CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-545

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: **21-545**	Submission Date(s): 08/15/02
Brand Name	[redacted]
Generic Name	Olopatadine Hydrochloride
Reviewer	Chandra S. Chaurasia, Ph. D.
Team Leader	E. Dennis Bashaw, Pharm.D.
OCPB Division	DPE III (HFD-880)
OND division	ODE V (HFD-550)
Sponsor	Alcon Research, Ltd., Fort Worth, TX 76134
Relevant IND(s)	60,991
Submission Type; Code	New formulation, Higher Strength
Formulation; Strength(s)	Ophthalmic Solution, 0.2%
Indication	Ocular itching associated with Allergic Conjunctivitis

1. EXECUTIVE SUMMARY

PATANOL (olopatadine hydrochloride) is a sterile ophthalmic solution containing olopatadine, a potent, selective H_1-receptor antagonist and a mast cell stabilizer. It is currently approved as 0.1% ophthalmic solution in the USA (Alcon Laboratories, PATANOL®, NDA 20-688) for the treatment of the signs and symptoms of allergic conjunctivitis with a twice daily dosing. In February 2001, Olopatadine in 2.5 mg and 5 mg oral tablets was approved as ALLELOCK in Japan for allergic rhinitis, urticaria and itching resulting from skin disease. Alcon is developing a new formulation Olopatadine QD Ophthalmic Solution 0.2% for once-daily administration under the proposed name [redacted]

The sponsor has not conducted any bioavailability study to assess pharmacokinetics of the Olopatadine HCl 0.2% solution. Instead the firm has requested for waiver citing section 21CFR 320.22(b)(1). However, the section cited by the sponsor is not applicable for a waiver request as the formulation for the 0.2% strength is different compared to the approved 0.1% strength PATANOL®. Nevertheless, the sponsor has provided supporting evidence of no significant systemic exposure following topical ocular administration of a 0.15% olopatadine hydrochloride ophthalmic solution having a dosage regimen of two drops into each eye twice daily for 2 weeks. Indeed, this study was considered a pivotal PK study for estimating bioavailability for PATANOL® (NDA 20-866) following topical ocular administration.

1.1. Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the information submitted to the Human Pharmacokinetics and Biopharmaceutics Section of NDA 21-545. The information submitted under this section is acceptable.

_____ Date: _____

Chandra S. Chaurasia, Ph.D.
Clinical Pharmacology Reviewer
Division of Pharmaceutical Evaluation III

RD/FT Initialed by E. Dennis Bashaw, Pharm.D. _____ Date: _____

2. TABLE OF CONTENTS

SUMMARY OF CPB FINDINGS

No studies have been conducted to assess the bioavailability of Olopatadine HCl Ophthalmic Solution, 0.2%. Pursuant to 21 CFR§320.22(b)(1)(i), the applicant requests a waiver from the requirements for submission of *in vivo* bioavailability or bioequivalence data. The applicant states that "*The drug product is an ophthalmic solution applied topically to the eye and is intended only for local therapeutic effect (i.e., antihistamine and mast cell stabilizer). It is not possible to measure the ocular bioavailability of olopatadine in humans by standard methods because of the unreasonable risk of obtaining the relevant biological fluids and tissues.*"

The firms states that "*the drug product is an ophthalmic solution thereby qualifying for a waiver of evidence of in vivo bioavailability or bioequivalence pursuant to 21 CFR 320.22(b)(1).*

As mentioned above, the section cited is misinterpreted by the sponsor, and is not applicable for this higher strength product. Furthermore, the Agency does not require intraocular sampling for PK measurement. However, it is noted that the sponsor has provided results from the following studies related to the systemic availability of olopatadine from ophthalmic and oral administration. It is further noted that these studies were reviewed as part of NDA 20-866 (Olopatadine HCl, 0.1% Ophthalmic Solution) by Dr. Dennis Bashaw.

Ophthalmic Dosing

Study No.

80:38610:0294:	Safety Evaluation and Plasma Levels of Topical AL4943A (Olopatadine 0.15%) in Normal Healthy Volunteers, N=15, Multiple Dose Study of Ocular BID for 15 Days.
17:38570:0594:	Safety Evaluation of Topical AL4943A (Olopatadine) in Japanese Normal Healthy Volunteers, N=9, Multiple Dose Study of Ocular BID for 14 Days.

Oral Dosing

Study No.

73:38570:0995	Pharmacokinetics of KW-4679 (olopatadine) in Healthy Japanese Adult Males after a Single Oral Administration: Dose Proportionality Study From 5-80 mg.
78:38570:0995	Pharmacokinetics of KW-4679 (olopatadine) in Healthy Caucasian Adult Males after a Single and Multiple Oral Administration.
32:33:0702	Pharmacokinetics of KW-4679 olopatadine) after Single Oral Dose in Renal Failure Patients.
31:33:0702	Pharmacokinetics of KW-4697 (olopatadine) in Young and Elderly Subjects Following a Single Dose.
C-00-23	Placebo-Controlled, Multiple Dose, Two-way Crossover, Safety and Pharmacokinetic Study of Oral Solution Doses of Olopatadine.

In Vitro Study

79:38570:0995	In Vitro Plasma Protein Binding
22:33:0400	In Vitro Study on Drug Interaction by Olopatadine in Human Liver Microsomes

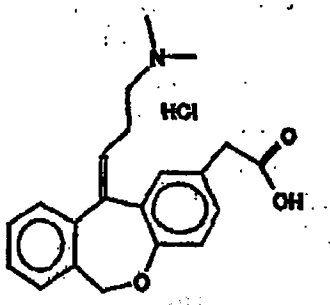
4. QUESTION-BASED REVIEW

4.1. General Attributes

What are the highlights of the physicochemical properties of —

— 0.2% is a sterile ophthalmic solution. Each mL of — contains 2.22 mg olopatadine hydrochloride equivalent to 2 mg olopatadine.

Chemical Structure of Olopatadine:



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

Physicochemical Properties: Olopatadine HCl is a white, crystalline, water-soluble powder with a molecular weight of 373.88. — has a pH of approximately 7 and osmolality of approximately 300 mOsm/kg.

What are the proposed therapeutic indication, dosage, route of administration, and mechanism of action of Olopatadine HCl?

Indication: Olopatadine HCl ophthalmic solution 0.2% is indicated for —

—

Dosage and Route of Administration: The recommended dose of Olopatadine HCl 0.2% solution is one drop to each affected eye once a day.

Mechanism of Action: Olopatadine is an inhibitor of the release of histamine from the mast cell and a relatively selective histamine H_1-antagonist that inhibits the *in vivo* and *in vitro* type 1 immediate hypersensitivity reaction including inhibition of histamine induced effects on human conjunctival epithelial cells. Olopatadine is devoid of effects on alpha-adrenergic, dopamine and muscarinic type 1 and 2 receptors.

4.2. General Clinical Pharmacology

Are the active moieties in the plasma or other biological fluid appropriately identified and measured to assess pharmacokinetic parameters?

Plasma samples were analyzed by validated GC/MS method with a quantitation limit of 0.50 ng/mL (Report Nos. 80:38610:0294 and 17:38570:0594) or by radioimmunoassay (Report Nos. 73:38570:0995 and 78:38570:0995) method with a detection limit of 0.1 ng/mL. The urine samples for olopatadine and its three metabolites (M1, M2 and M3) were analyzed using a validated HPLC

method with a detection limit of 0.2 μg/mL of urine for olopatadine, 0.4 μg/mL of urine metabolites M1 and M2, and 1.0 μg/mL for M2 (Report No. 73:38570:0995). Analytical method validation reports were submitted with NDA 20-866, and were found acceptable by the Biopharm reviewer, Dr. Dennis Bashaw.

What are the basic pharmacokinetic parameters of olopatadine (ADME)?
Olopatadine is predominately excreted as unchanged drug via the kidneys (~70% at oral doses of 5 and 10 mg). Further, liver metabolism represents a small fraction of olopatadine elimination, as evidenced by the N-desmethyl-olopatadine (M1) and Olopatadine N-oxide (M3) metabolites representing =1.6% and =4.1%, respectively, of the urinary recovery (Study No. 73:38570:0995). Since the systemic plasma levels after topical ocular administration are much lower than those observed after oral administration.

Are the study populations relevant to the proposed indication?
The pharmacokinetic studies following ocular or oral administrations were done in adult healthy Caucasian and Japanese volunteers to assess bioavailability of the drug product. Olopatadine HCl 0.2% is indicated for [redacted] Although the appropriate study population would have been subjects with conjunctivitis, given the known pharmacokinetics of the drug substance, the applied dose (1 drop) and dosing frequency (once daily), it is unlikely that subjects with conjunctivitis would have had a significantly different pharmacokinetic profile compared to healthy adults.

Are dose and dosing regimen appropriate for pharmacokinetic study?
The concentration chosen for Olopatadine 0.2% was based on data from a preclinical guinea pig model as well as from duration of action data observed from clinical Conjunctival Allergen Challenge (CAC) studies (C-00-36) with PATANOL. It is noted that at the EOP II Meeting on Jun 28, 2001, the Agency concurred with the sponsor that the pharmacokinetic studies conducted using 2 drops of Olopatadine Ophthalmic Solution 0.15% twice-daily to both eyes are sufficient to establish that once-daily dosing of one drop Olopatadine QD (0.2%) to both eyes will result in negligible plasma levels of Olopatadine. However, the Agency stated that the label for 0.2% Olopatadine ophthalmic solution would state that "*information regarding systemic bioavailability upon topical ocular administration from this formulation is not available.*"

4.3. Intrinsic Factors: Age, Sex, Race, Weight, Height and Disease States.
In the cardiovascular safety and pharmacokinetic study (Study No. C-00-23), mean Cmax and AUC_{0-12} values after 5 mg oral doses were not significantly ($p>0.05$) different between males (239.7 ng·hr/mL and 71.4 ng/mL, respectively) and females (253.3 ng·hr/mL and 79.0 ng/mL, respectively). The mean age or gender differences in plasma concentrations of olopatadine seen were small and not clinically significant as no QTc prolongation was seen in any of the 102 subjects in the study.

The effect of age (Study No. 32:33:0702) and renal disease (Study No. 31:33:0702) on the pharmacokinetics of olopatadine have been studied by Kyowa in Phase I studies involving small groups of male and female subjects. In elderly volunteers and patients with severe renal impairment, higher plasma levels of 1.3- and 3-fold, respectively, were observed compared to young healthy male subjects following 10 mg oral tablet doses. The magnitude of these mean differences in plasma were deemed not clinically meaningful. Since the systemic plasma levels after topical ocular

administration are much lower than those observed after oral administration, gender or age differences are not clinically relevant, and dose adjustments with Olopatadine Ophthalmic Solution, 0.2% are not needed in the elderly or renally impaired patients.

The effect of hepatic impairment on olopatadine pharmacokinetics has not been studied. This is justified since olopatadine is predominately excreted as unchanged drug via the kidneys (~70% at oral doses of 5 and 10 mg). Further, liver metabolism represents a small fraction of olopatadine elimination, as evidenced by the N-desmethyl- and N-oxide metabolites representing =1.6% and =4.1%, respectively, of the urinary recovery.

Pediatric Use:
Safety and effectiveness in pediatric patients below the age of 3 years have not been established.

Pursuant to 21 CFR§314.55(c)(3), the applicant requests a waiver of information regarding the use of Olopatadine HCl Ophthalmic Solution (0.2% as base) in pediatric patients under the age of 3 years.

Reviewer's Comments: It is noted that Olopatadine 0.1% labeling includes indication for using child 3 years or older. At the EOP II meeting on Jun 20, 2001, the Agency did not agree with the firm's approach that Alcon extend pediatric safety profile of olopatadine 0.1% bid dose to once daily dosing for the 0.2% strength. The Agency recommended that a separate pediatric safety studies in pediatric patients with Olopatadine HCl 0.2% ophthalmic solution. Since, the sponsor has not provided any pediatric study with the 0.2% strength, this should be addressed in the labeling.

Geriatric Use:
No overall differences in safety and effectiveness have been observed between elderly and younger patients

4.4. Extrinsic Factors: Drugs, Diets and Smoking
Considering the undetectable plasma concentrations of olopatadine after topical ocular administration, evaluation of the effect of any extrinsic factors on Olopatadine Ophthalmic Solution, 0.2% pharmacokinetics is not needed.

4.5 General Biopharmaceutics

What are the differences between approved, clinical, and to-be-marked formulations?
Pivotal ocular pharmacokinetic and bioavailability studies were conducted using olopatadine HCl 0.15% strength. The comparative formulations for Olopatadine HCl 0.1%, 0.15%, and 0.2% strengths are given below (Table 1). The proposed 0.2% strength contains sodium edetate, and povidone, which are not constituent parts in the approved 0.1% strength PATANOL®.
Table I. Component and Compositions of Olopatadine HCl 0.1%, 0.15% and 0.2% Ophthalmic Solutions.

Component	Olopatadine Ophthalmic Solution, 0.15%	Olopatadine Ophthalmic Solution, 0.1% (PATANOL®)	Olopatadine Ophthalmic Solution, 0.2%
	Percentage (w/v)		
Olopatadine			

Benzalkonium Chloride, NF			
Edetate Sodium, USP			
Povidone			
Sodium Chloride, USP			
Dibasic Sodium Phosphate USP			
Sodium Hydroxide, NF and/or Hydrochloric Acid, NF	pH adjust 7.0	pH adjust 7.0	pH adjust 7.0
Purified Water. USP	QS 100%	QS 100%	QS 100%

Are there any in vitro data for Olopatadine HCl?

- In vitro protein binding of olopatadine in human serum Study No. 79:38570:0995. Results summarized below in Section 4.6, Pharmacokinetic Data.
- In Vitro Study on Drug Interaction by Olopatadine in Human Liver Microsomes Study No. 22:33:0400. Results summarized below in Section 4.6, Pharmacokinetic Data.

4.6. Pharmacokinetic Data

Summary of the Study 80:38610:0294: Fifteen normal, healthy subjects instilled 2 drops of Olopatadine Ophthalmic Solution 0.15% twice daily in each eye for 15 days. The study subjects ranged in age from 22 to 47 years, 7 males (47%) and 8 females (53%), 13 Caucasians (86%), 1 Asian (7%) and 1 "Classified as Other" (7%). Blood samples for were taken before dosing and at 0.25, 0.5, 1, 2, 4, 6 and 8 hours after ocular instillation on Days 1, 8 and 15. Plasma concentrations measured after 15 days of topical, ocular dosing were typically at or below 0.5 ng/mL quantitation limit with only 3 of 375 samples being above 1 ng/mL.

Summary of the Study 17:38570:0594: Nine normal, healthy male Japanese subjects instilled 2 drops of Olopatadine Ophthalmic Solution 0.15% twice daily in each eye for 14 days. Plasma samples were obtained before dosing and at 0.25, 0.5, 1, 2, 4, 6 and 8 hours after dosing on Days 1 and 15. Plasma samples were also obtained on Day 8 at 0.25, 0.5 and 1 hour postdose.

Plasma samples were analyzed by a validated GC/MS spectrometric method with a quantitation limit of 0.50 ng/mL. Plasma concentrations of olopatadine were typically below 0.5 ng/mL. Only 2 out of 180 total samples were above 1 ng/mL with the highest concentration being ___ ng/mL. The results of this study demonstrate a very low systemic exposure of olopatadine during a multiple topical ocular dosing regimen.

Summary of the Study 73:38570:0995: The study was a single oral dose, dose proportionality study in 24 healthy Japanese males between 20 and 26 years of age. The design used for this study was an open-label, non-randomized, rising dose format. The subjects received either 5, 10, 20, 40, or 80 mg of olopatadine under fasted condition. An additional leg of the trial used a 10 mg dose under non-fasted condition to assess the food-effect on the pharmacokinetics of olopatadine. For all groups, blood samples were collected prior to the study and ant 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours postdose. Quantitative determination of olopatadine in plasma was carried out using a validated radioimmunoassay (RIA) method with a detection limit of 0.1 ng/mL.). The full data set had been reviewed under NDA 20-866. Relevant pharmacokinetics summary data of this study are provided below:

Dose	AUC0-inf (ng*hr/mL)	Cmax (ng/mL)	Tmax (hrs)	Cl/F (l/hr)	MRT (hrs)

5 mg	301±60	107.7±22	1±0.3	16.6±2.9	5.02±2.72
10 mg	614±137	191.8±43	0.9±0.5	17±3.4	4.29±0.53
10 mg (NON-FASTED)	537±104	170.8±45.3	1.3±0.5	19.3±3.6	5.01±1.31
20 mg	1217±124	324.4±50.1	0.9±0.6	16.6±1.8	5.6±1.3
40 mg	2805±371	882.6±202.3	1±0.6	14.5±1.9	5.07±0.61
80 mg	5176±1141	1711.6± 388.8	1.2±0.4	16.1±3.4	4.26±0.97

In addition to the analysis of plasma data, the sponsor collected time urine samples over 48 hours for olopatadine and its three metabolites (M1, M2 and M3). The samples were analyzed using a validated HPLC method with a detection limit of 0.2 µg/mL of urine for olopatadine, 0.4 µg/mL of urine metabolites M1 and M3, and 1.0 µg/mL for M2. The full data set from the time intervals has been reviewed under NDA 20-866. A summary data table is presented below:

Cumulative Urinary Excretion in % (Means S.D.)

Dose	Olopatadine	M1	M3*
5 mg	68.4±15.2	0.61±1.06	4.13±2.62
10 mg	71.7±5.2	1.09±1.6	2.28±1.34
20 mg	73.4±3.3	1.25±0.66	2.14±1.12
40 mg	62.2±3.4	0.9±0.46	3.15±0.57
80 mg	58.7±10.1	0.75±0.09	3.07±0.39

**M2 was not detected at any time in urine above the LLQ of 1.0 µg/mL.*

Summary of the Study 78:38570:0995: The study was a single oral 80 mg dose followed by a 2-day washout and the 80 mg tid dosing for 9 days and one dose on Day 10 in 20 Caucasian healthy adult males between 20 and 44 years of age. The trial itself was a double blind, placebo-controlled in which 12 subjects got olopatadine and 8 subjects got placebo. Quantitative determination of olopatadine in plasma was carried out using a validated radioimmunoassay (RIA) method with a detection limit of 0.1 ng/mL. The full data set had been reviewed under NDA 20-866. Relevant pharmacokinetics summary data of this study are provided below:

Study 78:38570:0995: Mean Pharmacokinetic Parameters (Mean ± S.D.)

	AUC0-8 (ng*hr/mL)	Cmax (ng/mL)	Tmax (hrs)	T1/2 (hrs)
Day 1	3877±1276	1625.8±759.7	1.04±0.58	9.68±3.79
Day 10	4235±1129	1728.8±684.7	1.04±0.45	12.2±3.9

Reviewer's Note: *Individual plasma-olopatadine-concentration vs. time plots submitted the above study reports were analyzed by Dr. Dennis Bashaw as part of NDA 20-688 review. Considering that topical ocular administration of olopatadine did not show any appreciable systemic absorption, the individual plasma concentration-time plots do not provide any meaningful information in the PK study.*

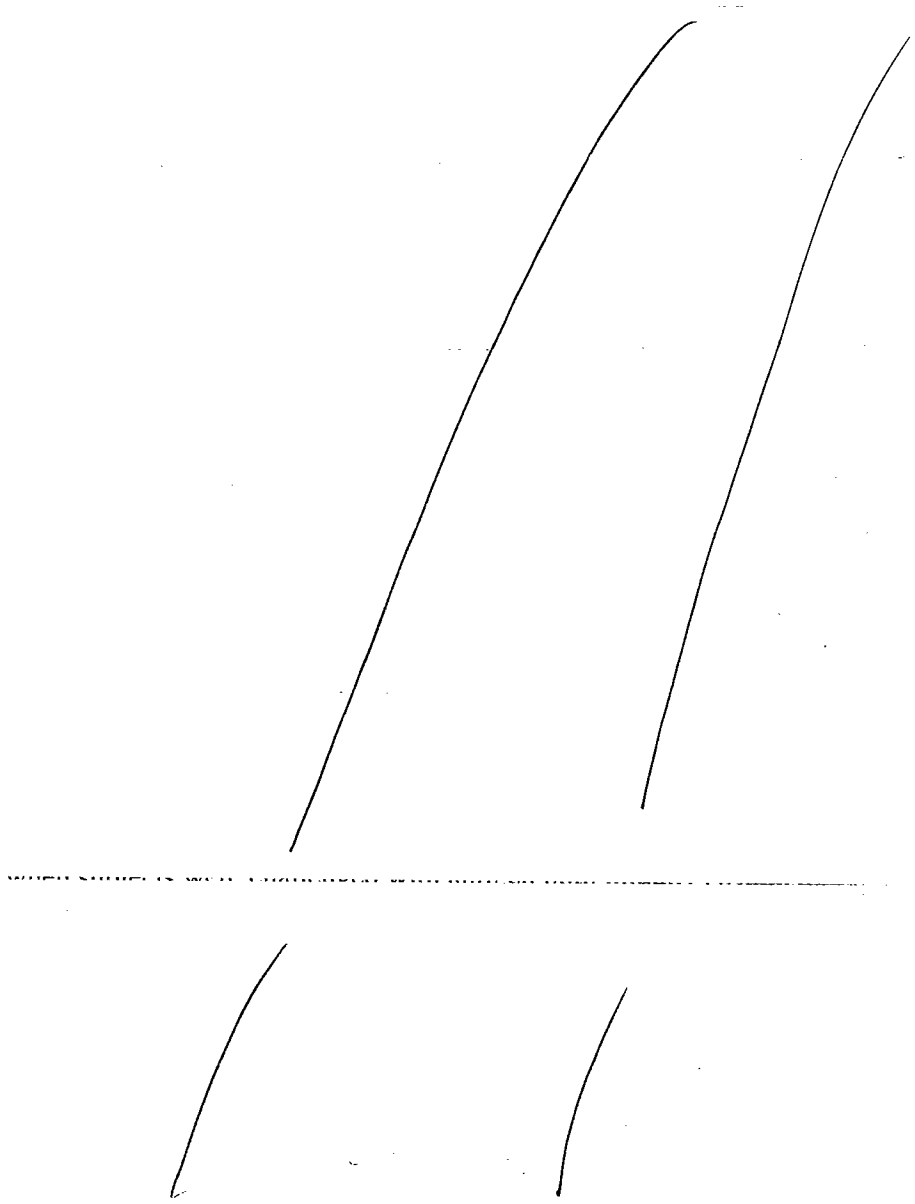
Summary of the Study 79:38570:0995: In vitro protein binding of olopatadine in human serum alone and in combination with drugs such as chlorpheniramine maleate, clenbuterol, prednisolone and theophylline was conducted using ultrafiltration as part of the NDA 20-866 The study has been reviewed by Dr. Dennis Bashaw. Based on the study results it was concluded that olopatadine is not highly protein bound with an unbound fraction (fu) of 45%, and that drug interactions based on protein binding displacement were not significant.

Summary of the Study No. 22:33:0400. The inhibitory activity of olopatadine on the metabolism of 6 cytochrome P-450 isozyme specific substrates was determined in human liver microsomes.

Olopatadine did not inhibit the metabolism of any isozyme specific substrate tested even at concentrations that were more than 4-orderes of magnitude higher than those found in humans after topical ocular administration of 0.15% olopatadine ophthalmic solution. These results demonstrate that exposure to olopatadine is unlikely to result in metabolic interactions with other concomitantly administered drugs through cytochrome P-450 inhibition.

5. DETAILED LABELING RECOMMENDATIONS

Most of the information in the pharmacokinetic section of the label is acceptable.
The following changes are recommended for the pharmacokinetic section of the labeling. ~~ABC~~ suggests deletion of text and **ABC** does insertion of new text.



5 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 1 of 1

6.2. OCPB Filing Review Form

Office of Clinical Pharmacology and Biopharmaceutics
NEW DRUG APPLICATION FILING AND REVIEW FORM

1.1.1.1.1 General Information About the Submission

	Information		Information
NDA Number	21-545	Brand Name	[redacted]
OCPB Division (I, II, III)	III	Generic Name	Olopatadine HCl
Medical Division	550	Drug Class	selective histamine H_1-antagonist
OCPB Reviewer	Tandon	Indication(s)	Ocular Itching associated with Allergic Conjunctivitis
OCPB Team Leader	Bashaw	Dosage Form	Ophthalmic Solution, 0.2%
		Dosing Regimen	1 drop once daily
Date of Submission	August 15, 2002	Route of Administration	Topical
Estimated Due Date of OCPB Review		Sponsor	Alcon
PDUFA Due Date		Priority Classification	P
1.1.1.2 Division Due Date			

1.1.1.2.1.1.1.1 Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	1.1.1.2.1.1.1.1			CTD format was used
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X	3		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:	X	3		• Oral solution 5 mg BID 2.5 days (done to demonstrate cardiac safety) • 0.15%, 2 drops BID for 14 days • 0.15%, 2 drops BID for 15 days
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				

fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	X	1		
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:	X	1		10 mg oral
renal impairment:	X	1		10 mg oral
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		9		
1.1.1.2.1.2				

1.1.1.2.1.3 Filability and QBR comments

	"X" if yes	1.1.1.3.1.1.1.1.1 Comments
1.1.1.3		
1.1.1.4 Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
1.1.1.5 Comments sent to firm ?	No	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
1.1.1.6		
QBR questions (key issues to be considered)	**Can a waiver be granted based on sponsor's request? What is the systemic exposure from 0.15% olopatadine ophthalmic solution? How do the daily doses from this study compare to that would be administered clinically using the 0.2% strength? What are the formulation differences between the one used in the biostudy and that to–be marketed?**	

Other comments or information not included above	**Olopatadine 0.1% ophthalmic solution has been approved in US for the treatment of allergic conjunctivitis** **The sponsor has requested a waiver for conducting PK study with 0.2% ophthalmic solution, however, BID dosing of 2 drops with 0.15% has been conducted. The dosing regimen for 0.2% Ophthalmic solution is once daily. So, the margin of safety can be assessed with the study conducted, as higher dose was administered in the study conducted. Looking at the previous label it appears that this study was reviewed for the NDA for olopatadine 0.1% ophthalmic solution, but it is not clear from the TOC. Differences in formulation and its impact should be noted.** **The sponsor has submitted several studies (n=10) with the oral formulation as it is approved in Japan for nasal indications. Most of these studies will not be relevant for review in this application, but some of them may elucidate the disposition characteristics and the need to review some of these can be ascertained at the time of review.**
Primary reviewer Signature and Date	**Veneeta Tandon, 9/10/02**
Secondary reviewer Signature and Date	**Dennis Bashaw, 9/10/02**

CC: NDA 21-545, HFD-850(Electronic Entry or Lee), HFD-550(Rodriguez), HFD-880 (Bashaw, Selen, Lazor),

End of Document

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Chandra S. Chaurasia
2/21/03 02:23:45 PM
BIOPHARMACEUTICS

Proposed Sponsor's Labeling included, pages 12-15. Table of Contents on page revised accordingly.

Dennis Bashaw
3/3/03 02:20:09 PM
BIOPHARMACEUTICS