Pharmacology

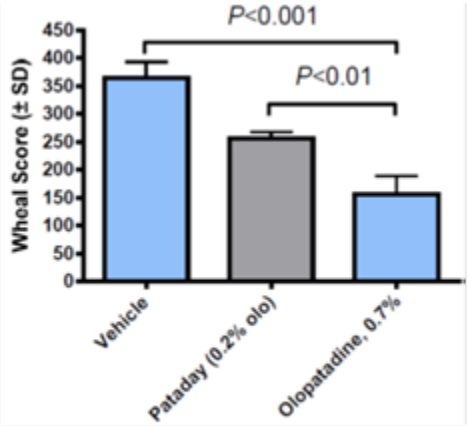
Olopatadine is a H1 receptor antagonist, an inhibitor of pro-inflammatory mediator release from human conjunctival mast cells, and an inhibitor of histamine stimulated cytokine production by human conjunctival epithelial cells. Most of the nonclinical studies to determine the pharmacologic properties of olopatadine were previously submitted under NDA 20-688 and 21-545. For this submission, the applicant conducted one preclinical efficacy pharmacology study, which compared efficacy of Pataday (olopatadine hydrochloride ophthalmic solution, 0.2%) with that of Olopatadine HCl Solution, 0.77% in a preclinical model of histamine-induced vascular permeability. Study results indicated that olopatadine, 0.77% significantly suppresses allergic conjunctival symptoms compared to Pataday and vehicle control.

TDOC-0016656: Preclinical pharmacology of high-dose (0.7%) olopatadine (AL-4943A) in an in vivo model of ocular allergy

Male Hartley VAF guinea pigs (250–300 g) received a single inferior subconjunctival injection of 300 ng histamine dissolved in saline to the right eye. Groups were given a 20 µL topical drop of olopatadine, 0.77%, olopatadine, 0.2% (Pataday) or corresponding vehicle to the right eye at 30 minutes or 24 hours prior to histamine challenge. At 30 minutes post challenge, guinea pigs were euthanized and the area of vascular leakage determined. Olopatadine exhibited significantly greater anti-allergy efficacy in vivo when administered topically in a 0.7% solution as compared with PATADAY® (olopatadine, 0.2%) or vehicle control, when administered either 30 minutes or 24 hours before histamine challenge.



30 minutes



24 hours

4.2 Secondary Pharmacology

Studies describing secondary pharmacology of olopatadine and its metabolites were previously reviewed under NDA 20-688 (Patanol) or NDA 21-545 (Pataday®). Briefly,

> The major olopatadine metabolites across species (including humans) are the N-oxide and N-desmethyl metabolites. Both metabolites showed affinity for the histamine H1 receptor but at lower concentrations than calculated for olopatadine. Weak interactions with the serotonin 5HT2A receptor and norepinephrine transporter were also observed. The N-oxide was evaluated for its ability to inhibit the release of histamine from human conjunctival mast cells. Inhibition was observed with an IC_{50} value of 3.07 mM. Comparing to the IC_{50} of 559 μM obtained for olopatadine in a separate study, the N-oxide showed lower potency than the parent compound. These findings, together with the low plasma levels detected for both metabolites, support that these metabolites are not expected to contribute significantly to olopatadine efficacy or side effects.

4.3 Safety Pharmacology

The effect of olopatadine (3, 10, 30, 100 mg/kg) on electrocardiogram, heart rate and blood pressure was determined in conscious dogs. Olopatadine significantly prolonged QTc by 20 – 40 msec at dose of 100 mg/kg. At the same dose, heart rate was also significantly increased while systolic blood pressure was decreased. At doses of 30 mg/kg or higher, olopatadine increased diastolic blood pressure. It is thought that olopatadine prolongation of the QTc interval was caused by the increase in heart rate. In a study to determine the effect of olopatadine on the central and peripheral nervous systems, olopatadine showed a sedative effect in mice at the highest dose tested, 300 mg/kg.

The doses at which these effects occurred are greatly in excess of therapeutic ophthalmic doses. Therefore, olopatadine is not expected to cause significant adverse effects in humans following topical ocular administration of 0.77% olopatadine hydrochloride ophthalmic solution

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Studies describing the pharmacokinetics, absorption, distribution, metabolism and excretion of olopatadine and its metabolites were previously reviewed under NDA 20-688 (Patanol) or NDA 21-545 (Pataday®). Briefly (from review of NDA 21-545):

> **Absorption**: Following i.v. administration, the elimination olopatadine from plasma was relatively rapid with a t½ of 0.7 hr in rabbits, 5 hr in rats, 7 hr in dogs, and 10

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hr in monkeys. The oral bioavailability of olopatadine was high, ranging from 70% in the rat to 100% in the monkey. In rats and dogs, both C_{max} and AUC increased in a dose-proportional manner over a dose range of 0.3 to 3 mg/kg/day. The volume of distribution at steady-state was moderately low, 1 – 2 L/kg. After a topical ocular dose of 0.15% olopatadine ophthalmic solution in rabbits, maximal plasma levels of 10 ng/mL were reached by 30 minutes, The elimination t½ of olopatadine from plasma following the topical ocular dose was similar to that observed following an i.v. dose (0.8hr).

Distribution: Ocular tissue distribution studies following a topical ocular dose of the 0.15% 14C-olopatadine ophthalmic solution in rabbits showed that radioactivity was absorbed into the eye and reached maximal tissue levels within 0.5 to 1 hour. Tissues at the site of dosing (i.e. cornea and conjunctiva) had the highest concentration of 1.85 µg equivalents/g and 0.398 µg equivalents/g, respectively. Posterior tissue (retina, vitreous humor) levels were 20- to 100-fold lower or not quantifiable. Radioactivity in the ocular tissues was eliminated with t½ of 1 to 2 hours except for the lens (9 hours). Although the lens has a somewhat longer t /12, the levels of radioactivity were 60-fold lower than those in aqueous humor. Half-lives of radioactivity in pigmented tissues of Dutch Belted rabbits were several fold longer than those observed in non-pigmented New Zealand white rabbits indicating some degree of melanin binding.

The distribution of radioactivity was studied in tissues of male rats following a single 1 mg/kg oral dose of 14C-olopatadine. Maximal concentrations in tissues, blood and plasma were generally found at 0.5 to 1 hr with the highest concentrations found in the GI tract (6.05 µg equivalents/g), liver (1.93 µg equivalents/g), and kidney (1.71 µg equivalents/g). The plasma C_{max} was 209 ng equivalents/mL at 0.5 hr. Concentrations of radioactivity in the brain (0.01 µg equivalents/g) were very low indicating little transfer across the blood/brain barrier. Radioactivity was eliminated from most tissues in parallel to plasma in a biphasic manner with an elimination t½ of 16.8 hours. There was no evidence of accumulation in any tissue with most of the radioactivity eliminated by 168 hours post-dose.

Radioactivity drug equivalents crossed the placental barrier and distribute into tissues of the fetus. However, the levels of radioactivity in the fetus were consistently lower than those in maternal plasma with tissue:plasma ratios of approximately ≤ 0.3. Olopatadine and radioactive drug equivalents were identified in the milk of lactating rats. Unchanged olopatadine was the major drug-related constituent in milk (approximately 74% of the total radioactivity in milk).

The distribution of radioactivity was also studied in male rats following daily 1 mg/kg oral doses of ^{14}C-olopatadine for 21 days. Accumulation of radioactive drug

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equivalents was observed in several tissues with the most notable being liver and kidney.

In vivo blood partitioning data showed no significant binding of radioactive drug equivalents in red blood cells following a single 1 mg/kg oral dose of 14C-olopatadine. Olopatadine was found to be moderately bound to rat (63%), guinea pig (67%), dog (56%), monkey (49%), and human (55%) plasma proteins in vitro. For all species, the percent of bound drug was independent of drug concentration over a range of 0.1 ng equivalents/mL to 1000 ng equivalents/mL.

Metabolism: The major metabolic pathways of olopatadine were found to involve N-demethylations and N-oxidation of the dimethylamino-propylidene side chain, hydroxylation of the dihydrodibenz[b,e]oxepine ring at C-8 and sulfate conjugation of the C-8 hydroxyl.

The metabolites formed in animals and humans are similar but do differ in the relative proportions of each. The major metabolites in animals and humans are N-desmethyl olopatadine and olopatadine N-oxide. N-desmethyl olopatadine is the major metabolite in rat plasma (7.7%), while in dogs olopatadine N-oxide is the major plasma metabolite (11%) (refer to the table below). In humans, the major plasma metabolite is olopatadine N-oxide (6.6% of 80 mg olopatadine oral dose). However, in both animals and humans olopatadine is not extensively metabolized and unchanged olopatadine is the major constituent in plasma, urine and excreta.

METABOLITES ON PLASMA, URINE, FECES, AND BILE FOLLOWING ORAL DOSES OF ^{14}C-OLOPATADINE (1 MG/KG) TO FASTING RATS AND DOGS

Matrix	Species Sex	Time (hr)	Olopatadine	M1	M2	M3	M4	M5	M6	Unknown
Plasma	Rat (M)	0.5	66.4 ± 5.8	7.7 ± 1.0	0.9 ± 0.5	0.5 ± 0.1	0.8 ± 0.2	1.8 ± 0.4	3.1 ± 1.9	19.0 ± 3.1
	Rat (M)	4	35.5 ± 11.6	7.2 ± 0.8	0.8 ± 0.5	0.7 ± 0.8	1.0 ± 0.7	1.3 ± 0.2	2.4 ± 1.3	51.1 ± 11.0
	Dog M)	0.5	71.1 ± 9.9	2.1 ± 1.4	1.1 ± 1.1	11.0 ± 2.2	N.D.	0.3 ± 0.5	N.D.	14.6 ± 6.7
	Dog M)	1[a]	53.7	3.1	0.6	8.8	N.D.	0.4	N.D.	33.6
	Dog M)	2[b]	56.3 ± 7.7	4.7 ± 1.1	0.5 ± 0.9	10.1 ± 1.3	0.5 ± 0.3	1.9 ± 1.7	1.0 ± 0.9	24.9 ± 5.2
Urine	Rat (M)	0 - 24	27.3 ± 3.4	6.0 ± 0.7	0.7 ± 0.2	0.5 ± 0.1	0.1 ± 0.0	1.1 ± 0.2	1.3 ± 0.3	4.7 ± 0.8
	Rat (F)	0 - 24	31.3 ±3.9	3.4 ± 0.7	0.5 ± 0.3	0.8 ± 0.1	0.1 ± 0.0	0.4 ± 0.2	0.6 ± 0.2	8.9 ± 1.3
	Dog M)	0 - 24	51.6 ± 5.3	4.5 ± 1.0	1.2 ± 0.3	1.9 ± 1.0	0.1 ± 0.1	1.3 ± 0.6	0.6 ± 0.3	10.8 ± 3.5
Feces	Rat (M)	0 - 24	19.4 ± 4.6	2.6 ± 0.7	0.4 ± 0.2	0.2 ± 0.1	0.6 ± 0.3	5.1 ± 0.9	4.1 ± 0.7	13.7 ± 1.8
	Dog (M)	0 - 48	6.0 ± 1.7	1.8 ± 0.5	0.2 ± 0.2	N.D.	0.4 ± 0.2	2.2 ± 0.9	0.8 ± 0.3	11.0 ± 0.3
Bile	Rat (M)	0 - 24	5.3 ±1.1	2.6 ± 0.2	0.3 ± 0.1	0.4 ± 0.1	6.3 ± 1.5	2.3 ± 0.7	7.3 ± 0.9	23.2 ± 3.2

Plasma values = mean % radioactivity in plasma ± S.D; Urine, feces, and bile values = mean % administered radioactivity ± S.D.; n = 5 (rats); n = 4 (dogs); [a]n=2; [b]n=3; N.D. = under detection limit

M1: N-Desmethyl olopatadine; **M2**: N-Didesmethyl olopatadine; **M3**: Olopatadine N-oxide; **M4**: 8-Hydroxy olopatadine sulfate; **M5**: 8-Hydroxy olopatadine; **M6**: 8-Hydroxy olopatadine N-oxide

Excretion: Olopatadine was excreted into the urine, feces, and bile. In rats following a 1 mg/kg i.v. dose, approximately equal amounts of the dose were recovered in urine (51%) and feces (44%). In bile duct cannulated rats, 45% of a 1 mg/kg oral dose was recovered in the bile. Thirty percent of the radioactivity in the bile was found to be reabsorbed, indicating that approximately 10% of the

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administered dose underwent enterohepatic recirculation. In dogs, the percent of dose recovered in urine was much higher than in feces (73% vs 23%) following a 1 mg/kg oral dose/ The constituent in the urine of rats, dogs, and monkeys was unchanged olopatadine. The percentages of dose recovered as unchanged olopatadine in the urine of these species art a 1 mg.kg oral dose, were 27%, 52%, and 40%, respectively.

The following studies were submitted to support the new formulation and API concentration:

Study A00304 (TDOC-0015572): Single dose ocular distribution comparison study between 0.2% Pataday® versus 0.77% high dose olopatadine (final formulation) in NZW male rabbits

Comparative tissue distribution of olopatadine was determined following topical ocular administration of 0.2% Pataday or 0.77% olopatadine to male New Zealand white rabbits (3 animals/time point/treatment). Test article was administered as a single 30 µL bilateral dose. Plasma and ocular tissues (aqueous humor, choroid, bulbar conjunctiva, cornea, iris-ciliary body, lens and retina) were collected up to 24 hours post-dose. Tissue concentrations of olopatadine were determined by a qualified liquid chromatography tandem mass spectrometry analytical method.

Plasma pharmacokinetic values remained low but were dose proportionately higher in the 0.77% olopatadine treated animals compared to 0.2% Pataday treated animals, indicating a low systemic exposure after topical ocular administration. In the ocular tissues, the C_{max} values, from highest to lowest, were observed in cornea, bulbar conjunctiva, aqueous humor, iris-ciliary body, choroid, retina and lens after the administration of the 0.2% PATADAY® formulation. The C_{max} values in ocular tissues following administration of 0.77% AL-4943A HD olopatadine formulation from highest to lowest were observed in bulbar conjunctiva, cornea, iris-ciliary body, aqueous humor, choroid, retina, and lens. Time to maximal tissue concentration (T_{max}) for each tissue ranged from 0.5 to 2 hours for most tissues, except the lens where T_{max} was not achieved until 4 or 8 hours for the 0.2% and 0.77% formulations, respectively. Generally, C_{max} and $AUC_{0\text{-last}}$ values in ocular tissues increased proportionally to dose when comparing the 0.2% formulation to the 0.77% formulation.

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Treatment	Matrix	C_{max} (ng/mL or ng/g)		T_{max} (h)	t½ alpha (h)	t½ *z* (h)	$AUC_{0\text{-last}}$ (ng·h/mL or ng·h/g)		T_{last} (h)
		Mean	Std dev.				Mean	Std dev.	
0.2% Pataday	Aqueous humor	80.0	15.1	2.00	NC	2.37	331	17.5	24
	Choroid	17.7	6.70	1.00	1.01	4.65	46.7	3.82	24
	Bulbar conjunctiva	609	212	0.500	0.806	NR	781	61.5	12
	Cornea	720	366	1.00	NC	2.82	1960	134	24
	Iris-Ciliary body	77.0	26.2	1.00	NC	2.47	297	15.3	24
	Lens	1.69	0.516	4.00	NC	NR	25.3	1.58	24
	Plasma	4.96	1.07	0.500	0.765	NR	9.81	0.699	24
	Retina	3.27	1.35	1.00	1.10	NR	8.34	0.665	24
0.77% formulation	Aqueous humor	206	36.6	2.00	NC	2.20	853	47.1	24
	Choroid	94.7	40.5	0.500	0.929	NR	202	19.5	24
	Bulbar conjunctiva	3000	1730	0.500	1.44	2.20	5750	748	12
	Cornea	2230	338	0.500	NC	2.78	5340	236	24
	Iris-Ciliary body	254	64.6	0.500	NC	3.02	857	43.2	24
	Lens	4.30	1.54	8.00	NC	NR	75.6	3.68	24
	Plasma	14.5	1.65	0.500	1.00	NR	29.7	1.60	24
	Retina	23.9	6.84	0.500	0.867	3.06	39.8	5.71	24

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Treatment	Matrix	Cmax	AUC
0.77% : 0.2% exposure ratio	Aqueous humor	2.6	2.6
	Choroid	5.4	4.3
	Bulbar conjunctiva	4.9	7.4
	Cornea	3.1	2.7
	Iris-Ciliary body	3.3	2.9
	Lens	2.5	3.0
	Plasma	2.9	3.0
	Retina	7.3	4.8

6 General Toxicology

6.1 Repeat-Dose Toxicity

Study title: AL4943A: Two-week topical ocular irritation and systemic toxicity study in pigmented rabbits

Study no.: A00304 (TDOC-0013437)
Study report location: N001 (eCTD0000) Section 4.2.3.2
Conducting laboratory and location: Alcon Research Ltd
6201 S. Freeway, Fort Worth, TX 76134
Date of study initiation: 1-26-2011
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity:
- Sulfobutylether beta Cyclodextrin (SBCD) formulation: 10-61663-1/
- Hydroxypropyl beta Cyclodextrin (HPBCD) formulation: 10-61509-1

Key Study Findings

- No ocular irritation or systemic toxicity was observed following four times daily, topical ocular (bilateral) administration of 0.7% HD Olopatadine (AL-4943A) in either Sulfobutylether beta Cyclodextrin (SBCD) or Hydroxypropyl beta

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Cyclodextrin (HPBCD) formulations. The HPBCD formulation is similar but not identical to the to-be-marketed clinical formulation.

Methods

Doses:	0.7%
Frequency of dosing:	QID (four times daily) for two weeks ~2.75 – 2.95 mg/animal/day
Route of administration:	Topical ocular drop
Dose volume:	Varied with formulation: 49.1 – 55 µL / drop
Formulation/Vehicle:	Sulfobutylether beta Cyclodextrin (SBCD) or hydroxypropyl beta Cyclodextrin (HPBCD)* based formulations
Species/Strain:	Pigmented (New Zealand White x Red, F1)
Number/Sex/Group:	4/sex/group
Age:	~7 months
Weight:	3.2 – 3.7 kg
Deviation from study protocol:	None which affected conduct or interpretability

Observations and Results

Mortality (days of clinical observations: once daily, all other days: twice daily)

- There were no deaths during the study

Clinical Signs (Prescreen, Days 3,7, and 10, and on the day of necropsy)

- No adverse clinical signs were attributed to the test article

Body Weights (Prescreen and on Study Days 7 and 14)

- There were no statistically significant or toxicologically relevant effects on body weight during the study.

Ophthalmology

- Slit lamp biomicroscopy [Prescreen and on Study Days 3, 7, 14; ocular scoring system by Hackett and McDonald (1996)]
  - No test article-related ocular findings

- Dilated lens evaluations (Prescreen and Study Day 14)
  - No test article-related ocular findings

- Indirect ophthalmoscopy (Prescreen, Study Day 14)
  - Normal fundi in both eyes of all animals, in all groups, was reported throughout the study

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- Pachymetry (Prescreen, Study Days 6 and 13)
  - No test article related changes in corneal thickness were reported

- Intraocular pressure (Prescreen, Study Days 6 and 13)
  - No test article related changes in intraocular pressure were reported.

Hematology (no more than two days prior to necropsy)

- No changes in hematological parameters were attributed to the test article

Clinical Chemistry (no more than two days prior to necropsy)

- No changes in clinical chemistry parameters were attributed to the test article

Gross Pathology (Day 15)

- No gross pathology was attributed to the test article

Organ Weights (Day 15)

- No changes attributed to the test article

Histopathology

Adequate Battery: Ocular tissues and adnexa only

Peer Review: No

Histological Findings: No microscopic findings were attributed to the test article

Toxicokinetics (Study Days 1 and 14)

Systemic exposure to olopatadine and its two metabolites, AL-24956 (M1; N-desmethyl olopatadine) and AL-38189 (M3; olopatadine-N-oxide) was assessed. Systemic exposure to olopatadine, M1 and M3 was demonstrated. There were no detectable levels of M3 on Study Day 1, although there were detectable levels on Study Day 14. No statistically significant gender differences for the C_{max} and $AUC_{0\text{-}4h}$ values were observed.

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Group	Day	Analyte	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-4h} (ng·h/mL)
0.7% olopatadine with SBCD*	1	Olopatadine	0.133	0.625	0.396
		AL-38189	BLQ	BLQ	NC
		AL-4943	8.79	0.500	21.7
	14	Olopatadine	0.215	1.13	0.629
		AL-38189	0.108	1.83	0.0876
		AL-4943	12.7	0.625	34.0
0.7% olopatadine with HPBCD*	1	Olopatadine	0.118	1.38	0.339
		AL-38189	BLQ	BLQ	NC
		AL-4943	8.79	0.688	25.9
	14	Olopatadine	0.241	1.13	0.681
		AL-38189	0.0999	1.50	0.0730
		AL-4943	15.2	0.500	39.2

*average drop size was 52.6µL for the SBCD formulation and 49.1µL for the HPBCD formulation
BLQ = below limit of quantitation (0.05 ng/mL); NC=not calculated

Dosing Solution Analysis

- All formulations were within specified acceptance limits

Study title: AL-4943A (High Dose Olopatadine): Three-month QID topical ocular irritation and systemic toxicity study in pigmented rabbits

Study no.:	N-11-110/TDOC-0015211
Study report location:	N001 (eCTD0000) Section 4.2.3.2
Conducting laboratory and location:	Alcon Research, Ltd., 6201 South Freeway, Fort Worth, TX 76134
Date of study initiation:	1-11-2012
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	HD Olopatadine Ophthalmic Solution, 0.7%, 1-501304-1, 99.36%

Key Study Findings

- No adverse or toxic effects were attributed to the test article
- The NOAEL, 0.77% QID, represents a ~4-fold ocular safety margin over the proposed clinical dose of 0.77%, QD.
- The clinical formulation used qualifies the excipients hydroxypropyl-γ-cyclodextrin and povidone K29/32 to (b) (4) %, respectively, for topical ophthalmic solutions.

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Methods

Doses:	0.77%
Frequency of dosing:	Bilateral, 4 times per day for 91 days Total daily dose: 1.23 mg/eye/day
Route of administration:	Topical ocular
Dose volume:	0.04 mL/drop
Formulation/Vehicle:	To-be-marketed formulation
Species/Strain:	Rabbit (pigmented), New Zealand White X Red, F1
Number/Sex/Group:	4/sex/group
Age:	4 – 5 months
Weight:	2.6 – 3.1 kg
Deviation from study protocol:	None which affected conduct or interpretability

Observations and Results

Mortality (Twice daily)

- There were no deaths during the study

Clinical Signs (Prescreen, once weekly thereafter, and on the day of necropsy)

- No adverse clinical signs were attributed to the test article

Body Weights (Prescreen and on Study Days 7, 13, 20, 27, 41, 55, 69, 87, and 92)

- There were no statistically significant or toxicologically relevant effects on body weight during the study.

Ophthalmology

- Slit lamp biomicroscopy [Prescreen and on Study Days 1, 7, 14, 21, 28, 42, 56, 70, and 91; ocular scoring system by Hackett and McDonald (1996)]
    - There were no test article-related ocular findings.

- Indirect ophthalmoscopy (Prescreen and on Study Days 28, 56, and 9)
    - Normal fundi in both eyes of all animals, in all groups, was reported throughout the study

- Pachymetry (Prescreen and on Study Days 7, 13, 27, 55, and 90)
    - No test article related changes in corneal thickness were reported

- Intraocular pressure (Prescreen and on Study Days 7, 13, 27, 55, and 90)
    - No test article related changes in intraocular pressure were reported.

Hematology (Study Day 90)

- No changes in hematological parameters were attributed to the test article

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Clinical Chemistry (Study Day 90)

- No changes in clinical chemistry parameters were attributed to the test article

Gross Pathology (Study Day 92)

- No gross pathology was attributed to the test article

Organ Weights (Study Day 92)

- No changes attributed to the test article

Histopathology

Adequate Battery: Yes

Peer Review: No

Histological Findings: Findings were limited and considered incidental. No microscopic pathology was attributed to the test article.

Toxicokinetics (Study Days 1, 44, and 91, prior to, 0.5, 1, and 4 hours after the last daily dose)

- Systemic exposure to olopatadine and its metabolites, AL-24956 (M1) and AL-38189 (M3), was demonstrated. No statistically significant gender differences in the C_{max} and $AUC_{0\text{-}4\ h}$ values were observed. Olopatadine concentrations were higher than the concentrations of its metabolites. AL- 38189 (M3) exhibited the lowest concentrations and was only slightly higher than the limit of quantitation for some animals up to 1 h post dose. The C_{max} and $AUC_{0\text{-}4\ h}$ values on Study Day 91 showed a statistically significant increase from Study Day 1 for olopatadine and its metabolite, AL-24956 (M1), indicating the possibility of accumulation. However, there was no statistically significant ($p > 0.05$) differences for the C_{max} and $AUC_{0\text{-}4\ h}$ values for AL-38189 (M3) between the Study Days 1 and 91.

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Analyte	Study Day	C_{max} (ng/mL)	AUC_{0-4h} (ng·h/mL)
Olopatadine (AL-4943)	1	9.46	25.8
	44	11.1	30.8
	91	15.1	37.4
M1 (AL-24956)	1	0.110	0.157
	44	0.158	0.369
	91	0.200	0.543
M3 (AL-38189)	1	0.110	0.0262
	44	0.117	0.120
	91	0.135	0.0598

Dosing Solution Analysis

- Test article remained within the set specification ([redacted] (b) (4) % of label), and therefore was considered stable for this study

7 Genetic Toxicology

The studies to determine genotoxic potential of olopatadine were previously reviewed under NDA 20-688 (Asoke Mukherjee, Ph.D., dated 7-16-1996). A summary of given in the following table.

GENOTOXICITY STUDIES WITH OLOPATADINE

Study	System	Concentration / Dose	Results
In vitro Bacterial Reverse Mutation, TR# A-88-93, Module 4, Vol. 17	*S. typhimurium* (TA98, TA100, TA1535, TA1537), *E. coli* (WP2 *uvrA*)	156.25-5000 μg/plate ± S9	Negative
In vitro Mutation Chromosome Aberration, TR# A-88-147, Module 4, Vol. 17	Chinese hamster lung cells	1.5-3.0 mM without S9 and 5.0-8.0 mM with S9	Negative
Micronucleus Assay, TR# A-90-17, Module 4, Vol. 17	Male S1c:ICR Mice	100, 200, 400 mg/kg (single dose); 400 mg/kg/day (4-days)	Negative

8 Carcinogenicity

The carcinogenicity studies conducted with olopatadine ([redacted] (b) (4) were previously reviewed under NDA 20-688 (Asoke Mukherjee, Ph.D., dated 7-16-1996). A summary of the studies is given in the following table.

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CARCINOGENICITY STUDIES WITH OLOPATADINE

Study	Route	Duration	Dose Levels	Results
Mouse/CD-1 TR #92/KKY009/1065 (Module 4, Vol. 18)	Oral/Diet	78-weeks	50, 160, 500 mg/kg/day	Negative
Rats/F344 TR# 93/KKY008/0386 (Module 4, Vol. 22)	Oral/Diet	104-weeks	0, 20, 65, 200 mg/kg/day	Negative

9 Reproductive and Developmental Toxicology

The studies conducted to determine the reproductive and developmental toxicity potential of olopatadine ((b) (4) were previously reviewed under NDA 20-688 (Asoke Mukherjee, Ph.D; 7-16-1996).

Fertility study in rats (segment I)

Groups of rats (22/sex) were orally dosed with 0, 6, 50 or 400 mg/kg. Male rats were treated for 9 weeks before mating and through the mating period. Female rats were treated during the 14 days prior to mating through gestation day 7. Pregnant dams were sacrificed on gestation day 20.

Three males at 400 mg/kg died on days 17, 26 and 90 of dosing though attribution to the test article was not established. Males showed mydriasis in all treated groups. Relaxation of the scrotum was also noted in some males after the second or third dose. Abnormal respiratory sounds occurred in females and males following drug administration. Body weight gain and food consumption were reduced in male and female rats at 400 mg/kg. At necropsy, male rats in the 400 mg/kg/day group showed dilatation of the renal pelvis.

Fertility results are shown in the following table. The number of corpora lutea and mean implantation were affected at the 400 mg/kg dose, however, the reviewer suggested that the dose is considered to have maternal toxicity. Male fertility was also affected at the 400 mg/kg dose. The reviewer states that the 50 mg/kg dose had no effect on male or female fertility.

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Dose	Control	6 mg/kg/day	50 mg/kg/day	400 mg/kg/day
# of dams	20	17	21	15
Mean implantation	16.1	14.9	15.0	13.7
% of corpora lutea	96.4	91.3	90.5	87.3
Live fetuses (m,f)	157,156	131, 107	152, 148	99, 89
Total live fetuses	312	238	300	188
Early death	10	15	11	16
% death to total	45%	64.7%	38.1%	53.3%
Late death	0	0	3	2
Corpora lutea	334	278	360	234
Body wt, live fetuses (m,f)	2.9, 2.7	3.0, 2.7	2.9, 2.7	3.0, 2.8

Segment II: Teratogenicity study of olopatadine in rats:
Pregnant female Jcl-Wistar rats were orally administered olopatadine (0, 60, 200 or 600 mg/kg/day) daily starting on gestation day 7 through gestation day 17 per standard protocol. Oxatomide served as the positive control. A subgroup of animals was sacrificed on Day 20 of gestation and fetuses removed by Caesarian section while another group was allowed to deliver, nurse and then sacrificed on Day 22 postpartum for the calculation of the number of implants and birth index. Weaned pups were raised and examined for behavioral, sensory and reproductive ability tests.

Maternal Toxicity: Mydriasis was observed at the 600 mg/kg dose. One rat at the 600 mg/kg dose died on Day 8, though attribution to the test article was not established.. Hyperemia and congestion of the ocular fundus were reported in one animal of each olopatadine treated group. At 200 and 600 mg/kg, abnormal respiratory sounds were reported.

The body weight and food consumption of dams did not change significantly from controls during gestation or lactation. The data suggests that olopatadine at all doses was related to an increase in post implantation loss based on early death. At the time, the applicant argued that the findings were within an acceptable range though the reviewer disagreed. Fetal body weight was also decreased by ~10% at the 600 mg/kg dose. Results are presented in the following table.

Dose (mg/kg/day)	Control	60	200	600	Oxatomide
# of dams	24	24	22	22	24
Implantations	314	340	308	324	354
Alive (% of implantations)	97	92.8*	93.5*	92.8	81.6**
Early death (% of implantations)	2.9	7.2*	6.3*	7.2	15.1**
Late death (% of implantations)	0	0	0.3	0	3.3**
B.W. (m, f)	3.1, 2.9	3.1, 2.9	3.0, 2.8	2.8**, 2.6**	2.8**, 2.6**

* $p<0.05$, ** $p<0.01$

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Skeletal and external abnormalities
At the 60 mg/kg dose, cleft palate was observed in 2 fetuses from two different litters, though no such findings were reported at higher doses. The reviewer of NDA 20-688 considered the finding incidental and that olopatadine was not associated with external abnormalities. At the 600 mg/kg dose, fusion of the ribs in two fetuses was observed. Among skeletal variation, delayed ossification of the metacarpus was noted in 11 pups from 2 litters in the 600 mg/kg/day group. These skeletal abnormalities did not reach statistical significance. Ossification of the coccygeal vertebra and sternebrae were also observed at the 600 mg/kg/day dose. Collectively, the skeletal findings suggest developmental delay at the highest dose tested.

Visceral abnormalities
The data suggest that visceral abnormalities occurred at the 200 and 600 mg/kg/day treatments.

	Control	60	200	600	Oxatomide
# fetuses	102 (24) *	106 (24)	97 (22)	98 (21)	95 (23)
Left umbilical artery	0	0	2 (2)	1 (1)	0
Bilateral azygos vein	1 (1)	0	3 (3)	4 (4)	3 (3)
Abnormal origin artery from arch	0	0	0	0	14 (5)
Right azygos vein	0	0	0	1 (1)	2 (2)

* (#) = number of litters

No effect on duration of pregnancy, nor viability, survival and development of the F_1 generation were reported. Body weight gain in the F_1 generation was not affected by treatment. Male rats in the F_1 generation showed shortening of the learning behavior (swimming time) after weaning in a dose related manner. However, the reproductive performance of F_1 male and female rats was not affected by treatment. The reviewer concluded that the highest dose tolerated in the study was 200 mg/kg and that the dose of 600 mg/kg was maternally toxic. Given the conclusion of maternal toxicity, the reviewer stated that the delayed ossification of the coccygeal vertebrae at the 600 mg/kg dose did not contribute in the determination of the teratogenic potential of olopatadine.

Reviewer's note: In this study, administration of 60 mg/kg/day olopatadine to pregnant rats on gestation days 7 – 17 resulted in an increase in post implantation loss based on early death and cleft palate in 2 fetuses. At the time of the original review of this study (see Asoke Mukherjee, 7-16-1996), the reviewer recommended that this LOAEL dose be used in the labeling to establish an exposure margin. In the review, the following text

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is recommended for the labeling describing these findings (text bolded for contrast with information below):

> Pregnancy Category C: Olopatadine was found not to be teratogenic in rats and rabbits. However, rats (b) (4) treated at (b) (4) (b) (4)

The recommended dosing regimen for Patanol (0.1% olopatadine) is 1 – 2 drops twice per day with bilateral administration if necessary. In order to yield the margins reported in the labeling, the reviewer must have assumed 2 drops per dose per eye, twice per day (4 drops/eye/day or 8 drops/day total when administered bilaterally) with a 45 µL drop size. At this amount, the maximum daily ocular dose would be 0.006 mg/kg for a 60 kg adult. Comparing this dose to the (b) (4) in the rat embryofetal development study would yield a margin o (b) (4).

However, in the current labeling for Patanol®, the following is stated (text bolded for contrast with above):

> Pregnancy Category C. Olopatadine was found not to be teratogenic in rats and rabbits. However, rats treated at **600 mg/kg/day**, or 93,750 times the MROHD and rabbits treated at 400 mg/kg/day, or 62,500 times the MROHD, during organogenesis showed a decrease in live fetuses

It is unknown why the current labeling does not include the findings at (b) (4) but lists the dose which decreased the number of live fetuses as 600 mg/kg.

Segment II oral teratogenicity study of olopatadine in rabbits

Female rabbits (KBL:JW) were orally treated with 25, 100 or 400 mg/kg/day from gestation day 6 to 18. Animals were sacrificed on Day 29.

At the time of Caesarian section, one fetus from an animal treated with 100 mg/kg was reported as descending into the vagina, suggesting premature delivery/abortion. Polypoid process of the endometrium was also reported at this dose. Body weight gain and food consumption were not affected by treatment. The litter data is shown in the following table. The reviewer stated that the data showed that the number of fetuses alive per litter or as a percentage of total implantation number were reduced in all treatment groups compared to control without statistical significance. At 400 mg/kg, there was an increase in the late death compared to control. The body weight of live fetuses was not changed. External examinations did not show any abnormalities compared to control dams. At the 100 and 400 mg/kg doses, abnormal alignment of the vertebrae was reported but did not reach statistical significance. No visceral abnormalities were observed. The reviewer concluded that no teratogenicity was shown up to 400 mg/kg.

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Dose (mg/kg)	Control	25	100	400
# of dams	16	13	15	15
Mean implantation	9.7	9.4	7.4	7.9
Total fetuses (alive)	137	99	99	98
Early death (% implantations)	10.6	16.9	8.5	13.2
Late death (% implantations)	2.3	5.5	2.3	7.4
Total corpora lutea	206	172	170	168
Body weight (fetuses)	43.3	44.47	45.81	47.19
Placental weight	5.02	5.12	5.44	5.77

Peri- and postnatal development of fetuses in rats treated with olopatadine (segment III):

Pregnant female rats (SPF jcl:Wistar) were orally treated with 60, 200 or 600 mg/kg/day olopatadine on gestation days 17 through post-partum day 21. At the end of lactation day 22, F_0 dams were sacrificed and corpora lutea and number of implantation sites were counted. Number of still births, the sex ratio and body weights of F_1 pups were noted. On the fourth day after birth, litters were culled. One male and one female from each litter were matured and allowed to mate at approximately week 10. The copulation and fertility index was calculated. Pregnant F_1 females were necropsied on Day 20 of gestation for examinations.

At 600 mg/kg/day dose, 6 animals F_0 dams died before sacrifice (1 on gestation day 19, 3 on gestation Day 18, and 1 on post-partum Days 9 and 11). This dose has been noted as intolerable in other studies and likely contributed to death. Surviving dams in the 600 mg/kg/day group showed poor lactation condition. During gestation, food consumption was reduced in dams treated with 600 mg/kg/day and all treated dams during lactation. The reviewer concluded that low food consumption impaired body weight gain at 600 mg/kg during the dosing period. A similar effect on food consumption was reported at the 200 mg/kg dose from post parturition day 15. However, the magnitude of changes in the body weight gain at 200 mg/kg dose was smaller than that for 600 mg/kg. The reviewer stated that the data clearly suggest that 600 mg/kg dose had maternal toxicity and the 200 mg/kg dose was tolerated.

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Mean Food consumption (g) during nursing period

Dose (mg/kg)	Day 1	Day 5	Day 8	Day 15	Day 22
Control	13.0	32.5	35.2	48.3	54.7
60	14.0	30.6	31.6	42.0	45.8*
200	13.9	28.5	29.2	37.4**	40.1**
600	12.4	20.8**	21.7**	29.4**	29.0**

* $p<0.05$, ** $p<0.01$

In the F_0 females treated with 600 mg/kg including dead animals, atrophy of the thymus and spleen, hemorrhage of the thymus, lungs, stomach and uterus, hydronephrosis, distension of ureter and bladder and lymph node swelling were reported.

The 600 mg/kg dose was toxic for delivery and nursing performance of the F_0 dams and pre- and post-natal survival of F_1 pups. At the 60 and 200 mg/kg doses, increased death among the weaning pups was also noticed. The reviewer concluded that based on the data, the 60 and 200 mg/kg doses should be considered toxic to the postnatal development of pups. The results of Caesarian section are presented in the following table.

	Control	60 mg/kg/day	200 mg/kg/day	600 mg/kg/day
# of dams	25	24	24	21
Duration of pregnancy	21.9	21.9	22	22
Birth to Day 4				
# of new births	330	322	314	261
# of still births (%)	9 (2.6%)	5 (1.4%)	6 (1.8%)	3 (1.1%)
Number of dead	22 (6.9%)	57 (18%)	88 (28.6%)	133 (51.6%)
# alive on Day 4	93.2%	82%	71.4%	48.4%
Days 4 – 22				
# new births (culling)	193	172	145	93
# dead	2	3	5	11
# weaning	191	169	140	82
After weaning				
# breeding	144	129	105	63
# of dead animals	0	0	0	5
# of live animals	144	129	105	58

At 600 mg/kg, delayed opening of the vagina was noted. No other external abnormalities were observed in the F_1 generation. Body weight gain of F_1 pups at 60 and 200 mg/kg were reduced from Day 14 onward though did not reach statistical significance through Day 21. Thereafter, a statistically significant decrease in body weight gain was also observed at 60 and 200 mg/kg doses. Changes in the body

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weight gain of F_1 pups at 600 mg/kg were more severe than the control from postnatal day 4 and statistically significant compared to control. F_1 pups did not show development anomalies in reflex and swimming activities. Relative organ weights of the spleen, lung, thymus and brain were increased for male F_1 rats at 600 mg/kg. The relative organ weights of the brain and ovary were increased in female F_1 rats at 600 mg/kg dose. No skeletal abnormalities were observed in F_1 rats. Reproductive performance of F_1 rats was not affected. F_2 pups were normal.

The experiment was repeated with 6 and 20 mg/kg doses. The food consumption of F_0 dams was decreased from post-partum day 11 at the 20 mg/kg dose. Body weight gain of F_1 pups was also reduced at 6 and 20 mg/kg doses during the weaning period. Number of variation in the cervical ribs was noted at the 20 mg/kg dose.

In a third Segment III study, doses of 2 mg/kg/day and 4 mg/kg/day were administered. Body weight gain was suppressed in the F_1 generation (up to 5%) at the 4 mg/kg dose, with peak effect occurring toward the end of the lactation period. This effect was fully recoverable during the post weaning period. At the 2 mg/kg dose, toxicity to F_1 pups was not evident, and this dose was considered by the sponsor to be the “non-toxic” dose for F_1 development. When dams of the 60 mg/kg dose group nursed F_1 pups from the control group, a similar effect on body weight gain was observed. Based on these data, it was concluded that olopatadine was excreted in breast milk and affected the weight gain of F_1 pups.

Reviewer’s note: In the current labeling for Pataday and that proposed for the current formulation, the following labeling statement has been proposed:

> Further, rats treated with 600 mg/kg/day of olopatadine during late gestation through the lactation period showed a decrease in neonatal survival and body weight.

However, it was established in the 3 separate Segment III studies that effects on weanlings were apparent at maternal doses as low as 4 mg/kg. A decrease in neonatal and weanling survival was observed at doses as low as 60 mg/kg/day, and decreases in body weight gain occurred at doses as low as 4 mg/kg/day. Therefore, the updated labeling suggested by the Agency is reflective of these reported observations.

10 Integrated Summary and Safety Evaluation

The applicant proposes a new formulation of olopatadine containing 0.77% of the active ingredient. The sponsor conducted pharmacology, ocular distribution and up to a 3-month ocular toxicity study to support the new formulation. Olopatadine exhibited significantly greater anti-allergy efficacy in vivo when administered topically in a 0.7% solution as compared with olopatadine, 0.2%. In pigmented rabbits, no adverse or toxic effects were attributed to olopatadine, 0.77% when administered up to four times daily for 3 months. The NOAEL, 0.77% QID, represents a ~4-fold ocular safety margin over the proposed clinical dose of 0.77%, QD. The formulation used also qualifies the

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excipients hydroxypropyl-γ-cyclodextrin and povidone K29/32 to (b) (4) %, respectively, for topical ophthalmic solutions. Changes to the labeling, particularly regarding pregnancy and teratogenicity, reflect an updated review of the presented data.

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/s/

AARON M RUHLAND
12/31/2014

LORI E KOTCH
12/31/2014

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 206276 **Applicant: Alcon Research Ltd.** **Stamp Date: 7-30-2014**

Drug Name: Olopatadine hydrochloride ophthalmic solution 0.77% (Pazeo®) **NDA Type: 505(b)(1); Original NDA submission; non-NME**

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	✓		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	✓		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	✓		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	✓		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	✓		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	✓		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	✓		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	✓		-Sponsor conducted ocular distribution study as requested at pre-NDA meeting on 7-30-2012
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?		✓	Current safety margins are based on direct dose comparison; recommendations for changes will be made as the review progresses.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	✓		P/T is not aware of any pending impurity issues. We defer to CMC for identification of impurities that exceed ICH Q3 limits, and require nonclinical qualification. This will occur during the review cycle.
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _YES

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

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

Reviewing Pharmacologist Date

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

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

Team Leader/Supervisor Date

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

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/s/

AARON M RUHLAND
10/06/2014

LORI E KOTCH
10/06/2014