CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-861s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	21-861 (Resubmission)
Proprietary Drug Name:	PATANASE
Generic Name:	Olopatadine HCL
Indication:	Seasonal Allergic Rhinitis (SAR)
Dosage Form:	Nasal Spray (solution)
Strength:	0.6%
Route of Administration:	Nasal
Applicant:	Alcon Research, Inc.
Clinical Division:	DPAP (HFD-570)
Submission Dates:	September 27, 2007
Reviewer:	Sandra Suarez-Sharp, Ph.D.
Team Leader (acting):	Wei Qiu, Ph. D.

TABLE OF CONTENTS

ITEM	PAGE NUMBER
1. Executive Summary	2
1.1 Recommendation	2
1.2 Phase IV commitments	2
1.3 Comment to the Medical Reviewer	2
1.4 Summary of Clinical Pharmacology	3
2. Question-Based Review	6
2.1 Patient compliance based on plasma concentrations determination	8
3. Labeling Recommendations	12
4. Appendix	16
4.1 Question based review for original submission	16

1. EXECUTIVE SUMMARY

1.1 Recommendation

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology II (OCP / DCPII) has reviewed the complete response to NDA 21-861 submitted on September 27, 2007. We found the complete response to the approvable letter dated October 27, 2005 acceptable from a Clinical Pharmacology standpoint provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert. The labeling comments (page 12) should be conveyed to the sponsor as appropriate.

1.2 Phase IV Commitments

None

1.3 Comments to the Medical Officer

- In Study C-05-69, more than 90% of patients (N = 159) who received olopatadine nasal spray and had blood samples taken for PK determination, had measurable olopatadine plasma concentrations at Months 1 and 5. This finding suggested a high degree of patient compliance. Considering this study was conducted in a randomized fashion, one can assume that this degree of compliance holds true for the entire population (890 patients) enrolled in the study.

- Based on the findings for mean QTc change from baseline (ΔQTc) (ΔQTcF were -2.9 msec and -3.5 msec for oloptadine and placebo, respectively), olopatadine is unlikely to have an effect on QTc interval at supratherapeutic doses. These findings suggest a lack of effect on QTc interval at therapeutic doses. It is noted that some placebo corrected ΔQTc values (ΔΔQTc) were higher than 10 msec at some time points due to large negative ΔQTc values for placebo. However, the lack of positive control makes the ΔΔQTc findings uninterpretable. Nevertheless, your findings on the lack of cardiovascular safety concerns from the phase 3 clinical trials, lack of postmarketing cardiovascular signal for the approved olopatadine tablet, no influence on the QT interval in hypokalemia-anesthetized dogs[1], and lack of potential for drug-drug interactions also suggest that olopatadine is unlikely to prolong QTc interval at the proposed therapeutic dose.

[1] Ken-ichiro Iwamoto, et al. Effect of olopatadine hydrochloride, a novel antiallergic agent, on the QT interval in dogs. Folia Pharmacologica Japonica. Vol 117 (2001) No. 6, pages 401-409.

1.4 SUMMARY OF CLINICAL PHARMACOLOGY

The present submission is a complete response to the approvable letter issued to the sponsor on October 27, 2005. The product under review has been reformulated to remove PVP. The sponsor conducted an additional long-term safety study (C-05-69) and an initial environmental exposure unit (EEU) efficacy study with the PVP-free formulation. This submission contains the results of a total of 5 clinical studies, two of which (Studies C-05-69 and C-04-45) pertain to Clinical Pharmacology as follows:

Study C-05-69 was a randomized, double-blind, vehicle-controlled, parallel-arm, long term safety study (b) (4) in patients with perennial allergic rhinitis (PAR). Patients (445 per arm) received either PVP-free (reformulated) Olopatadine 0.6% spray or placebo spray BID dosing, 2 sprays/nostril for up to 12 months. As part of patient compliance assessments, blood samples for olopatadine concentration determination were collected in a subset of patients (total N = 319; 159 received olopatadine nasal spray and 160 received placebo) at Months 1 and 5 Visits. Two blood samples were collected from each patient. Approximately 90% of these patients who received olopatadine showed quantifiable plasma concentration of olopatadine. This finding suggested high patient compliance.

Study C-04-45 was a phase I, randomized, double-blind, vehicle-controlled study in a total of 60 healthy volunteers (12 subjects/arm) conducted under the sponsor's own initiative. The purpose of this study was to evaluate the safety and pharmacokinetics of two degradation products of olopatadine, (b) (4) and (b) (4), at a concentration (b) (4) over 4-fold higher than the proposed specification limit of 0.2%. This study was considered irrelevant to the clinical pharmacology of the product, and therefore, was not reviewed.

Cardiovascular Safety

The original submission contained the results of two cardiovascular safety studies (C-0023 and C02-54). Study C-00-23 was a placebo-controlled cardiac repolarization study in healthy volunteers given olopatadine hydrochloride as an oral 5 mg solution twice daily for 3 days. This study was not reviewed because it did not provide additional information.

Study C-02-54 was a single-center, randomized, double-blind, crossover, cardiovascular safety and pharmacokinetic study in 34 healthy, male and female subjects, age 18 to 75 years. Subjects received twice-daily oral doses of 20 mg olopatadine solution or placebo for 14 days. Eighteen 12-lead ECGs were performed over the 24-hour period at baseline (Day -2 to -1), 15 ECGs over the 12-hour period on Day 12 and 18 ECGs over the 24-hour period after the last dose on Day 14 (Days 14/15) for each treatment.

In the review of this study as part of the original submission it was concluded that the mean QTc change from baseline showed an unlikely effect of olopatadine on QTc interval. The mean ΔQTcF values were -2.9 msec and -3.5 msec for oloptadine and placebo, respectively. The mean of maximum ΔQTcF were 17.4 msec and 15.9 msec for olopatadine and placebo, respectively. Current FDA guidelines for the analysis of QT data recommend the assessment of the QTc change from baseline corrected for placebo over time (ΔΔQTc). It is noted that some placebo corrected ΔQTc values (ΔΔQTc) were higher than 10 msec at some time points due to large negative ΔQTc values for placebo. The lack of positive control makes the ΔΔQTc findings uninterpretable. Nevertheless, your findings on the lack of cardiovascular safety concerns on the clinical trials and postmarketing assessment, and lack of potential for drug-drug interactions also suggest that olopatadine is unlikely to prolong QTc interval at the proposed therapeutic dose.

A summary of the Clinical Pharmacology findings previously reported in the Clinical Pharmacology review for the original submission of this NDA[1] is described below.

Pharmacokinetics in Healthy Volunteers

Single Dose

Following intranasal administration of olopatadine nasal spray 0.4% or olopatadine nasal 0.6%, olopatadine Cmax values were generally observed within 0.25 to 2 hours post-dose. Mean Cmax and AUC values were 12.5 ± 6.1 ng/mL and 42.5 ±16.0 ng*hr/mL and 17.5 ± 6.7 ng/mL and 60.3 ± 20.3 ng*hr/mL for olopatadine nasal 0.4% and olopatadine nasal 0.6%, respectively. The bioavailability of olopatadine was about 60 ± 20.8%. Olopatadine peak plasma concentrations increased in proportion to the intranasal dose. Similar dose-proportional increases were seen in mean AUC values.

Three minor metabolites (M1, M2, and M3) were identified in plasma, but only Ml and M3 were quantified following single intranasal doses of olopatadine nasal 0.4% or olopatadine nasal 0.6%. Peak plasma concentrations of Ml and M3 were low, accounting for ~ 2.0% and 3.0% of parent Cmax, respectively. $AUC_{0\text{-}inf}$ of Ml and M3 were low, accounting for ~ 6.0% and 9.0% of parent AUC_{inf}, respectively. M3 peak plasma concentrations and AUC_{inf} were approximately 1.5- to 3-fold higher and 1.5 higher, respectively than those for Ml.

Repeat Dose

Time to reach steady-state was not addressed; however, it is expected to be achieved within 2 to 3 days of repeated twice daily dosing, based on a half-life value of about 10 hrs. The mean accumulation ratio for olopatadine was 1.3. Olopatadine Tmax and half-life were similar to that after single dose administration.

Distribution

Following intranasal administration in SAR patients and healthy subjects, measurable plasma concentrations of olopatadine were observed in the systemic circulation within 5 minutes post-dose. Olopatadine was moderately bound (55%) to plasma proteins and the binding was independent of the concentration on the range of 0.1 to 1000 ng/mL.

Elimination

The CL/F and half-life of olopatadine following a single oral solution dose of 5 mg ^{14}C-Olopatadine Hydrochloride (200 μCi) averaged 15.3 (3.4) L/h and 7.9h (3.4), respectively. The mean total recovery of radioactivity in urine and feces was 70.5% and 17% of the dose, respectively indicating that urinary excretion was the major pathway of elimination. Urinary excretion of Ml and M3 accounted for about 7% of radiolabeled material recovered in the urine. Identified and unidentified metabolites accounted for <10% of the total radioactivity in urine. Unchanged olopatadine was the major component of radiolabeled material in plasma and urine. Ml, M2 and M3 metabolites accounted for less than 10% of circulating radioactivity in plasma.

In vitro studies with cDNA-expressed human cytochrome P450 isoenzymes (CYP) and flavin-containing monooxygenases (FMO) showed that the metabolism of olopatadine is a minor route of elimination. Two major different metabolites, M1 and M3, were identified. M1 formation was catalyzed mainly by CYP3A4, while M3 was primarily catalyzed by FMO1 and FMO. After incubation, M1 and M3 accounted for 5.2 and 30.5% of the initial olopatadine concentration, respectively. In addition, olopatadine did not inhibit the major CYP450 enzymes such as 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. The potential for olopatadine metabolites to act as an inducer of CYP enzymes was not evaluated.

Pharmacokinetics in Allergic Rhinitis Patients

The mean Cmax values in SAR patients were within the range of those observed in healthy volunteers (olopatadine 0.4%: mean 14.4 ± 4.4 ng/mL and 48.9 ± 12.5 ng*hr/mL); olopatadine 0.6%: mean 21.7 ± 8.7 ng/mL and 67.7 ± 21.1). The Cmax and AUC values for olopatadine metabolites did not appear to be

significantly different between SAR patients and healthy subjects. The mean Cmax (23.3 ± 6.2 ng/mL) and $AUC_{0\text{-}12h}$ (78.0 ± 13.9ng*hr/mL) of olopatadine following multiple administration of two sprays per nostril of 0.6% olopatadine twice daily increased up to 15% compared to those after single administration.

Pharmacokinetics in Special Populations

Gender, Age, and Race

The mean systemic exposure (Cmax and AUCt) in females following multiple administration of olopatadine in SAR patients was 40 % and 27% higher, respectively than those values observed in male SAR patients. This difference in systemic exposure may not be clinically relevant since multiple doses of oral olopatadine 20 mg BID appeared to be safe. Therefore, no dose adjustment is necessary based on gender differences in the PK of olopatadine. The effect of race and age on the PK of olopatadine was not evaluated.

Renal Impairment

Following single intranasal administration of two sprays per nostril of 0.6% olopatadine nasal spray to volunteers (25 subjects/patients), no meaningful differences were observed in the systemic exposure of olopatadine in patients with mild or moderate renal impairment compared to subjects with normal renal function. The plasma Cmax and AUC values in patients with severe renal impairment were approximately 1.2- and 2-fold higher than those in healthy subjects. Higher plasma concentrations of Ml and M3 metabolites were seen with increasing renal impairment, particularly those in severely-impaired patients with 2.6- and 3.6-fold higher mean Cmax values, respectively. Despite of the higher systemic exposure of parent drug and metabolites observed in patients with severe renal impairment following intranasal doses of olopatadine nasal spray 0.6%, these values are still 10- to 250-fold lower than peak concentrations observed following higher oral 20 mg to 400 mg doses which were safe and well-tolerated. Therefore, dosage adjustment of olopatadine based on renal impairment may not be necessary.

Hepatic Impairment

The effect of liver impairment on the PK of olopatadine and its metabolites was not evaluated. Olopatadine (and its metabolites) are mainly eliminated by the kidney. In fact, in a mass balance study total radioactivity was predominantly excreted in urine (70% of total administered dose) suggesting that liver metabolism is not an important route of elimination.

Drug/Drug Interactions (DDI)

DDI studies were not conducted with olopatadine. Drug interactions based on metabolic interaction are not anticipated because olopatadine is eliminated predominantly by renal excretion. In addition, olopatadine did not inhibit the *in vitro* metabolism of major CYP enzymes. The plasma protein binding of olopatadine is about 55%, thus, interactions through displacement from plasma proteins are not expected.

Dose-Response (Efficacy and Safety) Relationships

In the case of dose-response for efficacy, there was a trend for the higher doses of olopatadine to produce a bigger response; however a clear dose-ordering response (as shown for other nasal antihistamines) was not observed following either single administration of olopatadine 0.2-, 0.4-, or 0.6% nasal spray or after multiple administration of olopatadine 0.1 % and 0.2% nasal spray. Following single dose administration (two sprays per nostril) of either olopatadine 0.2%, 0.4%, 0.6% or vehicle, the mean decrease in TNSS (total nasal symptoms score) for the olopatadine nasal 0.6%, olopatadine nasal 0.4%, olopatadine nasal 0.2% or vehicle groups were 2.8-, 2.63-, 2.58-, and 1.52 units, respectively. This suggests that the use of lower doses than that proposed by the sponsor (two sprays per nostril twice a day of olopatadine 0.6%) may have the same clinical effect. In

general, based on two Phase II dose-response studies, systemic adverse events appeared not to be related to dose following single administration of olopatadine 0.2-, 0.4 or 0.6% nasal spray or multiple doses of olopatadine 0.1 or 0.2% nasal spray. However, nasal discomfort (2 events) appeared to be related to drug treatment, in this case the 0.2% olopatadine nasal spray.

Reviewer
Sandra Suarez-Sharp, Ph.D.
Office of Clinical Pharmacology
Division of Clinical Pharmaceutical Evaluation II

Final version signed by Qiu Wei, Ph.D., Acting Team leader
cc
DCPII: Sahajwalla, Doddapaneni, Qiu
HFD-570: Kaiser, Lee, Chowdhury, Raggio

2. QUESTION BASED REVIEW

This section focuses on a "question base review approach" considering the clinical pharmacology information submitted in the complete response. A comprehensive question base review done for the original submission can be found in the appendix.

2.1 General Attributes

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of Patanase Nasal Spray?

The original NDA 21-861 of Patanase® (olopatadine) Nasal Spray for the treatment of SAR was submitted in December 2004. The efficacy and safety of Patanase® in SAR patients was primarily assessed in three double-blind, placebo-controlled, multicenter studies. The clinical pharmacology program contained nine clinical pharmacology studies which focused on the evaluation of the systemic exposure, effect of renal impairment, and potential for QT prolongation. The original NDA submission was found acceptable from a Clinical Pharmacology standpoint with some labeling recommendations[2].

On October 2005, the Agency issued an approvable letter to the sponsor mainly due to safety concerns. Specifically, it was found that Patanase Nasal Spray caused nasal irritation and serious damage to the nasal mucosa. Preclinical information indicated that povidone (PVP), an inactive ingredient contained in Patanase Nasal Spray, caused irritation to the nasal mucosa. Based on these findings, the sponsor was recommended to reformulate the product to remove or reduce the concentration of PVP in the olopatadine nasal spray formulation.

The present submission is a complete response to the approvable letter issued to the sponsor on October 27, 2005. The product under review has been reformulated to remove PVP. This submission contains the results of a total of 5 clinical studies, one of which (Study C-05-69) contains Clinical Pharmacology information (see section 2.2).

[2] Clinical Pharmacology Review for NDA 21-861 (original submission) entered in DFS on 7/22/05 by Dr. Sandra Suarez

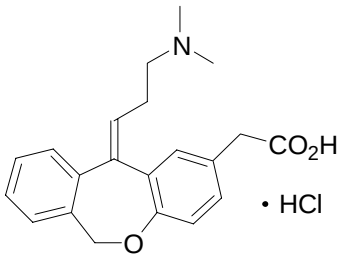
2.1.2. What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

The active component of PATANASE Nasal Spray is olopatadine hydrochloride, a specific histamine H_1 receptor antagonist.

Chemical name:

The chemical name for olopatadine hydrochloride is (*Z*)-11-[3-(dimethylamino)propylidene]-6,11-dihydrodibenz[*b*,*e*]-oxepin-2-acetic acid hydrochloride.

Structural formula:



Molecular formula: $C_{21}H_{23}NO_3 \bullet HCl$
Molecular weight: 373.88
Solubility: Olopatadine hydrochloride is a white, water-soluble crystalline powder.

Formulation

Olopatadine Hydrochloride Nasal Spray is a non-sterile, (b) (4), multiple-dose nasal spray solution containing 0.6% w/v olopatadine as base (equivalent to 0.665% w/v olopatadine hydrochloride). Each spray (100 microliters) delivers 665 mcg of olopatadine hydrochloride.

In the previously submitted formulation in original NDA 21-861, (b) (4). As a result of additional discussions with the Agency, a decision was made to remove PVP from the original formulation. The target pH of the formulation was (b) (4) 3.7 to (b) (4). Table 2.1.2.1 shows a comparison of the formulations used in the clinical pharmacology studies.

Table 2.1.2.1 Comparison of Olopatadine Nasal Spray Formulations Used in the Clinical Studies (%w/v)

Component	Series-1		Series-2			PVP-Free *	IV Solution	
	FID 100491	FID 101371	FID (b) (4)	FID (b) (4)	FID (b) (4)	FID 109941	FID 10503	FID 101688
Olopatadine Hydrochloride	0.111	0.222	0.222	0.443	0.665	0.665	0.222	0.0111
Olopatadine base	0.1%	0.2%	0.2%	0.4%	0.6%	0.6%	0.2%	0.01%
Benzalkonium Chloride	0.01 + (b) (4)	0.01 + (b) (4)	0.01	0.01	0.01	0.01	None	None
Edetate Disodium	None	None	(b) (4)			(b) (4)	None	None
Povidone	None.	None				0	None	None

Sodium Chloride	(b) (4)	-	-
Dibasic Sodium Phosphate		-	-
Sodium Hydroxide and/or Hydrochloric Acid		-	-
Purified Water		qs	qs

*Formulation used in the pivotal safety/PK study (Study c-05-69) included in the present submission

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Olopatadine, a structural analog of doxepin, is a non-steroidal, non-sedating, topically effective anti-allergic molecule that exerts its effects through multiple distinct mechanisms of action. The molecule possesses selective and specific histamine H_1 antagonist activity and is devoid of effects upon alpha adrenergic, dopaminergic and muscarinic receptors. Inhibitory effects upon expression of pro-inflammatory cytokines from epithelial cells and eosinophils have been reported. Inhibition of pro-inflammatory mediator release from human mast cells has also been observed. An intranasal study with olopatadine nasal spray has demonstrated decreases in albumin, lysozyme and leukotrienes.

The proposed indication is for the (b) (4) treatment of the symptoms of SAR such as (b) (4) in patients 12 years of age and older.

2.1.4 What are the proposed dosage(s) and route(s) of administration?

The proposed dose of PATANASE® Nasal Spray in patients 12 years and older is two sprays per nostril twice-daily.

2.2 Do the pharmacokinetic results support compliance of patients enrolled in the pivotal efficacy and safety study (C-05-69)?

Study C-05-69 was a randomized, double-blind, vehicle-controlled, parallel-arm, long term safety study (b) (4) in patients with perennial allergic rhinitis (PAR). Patients (890 total; 445 per arm) received either PVP-free Olopatadine 0.6% spray or placebo spray BID dosing, 2 sprays/nostril for up to 12 months. Patient compliance was assessed by dosing compliance, bottle weights, a global efficacy question and olopatadine plasma concentrations determined in a subset of patients at selected sites.

As part of patient compliance, plasma samples for olopatadine concentration determination were collected in a subset of patients (total N = 319; 159 received olopatadine and 160 received placebo) on two study visits (at Months 1 and 5) at pre-selected sites. Two blood samples were collected from each patient. Olopatadine concentrations were assayed using a validated LC/MS/MS method with a LOQ of 0.05 ng/mL, which is the same as that reported for study C-02-10. These olopatadine plasma concentrations were compared to the pharmacokinetic profile obtained in a subset of SAR patients from pivotal efficacy study C-02-10 (conducted using the previous formulation with (b) (4) PVP). Figure 2.2.1 shows that the PVP-free formulation presents a higher variability in the systemic exposure compared to that for the PVP formulation. It seems, however, that the ranges in olopatadine plasma concentrations from both formulations are similar. This

conclusion should be interpreted with caution since pharmacokinetic parameters were not reported because it was not in the scope of the study.

More than 90% of patients who received olopatadine and had blood samples drawn for PK determination had measurable olopatadine plasma concentrations. This finding suggested a high degree of patient compliance. Considering this was a randomized study, one can assume that this degree of compliance holds true for the entire population (890 patients) enrolled in the study.

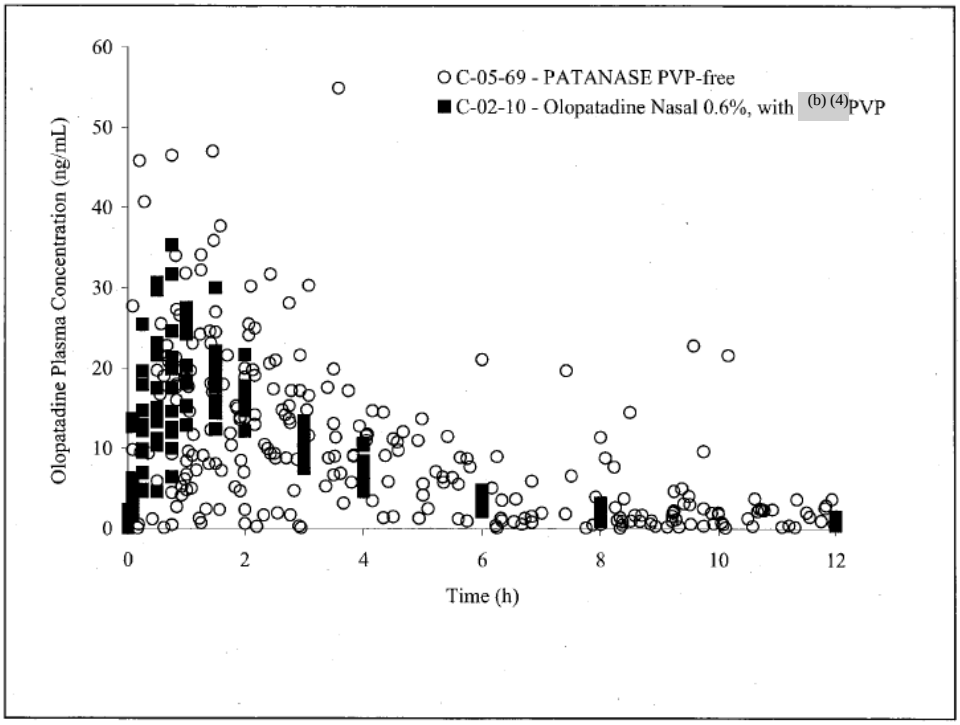


Figure 2.2.1 Olopatadine plasma concentration-time profiles after intranasal BID doses of PVP Free Olopatadine Nasal Spray 0.6% in PAR patients (C-05-69) and Olopatadine Nasal Spray 0.6% with (b) (4) PVP in SAR Patients (C-02-10).

The assessment of the pharmacokinetics of olopatadine for the reformulated PVP-free product was not requested in the approvable letter. The rationale was that for a nasal solution, the impact of the formulation difference on the deposition and PK of the drug is generally not expected. Of note, the pH value of the PVP-free formulation was (b) (4) than the previous one (3.7 (b) (4)). Pharmacokinetic assessment may be needed for a formulation change of a nasal solution involving pH changes since it has been shown that changes in the formulation pH may cause a slowing down of the cilia movement in the nasal cavity and this could result in a higher nasal residence time and therefore, a possibility for higher drug absorption.[3].

2.3 Does olopatadine prolong the QT or QTc interval?

The original submission contained the results of two cardiovascular safety studies (b) (4) and C-02-54). (b) (4)

[3] Aurora, J. Development of Nasal Delivery Systems: A Review. Drug Delivery.

Study C-02-54 was a single-center, randomized, double-blind, crossover, safety and pharmacokinetic study in 34 healthy, male and female subjects, age 18 to 75 years. Subjects received twice-daily oral doses of 20 mg olopatadine solution or placebo for 14 days. Eighteen 12-lead ECGs were performed over the 24-hour period at baseline (Day -2 to -1), 15 ECGs over the 12-hour period on Day 12 and 18 ECGs over the 24-hour period after the last dose on Day 14 (Days 14/15) for each treatment. The ECGs were forwarded to a centralized reading center for masked manual measurements to determine the ECG parameters.

Comparisons of the results of the analysis showed that Fridericia's correction formula (QTcF) yielded a slope closer to zero (-0.021) than Bazett's (-0.097).

Table 2.3.1 shows that all mean changes in QTcF from baseline were negative. No statistically significant ($p \geq 0.097$) differences were seen between olopatadine and vehicle in either the mean change or mean of maximum change.

Table 2.3.1. Mean, median, min and max QTc, Δ QTc change from baseline and mean of maximum Δ QTc following multiple administration of the treatments.

	QTcB		**QTcF**		**Δ QTB**		**Δ QTF**		**Mean of max Δ QTB**		**Mean of max Δ QTF**	
	OLOP	**PLB**	**OLOP**	**PLB**	**OLOP**	**PLB**	**OLOP**	**PLB**	**OLOP**	**PLB**	**OLOP**	**PLB**
Min (msec)	382.2	370.5	370.9	367.1	-12.9	-25.8	-22.5	-22.4	6.1	-11.5	-1.1	-6.1
Mean (msec)	409.6	408.9	401.2	401.5	3.14	0.09	-2.5	-3.9	30.68	29.4	17.4	15.9
Median (msec)	410.7	407.9	399.3	401	2.2	1.45	-3	-4.4	26.7	24.4	14.3	13.2
Max (msec)	463.5	455.7	450.9	446.2	35.8	27.9	20.7	13.7	91.22	94.8	63.1	52.1
N	81	79	81	79	81	79	81	79	81	79	81	79
SD	16.6	17.9	14.4	15.4	9.3	11.5	8.8	9.04	17.3	20.1	12.8	13.4

Several subjects on olopatadine and on placebo experienced a maximum change in QTc between 30 and 60 msec. Following olopatadine treatment, one subject experienced a QTcF change from baseline greater than 60 msec (63.1 msec) on Day 14 at 1.5 hours post-dose (Figure 2.3.1) and the highest QTcF absolute value was 518. The mean of maximum QTcF change from baseline was higher for the olopatadine group (17 msec ± 13 vs 16 msec ±13).

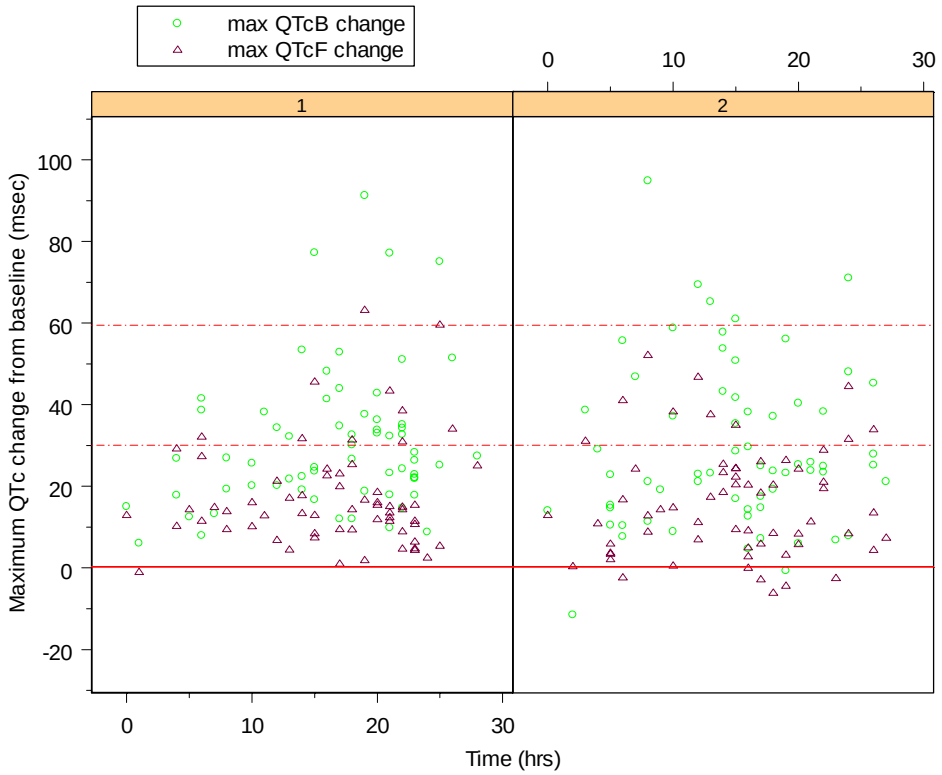


Figure 2.3.1. Individual maximum QTc change from baseline at steady state following multiple administration of the treatments (1=olopatadine and 2=placebo).

The mean QTc change from baseline (Table 2.3.1, Figure 2.3.1) findings showed an unlikely effect of olopatadine on QTc interval at supratherpeutic doses. Current FDA guidelines for the analysis of QT data recommend an assessment of the QTc change from baseline corrected for placebo over time (ΔΔQTc). It is noted that some placebo corrected ΔQTc values (ΔΔQTc) were higher than 10 msec at some time points due to large ΔQTc negative placebo values (Table 2.3.2). These larger than 10 msec ΔΔQTc values are uninterpretable since a positive control was not included in the study. Nevertheless, for a drug like olopatadine which has a low likelihood for potential drug-drug interactions, lack of cardiovascular concerns during the phase 3 trials, and lack of postmarketing cardiovascular safety signal, it is unlikely that it will prolong QTc interval at therapeutic doses. In addition, in a QT study in hypokalemia-anesthetized dogs using terfenadine as positive control, olopatadine (30 mg/kg, p.o. or 5 mg/kg i.v.) did not show any significant changes in QT interval[1] also suggesting an unlikely effect of olopatadine on QT interval as a result of clinically used of it.

Table 2.3.2. Mean (SD) QTF change from baseline corrected for placebo (ΔΔQTc) as a function of treatment and time following multiple administration of Patanase solution 20 mg BID

Time (hrs)	Mean Delta QTcF OLOP (msec)	Mean Delta QTcF PLB (msec)	ΔΔQTc (msec)
0	-8	-8	0
1	-13	-15	2
4	0	10	-10
5	5	-16	21
6	-0.33	-11.5	11.17
7	-4	-7.67	3.67
8	-4.5	6	-10.5
10	-3	-7	4
11	4	1	3
12	3	-2	5
13	-5	-5.67	0.67
14	-0.33	7.5	-7.83
15	-2.25	-0.67	-1.58
16	6	-2.67	8.67
17	-12.5	-9.6	-2.9
18	1.5	-4.25	5.75
19	-6.67	-9	2.33
20	-10.25	-8.33	-1.92
21	-0.6	1	-1.6
22	-0.83	-2.5	1.67
23	-7.33	5.67	-13
24	-9	-13	4

3. LABELING RECOMMENDATIONS

The following changes (underlined and strikethrough) were/are recommended for the *Drug Interactions (Section 7), Use in Specific Populations(Section 8) and Clinical Pharmacology/Pharmacodynamic/ Pharmacokinetic (section 12)* sections of the label based on the Clinical Pharmacology review of the original NDA submission:

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full following this page as B4 (CCI/ TS)

4. Appendix

4.1 Question-based review reported on the Clinical Pharmacology review for original NDA submission.

2. QUESTION BASED REVIEW

2.1 General Attributes

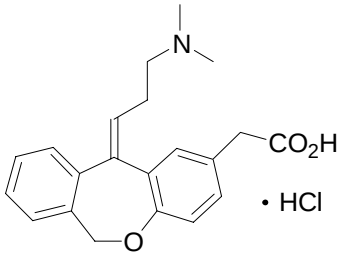
2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

The active component of PATANASE Nasal Spray is olopatadine hydrochloride, a specific histamine H_1 receptor antagonist.

Chemical name:

The chemical name for olopatadine hydrochloride is (*Z*)-11-[3-(dimethylamino)propylidene]-6,11-dihydrodibenz[*b*,*e*]-oxepin-2-acetic acid hydrochloride.

Structural formula:



Molecular formula: $C_{21}H_{23}NO_3 \bullet HCl$
Molecular weight: 373.88
Solubility: Olopatadine hydrochloride is a white, water-soluble crystalline powder.

FORMULATION

PATANASE® Nasal Spray contains 0.6% w/v olopatadine (base) in a (b) (4) nonsterile aqueous solution with a pH of approximately (b) (4). The components of PATANASE® Nasal Spray are shown in Table 2.1.1.1.

After initial priming (5 sprays), each metered spray from the nasal applicator delivers 100 mg of the aqueous solution containing 665 mcg of olopatadine hydrochloride, which is equivalent to 600 mcg of olopatadine (base). Each bottle of PATANASE® Nasal Spray provides 240 sprays after priming.

Table 2.1.1.1. Composition of Patanase Nasal Spray

Name of Ingredient	% w/v	Quantity (g) per batch (b) (4)	Quality Standard
Olopatadine HCl	0.665[a]	(b) (4)	NF
Benzalkonium Chloride	0.01		USP
Edetate Disodium	(b) (4)		USP
Povidone			USP
Sodium Chloride			USP
Dibasic Sodium Phosphate			NF
Sodium hydroxide and Hydrochloric Acid	Adjust to pH (b) (4)	Adjust to pH (b) (4)	NF
Purified Water	(b) (4)		USP

[a] 0.665% w/v olopatadine hydrochloride (665 mcg/spray) is equivalent to 0.6% w/v olopatadine as base (600 mcg/spray).
[b] (b) (4) benzalkonium chloride solution is used.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?
Mechanism of Action:

Olopatadine, a structural analog of doxepin, is a non-steroidal, non-sedating, topically effective anti-allergic molecule that exerts its effects through multiple distinct mechanisms of action. The molecule possesses selective and specific histamine H_1 antagonist activity and is devoid of effects upon alpha adrenergic, dopaminergic and muscarinic receptors. Inhibitory effects upon expression of pro-inflammatory cytokines from epithelial cells and eosinophils have been reported. Inhibition of pro-inflammatory mediator release from human mast cells has also been observed. An intranasal study with olopatadine nasal spray has demonstrated decreases in albumin, lysozyme and leukotrienes.

INDICATION (as per proposed label)

PATANASE® Nasal Spray is indicated in patients 12 years of age and older for the (b) (4) treatment of the symptoms of SAR (b) (4)

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dosage is a Nasal Spray and the proposed route of administration is by Nasal administration.

DOSAGE AND ADMINISTRATION (as per proposed label)

The recommended dose of PATANASE® Nasal Spray in patients 12 years and older is two sprays per nostril twice-daily.

2.2 General Clinical Pharmacology

2.2.1 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology and biopharmaceutics study data?

PATANASE® Nasal Spray for the treatment of seasonal allergic rhinitis (SAR) was studied in two randomized, double-blind, parallel, multicenter, vehicle placebo spray-controlled clinical trials conducted in the United States in 1,240 (406 patients received the 665 mcg dose) adolescent and adult patients 12 years of age and older. These trials evaluated the total nasal symptom scores (TNSS that included congestion (stuffy nose), rhinorrhea (runny nose), itchy nose and sneezing), as well as itchy and watery eyes, in known allergic patients who were treated for 2 weeks. (b) (4) .

The assessment of safety included the review of the frequency and incidence of adverse events, 12-lead ECG and vital signs and other laboratory analysis. The effect of PATANASE on the QT interval prolongation was studied in two placebo-controlled cardiac repolarization studies in 102 healthy volunteers given olopatadine hydrochloride as an oral 5 mg solution twice daily for 3 days, and in 32 healthy volunteers administered olopatadine hydrochloride 20 mg oral solution twice-daily for 14 days. In addition, the effect of olopatadine on cardiac repolarization was observed in 429 perennial allergic rhinitis patients given PATANASE® Nasal Spray, 665 micrograms twice daily for up to 1 year.

2.2.2 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

TNSS was selected as the primary endpoint because it is a well established and validated clinical efficacy endpoint in allergic rhinitis. However, it does not, by itself, fully describe the level of overall disease control. Therefore,

key secondary endpoints reflecting disease control, [redacted] (b) (4) As above mentioned, allergic rhinitis includes both nasal and non-nasal symptoms. The main nasal symptoms of allergic rhinitis are nasal itching (i.e., nasal pruritus), sneezing, rhinorrhea, and nasal congestion. Important non-nasal symptoms commonly associated with allergic rhinitis include itching eye, tearing eye, itching of ears and/or palate, and redness of the eye. The preferred measures of effectiveness in allergic rhinitis trials are patient self-rated instantaneous and reflective composite symptom scores. These summed scores generally include the following four nasal symptoms: rhinorrhea, nasal congestion, nasal itching, and sneezing, rated on a 0-3 scale of severity. While both patient self-rated symptom scores and physician-rated scores can be measured, the patient-rated scores are preferred as the primary measure of effectiveness.

A common allergic rhinitis rating system that has been used in clinical trials is the following 0-3 scale:

- 0 = absent symptoms (no sign/symptom evident)
- 1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated)
- 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable)
- 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Concentrations of olopatadine and its metabolites (M1, M2 and M3) were determined in plasma and urine samples from all human pharmacokinetic studies using LC/MS/MS and a HPLC-UV validated methods, respectively. The lower limits of quantification (LLOQ) were of 0.5 to 2 ng/mL and 200 to 1000 ng/mL for plasma and urine samples, respectively.

2.2.4 Exposure Response

2.2.4.1 What are the characteristics of the dose-systemic exposure relationships for efficacy?

Since systemic absorption of intranasally administered drugs is the result of nasal and gastrointestinal absorption, plasma concentrations cannot be correlated to efficacy (TNSS). In the case of dose-response for efficacy, there was a trend for the higher doses to produce a bigger response; however a clear dose-ordering response was not observed following either single dose administration of olopatadine 0.2-, 0.4-, or 0.6% nasal spray or after multiple dose administration of olopatadine 0.1- and 0.2% nasal spray (Figures 2.2.4.1.1 and 2.2.4.1.2, respectively).

Two dose-response studies were reported by the sponsor. Study C-01-83 was a single dose study in 320 (80 per arm) patients with AR. Patients received a single dose (2 sprays per nostril) of either olopatadine 0.2%, 0.4%, 0.6% or vehicle. The mean decrease in TNSS for the olopatadine nasal 0.6% group, olopatadine nasal 0.4% group, olopatadine nasal 0.2% group, and vehicle group were 2.8-, 2.63-, 2.58-, and 1.52 units, respectively (Table 2.2.4.1.1)

Table 2.2.4.1.1. Mean change from baseline in TNSS following single nasal administration (2 sprays per nostril) of olopatadine 0.2-, 0.4-, and 0.6% nasal solution (Data from Study C-01-83)

Statistics	Vehicle	Olopatadine 0.02%	Olopatadine 0.04%	Olopatadine 0.06%
Mean	-1.52	-2.58	-2.63	-2.8
Median	-1.0	-2.5	-2.0	-2.5
Minimum	-11	-12.0	-12	-11
maximum	6	4.0	4.0	5
SD	2.8	2.9	2.8	2.99

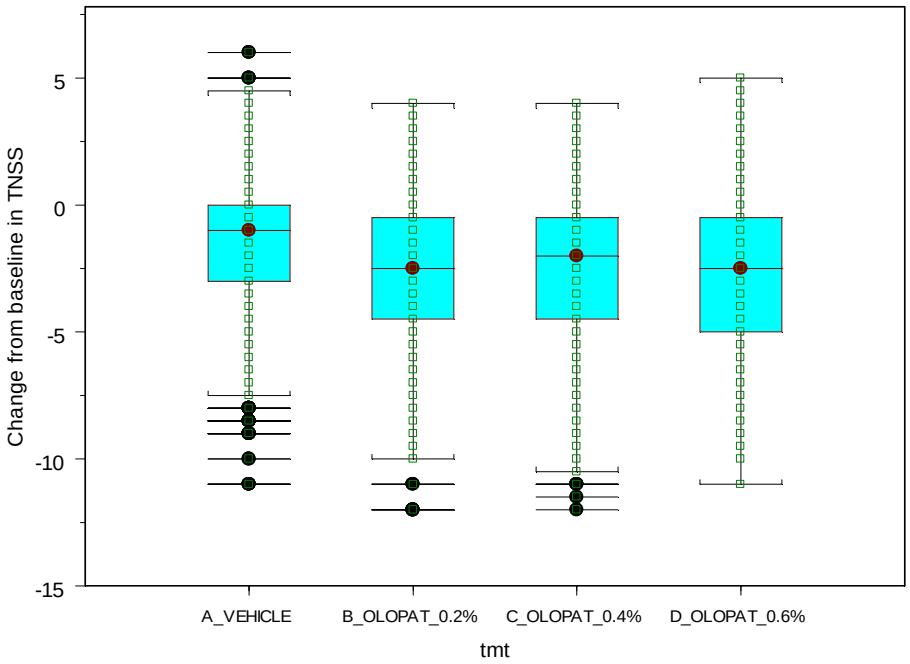


Figure 2.2.4.1.1. Change from baseline in TNSS following single nasal administration (2 sprays per nostril) of olopatadine 0.2-, 0.4-, and 0.6% nasal solution (Data from Study C-01-83).

Study C-00-10 was a placebo-controlled, parallel group study in 192 patients with AR. Patients received study drug (olopatadine 0.1% nasal spray or olopatadine 0.2% nasal spray, 2 sprays per nostril) either in BID (morning and evening) or QD (morning only) for 2 weeks. The primary efficacy variables analyzed were the AM and PM percent reduction in MRSC (Mayor Rhinitis Symptom Complex, averaged across all visits) from the average AM and PM MRSC baselines. No differences in percent reduction in either AM or PM MRSC were found for the BID or QD comparisons (Figure 2.2.4.1.2)

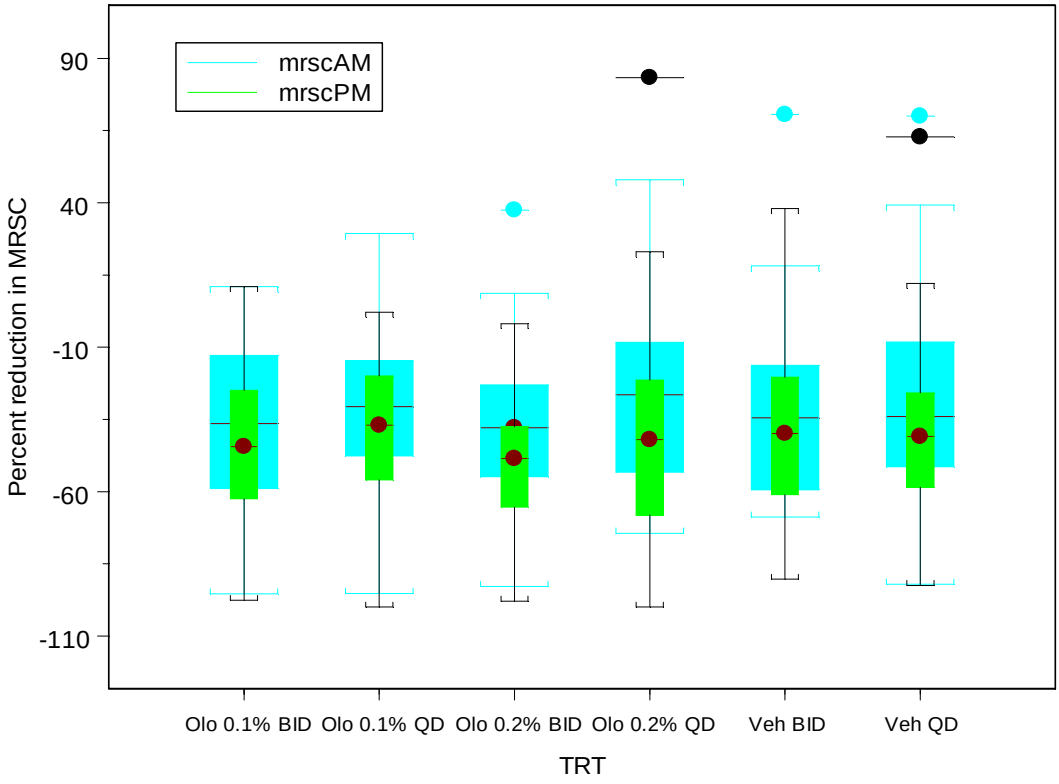


Figure 2.2.4.1.2. AM and PM percent reduction in MRSC (averaged across all visits) from the average AM and PM MRSC baselines following multiple administration of olopatadine 0.1 % and 0.2% nasal spray BID or QD (Data from Study C-00-10).

2.2.4.2 What are the characteristics of the dose-systemic exposure relationships for safety?

In general, based on two Phase II dose-response studies, systemic adverse events appeared not to be related to dose following single administration of olopatadine 0.2-, 0.4 or 0.6% nasal spray or multiple doses of olopatadine 0.1 or 0.2% nasal spray (Figure 2.2.4.2.1). However, nasal discomfort (2 events) appeared to be related to drug treatment, in this case the 0.2% olopatadine nasal spray.

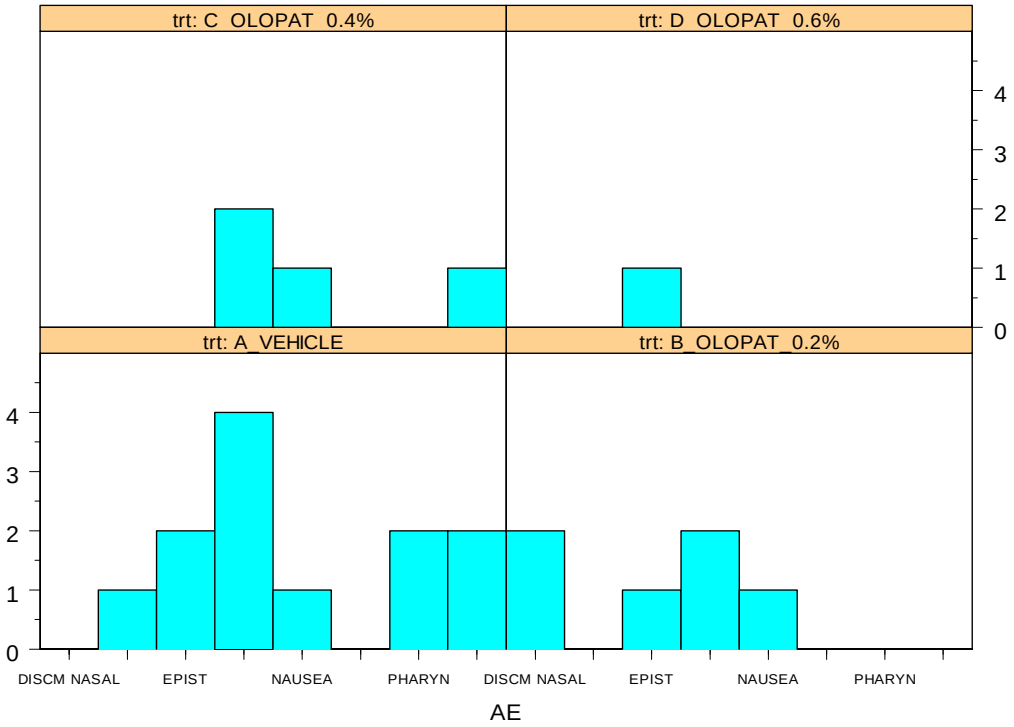


Figure 2.2.4.2.1. Adverse event frequency following single dose administration of olopatadine 0.2-, 0.4- and 0.6% to AR patients (Data from study C-01-83).

2.2.4.3 Does this drug prolong the QT or QTc interval?

Study C-02-54 was a single-center, randomized, double-masked, crossover design, safety and pharmacokinetic study in 34 healthy, male and female subjects, ages 18 to 75 years. Subjects received multiple twice-daily oral doses of 20 mg olopatadine solution or placebo for 14 days. Eighteen 12-lead ECGs were performed over the 24-hour period at baseline (Day -2 to -1), 15 ECGs over the 12-hour period on Day 12 and 18 ECGs over the 24-hour period after the last dose on Day 14 (Days 14/15) for each treatment. The ECGs were forwarded to a centralized reading center for masked manual measurements to determine the ECG parameters. The QT interval for three beats was averaged and corrected for rate (HR) using two fixed-exponent correction formula ($QTc=QT/RR^{\alpha}$) where $\alpha=0.500$ (Bazett's, QTcB) or $\alpha=0.333$ (Fridericia's, QTcF). In addition, an individual-derived regression approach (QTcI) was used. This method derives an α value for each subject that provides a slope ~ zero from the regression of 1/RR α versus QT using all the ECGs obtained at baseline and on each of the placebo study days. Mean steady-state (averaged across all time points on Day 12 and Days 14/15) changes from mean baseline (averaged from the 18 ECGs on Day -2) were calculated for each subject. The maximal change from mean baseline was defined as Emax. Categorical analysis of the Emax values into <30 msec, >30 to <60 msec and >60 msec for each subject. Plasma samples for olopatadine determination were obtained at the same time points as the ECG recordings on Days 12 and 14/15.

Comparisons of the results of the analysis showed that Fridericia's correction formula (QTcF) yielded a slope closer to zero (-0.02 1) than Bazett's (-0.097) (Figure 2.2.4.3.1). From the individual-regression rate-correction (QTcI) analysis, the mean of the individual subject exponent values (0.290) was closer to the 0.333 exponent used in Fridericia's formula compared to the 0.500 exponent used in Bazett's formula. These findings provided further support for the use of QTcF over QTcB along with the individual correction analysis (QTcI).

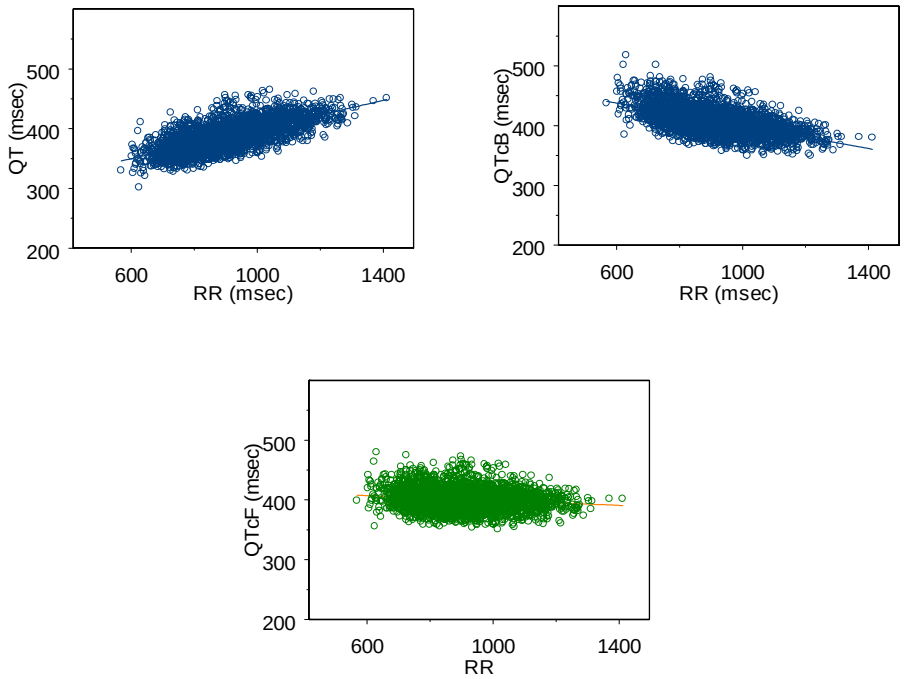


Figure 2.2.4.3.1. Individual QT, QTcB and QTcF as a function of RR following multiple administration of olopatadine 20 mg oral solution to male and female healthy volunteers.

Table 2.2.4.3.1 shows that all mean changes in QTcF from baseline were negative. No statistically significant (p≥0.097) differences were seen between olopatadine and vehicle in either the mean change or mean of maximum change.

Table 2.2.4.3.1. Mean, median, min and max QTc, Δ QTc change from baseline and mean of maximum Δ QTc following multiple administration of the treatments.

	QTcB		**QTcF**		**Δ QTB**		**Δ QTF**		**Mean of max Δ QTB**		**Mean of max Δ QTF**	
	OLOP	**PLB**	**OLOP**	**PLB**	**OLOP**	**PLB**	**OLOP**	**PLB**	**OLOP**	**PLB**	**OLOP**	**PLB**
Min (msec)	382.2	370.5	370.9	367.1	-12.9	-25.8	-22.5	-22.4	6.1	-11.5	-1.1	-6.1
Mean (msec)	409.6	408.9	401.2	401.5	3.14	0.09	-2.5	-3.9	30.68	29.4	17.4	15.9
Median (msec)	410.7	407.9	399.3	401	2.2	1.45	-3	-4.4	26.7	24.4	14.3	13.2
Max (msec)	463.5	455.7	450.9	446.2	35.8	27.9	20.7	13.7	91.22	94.8	63.1	52.1
N	81	79	81	79	81	79	81	79	81	79	81	79
SD	16.6	17.9	14.4	15.4	9.3	11.5	8.8	9.04	17.3	20.1	12.8	13.4

Several subjects on olopatadine and on placebo experienced a maximum change in QTc between 30 and 60 msec. On olopatadine, one subject experienced a QTcF Emax >60 msec (63.1 msec) on Day 14 at 1.5 hours post-dose (Figure 2.2.4.3.2). However, the QTcF values at the adjacent (1 and 2 hour) time points were 403 and 413 msec. Further, this subject did not have a Emax on Day 12. According to the sponsor, this isolated Emax was considered a random event and deemed not clinically meaningful in view of these findings. The highest QTF absolute value was 518 following olopatadine treatment. The mean of maximum QTF change from

baseline was highest for the olopatadine group (17 msec ± 13 vs 16 msec ±13) (Table 2.2.4.3.1). The maximum of the mean values over time was 18.8 msec and 14.9 msec for the olopatadine and placebo treatment, respectively (Figure 2.2.4.3.2 and Table 2.2.4.3.2).

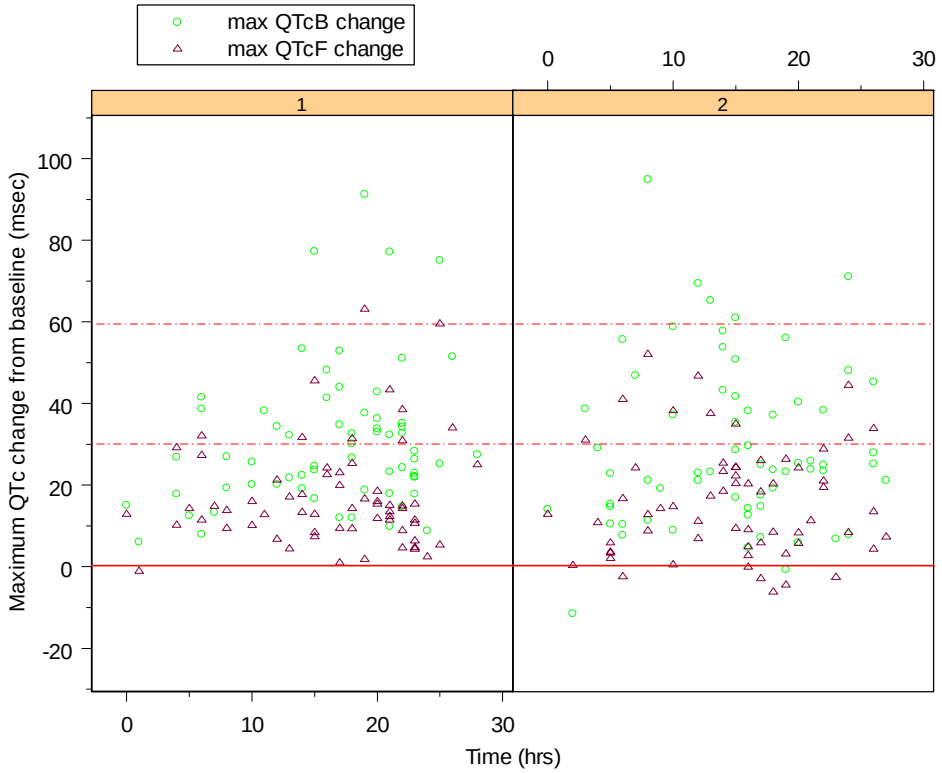


Figure 2.2.4.3.2. Individual maximum QTc change from baseline at steady state following multiple administration of the treatments (1=olopatadine and 2=placebo).

Although the QTc change from baseline and categorical analysis (**Table 2.2.4.3.1)** show an unlikely effect of olopatadine on QT prolongation, this conclusion should be interepreted with caution since the study did not include a positive control.

2.2.4.4 Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

As mentioned previously, the systemic absorption of intranasally administered drugs is the result of nasal and gastrointestinal absorption, and therefore plasma concentrations cannot be correlated to efficacy (TNSS). Thus, the appropriate dose and dosing regimen need to be based on dose-response relationships rather than exposure-response relationships. The proposed dose of Patanase in patients 12 years and older is two sprays per nostril (1 spray = 600 mcg of olopatadine base) twice-daily. In the case of dose-response for efficacy, there was a trend for higher doses to produce a bigger response; however a clear dose-ordering was not observed following either single administration of olopatadine 0.2-, 0.4-, or 0.6% nasal spray or after multiple administration of olopatadine 0.1- and 0.2% nasal spray. In general, based on Phase II dose-response studies, systemic adverse events appeared not to be related to dose following single administration of olopatadine 0.2-, 0.4 or 0.6% nasal spray or multiple doses of olopatadine 0.1 or 0.2% nasal spray. Based on phase III clinical trials, it appears that olopatadine 0.6% 2 sprays per nostril BID was efficacious in AR patients. Therefore, in terms of dose, it appears that

0.6% olopatadine may be the appropriate dose. In terms of dosing regimen, the dose-response studies did not evaluate BID vs QD regimen for higher doses, thus, conclusions in terms of appropriate dosing regimen cannot be made based on phase II dose-response information.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters? What are the characteristics of drug distribution? How do the PK parameters change with time following chronic dosing?

Single Dose

Single-dose pharmacokinetics was assessed following single intranasal administration of olopatadine nasal 0.4% or olopatadine nasal 0.6% in SAR patients and olopatadine nasal 0.1%, 0.2%, 0.4-, or 0.6% in healthy subjects. The mean PK parameters resulting from these studies are shown in Table 2.2.5.1.1. The mean and range in the olopatadine Cmax and AUC values in SAR patients following single intranasal doses (two sprays/nostril) of either olopatadine nasal 0.4% (1.6 mg) or olopatadine nasal 0.6% (2.4 mg) were comparable to those in healthy subjects.

Table 2.2.5.1.1. Mean ± SD (range) Pharmacokinetic Parameters of Olopatadine after Single Intranasal Doses

Study	Dose	Cmax (ng/mL)	Tmax (h)	AUC (ng*h/mL)	t_{112} (h)
Study C-02-10 SAR Patients	0.4% (N=14)	14.4 ± 4.4 (5.97 -21.9)	0.86 ± 0.41 (0.25 - 1.50)	48.9 ± 12.5 (23.3 - 67.4)	ND
	0.6% (N=13)	21.7 ± 8.7 (7.11 - 36.4)	1.00 ± 0.50 (0.25 - 2.00)	67.7 ± 21.1 (24.0 - 98.0)	ND
Study C-02-21 Healthy	0.6% (N=8)	29.3 ± 15.1 (13.6-58.4)	0.97 ± 0.54 (0.50 -2.00)	75.1 ± 29.4 (31.8 - 126)	ND
Study C-03-11 Healthy	0.4% (N=11)	12.5 ± 6.1 (1.98 -20.7)	1.04 ± 0.24 (0.75-1.50)	42.5 ± 16.0 (17.0-66.4)	8.6 ± 5.7 (1.75-17.9)
	0.6% (N=11)	17.5 ± 6.7 (6.37 -27.6)	1.05 ± 0.31 (0.75 - 1.50)	60.3 ± 20.3 (20.2 - 98.0)	10.0 ± 5.7 (3.2 -22.2)
Study C-02-46 Healthy	0.6% (N=6)	18.1±10.9 (3.80 - 29.9)	1.17±0.52 (0.50 - 2.00)	77.0±51.3 (17.0 - 139)	11.5±3.0 (7.2 - 14.5)

ND= not determined, sampling only out to 12 hours post-dose.

Three minor active metabolites (M1, M2, and M3) were identified in these PK studies, but only N-desmethyl olopatadine (Ml) and olopatadine N-oxide (M3) were quantified in plasma samples following single intranasal doses of olopatadine nasal 0.4% or olopatadine nasal 0.6%. The Cmax and AUC values for these metabolites did not appear to be markedly different between SAR patients and healthy subjects administered comparable single intranasal doses (Table 2.2.5.1.2)

Table 2.2.5.1.2. Mean ± SD (range) Pharmacokinetic Parameters of Metabolites Ml and M3 after Single Olopatadine Intranasal Doses

Study	Dose (N)	Analyte	Cmax (ng/mL)	Tmax (h)	AUC_{0-t} (ng*h/mL)	t_{112} (h)
Study C-02-10 SAR Patients	0.4% (N=14)	Ml	0.0861 ± 0.0431 (BLQ-0.163)	2.27 ± 0.87 (1.00-4.00)	0.546 ± 0.169[a] (0.366-0.702)	ND
	0.4% (N=14)	M3	0.357 ± 0.112 (0.153-0.581)	1.73 ± 0.77 (0.75-3.00)	1.42 ±0.24[a] (1.13-1.82)	ND
	0.6% (N=13)	Ml	0.150 ± 0.084 (BLQ-0.352)	2.41 ± 0.94 (1.50-4.00)	0.728 ± 0.121[a] (0.572-0.913)	ND
	0.6% (N=13)	M3	0.530±0.255 (0.115-1.16)	1.44±0.61 (0.75-3.00)	1.89±0.60[a] (0.5 14-2.60)	ND
Study C-03-11 Healthy Subjects	0.4% (N11)	Ml	0.138 ± 0.067 (0.0637-0.241)	4.82 ± 10.3 (1.50-36.0)	0.49 ± 0.32 (0.035-1.08)	5.5 ± 4.6 (2.5-13.6)
	0.4% (N=11)	M3	0.377±0.192 (0.0515-0.602)	1.18±0.32 (0.75-1.50)	1.00±0.62 (0.013-1.90)	1.6±0.4 (0.7-2.2)

	0.6% (N=11)	Ml	0.344±0.398 (0.800-1.34)	1.82±0.34 (1.00-2.04)	0.68±0.47 (0.094-1.38)	3.7± 1.8 (2.2-7.6)
	0.6% (N=1 1)	M3	0.511±0.229 (0.120-0.783)	1.25±0.37 (0.75-2.00)	1.38±0.65 (0.23-2.14)	1.7±0.4 (1.0-2.3)
Study C-02-46 Healthy Subjects	0.6% (N6)	Ml	0.192 ± 0.138 (BLQ-0.328)	2.60 ±0.55[b] (2.00-3.00)	2.09 ± 0.15[cd] (1.98-2.26)	4.0 ± 0.5[c] (3.5-4.4)
	0.6% (N=6)	M3	0.526 ± 0.348 (0.123-1.02)	1.88 ± 0.92 (0.75-3.00)	2.69 ± 1.98 (0.561-5.82)	2.5 ± 0.6 (1.9-3.3)

ND= not determined. [a]AUC0-6; [b]N=5; [c]N=3; [d]AUC $_{0\text{-}12h}$

Multiple Dose

The multiple-dose PK of olopatadine was examined in two studies following intranasal administration (Study C-02-10 and Study C-00-58) (two sprays/nostril) from 0.1% (0.4 mg), 0.2% (0.8 mg), 0.4% (1.6 mg) and 0.6% (2.4 mg). Comparison of the systemic exposure (Cmax and $AUC_{0\text{-}12}$) of olopatadine after single and multiple intranasal doses in SAR patients (C-02-10) indicate minimal accumulation (<1.3-fold) with twice-daily administration. Mean Tmax and t1/2 values were similar in healthy subjects and SAR patients.

Table 2.2.5.1.3. Mean ± SD (range) Pharmacokinetic Parameters of Olopatadine after Multiple QD or BID Intranasal Doses

Study	Dose/Regimen (N)	Cmax (ng/mL)	Tmax (h)	AUC0-$_{12}$ (ng*h/mL)	$t_{1/2}$ (h)
Study C-02-10 SAR patients	0.4%/BID x 14 days (N=14)	15.9 ± 6.4 (3.65-29.0)	1.00 ± 0.55 (0.25-2.00)	57.3 ± 24.5 (10.4-114)	8.3 ± 4.9 (2.1-21.3)
	0.6%/BID x 14 days (N=13)	23.3 ± 6.2 (14.4-35.3)	0.97 ± 0.52 (0.08 - 1.50)	78.0 ± 13.9 (54.4- 103)	10.4 ± 5.1 (4.0-21.8)
Study C-00-58 Healthy Subjects	0.1%/QD x 3 days (N12)	4.36 ± 2.27 (0.41 -7.92)	1.23 ± 0.59 (0.50 -2.00)	13.92± 5.90 (1.40 -20.67)	6.3 ± 4.1 (1.96 - 13.5)
	0.1%/BID x 3 days (N=12)	3.42 ± 1.31 (0.97 — 5.05)	1.06 ± 0.42 (0.50 - 1.50)	12.03 ± 3.66 (4.80 - 16.54)	8.3 ± 3.5 (3.06 - 13.3)
	0.2%/BID x 3 days (N=12)	8.48 ± 3.12 (2.77- 15.0)	1.25 ± 0.38 (0.75-2.00)	28.33 ± 9.88 (11.09- 14.03)	15.0 ± 9.6 (3.16-29.9)

The multiple-dose pharmacokinetics of olopatadine metabolites following intranasal administration of olopatadine nasal 0.6% was examined in SAR patients (Study C-02- 10). M2 was not quantifiable in any sample. For Ml and M3, peak plasma concentrations after BID dosing for 2 weeks were about 1.7-and 1.3-fold higher, respectively than those observed after the single dose. AUC values were 1.2- to 1.5-fold higher.

The PK of olopatadine following oral solution doses was examined as part of a cardiovascular safety study (Study C-02-54) following single and multiple twice-daily oral doses of the oral solution. The mean pharmacokinetic parameters following multiple twice-daily doses are presented in Table 2.2.5.1.4.

Table 2.2.5.1.4. Mean ± SD (range) Pharmacokinetic Parameters of Olopatadine after Multiple Twice- Daily Oral Solution Doses

Study	Dose/Day (N)	Cmax (ng/mL)	Tmax (h)	AUC $_{0\text{-}12h}$ (ng*h/mL)	T1/2 (h)
Study C-02-54 Healthy	20 mg/Day 14 (N32)	309 ± 57 (185 -436)	0.83 ± 0.40 (0.28-2.03)	997 ± 152 (689-1280)	11.2 ± 3.7 (5.4-18.5)

Mean Cmax values for metabolites Ml and M3 averaged 2.39 ± 0.65 ng/mL and 8.22 ± 1.83 ng/mL. Plasma concentrations of M3 were approximately 3-fold higher than those for Ml. M2 was not quantifiable (<0.250 ng/mL) in any sample. Measurable plasma concentrations of both Ml and M3 were obtained for up to 24 hours postdose. From these profiles, the estimated terminal half-life of Ml (9.1 ± 3.4 hours) and M3 (7.9 ± 2.4 hours) were not substantially different from that of the parent drug.

The absolute bioavailability of olopatadine as examined in a single center, open-label, randomized, crossover study (C-03-1 1). Twelve, healthy, adult, male and female subjects were randomized to receive either

a single intranasal dose (two sprays per nostril) of olopatadine nasal 0.4% (1.6mg) or olopatadine nasal 0.6% (2.4 mg) or a single intravenous infusion of olopatadine solution (1.5 mg). The mean absolute BA of olopatadine (based on dose-adjusted AUC ratios) was 61.3% for olopatadine nasal 0.4% and 56.6% for olopatadine nasal 0.6%. Similar absolute BA estimates were obtained based on ratios of the mean 48-hour urinary recovery of unchanged olopatadine, with values of 57% and 59%, respectively. Urinary recovery of unchanged olopatadine accounted for 61.5 ± 16.7% of the intravenous dose.

2.2.5.2 Are the PK of Patanase linear and dose-proportional?

Dose-proportionality following single and multiple intranasal administration of olopatadine nasal 0.4% or olopatadine nasal 0.6% in SAR patients and olopatadine nasal 0.2% or 0.6% in healthy subjects was evaluated in Studies C-03-10 and C-03-11, respectively.

Olopatadine peak plasma concentrations increased in proportion to the intranasal dose averaging 12.5 ± 6.1 ng/mL and 17.5 ± 6.7 ng/mL for olopatadine nasal 0.4% and olopatadine nasal 0.6%, respectively (Study C-03-11). Similar dose-proportional increases were seen in mean AUC values (an increase in 1.5 in dose resulted in a 1.4 increased in the olopatadine Cmax and AUC) (Refer to Table 2.2.5.1.1 and 2.2.5.1.2)

Following single intranasal doses of olopatadine nasal 0.4% and 0.6% plasma concentrations of M1 and M3 increased roughly in proportion to the olopatadine dose in both healthy subjects and SAR patients (refer to Table 2.2.5.1.2)

2.2.5.3 What are the mass balance characteristics of the drug?

Following a single oral administration of ^{14}C-olopatadine solution (5 mg/200 µCi/7.5 mL ^{14}C-olopatadine dosing solution) to 8 healthy volunteers, the overall mean total recovery of radioactivity (over the entire 192 hr postdose interval) in urine and feces was 70.5% and 17% of the dose, respectively indicating that urinary excretion was the major pathway of elimination of radioactivity with the majority recovered as unchanged olopatadine (Table 2.2.5.3.1). Together, urinary excretion of Ml and M3 accounted for about 7% of radiolabeled material recovered in the urine within 24 hours. Identified and unidentified metabolites accounted for <10% of the total radioactivity in urine. The majority of the cumulative % dose of radioactivity was recovered in the first 24 hours (67.4%) in the urine, and in the first 96 hours (16.0%) in the feces.

In plasma drug-related radioactivity was rapidly absorbed with peak total radioactivity in observed within 0.5 to 1 hours after dosing. Radioactivity was eliminated from plasma with a mean half-life of 7.94 hours. Unchanged olopatadine was the major component of radiolabeled material in plasma and urine. Olopatadine Ml, M2 and M3 metabolites accounted for less than 10% of circulating radioactivity in plasma (Table 2.2.5.3.2)

Table 2.2.5.3.1. Individual and Mean ± SD Cumulative Recovery of Total Radioactivity in Urine, Feces and Combined (Total) Following an Oral ^{14}C Olopatadine Dose, C-03-10

	Cumulative Urine		**Cumulative Feces**		**Cumulative Total**
Subject Number	**Ae (µg)**	**% Dose**	**Ae (µg)**	**% Dose**	**% Dose**
101					(b) (4)
102					
103					
104					
105					
106					
107					
108					
Mean	3493.3	70.5	841.7	17.0	87.5
SD	137.1	2.6	279.7	5.7	6.0
Min					(b) (4)

Max	(b) (4)

Table 2.2.5.3.2. Mean ± SD Plasma Total Radioactivity and Concentrations (ng eq./mL) at Selected Time points After a 5 mg ^{14}C-Olopatadine HCI Solution in Healthy Subjects

Peak	Component[a]	**Concentration (ng eq/mL) and Percent of Total Radioactivity (%)**								
		0.5 Hours			3 Hours			8 Hours		
		Mean	SD	%	Mean	SD	%	Mean	SD	%
	Total Radioactivity[b]	84.8	31.1	Ref	36.9	8.0	Ref	9.1	1.7	Ref
Mpl	Unidentified	1.63	0.66	1.9	0.86	031	2.3	BLQ	DLQ	ND
Mp2	Unidentified[c]	1.34	0.57	1.6	0.84	0.27	2.3	BLQ	BLQ	ND
Mp3	N-Desmethyl Olopatadine[d]	3.01	1.66	3.5	2.29	0.62	6.2	0.72	0.19	8.0
Mp4	Olopatadine	65.5	24.1	77.2	24.2	3.97	65.6	5.62	1.02	62.1
Mp5	Olopatadine N-Oxide	1.31	0.38	1.5	0.71	0.16	1.9	BLQ	BLQ	ND
Mp6	Unidentified	BLQ	BLQ	ND	0.68	0.20	1.8	BLQ	BLQ	ND
Mp7	Unidentified	1.39	0.35	1.6	0.71	0.23	1.9	BLQ	BLQ	ND

SD: Standard Deviation
BLQ: Below Limits of Quantitation (less than 0.34 ng eq/mE)
ND: Not determined since metabolite was below limit of quantitation. Ref: Reference concentration for calculation of olopatadine and metabolite percentages.
[a]identification of component in plasma based on retention time to authentic standards.
[b]Source: Study C-03-10, Alcon Clinical Study Report No.: TDOC 0001414
[c]Retention time corresponds to N-didesmethyl olopatadine standard. However, peak was not well resolved and presence of this compound at these levels is inconsistent with results of other clinical studies.
[d]Concentration may be an overestimate due to co-elution of other radioactive material under peak.

2.2.5.4 What are the characteristics of drug metabolism and excretion?

Data from the in-vitro metabolism of ^{14}C-olopatadine using microsomes prepared from: a) human B-lymphoblast cells expressing CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4; b) from baculovirus-infected insect cells expressing flavin-containing monooxygenase FMO1, FMO3, and FMO5 and microsomes from c) a mixed pool of human liver microsomes (0.53 nmol of P450/mg protein) prepared from six subjects showed that the metabolism of olopatadine is a minor route of elimination. Two different metabolites, M1 and M3, were formed when olopatadine was incubated with human liver microsomes in the presence of an NADPH-generating system. After 1-h incubation, M1 and M3 accounted for 5.2 and 30.5% of the initial olopatadine, respectively. M1 and M3 were identified tentatively as *N*-monodemethylolopatadine and olopatadine *N*-oxide, respectively. The formation of both M1 and M3 by human liver microsomes was found to be NADPH-dependent, and the formation rates of M1 and M3 were 0.330 and 2.50 pmol/min/mg protein, respectively.

Formation of Ml was decreased by the selective inhibitors of CYP3A4, troleandomycin and ketoconazole, by not by inhibitors of other P450 isozymes. The rate of M3 formation by FMO1 and FMO3 was about 4 times faster than by CYP1A2, CYP2B6 and CYP2E1. Other evaluated isozymes (CYP2A6, CYP2C9, CYP2C19, CYP2D6 and CYP2E1) did not catalyze the formation of either Ml or M3. This indicates that M1 formation is catalyzed primarily by CYP3A4, while M3 formation is catalyzed by FMO1 and FMO3.

After oral administration of [^{14}C]olopatadine to rats and dogs, the main metabolic pathways were 1) *N*-demethylation to M1 and M2, the *N*-monodemethyl and *N*-didemethyl analogs, respectively; 2) hydroxylation of dihydrodibenz[*b*,*e*]oxepin ring (M5); and 3) sulfoconjugation of M5 (M4) and *N*-oxidation (M3) (Fig.2.2.5.5.1). Following oral administration of 5 mg ^{14}C-olopatadine, olopatadine was the primary component circulating in plasma accounting for 77% of the peak total radioactivity. At least 6 metabolites were observed in plasma, of which M1 and M3 were the major metabolites. All were minor, representing 2 to 4.5% or less of parent circulating in plasma.

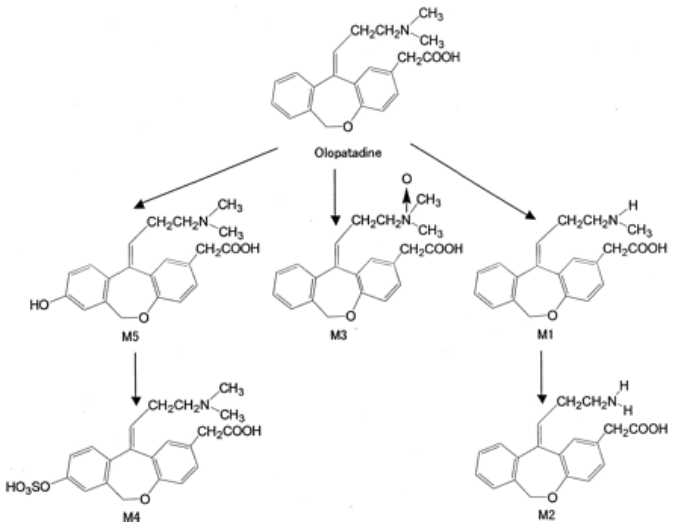


Fig. 2.2.5.4.1. Proposed metabolic pathway of olopatadine.

2.2.5.5 What are the inter- and intra-subject variabilities in PK parameters in volunteers and patients?

The CV% (intersubject variability) for the Cmax and AUC of olopatadine in healthy volunteers and AR patients was about 35%. Disease stage did not change the degree of variability.

2.3 Intrinsic Factors

2.3.1 Does age affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

2.3.1.1 Do race, gender, age, and disease status affect the PK and PD of the drug? What dosage regimen adjustments are recommended for each of these subgroups?

Gender

Alcon did not conduct any specific studies to investigate gender differences in the pharmacokinetics of parent drug or metabolites following intranasal administration of olopatadine nasal 0.6%. However, the mean systemic exposure (Cmax and AUCt) in females following multiple administration of olopatadine in SAR patients was 40 % and 27% higher, respectively than those values observed in male SAR patients. This increase in systemic exposure in females compared to males was lower following oral administration of olopatadine (13 to 20% higher in females) (Table 2.3.1.2.1). These differences in systemic exposure are not clinically relevant since multiple doses of oral olopatadine 20 mg BID appeared to be safe. Therefore, no dose adjustment is necessary based on gender difference in the PK of olopatadine.

Table 2.3.1.2.1. Mean ± SD (range) Olopatadine Pharmacokinetic Parameters by Gender

Study Population Dose	Gender Day	Parameters				
		Cmax (ng/mL)	Tmax (h)	AUC_{0-12} (ng*h/mL)	AUC0-inf (ng*h/mL)	$t_1/_2$ (h)
C-02-54 Healthy 20 mg oral BID x 14	Male Day 14	287 ± 56 (185-436)	0.76 ± 0.38 (0.28-1.53)	943 ± 143 (689-1250)	1070 ± 180 (743-1450)	10.0 ± 2.8 (5.4-15.6)
	Female Day 14	345 ± 53 (250-434)	0.88 ± 0.44 (0.53-2.03)	1070 ± 150 (734-1280)	1240 ± 180 (867-1630)	12.3 ± 4.1 (6.4- 18.5)
C-02-10 SAR patients Olopatadine 04% or Olopatadine 0.6%BIDx 14 days	Male Day 15 0.4%	22.4 ± 6.2 (14.4-21.7)	0.78 ± 0.64 (0.08-1.50)	82.9 ± 15.9 (57.5-103) .	97.5 ± 19.5 (66.0-116)	8.1 ± 3.0 (4.0-11.5)
	Female Day 15 0.4%	24.1 ± 6.5 (18.5-35.3)	1.14 ± 0.35 (0.75-1.50)	73.8 ± 11.5 (54.4-86.6)	85.9 ± 16.9 (59.3-108)	12.3 ± 6.0 (5.9-21.8)
	Male Day 15 0.6%	13.0±3.7 (7.00-18.1)	1.25±0.39 (0.75-1.50)	49.0±14.4 (34.5-69.6)	58.1±17.0 (40.7-81.0)	8.4±3.7 (5.2-15.0)
	Female Day 15 0.6%	18.1 ± 7.4 (3.65-29.0)	0.81 ± 0.59 (0.25-2.00)	63.6 ± 29.4 (10.4-114)	74.0 ± 35.3 (10.5-130)	8.3 ± 5.9 (2.1-21.3)

The effect of race and age (pediatric patients or elderly (>65 years)) on the PK of the drug has not been evaluated by the sponsor.

2.3.1.2. Does renal impairment affect the PK of the drug and its major metabolite? Is dosage regimen adjustment recommended?

After single intranasal administration of olopatadine nasal 0.6% to 25 subjects/patients (6 subjects with normal renal function, 7 patients with mild renal impairment, 6 patients with moderate renal impairment, and 6 patients with severe renal impairment) no clinically significant differences were observed in the systemic exposure of olopatadine in patients with mild or moderate renal impairment compared to subjects with normal renal function. The plasma Cmax and AUC values in patients with severe renal impairment were approximately 1.2- and 2-fold higher than those in healthy subjects. Higher plasma concentrations of the minor, active Ml and M3 metabolites were seen with increasing renal impairment particularly those in severely-impaired patients with 2.6- and 3.6-fold higher mean Cmax values, respectively. Urinary excretion of parent and metabolites was reduced in renally impaired patients. Despite of the higher systemic exposure of parent drug and metabolites observed in patients with severe renal impairment following intranasal doses of olopatadine nasal 0.6%, the extent of exposure is still 10- to 250-fold lower than that observed following higher oral 20 mg to 400 mg doses which were safe and well-tolerated. Therefore, dosage adjustment of olopatadine based on renal impairment may not be necessary.

2.3.1.3 Does liver impairment affect the PK of the drug? Is dosage adjustment recommended?

The effect of liver impairment on the PK of olopatadine and its metabolites was not evaluated. The rationale provided by the sponsor is that olopatadine (and its metabolites) are mainly eliminated by the kidney. In fact, in a mass balance study total radioactivity was predominantly excreted in urine (70% of total administered dose) suggesting that liver metabolism is not an important route of elimination.

2.3.1.4 What pregnancy and lactation use information is there in the application?

Olopatadine was non-teratogenic and did not affect reproductive function in animals. However, no adequate and well-controlled studies in pregnant women have been conducted. This drug should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the fetus.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The effects of herbal products, diet, smoking and alcohol used have not been evaluated.

2.4.2 Drug-Drug Interactions (DDI)

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Data from the in-vitro metabolism of ^{14}C-olopatadine showed that metabolism of olopatadine is a minor route of elimination. Two different metabolites, M1 and M3, were formed when olopatadine was incubated with human liver microsomes. After 1-h incubation, M1 and M3 accounted for 5.2 and 30.5% of the initial olopatadine concentration, respectively. M1 formation was catalyzed primarily by CYP2A4, while M3 formation is catalyzed by FMO1 and FMO3. Therefore, it is unlikely that substrates, inhibitors or inducers of these enzymes may affect the PK of olopatadine and its metabolites. In addition, olopatadine did not affect the activity of the major CYPP450 enzymes such as 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. Therefore, no major effects of olopatadine should be expected on the PK of other drugs.

2.4.2.2 Is the drug a substrate of CYP enzymes?

Data from the in-vitro metabolism of ^{14}C-olopatadine showed that the metabolism is a minor route of elimination. CYP3A4 appears to be the only CYP enzyme involved in the metabolism of olopatadine with an insignificant contribution to the overall elimination (~ 5%).

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

At concentrations as high as 100 μM (concentration was at least 3 times the maximum concentrations achieved *in vivo*), olopatadine failed to produce significant inhibition of the metabolism of any isozyme specific substrate tested (phenacetin for CYP1A2, tolbutamide for CYP2C8-9, S-mephenyltoin for CYP2C19, bufurol for CYP2D6, chloroxazone for CYP2E1 and testosterone for CYP3A4). The potential for olopatadine metabolites to act as inhibitors of CYP enzymes was not evaluated.

The potential for olopatadine or its metabolites to act as an inducer of CYP enzymes was not evaluated.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

This was not evaluated by the sponsor.

2.4.2.5. Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

No information on this issue was provided.

2.4.2.6 What is the effect of olopatadine on the PK of other drugs? What is the effect of other drugs on the PK of olopatadine?

No DDI studies were performed by the sponsor. Data from the in-vitro metabolism of ^{14}C-olopatadine showed that the metabolism of olopatadine is a minor route of elimination. Therefore, it is unlikely that substrates, inhibitors or inducers of these enzymes affect the PK of olopatadine and its metabolites. In addition, olopatadine did not inhibit the major CYPP450 enzymes such as 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. Therefore, no major effects of olopatadine should be expected on the PK of other drugs.

2.4.2.7 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

In-vitro metabolism studies using human microsomes indicated that olopatadine is metabolized into two major metabolites M1 and M3. M3 formation was catalyzed by FMO1 and FMO3. The contribution of these FMO enzymes is about 30% of the overall elimination of the drug. The sponsor did not conduct in vitro or in vivo DDI with inhibitors or inducers of these enzymes.

2.5 General Biopharmaceutics

2.5.1 What is the BCS Class classification for olopatadine?

This information was not provided by the sponsor. Also, this information may not be relevant since this is not a solid dosage form.

2.5.2 Was the to-be-marketed formulation used in the PK/clinical trials?

Two different series of nasal formulations were developed and used in subsequent clinical trials. The first series, with 0.1% or 0.2% w/v olopatadine as base, at neutral pH and without povidone or EDTA, was based upon the composition of PATANOL® (olopatadine hydrocloride ophthalmic solution) 0.1%. The Series 1 formulations were used in Phase II dose-ranging studies. The *in vivo* performance (systemic BA) and PK of the series 1 formulation at two strengths was evaluated after single and multiple intranasal doses in healthy subjects (Study C00-58). The second series, containing 0.2%, 0.4% and 0.6% w/v olopatadine as base, at acidic pH and with (b) (4) w/v povidone and (b) (4) EDTA, was based on the composition of olopatadine hydrochloride ophthalmic solution, 0.2%. The Series 2 formulations (drug product intended for market) were used in the pivotal safety and efficacy Phase III clinical trials. Furthermore, the *in vivo* bioavailability and pharmacokinetics of olopatadine from the drug product intended for market was studied in healthy subjects (C-03-11, C-02-21, and C-02-46), in SAR patients enrolled in the winter-cedar Phase III efficacy study (C-02-10) and in renal impairment study (C-02-46).

Two additional olopatadine formulations were used in clinical pharmacokinetic studies. An intravenous solution of 0.0 1% w/v olopatadine, without povidone, benzalkonium chloride (BAC) or EDTA, was used in absolute bioavailability study (C-03-l 1). An oral solution of 0.2% w/v olopatadine, without povidone or EDTA, was used in two cardiovascular safety/pharmacokinetic studies (C-00-23 and C-02-54) and in the ^{14}C-excretion study (C-03-10). Table 2.5.2.1-1 lists the formulations used in the clinical pharmacology studies.

Table 2.5.2.1. Comparison of Olopatadine Nasal Spray Formulations Used in Clinical Studies

Component	**Series 1**		**Series 2**			**Solution (oral)**	**Solution (IV)**
	FID 100491	FID 101371	FID (b) (4)	**FID** (b) (4)	**FID** (b) (4)	**FID** 101688	**FID** 105103
Olopatadine Hydrochloride	0.111	0.222	0.222	0.443	0.665	0.222	0.0111
Olopatadine base	0.1%	0.2%	0.2%	0.4%	0.6%	0.2%	0.01%
Benzalkonium Chloride	0.01+ (b) (4)	0.01 + (b) (4)	0.01	0.01	0.01	None	None
Edetate Disodium	None	None	(b) (4)			None	None
Povidone	None	None				None	None
Sodium Chloride	(b) (4)					-	-
Dibasic Sodium Phosphate						-	-
Sodium Hydroxide and/or Hydrochloric Acid						-	-
Purified Water						qs	qs

2.5.3 Are the method and dissolution specifications supported by the data provided by the sponsor?

This does not apply for orally inhaled drugs.

2.5.4 What is the effect of food on the BA of the drug?

This was not assessed. Generally, the effect of food on the PK of nasally administered drugs is not evaluated since the effect of these drugs is local. However, food may increase the systemic exposure of these drugs which may change its safety profile.

2.5.5 If different-strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product? Does the use of spacers affect the PK of the drug?

The sponsor is proposing only one strength of Patanase; 0.6%. Different strengths of olopatadine (0.1%, 0.2%, 0.4% and 0.6%) were used in Phase I, II and III PK studies. The sponsor studied the systemic exposure of the clinical trial batches that were used in pivotal safety and efficacy studies and intended for market. These studies were performed in both healthy subjects (C-02-21, C-03-11, C-02-46), and in the target population of allergic rhinitis patients (C-01-92, C-02-10), and utilized the bioavailability measures considered pivotal in single (Cmax and AUC0-inf) and multiple-dose studies (Cmax and AUCo-τ). The sponsor showed that the systemic exposure of olopatadine nasal spray increased in a roughly proportional manner with the dose.

2.6 Analytical Section

2.6.1 Was the suitability of the analytical method supported by the submitted information?

Bioanalytical methods for olopatadine and its metabolites

The sponsor did not mention if free, bound or total drug was measured. Therefore, it is assumed that total drug was measured. Concentrations of olopatadine and its metabolites were determined in plasma samples from all human pharmacokinetic studies considered in this review using an HPLC with tandem mass spectrometric detection (LC/MS/MS). The assay met all validation acceptance criteria with regard to precision, accuracy and specificity (Table 2.6.1.1). A working range of 0.050 ng/mL (quantitation limit) to 5.00 ng/mL was validated for olopatadine, Ml and M3. The working range for M2 was 0.250 ng/mL (quantitation limit) to 25.0 ng/mL. Mean absolute recoveries of olopatadine, Ml, M2 and M3 were 88.2%, 91.5%, 81.8 and 56.4, respectively. Stability of olopatadine and metabolites in plasma was demonstrated through five freeze/thaw cycles, up to six hours at room temperature, and in extracts for up to 19.5 hours at room temperature and 3.5 days at 1 to 8 degrees Celsius. Long-term storage stability of olopatadine and metabolites in human plasma at both -20 degrees Celsius and -70 degrees Celsius is ongoing.

Simultaneous analysis of olopatadine and M3 were conducted using a validated (b) (4) method. This method also met all acceptance criteria for linearity, precision and accuracy over the working ranges of 3.00 ng/mL (quantitation limit) to 1500 ng/mL for olopatadine and 1.00 ng/mL (quantitation limit) to 1500 ng/mL for M3 (Table 2.6.1.1). The mean absolute recoveries for olopatadine and M3 were 52.4% and 59.1%, respectively. There were no measurable peaks in control/blank urine. Stability of olopatadine and M3 in urine was demonstrated through four freeze/thaw cycles, up to six hours at room temperature, and in extracts for up to 92 hours at room temperature. Frozen long-term stability at both -20 degrees Celsius and -70 degrees Celsius is ongoing.

Table 2.6.1.1. Listing of Analytical Methods Used in Clinical Pharmacology/Bioavailability Studies Conducted by Alcon

Method	Matrix	Analyte(s)	Working Range (ng/mL)	Accuracy/RSD	Clinical Study
LC/MS/ MS	Human plasma	Olopatadine	0.05-25	Intra-day 98-1 12%/RSD ≤8.4% Inter-day l00-107%/RSD ≤l0.5%	C-00-58 Multiple dose-ranging PK (Alcon), Nasal, 0.1%, 0.2% BID C-02-2l Single dose PK (Alcon), Nasal, 0.6%
LC/MS/ MS	Human urine	Olopatadine	10-1500	Intra-day 94.3-98.2%/RSD ≤2.l% Inter-day 95.8-l00%/RSD ≤8.8%	C-00-58 Dose-ranging PK (Alcon) Nasal, Multiple-dose 0.1%, 0.2% BID
LC/MS/MS	Human plasma	Olopatadine Ml M2 M3	0.050-5 0.050-5 0.250-25 0.050-5	Intra-day 97.3-98.8%/RSD ≤5.6% Inter-day 96-l0l%/RSD≤6.2% Intra-day 108-1 12%/RSD ≤5.3% Inter-day 110-11 1%/RSD≤4.9% Intra-day 104-108%/RSD ≤6.2% Inter-day 106-1 l0%/RSD≤6.3% Intra-day 102-103%/RSD ≤4.4% Inter-day 100-l04%/RSD≤5.7%	C-02-lO Phase III Efficacy/PK (Alcon), Nasal, Multiple dose 0.4%, 0.6% BID C-02-54 Cardiovascular Safety/PK (Alcon), Oral Multiple dose 20 mg BID C-02-46 Renal Impairment, Nasal, Single dose 0.6% C-03-l 1 Absolute Bioavailability, Nasal/Intravenous
LC/MS/ MS	Human Urine	Olopatadine M3	3-1500 1-500	Intra-day l00-10l%/RSD ≤4.9% Inter-day 92-l00%/RSD≤9.5% Intra-day l02-l04%/RSD≤4.8% Inter-day 92-98%/RSD≤l 0.2%	C-02-46 Renal Impairment, Nasal, Single dose 0.6% C-03-1l Absolute Bioavailability, Nasal/Intravenous
LC/MS/ MS	Human Urine	Ml M2	0.50-250 0.50-250	Intra-day l0l-104%/RSD ≤8.9% Inter-day 9l-l03%/RSD≤5.7% Intra-day 103-l09%/RSD ≤l4.3% Inter-day 96-99%/RSD≤9.3%	C-02-46 Renal Impairment, Nasal, Single dose 0.6% C-03-1 1 Absolute Bioavailability, Nasal/Intravenous

---

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

/s/

Sandra Suarez
3/5/2008 01:58:13 PM
BIOPHARMACEUTICS

Wei Qiu
3/5/2008 02:01:10 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS TEAM LEADER'S MEMO

NDA:	21-861
Proprietary Drug Name:	PATANASE
Generic Name:	Olopatadine Hydrochloride
Indication:	Treatment of Seasonal Allergic Rhinitis (SAR) (b) (4) Allergic Rhinitis (b) (4)
Dosage Form:	Nasal Spray Solution
Strength:	0.6% solution (665 mcg)
Route of Administration:	Intranasal
Applicant:	Alcon, Inc.
Clinical Division:	DPADP (HFD-570)
Submission Dates:	December 21, 2004; April 11, 2005
Primary Reviewer:	Sandra Suarez-Sharp, Ph.D.
Team Leader:	Emmanuel O. Fadiran, Ph. D.

Recommendation

This memo summarises the findings and the conclusions of Dr. Sandra Suarez-Sharp's primary review of the clinical pharmacology and biopharmaceutics (CPB) studies submitted to NDA 21-861 for Patanase® (olopatadine hydrochloride) Nasal Spray. I concur with the conclusion that the the NDA is acceptable from a CPB standpoint provided that the sponsor agrees with the Agency's label recommendations. I also agree that new bioavailability studies may have to be conducted if a new formulation is developed. The labeling comments should be conveyed to the sponsor.

Summary of Clinical Pharmacology and Biopharmaceutics Findings

Patanase® Nasal Spray (olopatadine hydrochloride) is a selective histamine H_1 receptor antagonist proposed for the (b) (4) treatment of the symptoms of SAR (b) (4) in patients 12 years of age and older. Olopatadine is approved in a topical ophthalmic formulation for the treatment of allergic conjunctivitis under the trade name of PATANOL® (olopatadine hydrochloride ophthalmic solution) 0.1% in the US.

Patanase Nasal Spray will be available in one strength: 0.6% w/v olopatadine (base) in a (b) (4), nonsterile aqueous solution with a pH of approximately (b) After priming, each metered spray from the nasal applicator delivers 100 mg of the aqueous solution containing 665 µg of olopatadine hydrochloride, which is equivalent to 600 µg of olopatadine (base). Each bottle of Patanase® Nasal Spray provides 240 sprays after priming.

Alcon has conducted 9 Phase I, II and III studies to characterize the clinical pharmacology of olopatadine following administration of olopatadine solution via oral (C-00-23, C-02-54, C-03-10), intravenous (C-03-l 1) and nasal (C-00-58, C-02- 21, C-02-10, C-02-46, C-03-11) routes. Six studies (C-00-23, C-02-54, C-02-21, C-03-10, C-03-11) were conducted in healthy subjects while Study C-02-54 was a cardiovascular safety and PK study in healthy volunteers receiving multiple doses of olopatadine 20 mg BID oral solution. One study (C-02-46) was conducted in patients with varying degrees of renal impairment and; one study (C-02-10) was performed in the target population of SAR patients. Study C-00-23 was not reviewed because it did not provide

additional information. Information regarding protein binding, metabolism and inhibition of CYP enzymes was also reviewed.

Pharmacokinetics in Healthy Volunteers
Single Dose Pharmacokinetics

Following intranasal administration of 0.4 or 0.6% olopatadine nasal spray Tmax ranged from 0.25 to 2 hour. Mean Cmax and AUC values were 12.5 ± 6.1 ng/mL and 42.5 ±16.0 ng*hr/mL and 17.5 ± 6.7 ng/mL and 60.3 ± 20.3 ng*hr/mL for 0.4 and 0.6% olopatadine nasal spray respectively (Table 1, Study C-03-11). Olopatadine AUC and Cmax increased in proportion to the intranasal dose. The bioavailability of olopatadine was 60 ± 20.8%.

Single-dose pharmacokinetics was assessed following single intranasal administration of 0.4 or 0.6% olopatadine nasal spray in SAR patients (Table 1, Study C-03-10). The pharmacokinetics of olopatidine in SAR patients were comparable to those in healthy subjects.

Table 1. Mean ± SD (range) Pharmacokinetic Parameters of Olopatadine after Single Intranasal Doses

Study	**Dose**	**Cmax (ng/mL)**	**Tmax (h)**	**AUC (ng*h/mL)**	**t_{112} (h)**
Study C-02-10 SAR Patients	0.4% (N=14)	14.4 ± 4.4 (5.97 -21.9)	0.86 ± 0.41 (0.25 - 1.50)	48.9 ± 12.5 (23.3 - 67.4)	ND
	0.6% (N=13)	21.7 ± 8.7 (7.11 - 36.4)	1.00 ± 0.50 (0.25 - 2.00)	67.7 ± 21.1 (24.0 - 98.0)	ND
Study C-02-21 Healthy	0.6% (N=8)	29.3 ± 15.1 (13.6-58.4)	0.97 ± 0.54 (0.50 -2.00)	75.1 ± 29.4 (31.8 - 126)	ND
Study C-03-11 Healthy	0.4% (N=11)	12.5 ± 6.1 (1.98 -20.7)	1.04 ± 0.24 (0.75-1.50)	42.5 ± 16.0 (17.0-66.4)	8.6 ± 5.7 (1.75-17.9)
	0.6% (N=11)	17.5 ± 6.7 (6.37 -27.6)	1.05 ± 0.31 (0.75 - 1.50)	60.3 ± 20.3 (20.2 - 98.0)	10.0 ± 5.7 (3.2 -22.2)
Study C-02-46 Healthy	0.6% (N=6)	18.1±10.9 (3.80 - 29.9)	1.17±0.52 (0.50 - 2.00)	77.0±51.3 (17.0 - 139)	11.5±3.0 (7.2 - 14.5)

ND= not determined, sampling only out to 12 hours post-dose.

Three minor active metabolites (M1, M2, and M3) were identified in these PK studies, but only N-desmethyl olopatadine (Ml) and olopatadine N-oxide (M3) were quantified in plasma samples following single intranasal doses of 0.4 or 0.6% olopatadine nasal spray. The systemic exposures to the metabolites in SAR patients are similar to those in healthy subjects (Table 2).

Table 2. Mean ± SD (range) Pharmacokinetic Parameters of Metabolites Ml and M3 after Single Olopatadine Intranasal Doses

Study	Dose (N)	Analyte	Cmax (ng/mL)	Tmax (h)	AUC_{0-t} (ng*h/mL)	t_{112} (h)
Study C-02-10 SAR Patients	0.4% (N=14)	Ml	0.0861 ± 0.0431 (BLQ-0.163)	2.27 ± 0.87 (1.00-4.00)	0.546 ± 0.169[a] (0.366-0.702)	ND
	0.4% (N=14)	M3	0.357 ± 0.112 (0.153-0.581)	1.73 ± 0.77 (0.75-3.00)	1.42 ±0.24[a] (1.13-1.82)	ND
	0.6% (N=1 3)	Ml	0.150 ± 0.084 (BLQ-0.352)	2.41 ± 0.94 (1.50-4.00)	0.728 ± 0.121[a] (0.572-0.913)	ND
	0.6% (N=13)	M3	0.530±0.255 (0.115-1.16)	1.44±0.61 (0.75-3.00)	1.89±0.60[a] (0.5 14-2.60)	ND
Study C-03-11 Healthy Subjects	0.4% (N11)	Ml	0.138 ± 0.067 (0.0637-0.241)	4.82 ± 10.3 (1.50-36.0)	0.49 ± 0.32 (0.035-1.08)	5 5 ± 4.6 (2.5-13.6)
	0.4% (N=11)	M3	0.377±0.192 (0.0515-0.602)	1.18±0.32 (0.75-1.50)	1.00±0.62 (0.013-1.90)	1.6±0.4 (0.7-2.2)
	0.6% (N=11)	Ml	0.344±0.398 (0.800-1.34)	1.82±0.34 (1.00-2.04)	0.68±0.47 (0.094-1.38)	3.7± 1.8 (2.2-7.6)
	0.6% (N=1 1)	M3	0.511±0.229 (0.120-0.783)	1.25±0.37 (0.75-2.00)	1 38±0.65 (0.23-2.14)	1.7±0.4 (1.0-2.3)
Study C-02-46 Healthy Subjects	0.6% (N6)	Ml	0.192 ± 0.138 (BLQ-0.328)	2.60 ±0.55[b] (2.00-3.00)	2.09 ± 0 15[cd] (1.98-2.26)	4.0 ± 0.5[c] (3.5-4.4)
	0.6% (N=6)	M3	0.526 ± 0.348 (0.123-1.02)	1.88 ± 0.92 (0.75-3.00)	2.69 ± 1.98 (0.561-5.82)	2 5 ± 0.6 (1.9-3.3)

ND= not determined. [a]AUC0-6; [b]N=5; [c]N=3; [d]AUC_{0-12h}

Multiple Dose Pharmacokinetics

The multiple-dose PK of olopatadine was examined in two studies following intranasal administration olopatidine nasal solution (Table 3, Study C-02-10 and Study C-00-58). Comparison of the systemic exposure (Cmax and AUC_{0-12}) of olopatadine after single and multiple intranasal doses in SAR patients (Study C-02-10) indicates minimal accumulation (<1.3-fold) with twice-daily administration. Mean Tmax and $t_{1/2}$ values were similar in healthy subjects and SAR patients.

Table 3. Mean ± SD (range) Pharmacokinetic Parameters of Olopatadine after Multiple QD or BID Intranasal Doses

Study	Dose/Regimen (N)	Cmax (ng/mL)	Tmax (h)	$AUC0-_{12}$ (ng*h/mL)	$t_{1/2}$ (h)
Study C-02-10 SAR patients	0.4%/BID x 14 days (N=14)	15.9 ± 6.4 (3.65-29.0)	1.00 ± 0.55 (0 25-2.00)	57.3 ± 24.5 (10.4-114)	8.3 ± 4.9 (2.1-21.3)
	0.6%/BID x 14 days (N=13)	23.3 ± 6.2 (14.4-35.3)	0.97 ± 0.52 (0.08 - 1.50)	78.0 ± 13.9 (54.4- 103)	10.4 ± 5.1 (4.0-21.8)
Study C-00-58 Healthy Subjects	0.1%/QD x 3 days (N12)	4.36 ± 2.27 (0.41 -7.92)	1.23 ± 0.59 (0 50 -2.00)	13.92± 5.90 (1.40 -20.67)	6.3 ± 4.1 (1.96 - 13.5)
	0.1%/BID x 3 days (N=12)	3.42 ± 1.31 (0.97 — 5.05)	1.06 ± 0.42 (0.50 - 1.50)	12.03 ± 3.66 (4.80 - 16.54)	8.3 ± 3.5 (3.06 - 13.3)
	0.2%/BID x 3 days (N=12)	8.48 ± 3.12 (2.77- 15.0)	1.25 ± 0.38 (0.75-2.00)	28.33 ± 9.88 (11.09- 14.03)	15.0 ± 9.6 (3.16-29.9)

Time to reach steady-state was not addressed; however, it is expected to be achieved within 2 to 3 days of repeated twice daily dosing, based on a half-life value of about 10 hrs. Olopatadine Tmax and half-life after multiple dose administration were similar to those after single dose administration

The multiple-dose pharmacokinetics of olopatadine metabolites following intranasal administration of 0.6% olopatadine nasal spray was examined in SAR patients (Study C-02- 10). M2 was not quantifiable in any sample. For Ml and M3, peak plasma concentrations after BID

dosing for 2 weeks were about 1.7-and 1.3-fold higher, respectively than those observed after the single dose. AUC values were 1.2- to 1.5-fold higher.

Distribution

Following intranasal administration in SAR patients and healthy subjects, measurable plasma concentrations of olopatadine were observed in the systemic circulation within 5 minutes post-dose. Olopatadine was moderately bound (55%) to plasma proteins and the binding was independent of the concentration on the range of 0.1 to 1000 ng/mL.

Elimination

The mean (SD) apparent clearance (CL/F) and half-life ($t_{1/2}$) of olopatadine following admistration of a single dose of 5 mg ^{14}C-Olopatadine Hydrochloride (200 µCi) solution were 15.3 (3.4) L/h and 7.9 h (3.4), respectively. The mean total recovery of radioactivity in urine and feces was 70.5% and 17% of the dose, respectively indicating that urinary excretion was the major route of elimination (Table 4). Urinary excretion of Metabolites Ml and M3 accounted for about 7% of radiolabeled material recovered in the urine. Identified and unidentified metabolites accounted for <10% of the total radioactivity in urine. Unchanged olopatadine was the major component of radiolabeled material in plasma and urine. Metabolites Ml, M2 and M3 accounted for less than 10% of circulating radioactivity in plasma.

Table 4. Individual and Mean ± SD Cumulative Recovery of Total Radioactivity in Urine, Feces and Combined (Total) Following an Oral ^{14}C Olopatadine Dose, C-03-10

	Cumulative Urine		**Cumulative Feces**		**Cumulative Total**
Subject Number	**Ae (µg)**	**% Dose**	**Ae (µg)**	**% Dose**	**% Dose**
101					(b) (4)
102					
103					
104					
105					
106					
107					
108					
Mean	3493.3	70.5	841.7	17.0	87.5
SD	137.1	2.6	279.7	5.7	6.0
Min					(b) (4)
Max					

In vitro studies with cDNA-expressed human cytochrome P450 isoenzymes (CYP) and flavin-containing monooxygenases (FMO) showed that the metabolism of olopatadine is a minor route of elimination. Two major metabolites, M1 and M3, were identified. M1 formation was catalyzed mainly by CYP3A4, while M3 was primarily catalyzed by FMO1 and FMO. After incubation, M1 and M3 accounted for 5.2 and 30.5% of the initial olopatadine concentration, respectively.

Olopatadine did not inhibit the major CYP450 enzymes such as 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. The potential for olopatadine metabolites to act as an inducer of CYP enzymes was not evaluated.

Pharmacokinetics in Special Populations

Gender, Age, and Race

The mean systemic exposure (Cmax and AUCt) in females following multiple dose administration of 0.6% olopatadine nasal spray in SAR patients were 40% and 27% higher, respectively than those values observed in male SAR patients (Table 5, Study C-01-10). This difference in systemic exposure may not be clinically relevant since multiple doses of oral olopatadine 20 mg BID appeared to be safe. Therefore, no dose adjustment is necessary based on gender differences in the PK of olopatadine. The effect of race and age on the PK of olopatadine was not evaluated.

Table 5. Mean ± SD (range) Olopatadine Pharmacokinetic Parameters by Gender

Study Population Dose	**Gender Day**	**Parameters**				
		Cmax (ng/mL)	**Tmax (h)**	**AUC_{0-12} (ng*h/mL)**	**AUC0-inf (ng*h/mL)**	**$t_1/_2$ (h)**
C-02-54 Healthy 20 mg oral BID x 14	Male Day 14	287 ± 56 (185-436)	0.76 ± 0.38 (0.28-1.53)	943 ± 143 (689-1250)	1070 ± 180 (743-1450)	10.0 ± 2.8 (5.4-15.6)
	Female Day 14	345 ± 53 (250-434)	0.88 ± 0.44 (0.53-2.03)	1070 ± 150 (734-1280)	1240 ± 180 (867-1630)	12.3 ± 4.1 (6.4- 18.5)
C-02-10 SAR patients Olopatadine 04% or Olopatadine 0.6%BIDx 14 days	Male Day 15 0.4%	22.4 ± 6.2 (14.4-21.7)	0.78 ± 0.64 (0.08-1.50)	82.9 ± 15.9 (57.5-103) .	97.5 ± 19.5 (66.0-116)	8.1 ± 3.0 (4.0-11.5)
	Female Day 15 0.4%	24.1 ± 6.5 (18.5-35.3)	1.14 ± 0.35 (0.75-1.50)	73.8 ± 11.5 (54.4-86.6)	85.9 ± 16.9 (59.3-108)	12.3 ± 6.0 (5.9-21.8)
	Male Day 15 0.6%	13.0±3.7 (7.00-18.1)	1.25±0.39 (0.75-1.50)	49.0±14.4 (34.5-69.6)	58.1±17.0 (40.7-81.0)	8.4±3.7 (5.2-15.0)
	Female Day 15 0.6%	18.1 ± 7.4 (3.65-29.0)	0.81 ± 0.59 (0.25-2.00)	63.6 ± 29.4 (10.4-114)	74.0 ± 35.3 (10.5-130)	8.3 ± 5.9 (2.1-21.3)

Renal Impairment

Following single intranasal administration of two sprays per nostril of 0.6% olopatadine nasal spray to volunteers (25 subjects/patients), no significant differences were observed in the systemic exposure of olopatadine in patients with mild or moderate renal impairment compared to subjects with normal renal function. The plasma Cmax and AUC values in patients with severe renal impairment were approximately 2.6- and 5.6-fold higher than those in healthy subjects. Higher plasma concentrations of Ml and M3 metabolites were seen with increasing renal impairment, particularly those in severely-impaired patients with 2.6- and 3.6-fold higher mean Cmax values, respectively. The higher systemic exposure of parent drug and metabolites observed in patients with severe renal impairment following intranasal doses of 0.6% olopatadine nasal spray are 10- to 250-fold lower than peak concentrations observed following oral administration 20 mg to 400 mg doses which were safe and well-tolerated. Therefore, dosage adjustment of olopatadine based on renal impairment may not be necessary.

Hepatic Impairment

The effect of hepatic impairment on the PK of olopatadine and its metabolites was not evaluated. Olopatadine (and its metabolites) are mainly eliminated by the kidney. In fact, in a mass

balance study total radioactivity was predominantly excreted in urine (70% of total administered dose) suggesting that hepatic metabolism is a minor route of elimination.

Drug/Drug Interactions (DDI)

DDI studies were not conducted with olopatadine. Drug interactions based on metabolic interaction are not anticipated because olopatadine is eliminated predominantly by renal excretion. In addition, olopatadine did not inhibit the *in vitro* metabolism of major CYP enzymes.

Dose-Response (Efficacy and Safety) Relationships

In the case of dose-response for efficacy, there was a trend for the higher doses of olopatadine to produce a bigger response; however a clear dose-ordering response (as shown for other nasal antihistamines) was not observed following either single administration of 0.2-, 0.4-, or 0.6% olopatadine nasal spray or after multiple administration of 0.1 % and 0.2% olopatadine nasal spray. Following a single dose (two sprays per nostril) of either olopatadine 0.2%, 0.4%, 0.6% or vehicle, the mean decrease in TNSS for the 0.6% olopatadine nasal group, 0.4% olopatadine nasal group, 0.2% olopatadine nasal group or vehicle (placebo) group were 2.8-, 2.63-, 2.58-, and 1.52 units, respectively. This suggests that the use of lower doses (0.2% or 0.4%) than that proposed by the sponsor (two sprays per nostril twice a day of olopatadine 0.6%) may have significant clinical effect.

Effect of olopatidine on QT

The sponsor conducted a thorough Phase I cardiovascular study (Study C-02-54) in which 32 subjects received 20 mg oral doses of olopatadine solution BID. Plasma samples for olopatadine dtermination were obtained at the same time points as ECG recordings on Days 12 and 14/15 of the study.

Analysis of the results showed that Fridericia's correction formula (QTcF) yielded a slope closer to zero (-0.021) than Bazett's (-0.097). From the individual-regression rate-correction (QTcI) analysis, the mean of the individual subject exponent values (0.290) was closer to the 0.333 exponent used in Fridericia's formula compared to the 0.500 exponent used in Bazett's formula.

The mean changes in QTcF from baseline were negative. No statistically significant ($p \geq 0.097$) differences were seen between olopatadine and vehicle in either the mean change or mean of maximum change in. In addition, no linear correlation between QTc change from baseline and olopatadine systemic exposure (Cmax) was observed. A positive control was not included in the study. Current guidance requires the inclusion of a positive control.

General Biopharmaceutics

Formulations used in the PK/clinical trials

The sponsor is proposing to market only one strength of Patanase; 0.6%. Different strengths of olopatadine (0.1%, 0.2%, 0.4% and 0.6%) were used in Phase I, II and III PK studies. However, because this is a nasal solution, in vivo BE are not required. The sponsor studied the systemic exposure of the clinical trial batches that were used in pivotal safety and efficacy studies and to-be marketed formulation. These studies were performed in both healthy subjects (C-02-21, C-03-11, C-02-46), and in the target population of allergic rhinitis patients (C-01-92, C-02-10), and utilized the bioavailability measures considered pivotal in single (Cmax and

AUC0-inf) and multiple-dose studies (Cmax and AUCo-τ). The sponsor showed that the systemic exposure of olopatadine nasal spray increased in a roughly proportional manner with the dose.

Overall conclusions

The sponsor has conducted the appropriate studies to characterize the CPB of lopatadine nasal spray and have provided the appropriate information for the Clinical Pharmacology Section of the labeling. If however the application is not approved due to safety concerns because of the inclusion of povidone in the formulation the sponsor will need to conduct additional biovailability studies on the new formulation. The sponsor may submit the draft protocol(s) for OCPB comments before such studies are conducted.

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

/s/

Emmanuel Fadiran
10/5/2005 04:08:03 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-861
Proprietary Drug Name:	PATANASE
Generic Name:	Olopatadine Hydrochloride
Indication:	Treatment of Seasonal Allergic Rhinitis (SAR) (b) (4) Allergic Rhinitis (b) (4)
Dosage Form:	Nasal Spray Solution
Strength:	0.6% solution (665 mcg)
Route of Administration:	Intranasal
Applicant:	Alcon, Inc.
Clinical Division:	DPADP (HFD-570)
Submission Dates:	December 21, 2004, April 11, 2005
Reviewer:	Sandra Suarez-Sharp, Ph.D.
Team Leader:	Emmanuel O. Fadiran, Ph. D.

TABLE OF CONTENTS

ITEM	PAGE NUMBER
1. Executive Summary	4
1.1 Recommendation	4
1.2 Phase IV Commitments	4
1.3 Summary of Clinical Pharmacology and Biopharmaceuticals Findings	4
2. Question-Based Review	7
2.1 General Attributes	7
2.2 General Clinical Pharmacology	8
• Exposure-Response	9
o ER for Efficacy	9
o ER for Safety	11
• QTc Findings	12
• PK Characteristics of Drug and Metabolite	16
• Mass-balance	18
• Metabolism and Excretion	20
2.3 Intrinsic Factors	21
• Effect of Age, Race and Gender	21
• Renal Impairment	21
• Hepatic Impairment	21
2.4 Extrinsic Factors	22
• Metabolic Pathway	22
• Inhibition	23
2.5 General Biopharmaceutics	23
2.6 Analytical Section	25
3. Labeling Recommendations	26
4. Appendices	28
4.1 Proposed package insert	28
4.2 Individual Study Reviews	40
• Clinical ADME Study: Study C-03-10	40
• In vitro Metabolism Studies	45
o Metabolic Pathway	45
o Inhibition (PKDM 586)	50
• Protein Binding: Study Report 07038570:0995	55
• Pharmacokinetics-Healthy Volunteers	57
o Single Dose Studies	57
▪ Study C-02-21	57
▪ Study C-03-11: Absolute BA	59
▪ Study C-01-83 (Dose-Response)	65
o Multiple Doses	69
▪ Study C-02-54: Cardiovascular Safety	69
▪ Study C-0058 (Dose-Response)	79
• Pharmacokinetics-Special Populations	80
o Study C-02-10: SAR patients	82
o Study C-02-46: Renal dysfunction	87
4.3 CPB Filing/Review Form	95

1. EXECUTIVE SUMMARY

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-861 submitted on December 21, 2004 and we found it acceptable from a CPB standpoint provided that the sponsor agrees with the Agency's label recommendations. However, the clinical review has shown some local safety concerns (nasal perforation shown in 3 patients) which may preclude the approval of this formulation. New CPB studies may have to be conducted if a new formulation is developed. The labeling comments (page 26) should be conveyed to the sponsor.

1.2 Phase IV Commitments

None

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Patanase® Nasal Spray contains olopatadine hydrochloride, a specific histamine H_1 receptor antagonist. Patanase® Nasal Spray is proposed for the (b) (4) treatment of the symptoms of SAR (b) (4) such as (b) (4) in patients 12 years of age and older. Olopatadine hydrochloride received approval in Japan under the trade name ALLELOCK® by Kyowa for the oral treatment of allergic rhinitis, urticaria, and itching resulting from skin diseases such as eczema/dermatitis, prurius cutaneous, psoriasis vulgaris, and multiform exudative erythema. ALLELOCK® is administered as 5 mg tablets two times a day. In addition, the sponsor Alcon, Inc. is marketing olopatadine in a topical ophthalmic formulation for the treatment of allergic conjunctivitis under the trade name of PATANOL® (olopatadine hydrochloride ophthalmic solution, 0.1%) in the US and OPATANOL® in the EU.

Patanase Nasal Spray will be available in one strength: 0.6% w/v olopatadine (base) in a (b) (4) nonsterile aqueous solution with a pH of approximately (b) (4) After priming, each metered spray from the nasal applicator delivers 100 mg of the aqueous solution containing 665 µg of olopatadine hydrochloride, which is equivalent to 600 µg of olopatadine (base). Each bottle of Patanase® Nasal Spray provides 240 sprays after priming.

The efficacy and safety of Patanase® Nasal Spray in patients with AR was primarily assessed in 3 (2 studies in SAR and 1 study in PAR patients) randomized, double-blind, parallel, multicenter, vehicle placebo spray-controlled clinical trials conducted in the United States in 2164 (628 patients received the 665 mcg dose) adolescent and adult patients 12 years of age and older. These trials evaluated the total nasal symptom scores (TNSS) in known allergic patients who were treated for 2 weeks or one year (PAR Study) with two sprays per nostril of 0.6% olopatadine twice daily.

Alcon has conducted 9 Phase I, II and III studies to characterize the clinical pharmacology of olopatadine following administration of olopatadine solution via oral (C-00-23, C-02-54, C-03-10), intravenous (C-03-l 1) and nasal (C-00-58, C-02- 21, C-02-10, C-02-46, C-03-11) routes. Eight studies (C-00-23, C-02-54, C-02-21, C-03-10, C-03-11) were conducted in healthy subjects; Study C-02-54 was a cardiovascular safety and PK study in healthy volunteers receiving multiple doses of olopatadine 20 mg BID oral solution. One study (C-02-46) was conducted in patients with varying degrees of renal impairment and; one study (C-02-10) was performed in the target population of seasonal allergic rhinitis (SAR) patients. Study C-00-23

was not reviewed because it did not provide additional information. Information regarding protein binding, metabolism and inhibition of CYP enzymes was also reviewed. A summary of the clinical pharmacology and biopharmaceutics findings is presented below.

Pharmacokinetics in Healthy Volunteers

Single Dose

Following intranasal administration of olopatadine nasal spray 0.4% or olopatadine nasal 0.6%, Cmax values of olopatadine were generally observed within 0.25 to 2 hours post-dose. Mean Cmax and AUC values were 12.5 ± 6.1 ng/mL and 42.5 ±16.0 ng*hr/mL and 17.5 ± 6.7 ng/mL and 60.3 ± 20.3 ng*hr/mL for olopatadine nasal 0.4% and olopatadine nasal 0.6%, respectively. The bioavailability of olopatadine was about 60 ± 20.8%. Olopatadine peak plasma concentrations increased in proportion to the intranasal dose. Similar dose-proportional increases were seen in mean AUC values.

Three minor metabolites (M1, M2, and M3) were identified in plasma, but only Ml and M3 were quantified following single intranasal doses of olopatadine nasal 0.4% or olopatadine nasal 0.6%. Peak plasma concentrations of Ml and M3 were low, accounting for ~ 2.0% and 3.0% of parent Cmax, respectively. $AUC_{0\text{-}inf}$ of Ml and M3 were low, accounting for ~ 6.0% and 9.0% of parent AUC_{inf}, respectively. M3 peak plasma concentrations and AUC_{inf} were approximately 1.5- to 3-fold higher and 1.5 higher, respectively than those of Ml.

Repeat Dose

Time to reach steady-state was not addressed; however, it is expected to be achieved within 2 to 3 days of repeated twice daily dosing, based on a half-life value of about 10 hrs. The mean accumulation ratio for olopatadine was 1.3. Olopatadine Tmax and half-life were similar to that after single dose administration.

Distribution

Following intranasal administration in SAR patients and healthy subjects, measurable plasma concentrations of olopatadine were observed in the systemic circulation within 5 minutes post-dose. Olopatadine was moderately bound (55%) to plasma proteins and the binding was independent of the concentration on the range of 0.1 to 1000 ng/mL.

Elimination

The CL/F and half-life of olopatadine following a single oral solution dose of 5 mg ^{14}C-Olopatadine Hydrochloride (200 μCi) averaged 15.3 (3.4) L/h and 7.9h (3.4), respectively. The mean total recovery of radioactivity in urine and feces was 70.5% and 17% of the dose, respectively indicating that urinary excretion was the major pathway of elimination. Urinary excretion of Ml and M3 accounted for about 7% of radiolabeled material recovered in the urine. Identified and unidentified metabolites accounted for <10% of the total radioactivity in urine. Unchanged olopatadine was the major component of radiolabeled material in plasma and urine. Ml, M2 and M3 metabolites accounted for less than 10% of circulating radioactivity in plasma.

In vitro studies with cDNA-expressed human cytochrome P450 isoenzymes (CYP) and flavin-containing monooxygenases (FMO) showed that the metabolism of olopatadine is a minor route of elimination. Two major different metabolites, M1 and M3, were identified. M1 formation was catalyzed mainly by CYP3A4, while M3 was primarily catalyzed by FMO1 and FMO. After incubation, M1 and M3 accounted for 5.2 and 30.5% of the initial olopatadine

concentration, respectively. In addition, olopatadine did not inhibit the major CYP450 enzymes such as 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. The potential for olopatadine metabolites to act as an inducer of CYP enzymes was not evaluated.

Pharmacokinetics in Allergic Rhinitis Patients

The mean Cmax values in SAR patients were within the range of those observed in healthy volunteers (olopatadine 0.4%: mean 14.4 ± 4.4 ng/mL and 48.9 ± 12.5 ng*hr/mL); olopatadine 0.6%: mean 21.7 ± 8.7 ng/mL and 67.7 ± 21.1). The Cmax and AUC values for olopatadine metabolites did not appear to be markedly different between SAR patients and healthy subjects. The mean Cmax (23.3 ± 6.2 ng/mL) and $AUC_{0\text{-}12h}$ (78.0 ± 13.9ng*hr/mL) of olopatadine following multiple administration of two sprays per nostril of 0.6% olopatadine twice daily increased up to 15% compared to those after single administration.

Pharmacokinetics in Special Populations

Gender, Age, and Race

The mean systemic exposure (Cmax and AUCt) in females following multiple administration of olopatadine in SAR patients was 40 % and 27% higher, respectively than those values observed in male SAR patients. This difference in systemic exposure may not be clinically relevant since multiple doses of oral olopatadine 20 mg BID appeared to be safe. Therefore, no dose adjustment is necessary based on gender differences in the PK of olopatadine. The effect of race and age on the PK of olopatadine was not evaluated.

Renal Impairment

Following single intranasal administration of two sprays per nostril of 0.6% olopatadine nasal spray to volunteers (25 subjects/patients), no meaningful differences were observed in the systemic exposure of olopatadine in patients with mild or moderate renal impairment compared to subjects with normal renal function. The plasma Cmax and AUC values in patients with severe renal impairment were approximately 2.6- and 5.6-fold higher than those in healthy subjects. Higher plasma concentrations of Ml and M3 metabolites were seen with increasing renal impairment, particularly those in severely-impaired patients with 2.6- and 3.6-fold higher mean Cmax values, respectively. Despite of the higher systemic exposure of parent drug and metabolites observed in patients with severe renal impairment following intranasal doses of 0.6% olopatadine nasal spray these values are still 10- to 250-fold lower than peak concentrations observed following higher oral 20 mg to 400 mg doses which were safe and well-tolerated. Therefore, dosage adjustment of olopatadine based on renal impairment may not be necessary.

Hepatic Impairment

The effect of liver impairment on the PK of olopatadine and its metabolites was not evaluated. Olopatadine (and its metabolites) are mainly eliminated by the kidney. In fact, in a mass balance study total radioactivity was predominantly excreted in urine (70% of total administered dose) suggesting that liver metabolism is not an important route of elimination.

Drug/Drug Interactions (DDI)

DDI studies were not conducted with olopatadine. Drug interactions based on metabolic interaction are not anticipated because olopatadine is eliminated predominantly by renal excretion. In addition, olopatadine did not inhibit the *in vitro* metabolism of major CYP enzymes. The plasma protein binding of olopatadine is about 55%, thus, interactions through displacement from plasma proteins are not expected.

Dose-Response (Efficacy and Safety) Relationships

In the case of dose-response for efficacy, there was a trend for the higher doses of olopatadine to produce a bigger response; however a clear dose-ordering response (as shown for other nasal antihistamines) was not observed following either single administration of olopatadine 0.2-, 0.4-, or 0.6% nasal spray or after multiple administration of olopatadine 0.1 % and 0.2% nasal spray. Following a single dose (two sprays per nostril) of either olopatadine 0.2%, 0.4%, 0.6% or vehicle, the mean decrease in TNSS for the olopatadine nasal 0.6% group, olopatadine nasal 0.4% group, olopatadine nasal 0.2% group or vehicle group were 2.8-, 2.63-, 2.58-, and 1.52 units, respectively. This suggests that the use of lower doses than that proposed by the sponsor (two sprays per nostril twice a day of olopatadine 0.6%) may have significant clinical effect. In general, based on two Phase II dose-response studies, systemic adverse events appeared not to be related to dose following single administration of olopatadine 0.2-, 0.4 or 0.6% nasal spray or multiple doses of olopatadine 0.1 or 0.2% nasal spray. However, nasal discomfort (2 events) appeared to be related to drug treatment, in this case the 0.2% olopatadine nasal spray.

Based on data from one Phase I study in healthy males and females, olopatadine did not significantly affect QT or QTc following multiple BID doses of olopatadine 20 mg oral solution. A positive control was not included in the study. Current guidance requires the inclusion of a positive control.

Reviewer

Sandra Suarez-Sharp, Ph.D. _____
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Final version signed by Emmanuel Fadiran, Ph.D., Team leader _____

cc

NDA 21-861 :	Division File
HFD-870:	Malinowski, Hunt
HFD-570:	Fadiran, Lee, Chowdhury, Zeccola, Gilbert-McClain, Suarez-Sharp

2. QUESTION BASED REVIEW

2.1 General Attributes

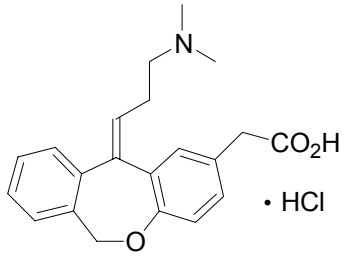
2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

The active component of PATANASE Nasal Spray is olopatadine hydrochloride, a specific histamine H_1 receptor antagonist.

Chemical name:

The chemical name for olopatadine hydrochloride is (*Z*)-11-[3-(dimethylamino)propylidene]-6,11-dihydrodibenz[*b,e*]-oxepin-2-acetic acid hydrochloride.

Structural formula:



Molecular formula: $C_{21}H_{23}NO_3 \bullet HCl$
Molecular weight: 373.88
Solubility: Olopatadine hydrochloride is a white, water-soluble crystalline powder.

FORMULATION

PATANASE® Nasal Spray contains 0.6% w/v olopatadine (base) in a (b) (4), nonsterile aqueous solution with a pH of approximately (b). The component of PATANASE® Nasal Spray are shown in Table 2.1.1.1.

After initial priming (5 sprays), each metered spray from the nasal applicator delivers 100 mg of the aqueous solution containing 665 mcg of olopatadine hydrochloride, which is equivalent to 600 mcg of olopatadine (base). Each bottle of PATANASE® Nasal Spray provides 240 sprays after priming.

Table 2.1.1.1. Composition of Patanase Nasal Spray

Name of Ingredient	% w/v	Quantity (g) per 400 L batch	Quality Standard
Olopatadine HCl	0.665[a]	(b) (4)	NF
Benzalkonium Chloride	0.01		USP
Edetate Disodium	(b) (4)		USP
Povidone			USP
Sodium Chloride			USP
Dibasic Sodium Phosphate			NF
Sodium hydroxide and Hydrochloric Acid	Adjust to pH (b)	Adjust to pH (b)	NF
Purified Water	(b)	(b) (4)	USP

[a] 0.665% w/v olopatadine hydrochloride (665 mcg/spray) is equivalent to 0.6% w/v olopatadine as base (600 mcg/spray).
[b] (b) (4)

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?
Mechanism of Action:

Olopatadine, a structural analog of doxepin, is a non-steroidal, non-sedating, topically effective anti-allergic molecule that exerts its effects through multiple distinct mechanisms of action. The molecule possesses selective and specific histamine H_1 antagonist activity and is devoid of effects upon alpha adrenergic, dopaminergic and muscarinic receptors. Inhibitory effects upon expression of pro-inflammatory cytokines from epithelial cells and eosinophils have been reported. Inhibition of pro-inflammatory mediator release from human mast cells has also been observed. An intranasal study with olopatadine nasal spray has demonstrated decreases in albumin, lysozyme and leukotrienes.

INDICATION (as per proposed label)

PATANASE® Nasal Spray is indicated in patients 12 years of age and older for the (b) (4) treatment of the symptoms of SAR (b) (4)

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dosage is a Nasal Spray and the proposed route of administration is by Nasal administration.

DOSAGE AND ADMINISTRATION (as per proposed label)

The recommended dose of PATANASE® Nasal Spray in patients 12 years and older is two sprays per nostril twice-daily.

2.2 General Clinical Pharmacology

2.2.1 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology and biopharmaceutics study data?

PATANASE® Nasal Spray for the treatment of seasonal allergic rhinitis (SAR) was studied in two randomized, double-blind, parallel, multicenter, vehicle placebo spray-controlled clinical trials conducted in the United States in 1,240 (406 patients received the 665 mcg dose) adolescent and adult patients 12 years of age and older. These trials evaluated the total nasal symptom scores (TNSS that included congestion (stuffy nose), rhinorrhea (runny nose), itchy nose and sneezing), as well as itchy and watery eyes, in known allergic patients who were treated for 2 weeks. (b) (4)

The assessment of safety included the review of the frequency and incidence of adverse events, 12-lead ECG and vital signs and other laboratory analysis. The effect of PATANASE on the QT interval prolongation was studied in two placebo-controlled cardiac repolarization studies in 102 healthy volunteers given olopatadine hydrochloride as an oral 5 mg solution twice daily for 3 days, and in 32 healthy volunteers administered olopatadine hydrochloride 20 mg oral solution twice-daily for 14 days. In addition, the effect of olopatadine on cardiac repolarization was observed in 429 perennial allergic rhinitis patients given PATANASE® Nasal Spray, 665 micrograms twice daily for up to 1 year.

2.2.2 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

TNSS was selected as the primary endpoint because it is a well established and validated clinical efficacy endpoint in allergic rhinitis. However, it does not, by itself, fully describe the level of overall disease control. Therefore, key secondary endpoints reflecting disease control, (b) (4) . As above mentioned, allergic rhinitis includes both nasal and non-nasal symptoms. The main nasal symptoms of allergic rhinitis are nasal itching (i.e., nasal pruritus), sneezing, rhinorrhea, and nasal congestion. Important non-nasal symptoms commonly associated with allergic rhinitis include itching eye, tearing eye, itching of ears and/or palate, and redness of the eye. The preferred measures of effectiveness in allergic rhinitis trials are patient self-rated *instantaneous* and *reflective* composite symptom scores. These summed scores generally include the following four nasal symptoms: rhinorrhea, nasal congestion, nasal itching, and sneezing, rated on a 0-3 scale of severity. While both patient self-rated symptom scores and physician-rated scores can be measured, the patient-rated scores are preferred as the primary measure of effectiveness.

A common allergic rhinitis rating system that has been used in clinical trials is the following 0-3 scale:

- 0 = absent symptoms (no sign/symptom evident)
- 1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated)
- 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable)
- 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Concentrations of olopatadine and its metabolites (M1, M2 and M3) were determined in plasma and urine samples from all human pharmacokinetic studies using LC/MS/MS and a HPLC-UV validated methods, respectively. The lower limits of quantification (LLOQ) were of 0.5 to 2 ng/mL and 200 to 1000 ng/mL for plasma and urine samples, respectively.

2.2.4 Exposure Response

2.2.4.1 What are the characteristics of the dose-systemic exposure relationships for efficacy?

Since systemic absorption of intranasally administered drugs is the result of nasal and gastrointestinal absorption, plasma concentrations cannot be correlated to efficacy (TNSS). In the case of dose-response for efficacy, there was a trend for the higher doses to produce a bigger response; however a clear dose-ordering response was not observed following either single dose administration of olopatadine 0.2-, 0.4-, or 0.6% nasal spray or after multiple dose administration of olopatadine 0.1- and 0.2% nasal spray (Figures 2.2.4.1.1 and 2.2.4.1.2, respectively).

Two dose-response studies were reported by the sponsor. Study C-01-83 was a single dose study in 320 (80 per arm) patients with AR. Patients received a single dose (2 sprays per

nostril) of either olopatadine 0.2%, 0.4%, 0.6% or vehicle. The mean decrease in TNSS for the olopatadine nasal 0.6% group, olopatadine nasal 0.4% group, olopatadine nasal 0.2% group, and vehicle group were 2.8-, 2.63-, 2.58-, and 1.52 units, respectively (Table 2.2.4.1.1)

Table 2.2.4.1.1. Mean change from baseline in TNSS following single nasal administration (2 sprays per nostril) of olopatadine 0.2-, 0.4-, and 0.6% nasal solution (Data from Study C-01-83)

Statistics	**Vehicle**	**Olopatadine 0.02%**	**Olopatadine 0.04%**	**Olopatadine 0.06%**
Mean	-1.52	-2.58	-2.63	-2.8
Median	-1.0	-2.5	-2.0	-2.5
Minimum	-11	-12.0	-12	-11
maximum	6	4.0	4.0	5
SD	2.8	2.9	2.8	2.99

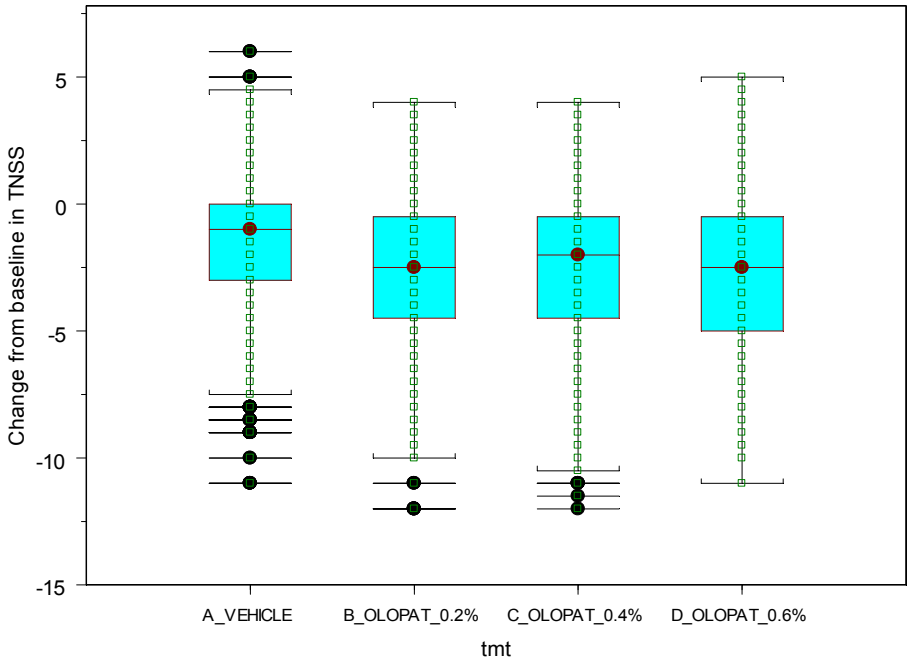


Figure 2.2.4.1.1. . Change from baseline in TNSS following single nasal administration (2 sprays per nostril) of olopatadine 0.2-, 0.4-, and 0.6% nasal solution (Data from Study C-01-83).

Study C-00-10 was a placebo-controlled, parallel group study in 192 patients with AR. Patients received study drug (olopatadine 0.1% nasal spray or olopatadine 0.2% nasal spray, 2 sprays per nostril) either in BID (morning and evening) or QD (morning only) for 2 weeks. The primary efficacy variables analyzed were the AM and PM percent reduction in MRSC (Mayor Rhinitis Sympton Complex, averaged across all visits) from the average AM and PM MRSC baselines. No differences in percent reduction in either AM or PM MRSC were found for the BID or QD comparisons (Figure 2.2.4.1.2)

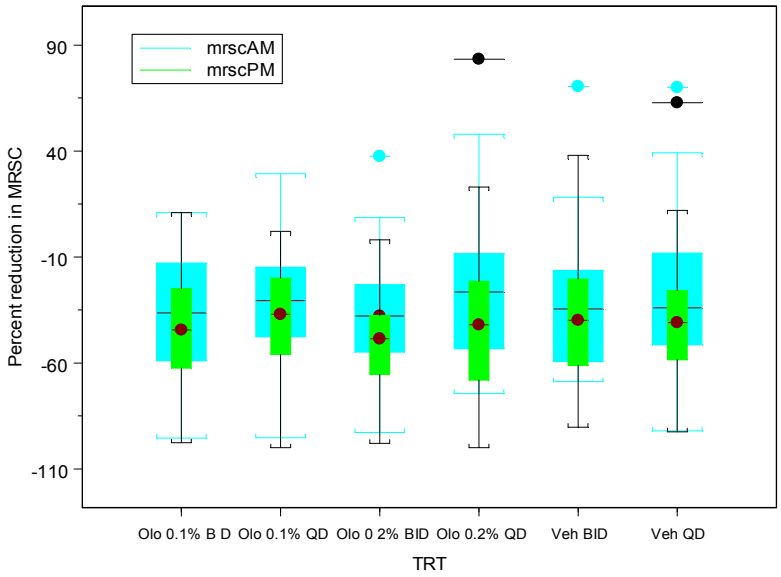


Figure 2.2.4.1.2. AM and PM percent reduction in MRSC (averaged across all visits) from the average AM and PM MRSC baselines following multiple administration of olopatadine 0.1 % and 0.2% nasal spray BID or QD (Data from Study C-00-10).

2.2.4.2 What are the characteristics of the dose-systemic exposure relationships for safety?

In general, based on two Phase II dose-response studies, systemic adverse events appeared not to be related to dose following single administration of olopatadine 0.2-, 0.4 or 0.6% nasal spray or multiple doses of olopatadine 0.1 or 0.2% nasal spray (Figure 2.2.4.2.1). However, nasal discomfort (2 events) appeared to be related to drug treatment, in this case the 0.2% olopatadine nasal spray.

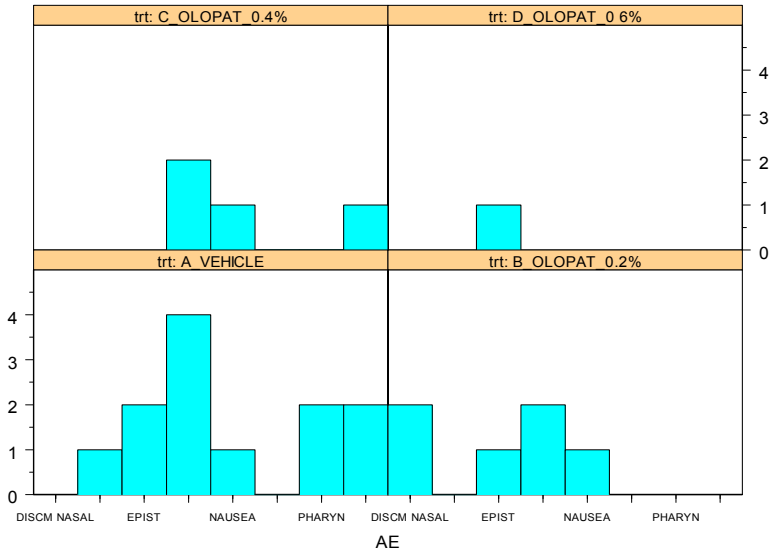


Figure 2.2.4.2.1. Adverse event frequency following single dose administration of olopatadine 0.2-, 0.4- and 0.6% to AR patients (Data from study C-01-83).

2.2.4.3 Does this drug prolong the QT or QTc interval?

Based on data from one thorough Phase I study (Study C-02-54), olopatadine and its metabolites did not significantly affect QT or QTc when multiple twice-daily oral doses of 20 mg olopatadine solution or placebo were administered to 32 healthy volunteers for 14 days. The mean change from baseline in QTF following olopatadine administration was -2.5 (8.8). In addition, no linear correlation between QTc change from baseline and olopatadine systemic exposure (Cmax) was observed. A positive control was not included in the study. Current guidance requires the inclusion of a positive control.

Study C-02-54 was a single-center, randomized, double-masked, crossover design, safety and pharmacokinetic study in 34 healthy, male and female subjects, ages 18 to 75 years. Eighteen 12-lead ECGs were performed over the 24-hour period at baseline (Day -2 to -1), 15 ECGs over the 12-hour period on Day 12 and 18 ECGs over the 24-hour period after the last dose on Day 14 (Days 14/15) for each treatment. The ECGs were forwarded to a centralized reading center for masked manual measurements to determine the ECG parameters. The QT interval for three beats was averaged and corrected for rate (HR) using two fixed-exponent correction formula ($QTc=QT/RR^{\alpha}$) where $\alpha=0.500$ (Bazett's, QTcB) or $\alpha=0.333$ (Fridericia's, QTcF). In addition, an individual-derived regression approach (QTcI) was used. This method derives an α value for each subject that provides a slope ~ zero from the regression of 1/RR α versus QT using all the ECGs obtained at baseline and on each of the placebo study days. Mean steady-state (averaged across all time points on Day 12 and Days 14/15) changes from mean baseline (averaged from the 18 ECGs on Day -2) were calculated for each subject. The maximal change from mean baseline was defined as Emax. Categorical analysis of the Emax values into <30 msec, >30 to <60 msec and >60 msec for each subject. Plasma samples for olopatadine determination were obtained at the same time points as the ECG recordings on Days 12 and 14/15.

Comparisons of the results of the analysis showed that Fridericia's correction formula (QTcF) yielded a slope closer to zero (-0.02 1) than Bazett's (-0.097) (Figure 2.2.4.3.1). From the individual-regression rate-correction (QTcI) analysis, the mean of the individual subject exponent values (0.290) was closer to the 0.333 exponent used in Fridericia's formula compared to the 0.500 exponent used in Bazett's formula. These findings provided further support for the use of QTcF over QTcB along with the individual correction analysis (QTcI).

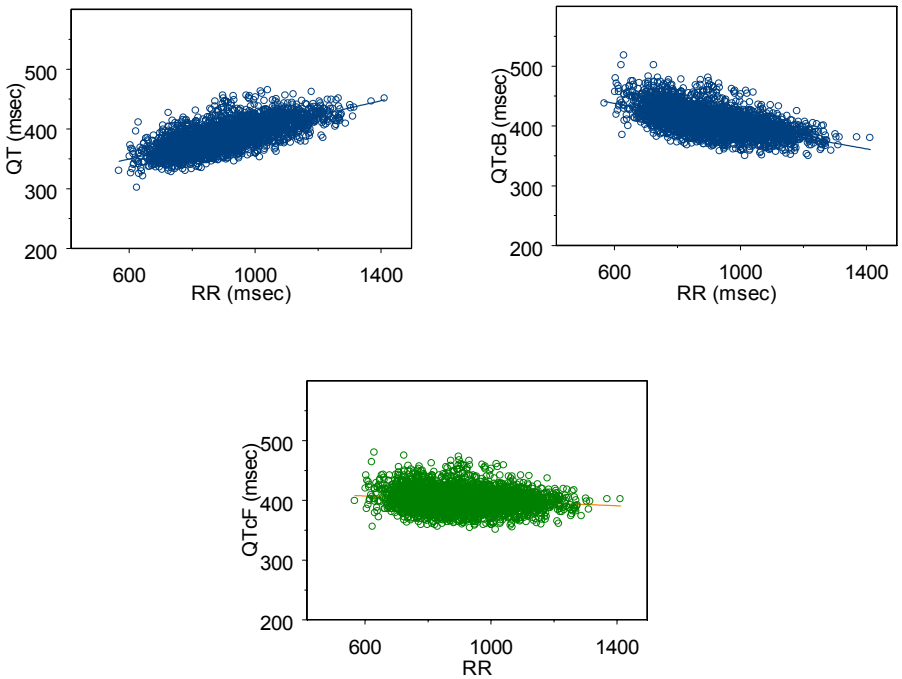


Figure 2.2.4.3.1. Individual QT, QTcB and QTcF as a function of RR following multiple administration of olopatadine 20 mg oral solution to male and female healthy volunteers.

Table 2.2.4.3.1 shows that all mean changes in QTcF from baseline were negative. No statistically significant ($p \geq 0.097$) differences were seen between olopatadine and vehicle in either the mean change or mean of maximum change.

Table 2.2.4.3.1. Mean, median, min and max QTc, Δ QTc change from baseline and mean of maximum Δ QTc following multiple administration of the treatments.

	QTcB		**QTcF**		**Δ QTB**		**Δ QTF**		**Mean of max Δ QTB**		**Mean of max Δ QTF**	
	OLOP	**PLB**	**OLOP**	**PLB**	**OLOP**	**PLB**	**OLOP**	**PLB**	**OLOP**	**PLB**	**OLOP**	**PLB**
Min (msec)	382.2	370.5	370.9	367.1	-12.9	-25.8	-22.5	-22.4	6.1	-11.5	-1.1	-6.1
Mean (msec)	409.6	408.9	401.2	401.5	3.14	0.09	-2.5	-3.9	30.68	29.4	17.4	15.9
Median (msec)	410.7	407.9	399.3	401	2.2	1.45	-3	-4.4	26.7	24.4	14.3	13.2
Max (msec)	463.5	455.7	450.9	446.2	35.8	27.9	20.7	13.7	91.22	94.8	63.1	52.1
N	81	79	81	79	81	79	81	79	81	79	81	79
SD	16.6	17.9	14.4	15.4	9.3	11.5	8.8	9.04	17.3	20.1	12.8	13.4

Several subjects on olopatadine and on placebo experienced a maximum change in QTc between 30 and 60 msec. On olopatadine, one subject experienced a QTcF Emax >60 msec (63.1 msec) on Day 14 at 1.5 hours post-dose (Figure 2.2.4.3.2). However, the QTcF values at the adjacent (1 and 2 hour) time points were 403 and 413 msec. Further, this subject did not have a Emax on Day 12. According to the sponsor, this isolated Emax was considered a random event and deemed not clinically meaningful in view of these findings. The highest QTF absolute value was 518 following olopatadine treatment. The mean of maximum QTF change from baseline was highest for the olopatadine group (17 msec ± 13 vs 16 msec ±13) (Table 2.2.4.3.1). The maximum of the mean values over time was 18.8 msec and 14.9 msec for the olopatadine and placebo treatment, respectively (Figure 2.2.4.3.2 and Table 2.2.4.3.2).

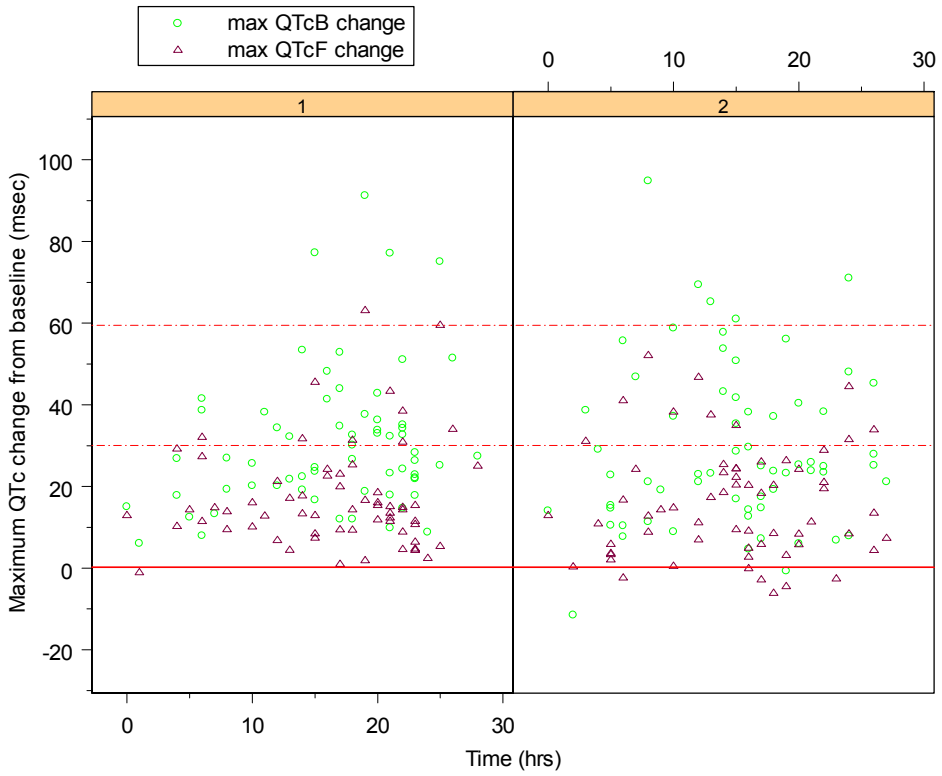


Figure 2.2.4.3.2. Individual maximum QTc change from baseline at steady state following multiple administration of the treatments (1=olopatadine and 2=placebo).

Table 2.2.4.3.2. Mean (SD) QTB change from baseline as a function of treatment and time following Patanase administration

Time	**Delta QTc (msec) Based on Fredericia's correction**	
	Placebo	320
0	0	0 (1.8)
1	-22.9	-12 (4.7)
6	-11.6 (15.9)	-2.5 (6.9)
8	12.4	-2.3 (8.7)
11	12.8 (8.8)	14.7 (2.9)
16	-3.5 (9.7)	14.04 (10.8)
20	6 (15.2)	-3.6 (5.8)
26	14.9 (16.8)	18.8 (28)
maximum	14.9	18.8

No linear correlation was observed between QTc change from baseline and systemic exposure (Cmax) of olopatadine at steady state (mean 309 ng/mL, range (b) (4) ng/mL) following multiple 20 mg oral solution doses for 14 days (Figure 2.2.4.3.3).

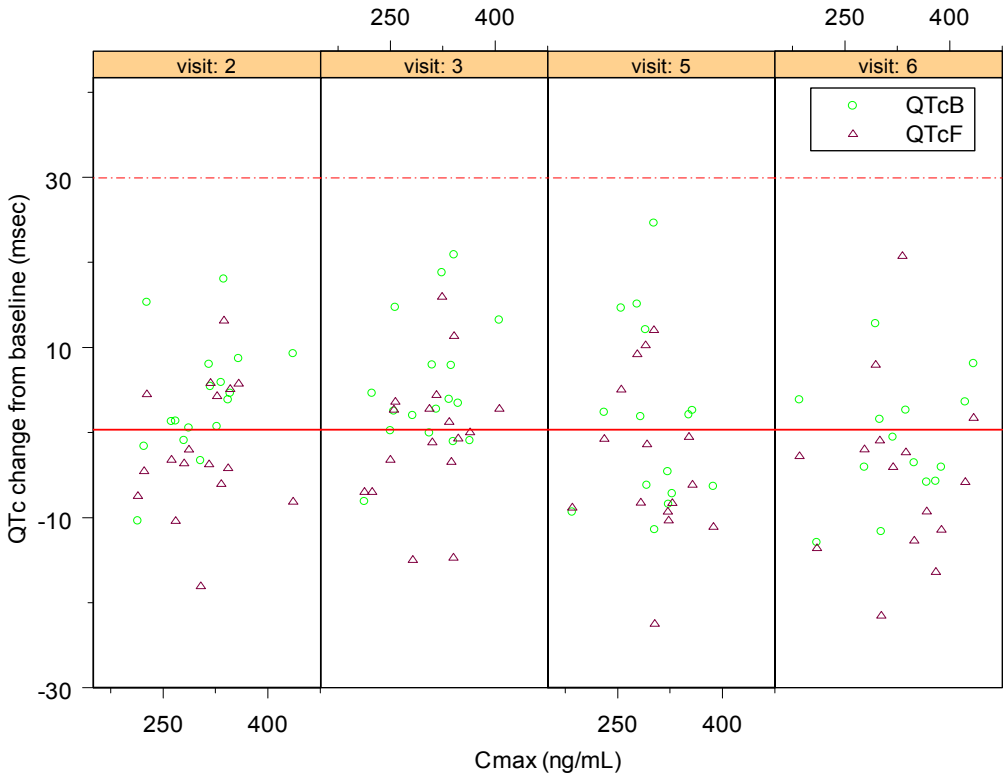


Figure 2.2.4.3.3. QTc change from baseline as a function of olopatadine systemic exposure (Cmax).

2.2.4.4 Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

As mentioned previously, the systemic absorption of intranasally administered drugs is the result of nasal and gastrointestinal absorption, and therefore plasma concentrations cannot be correlated to efficacy (TNSS). Thus, the appropriate dose and dosing regimen need to be based on dose-response relationships rather than exposure-response relationships. The proposed dose of Patanase in patients 12 years and older is two sprays per nostril (1 spray = 600 mcg of olopatadine base) twice-daily. In the case of dose-response for efficacy, there was a trend for higher doses to produce a bigger response; however a clear dose-ordering was not observed following either single administration of olopatadine 0.2-, 0.4-, or 0.6% nasal spray or after multiple administration of olopatadine 0.1- and 0.2% nasal spray. In general, based on Phase II dose-response studies, systemic adverse events appeared not to be related to dose following single administration of olopatadine 0.2-, 0.4 or 0.6% nasal spray or multiple doses of olopatadine 0.1 or 0.2% nasal spray. Based on phase III clinical trials, it appears that olopatadine 0.6% 2 sprays per nostril BID was efficacious in AR patients. Therefore, in terms of dose, it appears that 0.6% olopatadine may be the appropriate dose. In terms of dosing regimen, the dose-response studies did not evaluate BID vs QD regimen for higher doses, thus, conclusions in terms of appropriate dosing regimen cannot be made based on phase II dose-response information.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters? What are the characteristics of drug distribution? How do the PK parameters change with time following chronic dosing?

Single Dose

Single-dose pharmacokinetics was assessed following single intranasal administration of olopatadine nasal 0.4% or olopatadine nasal 0.6% in SAR patients and olopatadine nasal 0.1%, 0.2%, 0.4-, or 0.6% in healthy subjects. The mean PK parameters resulting from these studies are shown in Table 2.2.5.1.1. The mean and range in the olopatadine Cmax and AUC values in SAR patients following single intranasal doses (two sprays/nostril) of either olopatadine nasal 0.4% (1.6 mg) or olopatadine nasal 0.6% (2.4 mg) were comparable to those in healthy subjects.

Table 2.2.5.1.1. Mean ± SD (range) Pharmacokinetic Parameters of Olopatadine after Single Intranasal Doses

Study	**Dose**	**Cmax (ng/mL)**	**Tmax (h)**	**AUC (ng*h/mL)**	**t_{112} (h)**
Study C-02-10 SAR Patients	0.4% (N=14)	14.4 ± 4.4 (5.97 -21.9)	0.86 ± 0.41 (0.25 - 1.50)	48.9 ± 12.5 (23.3 - 67.4)	ND
	0.6% (N=13)	21.7 ± 8.7 (7.11 - 36.4)	1.00 ± 0.50 (0.25 - 2.00)	67.7 ± 21.1 (24.0 - 98.0)	ND
Study C-02-21 Healthy	0.6% (N=8)	29.3 ± 15.1 (13.6-58.4)	0.97 ± 0.54 (0.50 -2.00)	75.1 ± 29.4 (31.8 - 126)	ND
Study C-03-11 Healthy	0.4% (N=11)	12.5 ± 6.1 (1.98 -20.7)	1.04 ± 0.24 (0.75-1.50)	42.5 ± 16.0 (17.0-66.4)	8.6 ± 5.7 (1.75-17.9)
	0.6% (N=11)	17.5 ± 6.7 (6.37 -27.6)	1.05 ± 0.31 (0.75 - 1.50)	60.3 ± 20.3 (20.2 - 98.0)	10.0 ± 5.7 (3.2 -22.2)
Study C-02-46 Healthy	0.6% (N=6)	18.1±10.9 (3.80 - 29.9)	1.17±0.52 (0.50 - 2.00)	77.0±51.3 (17.0 - 139)	11.5±3.0 (7.2 - 14.5)

ND= not determined, sampling only out to 12 hours post-dose.

Three minor active metabolites (M1, M2, and M3) were identified in these PK studies, but only N-desmethyl olopatadine (Ml) and olopatadine N-oxide (M3) were quantified in plasma samples following single intranasal doses of olopatadine nasal 0.4% or olopatadine nasal 0.6%. The Cmax and AUC values for these metabolites did not appear to be markedly different between SAR patients and healthy subjects administered comparable single intranasal doses (Table 2.2.5.1.2)

Table 2.2.5.1.2. Mean ± SD (range) Pharmacokinetic Parameters of Metabolites Ml and M3 after Single Olopatadine Intranasal Doses

Study	Dose (N)	Analyte	Cmax (ng/mL)	Tmax (h)	AUC_{0-t} (ng*h/mL)	t_{112} (h)
Study C-02-10 SAR Patients	0.4% (N=14)	Ml	0.0861 ± 0.0431 (BLQ-0.163)	2.27 ± 0.87 (1.00-4.00)	0.546 ± 0.169[a] (0.366-0.702)	ND
	0.4% (N=14)	M3	0.357 ± 0.112 (0.153-0.581)	1.73 ± 0.77 (0.75-3.00)	1.42 ±0.24[a] (1.13-1.82)	ND
	0.6% (N=1 3)	Ml	0.150 ± 0.084 (BLQ-0.352)	2.41 ± 0.94 (1.50-4.00)	0.728 ± 0.121[a] (0.572-0.913)	ND
	0.6% (N=13)	M3	0.530±0.255 (0.115-1.16)	1.44±0.61 (0.75-3.00)	1.89±0.60[a] (0.5 14-2.60)	ND
Study C-03-11 Healthy Subjects	0.4% (N11)	Ml	0.138 ± 0.067 (0.0637-0.241)	4.82 ± 10.3 (1.50-36.0)	0.49 ± 0.32 (0.035-1.08)	5.5 ± 4.6 (2.5-13.6)
	0.4% (N=11)	M3	0.377±0.192 (0.0515-0.602)	1.18±0.32 (0.75-1.50)	1.00±0.62 (0.013-1.90)	1.6±0.4 (0.7-2.2)
	0.6% (N=11)	Ml	0.344±0.398 (0.800-1.34)	1.82±0.34 (1.00-2.04)	0.68±0.47 (0.094-1.38)	3.7± 1.8 (2.2-7.6)
	0.6% (N=1 1)	M3	0.511±0.229 (0.120-0.783)	1.25±0.37 (0.75-2.00)	1 38±0.65 (0.23-2.14)	1.7±0.4 (1.0-2.3)
Study C-02-46 Healthy Subjects	0.6% (N6)	Ml	0.192 ± 0.138 (BLQ-0.328)	2.60 ±0.55[b] (2.00-3.00)	2.09 ± 0.15[cd] (1.98-2.26)	4.0 ± 0.5[c] (3.5-4.4)
	0.6% (N=6)	M3	0.526 ± 0.348 (0.123-1.02)	1.88 ± 0.92 (0.75-3.00)	2.69 ± 1.98 (0.561-5.82)	2.5 ± 0.6 (1.9-3.3)

ND= not determined. [a]AUC0-6; [b]N=5; [c]N=3; [d]AUC_{0-12h}

Multiple Dose

The multiple-dose PK of olopatadine was examined in two studies following intranasal administration (Study C-02-10 and Study C-00-58) (two sprays/nostril) from 0.1% (0.4 mg), 0.2% (0.8 mg), 0.4% (1.6 mg) and 0.6% (2.4 mg). Comparison of the systemic exposure (Cmax and AUC_{0-12}) of olopatadine after single and multiple intranasal doses in SAR patients (C-02-10) indicate minimal accumulation (<1.3-fold) with twice-daily administration. Mean Tmax and t1/2 values were similar in healthy subjects and SAR patients.

Table 2.2.5.1.3. Mean ± SD (range) Pharmacokinetic Parameters of Olopatadine after Multiple QD or BID Intranasal Doses

Study	Dose/Regimen (N)	Cmax (ng/mL)	Tmax (h)	$AUC0-_{12}$ (ng*h/mL)	$t_{1/2}$ (h)
Study C-02-10 SAR patients	0.4%/BID x 14 days (N=14)	15.9 ± 6.4 (3.65-29.0)	1.00 ± 0.55 (0.25-2.00)	57.3 ± 24.5 (10.4-114)	8.3 ± 4.9 (2.1-21.3)
	0.6%/BID x 14 days (N=13)	23.3 ± 6.2 (14.4-35.3)	0.97 ± 0.52 (0.08 - 1.50)	78.0 ± 13.9 (54.4- 103)	10.4 ± 5.1 (4.0-21.8)
Study C-00-58 Healthy Subjects	0.1%/QD x 3 days (N12)	4.36 ± 2.27 (0.41 -7.92)	1.23 ± 0.59 (0.50 -2.00)	13.92± 5.90 (1.40 -20.67)	6.3 ± 4.1 (1.96 - 13.5)
	0.1%/BID x 3 days (N=12)	3.42 ± 1.31 (0.97 — 5.05)	1.06 ± 0.42 (0.50 - 1.50)	12.03 ± 3.66 (4.80 - 16.54)	8.3 ± 3.5 (3.06 - 13.3)
	0.2%/BID x 3 days (N=12)	8.48 ± 3.12 (2.77- 15.0)	1.25 ± 0.38 (0.75-2.00)	28.33 ± 9.88 (11.09- 14.03)	15.0 ± 9.6 (3.16-29.9)

The multiple-dose pharmacokinetics of olopatadine metabolites following intranasal administration of olopatadine nasal 0.6% was examined in SAR patients (Study C-02- 10). M2 was not quantifiable in any sample. For Ml and M3, peak plasma concentrations after BID dosing for 2 weeks were about 1.7-and 1.3-fold higher, respectively than those observed after the single dose. AUC values were 1.2- to 1.5-fold higher.

The PK of olopatadine following oral solution doses was examined as part of a cardiovascular safety study (Study C-02-54) following single and multiple twice-daily oral doses

of the oral solution. The mean pharmacokinetic parameters following multiple twice-daily doses are presented in Table 2.2.5.1.4.

Table 2.2.5.1.4. Mean ± SD (range) Pharmacokinetic Parameters of Olopatadine after Multiple Twice- Daily Oral Solution Doses

Study	Dose/Day (N)	Cmax (ng/mL)	Tmax (h)	AUC $_{0\text{-}12h}$ (ng*h/mL)	T1/2 (h)
Study C-02-54 Healthy	20 mg/Day 14 (N32)	309 ± 57 (185 -436)	0.83 ± 0.40 (0.28-2.03)	997 ± 152 (689-1280)	11.2 ± 3.7 (5.4-18.5)

Mean Cmax values for metabolites Ml and M3 averaged 2.39 ± 0.65 ng/mL and 8.22 ± 1.83 ng/mL. Plasma concentrations of M3 were approximately 3-fold higher than those for Ml. M2 was not quantifiable (<0.250 ng/mL) in any sample. Measurable plasma concentrations of both Ml and M3 were obtained for up to 24 hours postdose. From these profiles, the estimated terminal half-life of Ml (9.1 ± 3.4 hours) and M3 (7.9 ± 2.4 hours) were not substantially different from that of the parent drug.

The absolute bioavailability of olopatadine as examined in a single center, open-label, randomized, crossover study (C-03-1 1). Twelve, healthy, adult, male and female subjects were randomized to receive either a single intranasal dose (two sprays per nostril) of olopatadine nasal 0.4% (1.6mg) or olopatadine nasal 0.6% (2.4 mg) or a single intravenous infusion of olopatadine solution (1.5 mg). The mean absolute BA of olopatadine (based on dose-adjusted AUC ratios) was 61.3% for olopatadine nasal 0.4% and 56.6% for olopatadine nasal 0.6%. Similar absolute BA estimates were obtained based on ratios of the mean 48-hour urinary recovery of unchanged olopatadine, with values of 57% and 59%, respectively. Urinary recovery of unchanged olopatadine accounted for 61.5 ± 16.7% of the intravenous dose.

2.2.5.2 Are the PK of Patanase linear and dose-proportional?

Dose-proportionality following single and multiple intranasal administration of olopatadine nasal 0.4% or olopatadine nasal 0.6% in SAR patients and olopatadine nasal 0.2% or 0.6% in healthy subjects was evaluated in Studies C-03-10 and C-03-11, respectively.

Olopatadine peak plasma concentrations increased in proportion to the intranasal dose averaging 12.5 ± 6.1 ng/mL and 17.5 ± 6.7 ng/mL for olopatadine nasal 0.4% and olopatadine nasal 0.6%, respectively (Study C-03-11). Similar dose-proportional increases were seen in mean AUC values (an increase in 1.5 in dose resulted in a 1.4 increased in the olopatadine Cmax and AUC) (Refer to Table 2.2.5.1.1 and 2.2.5.1.2)

Following single intranasal doses of olopatadine nasal 0.4% and 0.6% plasma concentrations of M1 and M3 increased roughly in proportion to the olopatadine dose in both healthy subjects and SAR patients (refer to Table 2.2.5.1.2)

2.2.5.3 What are the mass balance characteristics of the drug?

Following a single oral administration of ^{14}C-olopatadine solution (5 mg/200 µCi/7.5 mL ^{14}C-olopatadine dosing solution) to 8 healthy volunteers, the overall mean total recovery of radioactivity (over the entire 192 hr postdose interval) in urine and feces was 70.5% and 17% of the dose, respectively indicating that urinary excretion was the major pathway of elimination of radioactivity with the majority recovered as unchanged olopatadine (Table 2.2.5.3.1). Together, urinary excretion of Ml and M3 accounted for about 7% of radiolabeled material recovered in the urine within 24 hours. Identified and unidentified metabolites accounted for <10% of the

total radioactivity in urine. The majority of the cumulative % dose of radioactivity was recovered in the first 24 hours (67.4%) in the urine, and in the first 96 hours (16.0%) in the feces.

In plasma drug-related radioactivity was rapidly absorbed with peak total radioactivity in observed within 0.5 to 1 hours after dosing. Radioactivity was eliminated from plasma with a mean half-life of 7.94 hours. Unchanged olopatadine was the major component of radiolabeled material in plasma and urine. Olopatadine Ml, M2 and M3 metabolites accounted for less than 10% of circulating radioactivity in plasma (Table 2.2.5.3.2)

Table 2.2.5.3.1. Individual and Mean ± SD Cumulative Recovery of Total Radioactivity in Urine, Feces and Combined (Total) Following an Oral ^{14}C Olopatadine Dose, C-03-10

	Cumulative Urine		**Cumulative Feces**		**Cumulative Total**
Subject Number	**Ae (µg)**	**% Dose**	**Ae (µg)**	**% Dose**	**% Dose**
101					(b) (4)
102					
103					
104					
105					
106					
107					
108					
Mean	3493.3	70.5	841.7	17.0	87.5
SD	137.1	2.6	279.7	5.7	6.0
Min					(b) (4)
Max					

Table 2.2.5.3.2. Mean ± SD Plasma Total Radioactivity and Concentrations (ng eq./mL) at Selected Time points After a 5 mg ^{14}C-Olopatadine HCI Solution in Healthy Subjects

Peak	Component[a]	**Concentration (ng eq/mL) and Percent of Total Radioactivity (%)**								
		0.5 Hours			3 Hours			8 Hours		
		Mean	SD	%	Mean	SD	%	Mean	SD	%
	Total Radioactivity[b]	84.8	31.1	Ref	36.9	8.0	Ref	9.1	1.7	Ref
Mpl	Unidentified	1.63	0.66	1.9	0.86	031	2.3	BLQ	DLQ	ND
Mp2	Unidentified[c]	1.34	0.57	1.6	0.84	0.27	2.3	BLQ	BLQ	ND
Mp3	N-Desmethyl Olopatadine[d]	3.01	1.66	3.5	2.29	0.62	6.2	0.72	0.19	8.0
Mp4	Olopatadine	65.5	24.1	77.2	24.2	3.97	65.6	5.62	1.02	62.1
Mp5	Olopatadine N-Oxide	1.31	0.38	1.5	0.71	0.16	1.9	BLQ	BLQ	ND
Mp6	Unidentified	BLQ	BLQ	ND	0.68	0.20	1.8	BLQ	BLQ	ND
Mp7	Unidentified	1.39	0.35	1.6	0.71	0.23	1.9	BLQ	BLQ	ND

SD: Standard Deviation

BLQ: Below Limits of Quantitation (less than 0.34 ng eq/mE)

ND: Not determined since metabolite was below limit of quantitation. Ref: Reference concentration for calculation of olopatadine and metabolite percentages.

[a]identification of component in plasma based on retention time to authentic standards.

[b]Source: Study C-03-10, Alcon Clinical Study Report No.: TDOC 0001414

[c]Retention time corresponds to N-didesmethyl olopatadine standard. However, peak was not well resolved and presence of this compound at these levels is inconsistent with results of other clinical studies.

[d]Concentration may be an overestimate due to co-elution of other radioactive material under peak.

2.2.5.4 What are the characteristics of drug metabolism and excretion?

Data from the in-vitro metabolism of ^{14}C-olopatadine using microsomes prepared from: a) human B-lymphoblast cells expressing CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4; b) from baculovirus-infected insect cells expressing flavin-containing monooxygenase FMO1, FMO3, and FMO5 and microsomes from c) a mixed pool of human liver microsomes (0.53 nmol of P450/mg protein) prepared from six subjects showed that the metabolism of olopatadine is a minor route of elimination. Two different metabolites, M1 and M3, were formed when olopatadine was incubated with human liver microsomes in the presence of an NADPH-generating system. After 1-h incubation, M1 and M3 accounted for 5.2 and 30.5% of the initial olopatadine, respectively. M1 and M3 were identified tentatively as *N*-monodemethylolopatadine and olopatadine *N*-oxide, respectively. The formation of both M1 and M3 by human liver microsomes was found to be NADPH-dependent, and the formation rates of M1 and M3 were 0.330 and 2.50 pmol/min/mg protein, respectively.

Formation of Ml was decreased by the selective inhibitors of CYP3A4, troleandomycin and ketoconazole, by not by inhibitors of other P450 isozymes. The rate of M3 formation by FMO1 and FMO3 was about 4 times faster than by CYP1A2, CYP2B6 and CYP2E1. Other evaluated isozymes (CYP2A6, CYP2C9, CYP2C19, CYP2D6 and CYP2E1) did not catalyze the formation of either Ml or M3. This indicates that M1 formation is catalyzed primarily by CYP3A4, while M3 formation is catalyzed by FMO1 and FMO3.

After oral administration of [^{14}C]olopatadine to rats and dogs, the main metabolic pathways were 1) *N*-demethylation to M1 and M2, the *N*-monodemethyl and *N*-didemethyl analogs, respectively; 2) hydroxylation of dihydrodibenz[*b*,*e*]oxepin ring (M5); and 3) sulfoconjugation of M5 (M4) and *N*-oxidation (M3) (Fig.2.2.5.5.1). Following oral administration of 5 mg ^{14}C-olopatadine, olopatadine was the primary component circulating in plasma accounting for 77% of the peak total radioactivity. At least 6 metabolites were observed in plasma, of which M1 and M3 were the major metabolites. All were minor, representing 2 to 4.5% or less of parent circulating in plasma.

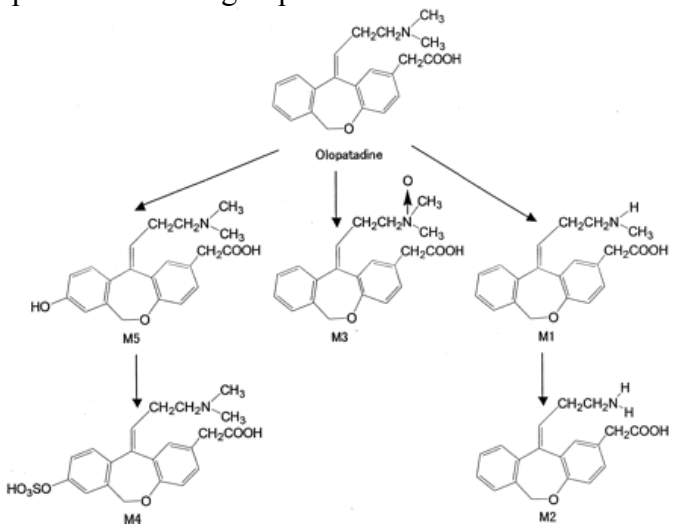


Fig. 2.2.5.4.1. Proposed metabolic pathway of olopatadine.

2.2.5.5 What are the inter- and intra-subject variabilities in PK parameters in volunteers and patients?

The CV% (intersubject variability) for the Cmax and AUC of olopatadine in healthy volunteers and AR patients was about 35%. Disease stage did not change the degree of variability.

2.3 Intrinsic Factors

2.3.1 Does age affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

2.3.1.1 Do race, gender, age, and disease status affect the PK and PD of the drug? What dosage regimen adjustments are recommended for each of these subgroups?

Gender

Alcon did not conduct any specific studies to investigate gender differences in the pharmacokinetics of parent drug or metabolites following intranasal administration of olopatadine nasal 0.6%. However, the mean systemic exposure (Cmax and AUCt) in females following multiple administration of olopatadine in SAR patients was 40 % and 27% higher, respectively than those values observed in male SAR patients. This increase in systemic exposure in females compared to males was lower following oral administration of olopatadine (13 to 20% higher in females) (Table 2.3.1.2.1). These differences in systemic exposure are not clinically relevant since multiple doses of oral olopatadine 20 mg BID appeared to be safe. Therefore, no dose adjustment is necessary based on gender difference in the PK of olopatadine.

Table 2.3.1.2.1. Mean ± SD (range) Olopatadine Pharmacokinetic Parameters by Gender

Study Population Dose	Gender Day	Parameters				
		Cmax (ng/mL)	Tmax (h)	AUC_{0-12} (ng*h/mL)	AUC0-inf (ng*h/mL)	$t_1/_2$ (h)
C-02-54 Healthy 20 mg oral BID x 14	Male Day 14	287 ± 56 (185-436)	0.76 ± 0.38 (0.28-1.53)	943 ± 143 (689-1250)	1070 ± 180 (743-1450)	10.0 ± 2.8 (5.4-15.6)
	Female Day 14	345 ± 53 (250-434)	0.88 ± 0.44 (0.53-2.03)	1070 ± 150 (734-1280)	1240 ± 180 (867-1630)	12.3 ± 4.1 (6.4- 18.5)
C-02-10 SAR patients Olopatadine 04% or Olopatadine 0.6%BIDx 14 days	Male Day 15 0.4%	22.4 ± 6.2 (14.4-21.7)	0.78 ± 0.64 (0.08-1.50)	82.9 ± 15.9 (57.5-103)	97.5 ± 19.5 (66.0-116)	8.1 ± 3.0 (4.0-11.5)
	Female Day 15 0.4%	24.1 ± 6.5 (18.5-35.3)	1.14 ± 0.35 (0.75-1.50)	73.8 ± 11.5 (54.4-86.6)	85.9 ± 16.9 (59.3-108)	12.3 ± 6.0 (5.9-21.8)
	Male Day 15 0.6%	13.0±3.7 (7.00-18.1)	1.25±0.39 (0.75-1.50)	49.0±14.4 (34.5-69.6)	58.1±17.0 (40.7-81.0)	8.4±3.7 (5.2-15.0)
	Female Day 15 0.6%	18.1 ± 7.4 (3.65-29.0)	0.81 ± 0.59 (0.25-2.00)	63.6 ± 29.4 (10.4-114)	74.0 ± 35.3 (10.5-130)	8.3 ± 5.9 (2.1-21.3)

The effect of race and age (pediatric patients or elderly (>65 years)) on the PK of the drug has not been evaluated by the sponsor.

2.3.1.2. Does renal impairment affect the PK of the drug and its major metabolite? Is dosage regimen adjustment recommended?

After single intranasal administration of olopatadine nasal 0.6% to 25 subjects/patients (6 subjects with normal renal function, 7 patients with mild renal impairment, 6 patients with moderate renal impairment, and 6 patients with severe renal impairment) no clinically significant

differences were observed in the systemic exposure of olopatadine in patients with mild or moderate renal impairment compared to subjects with normal renal function. The plasma Cmax and AUC values in patients with severe renal impairment were approximately 2.6- and 5.6-fold higher than those in healthy subjects. Higher plasma concentrations of the minor, active Ml and M3 metabolites were seen with increasing renal impairment particularly those in severely-impaired patients with 2.6- and 3.6-fold higher mean Cmax values, respectively. Urinary excretion of parent and metabolites was reduced in renally impaired patients. Despite of the higher systemic exposure of parent drug and metabolites observed in patients with severe renal impairment following intranasal doses of olopatadine nasal 0.6%, the extent of exposure is still 10- to 250-fold lower than that observed following higher oral 20 mg to 400 mg doses which were safe and well-tolerated. Therefore, dosage adjustment of olopatadine based on renal impairment may not be necessary.

2.3.1.3 Does liver impairment affect the PK of the drug? Is dosage adjustment recommended?

The effect of liver impairment on the PK of olopatadine and its metabolites was not evaluated. The rationale provided by the sponsor is that olopatadine (and its metabolites) are mainly eliminated by the kidney. In fact, in a mass balance study total radioactivity was predominantly excreted in urine (70% of total administered dose) suggesting that liver metabolism is not an important route of elimination.

2.3.1.4 What pregnancy and lactation use information is there in the application?

Olopatadine was non-teratogenic and did not affect reproductive function in animals. However, no adequate and well-controlled studies in pregnant women have been conducted. This drug should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the fetus.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The effects of herbal products, diet, smoking and alcohol used have not been evaluated.

2.4.2 Drug-Drug Interactions (DDI)

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Data from the in-vitro metabolism of ^{14}C-olopatadine showed that metabolism of olopatadine is a minor route of elimination. Two different metabolites, M1 and M3, were formed when olopatadine was incubated with human liver microsomes. After 1-h incubation, M1 and M3 accounted for 5.2 and 30.5% of the initial olopatadine concentration, respectively. M1 formation was catalyzed primarily by CYP2A4, while M3 formation is catalyzed by FMO1 and FMO3. Therefore, it is unlikely that substrates, inhibitors or inducers of these enzymes may affect the PK of olopatadine and its metabolites. In addition, olopatadine did not affect the activity of the major CYPP450 enzymes such as 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. Therefore, no major effects of olopatadine should be expected on the PK of other drugs.

2.4.2.2 Is the drug a substrate of CYP enzymes?

Data from the in-vitro metabolism of ^{14}C-olopatadine showed that the metabolism is a minor route of elimination. CYP3A4 appears to be the only CYP enzyme involved in the metabolism of olopatadine with an insignificant contribution to the overall elimination (~ 5%).

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

At concentrations as high as 100 µM (concentration was at least 3 times the maximum concentrations achieved *in vivo*), olopatadine failed to produce significant inhibition of the metabolism of any isozyme specific substrate tested (phenacetin for CYP1A2, tolbutamide for CYP2C8-9, S-mephenyltoin for CYP2C19, bufurol for CYP2D6, chloroxazone for CYP2E1 and testosterone for CYP3A4). The potential for olopatadine metabolites to act as inhibitors of CYP enzymes was not evaluated.

The potential for olopatadine or its metabolites to act as an inducer of CYP enzymes was not evaluated.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

This was not evaluated by the sponsor.

2.4.2.5. Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

No information on this issue was provided.

2.4.2.6 What is the effect of olopatadine on the PK of other drugs? What is the effect of other drugs on the PK of olopatadine?

No DDI studies were performed by the sponsor. Data from the in-vitro metabolism of ^{14}C-olopatadine showed that the metabolism of olopatadine is a minor route of elimination. Therefore, it is unlikely that substrates, inhibitors or inducers of these enzymes affect the PK of olopatadine and its metabolites. In addition, olopatadine did not inhibit the major CYPP450 enzymes such as 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. Therefore, no major effects of olopatadine should be expected on the PK of other drugs.

2.4.2.7 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

In-vitro metabolism studies using human microsomes indicated that olopatadine is metabolized into two major metabolites M1 and M3. M3 formation was catalyzed by FMO1 and FMO3. The contribution of these FMO enzymes is about 30% of the overall elimination of the drug. The sponsor did not conduct in vitro or in vivo DDI with inhibitors or inducers of these enzymes.

2.5 General Biopharmaceutics

2.5.1 What is the BCS Class classification for olopatadine?

This information was not provided by the sponsor. Also, this information may not be relevant since this is not a solid dosage form.

2.5.2 Was the to-be-marketed formulation used in the PK/clinical trials?

Two different series of nasal formulations were developed and used in subsequent

clinical trials. The first series, with 0.1% or 0.2% w/v olopatadine as base, at neutral pH and without povidone or EDTA, was based upon the composition of PATANOL® (olopatadine hydrocloride ophthalmic solution) 0.1%. The Series 1 formulations were used in Phase II dose-ranging studies. The *in vivo* performance (systemic BA) and PK of the series 1 formulation at two strengths was evaluated after single and multiple intranasal doses in healthy subjects (Study C00-58). The second series, containing 0.2%, 0.4% and 0.6% w/v olopatadine as base, at acidic pH and with (b) (4) w/v povidone and (b) (4) EDTA, was based on the composition of olopatadine hydrochloride ophthalmic solution, 0.2%. The Series 2 formulations (drug product intended for market) were used in the pivotal safety and efficacy Phase III clinical trials. Furthermore, the *in vivo* bioavailability and pharmacokinetics of olopatadine from the drug product intended for market was studied in healthy subjects (C-03-11, C-02-21, and C-02-46), in SAR patients enrolled in the winter-cedar Phase III efficacy study (C-02-10) and in renal impairment study (C-02-46).

Two additional olopatadine formulations were used in clinical pharmacokinetic studies. An intravenous solution of 0.0 1% w/v olopatadine, without povidone, benzalkonium chloride (BAC) or EDTA, was used in absolute bioavailability study (C-03-l 1). An oral solution of 0.2% w/v olopatadine, without povidone or EDTA, was used in two cardiovascular safety/pharmacokinetic studies (C-00-23 and C-02-54) and in the ^{14}C-excretion study (C-03-10). Table 2.5.2.1-1 lists the formulations used in the clinical pharmacology studies.

Table 2.5.2.1. Comparison of Olopatadine Nasal Spray Formulations Used in Clinical Studies

Component	**Series 1**		**Series 2**			**Solution (oral)**	**Solution (IV)**
	FID 100491	FID 101371	FID (b) (4)	**FID** (b) (4)	**FID** (b) (4)	**FID** 101688	**FID** 105103
Olopatadine Hydrochloride	0.111	0.222	0.222	0.443	0.665	0.222	0.0111
Olopatadine base	0.1%	0.2%	0.2%	0.4%	0.6%	0.2%	0.01%
Benzalkonium Chloride	(b) (4)	0.01 + (b) (4)	0.01	0.01	0.01	None	None
Edetate Disodium	None	None	(b) (4)			None	None
Povidone	None	None				None	None
Sodium Chloride	(b) (4)					-	-
Dibasic Sodium Phosphate						-	-
Sodium Hydroxide and/or Hydrochloric Acid						-	-
Purified Water						qs	qs

2.5.3 Are the method and dissolution specifications supported by the data provided by the sponsor?

This does not apply for orally inhaled drugs.

2.5.4 What is the effect of food on the BA of the drug?

This was not assessed. Generally, the effect of food on the PK of nasally administered drugs is not evaluated since the effect of these drugs is local. However, food may increase the systemic exposure of these drugs which may change its safety profile.

2.5.5 If different-strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product? Does the use of spacers affect the PK of the drug?

The sponsor is proposing only one strength of Patanase; 0.6%. Different strengths of olopatadine (0.1%, 0.2%, 0.4% and 0.6%) were used in Phase I, II and III PK studies. However, because this is a nasal solution, in vivo BE are not required. Nevertheless, based on the Agency's Guidance for Industry, Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, the sponsor studied the systemic exposure of the clinical trial batches that were used in pivotal safety and efficacy studies and intended for market. These studies were performed in both healthy subjects (C-02-21, C-03-11, C-02-46), and in the target population of allergic rhinitis patients (C-01-92, C-02-10), and utilized the bioavailability measures considered pivotal in single (Cmax and AUC0-inf) and multiple-dose studies (Cmax and AUCo-τ). The sponsor showed that the systemic exposure of olopatadine nasal spray increased in a roughly proportional manner with the dose.

2.6 Analytical Section

2.6.1 Was the suitability of the analytical method supported by the submitted information?

Bioanalytical methods for olopatadine and its metabolites

The sponsor did not mention if free, bound or total drug was measured. Therefore, it is assumed that total drug was measured. Concentrations of olopatadine and its metabolites were determined in plasma samples from all human pharmacokinetic studies considered in this review using an HPLC with tandem mass spectrometric detection (LC/MS/MS). The assay met all validation acceptance criteria with regard to precision, accuracy and specificity (Table 2.6.1.1). A working range of 0.050 ng/mL (quantitation limit) to 5.00 ng/mL was validated for olopatadine, Ml and M3. The working range for M2 was 0.250 ng/mL (quantitation limit) to 25.0 ng/mL. Mean absolute recoveries of olopatadine, Ml, M2 and M3 were 88.2%, 91.5%, 81.8 and 56.4, respectively. Stability of olopatadine and metabolites in plasma was demonstrated through five freeze/thaw cycles, up to six hours at room temperature, and in extracts for up to 19.5 hours at room temperature and 3.5 days at 1 to 8 degrees Celsius. Long-term storage stability of olopatadine and metabolites in human plasma at both -20 degrees Celsius and -70 degrees Celsius is ongoing.

Simultaneous analysis of olopatadine and M3 were conducted using a validated (b) (4) method. This method also met all acceptance criteria for linearity, precision and accuracy over the working ranges of 3.00 ng/mL (quantitation limit) to 1500 ng/mL for olopatadine and 1.00 ng/mL (quantitation limit) to 1500 ng/mL for M3 (Table 2.6.1.1). The mean absolute recoveries for olopatadine and M3 were 52.4% and 59.1%, respectively. There were no measurable peaks in control/blank urine. Stability of olopatadine and M3 in urine was demonstrated through four freeze/thaw cycles, up to six hours at room temperature, and in extracts for up to 92 hours at room temperature. Frozen long-term stability at both -20 degrees Celsius and -70 degrees Celsius is ongoing.

Table 2.6.1.1. Listing of Analytical Methods Used in Clinical Pharmacology/Bioavailability Studies Conducted by Alcon

Method	Matrix	Analyte(s)	Working Range (ng/mL)	Accuracy/RSD	Clinical Study
LC/MS/ MS	Human plasma	Olopatadine	0.05-25	Intra-day 98-1 12%/RSD ≤8.4% Inter-day l00-107%/RSD ≤l0.5%	C-00-58 Multiple dose-ranging PK (Alcon), Nasal, 0.1%, 0.2% BID C-02-2l Single dose PK (Alcon), Nasal, 0.6%
LC/MS/ MS	Human urine	Olopatadine	10-1500	Intra-day 94.3-98.2%/RSD ≤2.l% Inter-day 95.8-l00%/RSD ≤8.8%	C-00-58 Dose-ranging PK (Alcon) Nasal, Multiple-dose 0.1%, 0.2% BID
LC/MS/MS	Human plasma	Olopatadine Ml M2 M3	0.050-5 0.050-5 0.250-25 0.050-5	Intra-day 97.3-98.8%/RSD ≤5.6% Inter-day 96-l0l%/RSD≤6.2% Intra-day 108-1 12%/RSD ≤5.3% Inter-day 110-11 1%/RSD≤4.9% Intra-day 104-108%/RSD ≤6.2% Inter-day 106-1 l0%/RSD≤6.3% Intra-day 102-103%/RSD ≤4.4% Inter-day 100-l04%/RSD≤5.7%	C-02-lO Phase III Efficacy/PK (Alcon), Nasal, Multiple dose 0.4%, 0.6% BID C-02-54 Cardiovascular Safety/PK (Alcon), Oral Multiple dose 20 mg BID C-02-46 Renal Impairment, Nasal, Single dose 0.6% C-03-l 1 Absolute Bioavailability, Nasal/Intravenous
LC/MS/ MS	Human Urine	Olopatadine M3	3-1500 1-500	Intra-day l00-10l%/RSD ≤4.9% Inter-day 92-l00%/RSD≤9.5% Intra-day l02-l04%/RSD≤4.8% Inter-day 92-98%/RSD≤l 0.2%	C-02-46 Renal Impairment, Nasal, Single dose 0.6% C-03-1l Absolute Bioavailability, Nasal/Intravenous
LC/MS/ MS	Human Urine	Ml M2	0.50-250 0.50-250	Intra-day l0l-104%/RSD ≤8.9% Inter-day 9l-l03%/RSD≤5.7% Intra-day 103-l09%/RSD ≤l4.3% Inter-day 96-99%/RSD≤9.3%	C-02-46 Renal Impairment, Nasal, Single dose 0.6% C-03-1 1 Absolute Bioavailability, Nasal/Intravenous

3. LABELING COMMENTS

The following underlined changes are recommended for the Clinical Pharmacology Section of the label:

Pharmacokinetics and Metabolism

The pharmacokinetic properties of olopatadine have been studied following administration by the nasal, oral, intravenous and topical ocular routes.

Absorption: Following twice-daily intranasal administration of PATANASE® Nasal Spray to seasonal allergic rhinitis patients, the mean maximum plasma concentration (Cmax) and mean AUC were 23.3 ± 6.2 ng/mL and 78.0 ± 13.9 ng*hr/mL, respectively. Cmax occurred between 0.25 and 2 hours. The systemic absolute bioavailability of intranasal olopatadine was about 60%. The mean accumulation ratio following multiple intranasal administration of olopatadine was about 1.3.

Distribution: The protein binding of olopatadine was moderate at approximately 55% in human sera, and independent of drug concentration over the range of 0.1 to 1000 ng/mL.

Metabolism: Olopatadine is not extensively metabolized. Based on plasma metabolite profiles following oral administration of [^{14}C] olopatadine, at least six minor metabolites circulate in human plasma. Two of these have been identified as the olopatadine N-oxide and N-desmethyl

olopatadine. *In vitro* studies with cDNA-expressed human cytochrome P450 isoenzymes (CYP) and flavin-containing monooxygenases (FMO). N-desmethyl olopatadine (Ml) formation was catalyzed mainly by CYP3A4, while olopatadine N-oxide (M3) was primarily catalyzed by FMO1 and FMO. Olopatadine at concentrations up to 33,900 ng/mL did not inhibit the *in vitro* metabolism of specific substrates for CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. The potential for olopatadine and its metabolites to act as inducers of CYP enzymes has not been evaluated. Parent olopatadine was 77% of peak plasma total radioactivity and all metabolites amounted to <6% combined.

Excretion/Elimination: The plasma elimination half-life of olopatadine is 8 to 12 hours. Olopatadine is mainly eliminated through urinary excretion. Approximately 70% of a [^{14}C] olopatadine hydrochloride oral dose was recovered in urine with 17% in the feces. Of the drug-related material recovered within the first 24 hours in the urine, 86% was unchanged olopatadine with the balance comprised of olopatadine N-oxide and N-desmethyl olopatadine.

Special Populations
Gender: No specific pharmacokinetic study examining the effect of gender was conducted. However, sub-group analysis across three studies enrolling both males and females showed no clinically relevant difference in pharmacokinetics.

Age: The effect of age on the pharmacokinetics of olopatadine has not been evaluated.

Race: The effect of race on the pharmacokinetics of olopatadine has not been evaluated.

Renal Insufficiency: The mean Cmax values for olopatadine following single intranasal doses were not markedly different between healthy subjects (18.1 ng/mL) and patients with mild, moderate and severe renal impairment (range 15.5 to 21.6 ng/mL). Plasma AUC was two- to five-fold higher in patients with severe impairment (creatinine clearance <30 mL/min/1.73m^2). In these patients, predicted peak steady-state plasma concentrations of olopatadine are approximately 10-fold lower than those observed after higher 20 mg oral doses, twice daily, which were safe and well-tolerated. These findings indicate that no adjustment of the dosing regimen of PATANASE® Nasal Spray is warranted in patients with renal impairment.

Hepatic Insufficiency: No specific pharmacokinetic study examining the effect of hepatic impairment was conducted. Since metabolism of olopatadine is a minor route of elimination, no adjustment of the dosing regimen of PATANASE® Nasal Spray is warranted in patients with hepatic impairment.

Pharmacodynamics
Effects on cardiac repolarization (QTc): In one placebo-controlled cardiac repolarization studies, no increase in the QT or QTc interval was observed in any of the 32 healthy volunteers administered olopatadine hydrochloride 20 mg oral solution twice-daily for 14 days. In addition, no evidence of any effect of olopatadine on cardiac repolarization was observed in 429 perennial allergic rhinitis patients given PATANASE® (olopatadine HCl) Nasal Spray, 665 micrograms twice daily for up to 1 year.

11 pp withheld immed. after this page as (b)(4) Draft Labeling.

4.2 Individual Study Reviews

"An Open-Label, Single Dose, Mass Balance and Excretion Study of ^{14}C-Olopatadine Following Oral Administration in Healthy Subjects "

Study No. C-03-10

OBJECTIVE

- To determine the mass balance and excretion of olopatadine following a single oral dose of ^{14}C-olopatadine aqueous solution in healthy subjects.

STUDY DESIGN AND TREATMENT ADMINISTRATION

This was a single-center, single-dose pharmacokinetic study in 8 healthy, male subjects from 19 to 40 years of age. The excretion and recovery of drug-related radioactivity and metabolic profiles of olopatadine were characterized in plasma and urine samples obtained for 48 hours following a single oral dose of -^{4}C-olopatadine hydrochloride solution (approximately 5 mg olopatadine as base and 200 µCi).

All subjects received a single oral dose of 5 mg/200 µCi/7.5 mL ^{14}C-olopatadine dosing solution with the addition of cherry syrup. Following the administration of test article, 10 mL of water was added to rinse the container and ingested, then repeated for a second rinse.

FORMULATION/STUDY MEDICATION

[11-^{14}C] olopatadine hydrochloride solution in ethanol:water (1:9), (b) (4) vial, manufactured by (b) (4) batch no.: UA8961. Olopatadine oral solution 0.2%, 11 mL bottle, manufactured by Alcon Laboratories, Inc., lot no.: 03-500493-1. (b) (4) cherry syrup, 500 mL, manufactured by (b) (4) lot no.: SD0083.

PHARMACOKINETIC MEASUREMENTS
BLOOD AND PLASMA COLLECTION

Total radioactivity values were determined by liquid scintillation counting in plasma, urine, and feces at each collection time after administration of a 0.2% oral solution (5 mg) ^{14}C-olopatadine containing 200 µCi ^{14}C-olopatadine. The plasma pharmacokinetic (PK) parameters Cmax, Tmax, AUC(o-t), AUC(o-inf), T1/2, and Kel were determined for ^{14}C-olopatadine in terms of ng eq/mL and dpm/mL. Plasma CL/F was also determined in terms of ng eq/mL. Excretion parameters including cumulative recovery over the 48-hour recovery period were determined for feces and urine. The following excretion parameters were calculated and presented for the urine and feces data: concentration, volume (urine), weight (feces), Ae, cum. Ae, excretion rate, % Dose, and cum. % Dose. In addition, the renal clearance (CL_r) was estimated for each subject as the cum. Ae divided by the area under the concentration-time curve AUC(0inf). Recovery of total radioactivity was determined by comparing the total amount of radioactivity recovered in the urine and feces to the microcuries of ^{14}C-olopatadine administered. Metabolites in plasma and urine were determined by fraction collection and radiochromatographic analyses.

Safety

Safety evaluations were assessed on all subjects who were enrolled into the study and received a single dose of study drug. The frequency and incidence of adverse events are summarized by body system for all subjects. The safety assessment also includes an evaluation of physical exam parameters, cardiovascular parameters (pulse, blood pressure, and electrocardiogram [ECGI), oral body temperature, and clinical laboratory parameters (hematology, blood chemistry, and urinalysis).

Statistical Methods

For PK, descriptive statistics, including the mean, standard deviation (SD), coefficient of variation (CV), standard error of the mean (SEM), sample size (N), minimum and maximum (max), were calculated for concentrations. The same statistical parameters plus 95% confidence intervals were calculated for PK parameters.

RESULTS

ADME Evaluation

Total Radioactivity Concentrations in Plasma and Whole Blood

Following a single oral administration of the ^{14}C-olopatadine solution, drug-related radioactivity was rapidly absorbed with peak total radioactivity in plasma observed within 0.5 to 1 hours after dosing. Following the peak, plasma total radioactivity concentrations declined in a biphasic manner (Figure 1).

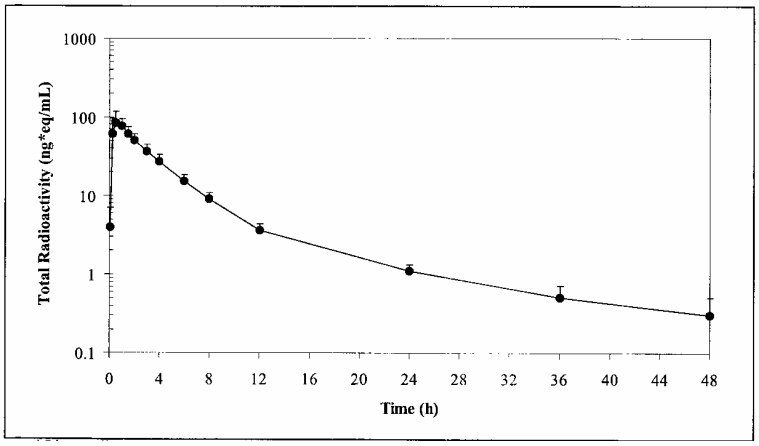


Figure 1. Mean ± SD plasma total radioactivity concentration (ng-eq/mL) after a single 5 mg oral dose of 14C-Olopatadine Hydrochloride solution (200 µCi).

Pharmacokinetic Parameters Based on Total Radioactivity

Individual and mean plasma total radioactivity pharmacokinetic parameters are presented in Table 1. The mean plasma Cmax was 89.1 ± 25.2 ng eq./mL and occurred at 0.59 ± 0.26 hours post-dose. Following the peak total radioactivity plasma levels declined in a biphasic manner with a mean elimination half-life of 7.92 ± 3.41 hours

Table 1. Individual and Mean ± SD Plasma Radioactivity Pharmacokinetic Parameters After a Single Oral Solution Dose of 5 mg ^{14}C-Olopatadine Hydrochloride (200 µCi)

Subject No.	Cmax (ng-eq/mL)	Tmax (h)	AUC_{0-t} (ng-eq*hr/mL)	AUC_0-inf (ng-eq*hr/mL)	$t_{1/2}$ (h)	CL/F (L/h)
101	(b) (4)		373.3	379.9	(b) (4)	13.10
102			279.4	283.0		17.67
103			466.9	472.0		10.53
104			324.6	340.8		14.67
105			330.3	336.5		14.86
106			391.8	394.6		12.67
107			278.6	284.7		17.56
108			227.2	233.9		21.38
Mean	89.1	0.59	334	340.7	7.9	15.3
SD	25.2	0.26	75.5	75.2	3.4	3.4
CV%	283	45	22.7	22.1	43	22
N	8	8	8	8	8	8
Min	(b) (4)		227 2	233.9	(b) (4)	10.6
Max			466.9	472		21.4

Excretion and Recovery of Radioactivity

Urinary Excretion

Figure 2 shows that urinary excretion of total radioactivity was fairly rapid with 30.4 ± 5.4 % of the dose recovered during the first collection (0-2 hour) interval. The majority of the cumulative recovery (% dose) of radioactivity in urine was within 12 hours (64.1 ± 4.8%). Beyond 132 hours post-dose, no further radioactivity was recovered in the urine. The cumulative total recovery of radiolabeled material in the urine accounted for 70.5 ± 2.6% (range 66.5 to 73.3%) of the dose.

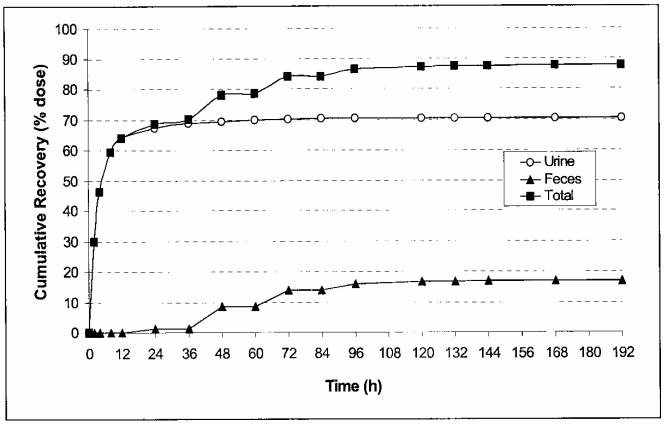


Figure 2. Mean Cumulative Recovery (% dose) of Total Radioactivity after a Single Oral Dose of '^{4}C-Olopatadine Hydrochloride Solution

Fecal Excretion

The recovery of radioactivity in feces during the first collection (0-24 hours) was low ranging from 0 to 4.2% (mean 1.6 ± 1.2%) of the dose in the 8 subjects (Figure 2). Over the 24-hour collection periods on subsequent days, the cumulative recovery of radioactivity in the feces increased to 17.0 ± *5.7%* (range 11.0 to 27.8%). Beyond 168 hours, no further radioactivity was recovered in feces.

Total Recovery

The individual cumulative recovery in urine and feces over the study period are presented in Table 2. The overall mean total recovery of radioactivity in the urine and feces accounted for 87.5 ± 6.0% of the dose (range 81.6 to 100.4%, N8).

Table 2. Individual and Mean ± SD Cumulative Recovery of Total Radioactivity in Urine, Feces and Combined (Total) Following an Oral ^{14}C Olopatadine Dose, C-03-10

	Cumulative Urine		**Cumulative Feces**		**Cumulative Total**
Subject Number	**Ae (µg)**	**% Dose**	**Ae (µg)**	**% Dose**	**% Dose**
101					(b) (4)
102					
103					
104					
105					
106					
107					
108					
Mean	3493.3	70.5	841.7	17.0	87.5
SD	137.1	2.6	279.7	5.7	6.0
Min					(b) (4)
Max					

Radiochromatographic Profiles of Olopatadine Metabolites

Radiochromatographic analysis of plasma samples obtained at 0.5, 3 and 8 hours showed the presence of 7 peaks labeled Mpl through Mp7 based on order of elution. Olopatadine was the primary component in plasma at each time point, representing about 77% of the total radioactivity in the 0.5 hour (peak total radioactivity) sample (Table 3). There were at least 6 metabolites in plasma, including Ml and M3. All the metabolites in plasma were minor, accounting ≤3.5% of the peak total radioactivity and in total representing <10% of the total radioactivity. At the 8 hour time point, only olopatadine and Ml were quantifiable (Table 3).

Table 3. Mean ± SD Plasma Total Radioactivity and Concentrations (ng eq./mL) at Selected Time points After a 5 mg ^{14}C-Olopatadine HCI Solution in Healthy Subjects

Peak	Component[a]	**Concentration (ng eq/mL) and Percent of Total Radioactivity (%)**								
		0.5 Hours			3 Hours			8 Hours		
		Mean	SD	%	Mean	SD	%	Mean	SD	%
	Total Radioactivity[b]	84.8	31.1	Ref	36.9	8.0	Ref	9.1	1.7	Ref
Mpl	Unidentified	1.63	0.66	1.9	0.86	031	2.3	BLQ	DLQ	ND
Mp2	Unidentified[c]	1.34	0.57	1.6	0.84	0.27	2.3	BLQ	BLQ	ND
Mp3	N-Desmethyl Olopatadine[d]	3.01	1.66	3.5	2.29	0.62	6.2	0.72	0.19	8.0
Mp4	Olopatadine	65.5	24.1	77.2	24.2	3.97	65.6	5.62	1.02	62.1
Mp5	Olopatadine N-Oxide	1.31	0.38	1.5	0.71	0.16	1.9	BLQ	BLQ	ND
Mp6	Unidentified	BLQ	BLQ	ND	0.68	0.20	1.8	BLQ	BLQ	ND
Mp7	Unidentified	1.39	0.35	1.6	0.71	0.23	1.9	BLQ	BLQ	ND

SD: Standard Deviation

BLQ: Below Limits of Quantitation (less than 0.34 ng eq/mE)

ND: Not determined since metabolite was below limit of quantitation. Ref: Reference concentration for calculation of olopatadine and metabolite percentages. [a]identification of component in plasma based on retention time to authentic standards.

[b]Source: Study C-03-10, Alcon Clinical Study Report No.: TDOC 0001414; [c]Retention time corresponds to N-didesmethyl olopatadine standard. However, peak was not well resolved and presence of this compound at these levels is inconsistent with results of other clinical studies.

[d]Concentration may be an overestimate due to co-elution of other radioactive material under peak.

Metabolic profile analysis of the urine samples at the 6 collection periods showed the presence of olopatadine and its two identified metabolites (Ml and M3) with parent drug accounting for the majority (about 86%) of the total radioactivity recovered within 24 hours post-dose. Metabolites Ml and M3 were minor, accounting for less than 7% of the dose recovered within 24 hours.

SUMMARY

- ^{14}C-Olopatadine was readily absorbed following oral administration of the 0.2% solution. Maximum plasma concentrations of total radioactivity were generally reached in approximately 0.5 hour.
- Radioactivity was eliminated from plasma with a mean half-life of 7.94 hours.
- Over the entire 192-hour postdose interval, an average of 17.0% of the radioactive dose was recovered in feces and 70.5% was recovered in urine, resulting in a cumulative total of 87.5% radioactivity recovery.
- The majority of the cumulative % dose of radioactivity was recovered in the first 24 hours (67.4%) In the urine, and in the first 96 hours (16.0%) in the feces.

CONCLUSIONS

- Unchanged olopatadine was the major component of radiolabeled material in plasma and urine.
- Olopatadine Ml, M2 and M3 metabolites accounted for less than 10% of circulating radioactivity in plasma.
- Urinary excretion was the major pathway of elimination of radioactivity with the majority recovered as unchanged olopatadine.
- Together, urinary excretion of Ml and M3 for about 7% of radiolabeled material recovered in the urine within 24 hours.
- Identified and unidentified metabolites only accounted for <10% of the total radioactivity in urine.

COMMENTS

a) Validation of the analytical methods used to assess total radioactivity, radiolabeled drug, unlabeled drug and metabolites in urine and feaces is not provided in this NDA submission.

"Effects of Olopatadine, a New Antiallergic Agent, on Human Liver Microsomal Cytochrome P450 Activities"

Objective

- to identify the cytochrome(s) P450 involved in the metabolism of olopatadine and to determine the potential of olopatadine to inhibit the human cytochromes P450 enzymes.

Materials

Analytes and Chemicals

(b) (4)

Preparation of Hepatic Microsomal Fractions. Male Wistar rats (7 weeks old) were obtained from (b) (4) and were held in cages under constant temperature and lighting (12-h light/dark cycle). Rats were killed under ether anesthesia and washed hepatic microsomes were isolated by differential ultracentrifugation (Guengerich et al., 1994). Microsomal fractions were resuspended in 10 mM potassium phosphate, pH 7.4, containing 20% glycerol and 0.1 mM EDTA and were stored at −80°C until required for experiments.

Incubation Conditions. Preliminary results indicated that the rate of formation of M1 and M3 at 10 µM olopatadine was linear at 37°C for an incubation time of up to 1 h and for a microsomal protein concentration up to 2 mg/ml. More than 90% of the initial amount of olopatadine remained after 2-h incubation with 2 mg protein/ml. The concentration of 10 µM olopatadine was chosen for these in vitro incubations because this was the maximum plasma concentration achieved in a phase I clinical study, and also because of a low limit of quantitation for M1 and

M3. [^{14}C]Olopatadine (10 µM, 6.7 kBq/ml final concentration) was incubated with liver microsomes (1 mg protein/ml final protein concentration) in phosphate buffer (100 mM, pH 7.4) at 37°C. For structural elucidation of olopatadine metabolites by HPLC with tandem mass spectrometry (LC/MS/MS), samples were prepared by extracting a large-scale incubation (12.5 ml) using a (b) (4) cartridge (b) (4)

For metabolism by recombinant P450 and FMO expression systems, [^{14}C]olopatadine (10 µM, 6.7 kBq/ml) or olopatadine (10 µM) was incubated with a NADPH-generating system in phosphate buffer, pH 7.4, at 37°C. Reactions were initiated by addition of microsomes of recombinant P450 or FMO (1 mg protein/ml) at 37°C. All incubations were conducted in duplicate and the duplicate values agreed within 85 to 115% of each other; the results are presented as the mean of the duplicate data.

Effects of Enzyme Inhibitors and Activators on the Formation of M1 and M3. To determine the effect of compounds on the metabolism of olopatadine, [^{14}C]olopatadine (10 µM, 6.7 kBq/ml), enhancers or inhibitors, microsomes (1 mg/ml), and NADPH-generating system were mixed and incubated at 37°C for 1 h in a final volume of 100 µl. In the cases of furafylline, diethyldithiocarbamate, troleandomycin, SKF-525A, *N*-octylamine, and thiourea, the mixture of microsomes and these compounds was preincubated in the presence of a NADPH-generating system at 37°C for 15 min and then the reaction was initiated by addition of [^{14}C]olopatadine. The concentration of added compounds was 10 µM except for *N*-octylamine, which was added at 100 µM. All inhibitors were dissolved in methanol; the final concentration of methanol was 1.0 vol% in the reaction mixture.

Effects of Olopatadine on P450 Isozyme-Specific Activities. The effect of olopatadine on the activity of all P450 enzymes was examined using two different incubation methods. A pretreatment method was used to estimate the metabolism-dependent inhibition, e.g., suicidal inhibition, and a simultaneous incubation method was used to assess metabolism-independent inhibition (e.g., competitive inhibition). The following activities were measured for the respective P450 isozymes: phenacetin *O*-deethylation for CYP1A2 (phenacetin concentration; 100 µM), tolbutamide methylhydroxylation for CYP2C8/9 (tolbutamide concentration; 500 µM), *S*-mephenytoin 4'-hydroxylation for CYP2C19 (*S*-mephenytoin concentration; 200 µM), bufuralol 1'-hydroxylation for CYP2D6 (bufuralol concentration; 100 µM), chlorzoxazone 6-hydroxylation for CYP2E1 (chlorzoxazone concentration; 500 µM), and testosterone 6β-hydroxylation for CYP3A4 (testosterone concentration; 250 µM). In the preincubation method, incubation of olopatadine was carried out in the presence of the NADPH-generating system at 37°C for 30 min before the addition of the specific probe substrates. In the simultaneous incubation method, olopatadine was added with the specific probe substrates to the microsomal incubation mixture and then the reaction was initiated by addition of the NADPH-generating system.

RESULTS

Olopatadine Metabolism. Two different metabolites, M1 and M3, were formed when olopatadine was incubated with human liver microsomes in the presence of an NADPH-generating system: after 1-h incubation, M1 and M3 accounted for 5.2 and 30.5% of the initial olopatadine, respectively. Structural information for these metabolites was obtained by LC/MS/MS analysis with electrospray ionization (ESI). M1 and M3 were identified tentatively as *N*-monodemethylolopatadine and olopatadine *N*-oxide, respectively, and this assignment was confirmed by demonstrating that these metabolites had identical retention times and mass spectra to the respective authentic standards. The formation of both M1 and M3 by human liver microsomes was found to be NADPH-dependent, and the formation rate of M1 and M3 was 0.330 and 2.50 pmol/min/mg protein, respectively. Kinetic parameters could not be calculated for the metabolites, because only low amounts of the metabolites were formed. In addition, M3 was reduced to olopatadine during incubation with human liver microsomes in the presence of NADPH under aerobic condition (data not shown). Therefore, according to the sponsor, the kinetic parameters could not be calculated accurately.

After oral administration of [^{14}C]olopatadine to rats and dogs, the main metabolic pathways were 1) *N*-demethylation to M1 and M2, the *N*-monodemethyl and *N*-didemethyl analogs, respectively; 2) hydroxylation of dihydrodibenz[*b*,*e*]oxepin ring (M5); and 3) sulfoconjugation of M5 (M4) and *N*-oxidation (M3) (Fig.1). After oral administration of olopatadine to human subjects, the metabolites detected in plasma were M1 and M3, but the areas under the plasma concentration-time curve of both M1 and M3 were lower than that of unchanged drug.

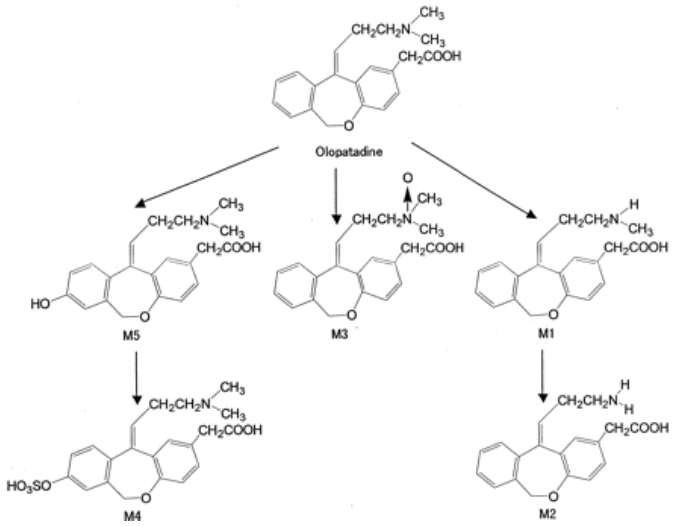


Fig. 1. Proposed metabolic pathway of olopatadine.

Inhibition of olopatadine Metabolism with Form-Selective P450 Inhibitors

Selective inhibitors of P450 isozymes were used in this study to determine the potential roles of P450 isozymes in the formation of M1 and M3 (Fig. 2). SKF-525A, a nonspecific inhibitor of P450, and both troleandomycin and ketoconazole, which are inhibitors of CYP3A,

markedly inhibited M1 formation. Selective inhibitors of other P450 enzymes, furafylline, sulfaphenazole, tranylcypromine, quinidine, and diethyldithiocarbamate, had little effect on M1 formation. However, according to the sponsor, none of the P450 inhibitors had significant effects on the formation of M3. In addition, the effects of *N*-octylamine and thiourea on the formation of M1 and M3 were examined (Fig. 2). M1 formation was inhibited by *N*-octylamine and thiourea but M3 formation was enhanced by *N*-octylamine and inhibited by thiourea, suggesting that M3 was formed by FMO.

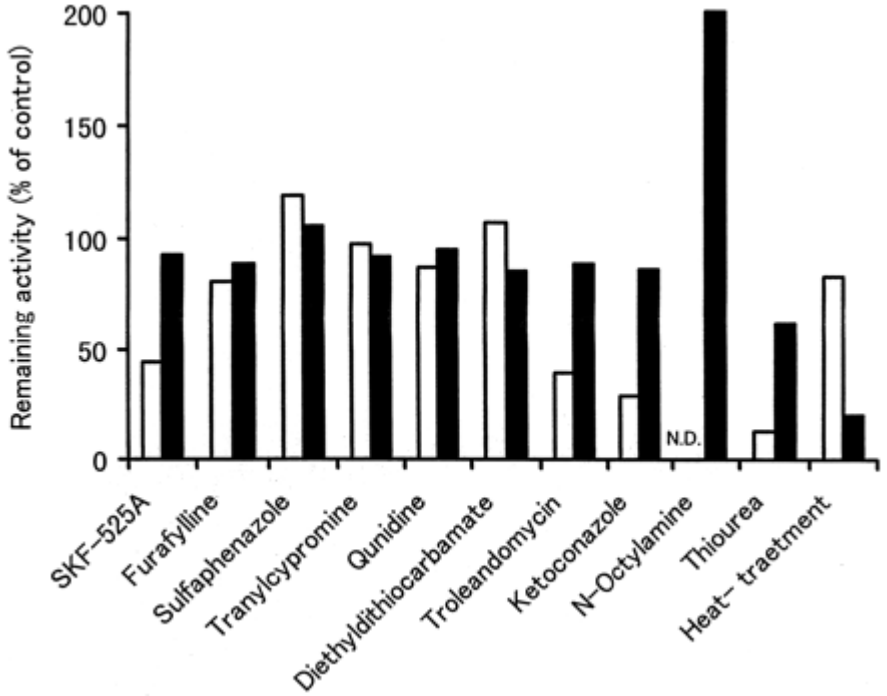


Fig. 2 **Effects of various compounds on M1 (□) and M3 (■) formation by human liver microsomes.**

There was little difference in M1 formation by human liver microsomes treated without and with mild heat (45°C for 2 min); however, mild heat treatment of microsomes markedly lowered M3 formation (Fig. 3). Because, in contrast to P450, FMO is heat-labile these data provide further evidence that M3 formation is catalyzed by FMO.

The formation of M1 and M3 catalyzed by specific human P450 isozymes and FMO is shown in Fig. 2. The velocity of M1 formation by CYP3A4 was 0.00242 nmol/min/nmol P450. CYP1A2 generated small amounts of M1, but CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and FMO did not catalyze M1 formation. The velocities of M3 formation by FMO1 and FMO3 were 0.815 and 0.215 pmol/min/mg protein, respectively. The velocities of M3 formation by CYP1A2, CYP2B6, and CYP2E1 were less than one-fourth of the rate catalyzed by FMO3. The other P450 isozymes, CYP2A6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, did not form M3.

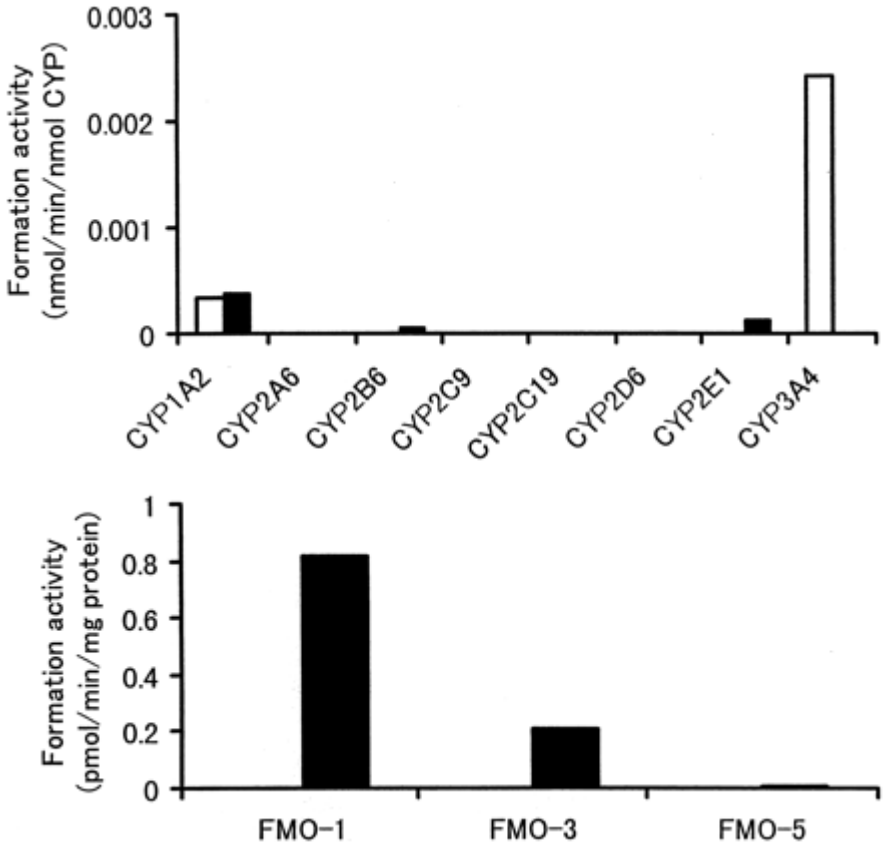


Fig. 3. **Formation of M1 (□) and M3 (■) by microsomes from cells expressing the specified recombinant P450 and FMO isozymes.**

SUMMARY OF FINDING

- Olopatadine is metabolized to two metabolites, M1 (*N*-monodemethylolopatadine) and M3 (olopatadine *N*-oxide) at rates of 0.330 and 2.50 pmol/min/mg protein, respectively.
- Troleandomycin and ketoconazole, which are both selective inhibitors of CYP3A, significantly reduced M1 formation but specific inhibitors of other P450 isozymes did not decrease M1 formation.
- Incubation of olopatadine with cDNA-expressed human P450 isozymes confirmed that M1 formation was almost exclusively catalyzed by CYP3A4.
- The formation of M3 was enhanced by *N*-octylamine and was inhibited by thiourea.
- High specific activity of M3 formation was exhibited by cDNA-expressed flavin-containing monooxygenase FMO1 and FMO3.

"Study of Drug Interaction (by olopatadine) in Human Liver Microsones"

Protocol No.: PKDM 586
Technical Report No.: 0:33:0400

Objective

- to determine the potential of olopatadine to inhibit the human cytochromes P450 1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4.

Methods

The effect of olopatadine on the activity of all P450 enzymes was examined using two different incubation methods. A pretreatment method was used to estimate the metabolism-dependent inhibition, e.g., suicidal inhibition, and a simultaneous incubation method was used to assess metabolism-independent inhibition (e.g., competitive inhibition). The following activities were measured for the respective P450 isozymes: phenacetin *O*-deethylation for CYP1A2 (phenacetin concentration; 100 µM), tolbutamide methylhydroxylation for CYP2C8/9 (tolbutamide concentration; 500 µM), *S*-mephenytoin 4'-hydroxylation for CYP2C19 (*S*-mephenytoin concentration; 200 µM), bufuralol 1'-hydroxylation for CYP2D6 (bufuralol concentration; 100 µM), chlorzoxazone 6-hydroxylation for CYP2E1 (chlorzoxazone concentration; 500 µM), and testosterone 6β-hydroxylation for CYP3A4 (testosterone concentration; 250 µM). In the preincubation method, incubation of olopatadine was carried out in the presence of the NADPH-generating system at 37°C for 30 min before the addition of the specific probe substrates. In the simultaneous incubation method, olopatadine was added with the specific probe substrates to the microsomal incubation mixture and then the reaction was initiated by addition of the NADPH-generating system.

Olopatadine was incubated at concentrations of 0 (control) to 100 mcM (33900 ng/mL). Selective inhibitors for each specific CYP isozyme, furafylline (CYP1A2), sulfaphenazole (CYP2C8-9), tranylcypromine (CYP2C19), quinidine (CYP2D6), diethyldithiocarbamate (CYP2EI) and ketoconazole (CYP3A4) were also incubated with the human liver microsomes to serve as positive controls.

Materials

Analytes and Chemicals

Olopatadine, lot No.P-O0S, which was used for this study, had been synthesized at the (b) (4) (b) (4) were purchased from (b) (4) (b) (4) from (b) (4) (b) (4) from (b) (4) (b) (4) from (b) (4) (b) (4) from (b) (4) (b) (4) (b) (4) (b) (4) and (b) (4) from (b) (4).

Human liver microsomes (lot HHM-0121) from were obtained from (b) (4) through (b) (4) The donor information of human liver microsomes is shown in Table 1. The other reagents and solvents used were commercially available and analytical grade reagents.

Table 1. Donor information of human liver microsomes

Donor No.	Age	Race	Sex
(b) (6)		Black	Femal
		Black	Male
		Black	Male
		Black	Femal
		Black	Male
		Black	Femal

RESULTS

Figures 1 through 6 showed the influence of olopatadine on the metabolism of known substrates for the enzymes evaluated. Olopatadine did not appear to affect the activity of the enzymes tested. Therefore, it can be concluded that olopatadine does significantly inhibit the activity of major CYP450 enzymes. Activities are expressed as a percentage relative to the control experiment. The control activities of phenacetin *O*-deethylation, tolbutamide methylhydroxylation, *S*-mephenytoin 4'-hydroxylation, bufuralol 1'-hydroxylation, chlorzoxazone 6-hydroxylation, and testosterone 6β-hydroxylation were (b) (4) pmol/min/mg protein, respectively. Values are the mean of two incubations.

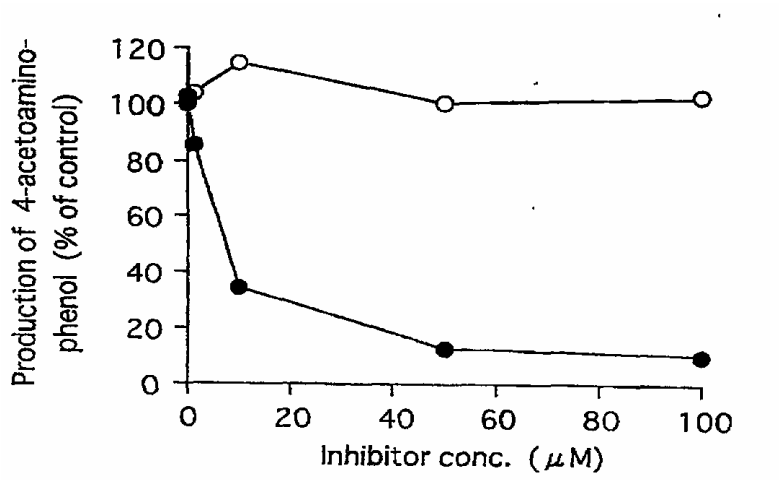


Figure 1. Inhibitory effects of olopatadine (open circle) and furafylline (closed circle) on the phenacetin O-deethylation by human liver microsomes.

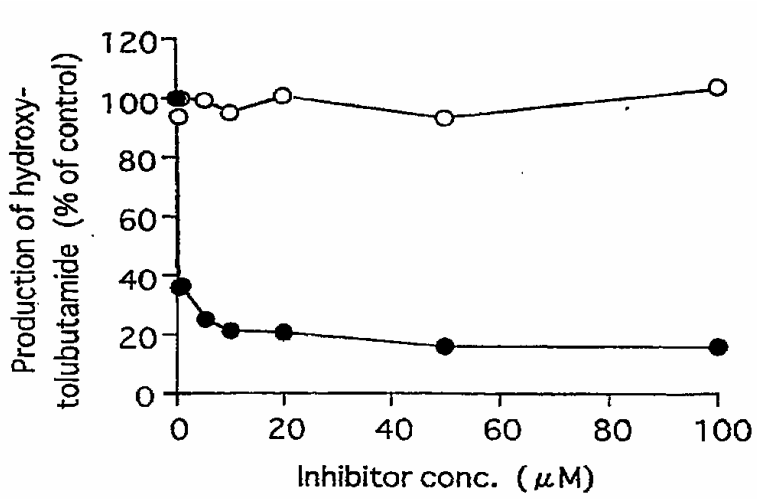


Figure 2. Inhibitory effects of olopatadine (open circle) and sulfaphenazole (closed circle) on the tolbutamide hydroxylation by human liver microsomes.

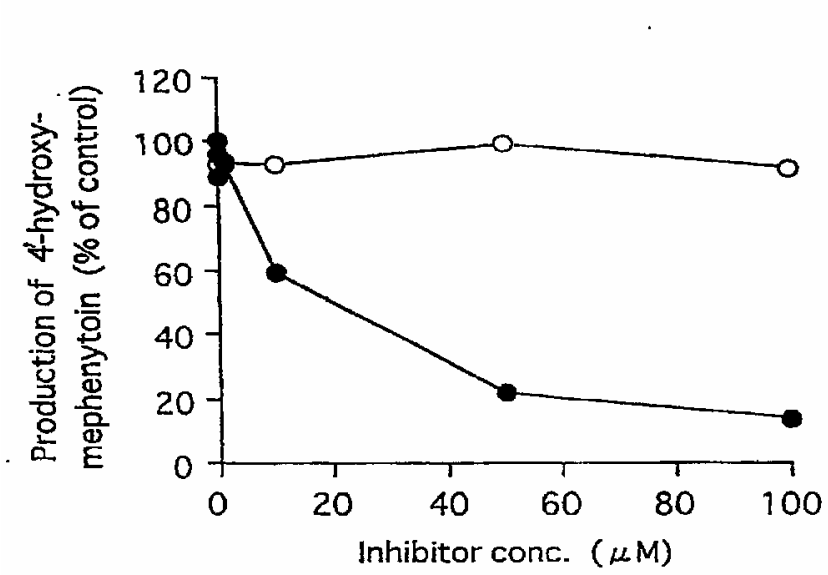


Figure 3. Inhibitory effects of olopatadine (open circle) and tranylcypromide (closed circle) on the S-mephenytoin 4'-hydroxylation by human liver microsomes.

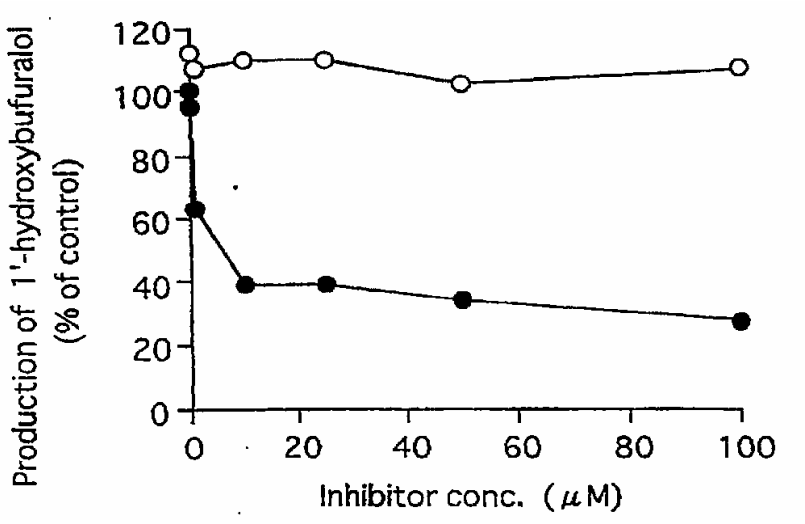


Figure 4. Inhibitory effects of olopatadine (open circle) and quinidine (closed circle) on bufuralol 1'-hydroxylation by human liver microsomes.

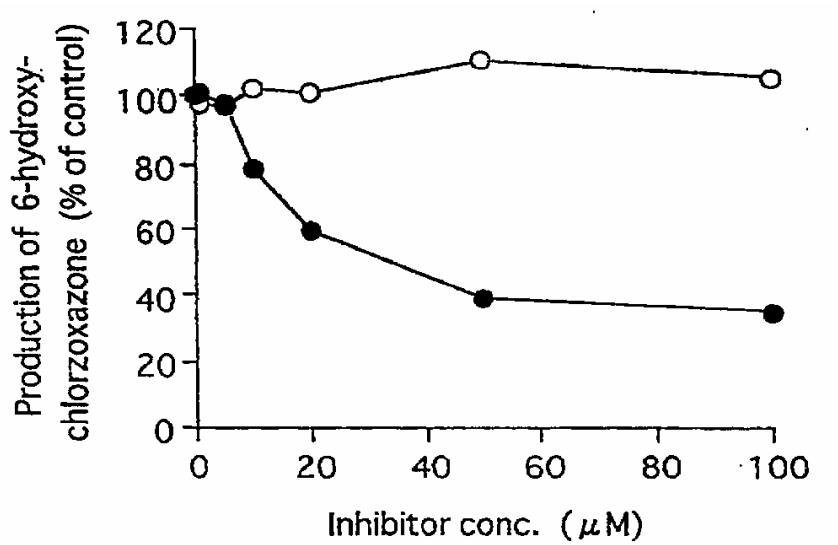


Figure 5. Inhibitory effects of olopatadine (open circle) and diethyldithiocarbamate (closed circle) on chlorzoxazone 6-hydroxylation by human liver microsomes.

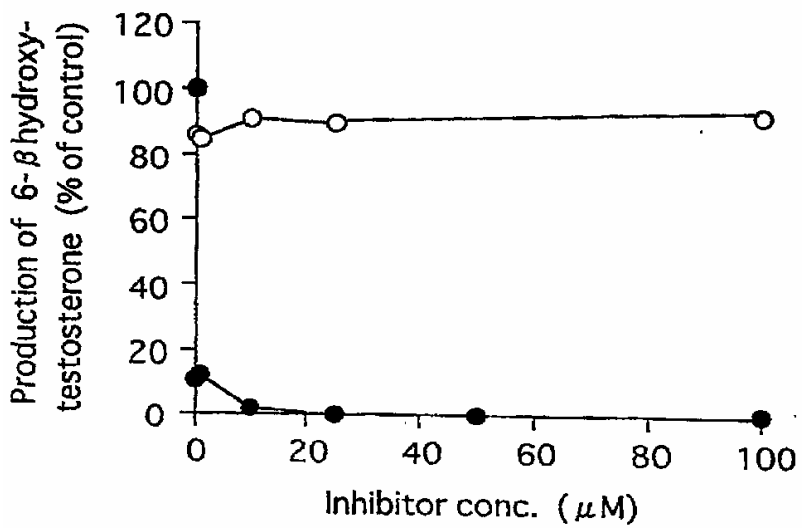


Figure 6. Inhibitory effects of olopatadine (open circle) and ketoconazole (closed circle) on testosterone 6β-hydroxilation by human liver microsomes.

Conclusions

- Olopatadine did not show significant inhibition of any of the P450 activities investigated in human liver microsomes.

Reviewer's Comments

- Olopatadine has a molecular weight of 343.4. The IC50 value exceeded 100 μM (33900 ng/mL), much higher than the highest concentrations achieved clinically (a dose of 0.6% corresponds to a concentration range of 1.856 to 2.665 μg/mL). Thus, the concentrations used in this study were at least 14 times the minimum concentrations achieved *in vivo*.
- Optimal substrate, inhibitor and substrate and inhibitor concentrations were used for preferred substrate reactions in this study.
- The potential induction properties of the drug and its metabolites were not evaluated in vitro.

"*IN VITRO* PROTEIN BINDING OF OLOPATADINE"

Clinical Study Report no.: 07038570:0995

Objectives

- to determine the in vitro protein binding of olopatadine in human serum albumin.

METHODS AND RESULTS

The *in vitro* protein binding of Olopatadine was determined by equilibrium dialysis using human serum albumin (HSA), rat serum albumin (RSA) and bovine serum albumin (HAS). The effect of pH on the protein binding of ^{14}C-olopatadine was investigated in BSA at pH 6, 7 and 8. Equilibrium dialysis conditions were 3 hr at pH 7.4 at 37°C. The unbound fraction was calculated by radioactivities in the albumin solution and in the buffer after equilibrium. Radioactivity was measured using liquid scintillation counter.

Because of variability in olopatadine binding to RSA of different lot numbers, the free fatty acid (non-esterified fatty acids or NEFA) concentrations in the different lots of RSA were measured and compared to the binding of olopatadine.

The amount of unbound (free) (b) (4)-4679 in 4% human serum albumin increased from 49% to 59% over the concentration range of 1 mcg/mL to 2.0 x 103 mcg/mL (Table 1). The number of binding sites for HSA were calculated to be 6.97 and the binding site association constant (Ka) was 2.40 x 10 M-^{1} (Table 2). The amount of unbound olopatadine in 4% bovine serum albumin decreased as the pH increased over the concentration range of 1 mcg/mL to 2.0 x 103 mcg/mL. The change in binding was primarily attributed to a change of affinity at the high affinity binding site, i.e., as pH increased, the affinity of the high affinity binding site increased. A species difference in the high affinity binding was noted between HSA and BSA.

Free fatty acids in RSA affected the binding of olopatadine (100 mcg/mL). As the concentration of free fatty acids in 4% RSA increased, the amount of olopatadine bound decreased.

Table 1. Unbound fraction of 14C-olopatadine in human serum albumin (HAS) solution (4%)

D (mcg/mL)	Ct (mcg)	fu
1	1.78	0.49
25	4.46 x 10	0.489
50	8.82 x 10	0.509
100	1.77×10^2	0.503
20	3.51×10^2	0.516
300	5.27×10^2	0.514
500	8.7×10^2	0.529
700	1.21×10^2	0.536
1000	1.71×10^2	0.553
2000	3.35×10^2	0.590

D: Initial 14C-olopatadine concentration of HAS side
Ct: Final 14C-olopatadine concentration of HAS side
Fu: unbound fraction

Table 2. Binding parameters of 14C-olopatadine to human serum albumin

n	Ka (h^{-1})	n*Ka (h^{-1})
6.97	2.40×10^2	1.67×10^3

GENERAL COMMENTS

1. The total compound recovery from the equilibrium dialysis system beyond 3 hrs is not reported; thus, it is not known if equilibrium was reached at this time. Therefore, the results of protein binding from this study should be interpreted with caution.

"Single-Dose Study Following Intranasal Administration of Olopatadine 0.6% in Healthy Subjects"

Protocol No.: C-02-21
Technical Report No.: 0001383

Objective

- to determine safety and the single dose pharmacokinetics of olopatadine hydrochloride nasal spray 0.6% in healthy volunteers.

Study Design and Methods

The safety and systemic exposure of olopatadine using the pump and concentration intended for market was examined in a single center, double-masked, placebo-controlled, randomized, parallel-group study. Twelve healthy, adult, male and female subjects were randomized to receive either a single intranasal dose (two 100 mcL sprays per nostril) of olopatadine vehicle (N=4) or Olopatadine Nasal Spray, 0.6% (N=8). Based on the nominal volume, 0.6% concentration and replicate sprays, the delivered dose was 2.4 mg. Serial plasma samples were collected up to 12 hours post-dose and measured for olopatadine using a validated HPLC/MS/MS method with a LOQ of 0.050 ng/mL.

RESULTS

Figures 1 shows the mean olopatadine plasma concentrations following single administration of olopatadine 0.6% to healthy volunteers. Table 1 summarizes the mean olopatadine pharmacokinetic parameters. Across the 8 subjects, peak olopatadine plasma concentrations varied from 13.6 to 58.4 ng/mL and averaged 29.3 ± 15.1 ng/mL.

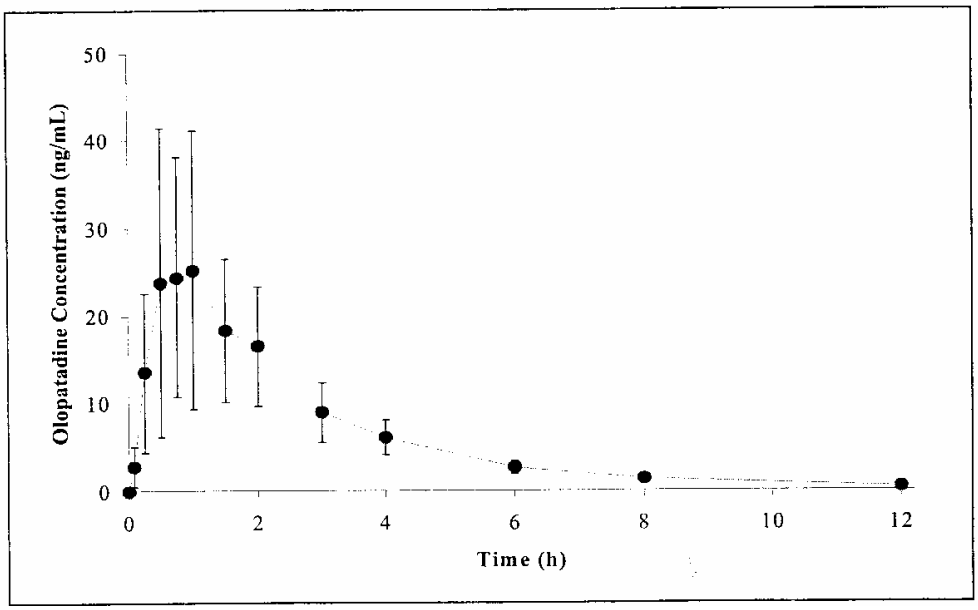


Figure 1. Mean olopatadine plasma concentrations (ng/mL) profiles after single intranasal dosing of olopatadine nasal 0.06 % in healthy subjects.

Table 1. Mean ± SD (range) Olopatadine Pharmacokinetic Parameters in Healthy Subjects after Single Intranasal Dose of 0.6%

Subject Number	Gender	Cmax (ng/mL)	Tmax (h)	AUC_{0-12} (ng•h/mL)
102	Female	(b) (4)		90.1
103	Female			99.4
104	Female			70.3
106	Female			126
202	Male			57.9
203	Male			53.9
205	Male			71.4
206	Male			31.8
Mean		29.3	0.97	75.1
SD		15.1	0.54	29.4
N		8	8	8
Mm		(b) (4)		31.8
Max				126

Conclusions

- Following single intranasal administration of the highest clinical dose (0.6%) used in Phase III trials, the Cmax and AUC0-12h of olopatadine were 29.3 ng/mL (±15.1) and 75.1 ng*hr/mL (±29.4), respectively.

General Comments

- The pharmacokinetics of the major metabolites were not assessed.
- AUCinf was not reported

"Single-Dose Absolute Bioavailability Study of intranasal Olopatadine 0.4% and 0.6% versus Olopatadine IV infusion in Healthy Subjects"

Protocol No.: C-03-11
Technical Report No.: 0001417

Objective

- to determine the absolute BA of olopatadine following intranasal administration.

Study Design and Methods

The absolute bioavailability of olopatadine using the pump and two concentrations studied in clinical efficacy studies was examined in a single center, open-label, randomized, crossover study. Twelve healthy, adult, male and female subjects were randomized to receive either a single intranasal dose (two 100 mcL sprays per nostril) of Olopatadine Nasal 0.4% (1.6 mg) or Olopatadine Nasal 0.6% (2.4 mg) or a single intravenous infusion of Olopatadine solution (1.5 mg) delivered over 30 minutes. Serial plasma samples and urine collections were obtained out to 48 hours post-dose and measured for olopatadine and its minor metabolites (Ml, M2, M3) using a validated HPLC/MS/MS method with a LOQ of 0.050 ng/mL for olopatadine, Ml and M3 and 0.250 ng/mL for M2.

RESULTS

Figures 1 shows the mean olopatadine plasma concentrations following single administration of the treatments to healthy volunteers. Table 1 summarizes the mean olopatadine pharmacokinetic parameters.

Peak plasma concentrations increased in proportion to the intranasal dose averaging 12.5 ± 6.1 ng/mL and 17.5 ± 6.7 ng/mL for Olopatadine Nasal 0.4% and olopatadine Nasal 0.6%, respectively (Table 1). Similar dose-proportional increases were seen in mean AUC values. Elimination half-lives ranged considerably across the 11 subjects within each treatment. Mean t1/2 values ranged 6 to 10 hours across treatments.

Cumulative urinary recovery of unchanged olopatadine accounted for 61.5 ± 16.7% of the intravenous dose. Cumulative recoveries of olopatadine over the 48-hour collection period were dose-related for the two intranasal treatments (Table 1). For all three treatments, the majority of unchanged olopatadine was excreted in the urine within 8-12 hours post-dose.

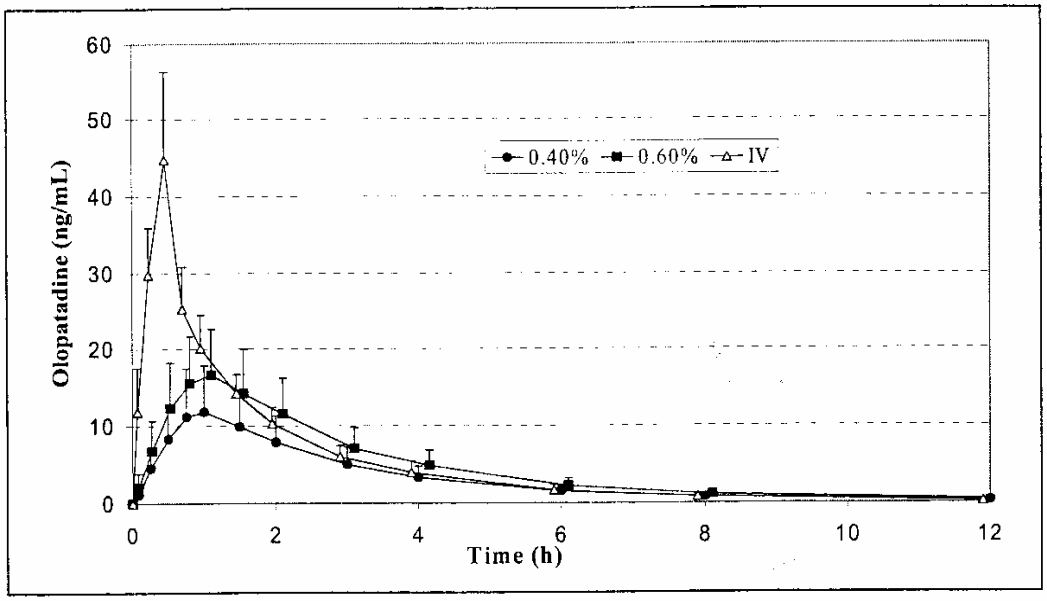


Figure 1. Mean olopatadine plasma concentrations (ng/mL) profiles after single intranasal dosing of olopatadine nasal 0.04 % and 0.06 % and single 1.5 mg IV infusion in healthy subjects.

Table 1. Mean ± SD (range) Olopatadine Pharmacokinetic Parameters in Healthy Subjects after Single Intranasal Dose of 0.6%

Parameter	**Olopatadine Nasal 0.4% (1.6 mg) (N=11)**	**Olopatadine Nasal 0.6% (2.4 mg) (N=11)**	**Olopatadine LV Infusion (1.5 mg) (N=11)**
Cmax (ng/mL)	12.5 ± 6.1 (1.98-20.7)	17.5 ± 6.7 (6.37-27.6)	44.8 ± 11.5 (30.8-63.7)
Tmax (h)	1.04 ± 0.24 (0.75-1.50)	1.05 ± 0.31 (0.75-1.50)	0.50 ± 0.01 (0.49-0.52)
AUC0-inf (ng*h/mL)	45.7 ± 15.3 28.2-67.7)	61.8 ± 30.8 (21.1-101)	68.2 ± 13.6 (50.6-95.3)
T1/2 (h)	8.65 ± 5.67 (1.75-17.9)	10.0 ± 5.7 (3.2-22.2)	6.12 ± 9.34 (2.1-33.2)
Ae0-48h (ug)	558± 202 (283-813)	871±305 (387-1324)	922±251 (483-1 195)
Ae (% dose)	34.9± 12.6 (17.7-50.8)	36.3 ± 12.7 (16. 1-55.2)	61.5 ± 16.7 (32.2-79.6)
CLr (L/h)	12.8 ± 5.0 (6.7-193)	14.8 ± 4.5 (8.8-21.7)	13.8 ± 4.0 (7.7-20.8)
F (AUC) (%)	61.3 ± 20.8 (30.9-87.5)	56.6 ± 17.3 (26.0-83.6)	Reference
F (Ae) (%)	57[a]	59 [a]	Reference

[a]Ratio of dose-adjusted mean $Ac_{0\text{-}48}$ values

M1 metabolite Pharmacokinetics

Figures 2 shows the mean metabolite M1 plasma concentrations following single administration of the treatments to healthy volunteers. Table 2 summarizes the mean M1 pharmacokinetic parameters.

Mean plasma concentrations of Ml following intranasal administration of Olopatadine Nasal **0.4%** and 0.6% were dose-related, but did not increase proportionally to the dose (Figure 2*)*. Quantifiable plasma concentrations of Ml were observed out to 8 hours in some subjects for all 3 treatments. Mean Cmax values increased greater than in proportion to the intranasal dose. Mean AUC values did not increase with dose. The mean estimated half-life of Ml ranged from approximately 3-6 hours.

Cumulative urinary recovery of Ml was low, accounting for 0.8% of the intravenous olopatadine dose (Table 2).

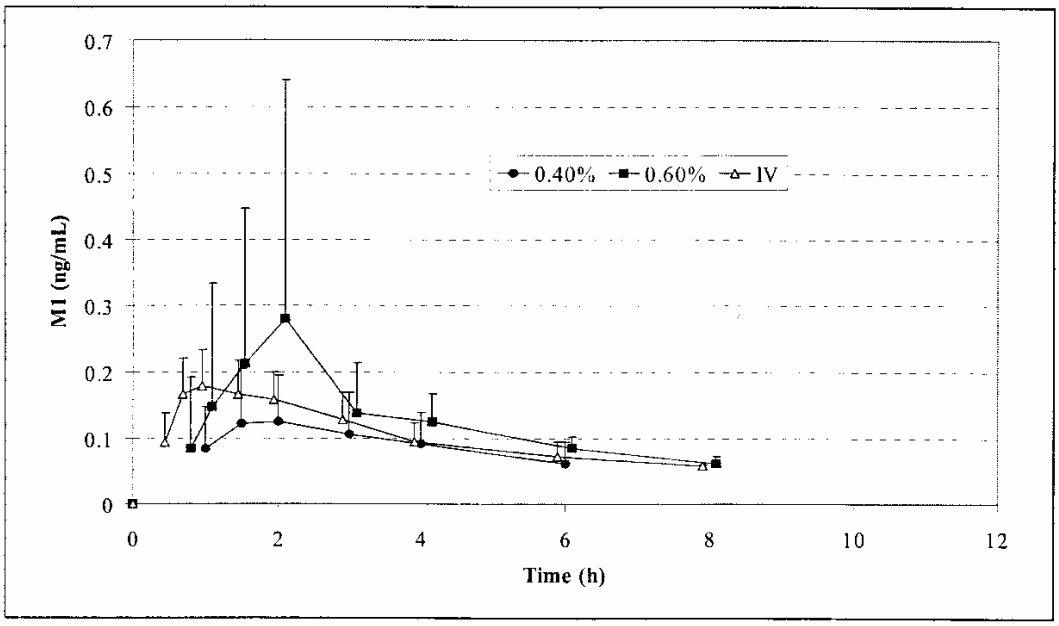


Figure 2. Mean M1 plasma concentrations (ng/mL) profiles after single intranasal dosing of olopatadine nasal 0.04 % and 0.06 % and single 1.5 mg IV infusion in healthy subjects.

Table 2. Mean ± SD (range) M1 Pharmacokinetic Parameters in Healthy Subjects after Single Intranasal Dose of 0.6%

Parameter	Olopatadine Nasal 0.4% (N=l1)	Olopatadine Nasal 0.6% (N=11)	Olopatadine IV Infusion (1.5 mg) (N=11)
Cmax (ng/mL)	0.138 ± 0.067 (0.0637-0.241)	0.344 ± 0.398 (0.0800-1.34)	0.184 ± 0.053 (0.108-0.253)
Tmax (h)	4.8 ± 10.3 (1.50-36.0)	1.82 ± 0.34 (1.00-2.04)	1.16 ± 0.36 (0.77-2.00)
AUC 0-inf (ng*h/mL)	1.11 ± 0.40 (0.57-1.83)	1.17 ± 0.36 (0.71-1.69)	0.94 ± 0.25 (0.71-1.38)
T1/2 (h)	5.50 ±4.60 (2.48-13.6)	3.73 ± 1.81 (2.25-7.63)	2.96±0.86 (1.81-4.46)
Ae (ug)	9.11 ± 5.96 (2.75-21.1)	11.53 ± 5.70 (2.61-22.8)	11.28 ± 5.10 (4.53-21.4)
Ae (% dose)	0.6 ± 0.4 (0.2-1.3)	0.5 ± 0.2 (0.1-0.9)	0.8 ± 0.3 (0.3-1.4)
CLr (L/h)	10.8 ± 6.8 (2.2-20.0)	10.2 ± 2.2 (7.1-13.9)	12.7 ± 5.9 (6.4-23.3)

M2 metabolite Pharmacokinetics

Except for a single time point (5.84 ng/mL at 2 hours) in one subject administered Olopatadine Nasal 0.6%, no measurable (<0.250 ng/mL) M2 was found in any other plasma sample collected for the three treatments.

Urinary excretion of M2 was observed in 8/12, 4/12 and 6/12 subjects administered 1.5 mg IV infusion, Olopatadine Nasal 0.4% and Olopatadine Nasal 0.6% treatments, respectively.

Cumulative recovery of M2 was very low, with mean values ranging from 0.12 to 0.34 ug (<0.1% of olopatadine dose) across the three treatments (Table 3).

Table 3. Mean ± SD (range) M2 Pharmacokinetic Parameters in Healthy Subjects after Single Intranasal Dose of 0.6%

Parameter	Olopatadine Nasal 0.4% (N=11)	Olopatadine Nasal 0.6% (N=11)	Olopatadine IV Infusion (1.5 mg) (N=11)
C_{max} (ng/mL)	BLQ	5.84[a]	BLQ
T_{max} (h)	ND	2.0[a]	ND
$AUC_{0\text{-}inf}$ (ng*h/mL)	ND	ND	ND
$t_{½}$ (h)	ND	ND	ND
Ae (ug)	0.12 ± 0.19 [b] (0.00-0.54)	0.23 ± 0.33 [c] (0.00-0.97)	0.34 ± 0.31 [d] (0.00-0.79)
Ae (% dose)	ND	ND	ND
CLr (L/h)	ND	ND	ND

[a]N=1, [b]N=4, [c]N= 6, [d]N=8
BLQ <0.250 ng/mL
ND= not determined

M3 Metabolite Pharmacokinetics

Figures 3 shows the mean metabolite M1 plasma concentrations following single administration of the treatments to healthy volunteers. Table 4 summarizes the mean M3 pharmacokinetic parameters.

Mean M3 plasma concentrations of the two nasal treatments were dose-related. Measurable M3 plasma concentrations were observed out to 6 hours in 5/12 subjects following the intravenous dose and out to 6-8 hours for the two nasal treatments.

Peak plasma concentrations of M3 were low averaging 0.562 ± 0.350 ng/mL following the IV infusion dose (Table 4). For the nasal treatments, mean M3 **Cmax** values appeared to be dose-related. Peak M3 concentrations were observed within 0.75 to 2.0 hours following the intranasal doses. Mean AUC values increased in proportion to the nasal dose. Estimated **t1/2** values for M3 averaged 1.5-1.7 hours for the 3 treatments.

Mean urinary recovery of M3 increased in proportion to the olopatadine nasal doses. Urinary recovery of M3 was small, ranging from 1.6-2.0% of the olopatadine dose.

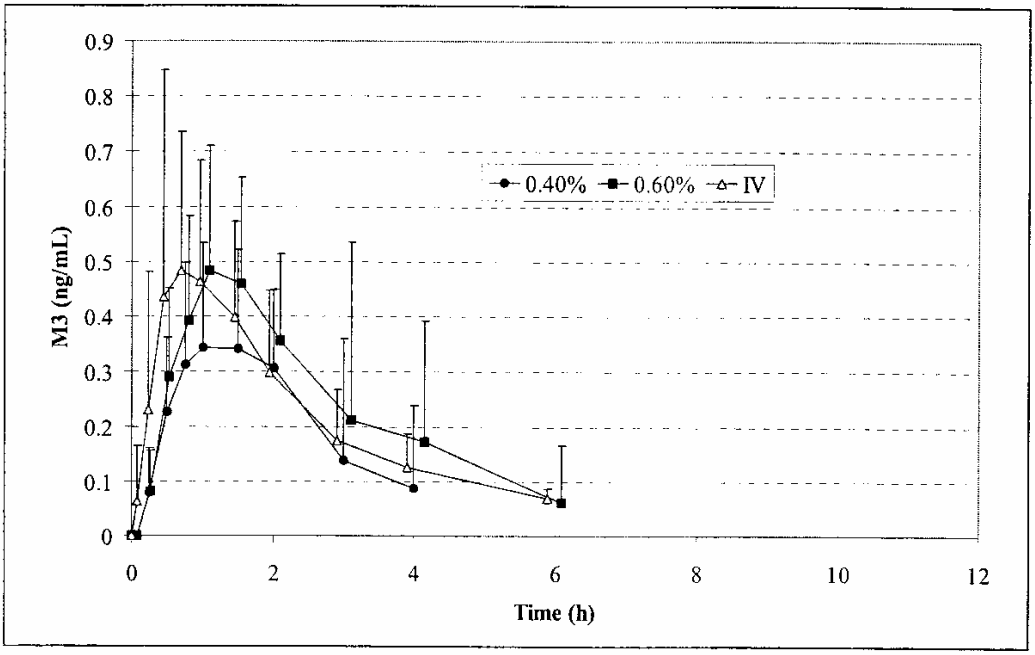


Figure 3. Mean M3 plasma concentrations (ng/mL) profiles after single intranasal dosing of olopatadine nasal 0.04 % and 0.06 % and single 1.5 mg IV infusion in healthy subjects.

Table 4. Mean ± SD (range) M3 Pharmacokinetic Parameters in Healthy Subjects after Single Intranasal Dose of 0.6%

Parameter	**Olopatadine Nasal 0.4%** (N=11)	**Olopatadine Nasal 0.6%** (N=Il)	**Olopatadine IV Infusion (1.5 mg)** (N=11)
Cmax (ng/mL)	0.377 ± 0.192 (0.052-0.602)	0.511 ± 0.229 (0.120-0.783)	0.562 ± 0.350 (0.319-1.49)
Tmax (h)	1.18 ± 0.32 (0.75-1.50)	1.25 ± 0.37 (0.75-2.00)	0.85 ± 0.30 (0.50-1.50)
AUC 0-inf (ng*h/mL)	1.26 ± 0.56 (0.500-2.08)	1.55 ± 0.68 (0.33-228)	1.38 ± 0.70 (0.75-2.74)
T1/2 (h)	1.57 ± 0.43 (0.73-2.25)	1.68 ± 0.41 (0.96-2.31)	1.50 ± 0.32 (0.94-1.91)
Ae (ug)	25.9 ± 14.7 (9.3-52.0)	41.2 ±18.7 (170-79.1)	30.5 ± 8.3 (9.63-42.8)
Ae (% dose)	1.6 ± 0.9 (0.6-3.3)	1.7 ± 0.8 (0.7-3.3)	2.0 ± 0.6 (0.6-2.9)
CLr (L/h)	21.2 ± 4.1 (14.3-27.5)	30.4 ± 11.4 (15.6-55.4)	25.6 ± 11.2 (10.9-41.6)0.344

Summary of Findings

- Plasma concentrations of olopatadine following single intranasal administration of olopatadine Nasal 0.4% and Olopatadine Nasal 0.6% were dose-related. An increase in 1.5 in dose resulted in a 1.4 increased in the olopatadine Cmax and AUC.
- Urinary recovery of unchanged olopatadine following intranasal administration of 0.4% and 0.6% was approximately 35-36% as compared to 61% of the intravenous dose.

- The mean absolute bioavailability of olopatadine (based on dose-adjusted AUC ratios) was 61.3% for Olopatadine Nasal 0.4% and 56.6% for Olopatadine Nasal 0.6%.
- Peak plasma concentrations of the active metabolites Ml and M3 were low, accounting for ~ 2.0% and 3.0% of parent Cmax, respectively.
- AUC 0-inf of the active metabolites Ml and M3 were low, accounting for ~ 6.0% and 9.0% of parent AUCinf, respectively.
- M3 peak plasma concentrations and AUCinf were approximately 1.5- to 3-fold higher and 1.5 higher, respectively than those of Ml.
- Differences in the ratios of metabolites/parent between intravenous and nasal doses may suggest some first-pass metabolism of the intranasal dose.

"Dose-Response of Olopatadine Hydrochloride Nasal Spray vs. Placebo in Treating Seasonal Allergic Rhinitis in an Environmental Exposure Chamber (EEC)"

Protocol No.: C-01-83
Technical Report No.: 0001300

Objective

- To determine whether a dose-response relationship exists for Olopatadine Hydrochloride Nasal Spray administered as 0.6%, 0.4%, 0.2% versus placebo

Study Design and Methods

Patients of either sex, aged 16 and older, who had a history of seasonal allergic rhinitis (SAR) were enrolled. Patients who met the inclusion criteria on 2 priming visits were enrolled in order as they qualified, so that treatment groups were equally enrolled.. At Visit 3 (treatment visit), patients were exposed to allergen in the EEC, PNIF was measured, and diary cards were completed at various intervals during the study period. Data on concomitant medications, adverse events, vital signs, and blood pressure were recorded at all visits. Patients exited the stud at Visit 3.

Number of Patients Planned/Analyzed: 320 patients (80/arm) were planned, 320 were enrolled and analyzed.

Test Product, Dose and Mode of Administration, Batch Number(s): Olopatadine Hydrochloride Nasal Spray 0.6%, metered-dose manual spray pump (2 sprays/nostril), Lot #02-600082-1; Olopatadine Hydrochloride Nasal Spray 0.4%, metered-dose manual spray pump (2 sprays/nostril), Lot #02-600081-1; Olopatadine Hydrochloride Nasal Spray 0.2%, metered-dose manual spray pump (2 sprays/nostril), Lot #02-600080-1. Use of the highest concentration of Olopatadine Nasal Spray 0.6% as a single dose of 2 sprays/nostril results in a total dose of 2.66 mg olopatadine hydrochloride, or 2.4 mg of olopatadine as free base.
Reference Therapy, Dose and Mode of Administration, Batch Number(s): Olopatadine Hydrochloride Nasal Spray Vehicle (Placebo), metered-dose manual spray pump (2 sprays/nostril), Lot #02-600079-1.

Duration of Treatment: Patients received a single dose (2 sprays per nostril) on one day.

Criteria for Evaluation: All patients who received drug were evaluable for safety analysis. All patients who received drug and had at least one on-therapy visit were evaluable for intent-to-treat (ITT) analysis. All patients who received drug and met inclusion and exclusion criteria were evaluable for the per protocol (PP) analysis. Evaluability was also performed on a by-visit basis for all patients with one or more on-therapy visits. Final patient evaluability was performed prior to locking the database and breaking treatment codes.

Statistical Methods:

The primary statistical objective of this study was to describe a dose response relationship for Olopatadine Hydrochloride Nasal Spray administered as 0.6%, 0.4%, and 0.2% when compared to Olopatadine Hydrochloride Nasal Spray Vehicle (placebo). A test of superiority was performed for the primary efficacy variable. Two-sample t-tests were used to determine statistical significance for the primary and the secondary variables for the patients' assessments of runny nose, stuffy nose, itchy nose, and sneezing. Primary and secondary conclusions were based on the ITT data set.

Efficacy

The primary efficacy variable was the mean change from baseline in TNSS, defined as the sum of the patients' diary assessments of runny nose, stuffy nose, itchy nose, and sneezing at each time point. There were 2 types of secondary efficacy variables:. 1) Changes from baseline in the severity scores for patient diary assessments of runny nose, stuffy nose, itchy nose and sneezing. 2) Changes from baseline in nasal inspiratory flow. The exploratory efficacy variable was the Patient Global Rating Scale.

RESULTS

Out of the 320 patients enrolled in this study, all were evaluable for the safety, intent-to-treat (ITT), and per protocol (PP) analyses. The average age was 36 years (range 17-65 years). Males comprised 48.4%, 58.8% were Caucasian, 15.6% were Black, 18.4% were Asian, and 7.2% were Hispanic. Figure 1 shows a box plot of the individual change from baseline in TNSS as a function of treatment. The mean decrease in TNSS for the olopatadine nasal 0.6% group, olopatadine nasal 0.4% group, olopatadine nasal 0.2% group, and vehicle group were 2.8-, 2.63-, 2.58-, and 1.52 units, respectively (Table 1).

Table 1. Mean change from baseline in TNSS following single nasal administration (2 sprays per nostril) of olopatadine 0.2-, 0.4-, and 0.6% nasal solution (Data from Study C-01-83)

Statistics	**Vehicle**	**Olopatadine 0.02%**	**Olopatadine 0.04%**	**Olopatadine 0.06%**
Mean	-1.52	-2.58	-2.63	-2.8
Median	-1.0	-2.5	-2.0	-2.5
Minimum	-11	-12.0	-12	-11
maximum	6	4.0	4.0	5
SD	2.8	2.9	2.8	2.99

Figure 2 shows a frequency plot of adverse events as a function of treatment. In general, systemic adverse events appeared not to be related to dose following single administration of olopatadine 0.2-, 0.4 or 0.6% nasal spray or multiple doses of olopatadine 0.1 or 0.2% nasal spray. However, nasal discomfort (2 events) appeared to be related to drug treatment, in this case the 0.2% olopatadine nasal spray.

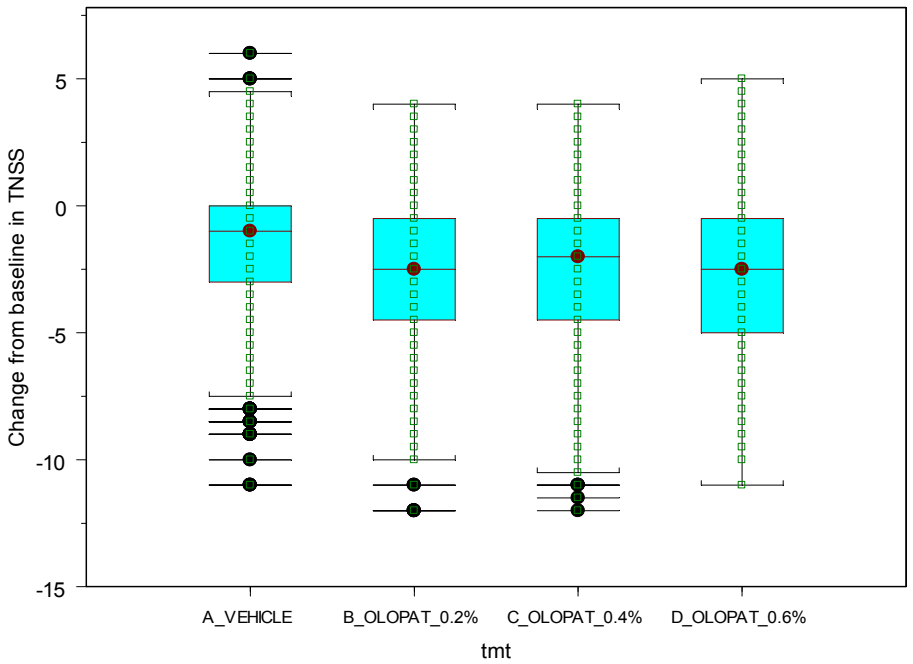


Figure.1. . Change from baseline in TNSS following single nasal administration (2 sprays per nostril) of olopatadine 0.2-, 0.4-, and 0.6% nasal solution (Data from Study C-01-83).

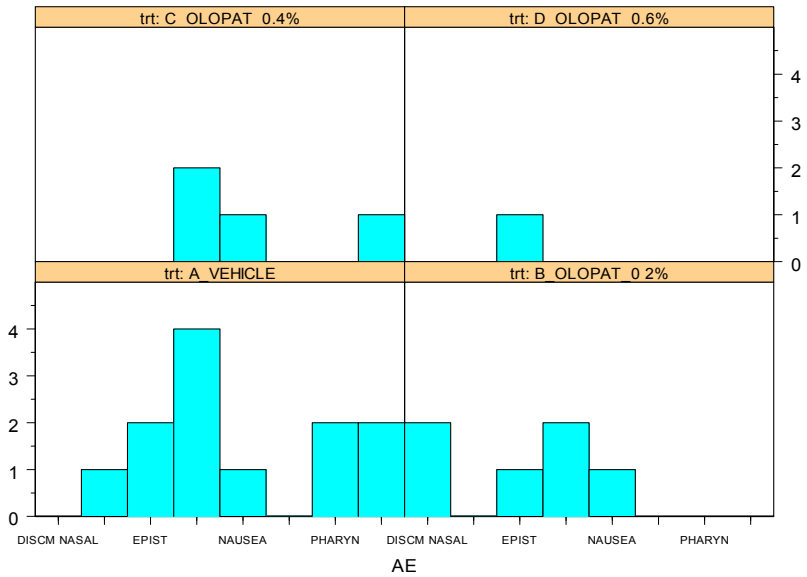


Figure 2. Adverse event frequency following single dose administration of olopatadine 0.2-, 0.4- and 0.6% to AR patients (Data from study C-01-83).

Conclusions

- In the case of dose-response for efficacy, there was a trend for the higher doses to produce a bigger response; however a clear dose-ordering response was not observed following either single administration of olopatadine 0.2-, 0.4-, or 0.6% nasal spray.
- Systemic adverse events appeared not to be related to dose following single administration of olopatadine 0.2-, 0.4 or 0.6% nasal spray

" Multiple--Dose Cardiovascular Safety/PK Study after 20 mg Oral Doses"

Study no.: C-02-54
Development Phase of Study: Phase I

This was a single-center, randomized, double-masked, crossover design, safety and pharmacokinetic study in 34 healthy, male and female subjects, ages 18 to 75 years. The primary objective of this study was to evaluate the cardiovascular effects of olopatadine following multiple twice-daily oral doses of 20 mg olopatadine solution versus olopatadine vehicle for 13 days with a single morning dose on Day 14. Of the 34 subjects, 32 completed both active and placebo treatments. To examine the effect of olopatadine on the QT interval, eighteen 12-lead ECGs were performed over the 24-hour period at baseline (Day -2 to -1), 15 ECGs over the 12-hour period on Day 12 and 18 ECGs over the 24-hour period after the last dose on Day 14 (Days 14/15) for each treatment. The ECGs were forwarded to a centralized reading center for masked manual measurements to determine the ECG parameters. The QT interval for three beats was averaged and corrected for rate (RR) using two fixed-exponent correction formula (QTcQT/RRU) where cz=0.500 (Bazett's, QTcB) or u=0.333 (Fridericia's, QTcF). In addition, an individual-derived regression approach (QTcI) was used. This method derives an a value for each subject that provides a slope -~ zero from the regression of 1/RRU versus QT using all the ECGs obtained at baseline and on each of the placebo study days. Mean steady-state (averaged across all time points on Day 12 and Days 14/15) changes from mean baseline (averaged from the 18 ECGs on Day -2) were calculated for each subject. The maximal change from mean baseline was defined as Emax. Categorical analysis of the Emax values into <30 msec, _30 to _60 msec and >60 msec for each subject. Plasma samples for olopatadine determination were obtained at the same time points as the ECG recordings on Days 12 and 14/15.

QT Study Report

The document is created by QTech on 5/16/2005 1:03:36 PM.

I. STUDY INFORMATION

Table 1. Study Details

Study Name	Patanase5
Study#	
NDA/IND#	NDA21861
Submission Date	
Class	
Crossover	True
Comment	
Analysis Method	Baseline Method: Mean Baseline has same name as other regimens

Baseline Definition	General Baselines: 0:Day==1;Period==1:Day>1;Period==1 2:Day==1;Period==1:Day>4;Period==2 Mean of Delta QTc: 0:Day==1;Period==1:Day>1;Period==1 2:Day==1;Period==1:Day>4;Period==2
Unique Values	(b) (4)
	Regimen: 1, 2 Period: 1, 2 Day: 1, 2, 3, 5, 6 Time: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28

II. OUTLIER ANALYSIS

Table 2.1 Frequency for QTc > 450 msec.

(b) (4)

Table 2.2 Frequency for QTc > 500 msec.

(b) (4)

QTcF

(b) (4)

Table 2.3 Frequency for Delta QTc: 30~60 msec.

(b) (4)

Table 2.4 Frequency for Delta QTc > 60 msec.

(b) (4)

III. MEAN OBSERVATIONS

Table 3.1 Mean Observations (Average Across Subject)

Treatment	Time	# of Subj.	Mean HR	SD of HR	Mean QTcB	SD of QTcB	Mean QTcF	SD of QTcF
Baseline- 1	0.00	1	53.05	NA	382.00	NA	390.00	NA
Baseline- 1	1.00	1	54.05	NA	387.00	NA	394.00	NA
Baseline- 1	3.00	1	54.89	NA	404.00	NA	411.00	NA
Baseline- 1	4.00	1	57.47	NA	411.00	NA	414.00	NA
Baseline- 1	6.00	1	59.17	NA	391.00	NA	392.00	NA
Baseline- 1	7.00	1	60.18	NA	384.00	NA	384.00	NA
Baseline- 1	8.00	1	61.48	NA	414.00	NA	412.00	NA
Baseline- 1	9.00	1	61.73	NA	411.00	NA	409.00	NA
Baseline- 1	10.00	3	62.33	0.77	390.67	5.86	388.00	6.08
Baseline- 1	11.00	2	63.26	0.24	406.50	7.78	403.00	7.07
Baseline- 1	16.00	1	68.26	NA	425.00	NA	416.00	NA
Baseline- 1	21.00	1	74.07	NA	429.00	NA	414.00	NA

Baseline- 1	22.00	1	75.28	NA	411.00	NA	396.00	NA
Baseline- 1	23.00	1	76.34	NA	411.00	NA	395.00	NA
Baseline- 2	1.00	1	53.29	NA	399.00	NA	407.00	NA
Baseline- 2	2.00	1	54.79	NA	393.00	NA	399.00	NA
Baseline- 2	4.00	1	57.20	NA	411.00	NA	415.00	NA
Baseline- 2	6.00	1	59.58	NA	417.00	NA	417.00	NA
Baseline- 2	7.00	1	60.42	NA	412.00	NA	412.00	NA
Baseline- 2	8.00	1	61.10	NA	408.00	NA	407.00	NA
Baseline- 2	9.00	1	61.98	NA	377.00	NA	375.00	NA
Baseline- 2	10.00	1	63.09	NA	381.00	NA	378.00	NA
Baseline- 2	11.00	1	63.63	NA	399.00	NA	396.00	NA
Baseline- 2	13.00	1	65.22	NA	447.00	NA	441.00	NA
Baseline- 2	18.00	2	70.80	0.65	438.00	15.56	426.00	15.56
Baseline- 2	19.00	1	71.34	NA	420.00	NA	408.00	NA
Baseline- 2	20.00	1	72.90	NA	412.00	NA	399.00	NA
Baseline- 2	23.00	1	75.95	NA	419.00	NA	403.00	NA
1	0.00	1	53.10	NA	391.00	NA	399.00	NA
1	1.00	1	53.86	NA	387.00	NA	394.00	NA
1	4.00	1	57.23	0.35	395.50	0.71	399.00	0.00
1	5.00	1	58.42	NA	415.00	NA	417.00	NA
1	6.00	3	58.67	0.35	399.67	13.50	401.33	13.50
1	7.00	1	59.82	NA	410.00	NA	410.00	NA
1	8.00	2	60.70	0.74	408.00	9.90	407.00	8.49
1	10.00	2	62.57	0.46	399.50	21.92	396.50	21.92
1	11.00	1	64.31	NA	402.00	NA	398.00	NA
1	12.00	2	64.83	0.05	394.00	1.41	389.00	1.41
1	13.00	2	65.79	0.20	403.50	31.82	397.50	31.82
1	14.00	2	66.52	0.13	411.33	0.58	404.33	0.58
1	15.00	3	68.05	0.50	411.25	11.56	403.25	11.56
1	16.00	2	68.65	0.78	400.00	8.49	391.00	7.07
1	17.00	3	69.11	0.88	403.00	9.93	393.75	9.29
1	18.00	3	70.67	0.48	432.25	32.26	420.75	31.10
1	19.00	3	71.01	0.47	409.33	16.44	398.00	15.87
1	20.00	4	72.25	1.53	411.25	13.38	398.50	12.23
1	21.00	5	73.46	0.37	423.60	9.04	409.60	8.59
1	22.00	5	74.60	0.56	404.50	8.04	390.17	7.83
1	23.00	5	75.63	0.36	411.67	23.31	396.17	21.96
1	24.00	1	77.22	NA	407.00	NA	390.00	NA
1	25.00	2	78.07	0.07	429.50	21.92	411.00	21.21
1	26.00	1	78.84	NA	430.00	NA	411.00	NA
1	28.00	1	81.52	NA	429.00	NA	408.00	NA
2	0.00	1	53.29	NA	391.00	NA	399.00	NA
2	2.00	1	54.79	NA	391.00	NA	397.00	NA
2	3.00	1	55.81	NA	389.00	NA	394.00	NA
2	4.00	1	56.71	NA	388.00	NA	391.00	NA
2	5.00	4	57.49	0.20	392.75	13.45	395.50	13.92
2	6.00	3	58.94	0.15	385.33	14.19	386.67	14.29
2	7.00	1	60.54	NA	406.00	NA	405.00	NA

2	8.00	3	60.54	1.11	400.00	7.00	399.33	7.64
2	9.00	1	62.50	NA	401.00	NA	399.00	NA
2	10.00	3	62.98	0.40	402.00	8.19	398.67	8.74
2	12.00	3	64.70	0.56	411.00	6.08	406.00	6.08
2	13.00	2	65.50	0.51	409.00	0.00	402.50	0.71
2	14.00	3	66.82	0.32	406.00	16.37	399.00	15.72
2	15.00	6	67.56	0.42	413.17	23.09	405.17	22.87
2	16.00	4	68.67	0.27	405.00	31.28	396.20	30.55
2	17.00	4	69.53	0.68	410.75	5.56	401.00	5.03
2	18.00	3	70.15	0.85	405.67	10.97	395.33	10.21
2	19.00	3	71.46	0.76	410.67	3.79	399.00	3.46
2	20.00	3	72.55	0.18	400.67	13.32	388.33	12.90
2	21.00	1	73.90	0.77	427.50	0.71	412.50	0.71
2	22.00	3	74.60	0.46	420.00	5.29	405.33	5.13
2	23.00	1	75.28	NA	401.00	NA	386.00	NA
2	24.00	2	76.47	0.15	403.67	5.51	387.33	5.03
2	26.00	3	79.05	0.37	434.00	14.00	414.00	13.08
2	27.00	1	79.05	NA	449.00	NA	428.00	NA

Table 3.2 Mean of Maximum Observations

Treatment	# of Subj.	Mean HR	SD of HR	Mean QTcB	SD of QTcB	Mean QTcF	SD of QTcF
Baseline- 1	17	62.91	7.00	402.65	14.47	399.82	11.36
Baseline- 2	15	64.14	6.87	411.40	20.45	407.27	17.81
1	32	70.10	6.71	411.84	17.15	402.63	15.16
2	32	68.55	6.49	408.97	16.96	401.28	14.01

Table 3.3 Maximum of Mean Observations

Treatment	# of Subj.	Mean HR	SD of HR	Mean QTcB	SD of QTcB	Mean QTcF	SD of QTcF
Baseline- 1	17	76.34	NA	429.00	NA	416.00	NA
Baseline- 2	15	75.95	NA	447.00	NA	441.00	NA
1	32	81.52	NA	456.00	NA	443.00	NA
2	32	79.26	NA	449.00	NA	428.00	NA

IV. QTc CHANGES FROM BASELINE (DeltaQTc)

Table 4.1 Mean QTc Changes From Baseline (DeltaQTc)

Treatment	Time	# of Subj.	Mean Delta QTcB	SD of Delta QTcB	Mean Delta QTcF	SD of Delta QTcF
1	0.00	1	-8.00	NA	-8.00	NA
1	1.00	1	-12.00	NA	-13.00	NA
1	4.00	1	2.50	0.71	0.00	0.00
1	5.00	1	1.00	NA	5.00	NA
1	6.00	3	-3.33	6.81	-0.33	6.66
1	7.00	1	-1.00	NA	-4.00	NA

1	8.00	2	-3.00	9.90	-4.50	4.95
1	10.00	2	2.00	2.83	-3.00	0.00
1	11.00	1	15.00	NA	4.00	NA
1	12.00	2	10.00	2.83	3.00	9.90
1	13.00	2	7.00	11.31	-5.00	14.14
1	14.00	2	3.00	6.08	-0.33	5.51
1	15.00	3	5.25	10.31	-2.25	9.00
1	16.00	2	14.00	1.41	6.00	2.83
1	17.00	3	0.50	6.19	-12.50	5.45
1	18.00	3	5.25	9.43	1.50	6.35
1	19.00	3	0.67	10.69	-6.67	12.42
1	20.00	4	-3.75	5.25	-10.25	10.90
1	21.00	5	3.20	7.46	-0.60	5.13
1	22.00	5	6.83	10.09	-0.83	9.56
1	23.00	5	-1.00	4.90	-7.33	3.67
1	24.00	1	-5.00	NA	-9.00	NA
1	25.00	2	16.50	28.99	5.00	22.63
1	26.00	1	19.00	NA	16.00	NA
1	28.00	1	18.00	NA	13.00	NA
2	0.00	1	-8.00	NA	-8.00	NA
2	2.00	1	-23.00	NA	-15.00	NA
2	3.00	1	5.00	NA	10.00	NA
2	4.00	1	-11.00	NA	-16.00	NA
2	5.00	4	-12.75	7.32	-11.50	4.51
2	6.00	3	-11.00	13.75	-7.67	13.05
2	7.00	1	13.00	NA	6.00	NA
2	8.00	3	-0.67	5.77	-7.00	3.61
2	9.00	1	0.00	NA	1.00	NA
2	10.00	3	5.00	11.53	-2.00	7.94
2	12.00	3	-0.67	6.43	-5.67	3.06
2	13.00	2	13.00	7.07	7.50	4.95
2	14.00	3	9.33	2.08	-0.67	4.51
2	15.00	6	4.83	5.88	-2.67	8.07
2	16.00	4	-3.00	9.82	-9.60	8.14
2	17.00	4	-5.00	7.79	-4.25	11.76
2	18.00	3	-5.00	6.56	-9.00	6.24
2	19.00	3	-5.67	16.92	-8.33	11.72
2	20.00	3	6.00	15.39	1.00	11.36
2	21.00	1	0.50	0.71	-2.50	0.71
2	22.00	3	6.00	1.00	5.67	2.52
2	23.00	1	-11.00	NA	-13.00	NA
2	24.00	2	15.00	15.87	4.33	10.26
2	26.00	3	7.33	6.03	0.33	8.50
2	27.00	1	0.00	NA	-9.00	NA

Table 4.2 Mean of Maximum QTc Changes From Baseline (DeltaQTc)

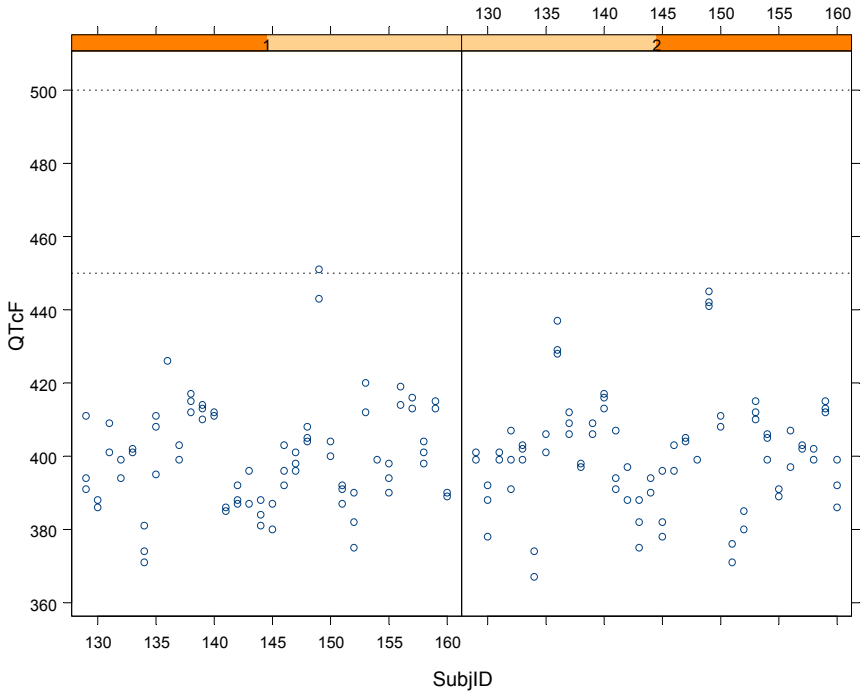
Treatment	# of Subj.	Mean Delta	SD of Delta	Mean Delta	SD of Delta

		QTcB	QTcB	QTcF	QTcF
1	32	5.09	9.96	-0.69	9.11
2	32	2.22	11.07	-2.03	8.67

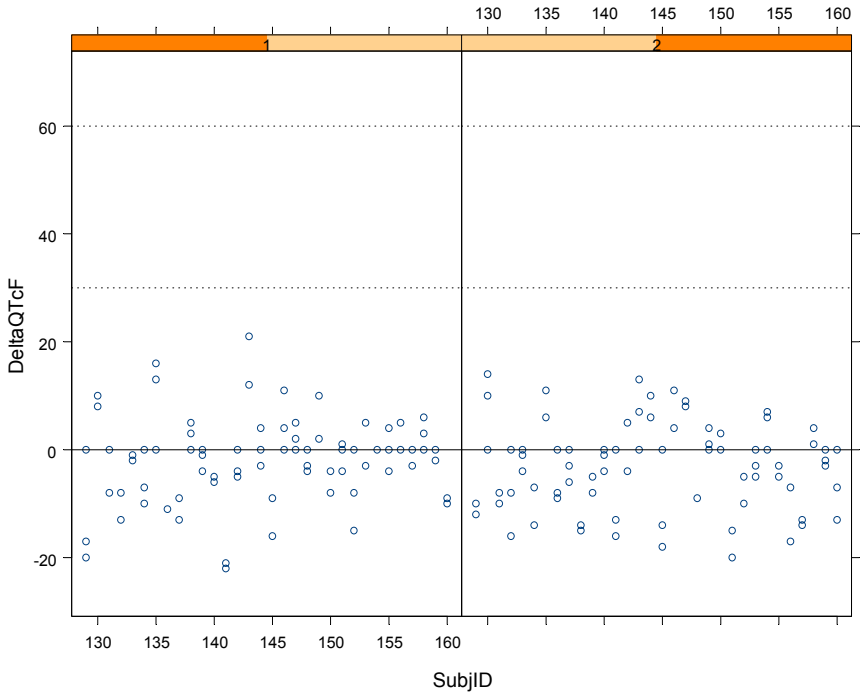
Table 4.4 Maximum of Mean QTc Changes From Baseline (DeltaQTc)

Treatment	# of Subj.	Mean Delta QTcB	SD of Delta QTcB	Mean Delta QTcF	SD of Delta QTcF
1	32	25.00	NA	16.00	NA
2	32	21.00	NA	11.00	NA

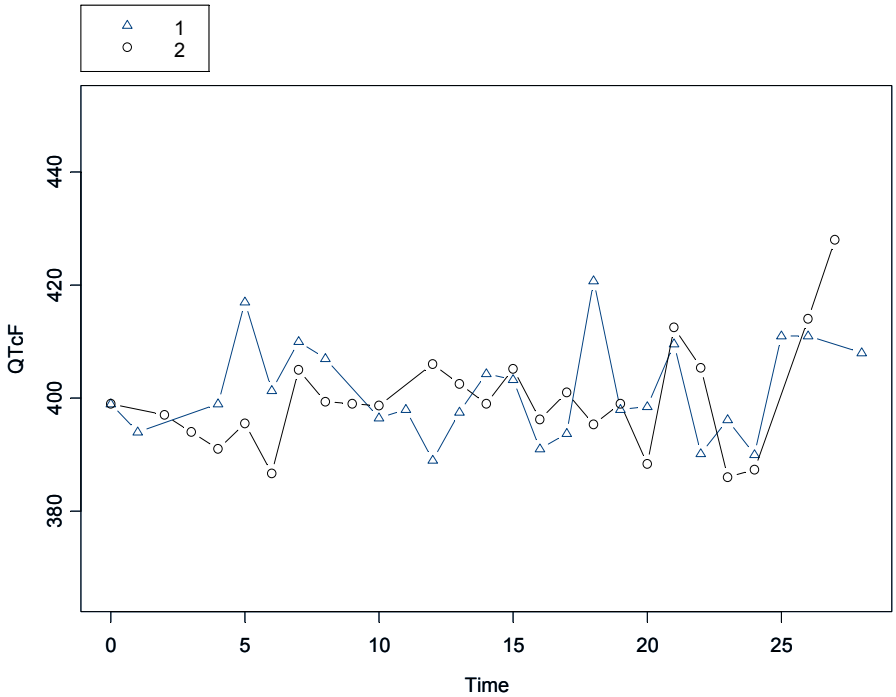
Outlier



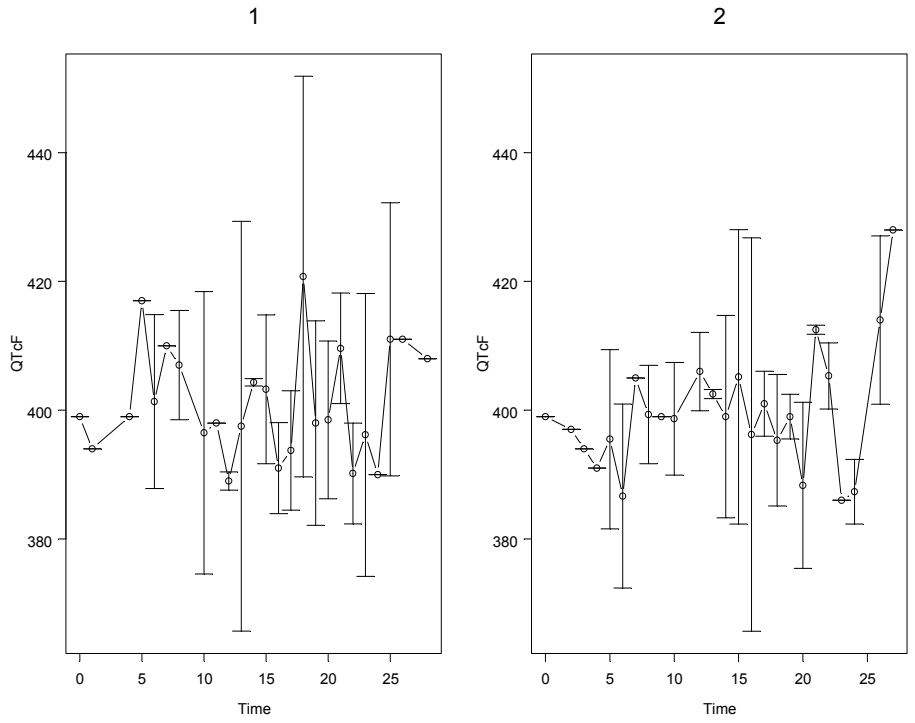
Outlier


130
135
140
145
150
155
160
1
2
60
40
20
0
-20
DeltaQTcF
SubjID

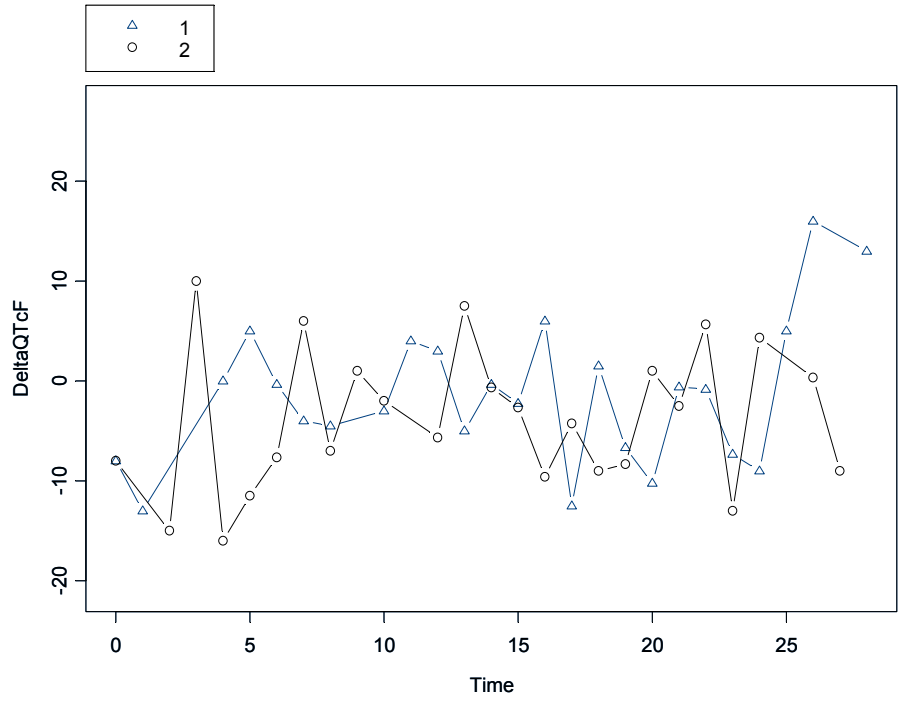
Mean


1
2
440
420
400
380
QTcF
0
5
10
15
20
25
Time

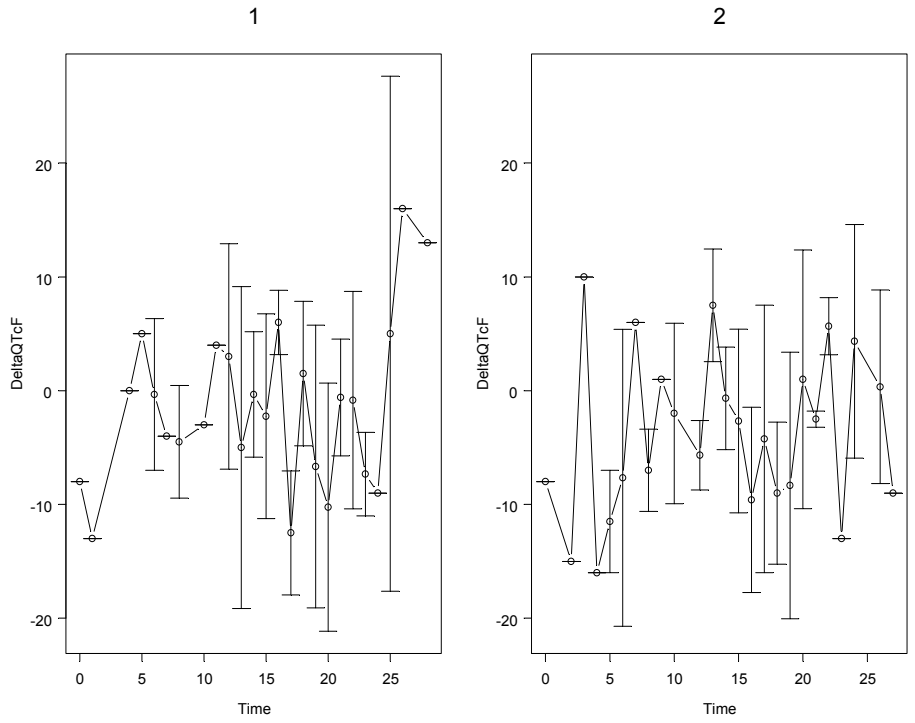
Mean&SD


1
2
QTcF
440
420
400
380
0
5
10
15
20
25
Time

Mean


1
2
DeltaQTcF
20
10
0
-10
-20
0
5
10
15
20
25
Time

Mean&SD



CONCLUSION

- Olopatadine and its metabolites did not significantly affect QT or QTc when multiple twice-daily oral doses of 20 mg olopatadine solution or placebo were administered to 34 healthy volunteers for 14 days. The mean change from baseline in QTF following olopatadine administration was -2.5 (8.8). In addition, no linear correlation between QTc change from baseline and olopatadine systemic exposure (Cmax) was observed.

"Multiple-Dose Study Following Intranasal Administration of Olopatadine 0.1% and 0.2% in Healthy Subjects"

Protocol No.: C-00-58
Technical Report No.: 0001300

Objective

- to determine safety and the single- and multiple-dose pharmacokinetics of olopatadine hydrochloride nasal spray 0.1% and 0.2%.

Study Design and Methods

The safety and the single- and multiple-dose pharmacokinetics of olopatadine hydrochloride nasal spray 0.1% and 0.2% were evaluated in an open-label, randomized, parallel-group, multiple-dose study in healthy volunteers. This study used Series 1 formulations employed in Alcon Phase II dose-ranging studies but not intended for marketing. Thirty-six, male and female subjects, ages 18 to 45 years, received QD or BID intranasal doses (two 100 mcL sprays/nostril) of Olopatadine Nasal 0.1% or BID doses of Olopatadine Nasal 0.2% for 2 1/2 days. Based on the delivered volume, concentrations and replicate sprays, the dose at each administration of 0.1% and 0.2% concentrations was 0.4 mg and 0.8 mg, respectively. Serial plasma samples were collected up to 12 hours post-dose after the first dose on Day 1 and up to 24 hours after the last dose on the morning of Day 3. Urine samples were collected up to 24 hours post-dose on Day 3. Samples were analyzed for olopatadine using a validated HPLC/MS/MS method. The LOQ for olopatadine was 0.050 ng/mL in plasma and 10 ng/mL in urine.

RESULTS

Figures 1 shows the mean olopatadine plasma concentrations following multiple administration of the treatments to healthy volunteers. Table 1 summarizes the mean olopatadine pharmacokinetic parameters at Day 3. Across the dose groups, peak olopatadine plasma concentrations were seen within 0.5 to 2 hours post-dose. Mean AUC values were also dose-related. Mean half-lives varied across the groups (range 6.3 to 15.0 hours); according to the sponsor these finding are attributed to differences in the number of quantifiable plasma data in the terminal phase between the dose groups.

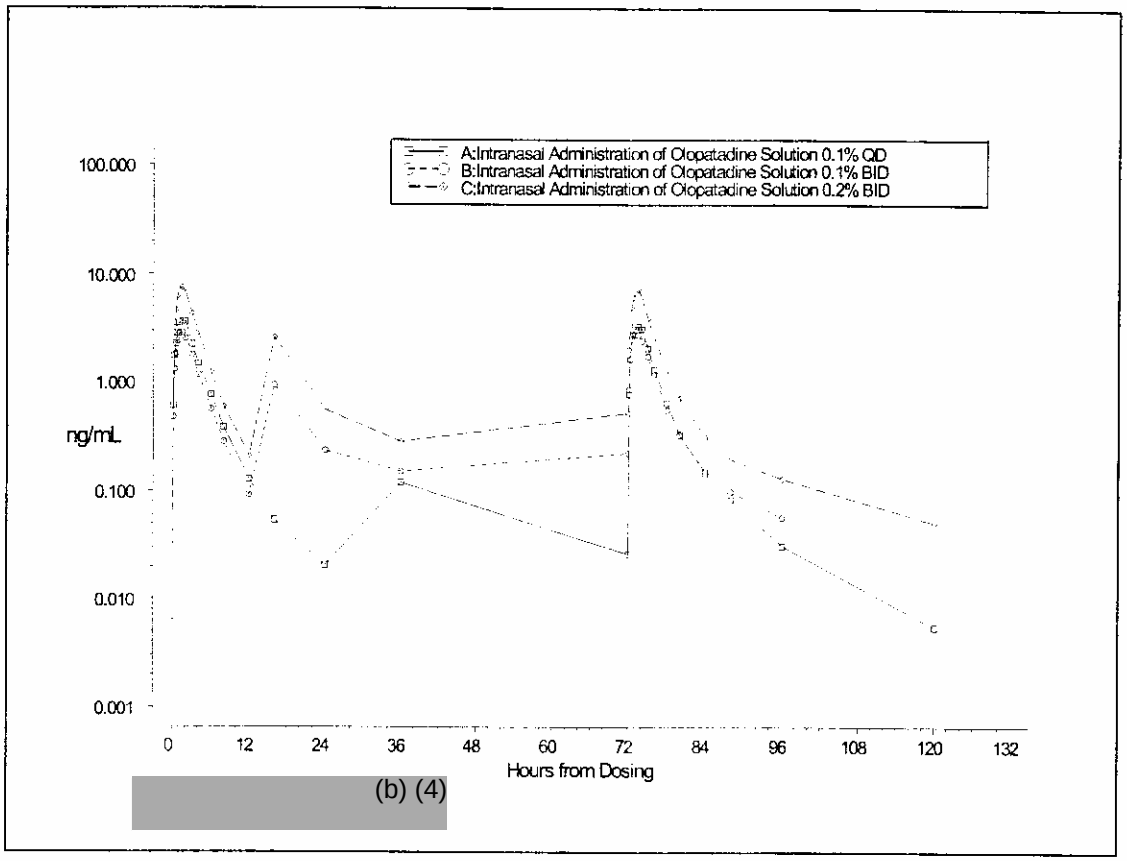


Figure 1. Mean olopatadine plasma concentrations (ng/mL) profiles after single or multiple intranasal dosing of olopatadine nasal 0.01 % (QD or BID) or 0.2% BID for 2.5 Days in healthy subjects.

Table 1. Mean ± SD (range) Day 3 Olopatadine Pharmacokinetic Parameters in Healthy Subjects after Multiple QD or BID Intranasal Doses for 2.5 Days

Parameter	**0.1% QD**	**0.1% BID**	**0.2% BID**
	0.4mg	**0.8 mg**	**1.6mg**
Cmax (ng/mL)	4.36 ± 2.27 (0.41 -7.92)	3.42 ± 1.31 (0.97 -5.05)	8.48 ± 3.12 (2.77- 15.0)
Tmax (h)	1.23 ± 0.59 (0.50-2.00)	1.06 ± 0.42 (0.50- 1.50)	1.25 ± 0.38 (0.75 -2.00)
AUC(0-12) **(ng*h/mL)**	13.92 ± 5.90 (1.40-20.67)	12.03 ± 3.66 (4.80- 16.54)	28.33 ± 9.88 (11.09- 14.03)
AUC(0-inf) **(ng*hr/mL)**	15.45 ± 6.81 (1.54-23.91)	14.04 ± 4.17 (5.08 - 19.04)	33.84 ± 12.66 (12.92-51.32)
$T_{(1/2}$ (h)	6.32 ± 4.07 (1.96-13.5)	8.31 ± 3.48 (3.06-13.3)	15.0 ± 9.56 (3.16-29.9)
Ae (% dose)	60.4 ± 24.8 (2.7 -84.8)	56.2 ± 15.1 (24.7 -76.9)	67.4 ± 20.6 (23.9-94.7)
CLr (L/h)	16.2a	17.0a	17.6a

[a]Estimated from mean recovery and mean AUC

Conclusions

- Dose-related systemic exposure of olopatadine following single and multiple intranasal doses was observed for the BID administration. Two fold increase in the dose resulted in 2.35-fold increase in the AUCinf.
- No appreciable plasma accumulation of olopatadine was seen with BID dosing for 2.5 days (mean accumulation ratio ranged from 1.16 to 1.19)

"Multiple-Dose Study Following Intranasal Administration in SAR Patients "

Study No. C-02-10
Technical document: 0000533

OBJECTIVE

- To determine the pharmacokinetic of olopatadine and its metabolites following single and multiple administration of olopatadine in SAR patients.

STUDY DESIGN AND TREATMENT ADMINISTRATION

The single- and multiple-dose pharmacokinetics of olopatadine and its metabolites were examined in a sub-group of adult, male and female seasonal allergic rhinitis (SAR) patients who participated in a double-masked, multiple-dose, placebo-controlled, parallel-design, Phase III winter cedar pollen efficacy study. At a single center, 42 SAR patients were randomized to receive BID intranasal doses (two 100 mcL sprays per nostril) of Olopatadine Vehicle, Olopatadine Nasal 0.4% or Olopatadine Nasal 0.6% for 14 days. Of the 42 patients, 27 patients were randomized to active treatment, 14 to Olopatadine Nasal 0.4% and 13 to Olopatadine Nasal 0.6%. Based on the nominal volume, concentrations and replicate sprays, the dose delivered at each administration of Olopatadine Nasal 0.4% or Olopatadine Nasal 0.6% was 1.6mg and 2.4 mg, respectively.

Serial plasma samples were obtained for 12 hours after the first dose (Day 0), prior to the morning dose on Day 7 and for the 48-how period following the last intranasal dose (Days 15-17). Samples were measured in patients who received active drug for olopatadine, Ml, M2 and M3 using a validated HPLC/MS/MS method. The LOQ was 0.050 ng/mL for olopatadine, Ml and M3 and 0.250 ng/mL for M2. Pharmacokinetic parameters on Days 0 and 15 were determined using model-independent methods.

RESULTS

Single-Dose Data

Olopatadine

Figures 1 shows the mean olopatadine plasma concentrations following single administration of the treatments to SAR patients. Table 1 summarizes the mean olopatadine pharmacokinetic parameters. Following the first intranasal dose, peak plasma concentrations of olopatadine were observed 0.25 h to 2 hours post-dose and were related to the dose. Similarly, the AUC over the dosing interval (AUC_{012}) increased in proportion to the dose (Table 1).

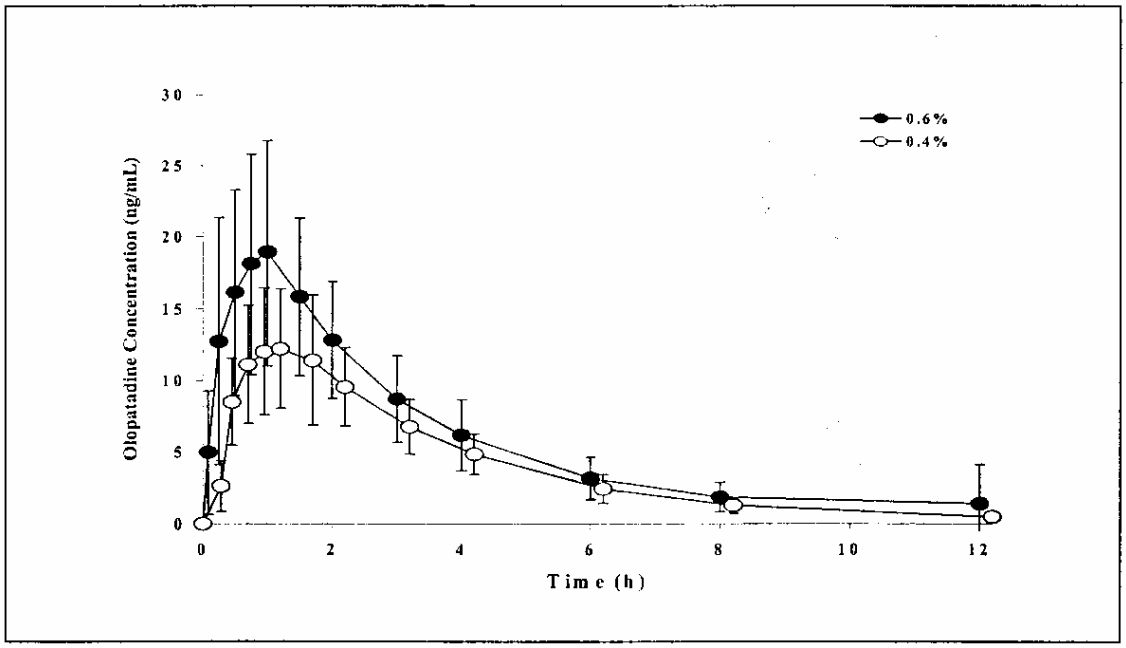


Figure 1. Mean ± SD plasma concentrations \in SAR patients after single administration of olopatadine nasal 0.4% or olopatadine 0.6%.

Table 1. Mean ± SD (range) Single-Dose (Day-O) Olopatadine Pharmacokinetic Parameters in SAR Patients

Parameter	Treatment	Olopatadine
Cmax (ng/mL)	Olopatadine 0.4%	14.4 ± 4.4 (5.97 -21.9)
	Olopatadine 0.6%	21.7 ± 8.7 (7.11 -36.4)
T1/2 (h)	Olopatadine 0.4%	0.86 ± 0.41 (0.25-1.50)
	Olopatadine 06%	1.00 ± 0.50 (0.25-2.00)
AUC $_{0-12}$ (ng*h/mL)	Olopatadine 0.4%	48.9 ± 12.5 (23.3 - 67.4)
	Olopatadine 0.6%	67.7 ± 21.1 (24.0-98.0)

Metabolite M2

No quantifiable plasma concentrations (<0.250 ng/mL) of the metabolite M2 were seen in any sample after the single administration dose for either dose.

Metabolites Ml and M3

Plasma concentrations of olopatadine metabolites M1 and M3 were low, with peak values ranging from <0.0500 ng/mL to 0.352 ng/mL for Ml and <0.0500 to 1.16 ng/mL (Table 2). Mean Cmax and AUC values were dose-related with those for M3 about 3-fold greater than those of Ml. Mean Ml and M3 Cmax values were approximately 0.7% and 2.9% of parent Cmax.

Table 2. Mean ± SD (range) Single-Dose (Day-O) M1 and M3 Pharmacokinetic Parameters in SAR Patients

Parameter	Treatment	Desmethyl Olopatadine (M1)	Olopatadine N-Oxide (M3)
C_{max} (ng/mL)	Olopatadine 0.4%	0.0861 ± 0.0431 (<0.0500 – 0.163)	0.357 ± 0.112 (0.153 - 0.581)
	Olopatadine 0.6%	0.150 ± 0.084 (<0.0500 – 0.352)	0.530 ± 0.255 (0.115 - 1.16)
T_{max} (h)	Olopatadine 0.4%	2.27 ± 0.87 (1.00 – 4.00)	1.73 ± 0.77 (0.75 - 3.00)
	Olopatadine 0.6%	2.41 ± 0.94 (1.50 – 4.00)	1.44 ± 0.61 (0.75 - 3.00)
AUC_{0-4} (ng*h/mL)	Olopatadine 0.4%	0.315 ± 0.079 (0.208 – 0.427)	0.942 ± 0.277 (0.502 - 1.49)
	Olopatadine 0.6%	0.462 ± 0.127 (0.252 - 0.680)	1.33 ± 0.52 (0.351 - 1.95)
AUC_{0-6} (ng*h/mL)	Olopatadine 0.4%	0.546 ± 0.169 (0.366 - 0.702)	1.42 ± 0.24 (1.13 - 1.82)
	Olopatadine 0.6%	0.728 ± 0.121 (0.572 - 0.913)	1.89 ± 0.60 (0.514 - 2.60)

Multiple-Dose
Olopatadine

Mean trough (Cmin) plasma concentrations of olopatadine indicated that steady-state was achieved during the 14-day dosing period. Table 3 shows the PK parameters of olopatadine following multiple administration of the treatments. Dose-related increases were observed in the mean steady-state values for Cmax, AUC0-12h and AUCinf (Table 2). Following the peak, plasma concentrations of olopatadine declined in a biphasic manner over the 48-hour sampling period with a mean elimination half-life of 8.3 ± 4.9 hours and 10.4 ± *5.1* hours for the two treatments. Mean plasma concentrations, Cmax and AUC_{0-12h} values for olopatadine were approximately 1.3-fold higher than those after the single dose indicating minimal accumulation in plasma.

Table 3. Mean ± SD (range) Day-15 Olopatadine Pharmacokinetic Parameters in SAR Patients

Parameter	Treatment	Olopatadine
C_{max} (ng/mL)	Olopatadine 0.4%	15.9 ± 6.4 (3.65 - 29.0)
	Olopatadine 0.6%	23.3 ± 6.2 (14.4 - 35.3)
T_{max} (h)	Olopatadine 0.4%	1.00 ± 0.55 (0.25 - 2.00)
	Olopatadine 0.6%	0.97 ± 0.52 (0.08 - 1.50)
AUC_{0-12} (ng*h/mL)	Olopatadine 0.4%	57.3 ± 24.5 (10.4 – 114)
	Olopatadine 0.6%	78.0 ± 13.9 (54.4 – 103)
$AUC_{0-\infty}$ (ng*h/mL)	Olopatadine 0.4%	67.2 ± 29.1 (10.5 – 130)
	Olopatadine 0.6%	91.2 ± 18.4 (59.3 – 116)
$T_{1/2}$ (h)	Olopatadine 0.4%	8.3 ± 4.9 (2.1 - 21.3)
	Olopatadine 0.6%	10.4 ± 5.1 (4.0 - 21.8)

Metabolite M1

Plasma concentrations of Ml reached maximal levels on average within 1 to 4 hours post-dose for both dose levels (Table 4). Mean values for Cmax and AUC increased in proportion to the 0.4% and 0.6% dose levels, respectively. Ml Cmax and AUC0-inf values represented approximately 0.7-0.8% and 1.3-1.4% of the respective parent mean values at the two doses. Following the peak, Ml plasma concentrations declined in an apparent monophasic manner with a mean half-life of 3.3 hours.

Metabolite M2

According to the sponsor, no quantifiable plasma concentrations (<0.250 ng/mL) of the metabolite M2 were seen in any sample after the multiple administration dose for either dose.

Metabolite M3

Plasma concentrations of M3 reached maximal levels within 0.75 to 2 hours (mean values ranging from 1.41 to 1.56 hours) post-dose for both (Table 4). M3 Cmax and AUC_{0-inf} values were approximately 3-fold and 2.2-fold higher than the respective values for Ml. Further, mean M3 Cmax and AUC_{0-inf} values represented about 2.8% and 3.0% of the respective parent mean values at the two doses. Following the peak, M3 plasma concentrations declined in a monophasic manner with a mean half-life of 2.2-2.3 hours.

Table 4. Mean ± SD (range) Day-15 MI and M3 Plasma Pharmacokinetic Parameters in SAR Patients

Parameter	Treatment	Desmethvl Olopatadine (Ml)	Olopatadine N-Oxide (M3)
Cmax (ng/mL)	Olopatadine 0.4%	0.115 ± 0.072 (<0.0500 - 0.307)	0.466 ± 0.246 (0.0765 - 0.993)
	Olopatadine 0.6%	0.183 ± 0.062 (0.110 - 0.283)	0.629 ± 0.241 (0.302 - 1.08)
Tmax (h)	Olopatadine 0.4%	2.23 ± 0.78 (1.50-4.00)	1.56 ± 0.46 (0.75 -2.00)
	Olopatadine 0.6%	2.15 ±0.80 (1.00-4.00)	1.41 ± 0.37 (0.75 -2.00)
AUC0-4h (ng*h/mL)	Olopatadine 0.4%	0.403 ± 0.195 (0.198 - 0.845)	1.34 ± 0.60 (0.636-2.73)
	Olopatadine 0.6%	0.529 ± 0.177 (0.334 - 0.867)	1.64 ± 0.55 (0.823 - 2.43)
AUC0-6h (ng*h/mL)	Olopatadine 0.4%	0.681 ± 0.258 (0.380 - 1.11)	1.81 ± 0.75 (0.841 -3.50)
	Olopatadine 0.6%	0.762 ± 0.243 (0.508-1.27)	2.02 ± 0.65 (1.01 -2.92)
AUC0-inf (ng*h/mL)	Olopatadine 0.4%	0.939 ± 0.393 (0.459 - 1.51)	2.10 ± 1.01 (0.946 -4.68)
	Olopatadine 0.6%	1.16 ± 0.54 (0.531 -2.52)	2.52 ± 0.83 (1.17-3.48)
T1/2 (h)	Olopatadine 0.4%	3.3 ± 1.0 (2.0-4.9)	2.2 ± 0.6 (1.0-3.0)
	Olopatadine 0.6%	3.3 ± 1.1 (1.9-5.0)	2.3 ± 0.6 (1.4-3.0)

SUMMARY

- Plasma concentrations of olopatadine and its metabolites (Ml and M3) were dose-related. An increase in 1.5 in dose resulted in a 1.4-1.5 increase in the olopatadine Cmax and AUCinf.
- Steady-state values for Ml and M3 were low relative to parent, accounting for ≤0.8 and ≤2.9% of olopatadine Cmax, respectively. AUCinf of M1 or M3 accounted for less than 3% of olopatadine AUCinf.
- M3 Cmax and $AUC_{0\text{-}inf}$ values were approximately 3-fold and 2.2-fold higher than the respective values for Ml.
- Accumulation of parent drug and metabolites in plasma with BID dosing was minimal (less than 1.5 fold)

" An Open Label, Single-Dose Pharmacokinetic Study of Olopatadine 0.6% Nasal Spray in Healthy Subjects and in Subjects With Renal Impairment"

Study no.: C-02-46
Development Phase of Study: Phase I

Objectives

- to characterize the plasma pharmacokinetics and urinary excretion of olopatadine and its major metabolites following a single dose of Olopatadine Hydrochloride Nasal Spray 0.6% in subjects with varying degrees of renal impairment compared to subjects with normal renal function

STUDY DESIGN, TREATMENT AND ADMINISTRATION

This was a single-center, single-dose pharmacokinetic study in subjects with normal renal function and in patients with varying degrees of renal impairment. Twenty-five subjects/patients (18 years or older) were administered a single dose (two 100 uL sprays/nostril) of Olopatadine Nasal 0.6% (equivalent to 2.4mg olopatadine base).

PHARMACOKINETIC MEASUREMENTS

Blood Sampling

Blood samples for plasma were collected pre-dose and out to 48 hours post-dose.

Urine Sampling

Urine samples were collected pre-dose and at 0-2, 2-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-60, 60-72, 72-96, 96-120, 120-132, 132-144, 144-156, 156-168, 168-180 and 180-192 hours post-dose.

Analytical Method

Plasma concentrations of olopatadine, Ml, M2 and M3 were determined using validated UPLC-MS/MS method. The LOQ for olopatadine, Ml and M3 were 0.0500 ng/mL, and that for M2 was 0.250 ng/mL.

SAFETY MEASUREMENTS

Safety was evaluated in this study by monitoring of adverse events, laboratory safety data, physical examinations, and vital sign evaluations.

DATA ANALYSIS

Pharmacokinetic Data Analysis

Pharmacokinetic:

Model-independent pharmacokinetic parameters were calculated for olopatadine, Ml, M2 and M3. Where applicable, for olopatadine and its human plasma metabolites: N-desmethyl olopatadine (M1), N-didesmethyl olopatadine (M2) and olopatadine N-oxide (M3), the plasma pharmacokinetic assessments included the observed Cmax, Tmax, AUC, non-parenteral clearance (CL/F for parent only) and elimination half-life. Urinary excretion parameters included urinary recovery (amount and percent dose) and renal clearance (CLr).

Safety

Safety criteria included an assessment of nasal examination parameters (significant anatomic abnormalities, evidence of infection, bleeding, ulcerations of the mucosa), physical examination parameters, cardiovascular parameters (pulse, systolic blood pressure, diastolic blood pressure); eletrocardiographic parameters (QTc interval, PR interval, QRS interval, RR interval, QT interval, rhythm, arrhythmia, conduction, morphology, MI, ST segment, T wave, and U wave); clinical laboratory parameters (hematology, blood chemistry, urinalysis); and adverse event monitoring.

Statistical Methods

The pharmacokinetic analysis consisted of describing the data with means and 95% confidence intervals. Descriptive statistics were provided for each renal impairment group for olopatadine and other key metabolites for the following: plasma concentrations at each sampling time; plasma pharmacokinetic assessments of the observed maximum drug concentration (Cmax), time of the maximum drug concentration (Tmax), area under the drug concentration-time curve (AUC), and elimination half-life (t1/2); urinary recovery (Ae); and, renal clearance (CLr).

RESULTS

Pharmacokinetic Results

Twenty-five subjects/patients were enrolled in the study. As assessed by creatinine clearance (CLcr) at the Screening Visit, 6 subjects with normal renal function (CLcr = 80.1 to 114 mL/min/1.73m^2), 7 patients with mild renal impairment (CLcR = *53.5* to 76.2 mL/min/l.73m^2), 6 patients with moderate renal impairment (CLcr = 33.4 to 49.1 mL/min/l.73m^2), and 6 patients with severe renal impairment (CLcr 5.2 to 29.9 mL/min/173m^2) were administered a single intranasal dose (two 100 uL sprays/nostril for a total dose of 2.4 mg) of Olopatadine Nasal 0.6%.

The mean pharmacokinetic parameters for olopatadine in the 6 healthy subjects and 19 patients with varying degrees of renal impairment are presented in Table 1. Peak plasma concentrations of olopatadine averaged 18.1 ± 10.9 ng/mL in healthy subjects. No significant (p = 0.8166) differences were seen in mean Cmax values among the 4 study groups. Mean AUC values were similar in healthy subjects and patients with either mild or moderate impairment, whereas a 2.5-fold higher mean in severely impaired patients was significantly (p = 0.0009) different.

Figure 1 shows the mean plasma concentrations of olopatadine following single dose administration of olopatatine in patients with various degrees of renal impairment. Plasma concentrations were comparable in subjects with normal renal function and in patients with mild or moderate renal impairment, whereas in severely impaired patients olopatadine plasma concentrations were much higher and more prolonged.

The mean PK parameters for olopatadine in the 6 healthy subjects and 19 patients with varying degrees of renal impairment are presented in Table 1. Peak plasma concentrations of olopatadine averaged 18.1 ± 10.9 ng/mL in healthy subjects. No significant (p = 0.8166) differences were seen in mean Cmax values among the 4 study groups. Mean $AUC_{0\text{-}inf}$ values were similar in healthy subjects and patients with either mild or moderate impairment, whereas a 2.5-fold higher mean in severely impaired patients was significantly (p = 0.0009) different.

Urinary recovery of olopatadine averaged 39.2 ± 19.8% of the nasal dose in healthy

subjects as compared to 10.6 ± 7.1% of the dose in severely impaired patients. Renal clearance significantly decreased about 13-fold with increasing renal impairment.

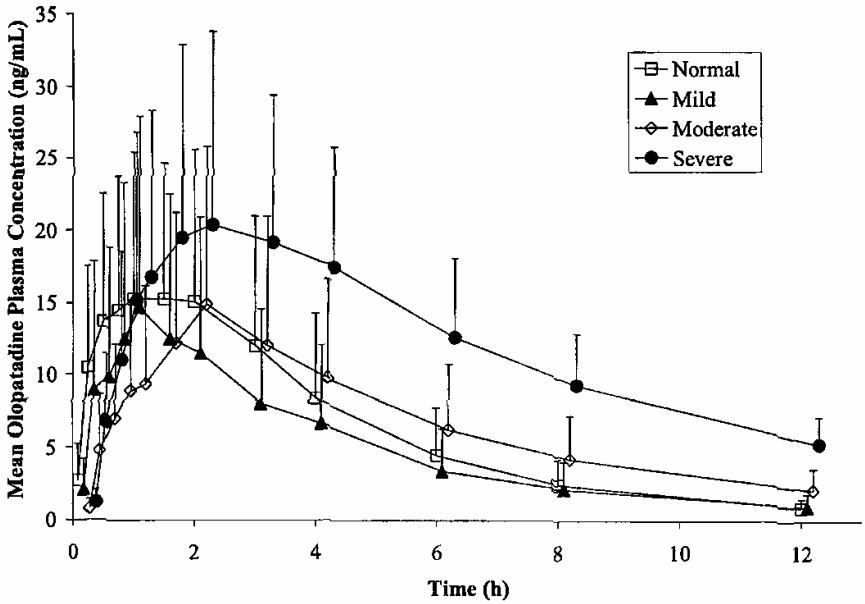


Figure 1. Mean plasma concentrations of olopatadine (ng/ mL) in subjects with normal and impaired renal function following single administration of olopatadine 0.6%

Table 1. Summary of Olopatadine mean ± SD (range) PK parameters in Patients With Impaired Renal Function and Subjects with Normal Renal Function Following Intranasal Administration of Olopatadine Nasal 0.6% (ITT analysis)

Pharmacokinetic Parameter	**Healthy Subjects (N=6)**	**Mild Impairment (N=7)**	**Moderate Impairment (N=6)**	**Severe Impairment (N=6)**
Cmax (ng/mL)	18.1 ± 10.9 (3.80-29.9)	15.5± 13.4 (0.884-33.5)	16.2± 11.3 (3.40 -31.1)	21.6± 13.1 (4.82-38.1)
Tmax (h)	1.17 ± 0.52 (0.50-2.00)	0.93 ± 0.28 (0.75-1.50)	1.67 ± 0.26 (1.50-2.00)	2.75 ± 1.08 (1.50- 4.00)
AUC_{0-12} (ng*h/mL)	77.0 ± 51.3 (17.0- 139)	61.3 ± 50.9 (5.42- 126)	81.7 ± 53.6 (17.6- 154)	149 ± 72 (46.6-240)
AUC_{0-inf} (ng*h/mL)	89.7±59.0 (20.5-155)	74.4± 61.9 (9.66- 157)	117±72 (26.4-214)	251 ±93 (113-374)
CL/F (L/h)	45.4 ± 39.0 (15.5-117)	80.9 ± 85.3 (15.3 -248)	34.9 ± 31.4 (11.2-91.0)	11.1 ± 5.3 (6.42-21.2)
T1/2 (h)	11.5±3.0 (7.2- 14.5)	10.2± 1.7 (7.9-12.5)	12.6±2.4 (10.2- 15.6)	15.5±2.0 (12.9-18.4)
$Ae_{0-48\ h}$ (ug)	940±474 (264- 1410)	525±452 (63.2-1290)	463±367 (58.1 -956)	253±170 (16.7-479)
Ae (% dose)	39.2± 19.8 (11.0- 58.7)	21.9± 18.9 (2.63-53.9)	19.3± 15.3 (2.42-39.8)	10.6±7.1 (0.697-20.01
CL_R (L/h)	12.4±5.9 (7.98-24.0)	7.08± 1.23 (5.23-8.68)	4.05±2.00 (1.37-6.55)	0.97±0.51 (0.17-1.59)

The N-desmethyl metabolite of olopatadine (Ml) is a minor active metabolite of olopatadine in human plasma. Following administration of Olopatadine Nasal 0.6%, peak plasma

concentrations of M1 were seen within 6 to 24 hours post-dose. Similar to olopatadine, mean plasma M1 concentrations were not greatly different between subjects with normal renal function and patients with mild or moderate renal impairment, whereas they were markedly higher and prolonged in severely impaired patients (Table 2).

Table 2. Mean ± SD (range) M1 Pharmacokinetic Parameters in Patients With Impaired Renal Function and Subjects with Normal Renal Function Following Intranasal Administration of Olopatadine Nasal 0.6% (ITT analysis)

Pharmacokinetic Parameter	**Healthy Subjects** (N=6)	**Mild Impairment** (N=7)	**Moderate Impairment** (N=6)	**Severe Impairment** (N=6)
Cmax (ng/mL)	0.192 ± 0.138 (BLQ—0.328)	0.148 ± 0.093 (BLQ—0.251)	0.247 ± 0.226 (BLQ—0.540)	0.497 ± 0.447 (0.077—1.28)
Tmax (h)	2.60 ± 0.55 (2.00—3.00)	3.33 ± 0.82 (2.00—4.00)	3.25 ± 0.50 (3.00—4.00)	9.00 ± 7.35 (6.00—24.0)
AUC_{0-12h} (ng*h/mL)	2.09±0.15 (1.98—2.26)	1.69±0.42 (1.21—1.93)	2.53± 1.18 (0.916—3.54)	4.40± 3.90 (0.618—11.0)
AUCo-inf (ng*h/mL)	2.49±0.22 (2.27—2.71)	2.08±0.65 (1.34—2.55)	3.99± 1.86 (1.93 —5.94)	13.5±8.9 (5.69—26.5)
$T_{1/2}$(h)	4.0±0.5 (3.5—4.4)	4.2± 1.2 (3.1—5.4)	7.3±2.9 (4.2—11.2)	14.9±3.7 (9.1—18.1)
Ae_{O-48h} (ug)	14.3 ± 9.4 (3.90—24.7)	10.2 ± 9.85 (0.61 —23.2)	12.6 ± 13.6 (1.38—34.3)	13.9 ± 8.45 (5.41 —23.5)
Ae (%)	0.60 ± 0.39 (0.16— 1.03)	0.425 ± 0.4 (0.03— 0.965)	0.53 ± 0.565 (0.06— 1.43)	0.58 ± 0.35 (0.23—0.98)
CLr (L/h)	10.8±2.1 (8.78— 13.3)	7.55±2.7 (3.56—9.50)	4.2±1.4 (2.88—5.85)	1.09±0.33 (0.77— 1.53)

Metabolite M2

The N-didesmethyl metabolite of olopatadine (M2) was not quantifiable (≤0.250 ng/mL) in any plasma sample in all subjects/patients except at one time point (0.370 ng/mL at 4 hours) in one severe renal impairment patient. Although renal clearance of M2 decreased with decreasing creatinine clearance, urinary recovery of M2 was very minor, accounting for <0.06% of the dose across the study groups.

Metabolite M3

Following administration of Olopatadine Nasal 0.6%, measurable plasma concentrations of M3 were seen within 0.25 to 4 hours post-dose. Maximal plasma concentrations were seen within 45 minutes to 4 hours post-dose in healthy subjects and patients with mild or moderate impairment whereas, peak concentrations were observed at later time points (4 to 12 hours) in patients with severe impairment (Table 3).

Table 3. Mean ± SD (range) M3 Pharmacokinetic Parameters in Patients With Impaired Renal Function and Subjects with Normal Renal Function Following Intranasal Administration of Olopatadine Nasal 0.6% (ITT analysis)

Pharmacokinetic	**Healthy Subjects** (N=6)	**Mild Impairment** (N =7)	**Moderate Impairment** (N=6)	**Severe Impairment** (N=6)
Cmax (nglmL)	0.526 ± 0.348 0.123 to 1.02	0.373 ± 0.3 17 0.083 to 0.838	0.697 ± 0.549 0.074 to 1.34	1.89 ± 1.20 0.607 to 3.94
Tmax (h)	1.88 ± 0.92 (0.75-3.00)	2.50 ± 1.04 (1.5-4.00)	2.33 ± 0.52 (2.00-3.00)	6.33 ± 2.94 (4.00 -12.00)
AUC $_{0\text{-}12}$(ng*hr/mL)	2.69 ± 1.98 (0.561 -5.29)	2.72 ± 2.03 (0.511 -4.89)	4.7±3.53 (0.457-8.78)	16.3 ± 99 (4.99—31.8)
AUCo-inf (ng*h/mL)	2.89 ± 2.18 (0.581 -5.82)	3.08 ± 2.47 (0.518—5.95)	7.84 ± 5.16 (0.525 — 13.0)	36.9 ± 12.6 (19.7—51.5)
T1/2 (h)	2.5 ± 0.6 (1.9—3.3)	2.8 ± 1.1 (1.7—4.5)	6.0 ± 2.5 (3.4—9.3)	15.7 ± 59 (11.9—27.4)
Ae $_{0\text{-}48h}$ (ug)	58.1 ±35.8 (16.2 — 104)	35.4±36.1 (3.05—93.1)	45.0 ±33.8 (3.79—85.4)	61.2 ±4l.2 (5.97— 107)
Ae (%)	2.42± 1.49 (0.674—4.33)	1.48± 1.50 (0.127—3.88)	1.87± 1.41 (0.158—3.56)	2.56±1.72 (0.249—4.48)
CLr (L/h)	22.8±4.9 (17.3 —28.9)	15±3.9 (8.45— 19.6)	7.1 ±4.4 (1.0— 12.2)	1.6±0.9 (0.293—2.86)

Figures 2, 3 and 4 show the individual Cmax, AUC and Ae, respectively of the parent compound and major metabolites following single administration of olopatadine in subjects with various degrees of renal impairment.

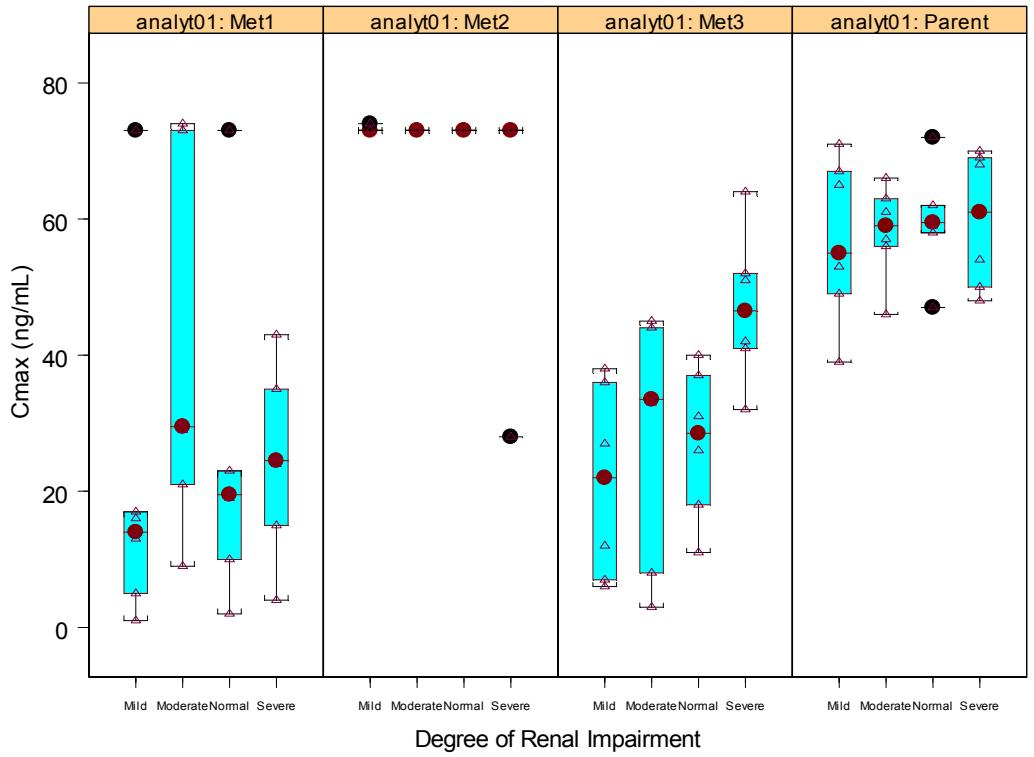


Figure 2. Individual Cmax (ng/mL) of parent compound and major metabolites following single administration of olopatidine 0.6% nasal spray in healthy subjects with various degrees of renal impairment

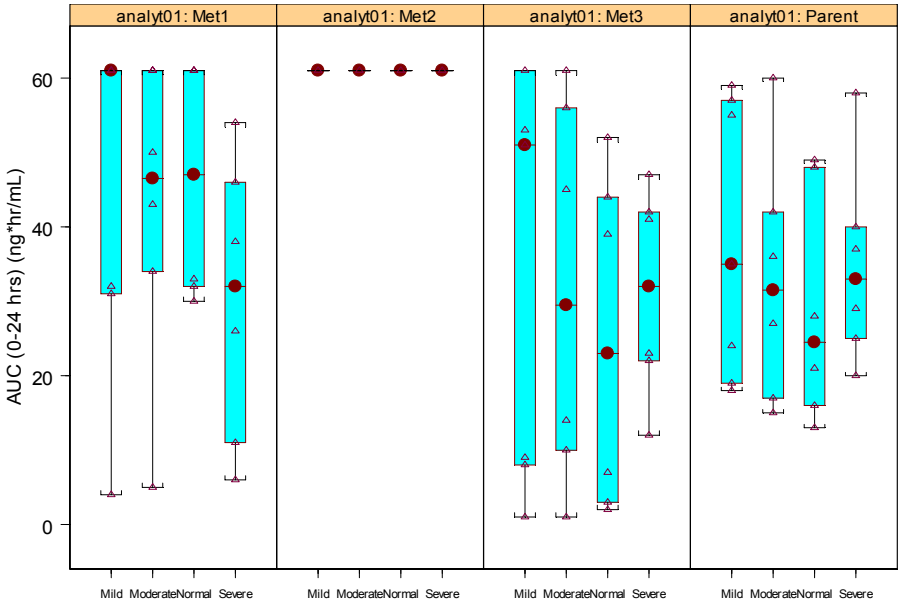


Figure 3. Individual AUC0-24h (ng/mL) of parent compound and major metabolites following single administration of olopatidine 0.6% nasal spray in healthy subjects with various degrees of renal impairment

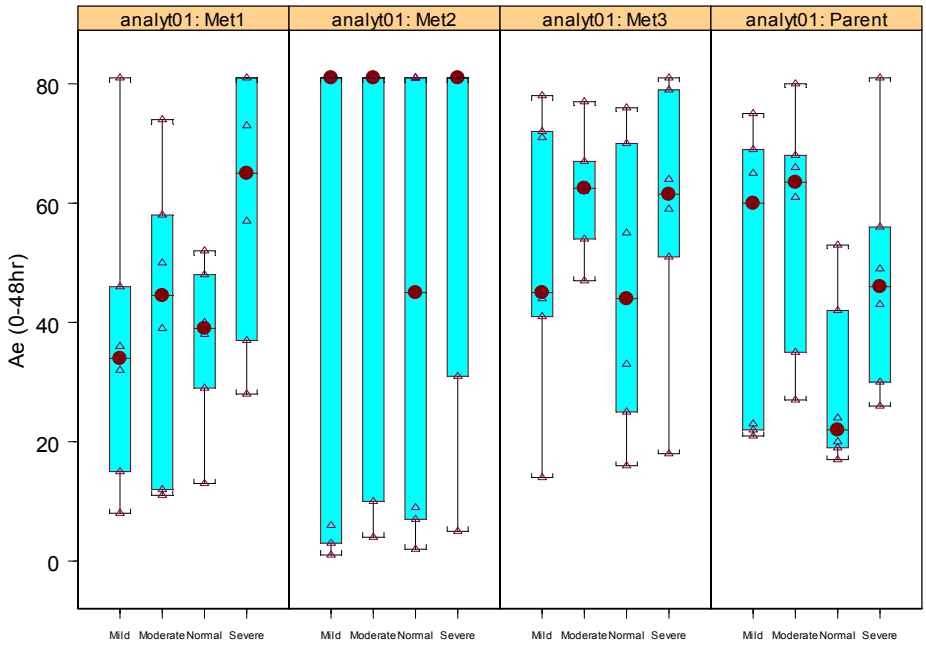


Figure 4. Individual Ae $_{(0\text{-}48hr)}$ of parent compound and major metabolites following single administration of olopatidine 0.6% nasal spray in healthy subjects with various degrees of renal impairment

Multiple Dose Predictions Based on the Principle of Superposition

Since the plasma concentrations of olopatadine and its minor metabolites have been shown to exhibit linear pharmacokinetics, the concentrations of parent drug and metabolites in plasma on multiple dosing were predicted based on the principle of superposition. For each study group, the mean single-dose plasma concentration versus time profile was superimposed every dosing interval (12 hours) until steady-state was achieved. The findings from the superposition analysis showed that the predicted steady-state plasma levels of olopatadine in subjects with normal renal function and in patients with mild and moderate impairment were similar to those observed after the single intranasal dose. In patients with severe impairment, superposition predicted steady-state levels to be approximately 1.5-fold higher than those observed after a single intranasal dose. Applying this difference to the mean single-dose Cmax values, the predicted mean steady-state Cmax of olopatadine in patients with severe renal impairment administered BID intranasal doses of Olopatadine Nasal 0.6% would be approximately 30 ng/mL. Thus, even in patients with severe renal impairment, the predicted peak systemic exposure is approximately 10-to 250-fold lower than the mean Cmax values observed after safe and well-tolerated 20 mg (309 ng/mL) to 400 mg (7700 ng/mL) oral doses. For metabolites Ml and M3, superposition would predict steady-state plasma levels approximately *2.5*- and 2-fold higher in patients with severe renal impairment, respectively than those observed after the single intranasal dose. However, these predicted peak steady-state levels would still be less than I and *5* ng/mL, respectively

SUMMARY OF FINDINGS

- After intranasal administration of Olopatadine Nasal 0.6%, no meaningful -differences were observed in the plasma pharmacokinetics of olopatadine in patients with mild or moderate renal impairment compared to subjects with normal renal function.
- The plasma Cmax and AUC values in patients with severe renal impairment were approximately 2.6- and 5.6-fold higher than those in healthy subjects.
- Higher plasma concentrations of the minor, active Ml and M3 metabolites were seen with increasing renal impairment particularly those in severely-impaired patients with 2.6- and 3.6-fold higher mean Cmax values, respectively.
- Urinary excretion of parent and metabolites was reduced in renally impaired patients.

CONCLUSIONS

- Overall, the observed or predicted higher systemic exposure of parent drug and metabolites seen in patients with severe renal impairment following intranasal doses of Olopatadine Nasal 0.6% are still 10- to 250-fold lower than peak concentrations observed following higher oral 20 to 400 mg doses which were safe and well-tolerated.

4.3 CPB Filing/Review Form

Clinical Pharmacology and Biopharmaceutics Review

"Patanase Nasal Spray"

NDA	21-861
Sponsor:	Alcon Research, Ltd.
Type:	NDA filing meeting package
Drug:	Olopatadine HCl
Submission date:	Dec 30, 2004
Draft review:	Feb 1, 2005
Review date:	Feb 4, 2005
Reviewer:	Sandra Suarez-Sharp, Ph.D.

BACKGROUND

Alcon has developed Olopatadine Hydrochloride Nasal Spray for the treatment and prevention of seasonal (b) (4) allergic rhinitis. Olopatadine Nasal Spray contains olopatadine hydrochloride 0.6% in an aqueous buffered solution. Dosing of Olopatadine Nasal Spray is proposed at 2 sprays per nostril, twice daily. Olopatadine is an inhibitor of the release of histamine from the mast cells and a relatively selective histamine H_1 - antagonist that inhibits the *in vivo* and *in vitro* type 1 immediate hypersensitivity reaction including inhibition of histamine induced cytokine secretion by epithelial cells.

Alcon received FDA approval for an identical formulation, Patanol® (Olopatadine Hydrochloride Ophthalmic Solution 0.1%), NDA 20-688 on December 18, 1996. Patanol is approved for the treatment of the signs and symptoms of allergic conjunctivitis.

INTRODUCTION

Chemistry

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

Molecular Formula: $C_{21}H_{23}NO_3$*HCl

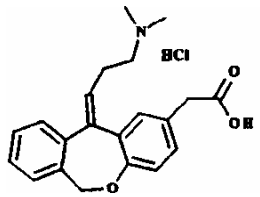


Figure 1. Structural formula for Olopatadine Hydrochloride

Molecular Weight: 373.88

Inhalation Device Composition

Olopatadine Hydrochloride Nasal Spray is a non-sterile, (b) (4) multiple-dose nasal spray solution containing 0.6% w/v olopatadine as base (equivalent to 0.665% w/v olopatadine hydrochloride). The excipients in the formulation include benzalkonium chloride, edetate disodium, povidone, sodium chloride, dibasic sodium phosphate, sodium hydroxide and hydrochloric acid (to adjust pH) and purified water. All excipients are compendial materials. According to the sponsor, this formulation is very similar to that of Olopatadine Ophthalmic Solution, 0.2%. (NDA 21-545).

The packaging system consists of a 30 mL white oval high-density polyethylene (HDPE) bottle, (b) (4) with a (b) (4) pump. The sealed bottle with pump is fitted with a white (b) (4) actuator and blue HDPE overcap.

Clinical pharmacology studies included in the NDA at the time of submission

Phase I Studies

- Study C-00-58 was a pharmacokinetic study of nasal administration of 0.1%, dosed QD and BID and 0.2% dosed QD for 2.5 days in healthy subjects.
- Study C-02-21 was a parallel-design, double-masked, placebo-controlled study using Olopatadine Nasal Spray 0.6% in healthy subjects.
- Study C-03-11 was a randomized, three-way crossover, absolute bioavailability study of Olopatadine Nasal 0.6% and Olopatadine Nasal 0.4% versus intravenous infusion of olopatadine sterile solution (1.5 mg) in healthy subjects.
- Study C-02-46 was a parallel-design, open-label of Olopatadine Nasal Spray 0.6% in renal impaired patients and subjects with normal renal function.
- Study C-03-10 was an excretion study of oral ^{14}C-olopatadine in healthy subjects.
- Study C-02-54 evaluated the possibility of QTc prolongation. This study was a crossover, cardiovascular safety and pharmacokinetic study of placebo or 20 mg olopatadine oral BID doses for 13.5 days in healthy subjects.
- Study C-00-23 evaluated the possibility of QTc prolongation. This study was a crossover, cardiovascular safety and pharmacokinetic study of placebo or 5 mg olopatadine oral BID doses for 2.5 days in healthy subjects.

Phase II and Phase III Clinical Studies

A total of 11 clinical efficacy and safety studies have been conducted with Olopatadine Nasal Spray in varying concentrations. Early studies evaluated concentrations of Olopatadine Nasal Spray 0.1% and 0.2%, however, results suggested sub-therapeutic efficacy. Later trials demonstrated consistent efficacy of olopatadine nasal spray when reformulated to achieve higher concentrations up to 0.6%.

PK/PD Related Studies of Olopatadine Nasal 0.1% and 0.2%

- Study C-00-10 was a US dose response study conducted in SAR patients. Olopatadine 0.1%, 0.2% and vehicle sprays were dosed QD and BID.
- Study C-00-70 was a US crossover dose-response study using antigen challenges in asymptomatic SAR patients in a clinic. Olopatadine 0.1%, 0.2%, azelastine 0.1% and vehicle were dosed prior to the antigen challenge.

Studies of Olopatadine Nasal 0.2%, 0.4%, and 0.6%

- Study C-01-83 was a Canadian dose response, onset of action, and duration of action study in SAR patients in a single site EEU. Olopatadine 0.2%, 0.4% and 0.6% were compared to vehicle. Patients were dosed once in the morning followed by a 12-hour assessment.

- **C-02-10:** Multiple dose study in SAR patients

Other Studies

TDOC-0000808: Metabolite profiles of ^{14}C-Olopatadine Hydrochloride in Human Plasma and Urine.

TR:022:33:0400: Study of drug interaction in human liver microsomes.

TR-94-644: In vitro protein binding
TR-89-88: In vitro protein binding
TR-90-73: In vitro protein binding

This reviewer's Comments

The table below summarizes the overall content of the clinical pharmacology and biopharmaceutics information (mainly paper submission) provided by the sponsor to support the request for the approval of this NDA. Phase I PK studies were conducted using a different formulation than that in the to-be marketed formulation. Since the drug product is a nasal solution, the impact of the formulation difference in deposition and PK of the drug is considered of non-clinical relevance. The sponsor has submitted a reviewable package for this NDA and therefore, there are no filing issues.

Study Title/Description	Tabular listing/PKPD summary	Analytical method	PK/PD parameters	Statistical analysis
All PK/PD studies	√	√	√	√

COMMENTS TO SPONSOR

The following comments should be conveyed to the sponsor:

- For studies C-02-54 and C-00-23 (cardiovascular safety and pharmacokinetic studies) submit the following information in a tabulated form and as SAS transport files: ID, Study, Day, Time (actual time), Treatment, RR, HR, QT, QTB, QTF, ΔQTB, ΔQTF (change from baseline), parent drug concentration, major metabolite concentration, time of PK samples, and other relevant parameters useful to evaluate QT prolongation.
- For the dose response studies (C-00-10, C-00-70, and C-01-83) submit the following information in a tabulated form and as SAS Transport files: ID, Treatment, Dose, Time, primary end point for efficacy and most relevant AEs, and other relevant information useful to evaluate Dose-Response.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics, the Division of Pharmaceutical Evaluation II (OCPB/DEP-II) has reviewed the NDA package for filing. The OCPB/DEP-II is aware of the pharmacokinetic studies that the sponsor submitted to the NDA. The NDA is filable from a CPB standpoint. Please convey the comments above to the sponsor.

Sandra Suarez-Sharp, Ph.D.
Pharmacokinetics Reviewer, DPEII, OCPB

Concurrence:

Emmanuel Fadiran Ph. D.
Team Leader, DPEII, OCPB

cc:
HFD-570 Div., Lee, Jafari
HFD-870 Malinowski, Hunt, Fadiran, Suarez-Sharp

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-861	**Brand Name**	Patanase
OCPB Division (I, II, III)	II	**Generic Name**	Olopatadine Hydrochloride
Medical Division	DPADP	**Drug Class**	**Antihistamine**
OCPB Reviewer	**Sandra Suarez-Sharp**	**Indication(s)**	**Seasonal Allergic Rhinitis**
OCPB Team Leader	**Emmanuel Fadiran**	**Dosage Form**	Nasal solution
PM Reviewer		**Dosing Regimen**	Adults >12 years: 2 sprays per nostril, twice daily
Date of Submission	December 30th, 2005	**Route of Administration**	Nasal administration
Estimated Due Date of OCPB Review	**August 2005**	**Sponsor**	Alcon Research, Ltd.
PDUFA Due Date	October 30, 2005	**Priority Classification**	**Standard**
Division Due Date	**September, 2005**		

3 Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:	**x**	**1**	**1**	**Study C-03-10**
Isozyme characterization:	**x**	**2**		
Blood/plasma ratio:				
Plasma protein binding:	**x**	**3**		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-	**x**	**6**		
single dose:	**x**	**4**		
multiple dose:	**x**	**3**		
Patients-	**x**			
single dose:	**x**	**1**	1	
multiple dose:	**x**	**3**	3	**C-02-10, C-0010, C-1-83**
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**2**	2	**C-00-58, C-02-10**
fasting / non-fasting multiple dose:	**x**	**2**	2	**C-00-58, C-02-10**
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	**X**	**1**	1	C-02-46
hepatic impairment:				
PD:				
Phase 2:	**X**	**3**	**2**	**C-02-10, C-0070, C-01-83**
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				

Population Analyses -				
Data rich:				
Data sparse:	**X**	**1**		
II. Biopharmaceutics	**X**	**1**	**1**	**C-00-58**
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
QTC STUDIES (PHASE 1)	**X**	**2**	**1**	**C-02-54, C-00-23**
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**10**	**9**	

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	**X**	Comments have been sent to firm (or attachment included). FDA letter date if applicable. **See review**
QBR questions (key issues to be considered)	1. Metabolic pathway 2. Inhibition/induction of drug of CYP enzymes 3. Drug-drug interaction 4. Effect of hepatic impairment on PK of drug 5. Gender, race, age, effect on the PK of the drug 6. Dose-response **7.** QT prolongation	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-861, HFD-570 (Zeccola, Lee), HFD-870 (Fadiran, Hunt, Malinowski)

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

/s/

Sandra Suarez
7/22/05 11:19:20 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
7/22/05 02:08:13 PM
BIOPHARMACEUTICS
I concur

"Patanase Nasal Spray"

NDA	**21-861**
Sponsor:	**Alcon Research, Ltd.**
Type:	**NDA filing meeting package**
Drug:	**Olopatadine HCl**
Submission date:	**Dec 30, 2004**
Draft review:	**Feb 1, 2005**
Review date:	**Feb 4, 2005**
Reviewer:	**Sandra Suarez-Sharp, Ph.D.**

BACKGROUND

Alcon has developed Olopatadine Hydrochloride Nasal Spray for the treatment and prevention of seasonal (b) (4) allergic rhinitis. Olopatadine Nasal Spray contains olopatadine hydrochloride 0.6% in an aqueous buffered solution. Dosing of Olopatadine Nasal Spray is proposed at 2 sprays per nostril, twice daily. Olopatadine is an inhibitor of the release of histamine from the mast cells and a relatively selective histamine H_1 - antagonist that inhibits the *in vivo* and *in vitro* type 1 immediate hypersensitivity reaction including inhibition of histamine induced cytokine secretion by epithelial cells.

Alcon received FDA approval for an identical formulation, Patanol® (Olopatadine Hydrochloride Ophthalmic Solution 0.1%), NDA 20-688 on December 18, 1996. Patanol is approved for the treatment of the signs and symptoms of allergic conjunctivitis.

INTRODUCTION

Chemistry

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

Molecular Formula: $C_{21}H_{23}NO_3$*HCl

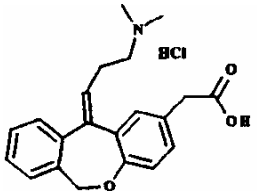


Figure 1. Structural formula for Olopatadine Hydrochloride

Molecular Weight: 373.88

Inhalation Device Composition

Olopatadine Hydrochloride Nasal Spray is a non-sterile, (b) (4) multiple-dose nasal spray solution containing 0.6% w/v olopatadine as base (equivalent to 0.665% w/v olopatadine hydrochloride). The excipients in the formulation include benzalkonium chloride, edetate disodium, povidone, sodium chloride, dibasic sodium phosphate, sodium hydroxide and hydrochloric acid (to adjust pH) and purified water. All excipients are compendial materials. According to the sponsor, this formulation is very similar to that of Olopatadine Ophthalmic Solution, 0.2%. (NDA 21-545).

The packaging system consists of a 30 mL white oval high-density polyethylene (HDPE) bottle, (b) (4) with a (b) (4) pump. The sealed bottle with pump is fitted with a white (b) (4) actuator and blue HDPE overcap.

Clinical pharmacology studies included in the NDA at the time of submission

Phase I Studies

- Study C-00-58 was a pharmacokinetic study of nasal administration of 0.1%, dosed QD and BID and 0.2% dosed QD for 2.5 days in healthy subjects.
- Study C-02-21 was a parallel-design, double-masked, placebo-controlled study using Olopatadine Nasal Spray 0.6% in healthy subjects.
- Study C-03-11 was a randomized, three-way crossover, absolute bioavailability study of Olopatadine Nasal 0.6% and Olopatadine Nasal 0.4% versus intravenous infusion of olopatadine sterile solution (1.5 mg) in healthy subjects.
- Study C-02-46 was a parallel-design, open-label of Olopatadine Nasal Spray 0.6% in renal impaired patients and subjects with normal renal function.
- Study C-03-10 was an excretion study of oral ^{14}C-olopatadine in healthy subjects.
- Study C-02-54 evaluated the possibility of QTc prolongation. This study was a crossover, cardiovascular safety and pharmacokinetic study of placebo or 20 mg olopatadine oral BID doses for 13.5 days in healthy subjects.
- Study C-00-23 evaluated the possibility of QTc prolongation. This study was a crossover, cardiovascular safety and pharmacokinetic study of placebo or 5 mg olopatadine oral BID doses for 2.5 days in healthy subjects.

Phase II and Phase III Clinical Studies

A total of 11 clinical efficacy and safety studies have been conducted with Olopatadine Nasal Spray in varying concentrations. Early studies evaluated concentrations of Olopatadine Nasal Spray 0.1% and 0.2%, however, results suggested sub-therapeutic efficacy. Later trials demonstrated consistent efficacy of olopatadine nasal spray when reformulated to achieve higher concentrations up to 0.6%.

PK/PD Related Studies of Olopatadine Nasal 0.1% and 0.2%

- Study C-00-10 was a US dose response study conducted in SAR patients. Olopatadine 0.1%, 0.2% and vehicle sprays were dosed QD and BID.
- Study C-00-70 was a US crossover dose-response study using antigen challenges in asymptomatic SAR patients in a clinic. Olopatadine 0.1%, 0.2%, azelastine 0.1% and vehicle were dosed prior to the antigen challenge.

Studies of Olopatadine Nasal 0.2%, 0.4%, and 0.6%

- Study C-01-83 was a Canadian dose response, onset of action, and duration of action study in SAR patients in a single site EEU. Olopatadine 0.2%, 0.4% and 0.6% were compared to vehicle. Patients were dosed once in the morning followed by a 12-hour assessment.

- **C-02-10:** Multiple dose study in SAR patients

Other Studies

TDOC-0000808: Metabolite profiles of ^{14}C-Olopatadine Hydrochloride in Human Plasma and Urine.

TR:022:33:0400: Study of drug interaction in human liver microsomes.

TR-94-644: In vitro protein binding
TR-89-88: In vitro protein binding
TR-90-73: In vitro protein binding

This reviewer's Comments

The table below summarizes the overall content of the clinical pharmacology and biopharmaceutics information (mainly paper submission) provided by the sponsor to support the request for the approval of this NDA. Phase I PK studies were conducted using a different formulation than that in the to-be marketed formulation. Since the drug product is a nasal solution, the impact of the formulation difference in deposition and PK of the drug is considered of non-clinical relevance. The sponsor has submitted a reviewable package for this NDA and therefore, there are no filing issues.

Study Title/Description	Tabular listing/PKPD summary	Analytical method	PK/PD parameters	Statistical analysis
All PK/PD studies	√	√	√	√

COMMENTS TO SPONSOR

The following comments should be conveyed to the sponsor:

- For studies C-02-54 and C-00-23 (cardiovascular safety and pharmacokinetic studies) submit the following information in a tabulated form and as SAS transport files: ID, Study, Day, Time (actual time), Treatment, RR, HR, QT, QTB, QTF, ΔQTB, ΔQTF (change from baseline), parent drug concentration, major metabolite concentration, time of PK samples, and other relevant parameters useful to evaluate QT prolongation.
- For the dose response studies (C-00-10, C-00-70, and C-01-83) submit the following information in a tabulated form and as SAS Transport files: ID, Treatment, Dose, Time, primary end point for efficacy and most relevant AEs, and other relevant information useful to evaluate Dose-Response.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics, the Division of Pharmaceutical Evaluation II (OCPB/DEP-II) has reviewed the NDA package for filing. The OCPB/DEP-II is aware of the pharmacokinetic studies that the sponsor submitted to the NDA. The NDA is filable from a CPB standpoint. Please convey the comments above to the sponsor.

Sandra Suarez-Sharp, Ph.D.
Pharmacokinetics Reviewer, DPEII, OCPB

Concurrence:

Emmanuel Fadiran Ph. D.
Team Leader, DPEII, OCPB

cc:
HFD-570 Div., Lee, Jafari
HFD-870 Malinowski, Hunt, Fadiran, Suarez-Sharp

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-861	**Brand Name**	Patanase
OCPB Division (I, II, III)	II	**Generic Name**	Olopatadine Hydrochloride
Medical Division	DPADP	**Drug Class**	Antihistamine
OCPB Reviewer	Sandra Suarez-Sharp	**Indication(s)**	Seasonal Allergic Rhinitis
OCPB Team Leader	Emmanuel Fadiran	**Dosage Form**	Nasal solution
PM Reviewer		**Dosing Regimen**	Adults >12 years: 2 sprays per nostril, twice daily
Date of Submission	December 30th, 2005	**Route of Administration**	Nasal administration
Estimated Due Date of OCPB Review	August 2005	**Sponsor**	Alcon Research, Ltd.
PDUFA Due Date	October 30, 2005	**Priority Classification**	Standard
Division Due Date	September, 2005		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:	**x**	**1**		**Study C-03-10**
Isozyme characterization:	**x**	**2**		
Blood/plasma ratio:				
Plasma protein binding:	**x**	**3**		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-	**x**	**6**		
single dose:	**x**	**4**		
multiple dose:	X	**3**		
Patients-	**x**			
single dose:	**x**	**1**		
multiple dose:	**x**	**3**		**C-02-10, C-0010, C-1-83**
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**2**		**C-00-58, C-02-10**
fasting / non-fasting multiple dose:	**x**	**2**		**C-00-58, C-02-10**
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

pediatrics:				
geriatrics:				
renal impairment:	**X**	**1**		C-02-46
hepatic impairment:				
PD:				
Phase 2:	**X**	**3**		**C-02-10, C-0070, C-01-83**
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	**X**	**1**		
II. Biopharmaceutics	**X**	**1**		**C-00-58**
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
QTC STUDIES (PHASE 1)	**X**	**2**		**C-02-54, C-00-23**
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**16**	**16**		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	**X**	Comments have been sent to firm (or attachment included). FDA letter date if applicable. See review
QBR questions (key issues to be considered)	1. Metabolic pathway 2. Inhibition/induction of drug of CYP enzymes 3. Drug-drug interaction 4. Effect of hepatic impairment on PK of drug 5. Gender, race, age, effect on the PK of the drug 6. Dose-response **7.** QT prolongation	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-861, HFD-570 (Zeccola, Lee), HFD-870 (Fadiran, Hunt, Malinowski)

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

/s/

Sandra Suarez
3/11/05 11:03:11 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
3/11/05 11:48:31 AM
BIOPHARMACEUTICS
I concur