CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-545

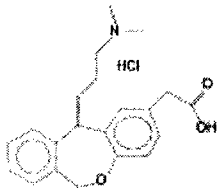
PHARMACOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY AMENDMENT REVIEW

NDA number: 21-545
Review number: 2
Sequence number/date/type of submission: 000/December 11, 2003/AZ
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Alcon, Inc
Reviewer name: María I. Rivera
Division name: Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products
HFD #: 550
Review completion date: April 22, 2004

Drug:

Trade name:
Generic name: Olopatadine Hydrochloride Ophthalmic Solution, 0.2%
Chemical name: 11-[(Z)-3-(Dimethylamino)propylidene]-6,11-dihydrodibenz[*b,e*]oxepin-2-acetic acid hydrochloride
CAS registry number: 140462-76-6 (hydrochloride); 113806-05-6 (base)
Molecular formula/molecular weight: $C_{21}H_{23}NO_3 \bullet HCl/373.88$
Structure:



Drug class: H1-receptor antagonist

Indication: treatment of ocular itching associated with allergic conjunctivitis

In this amendment, Alcon submitted the final reports of two nonclinical topical ocular repeated-dose toxicity studies and five genotoxicity studies to assess the toxicity potential of degradation products found in stability batches of olopatadine hycrochloride. The degradations products are the

Proposed specifications are the following:

Degradation Product	Specification	
	% active	Exposure, µg/day*

All these specifications are below the ICH threshold for biological qualification, which is 1% for a maximum daily dose of < 10 mg of drug substance.

The repeated dose ocular/systemic toxicity studies are summarized below:

Study	Key Findings
Title: One Month Topical Ocular Irritation and Systemic Toxicity Evaluation of AL-4943A (Olopatadine) Ophthalmic Solution Degradation Products [redacted] in New Zealand Rabbits **Objective:** Designed to assess the local topical ocular toxicity potential of olopatadine degradation products found in Olopatadine Ophthalmic Solution (0.1% and 0.2%). **Study no.**: TDOC-0000353 **Module # and Volume #**: 4, 1 **Conducting laboratory and location:** Alcon Research Ltd., 6201 S. Freeway, Forth Worth, TX 76134 **Date of study initiation:** May 7, 2003 **GLP/QA**: Yes **Drug, lot #, and % purity**: AL-4943A, 0.1%, lot # 03-33402, [redacted] AL-4943A, 0.1% [redacted] AL-4943A, 0.1% + [redacted] Individual degradation products were [redacted] **Methods** **Doses:** Given daily for 34 days Group 1: Vehicle Group 2: AL-4943A, 0.1% Group 3: AL-4943A, 0.1% [redacted] Group 4: AL-4943A, 0.1% [redacted] **Species/strain:** Rabbit/New Zealand White **Number/sex/group:** 4 **Route, volume, infusion rate:** Two drops were administered to the superior corneo-scleral junction of the right eye 4x/day. The total dose volume was ~ 70 • l at each treatment interval. **Age:** 5 months **Weight:** 3.0-3.8 kg **Observations:** Clinical signs, detailed health examinations, body weight, inappetence, ophthalmoscopy including slit-lamp biomicroscopic examinations, indirect	➢ The concentration of [redacted] decreased [redacted] over the course of the 1-mo study period [redacted] in pre-study analysis to [redacted] in post-study analysis). The decrease was associated with a concomitant increase in an unidentified peak (HPLC). ➢ Minimal conjunctival congestion (score = 1) was observed sporadically in both test-article and vehicle treated eyes as well as in the non-treated eyes. Moderate congestion (score = 2) was observed on Day 21 in the treated eye of one male each in Groups 1, 2, and 3. The congestion resolved by the next evaluation (Day 34) for the animals in Groups 1 and 3 and was reduced to minimal in the animal in Group 2. On Day 34, one male in Group 3 had moderate congestion in the treated eye and a second male in Group 4 had moderate congestion on both eyes. Because of the sporadic occurrence, these findings were not considered test-article related. ➢ No test-article related effects were observed in corneal pachymetry or IOP measurements, and gross pathology or histopathology. **Conclusions:** ➢ Administration of 2 drops of 0.1% Olopatadine Ophthalmic Solution containing [redacted], or a combination o[redacted] to the right eye of rabbits 4x/day for 1-month did not result in any biologically significant finding. ➢ In this study, two drops of test-article were given 4x/day to one eye. Therefore, the daily exposure (based on a dose volume of 70 µl/treatment) was [redacted] respectively. ➢ On a body weight basis (µg/kg/day), using a human weight of 50 kg and a rabbit weight of 3.4 kg, the safety factors are 416, 257, and 121 for the [redacted], respectively, based on the exposure levels of [redacted] µg/day proposed for the commercial product. ➢ Considering the [redacted]-decrease in [redacted] concentration at the end of study, then the safety margin is between 60 and 121. Note: The Sponsor calculations for the daily exposure were [redacted] for the [redacted]

ophthalmoscopic examinations [the fundus of each eye was evaluated in respect to the optic nerve head characteristics, fundic vascular pattern (retinal and choroidal), and pigmentation/ coloration characteristics], corneal pachymetry and intraocular pressure, gross necropsy and histopathology of eyes and adnexa

[redacted], respectively. The safety margins were 23-42-fold on a body weigh basis. In spite of the discrepancies in the calculations, there is no safety concern.

Title: Four-Week Topical Ocular Irritation and Systemic Toxicity Evaluation of Olopatadine (AL-4943A) Ophthalmic Solution Degradation Products [redacted] in New Zealand White Rabbits

Objective: Designed to assess the local topical ocular toxicity potential of olopatadine degradation products [redacted] which have been found in stability lots of PATANOL (Olopatadine Ophthalmic Solution 0.1%).

Study no.: TR 024:30:0303
Module # and Volume #: 4, 1
Conducting laboratory and location: Alcon Research Ltd., 6201 S. Freeway, Forth Worth, TX 76134
Date of study initiation: Dec. 11, 2002
GLP/QA: Yes
Drug, lot #, and % purity:
AL-4943A, 0.1%, lot # 02-32752
AL-4943A, 0.1% [redacted]
AL-4943A, 0.1% [redacted]
AL-4943A, 0.1% + [redacted]

AL-4943A and the individual degradation products were [redacted] pure.

Methods

Doses: Given daily for 28 days

Group	Opthalmic Solution
1	Vehicle
2	AL-4943A, 0.1%
3	AL-4943A, 0.1% [redacted]
4	AL-4943A, 0.1% [redacted]
5	AL-4943A, 0.1% + [redacted]

[redacted]

Species/strain: Rabbit/New Zealand White
Number/sex/group: 4
Route, volume, infusion rate: Two drops were administered to the superior corneo-scleral junction of the right eye 4x/day. The total dose volume was ~ 66 • l at each treatment interval.

- The concentration of [redacted] decreased [redacted]% over the course of the 1-mo study period [redacted] in pre-study analysis to [redacted] in post-study analysis). The decrease was associated with a concomitant increase in an unidentified peak (HPLC).
- Minimal conjunctival congestion (score = 1) was observed sporadically in both test-article and vehicle treated eyes as well as in the non-treated eyes. One case of moderate congestion (score = 2) was observed on Day 28 in the treated eye of one female in Group 5. Because of the sporadic occurrence, these findings were not considered test-article related.
- No test-article related effects were observed in corneal pachymetry or IOP measurements, clinical pathology, organ weights, gross pathology, and histopathology.
- Pitted or mottled kidneys were observed in one female each in Groups 2, 3, and 5. Microscopically, moderate multifocal fibrosis and moderate to moderately severe multifocal lymphoid infiltrates were observed in the kidneys. Perivascular lymphoid cuffing accompanied by moderate to moderately severe multifocal granulomatous inflammation was identified in the brains of the affected animals. The Sponsor considered these findings to be the result of infection by *Encephalitozoon cuniculi.*

Conclusions:

- Administration of 2 drops of 0.1% Olopatadine Ophthalmic Solution containing [redacted], or a combination of [redacted] to the right eye of rabbits 4x/day for 4 weeks did not result in any biologically significant finding.
- In this study, two drops or test-article were given 4x/day to one eye. Therefore, the daily exposure (based on a dose volume of 66 µl/treatment) was [redacted] respectively.
- On a body weight basis (µg/kg/day), using a human weight of 50 kg and a rabbit weight of 2.85 kg, the safety factors are 292 and 136 for [redacted] respectively, based on the exposure levels of [redacted] µg/day proposed for the commercial product.

	↑ frequency of small colonies consistent with damage to multiple loci on chromosome 11 in addition to functional loss of the TK locus **Conclusion:** — was determined to give a positive mutagenic result at ≥ 1250 µg/ml (-S9) and ≥ 250 µg/ml (+S9).
Title: *In vitro* Mammalian Cell Mutation Test (L5178Y/TK$^{+/-}$ Mouse Lymphoma Assay) using — a Degradation Product of AL-4943A (Olopatadine) **Study #:** TR 018:30:0203 **Module # and Volume #:** 4, 2 **Compound:** —, lot#: 10258:002, — pure **Doses:** 10-40 µg/ml (-S9; 4 hr); 50-130µg/ml (+S9; 4 hr); 7.5-25 µg/ml (-S9; 24 hr)	Equivocal[a] at ≥15 µg/ml (–S9, 4hr) 100 and 110 µg/ml (+S9, 4 hr;) 15 µg/ml (–S9, 24 hr) Positive[a] at 30 µg/ml (–S9, 4hr) ≥ 110 µg/ml (+S9, 4hr) Toxic[b] at ≥ 30 µg/ml (-S9; 4 hr) ≥ 110 µg/ml (+S9; 4 hr) ≥ 15 µg/ml (-S9; 24 hr) ↑ frequency of small colonies consistent with damage to multiple loci on chromosome 11 in addition to functional loss of the TK locus **Conclusion:** — was concluded to be equivocal without S9 with a 4 hr exposure, negative without S9 with a 24-hr exposure, and positive with S9 at ≥ 110 µg/ml.
Title: Mouse Micronucleus Test Using — and AL-4943A (Olopatadine) **Species:** ICR mice; n=5/sex/group for bone marrow collection at 24 and 48 hr after dosing **Study #:** TDOC 0000653 **Module # and Volume #:** 4, 2 **Compounds:** AL-4943A-09 — pure Lot#: 110013 Lot#: 10489:030 **Doses:** Both compounds were combined in a ratio of 88:12 (w/w) and administered as a single ip injection. The doses were: AL-4943A: 22, 73, or 220 mg/kg — 3, 10, or 30 mg/kg Untreated, vehicle, and CP (50 mg/kg) controls were included.	Mortality was observed in 1/15 male and 1/15 female mice receiving the high dose. Clinical signs included: lethargy and piloerection in males and female mice at all doses and irregular breathing and convulsions in male an females at the high dose. There was no increase in the number of micronucleated polychromatic erythrocytes. There was no reduction in the ratio of PCE/total erythrocytes in all test-article treated mice. **Conclusion:** AL-4943A and — when administered together up to doses of 220 mg/kg and 30 mg/kg, respectively, were concluded to be negative in the mouse micronucleus assay.

[a]Positive = ≥ 100 mutants/10^6 clonable cells over that of solvent control; equivocal = mutant frequency between 55 and 99 mutants/10^6 clonable cells over that of solvent control; negative = mutant frequency of ≤ 55 mutants/10^6 clonable cells over that of the solvent control; [b]Toxicity defined as total growth of ≤50% of the solvent control

All these GLP studies were reviewed and found valid according to standard criteria. The results for the mouse lymphoma studies are presented in the table below.

Results of Mammalian Cell Forward Mutation Assays with — (4-hr exposures)

Test Article	—									
	Concentration or Dose Level (µg/ml)									
Without Activation	**DMSO**		**250**	**500**		**750**		**1000**		**1250**
Cytotoxicity	NA		113, 103	88, 89		72, 78		41, 55		11, 26
Genotoxicity	88, 99		-16, -13	-14, -19		33, 24		77, 56		176, 100
With Activation	**DMSO**		**50**	**100**		**250**		**500**		
Cytotoxicity	NA		98, 92	55, 101		61, 50		35, 41		
Genotoxicity	76, 75		-4, 4	-15, 15		55, 101		145, 102		
Test Article	—									
	Concentration or Dose Level (µg/ml)									
Without Activation	**Water**	**7.5**	**10**	**12.5**	**15**	**20**	**25**	**30**	**40**	**50**
Cytotoxicity	NA	ND	63, 43	ND	80, 59	70, 83	75, 66	35, 53	10, x	x, x
Independent Repeat	NA	110, 90	104, 90	82, 62	52, 48	29, 37	x, 9	ND	ND	x, x
Genotoxicity	102, 55	ND	50, -35	ND	37, 57	68, 26	35, 64	76, 104	19, x	x, x
Independent Repeat	79, 76	8, 1	-18, -4	-16, 10	-15, 86	11, -30	x, x	ND	ND	x, x
With Activation	**Water**	**50**	**75**	**100**	**110**	**120**	**125**	**130**	**150**	
Cytotoxicity	NA	78, 77	60, 80	63, 60	38, 50	ND	15, 25	ND	x, x	
Independent repeat	NA	73, 76	ND	58, 41	33, 38	19, 13	11, 12	10, x	x,, x	
Genotoxicity	68, 52	-41, 1	-28, -34	90, 2	127, 60	ND	139, 41	ND	x, x	
Independent repeat	64, 57	44, 39	ND	40, 45	18, 12	21, 53	172, 51	188, x	x,x	

NA = not applicable; ND = not determined; x = too toxic to clone

Cytotoxicity = % total growth = (% suspension growth * % cloning growth)/100

Genotoxicity = Control values represent the mutant frequency/10^6 cells whereas the test-article values represent the mutant frequency over controls/10^6 cells, i.e, mutant frequency in test-article samples – average mutant frequency of solvent control; Positive = ≥ 100 mutants/10^6 clonable cells over that of solvent control; Equivocal = mutant frequency between 55 and 99 mutants/10^6 clonable cells over that of solvent control; Negative = mutant frequency of ≤ 55 mutants/10^6 clonable cells over that of the solvent control

The Sponsor made the following comments: *"Much variability was encountered, and in many cases the induced mutation frequency was categorized differently for two cultures within the same assay. For example, the initial assays with activation for — at the 125 µg/ml concentration resulted in induced mutation frequencies of 41 (negative) and 139 (positive), and the independent repeat assay at the same concentration gave frequencies of 51 (negative) and 172 (positive). The results were inconsistent between tests. Based on the equivocal or weak nature of the responses, and with negative results from other*

genotoxicity assays, it is considered that the results give a weak signal, if any, for genotoxicity".

"These increased frequencies were variable, and especially in the case of — significant cytotoxicity may have been present at or near the concentrations tested".

Reviewer's Comments: The results of the mouse lymphoma (ML) assay, although highly variable, do show that there is a genotoxic response (equivocal or positive) for —. A subsequent *in vivo* genotoxicity assay, the mouse micronucleus, was conducted with — (as a mixture of 88% olopatadine:12% — and — was shown to be non-genotoxic with overall dose levels of up to 250 mg/kg (approximately 220 mg olopatadine, 30 mg/kg —). Based on a — µg/day patient dose of — from clinical use of Olopatadine HCl Ophthalmic Solution, 0.2% and a patient weight of 50 kg (— µg/kg/day), this represents an exposure margin of ~ 72000-fold on a body weight basis.

Evaluation: Olopatadine degradation products — did not cause any significant local or systemic toxicity after ocular administration for 1-month and therefore, are not expected to be associated with major ocular or systemic side effects in humans at the specifications limits established. — were equivocal or positive in the mouse lymphoma assay. However, based on the following rationale, it is concluded that these degradation products pose minimal genotoxic risk to humans:

1. — was negative in the Ames test and positive in the ML assay at concentrations ≥ 250 µg/ml (+S9). The human exposure for — is — µg/kg (50 kg person). Therefore, the human exposure is minimal.
2. — was also positive in the ML assay. The lowest dose at which a positive response was observed was 30 µg/ml (-S9, 4hr). However, — was negative in the Ames test and in the mouse micronuclei assay. The mouse micronuclei assay provided a safety margin of over 70000-fold. The human exposure for — — µg/kg (50 kg person). Therefore, the human exposure is minimal.
3. The specifications for the — degradation products are below the ICH threshold for biological qualification, which is 1% for a maximum daily dose of < 10 mg of drug substance. No further studies are then considered necessary to qualify these degradations products.
4. These degradation products are also present in the Olopatadine HCl Ophthalmic Solution, 0.1% (PATANOL®). The marketing experience with PATANOL® (approved in 1996) further supports the safety of these degradation products.

Signature:

Reviewer's Signature: _____
María I. Rivera, PhD

Supervisor's Signature:_____ Concurrence Yes ___ No ___
Josie Yang, PhD

cc: list:

NDA 21-545 N-000 (AZ)
HFD-550/Division File
/PM/R. Rodriguez
/MO/W. Boyd
/Pharm-Tox TL/J. Yang
/Pharm-Tox/M.I. Rivera

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

/s/

Maria I. Rivera
8/31/04 12:59:52 PM
PHARMACOLOGIST

Josie Yang
8/31/04 01:51:53 PM
PHARMACOLOGIST

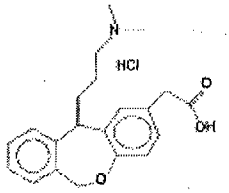
PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-545
Review number: 001
Sequence number/date/type of submission: 000/August 14, 2002/Original NDA
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Alcon, Inc
Manufacturer for drug substance: Alcon Manufacturing, Ltd.

Reviewer name: María I. Rivera
Division name: Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products
HFD #: 550
Review completion date: February 24, 2003

Drug:

Trade name:
Generic name: Olopatadine Hydrochloride Ophthalmic Solution, 0.2%
Chemical name: 11-[(Z)-3-(Dimethylamino)propylidene]-6,11- dihydrodibenz[*b,e*]oxepin-2-acetic acid hydrochloride
CAS registry number: 140462-76-6 (hydrochloride); 113806-05-6 (base)
Molecular formula/molecular weight: $C_{21}H_{23}NO_3 \bullet HCl/373.88$
Structure:



Relevant INDs/NDAs/DMFs: IND 60,991, NDA 20-688, DMFs

Drug class: H1-receptor antagonist

Indication: treatment of ocular itching associated with allergic conjunctivitis

Clinical formulation: Based on that of PATANOL® with the following exceptions: (1) The concentration of olopatadine was increased from 0.1% to 0.2%; (2) Edetate disodium

and (3) Povidone . Both edetate disodium and povidone are accepted ophthalmic pharmaceutical ingredients.

Component	% w/v	Function	Compendial Status
Olopatadine Hydrochloride		Active	
Benzalkonium Chloride			
Edetate Disodium			USP
Povidone			USP
Sodium Chloride			USP
Dibasic Sodium Phosphate,			USP
Sodium Hydroxide and Hydrochloric Acid			NF NF
Purified Water			USP

[a]Specified amounts of sodium hydroxide and hydrochloric acid are added for final solution pH adjustment to 7.0

Route of administration: Topical ocular

Proposed use: One drop in each affected eye once a day

Disclaimer: Sponsor's material has been used in this review.

APPEARS THIS WAY
ON ORIGINAL

Executive Summary

I. Recommendations

A. Recommendation on Approvability: Approval

B. Recommendation for Nonclinical Studies: No additional nonclinical studies are required.

C. Recommendations on Labeling: (1) Correction of the safety factors calculated in the Carcinogenesis, Mutagenesis, and Impairment of Fertility and Pregnancy Sections, and (2) Revision of the Pregnancy Section regarding non-teratogenic effects of olopatadine.

Under label Section "Carcinogenesis, Mutagenesis, Impairment of Fertility"
Olopatadine administered orally was not carcinogenic in mice and rats in doses up to 500 mg/kg/day and 200 mg/kg/day, respectively. Based on a 40 μl drop size and a 50 kg person, these doses were [redacted] and [redacted] times higher than the maximum recommended ocular human dose (MROHD). No mutagenic potential was observed when olopatadine was tested in an *in vitro* bacterial reverse mutation (Ames) test, an *in vitro* mammalian chromosome aberration assay or an *in vivo* mouse micronucleus test. Olopatadine administered to male and female rats at oral doses of [redacted] times MROHD level resulted in a slight decrease in the fertility index and reduced implantation rate; no effects on reproductive function were observed at doses of [redacted] times the maximum recommended ocular human use level.

Under label Section "Pregnancy"
Pregnancy Category:C
Olopatadine was found not to be teratogenic in rats and rabbits. However, rats treated at 600 mg/kg/day, or [redacted] times the MROHD and rabbits treated at 400 mg/kg/day, or

[redacted]

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings

The nonclinical profile of olopatadine hydrochloride has been established under the program development for NDA 20-688, PATANOL® (Olopatadine Hydrochloride Ophthalmic Solution, 0.1%), approved in 1996. The new product differs from PATANOL® in the increased

concentration of drug substance and the additional pharmaceutical excipients, povidone [redacted] and edetate disodium [redacted]). Both excipients are accepted ophthalmic ingredients.

During the program development for NDA 20-688, the Sponsor conducted 3 topical ocular studies in 2 species, a 1-month and a 6-month study in rabbits utilizing concentrations up to 0.2% and 1%, respectively, and a 6-month study in monkeys utilizing concentrations up to 0.5%. At the End of Phase II Meeting held on March 14, 2001, the Division agreed that to support the new formulation, an acute local tolerance study and a 3-month topical ocular safety and systemic toxicity study could be bridged to the studies previously submitted with NDA 20-688. The Sponsor also conducted an acute local tolerance study using a 6-month old clinical formulation.

Daily ocular administration of 0.2% or 0.4% Olopatadine QD Ophthalmic Solution (one drop t.i.d. to both eyes) for up to 3 months did not elicit any systemic or significant ocular toxicity except for minimal conjunctival congestion and aqueous flare in some rabbits. Minimal conjunctival congestion was also observed in vehicle controls. In the acute local tolerance studies, minimal to moderate conjunctival congestion, minimal discharge, and acceptable discomfort were observed in some animals following a dosing regimen of 2 drops every 30 min for a total of 10 doses. The intended clinical dose is one drop/eye/day. Therefore, the nonclinical findings support that the intended dose of 0.2% Olopatadine Ophthalmic Solution is not expected to be associated with major ocular or systemic side effects in humans.

Studies using an [redacted] old formulation indicated that degradation products up to a level of [redacted] (percent active) did not present any safety concern. The levels of the [redacted] degradation products were [redacted] of the active ingredient. The clinical product specifications for [redacted] degradation products is no more than (NMT [redacted] each and NMT [redacted] for total impurities (Module 2.3.P.5, p. 24). Since animals received 20x the proposed clinical dose, a safety factor of ~5x is provided by the nonclinical data. In addition, the specifications fall below the ICH threshold for biological qualification (1%) and thus, the impurities are not considered to present a safety concern. Further studies were conducted to evaluate the toxicity of four olopatadine derivatives: [redacted] , and the N-oxide and N-monodesmethyl metabolites. None of these olopatadine derivatives were toxic following a single oral dose of approximately 2,000 mg/kg to mice.

An *in vivo* and an *in vitro* studies were conducted to address possible interactions of olopatadine with the CYP450 metabolizing system. In the *in vivo* study, female Sprague-Dawley rats were given a single oral dose of 0.1, 1, or 25 mg/kg olopatadine daily for 7 consecutive days. In olopatadine-treated groups, there was no significant effect on body weight, microsomal protein content, CYP450 levels, cytochrome b_5 levels, and aniline hydroxylase, aminopyrine N-demethylase, and 7-ethoxycoumarin o-deetylase activities. In the *in vitro* study, the inhibitory activity of olopatadine on the metabolism of the following six CYP450 isozymes specific substrates was determined in human liver microsomes: phenacetin (CYP1A2), tolbutamine (CYP2C8-9), S-mephenytoin (CYP2C19), bufuralol (CYP2D6), chlorzoxazone (CYP2E1), and testosterone (CYP3A4). Olopatadine did not inhibit the metabolism of any CYP450 isozyme specific substrate at concentrations up to 100 μM (33900 ng/ml). Therefore, these findings

suggest that olopatadine has low potential to affect the activity of the CYP450 drug metabolizing system.

B. Pharmacologic Activity

Olopatadine is a relatively selective 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 antihistaminic and antiallergic properties of olopatadine *in vivo* and *in vitro* were previously submitted under NDA 20-688 and were reviewed by Asoke Mukherjee, Ph.D. (review date, July 16, 1996).

The new formulation was compared to that of PATANOL® for efficacy and duration of action. Olopatadine QD showed superior efficacy compared to PATANOL® in the model of histamine-stimulated conjunctival vascular permeability in guinea pigs. The proposed formulation: (1) inhibited the histamine-induced response by 72% compared to 55% inhibition by PATANOL® at 24 hr post-dosing, (2) exhibited significant efficacy through 30 hr (~50% inhibition), and (3) exhibited significant activity within 5 min, demonstrating similar onset of action to that of PATANOL®.

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 concentrations higher than those previously calculated for olopatadine (Ref. 13). 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 (Ref. 4), 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.

C. Nonclinical Safety Issues Relevant to Clinical Use

Olopatadine caused untoward pharmacologic effects on respiratory, behavioral, and cardiovascular (including a 20-40 msec prolongation of the QTc interval in dogs) systems following oral or i.v. doses. Pathological changes in the liver, kidney, heart, among other organs, were also observed. 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 0.2% Olopatadine Hydrochloride Ophthalmic Solution. The maximum daily dose of [redacted] is the same as that of PATANOL®. The marketing experience with PATANOL® further supports the safety of the dose.

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:
NDA 21-545/Original NDA
HFD-550/Division File
/PM/R. Rodriguez
/MO/W. Chambers
/MO/M. Feinsod
/Pharm-Tox TL/J. Yang
/Pharm-Tox/M.I. Rivera

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Olopatadine is a relatively selective 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 antihistaminic and antiallergic properties of olopatadine *in vivo* and *in vitro* were previously submitted under NDA 20-688 and were reviewed by Asoke Mukherjee, Ph.D. (review date, July 16, 1996). One new study was conducted with the proposed clinical formulation and is summarized below. Two additional studies considered relevant to the current NDA were reviewed in detail. Literature references were also provided in the current NDA to support the pharmacology of olopatadine.

STUDY TITLE: PRECLINICAL EVALUATION OF THE ANTI-HISTAMINE EFFICACY OF THE PROPOSED QD —— CLINICAL FORMULATION

This study was reviewed during the IND stage of the current application (IND 60,991) by Susan Wilson, Ph.D. (review date, April 18, 2001). The following evaluation was copied from Dr. Wilson's review.

Study no: TR#033:32:0600
Volume #: Module 4, Volume 1
Objective: To identify a modified PATANOL formulation which would achieve duration of action sufficient to support a once-a-day clinical dosing regimen.

Method: Twenty μl of either Patanol vehicle, Patanol (0.1% Olopatadine), or 0.2% Olopatadine QD was applied to one eye of male Dunkin Hartley guinea pigs (n=5-6/group) 45 min following an i.v. injection of Evans Blue dye. Anesthetized animals were challenged with histamine instilled into the conjunctiva 24 hr following instillation of test articles. Thirty minutes following challenge, the guinea pigs were sacrificed and the area of extravasated blue dye measured. Olopatadine QD was also assessed using pretreatment times of 15 min to 30 hr. Permeability score was calculated by multiplying the area of blue dye by the color intensity (Grade of 1-6). Onset of action was also determined using a 5-min pretreatment interval.

Results and Concusions: The onset of action with Olopatadine QD was quick (e.g. within 5 min) and comparable to PATANOL. The activity of Olopatadine QD was greater than PATANOL 24 hr after administration (72% vs 55% inhibition of histamine-stimulated response, respectively). Olopatadine QD exhibited efficacy up to 30 hr following treatment. These data support a once a day administration of the new formulation.

STUDY TITLE: —— AL-18876-01 AND AL-24956A DATA

Study no: TR# 020:32:1101
Volume #: Module 4, Volume 1

Objective: To characterize the selectivity of two olopatadine metabolites, olopatadine N-oxide (AL-18876-01) and N-desmethyl-olopatadine (AL-24956A) in a panel of 40 physiological receptors or potential binding sites.
Method: Compounds were tested for receptor binding inhibition assays at three concentrations, 10^{-9}, 10^{-7}, and 10^{-5} M. [redacted] used a criteria of 50% inhibition to qualify a compound as active.
Results and Conclusions: Al-18876-01 showed 87% inhibition of histamine H1 receptor binding at 10 μM. Other receptors that showed ~ 30% inhibition at 10 μM were histamine H2, muscarinic M1 and M2, and serotonin 5HT2A (these are not considered relevant interactions according to the assay criteria). AL-24956A showed 70% inhibition (0.1 μM) and 96% inhibition (10 μM) of histamine H1 receptor, and ~70% inhibition of both the norepinephrine transporter and the serotonin 5HT2A receptor at 10 μM. In a separate study (Ref. 13), olopatadine IC_{50} value for the histamine H1 receptor was 10 – 50 nM. Interaction was also observed with the serotonin 5HT2A (IC_{50} = 1 μM) and serotonin uptake (IC_{50} = 10 μM) receptors. The lower affinity of olopatadine metabolites for the H1 receptor compared to that of olopatadine, together with the minimal systemic exposure (refer to Pharmacokinetics/Toxicokinetics Section), supports that these metabolites are not expected to contribute significantly towards the antihistaminic efficacy. The findings also support that these metabolites are not expected to show significant *in vivo* interactions with the other physiological receptors tested.

STUDY TITLE: AL-18876 (OLOPATADINE N-OXIDE): EFFECT ON HISTAMINE RELEASE FROM HUMAN CONJUNCTIVAL MAST CELLS

Study no: TR# 012:32:0300
Volume #: Module 4, Volume 1
Objective: To evaluate the ability of the N-oxide derivative of olopatadine to inhibit histamine release from conjunctival mast cells *in vitro.*
Method: Conjunctival mast cells were treated with 0.2 – 10 mM olopatadine N-oxide 15 min prior to challenge with anti-human IgE. Ketotifen (30 μM) was used as the reference compound. Histamine release was determined by radioimmunoassay.

Results and Conclusions: Olopatadine N-oxide inhibited the release of histamine from conjunctival mast cells at concentrations > 0.2 mM with almost 100% inhibition observed at 10 mM. The IC_{50} value was 3.07 mM. Ketotifen (30 μM) showed 61 % inhibition, consistent with previous findings (Ref. 4). The Sponsor mentioned that in a separate study (Ref. 4), the IC_{50} of olopatadine was calculated to be 559 μM. Therefore, olopatadine N-oxide, the main metabolite of olopatadine identified in human plasma following oral administration, inhibited the release of histamine from conjunctival mast cells but appeared to be less potent than the parent compound.

Pharmacology summary: Olopatadine's antihistaminic effect and its duration of action *in vivo* following topical ocular administration have been demonstrated in guinea pig models of histamine-induced vascular permeability (Ref. 2, 3) and passive anaphylaxis in conjunctiva (Ref. 4). *In vitro* receptor binding studies and functional potency studies have demonstrated the affinity of olopatadine for the H1-histamine receptor (Ref. 10, 1, 13, 14, 17). Additionally, these studies have shown the selectivity of olopatadine for the H1-histamine receptor, demonstrating its lack of significant interaction with α-adrenergic, muscarinic, dopaminergic, and numerous other

receptors and its absence of *in vivo* anti-cholinergic activity at effective anti-allergic/antihistaminic concentrations (Ref. 29 – 31). Olopatadine's antihistaminic activity has also been demonstrated *in vivo* following systemic administration (Ref. 16 – 20, 22). Studies using human conjunctival mast cells showed olopatadine inhibited the release of histamine, tryptase, PGD_2, and TNFα upon immunologic stimulation (Ref. 4-9).

The new study (TR# 033:32:0600) showed that 0.2% Olopatadine QD had superior efficacy compared to PATANOL® in the model of histamine-stimulated conjunctival vascular permeability in guinea pigs. The proposed formulation: (1) inhibited the histamine-induced response by 72% compared to 55% inhibition by PATANOL® at 24 hr post-dosing, (2) exhibited significant efficacy through 30 hr (~50% inhibition), and (3) exhibited significant activity within 5 min, demonstrating similar onset of action to that of PATANOL®.

The N-oxide- and N-desmethyl-olopatadine metabolites showed affinity for the histamine H1 receptor but at concentrations higher than those previously reported for olopatadine (Ref. 13). 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 (Ref. 4), the N-oxide showed lower potency than the parent compound.

Pharmacology conclusions: The nonclinical studies support that the new formulation [redacted] and may be effective at the once a day dose regimen. Olopatadine N-oxide and N-desmethyl metabolites showed lower affinity for the histamine H1 receptor than that reported for olopatadine. These findings, together with the low plasma levels of both metabolites, support that these metabolites are not expected to contribute significantly to olopatadine efficacy or side effects.

II. SAFETY PHARMACOLOGY:

Pharmacology studies to assess potential neurological and cardiovascular effects of olopatadine have been previously submitted under NDA 20-688. Two studies were submitted during the IND stage of the current NDA and were previously reviewed by Susan Wilson, Ph.D. (review date, April 18, 2001). An additional pharmacodynamic drug interaction study was submitted with the current NDA.

In Vitro Study

STUDY TITLE: EFFECTS OF OLOPATADINE HYDROCHLORIDE ON CLONED HERG CHANNELS

The study evaluation was copied from Dr. Wilson's IND 60, 991 review.

Study no: TR# 137:30:0700
Volume #: Module 4, Volume 2
Objective: To measure the effects of olopatadine on cloned human ether-a-go-go (hERG) channels.
Method: Olopatadine at 0.3, 1, and 7 mM (3 replicates/concentration) was applied to hERG transfected HEK293 cells. The positive control was terfenadine (Seldane) at 500 nM, which has been removed from the market because of its prolongation of the cardiac potential and QT

interval. The concentration-response was used to establish an IC_{50}. The frequency of stimulation (0.3-3 Hz) and temperature (22-32.4°C) were varied to determine use-dependence and temperature-dependence.

Results and Conclusions: Based on the concentration response, the IC_{50} was 1.1 mM. The response was use- and temperature-independent. The Sponsor states that the "IC_{50} should be interpreted in light of the IC_{50} that has been established for therapy. The ratio of IC_{50} hERG/IC_{50} therapy should be 100 or more ideally." A 1.1 mM concentration of Olopatadine would be approximately 410 μg/ml. An IC_{50} for Olopatadine QD has not been determined. However, at a dose of 1-2 drops (approximately 50 μl/drop) of a 0.2% Olopatadine solution, the total dose administered in a 24-hr period would only be about 400 μg. Therefore, the IC_{50} for Olopatadine-induced hERG blockade should exceed the IC_{50} by a factor larger than 100.

In Vivo Studies

STUDY TITLE: EFFECTS OF KW-4679 ON ELECTROCARDIOGRAM, HEART RATE AND BLOOD PRESSURE IN CONSCIOUS DOG

The study evaluation was copied from Dr. Wilson's IND 60, 991 review.

Study no: ---- , 1995 (Final Report, Pharmaceutical Research Institute, Kyowa Hakko Kogyo Co., Ltd.)

Volume #: Module 4, Volume 2

Objective: To evaluate the effects of orally administered KW-4679 on ECG, heart rate, and blood pressure of conscious dogs compared to terfenadine and epinastine.

Method: Instrumented male and female beagle dogs (5-6 months; n=4-6/group) were administered 0, 3, 10, 30, or 100 mg/kg of KW-4679; 10, 30, or 100 mg/kg of terfenadine; and 10 or 30 mg/kg of epinastine. ECG, blood pressure, and heart rate were measured for 12 hours after dosing.

Results: At 100 mg/kg of KW-4679, heart rate was significantly increased for 1-5 hr compared to vehicle control. Heart rate in the vehicle control was generally < 90 bpm. Heart rate for KW-4679 was 130 bpm at 1 hr after dosing and gradually decreased to about 97 bpm at 5 hr. ECG findings at 100 mg/kg included (1) a slight statistically nonsignficant decrease in the PQ interval 1-4 hr after dosing and (2) a statistically significant increase in QTc 1-6 hr and 12 hr after dosing. There was approximately a 20-40 msec change in QTc compared to baseline. There was a slight statistically nonsignicant decrease in mean systolic blood pressure and an increase in mean and diastolic blood pressure at 100 mg/kg of KW-4679.

Sponsor's Conclusions (numbered) and Reviewer's Comment

1. The increase in QTc observed at 100 mg/kg of KW-4679 was " an apparent effect caused by increase in heart rate" and there was actually a decrease in the uncorrected QT interval.

Reviewer's Comment – The corrected QT interval more accurately reflects a drug's effect on this interval because it does correct for changes in heart rate. The NOAEL for this effect, based on the graphs, was 30 mg/kg. This dose far exceeds the dose to be administered in the clinical setting for this application. Therefore, potential prolongation of the QT interval is not a major concern for the ocular product.

2. KW-4679 administration at 100 mg/kg resulted in a significant increase in heart rate for up to 5 hr after dosing. Marginal effects were observed on mean, systolic and diastolic blood pressure suggesting a mild vasoactive activity. **Reviewer's Comment** – The Reviewer concurs.

STUDY TITLE: EFFECT OF COMBINATION OF KW-4679 AND ITRACONAZOLE ON THE ECG IN CONSCIOUS DOGS

Study no: —— , 1999 (Report, Pharmaceutical Research Institute, Kyowa Hakko Kogyo Co., Ltd)
Volume #: Module 4, Volume 2
Objective: To determine the effect of olopatadine in combination with itraconazole, a CYP3A4 inhibitor, on the QT interval in conscious dogs.
Method: Treatment was done on the same group of animals with at least a 1-week washout period between treatments. Drugs were administered orally in gelatin capsules. Instrumented male beagle dogs (7-9 months; n = 6) were treated first with vehicle (0.3% sodium carboxymethylcellulose). ECG, blood pressure, and heart rate measurements were taken for 24 hr. On the second phase of treatment, dogs were administered 30 mg/kg of olopatadine. ECG, blood pressure, and heart rate were measured for 24 hr after dosing. On the third phase of treatment, animals were treated with 100 mg/kg itraconazole 1 hr before olopatadine treatment (30 mg/kg). ECG, blood pressure, and heart rate measurement were taken before dosing and 24 hr post-dose.
Results: Olopatadine alone significantly increased ΔHR ($AUC_{0\text{-}10hr}$; the area under the 0 – 10 hr post-dose curve for the Δ value). Compared to vehicle values, ΔHR increased from -1.4 ± 7.4 to 54.8 ± 17.5 beats/min.hr (p = 0.048). A trend towards lower ΔQT ($AUC_{0\text{-}10hr}$) values was observed in olopatadine-treated dogs compared to controls (35.5 ± 27.4 vs 66.9 ± 26.4 msec.hr, respectively; p = 0.216). After olopatadine treatment, ΔmBP ($AUC_{0\text{-}10hr}$) showed a trend towards increasing values (mean systolic, mean diastolic, and mean blood pressure all tended to increase 3-6 hr post-dosing with statistically significant changes at some time points). No significant changes were observed in ΔHR ($AUC_{0\text{-}10hr}$), ΔQT ($AUC_{0\text{-}10hr}$), and ΔmBP ($AUC_{0\text{-}10hr}$) between treatment with olopatadine alone and in combination with itraconazole.
Sponsor's Conclusion and Reviewer's Comment: There is very little possibility of QT prolongation as a result of using olopatadine in combination with a CYP3A4-inhibiting drug such as itraconazole. **Reviewer's Comments:** The study did not include a positive control to demonstrate that there was CYP3A4 inhibition following the dose regimen and form of administration of itraconazole. The dose of olopatadine used (30 mg/kg) was a NOAEL in the study reviewed above. At 100 mg/kg some effects were seen in QTc interval. Thus, 30 mg/kg may have not been a high enough dose to reproduce the prolongation of QTc interval observed previously. On the other hand, at the proposed therapeutic ophthalmic doses, it is unlikely that there will be an effect on hepatic metabolism because of the low systemic exposure. Studies summarized under Section III (Pharmacokinetics/Toxicokinetics) of this review, also demonstrate a lack of significant interaction of olopatadine with the CYP450 drug metabolizing system.

Studies previously submitted under NDA 20-688 and publications submitted with the current NDA are summarized in the following tables.

EFFECTS OF OLOPATADINE IN GENERAL SYMPTOMS, BEHAVIOUR, CENTRAL AND PERIPHERAL NERVOUS SYSTEMS

Ref. no	Test	Method of Assessment	Species	Route	Dose (mg/kg)	Results
29,30	Behavioral Observations	Irwin Screen	Mouse (n = 3/grp)	p.o.	10, 30, 100, 300	No effects at doses ≤ 30 mg/kg 100 mg/kg: transient ↑in respiratory rate 300 mg/kg: ↑respiratory rate, slight sedative effect, ↓ muscle tone, ↓ spontaneous movement (symptoms disappeared within 3 hrs after administration)
	Muscle relaxation	Traction and slant tests	Mouse (n = 10)	p.o.	10, 30, 100, 300	No effect
	Motor coordination	Rotarod test	Mouse (n = 10)	p.o.	10, 30, 100, 300	No effect
	Sleep time prolongation	Pentobarbital-induced	Mouse (n = 10)	p.o.	10, 30, 100, 300	No effect
	Analgesic activity	Phenylbenzo-quinone writhing	Mouse (n = 10)	p.o.	100, 300	No effect
	Anti-convulsant activity	Electroshock and PTZ-induced convulsions	Mouse (n = 10)	p.o.	10, 30, 100, 300	No effect
	Body temperature	Rectal probe	Rat (n = 10)	p.o.	30, 100, 300	No effect
	Blepharoptosis	Reserpine-induced	Mouse (n = 10)	p.o.	300	No effect
	Lethality	Physostigmine-induced	Mouse (n = 10)	p.o.	30, 100, 300	One survival at 300 mg/kg, otherwise no effect
29, 30, 31	Anti-cholinergic activity	Physostigmine-induced lethality	Mouse (n = 10)	p.o.	10, 30, 100, 300	No effect
	EEG	Spontaneous activity & arousal response	Rabbit (n = 4-5)	i.v.	2, 4	No effect
29, 30	EEG	Spontaneous activity & spectral powers	Rat (n = 4-5)	p.o.	20	No effect
29, 30	Spinal Reflex	Responsive to dorsal root stim.	Cat (n = 3)	i.v.	1, 5	No effect
29, 30	Pupil Diameter	Observational	Mouse (n =10)	p.o.	10, 30, 100, 300	Modest dilation at 100 & 300 mg/kg
29, 30	Nictitating Membrane	Contraction Response	Cat (n = 4)	i.v.	0.1, 1	No effect
33	Sleep-wake cycle	EEG, behavior	Cat (n = 5 -6)	p.o.	3, 30	No effect on EEG at any dose Early vomiting noted at 30 mg/kg ↑ slow wave sleep (not stat. significant)
29, 30	Local anesthetic action	Corneal reflex	Guinea Pig (n = 3-5)	Topical ocular	1%, 2%	No effect
		Infiltration anesthesia	Guinea Pig (n = 8)	Intra-cutaneous	0.5%, 1%, 2%	No effect at 0.5 and 1% Anesthetic action in 1 out of 8 guinea pigs at 2%
29, 30	Ischiatic Nerve – anterior tibial muscle	Responsiveness	Rabbit	i.v.	3, 10	No effect
29, 30	Phrenic nerve-diaphragm prep	Responsiveness	Rat	*In Vitro*	$10^{-6} - 10^{-4}$ M	No effect

EFFECTS OF OLOPATADINE ON CARDIOVASCULAR, RESPIRATORY, AND AUTONOMIC NERVOUS SYSTEM

Ref. no	Test	Species	Route	Dose (mg/kg)	Results
34	Rate & contractile force of isolated atria	Guinea Pig (n = 6)	*In vitro*	10^{-6} –10^{-4} M	No significant effects
35	Action potential in isolated ventricular myocytes	Guinea Pig (n = 9)	*In vitro*	10^{-7} –10^{-4} M	No significant effects
34, 36, 37	Acute cardiovascular & respiratory effects	Dog (anesthetized) (n = 4-7)	i.v.	0.1, 0.3, 1, 5, 20, 50, 100	Doses of 0.1-1.0 mg/kg had no effect on respiratory rate, heart rate, or ECG
	Heart rate				No effect observed at doses of 0.1-1.0 mg/kg. Transient ↑ at 5-100 mg/kg, not dose-dependent
	ECG				No effect observed at doses of 0.1-1.0 mg/kg. Changes observed with doses ≥ 5 mg/kg as follows: 5 mg/kg – Transient shortening of R-R interval 20 mg/kg – Transient ↑ in T wave amplitude. 50 mg/kg – Transient prolongation of PR interval and P wave duration 100 mg/kg – Transient prolongation of QRS interval
	Blood pressure				At doses ≤ 5 mg/kg, non dose-dependent ↑ (1-7 mm Hg). At 20-100 mg/kg, dose dependent ↓ (10.7-59%) within 5 min of dosing; recovery time dose-dependent.
	Peripheral vascular Resistance				↓ (50%) at 100 mg/kg
	Femoral blood flow (n = 3-7)				Initial ↑ (15, 39%) at 1 and 5 mg/kg, respectively, were transient (within 1 min), but statistically significant. Decreases (21-30%) at doses ≥ 20 mg/kg were not dose-dependent, but the effect was more sustained at higher doses.
36	Renal blood flow	Dog (anesthetized) (n= 4)	i.v.	5, 20, 50	Significant reversible ↓ at 50 mg/kg (25% at 10 min, 8.5% at 30 min)
34, 36	Respiratory rate	Dog (anesthetized) (n = 4)	i.v.	0.1, 0.3, 1, 5	At 5 mg/kg, significant ↑ 10-15 min post dosing; no effect at lower doses.
36	Blood pressure responses to:	Dog (anesthetized) (n = 3-9)	i.v.	0.1, 0.3, 1, 5	
	Histamine				Hypotensive effect antagonized by doses ≥ 0.1 mg/kg.
	Norepinephrine				Hypertensive effect enhanced by doses ≥ 0.1 mg/kg.
	Isoproterenol				Hypotensive effect enhanced by doses ≥ 0.3 mg/kg.
	Acetylcholine				Hypotensive effect not altered
	Angiotensin II				Hypertensive effect enhanced at 0.1 and 1

Other General/Safety Pharmacological effects of Olopatadine are summarized below.

Ref. no	Test	Species	Route	Dose (mg/kg)	Results
34	**GI System**				
	Gastrointestinal Propulsion	Mouse (n = 10-15)	p.o.	10, 30, 100, 300	No effect on gastrointestinal propulsion at doses ≤ 300 mg/kg
	Saliva secretion				Inhibited by 38% at 300 mg/kg
34	**Water and Electrolyte**				
	Urine volume and electrolyte excretion	Rat (n = 3)	p.o.	3, 30, 100, 300	Potassium ion excretion slightly but significantly ↑ (60%) at 300 mg/kg. No effect on urine volume, Na^+ or Cl^- ion concentrations at doses ≤ 300 mg/kg.
34	**Isolated Smooth Muscle Preps**				
	Uterus	Rat (n = 4-5)	i.v.	1, 5 mg/kg	Slight ↓ in contractile force (25%) and frequency (17%) at 5 mg/kg
		Guinea pig extracted uteri (n=4-5)	*In vitro*	10^{-6}-10^{-4} M	No effect on spontaneous contraction at doses ≤ 10^{-5} M. Slight inhibition on contractile force at 10^{-4} M. Inhibited oxytocin- induced contractions (IC_{50} = 3.2 X 10^{-5} M).
	Vas deferens	Guinea Pig (n = 4)	*In vitro*	10^{-6}-10^{-4} M	No effect on muscle tension. At concentrations ≥ 10^{-4} M, inhibited norepinephrin-induced contractile response.
	Ileum	Rabbit (n = 4)	*In vitro*	10^{-6}-10^{-4} M	Significant effect on force and frequency of spontaneous contractions at 10^{-4} M.
	Ileum	Guinea pig (n = 3-19)	*In vitro*	10^{-9}-10^{-4} M	Inhibited contractions induced by histamine (pA2 = 7.69), acetylcholine (IC_{50} = 1.6 x 10^{-4} M), and serotonin (IC_{50} = 3.3 x 10^{-5} M). No effect on bradykinin or LTD_4 induced contractions at doses ≤ 10^{-4} M
39	Trachea	Guinea pig (n = 4-11)	*In vitro*	10^{-9}-10^{-4} M	Competitive antagonism (pA2 = 8.59); noncompetitive antagonism (pD'2 = 7.00)
34	**Hematology**				
	Coagulation	Rabbit blood (n = 6)	*In vitro*	10^{-5}-10^{-3} g/mL	No effect.
	Hemolytic action	Human RBCs (n = 1; multiple Human RBCs)	*In vitro*	10^{-5}-10^{-3} g/mL	Hemolytic activity at 10^{-4} g/mL or greater.

The Sponsor mentioned that the Safety Pharmacology studies were not conducted according to GLP but incorporated most of the GLP standards.

Safety pharmacology summary: Olopatadine elicited effects on respiration and behavior in rodents, but only at oral doses of 100 mg/kg and 300 mg/kg, respectively. The human equivalent doses are 8.13 mg/kg (300 mg/m^2) and 24.4 mg/kg (900 mg/m^2), respectively. Therefore, these effects occurred at doses which are more than 3 orders of magnitude above the proposed maximum daily ophthalmic dose (3.2 μg/kg, 40 μl drop size, 50 kg person). Because some drugs of this class (antihistamines) are recognized as having a potential to precipitate cardiac arrhythmias (e.g., prolongation of the QTc interval) in susceptible individuals, studies were also conducted to address the potential of olopatadine to affect cardiac electrophysiology. In anesthesized dogs, no effects on heart rate, ECG, or respiratory rate were observed after intravenous doses < 5 mg/kg. At i.v. doses > 5 mg/kg, transient effects on heart rate, blood pressure, ECG, or respiratory rate were observed. Effects were also observed in peripheral vascular resistance (↓ at 100 mg/kg), femoral blood flow (↓ at ≥ 20 mg/kg), and renal blood flow (↓ at 50 mg/kg) suggesting a vasoactive activity. The two new *in vitro* and *in vivo* cardiovascular

studies submitted showed that olopatadine blocks hERG channels and prolonged the QTc interval in conscious dogs. However, the doses and concentrations at which these effects were observed significantly exceed anticipated human exposure following topical ocular administration (> 800 fold for the *in vivo* study). *In vitro* studies showed that olopatadine did not show any changes in the rate and contractility in guinea pig right atrium preps at 1-100 μM (Ref. 34) and exerted no significant effects on action potential parameters in guinea pig ventricular myocytes at 0.1 μM – 100 μM (Ref. 35), supporting that olopatadine has low potential to cause ventricular arrhythmias. ECG profiles observed following oral dosing with olopatadine alone or concomitantly with the CYP3A4 inhibitor, itraconazole, were similar, suggesting that the pharmacologic effects of olopatadine at therapeutic ophthalmic doses are unlikely to be altered by drugs causing inhibition of this CYP450 isozyme. In spite of the deficiencies in the study design (refer to Reviewer's comments above), additional studies summarized under Pharmacokinetics/Toxicokinetics Section of this review, support that olopatadine does not have significant effects on CYP450 activity.

Safety pharmacology conclusions: Olopatadine caused untoward pharmacologic effects in respiratory, behavioral, and cardiovascular systems following systemic doses. However, the doses at which these effects were observed are greatly in excess of therapeutic ophthalmic doses. Therefore, olopatadine is not expected to cause significant pharmacological adverse effects in humans following topical ocular administration of 0.2% Olopatadine Hydrochloride Ophthalmic Solution. The maximum daily dose of [redacted] is the same as that of PATANOL®. The marketing experience with PATANOL® futher supports the safety of the proposed human maximal dose.

III. PHARMACOKINETICS/TOXICOKINETICS:

Extensive studies to address the PK/TK of olopatadine in several species (rats, rabbits, dogs, and monkeys) were submitted under NDA 20-688 and reviewed by Asoke Mukherjee, Ph.D. (review date, July 16, 1996). A general summary of the findings follows (refer to Dr. Mukherjee's review for more details). Studies are included in Ref. 43 –76 (See Appendix).

Absorption: Following i.v. administration, the elimination of olopatadine from plasma was relatively rapid with $t_{1/2}$ of 0.7 hr in rabbits, 5 hr in rats, 7 hr in dogs, and 10 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. 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 $t_{1/2}$ of olopatadine from plasma following the topical ocular dose was similar to that observed following an i.v. dose (0.8 hr).

Distribution: Ocular tissue distribution studies following a topical ocular dose of the 0.15% ^{14}C-Olopatadine Ophthalmic Solution in rabbits showed that radioactivity was absorbed into the eye and reached maximal tissue levels within 0.5 to 1 hr. Tissues at the site of dosing (i.e., cornea and conjunctiva) had the highest concentrations at 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 $t_{1/2}$ of 1 to 2 hr,

except for lens (9 hr). Although the lens had a somewhat longer $t_{1/2}$, 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 ^{14}C-olopatadine. Maximal concentrations in tissues, blood and plasma were generally found at 0.5 to 1 hr with highest concentrations found in the GI tract (6.05 µg eq/g), liver (1.93 µg eq/g), and kidney (1.71 µg eq/g). The plasma C_{max} was 209 ng.eq/ml at 0.5 hr. Concentrations of radioactivity in brain (0.01 µg eq/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 $t_{1/2}$ of 16.8 hr. There was no evidence of accumulation in any tissue with most of the radioactivity eliminated by 168 hr post-dose.

Radioactive 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 the 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 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 ^{14}C-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 eq/mL to 1000 ng eq/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 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 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 major 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 after a 1 mg/kg oral dose, were 27%, 52%, and 40%, respectively.

The following nonclinical PK/TK studies was conducted with the new 0.2% Olopatadine Hydrochloride formulation.

STUDY TITLE: OCULAR TISSUE DISTRIBUTION OF OLOPATADINE FOLLOWING A SINGLE TOPICAL OCULAR DOSE OF A 0.2% OLOPATADINE OPHTHALMIC SOLUTION TO MALE NEW ZEALAND WHITE RABBITS

Study #: TR# 023:33:0502
Volume #: Module 4, Volume 4
Objective: To determine the concentration of olopatadine in anterior-segment ocular tissues (aqueous humor, conjunctiva, cornea, iris-ciliary body, lens) and plasma following a single topical ocular dose of the proposed 0.2% Olopatadine QD Ophthalmic Solution
Drug, lot #: 0.2% Olopatadine Ophthalmic Solution, lot # 17033
Method: Male New Zealand White Rabbits (4/time point) received a topical ocular dose (30 μl) in the right eye. Aqueous humor, conjunctiva, cornea, iris-ciliary body, lens, and plasma were collected up to 48 hr post-dose. Olopatadine concentrations were determined by LC/MS/MS.
Results: Olopatadine was absorbed into the eyes following a single topical ocular dose of 0.2% Olopatadine Ophthalmic Solution (refer to table below). The highest concentrations of olopatadine were found in tissues associated with the site of dosing (conjunctiva and cornea). In most tissues, maximal levels were reached within 0.5 – 1 hr, except for the lens (4 hr).

Concentrations of olopatadine declined with $t_{1/2}$ of 1 – 2 hr. The $t_{1/2}$ in the lens was 8 hr, but the $AUC_{0\text{-}8hr}$ was 26-fold lower than that in aqueous humor, indicating relatively low uptake. The plasma $AUC_{0\text{-}8hr}$ value was 900- and 400-fold lower than the values in cornea and conjunctiva, respectively.

PK PARAMETERS OF OLOPATADINE IN OCULAR TISSUES AND PLASMA FOLLOWING A SINGLE TOPICAL OCULAR DOSE OF A 0.2% OLOPATADINE OPHTHALMIC SOLUTION TO RABBITS

PK Parameter	Aqueous Humor	Conjunctiva	Cornea	ICB*	Lens	Plasma
T_{max} (hr)	1.0	0.5	0.5	0.5	4.0	0.5
C_{max} (ng/g or ml)	87.4	931	1230	82.2	1.70	1.85
$t_{1/2}$ (hr)	1.3	2.0	1.4	1.5	8.0	2.5
$AUC_{0\text{-}8hr}$ (ng•hr/g or ml)	292	995	2280	219	11.2	2.5

*ICB = iris-ciliary body

Conclusions: Olopatadine was absorbed into eye tissues following a single topical ocular dose of 0.2% Olopatadine Ophthalmic Solution. The distribution was primarily to cornea and conjunctiva with little systemic distribution. In a previous study (Ref. 49), similar pattern of distribution and $t_{1/2}$ values were obtained after topical ocular administration of 0.15% Olopatadine Ophthalmic Solution. Therefore, the additional excipients found in the 0.2% Olopatadine QD Ophthalmic Solution (— povidone and —, edetate disodium) did not affect the ocular distribution of olopatadine.

Findings from studies that evaluated the effects of olopatadine on CYP450 are summarized in the following table:

Study Tittle	Species/Test system	Dose	Results
Disposition of KW-4679 (olopatadine): Effect of Repeated Oral Administrations of KW-4679 to Rats on the Hepatic Drug-Metabolizing Enzymes TR# 059:38570:0995 Module 4, Volume 5	Sprague-Dawley ♀ Rats (n=6/group)	Olopatadine: 0.1, 1, 25 mg/kg, p.o. for 7 days Phenobarbital: 80 mg/kg, p.o. for 7 days	Olopatadine had no significant effect on body weight, microsomal protein content, CYP450 levels, cytochrome b_5 levels, and aniline hydroxylase, aminopyrine N-demethylase, and 7-ethoxycoumarin o-deetylase activities. The expected response was observed with the positive control (phenobarbital) except for cytochrome b_5 content (was higher than the control group but not statistically significant).
Study of Drug Interaction (by Olopatadine) in Human Liver Microsomes TR# 022:33:0400 Module 4, Volume 5	Human liver microsomes	0 – 100 μM (0-33900 ng/ml)	No inhibition of the metabolism of any isozyme specific substrate: phanacetin (CYP1A2), tolbutamine (CYP2C8-9), S-mephenytoin (CYP2C19), bufuralol (CYP2D6), chlorzoxazone (CYP2E1), and testosterone (CYP3A4) Inhibition was observed with the positive controls (inhibitors of each isozyme).

PK/TK summary: Most of the PK/TK studies submitted with the current NDA were previously submitted with NDA 20-688 and reviewed by Asoke Mukherjee, Ph.D. (review date, July 16, 1996). A summary of these studies was provided above. Concerning the proposed 0.2 % Olopatadine QD Ophthalmic Solution, a study was conducted to determine the concentration of

olopatadine in anterior-segment ocular tissues (aqueous humor, conjunctiva, cornea, iris-ciliary body, lens) and plasma following a single topical ocular dose in rabbits. The highest concentrations of olopatadine were found in tissues associated with the site of dosing (conjunctiva and cornea). In most tissues, maximal levels were reached within 0.5 - 1 hr, except for the lens (4 hr). Concentrations of olopatadine declined with $t_{1/2}$ of 1 – 2 hr. Low levels of olopatadine were detected in plasma with a C_{max} of 1.85 ng/ml and $t_{1/2}$ of 2.5 hr. The plasma $AUC_{0\text{-}8hr}$ value was 900- and 400-fold lower than the values in cornea and conjunctiva, respectively.

An *in vivo* and an *in vitro* studies were conducted to address possible interactions of olopatadine with the CYP450 metabolizing system. In the *in vivo* study, female Sprague-Dawley rats were given a single oral dose of 0.1, 1 or 25 mg/kg olopatadine daily for 7 consecutive days. Animals dosed with 80 mg/kg phenobarbital were used as positive controls for CYP450 induction. In olopatadine-treated groups, there was no significant effect on body weight, microsomal protein content, CYP450 levels, cytochrome b_5 levels, and aniline hydroxylase, aminopyrine N-demethylase, and 7-ethoxycoumarin o-deetylase activities. In the phenobarbital-treated animals, all the parameters and enzyme activities measured were significantly increased compared to the control group ($p<0.01$) with the exception of cytochrome b_5 content (was higher than the control group but not statistically significant). In the *in vitro* study, the inhibitory activity of olopatadine on the metabolism of the following six CYP450 isozymes specific substrates was determined in human liver microsomes: phanacetin (CYP1A2), tolbutamine (CYP2C8-9), S-mephenytoin (CYP2C19), bufuralol (CYP2D6), chlorzoxazone (CYP2E1), and testosterone (CYP3A4). Olopatadine did not inhibit the metabolism of any isozyme specific substrate at concentrations up to 100 μM (33900 ng/ml). The positive controls (selective inhibitors for each isozyme) showed inhibition of enzymatic activity.

PK/TK conclusions: Olopatadine was absorbed into rabbit eye tissues following a single topical ocular dose of 0.2% Olopatadine QD Ophthalmic Solution. The distribution was primarily to cornea and conjunctiva with minimal amounts found in plasma (C_{max} of 1.85 ng/ml). In a previous study (Ref. 49), similar pattern of distribution and $t_{1/2}$ values were obtained after topical ocular administration of 0.15% Olopatadine Ophthalmic Solution. Therefore, the findings suggest that the additional excipients found in the 0.2% Olopatadine Ophthalmic Solution (— povidone and — edetate disodium) may not affect the ocular distribution of olopatadine in humans. Olopatadine demonstrated a lack of effect on CYP450 drug metabolism system *in vitro* (human liver microsomes) at concentrations up to 100 μM (33900 ng/ml) and *in vivo* (female rats treated with 0.1 - 25 mg/kg for 7 days). The maximum plasma concentrations found in human after topical ocular administration of 0.15% Olopatadine Ophthalmic Solution, twice daily for 15 days, were generally below the quantitation limit (<0.5 ng/ml to 1.28 ng/ml)[1]. Therefore, the lack of an effect on CYP450 activity in the nonclinical studies at concentrations up to 25 mg/kg (*in vivo*) or 100 μM (*in vitro*), and the low olopatadine levels achieved systemically after ocular administration to humans, suggest that olopatadine has low potential to affect the activity of the CYP450 enzymes after a once a day ocular administration of 0.2% Olopatadine Ophthalmic Solution.

IV. GENERAL TOXICOLOGY:

[1]PDR Drug Information for PATANOL, TR# 080:38610:0294, TR# 002:38610:0195

A three-month ocular and systemic toxicity study, as proposed at the End of Phase II Meeting held on March 14, 2001, was conducted. Additional General Toxicology Studies submitted under this NDA were previously submitted under NDA 20-688 and reviewed by Asoke Mukherjee, Ph.D. (review dated July 16, 1996). A summary of the studies is presented in a table at the end of this section.

STUDY TITLE: THREE-MONTH TOPICAL OCULAR SAFETY TOXICITY EVALUATION OF OLOPATADINE QD OPHTHALMIC SOLUTIONS IN RABBITS WITH A SIX-WEEK INTERIM EVALUATION

Key study findings: Daily ocular administration of 0.2% or 0.4% Olopatadine QD Ophthalmic Solution did not elicit any systemic or significant ocular toxicity. Minimal conjunctival congestion and aqueous flare occurred in some animals. Minimal conjunctival congestion was also noted in the vehicle controls.

Study no: TR #034:30:0402
Volume #, and page #: Volume 12, Module 4
Conducting laboratory and location: Alcon Research Ltd., 6201 S. Freeway, Forth Worth, TX 76134
Date of study initiation: 3-21-01
GLP compliance: Yes
QA report: Yes
Drug, and lot #:
0.2% Olopatadine QD Ophthalmic Solution, lot # 01-28526-1
0.4% Olopatadine QD Ophthalmic Solution, lot # 01-28528-1

Chemical analysis was performed prior to initiation and at the completion of the study. Olopatadine concentration was [redacted] of the label at the start of the study and remained at similar concentrations at the completion of the study. The concentration of benzalkonium chloride in the test and control article was [redacted] of label in the pre- and post-study samples. A slight amount of [redacted] was detected in the pre-study samples ([redacted]) in both olopatadine solutions. At completion of the study, degradation products were detected in both olopatadine solutions as shown in the table below.

Component	0.2%	0.4%
[redacted]		

Formulation/vehicle: Olopatadine QD Vehicle, lot # 01-28524-1

Methods (unique aspects): Rabbits were divided into two control groups (an untreated and a vehicle control) and two treatment groups. Three rabbits/sex/groups were treated for six weeks while the remaining rabbits/group were treated for 13 weeks.

Dosing:

Species/strain: Rabbits/F_1 cross of New Zealand Red x New Zealand White
#/sex/group or time point (main study): 8/sex/group
Satellite groups used for toxicokinetics or recovery: None
Age: 3 – 4 months
Weight: 2.1 – 2.9 kg
Doses in administered units: 0, 0.2, and 0.4%
Route, form, volume, and infusion rate: One drop (~ 30 μl) was administered to the superior corneo-scleral junction of both eyes t.i.d.

Observations and times:

Clinical signs: Twice daily for morbidity, morbundity, general heath and well being, and overt signs of toxicity. A detailed health examination was also performed twice/week.
Body weights: On Day 0, weekly afterwards, and prior to necropsy
Food consumption: Not measured
Ophthalmoscopy:
Slit-lamp biomicroscopic examinations: On Day 0 and during Weeks 1, 2, 3, 4, 6, 9, and 13
Indirect ophthalmoscopic examinations: At pre-treatment and after 6 and 13 weeks of treatment; the fundus of each eye was evaluated in respect to the optic nerve head characteristics, fundic vascular pattern (retinal and choroidal), and pigmentation/ coloration characteristics.
Pachymetry: On Day 0 and after 6 and 13 weeks of treatment
Intraocular pressure: On Day 0 and after 6 and 13 weeks of treatment
EKG: Not performed
Hematology: After 6 and 13 weeks of treatment
Clinical chemistry: After 6 and 13 weeks of treatment
Urinalysis: Not performed
Gross pathology: At end of 6 and 13 week treatment periods
Organs weighed: Adrenals, liver, spleen, kidneys, heart, gonads, and brain
Histopathology: Eyes, eyelids, nictitating membrane, Harderian glands, lacrimal glands, nasal-lacrimal tissue, adrenals, aorta, bone and bone marrow (femur, rib, sternum), brachial plexus, brain, cecum, colon, duodenum, cervix, epididymides, esophagus, gallbladder, heart, ileum, jejenum, kidneys, larynx, liver, lungs, lymph nodes (cervical and mesenteric), mammary glands, oviducts, ovaries, pancreas, parathyroids, peripheral nerve (sciatic), Peyer's patch, pituitary, prostate, rectum, sacculus rotundus, salivary glands, seminal vesicle, skeletal muscle, skin, spleen, spinal cord (cervical, midthoracic, lumbar), stomach (cardia, fundus, pylorus), testes, thymus, thyroids, tongue, trachea, ureter, urethra, urinay bladder, uterus, vagina, and gross lessions

Results:

Mortality: None
Clinical signs: No treatment-related effects
Body weights: No treatment-related effects

Ophthalmoscopy:

Slit-lamp biomicroscopic examinations: No treatment-related alterations in conjunctival swelling, conjunctival discharge, light reflex, or iritis were observed in any group. In addition, there were no corneal abnormalities or signs or neovascularization. The following effects were observed:

Conjunctival congestion: Minimal congestion (score = 1, scale max. = 3) was observed in some animals from both vehicle and test-article treated eyes on Day 63 and Day 91.

Aqueous flare: Three rabbits treated with 0.4% test-article had mild aqueous flare (score = 1, scale max. = 3) on Day 42. The finding was not apparent on subsequent examinations.

Lens abnormalities: One vehicle-treated ♀ developed anterior capsular opacity on the OD lens on Day 7. On Day 63, a ♂ rabbit developed focal nuclear cataract on the OD eye. Both observations remained until the end of the study.

Indirect ophthalmoscopic examinations: All animals were normal.

Pachymetry: No treatment-related effects

Intraocular pressure: On Day 90, a statistically significant decrease ($p < 0.05$) was observed in ♀ at both 0.2 and 0.4% test-article (25.7% and 21.0% ↓ from untreated controls, respectively). In males, IOP was decreased by ~25% in both test-article treated-groups at Day 90, but the decrease was not statistically significant.

Hematology: No treatment-related effects

Clinical chemistry: No treatment-related effects

Organ weights: No treatment-related effects

Gross pathology: No treatment-related effects

Histopathology: All findings were considered incidental as they showed minimal severity and/or there was no dose response.

Summary of study findings: Rabbits were treated with Olopatadine Ophthalmic Solution (0.2 or 0.4%) which contains — povidone and — edetate disodium as additional excipients compared to the approved product PATANOL®. Topical ocular administration (one drop t.i.d. to both eyes, for up to 3 months) did not elicit any systemic or significant ocular toxicity. Minimal conjunctival congestion and aqueous flare occurred in some animals. Minimal conjunctival congestion was also observed in vehicle controls. Chemical analysis of the test-article showed that a slight amount of — was present in the pre-study samples in both olopatadine solutions. At the completion of the study, — were present at concentrations of — label. The total amount of degradation products detected was —

The study was deficient in that PK measurements were not done to determine systemic exposure. However, on study TR# 023:33:0502 (refer to Pharmacokinetics/Toxicokinetics Section) low levels (C_{max} = 1.85 ng/ml) of olopatadine were found in plasma after single ocular administration of 0.2% Olopatadine QD Ophthalmic Solution. In a multiple dose study for up to 1 month, mean peak plasma concentrations for the 0.1% q.i.d, 0.2% q.i.d., and 0.2% h.i.d. (six times a day) dose groups were 1.26 ± 0.86 ng/ml, 2.57 ± 1.49 ng/ml, 2.49 ± 1.33 ng/ml, respectively (Ref. 72).

Conclusions: Daily ocular administration of 0.2% or 0.4% Olopatadine QD Ophthalmic Solution did not elicit any systemic or significant ocular toxicity except for minimal conjunctival congestion (also observed in vehicle controls) and aqueous flare in some animals. The results support that a single daily dose of 0.2 % Olopatadine QD Ophthalmic Solution is expected to be well-tolerated in humans. The study also support that — degradations products up to a level of — are acceptable — x 3 doses/day), which is slightly higher than the clinical product specifications of NMT — (Module 2.3.P.5, p. 24). Refer to study TR# 039:30:0501 and report by — on Section VIII of this review, Special Toxicology Studies, for further evaluation of degradation products.

General Toxicology Studies previously submitted under NDA 20-688 are summarized in the following table. Studies are included in Ref. 77 – 92 (See Appendix).

TOXICOLOGY STUDIES WITH OLOPATADINE

Study	Species	Dose (mg/kg/day)	Route	Major Findings
Single Dose[a]	Mouse/Slc:ICR (n=5/sex/grp)	250 - 2000	p.o.	LD_{50} = 1.15 g/kg for ♂ LD_{50} = 1.83 g/kg for ♀ ↓ spontaneous activity, blepharoptosis, mydriasis and hydronephrosis at most doses; abnormal gait, slow respiration, dyspnea, abnormal respiratory sounds, tremors, convulsions, and hypothermia, at ≥ 1000
	Rat/Wistar (n=10/sex/grp)	800 - 5000	p.o.	LD_{50} > 5 g/kg for ♂ LD_{50} = 3.87 g/kg for ♀ Mydriasis, relaxation of scrotum, abnormal respiratory sounds at all doses; ↓ spontaneous activity, blepharoptosis, and hypothermia, at ≥ 3000; tremor, jumping, dyspnea, renal infarct in dead animals, fading and swelling of kidneys and hydronephrosis in survivors
	Rat/Wistar (n=10/sex/grp)	110 - 150	i.v.	LD_{50} = 127.5 g/kg for ♂ LD_{50} = 144.1 g/kg for ♀ Mydriasis, relaxation of scrotum, ↓ spontaneous activity, ↑ respiratory rate, abnormal respiratory sounds at all doses; straub tail (at ≥125 in ♂, at ≥146 in ♀); dyspnea and jumping in dead animals, fading and swelling of kidneys in survivors
	Dog/Beagle (n=2/sex)	5000	p.o.	No deaths, animals vomited within 30 min post-dose; mydriasis, dry muzzle
	Dog/Beagle (n=2 ♂/grp	150, 300	i.v.	One death due to respiratory arrest at 300; spasm, tonic and clonic convulsions, mydriasis, vomiting, dry muzzle
Repeated Dose[a] Systemic	Rat/Wistar (n=10/sex/grp)	0, 20, 60, 200, 600	p.o., 4 weeks	Abnormal respiratory sounds: ♂ at ≥200, ♀ at ≥ 60; lacrimation ≥ 200; mydriasis ≥ 600; slight centrilobular hepatocytes swelling at 600 NOEL = 20 mg/kg/day
	Rat/Wistar (n=15/sex/grp)	0, 6, 25, 100, 400	p.o., 13 weeks	Abnormal respiratory sounds at ≥100; ↑ ALP at 400; Microscopic lesions in liver (slight hepatocyte necrosis and swelling, hyperplasia of bile duct) at ≥ 6; stomach (degeneration of mucosal epithelium) at 6 – 100; kidney (degeneration and necrosis), prostate (inflammatory cell infiltration and ↓ gland secretion) at

				400; seminal vesicle (decreased secretion) at 6, 100, and 400; uterus (atrophy at 400, dilatation in the uterine horn at 6, 25, 400)
	Dog/Beagle (n=4/sex/grp)	2, 10, 50, 250	p.o., 4 weeks	Mydriasis at ≥ 50; salivation at 250; gallbladder enlargement at 250; fatty degeneration of the hepatocytes and renal tubular epithelium, vacuolar degeneration of pancreatic exocrine cells, ↓ cells in bone marrow and thymus, ↓ parotid gland zymogen granules, atrophy of testes and prostate at 250 (n = 1-2)
	Dog/Beagle (n=3-5/sex/grp)	0, 0.6, 10, 40, 160	p.o., 13 weeks	One ♀ at 160 found dead with microscopic findings of hepatic and renal congestion, thymic hemorrhage and fibrosis, and degeneration and necrosis of coronary and renal arteries; conjunctival hyperemia in all grps; slight ↑ in SGPT in one ♀ at 0.6, one ♂ at 10, and one ♂ at 160; gall bladder fading and swelling at 160; renal swelling at ≥ 40; microscopic findings included slight clarification of hepatocytes in all grps, slight clarification of renal tubular epithelium at 160, fatty degeneration of renal tubular epithelium in ♀ at 160; ↓ R- and S-wave in one out of two ♂ at 160
	Rat/Wistar (n = 30)	0, 1, 10, 100	p.o., 52 weeks	Abnormal respiratory sounds at 100; mydriasis in ♀ ≥ 10 and in ♂ at 100; ↑ ALP at 100; hepatocyte vacuolar degeneration in ♂ at 100; microgranuloma in the liver in ♀ at 100; ↓ hematopoietic bone marrow cells in ♀ at 100; atrophy of the thymus in ♂ at ≥ 10
	Dog/Beagle (n=4/sex/grp)	0, 0.6, 5, 40	p.o., 52 weeks	Abnormalities in EKG in the heart: ↑ R-wave height in one ♂ at 5, ↓ Q-wave height in two ♂ at 40, prolongation of P-wave in one ♀ at 5 and one ♀ at 40; focal fibrosis and deposition of brown pigment in the heart in one ♀ at 40; dry oral mucosa cavity and muzzle at 40
Repeated Dose[b] Ocular	Rabbit/NZW	0, 0.1, 0.2%, 2 drops q.i.d 0.2%, 2 drops 6 times/day (0.09 – 0.28 mg/kg/day)	1 month	Minimal conjunctival congestion (hyperemia)
	Rabbit/NZW	0, 0.15, 0.5, 1.0 %, 2 drops q.i.d. (0.13 – 0.87 mg/kg/day)	6 months	Minimal conjunctival congestion (hyperemia)
	Monkey/ Cynomolgus (n=4/sex/grp)	0, 0.1, 0.2, 0.5%, 2 drops q.i.d. (0.096–0.53 mg/kg/day)	6 months	No treatment-related effects

[a]Drug substance; [b]Drug product

Toxicology summary: Daily ocular administration of 0.2% or 0.4% Olopatadine QD Ophthalmic Solution (one drop t.i.d. to both eyes, for up to 3 months) did not elicit any systemic

or significant ocular toxicity except for minimal conjunctival congestion (also observed in vehicle controls) and aqueous flare in some rabbits. Olopatadine, like other agents of this class, caused symptoms of CNS inhibition (e.g., ↓ spontaneous movements) or CNS excitement (e.g., tremor or spasm) at high oral or i.v. doses. Dryness of oral mucosa, nose tip, and abnormal respiratory sounds were other clinical signs observed. Pathological changes in the liver, kidney, heart, etc., occurred at doses much higher than those that could be achieved by the therapeutic ocular dose of 0.2% Olopatadine Ophthalmic Solution in humans (> 300- or 800-fold in rats and dogs, respectively). Chemical analysis of the 0.2% and 0.4% Olopatadine Ophthalmic Solutions used in study TR #034:30:0402, showed that a slight amount of [redacted] was present in the pre-study samples in both olopatadine solutions. At the completion of the 3-month study, [redacted] were present at concentrations of [redacted] label. The total amount of degradation products detected was [redacted].

Toxicology conclusions: The only ocular side effects observed after daily administration of 0.2% Olopatadine Ophthalmic Solution (one drop t.i.d. to both eyes, for up to 3 months) were minimal conjunctival congestion (also observed in vehicle controls) and aqueous flare; there was no systemic toxicity. Therefore, the nonclinical findings support that administration of 0.2% Olopatadine Ophthalmic Solution (one drop/eye once a day) is not expected to be associated with major ocular or systemic side effects. The nonclinical data also support that [redacted] degradations products up to a level of [redacted] are acceptable [redacted] x 3 doses/day). In addition, the safety of these degradation products has been established through the approved product, PATANOL®. Studies summarized under Section VIII of this review, add further evidence to the low toxicity of these olopatadine derivatives.

V. GENETIC TOXICOLOGY:

The studies conducted to determine the genotoxic potential of olopatadine (KW-4679) were previously submitted under NDA 20-688 and were reviewed by Asoke Mukherjee, Ph.D. (review dated July 16, 1996). A summary of the studies is 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

Studies with [redacted] (not submitted with NDA 20-688)

[redacted] is one of the impurities found in the drug substance and the specification limit for the proposed product has been set at NMT [redacted] (Module 2.3.S.4, p. 7). This specification limit is the same as that established for olopatadine hydrochloride under NDA 20-688. The studies were not reviewed in detail because (1) the safety of this impurity has been

established through the approved product, PATANOL®, and (2) the specification limit is below the ICH guideline threshold for biological qualification (1%).

GENOTOXICITY STUDIES WITH [redacted]

Study	System	Concentration / Dose	Results
In vitro Bacterial Reverse Mutation (Module 4, Vol. 17)	*S. typhimurium* (TA98, TA100, TA1535, TA1537), *E. coli* (WP2 *uvrA*)	156-5000 μg/plate ± S9	Negative
In vitro Mutation Chromosome Aberration (Module 4, Vol. 17)	Chinese hamster lung cells	0.35, 0.70, and 1.40 Mm (continuous treatment for 24 or 48 hr) 2.5, 5.0, and 10 mM ± S9 (6 hr treatment, 24 hr total incubation time)	12% at 24 hr at 1.4 mM 12% at 48 hr at 0.70 mM 37% at 48 hr at 1.4 mM 18.5% (-S9) and 10.5 % (+S9) at 10 mM
Micronucleus Assay (Module 4, Vol. 17)	Male [redacted] CD-1 Mice	500, 1000, 2000 mg/kg (single oral dose)	Negative

Genetic toxicology summary: [redacted] was not mutagenic in the Amest Test and did not cause micronuclei formation *in vivo*. Blood levels of olopatadine were not determined in the *in vivo* assay, but previous PK studies have shown that olopatadine has high oral bioavailability (refer to Pharmacokinetics/Toxicokinetics Section). The chromosomal aberration assay was positive for [redacted] at concentrations ≥ 0.70 mM (continuous treatment for 24 or 48 hr without S9) and at 10 mM ± S9 (6 hr treatment).

Genetic toxicology conclusions: The reviewer considers there is no safety concern because the specification limits for [redacted] at NMT [redacted] is much lower than the concentration at which a positive finding was observed in the *in vitro* chromosomal aberration assay (≥ 0.70 mM or > 262 μg/ml). In addition, the *in vivo* micronuclei assay was negative at concentrations up to 2,000 mg/kg.

Labeling recommendations: No changes are recommended.

VI. CARCINOGENICITY:

The carcinogenicity studies conducted with olopatadine (KW-4679) were previously submitted under NDA 20-688 and were reviewed by Asoke Mukherjee, Ph.D. (review dated July 16, 1996). A summary of the studies is given in the following table.

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

Labeling Recommendations: The calculations of Safety Factors needs to be corrected. In NDA 20-688, the factors were calculated based on a total of 8 drops, 40 μl size, and a 50 kg person. The new product has a maximum recommended dose of 1 drop/eye/day. Therefore, a total of 2 drops/day is the maximum human dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

The studies conducted to determine the reproductive and developmental toxicity potential of olopatadine (KW-4679) were previously submitted under NDA 20-688 and were reviewed by Asoke Mukherjee, Ph.D. (review dated July 16, 1996). In NDA 20-688 review, it was concluded that the rabbit teratogenicity study (TR# A-89-59) showed a decrease in the number of live fetuses. However, taking into consideration the high variability within each group, the lack of a dose-response, and the low number of dams tested, it is difficult to conclude that there is a drug-related effect in the number of live fetuses. In teratogenicity study TR # A-89-52, there was a significant decrease in fetal weight from dams treated with 600 mg olopatadine/kg. In addition, rats treated with 600 mg/kg/day of olopatadine during late gestation throughout the lactation period (TR # D-2525) showed a decrease in pup survival and body weight. Label modifications are recommended to reflect these findings. A summary of the studies is given in the following table.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY STUDIES WITH OLOPATADINE

Study	Species	Treatment Duration	Dose Levels/Route	Major Findings
Segment I TR# A-89-26 (Module 4, Vol. 27)	Rats/ Wistar	M: 9th week through mating F: 14th day before mating until Gestation Day 7	0, 6, 50, 400 mg/kg/day, p.o. (gavage)	↓ implantation, corpora lutea, and fertility at 400, ↓ body weight and food consumption at the same dose
Segment II TR# A-89-52 (Module 4, Vol. 27)	Rats/ Wistar	Gestation Day 7-17	0, 60, 200, 600 mg/kg/day, p.o. (gavage)	↑ post-implantation loss at all doses, skeletal anomalies at 600 (delayed ossification of metacarpus and metatarpus, but not statistically significant), ↓ fetal weight by 10% at 600
Segment III TR# D-2525 (Module 4, Vol. 28)	Rats/ Wistar	Gestation Day 17- Lactation Day 21	0, 60, 200, 600 mg/kg/day, p.o. (gavage)	↓ # of pups and pup body weight at 600, ↓ maternal BW and food consumption at the same dose
Segment III TR# D-3289 (Module 4, Vol. 29)	Rats/ Wistar	Gestation Day 17- Lactation Day 21	0, 6, 20 mg/kg/day, p.o. (gavage)	No effect
Segment III TR# A-95-07 (Module 4, Vol. 30)	Rats/ Wistar	Gestation Day 17- Lactation Day 21	2, 4 mg/kg/day, p.o. (gavage)	No effect
Segment II TR# A-89-59 (Module 4, Vol. 27)	Rabbits/ Japanese White	Gestation Day 6-18	0, 25, 100, 400 mg/kg/day, p.o. (gavage)	No effect

Labeling recommendations:

VIII. SPECIAL TOXICOLOGY STUDIES:

STUDY TITLE: ONE-DAY TOPICAL OCULAR IRRITATION (LOCAL TOLERANCE) EVALUATION OF OLOPATADINE/POVIDONE OPHTHALMIC SOLUTIONS IN RABBITS

Key study findings:

- Olopatadine 0.2% Ophthalmic Solution containing — povidone (PVP) did not elicit any significant ocular irritation or systemic toxicity but was less comfortable compared to the vehicle containing — PVP.
- Olopatadine 0.4% Ophthalmic Solution containing — PVP showed a higher incidence of minimal conjunctival discharge and, like 0.2% Olopatadine, was less comfortable compared to the vehicle control.

Study no: TR #162:30:0800
Volume #: Module 4, Volume 30
Conducting laboratory and location: Alcon Research Ltd., 6201 S. Freeway, Fort Worth, TX 76134
Date of study initiation: 7-25-00
GLP compliance: Yes
QA reports: Yes
Drug and lot #:
0.2% Olopatadine/PVP Ophthalmic Solution, lot # 00-26820, % purity = —
0.4% Olopatadine/PVP Ophthalmic Solution, lot # 00-26979, % purity = —

Formulation/vehicle: PVP vehicle

Methods: Three treatment groups were included: PVP vehicle, 0.2% Olopatadine/PVP Ophthalmic Solution, and 0.4% Olopatadine/PVP Ophthalmic Solution. Eight New Zealand White rabbits/group were used (4/sex). Chemical analysis of the test-article solutions as well as of the PVP vehicle control was performed prior to initiation of the study and found to be within acceptable limits.

Dosing: Two drops (~ 60 μl) of test-article or vehicle were administered to the superior corneoscleral junction of the right eye of each animal. The dosing was repeated every 30 min for a total of 10 doses. Animals were observed up to three days post-dose.

Observations and times:

Clinical signs: Observed twice daily for morbidity, morbundity, general heath and well being, and overt signs of toxicity. A detailed health examination was also performed prior to the start of the study and at the termination of the study on Day 4.
Body weights: On Day 0 and on Day 4
Ophthalmoscopy:

Slit-lamp biomicroscopic examinations: Performed on Day 0, 1 hr after the last dose on Day 1 and 24, 48, and 72 hr after the first dose. Normal limits were defined as scores of 0 for all parameters and 0 – 1 for conjunctival congestion.

Comfort Evaluations: After the first and last drug administration, scoring ranged from 0 – 4 with 4 being the least comfortable

Gross pathology: At termination of study on Day 4

Histopathology: At termination of study on Day 4, eyes and adnexa from all animals

Results:

Mortality: None

Clinical signs: No treatment-related effects

Body weights: No treatment-related effects

Ophthalmoscopy:

Slit-lamp biomicroscopic examinations: The following findings were observed on Day 1:

- Moderate conjunctival congestion (score = 2) in 1 ♀ dosed with 0.2% test-article and in 1 ♀ and 1 male dosed with 0.4% test-article
- Minimal conjunctival discharge (score = 1) in 1 ♂ treated with vehicle control, 1 ♂ treated with 0.2 % test-article, 5 rabbits (3♂ and 2 ♀) treated with 0.4% test-article, and in the untreated eye of 1 ♀ in the 0.2% test-article group.

These effects were reversible. No signs of conjunctival swelling, aqueous flare, iritis, loss of light reflex or any corneal abnormalities were observed.

Comfort Evaluations: Both 0.2% and 0.4% test-article were less comfortable than PVP vehicle after both the first and last drug applications (refer to table below). The mean values were similar for both test-article concentrations.

Group	First Dose		Last Dose	
	Mean	Incidence	Mean	Incidence
PVP Vehicle	0.74	6/8	1.63	8/8
0.2 % Olopatadine	1.25	8/8	2.13	8/8
0.4% Olopatadine	1.25	7/8	2.0	8/8

Gross pathology: No gross pathology was observed in any rabbit.

Histopathology: Because no untoward findings were observed, histopathology was not performed. The eyes and adnexa were retained for possible future histological examinations.

Summary: A local tolerance study was conducted with the new clinical formulation of 0.2% Olopatadine Ophthalmic Solution as proposed to the Division at the End of Phase II meeting (March 14, 2001). Animals were treated in the right eye with test-article concentrations of 0.2% or 0.4% Olopatadine/ ⟵ PVP or PVP vehicle control. The dosing was repeated every 30 min for a total of 10 doses. Olopatadine 0.2% Ophthalmic Solution containing ⁀ PVP did not elicit any significant ocular irritation or systemic toxicity but was less comfortable compared to the PVP vehicle. Olopatadine 0.4% Ophthalmic Solution containing ⁀ PVP showed a higher

incidence of minimal conjunctival discharge and, like 0.2% Olopatadine, was less comfortable compared to the vehicle control.

Conclusions: Minimal to moderate conjunctival congestion, minimal discharge, and acceptable discomfort were observed in some animals following a dosing regimen of 2 drops every 30 min for a total of 10 doses. The intended clinical dose is one drop/eye/day. Therefore, the findings support that Olopatadine 0.2% Ophthalmic Solution has a low potential to induce ocular irritation and discomfort in humans.

STUDY TITLE: ONE-DAY TOPICAL OCULAR IRRITATION (LOCAL TOLERANCE) EVALUATION OF OLOPATADINE/POVIDONE OPHTHALMIC SOLUTIONS IN RABBITS

Key study findings: An — old clinical formulation of 0.2% Olopatadine/ — Povidone (PVP) Ophthalmic Solution with degradation products (— of active) did not elicit any significant ocular or systemic toxicity up to 3 days post-dose.

Study no: TR #039:30:0501
Volume #: Module 4, Volume 30
Conducting laboratory and location: Alcon Research Ltd., 6201 S. Freeway, Fort Worth, TX 76134
Date of study initiation: 5-01-01
GLP compliance: Yes
QA reports: Yes
Drug, lot #, and % purity:
0.2% Olopatadine/PVP Ophthalmic Solution, lot # 00-500195-1, % purity = not specified

Formulation/vehicle: PVP vehicle

Methods: The study objective was to determine the ocular irritation potential and comfort of an — old preparation of the proposed clinical formulation. Only one treatment group was included, 0.2% Olopatadine/PVP Ophthalmic Solution. Eight New Zealand White rabbits were used (4/sex). Chemical analysis was performed prior to initiation of the study to analyze the strength and identity of olopatadine, benzalkonium chloride (BAC) preservative, and degradation products.

Dosing: Two drops (~ 60 μl) of test-article were administered to the superior corneoscleral junction of the right eye of each animal. The dosing was repeated every 30 min for a total of 10 doses. Animals were observed up to three days post-dose.

Observations and times:
Clinical signs: Observed twice daily for morbidity, morbundity, general heath and well being, and overt signs of toxicity. A detailed health examination was also performed prior to the start of the study and at the termination of the study on Day 4.
Body weights: On Day 0 and at termination of the study
Ophthalmoscopy:

Slit-lamp biomicroscopic examinations: Performed 1 hr after the last dose on Day 1 and on Day 24. Normal limits were defined as scores of 0 for all parameters and 0 – 1 for conjunctival congestion.

Comfort Evaluations: After the first and last drug administration, scoring ranged from 0 – 4 with 4 being the least comfortable

Gross pathology: Not performed

Histopathology: Not performed

Results:

Chemical analysis: The strength and identity of the test-article and BAC preservative were close to —. The total concentration of degradation products (known and unknown) of olopatadine (AL-4943) amounted to — of the test-article, with amounts of — of the active ingredient found for the — degradation products.

Component	Result Value
AL-4943[a]	

Clinical signs: No treatment-related effects

Body weights: No treatment-related effects

Ophthalmoscopy:

Slit-lamp biomicroscopic examinations: No signs of conjunctival swelling, aqueous flare, iritis, loss of light reflex or any corneal abnormalities were observed. Conjunctival congestion scores of 0 – 1 (minimal) were observed in most treated and some untreated eyes. Minimal conjunctival discharge (score = 1) was observed in one ♂ treated-eye on Day 1 and in one ♀ untreated eye on Day 4.

Comfort Evaluations: The mean comfort score rouse from 1.25 after the first dose to 1.63 after the last dose. Two rabbits have scores of 2 after the first dose compared to 5 rabbits after the last dose. According to the assay standards, the scores are still within the acceptable range.

Summary: A tolerance study was conducted with an — old clinical formulation containing a total of — degradation products (percent of active). Two drops (~ 60 μl) of test-article were administered to the right eye every 30 min for a total of 10 doses. Minimal conjunctival discharge was observed in one male treated-eye on Day 1 and in one female untreated eye on Day 4. The mean comfort score increased from 1.25 after the first dose to 1.63 after the last dose. According to the assay criteria, the comfort scores obtained in both studies are considered acceptable.

Conclusions: The findings indicate that degradation products up to a level of — (percent active) did not present any safety concern. Amounts of — of the active ingredient were found for the — degradation products in the animals studies. The clinical product specifications for — degradation products are NMT — each and NMT — for total impurities (Module 2.3.P.5, p. 24). Since animals received 20x the proposed clinical dose, a safety factor for these impurities of ~5x is provided by the nonclinical data. In addition, the specifications fall below the ICH threshold for biological qualification (1%) and thus, the impurities are not considered to present a safety concern.

STUDY TITLE: TOXICITY OF SINGLE-DOSE ORAL ADMINISTRATION OF RELATED COMPOUNDS —, N-OXIDE DERIVATIVE, N-MONODESMETHYL DERIVATIVE, AND — TO MICE

Key study findings: Olopatadine derivatives were not toxic following a single oral dose of up to 1800 – 1900 mg/kg to mice.

Study no: — , 1995
Volume #: Module 4, Volume 31
Conducting laboratory and location: Safety Research Laboratory, Kyowa Hakko Kogyo Co., Ltd.
Date of study initiation: February 1995
GLP compliance: No
QA Reports: No
Drug and lot #: — , lot # M-940622; N-oxide, lot # 930594-71; N-monodesmethyl, M-22-CAKE-2; —

Formulation/vehicle: Distilled water

Methods:. Scl:ICR (SPF) mice (5/sex/group) were given a single oral administration of the test-article and observations were conducted for a period of 14 days post-dose. — , and the N-oxide and N-monodesmethyl metabolites were the test-articles evaluated.

Dosing: — 225, 450, 900, and 1800 mg/kg
N-oxide, N-monodesmethyl, and — derivatives: 237, 475, 950, and 1900 mg/kg
Control: Untreated group

Observations and times:
Clinical signs: Daily
Body weights: Days 1, 3, 7, and 14
Organ Weights: kidney only
Gross pathology: At termination
Histopathology: At termination

Results:

Mortality: None
Clinical signs: None treatment-related
Body Weights: No treatment-related effects
Organ Weights: No treatment-related changes
Gross pathology: No treatment-related effects
Histopathology: All olopatadine derivatives caused slight to moderate swelling and vacuolation of tubular epithelium. Because of a lack of a dose-response, the finding was not considered toxicological significant.

Summary and Conclusion: None of olopatadine derivatives was toxic following administration of a single oral dose of up to 1800 – 1900 mg/kg to mice. In a previously conducted study, deaths were observed in mice treated with a single olopatadine oral dose ≥ 500 mg/kg (Ref. 77). Therefore, the toxicity of these olopatadine-derivatives is extremely low.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions: Daily ocular administration of 0.2% or 0.4% Olopatadine QD Ophthalmic Solution (one drop t.i.d. to both eyes) for up to 3 months did not elicit any systemic or significant ocular toxicity except for minimal conjunctival congestion (also observed in vehicle controls) and aqueous flare in some rabbits. Minimal to moderate conjunctival congestion, minimal discharge, and acceptable discomfort were observed in acute studies following a dosing regimen of 2 drops every 30 min for a total of 10 doses, which is an exaggerated dose regimen compared to the intended human dose of one drop/eye/day. Therefore, the nonclinical findings support that administration of 0.2% Olopatadine Ophthalmic Solution (one drop/eye once a day) is not expected to be associated with major ocular or systemic side effects.

General Toxicology Issues: Systemic administration of olopatadine have been associated with untoward effects in the CNS, respiratory, and cardiovascular (including a 20-40 msec prolongation of the QTc interval in dogs) systems and pathological changes in the liver, kidney, and heart, among other organs. However, the doses at which these effects occurred are greatly in excess of therapeutic ophthalmic doses and were associated with plasma levels much higher than those detected after ocular administration of 0.15% Olopatadine Hydrochloride Ophthalmic Solution (refer to table below). Therefore, olopatadine is not expected to cause significant adverse effects in humans following topical ocular administration of 0.2% Olopatadine Hydrochloride QD Ophthalmic Solution. The maximum daily dose of [redacted] is the same as that of PATANOL®. The marketing experience with PATANOL® further supports the safety of the dose.

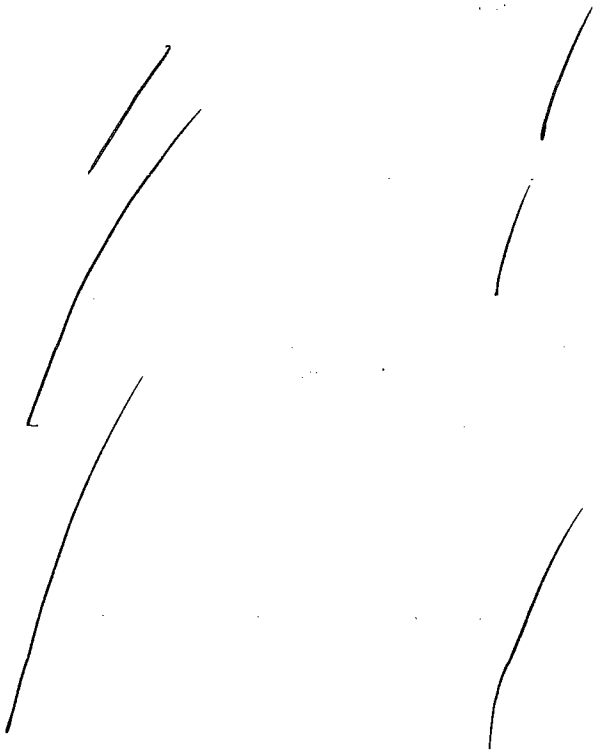
COMPARISON OF MAXIMAL PLASMA LEVELS AT NO EFFECT DOSE LEVELS IN ANIMAL SPECIES WITH HUMANS EXPOSURE FOLLOWING TOPICAL OCULAR ADMINISTRATION

Dose Route	Species	Dose Regimen[a]	C_{max}[b] (ng/mL)	Safety Margin[c]
Oral	Rat	6 mg/kg q.d. 7 Days	566	1132
	Dog	5 mg/kg q.d. 14 Days	2680	5360
Topical ocular	Rabbit	1.0% q.i.d. 6 Months	10.4	21
	Monkey	0.5% q.i.d. 6 Months	7.60	15
	Human	0.15%	<0.5	-

[a]In animal studies, each animal received 2 drops of the test formulation in one eye. In human studies, each subject received 1 drop of the test formulation in one eye.
[b]Values are for plasma.
[c]Safety Margin defined as the ratio of maximal plasma concentration of olopatadine in toxicology species to that in human plasma. Since maximal plasma concentrations of olopatadine in human subjects were typically below the quantitation limit of the assay (0.5 ng/mL), the value of the quantitation limit was used for calculating the margin of safety ratio.

Recommendations: Approval

Labeling with basis for findings: The following changes are recommended: (1) corrections of the safety factors calculated in the Carcinogenesis, Mutagenesis, Impairment of Fertility and Pregnancy Sections, and (2) revision of the Pregnancy Section regarding non-teratogenic effects of olopatadine.



X. APPENDIX/ATTACHMENTS:

STUDIES AND PUBLICATIONS SUBMITTED WITH THIS NDA (Includes reference to studies submitted previously under NDA 20-688)

Ref. No.	Report # or Publication	Section / Subsection / TR Title	In NDA 20-688
		PHARMACOLOGY	
		Primary Pharmacodynamics	
1	Yanni et al., 1996	Yanni JM, Stephens DJ, Miller ST, Weimer LK, Graff G, Parnell D, Lang LS, Spellman, JM, Brady MT, Gamache DA. The in vitro and in vivo ocular pharmacology of olopatadine (AL-4943A), an effective anti-allergic/antihistaminic agent. *J Ocular Pharmacol Ther* 1996;**12(4)**:389-400.	No
2	TR# 039:39900:1093	Preclinical evaluation of the anti-histaminic activity of AL-4943A clinical formulations	Yes
3	TR# 033:32:0600	Preclincal evaluation of the anti-histaminic efficacy of the proposed QD PATANOL clinical formulation	No
4	TR# 017:39900:0693	AL-4943A (KW-4679): Summary of preclinical pharmacology evaluation	Yes
5	Sharif et al., 1996a	Sharif NA, Xu SX, Miller ST, Gamache DA, Yanni JM. Characterization of the ocular antiallergic and antihistaminic effects of olopatadine (AL-4943A), a novel drug for treating ocular allergic diseases. J Pharmacol Exp Ther 1996;278:1252-61.	No
6	Miller et al., 1996	Miller S, Cook E, Graziano F, Spellman J, Yanni J. Human conjunctival mast cell responses in vitro to various secretagogues. Ocular Immunol Inflamm 1996;4(1):39-49.	No
7	Cook et al., 2000	Cook EB, Stahl JL, Barney NP, Graziano FM. Olopatadine inhibits TNFα release from human conjunctival mast cells. Ann Allergy Asthma Immunol 2000;84:504-8.	No
8	Yanni et al., 1997	Yanni JM, Miller ST, Gamache DA, Spellman JM, Xu S, Sharif NA. Comparative effects of topical ocular anti-allergy drugs on human conjunctival mast cells. Ann Allergy Asthma Immunol 1997;79(6):541-5.	No
9	Yanni et al., 1999	Yanni JM, Weimer LK, Sharif NA, Xu SX, Gamache DA, Spellman JM. Inhibition of histamine-induced human conjunctival epithelial cell responses by ocular allergy drugs. Arch Ophthalmol 1999;117:643-7.	No
10	Sharif et al., 1996b	Sharif NA, Xu SX, Yanni JM. Olopatadine (AL-4943A). Ligand binding and functional studies on a novel, long acting H1-selective histamine antagonist and anti-allergic agent for use in allergic conjunctivitis. J Ocular Pharm Ther 1996;12(4):401-407.	No
11	TR# 012:39730:0895	Olopatadine (AL-4943A): Ligand binding and functional studies on a novel, long-acting H_1 selective histamine antagonist/anti-allergic agent for use in allergic conjunctivitis	Yes
12	TR# 020:32:1101	AL-18876-01 and AL-24956A data.	No
13	TR# 030:39900:0892	*In vitro* receptor binding profiles of ALO4943A (KW-4679) and ALO3024 (ketotifen)	Yes
14	TR# 005:39930:1093	Affinity and potency of KW-4679 (ALO4943A) for histamine receptor subtypes determined by receptor binding and phosphoinositide turnover techniques	Yes
15	TR# 012:32:0300	AL-18876 (Olopatadine N-Oxide): Effect on histamine release from human conjunctival mast cells.	No

Ref. No.	Report # or Publication	Section / Subsection / TR Title	In NDA 20-688
		Secondary Pharmacodynamics	
16	Kaise et al., 1995	Kaise T, Manabe H, Ohmori K. The effect of KW-4679, an antiallergic drug, on experimental allergic rhinitis. Allergy 1995: 44(10):1229-1233.	No
17	[redacted]	[redacted] Effect of [redacted] on experimental allergic conjunctivitis and rhinitis in rats and guinea pigs.	No
18	TR# 89-111(Y)	Pharmacological properties of KW4679 – Effects on passive cutaneous anaphylaxis in rats	Yes
19	TR# 89-108(Y)	Pharmacological properties of KW4679 – Effects on bronchial anaphylactic reactions	Yes
20	Ishii et al., 1995a	Ishii H, Sasaki Y, Ikemura T, Kitamura S, Ohmori K. Pharmacological studies on KW-4679, an antiallergic drug (1): Inhibitory effect on passive cutaneous anaphylaxis (PCA) and experimental asthma in rats and guinea pigs. Folia Pharmacol Jpn 1995;106:289-298.	No
21	TR # 039:32:0900	Olopatadine (KW-4679): Effect on bronchoalvelolar lavage (BAL)-derived leukocyte counts following aerosol antigen challenge studies by Kyowa Hakko (1993)	Yes
22	Ohmori et al., 1996	Ohmori K, Ishii H, Sasaki Y, Ikemura T, Manabe H, Kitamura S. Effects of KW-4679, a new orally active antiallergic drug, on antigen-induced bronchial hyperresponsiveness, airway inflammation and immediate and late asthmatic responses in guinea pigs. Int Arch Allergy Immunol 1996;110:64-72.	No
23	TR# 89-72(Y)	Occupancy of histamine H1 receptors in guinea pigs after oral administration of KW4679, an antiallergic agent	No
24	Sasaki et al., 1995a	Sasaki Y, Ishii H, Ikemura T, Miki I, Tamura T, Sitamura S, Ohmori K. The antihistaminic effect of KW-4679, a novel antiallergic drug. Clin Pharm Ther 1995;5(10):1825-35.	No
25	Sasaki et al., 1995b	Sasaki Y, Ikeda Y, Ikemura T, Okamura K, Miyake K, Ishii H, Ohmori K. Effect of the new antiallergic drug KW-4679 on histamine and leukotoleuen released by the abdominal cavity effusion cells in rats. Clin Pharm Ther 1995;5(10):1837-1850.	No
26	Ikemura et al., 1996	Ikemura T, Manabe H, Sasaki Y, Ishii H, Onuma K, Miki I, Kase H, Sato S, Kitamura S, Ohmori K. KW-4679, an antiallergic drug, inhibits the production of inflammatory lipids in human polymorphonuclear leukocytes and guinea pig eosinophils. Int Arch Allergy Immunol 1996;110:57-63.	No
27	TR# 90-131(Y)	Biochemical characterization of KW4679, an antihistaminic and antiallergic agent	Yes
		SAFETY PHARMACOLOGY	
28	TR# 137:30:0700	Effects of olopatadine hydrochloride on cloned hERG channels	No
29	TR# 89-121(Y)	Pharmacological properties of KW4679 – Effects on the central and peripheral nervous systems	Yes
30	Ishii et al., 1995b	Ishii KKH, Sasaki Y, Manabe H, Ikemura T, Satou H, Ichikawa S, Shiozaki S, Kitamura S, Oumori K. General pharmacology of KW-4679, a new antiallergic drug (1st report) – Effects on the central nervous system, autonomic nervous system and peripheral nervous system. Clin Pharm Therap 5(8):1421-40, 1995.	No
31	TR# A-88-67	Study of anticholinergic effect of KW-4679	Yes
32	Kamei et al., 1996	Kamei C, Ichiki C, Yoshida T, Tsujimoto S. Effect of the new antiallergic agent olopatadine on EEG spectral powers in conscious rats. Arzneim-Forsch/Drug Res 1996;46(II,8):789-93.	No
33	TR# 1156	Pharmacological properties of KW4679 – Effects of KW4679 on the sleep-wakefulness cycle in cats	Yes

Ref. No.	Report # or Publication	Section / Subsection / TR Title	In NDA 20-688
34	Ishii et al., 1995c	Ishii H, Sasaki Y, Manabe H, Sato H, Fuji M, Iketa J, Kitamura S, Ohmori T. General pharmacology of KW-4679, an antiallergic drug (2nd report) – effects on respiratory, circulatory system, urogenital system and digestive system. Clin Pharmacol Ther 1995;5(12):53-71.	No
35	Kato et al., 1996	Kato Y, Mori T, Ohmori K, Ichimura M. Effect of terfenadine and KW-4679, a novel antiallergic compound, on action potential of guinea pig ventricular myocytes. Jpn J Pharmacol 1996;70:199-202.	No
36	TR# 91-58(Y)	Pharmacological properties of KW4679 – Effects on respiratory and cardiovascular systems	Yes
37	TR# A-88-73	Effects of KW4679 on cardiovascular system in dogs	Yes
38	Nito et al., 1995	Effects of KW-4679 on electrocardiogram, heart rate, and blood pressure in conscious dogs.	No
39	TR# 89-110(Y)	Pharmacological properties of KW4679 – Effects of KW4679 on contraction of tracheal smooth muscle	Yes
40	TR# 019:39900:0895	Effects of olopatadine on contralateral eye responses in a model of histamine-induced vascular permeability	Yes
		PHARMACODYNAMIC DRUG INTERACTIONS	
41	Honig et al., 1993	Honig PK, Wortham DC, Zamani K, Conner DP, Mullin JC, Cantilena LR. Terfenadine-ketoconazole interaction. Pharmacokinetic and electroretinographic consequences. JAMA 1993 Mar;269(12):1513-8.	No
42	Iwamoto et al., 1999	Effect of combination of KW-4679 and itraconazole on the ECG in conscious dogs.	No
		PHARMACOKINETICS	
		Analytical Methods and Validation Reports	
43	TR# 067:38570:0995	Radioimmunoassay of KW-4679 (olopatadine): Determination of KW-4679 in rat and dog plasma (Kyowa Hakko Kogyo TR# 89-103(Y))	Yes
44	TR# 068:38570:0995	Radioimmunoassay of KW-4679 (olopatadine): Determination of KW-4679 and — in rat plasma by radioimmunoassay combined with HPLC (Kyowa Hakko Kogyo TR# 90-43(Y))	Yes
45	TR# 028:38570:0894	Validation of Alcon Technical Procedure — or the determination of ALØ4943A (KW4679) in rabbit plasma by gas chromatography with mass selective detection	Yes
46	TR# 090:38570:1095	Validation of Alcon Technical Procedure — for the determination of ALØ4943A (KW4679) in Cynomolgus monkey plasma by gas chromatography with mass selective detection	Yes
47	TR# 025:33:0600	Validation of an HPLC/MS/MS method for the determination of olopatadine and metabolites in dog plasma at —	No
		Absorption	
48	TR # 046:38570:0995	Disposition of KW-4679 (olopatadine): Pharmacokinetics of KW-4679 in rats (Kyowa Hakko Kogyo TR # 95-94)	Yes
49	TR# 033:38570:0994	Plasma pharmacokinetics of ALØ4943A following either a single topical ocular or intravenous dose to New Zealand white rabbits	Yes
50	TR #051:38570:0995	Disposition of KW-4679 (olopatadine): Disposition of KW-4679 pharmacokinetics in dogs (Kyowa Hakko Kogyo TR #95-95)	Yes
51	TR #052:38570:0995	Disposition of KW-4679 (olopatadine): Comparison of KW-4679 pharmacokinetics in monkeys (Kyowa Hakko Kogyo TR #95-137)	Yes
52	TR #055:38570:0995	Disposition of KW-4679 (olopatadine): Comparison of KW-4679 pharmacokinetics in male and female rats (Kyowa Hakko Kogyo TR #95-96)	Yes

Ref. No.	Report # or Publication	Section / Subsection / TR Title	In NDA 20-688
53	TR# 043:38570:0995	Disposition of KW-4679 (olopatadine): Absorption, distribution, and excretion of ^{14}C-KW-4679 in rats (Kyowa Hakko Kogyo TR # 94-243)	Yes
		Distribution	
54	TR# 014:38570:0395	Ocular tissue distribution of radioactivity following single topical ocular doses of 0.15% ^{14}C-ALØ4943A ophthalmic solution to male New Zealand white rabbits	Yes
55	TR# 015:38570:0395	Ocular tissue distribution of radioactivity following single topical ocular doses of 0.15% ^{14}C-ALØ4943A ophthalmic solution to male Dutch Belted rabbits	Yes
56	TR# 023:33:0502	Ocular tissue distribution of olopatadine following a single unilateral topical ocular dose of 0.2% AL-4943A ophthalmic solution to male New Zealand albino rabbits	No
57	TR# 043:38570:0995	Disposition of KW-4679 (olopatadine): Absorption, distribution, and excretion of ^{14}C-KW-4679 in rats (Kyowa Hakko Kogyo TR # 94-243)	Yes
58	TR# 060:38570:0995)	Disposition of KW-4679 (olopatadine): Distribution of 14C-KW-4679 administered in pregnant rats by whole-body autoradiography and radioluminography (Kyowa Hakko Kogyo TR #92-234)	Yes
59	Ohishi et al., 1995b	Ohishi T, Nishiie H, Fuse E, Kobayashi H, Kobayashi S. Pharmacokinetics of the new anti-allergy drug KW-4679 (Part 2): Absorption, excretion, and distribution of 14C-KW-4679 in repeated oral administration to rats and its effect on the drug-metabolizing enzyme system. Xenobio Metab Dispos 1995;10(5):669-682.	No
60	TR# 056:38570:0995	Disposition of KW-4679 (olopatadine): *In vitro* protein binding of KW-4679 (Kyowa Hakko Kogyo RE #94-644)	Yes
61	TR# 069:38570:0995	*In vitro* protein binding of KW-4679 (olopatadine) (Kyowa Hakko Kogyo TR# 89-88(Y))	Yes
62	TR# 070:38570:0995	Disposition of KW-4679 (olopatadine): *In vitro* protein binding of KW-4679 (Kyowa Hakko Kogyo RE #90-73(Y))	Yes
63	TR #061:38570:0995	Disposition of KW-4679 (olopatadine): Transfer into the fetus of rats (Kyowa Hakko Kogyo TR #93-246)	Yes
64	TR #062:38570:0995	Disposition of KW-4679 (olopatadine): Milk transfer of ^{14}C-KW-4679 after oral administration (Kyowa Hakko Kogyo TR #94-106)	Yes
		Metabolism	
65	Ohishi et al., 1995a	Ohishi T, Magara H, Yasuzawa T, Kobayashi H, Yamaguchi K, Kobayashi S. Disposition of KW-4679 (4): Metabolism of KW-4679 in rats and dogs. Xenobio Metab Dispos 1995;10(5):1-18.	No
66	TR# 059:38570:0995	Disposition of KW-4679 (olopatadine): Effect of repeated oral administrations of KW-4679 to rats on the hepatic drug-metabolizing enzymes (Kyowa Hakko Kogyo TR# 93-3)	Yes
67	TR# 022:33:0400	Study on drug interaction of olopatadine in human liver microsomes	No
		Excretion	
68	TR# 043:38570:0995	Disposition of KW-4679 (olopatadine): Absorption, distribution, and excretion of ^{14}C-KW-4679 in rats (Kyowa Hakko Kogyo TR # 94-243)	Yes
69	TR# 053:38570:0995	Disposition of KW-4679 (olopatadine): Absorption and excretion of 14C-KW-4679 after oral administration to dogs (Kyowa Hakko Kogyo TR # 94-647)	Yes
70	TR# 063:38570:0995	Disposition of KW-4679 (olopatadine): Renal clearance of KW-4679 in rats (Kyowa Hakko Kogyo TR#95-10)	Yes
71	TR #052:38570:0995	Disposition of KW-4679 (olopatadine): Comparison of KW-4679 pharmacokinetics in monkeys (Kyowa Hakko Kogyo TR #95-137)	Yes
		Other Pharmacokinetic Studies	
72	TR# 030:38570:0994	ALØ4943A plasma concentrations following one-month QID and HID topical ocular dosing regimens in New Zealand albino rabbits	Yes
73	TR# 031:38570:0994	ALØ4943A plasma concentrations following a six-month QID topical ocular dosing regimen in New Zealand albino rabbits	Yes

Ref. No.	Report # or Publication	Section / Subsection / TR Title	In NDA 20-688
74	TR# 097:38570:1295	ALØ4943A plasma concentrations following a six-month QID topical ocular dosing regimen in Cynomolgus monkeys	Yes
75	TR# 019:33:0400	Toxicokinetics of KW-4679 (Olopatadine) (I): Toxicokinetics of KW-4679 after repeated oral administration to rats for 7 days.	No
76	TR# 002:33:0100	Pharmacokinetics of olopatadine, N-desmethyl olopatadine and olopatadine N-oxide in male Beagle dogs following oral administration of olopatadine	No
		TOXICOLOGY	
		Single-Dose Toxicity	
77	TR# A-89-69	Toxicological studies of KW4679; acute oral toxicity study of KW4679 in mice	Yes
78	TR# A-89-68	Toxicological studies of KW4679; acute oral and intravenous study of KW4679 in rats	Yes
79	TR# 89-62	Toxicological studies of KW4679; acute oral and intravenous toxicity study of KW4679 in dogs	Yes
		Repeat-Dose Toxicity	
80	TR# A-88-80)	Toxicological study of KW4679; 4-week subchronic oral toxicity study of KW4679 in rats	Yes
81	TR# A-89-65	Toxicological study of KW4679; 13-week subacute oral toxicity study of KW4679 in rats	Yes
82	TR# A-90-82	Toxicological study of KW4679; 52-week chronic oral toxicity study of KW4679 in rats	Yes
83	TR# 099:38520:1293	One-month topical ocular irritation and systemic toxicity evaluation of AL-4943A ophthalmic solution in rabbits	Yes
84	TR# 030:38570:0994	ALØ4943A plasma concentrations following one-month QID and HID topical ocular dosing regimens in New Zealand albino rabbits	Yes
85	TR# 034:30:0402	Three month topical ocular safety and systemic toxicity evaluation of olopatadine QD ophthalmic solution in rabbits with a six week interim evaluation (N-01-028)	No
86	TR# 030:38520:0395	Six-month topical ocular irritation and systemic toxicity evaluation of AL-4943A ophthalmic solution in rabbits	Yes
87	TR# 031:38570:0994	ALØ4943A plasma concentrations following a six-month QID topical ocular dosing regimen in New Zealand albino rabbits	Yes
88	TR# KH-4W-D	Research on the safety of KW-4679: Four week, repeated dose, oral administration toxicity study in dogs	No
89	TR# A-89-66	Toxicological study of KW4679; 13-week subacute oral toxicity study of KW4679 in dogs	Yes
90	TR# A-90-92	Toxicological study of KW4679; 52-week chronic oral toxicity study of KW4679 in dogs	Yes
91	TR# 102:38520:0895	Six-month chronic topical ocular irritation and systemic toxicity evaluation of AL-4943A ophthalmic solution in primates	Yes
92	TR# 097:38570:1295	ALØ4943A plasma concentrations following a six-month QID topical ocular dosing regimen in Cynomolgus monkeys	Yes
		GENOTOXICITY	
		In vitro	
93	TR# A-88-93	Toxicological study of KW4679; bacterial reverse mutation assay of KW4679	Yes
94	TR# A-88-147	Toxicological study of KW4679; chromosomal aberration test of KW4679 on CHL cells in vitro	Yes
		In vivo	
95	TR# A-90-17	Toxicological study of KW4679; micronucleus test of KW4679 administered orally to mice	Yes

Ref. No.	Report # or Publication	Section / Subsection / TR Title	In NDA 20-688
96	—	Mutagenicity study of — (report from Kyowa Hakko Kogyo Co., Ltd.)	No
		CARCINOGENICITY	
		Long-Term Studies	
97	TR# 92/KKY009/1065	KW4679: oncogenicity study by dietary administration to CD-1 mice for 78 weeks	Yes
98	TR# 93/KKY008/0386)	KW4679: oncogenicity study by dietary administration to F-344 rats for 104 weeks	Yes
		REPRODUCTIVE AND DEVELOPMENTAL TOXICITY	
		Fertility and Early Embryonic Development	
99	TR# A-89-26	Toxicological study of KW4679; fertility study of KW4679 in rats	Yes
		Embryo-Fetal Development	
100	TR# A-89-52	Reproduction study of KW4679; teratogenicity study of KW4679 in rats	Yes
101	TR# A-89-59	Reproduction study of KW4679; teratogenicity study of KW4679 in rabbits	Yes
		Prenatal and Postnatal Development Including Maternal Function	
102	TR# D-2525	Reproductive and development toxicology study of KW4679 in rats by oral administration; peri- and postnatal toxicity study	Yes
103	TR# D-3289	Reproductive and development toxicity study of KW4679 in rats by oral administration; peri- and postnatal toxicity study	Yes
104	TR# A-95-07	Supplemental study for body weight gain of F1 pups in peri- and postnatal study of KW4679 administered orally in rats	Yes
		LOCAL TOLERANCE	
105	TR# 162:30:0800	One-day topical ocular irritation (local tolerance) evaluation of olopatadine/povidone ophthalmic solutions in rabbits (protocol N-00-159)	No
106	TR# 039:30:0501	One-day topical ocular irritation (local tolerance) evaluation of olopatadine/povidone ophthalmic solutions in rabbits (protocol N-01-055)	No
		ANTIGENICITY	
107	TR# 136:30:0600	A dermal sensitization study in guinea pigs with olopatadine HCl (maximizaton design)	No
108	TR# A-90-43	Toxicological study of KW4679; antigencity test of KW4679	No
		IMPURITIES	
109	—	Toxicitv study of single-dose oral administration of related compounds / — N-oxide derivative, N-monodesmethyl derivative, and — to mice (report from Kyowa Hakko Kogyo Co., Ltd.)	No

Addendum to review: None

Other relevant materials (Studies not reviewed, appended consults, etc.): None

Any compliance issues: None

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/s/

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