# CLINICAL PHARMACOLOGY REVIEW

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| **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**



## 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 ) pertain to Clinical Pharmacology as follows:

**Study C-05-69** was a randomized, double-blind, vehicle-controlled, parallel-arm, long term safety study with efficacy component 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.

**Cardiovascular Safety**

The original submission contained the results of two cardiovascular safety studies and C02-54).

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

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

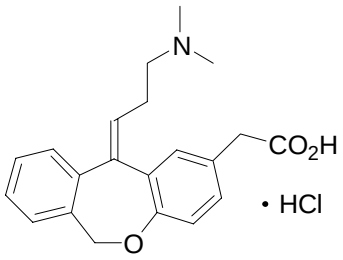
**2.1.2. What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?**

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, [redacted], multiple-dose nasal spray solution containing 0.6% w/v olopatadine as base (equivalent to [redacted] olopatadine hydrochloride). Each spray (100 microliters) delivers 665 mcg of olopatadine hydrochloride.

In the previously submitted formulation in original NDA 21-861, [redacted]. 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 [redacted] 3.7 to [redacted]. 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 103716 | FID 103717 | FID 103718 | 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 | [redacted] | | 0.01 | 0.01 | 0.01 | 0.01 | None | None |
| Edetate Disodium | None | None | [redacted] | | | [redacted] | None | None |
| Povidone | None. | None | | | | 0 | None | None |

| | | | | |
|---|---|---|---|---|
| Sodium Chloride<br>Dibasic Sodium Phosphate | | | -<br>- | -<br>- |
| 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 of the symptoms of SAR such as in patients 12

**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 with efficacy component 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 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.

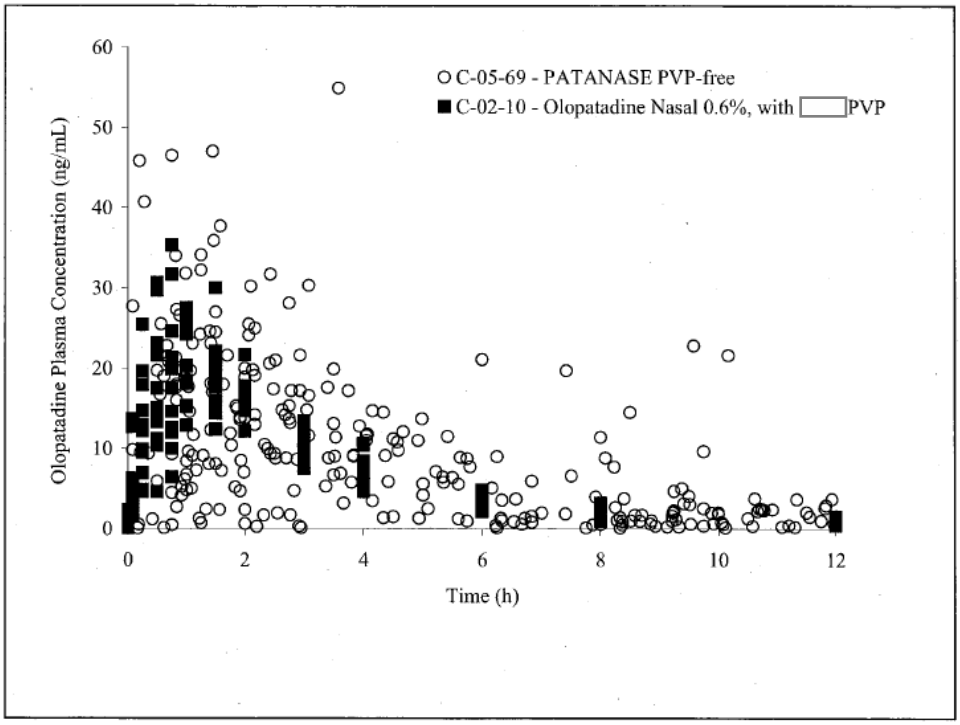



**Figure 2.2.1** Olopatadine plasma concentration-time profiles after intranasal BID doses of PVP Free Olopatadine Nasal Spray 0.6% in PAR patients (C-05-69) and Olopatadine Nasal Spray 0.6% with PVP in SAR Patients (C-02-10).

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 than the previous one (3.7 ). 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 ( and C-02-54).

[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).

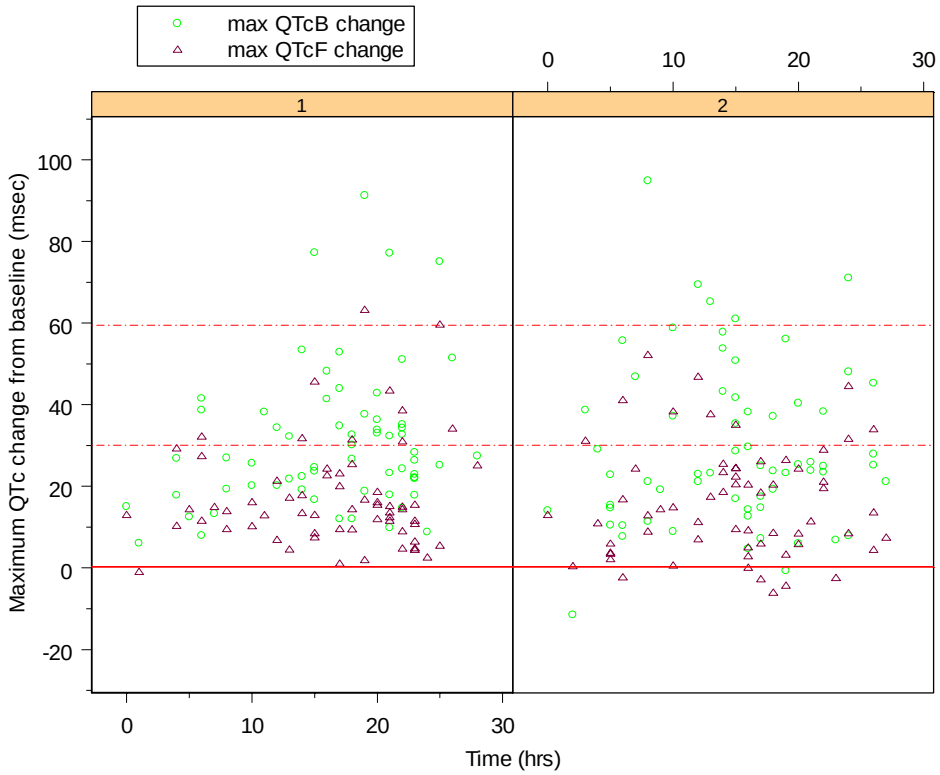



**Figure 2.3.1**. Individual maximum QTc change from baseline at steady state following multiple administration of the treatments (1=olopatadine and 2=placebo).

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:

Pages 13 through 15 redacted for the following reasons:
- - - - - - - - - - - - - - - - - - - - - - - - - - - -

## 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

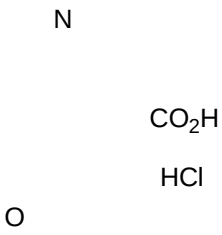
**2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?**

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 [redacted], nonsterile aqueous solution with a pH of approximately [redacted] 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 [redacted] L batch | Quality Standard |
|---|---|---|---|
| Olopatadine HCl | 0.665[a] | [redacted] | NF |
| Benzalkonium Chloride | 0.01 | | USP |
| Edetate Disodium | [redacted] | | USP |
| Povidone | | | USP |
| Sodium Chloride | | | USP |
| Dibasic Sodium Phosphate | | | NF |
| Sodium hydroxide and Hydrochloric Acid | Adjus pH [redacted] | Adju H [redacted] | NF |
| Purified Water | [redacted] | [redacted] | 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] [redacted] 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 [redacted] of the symptoms of SAR [redacted]

**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. [redacted]

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]. 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 |

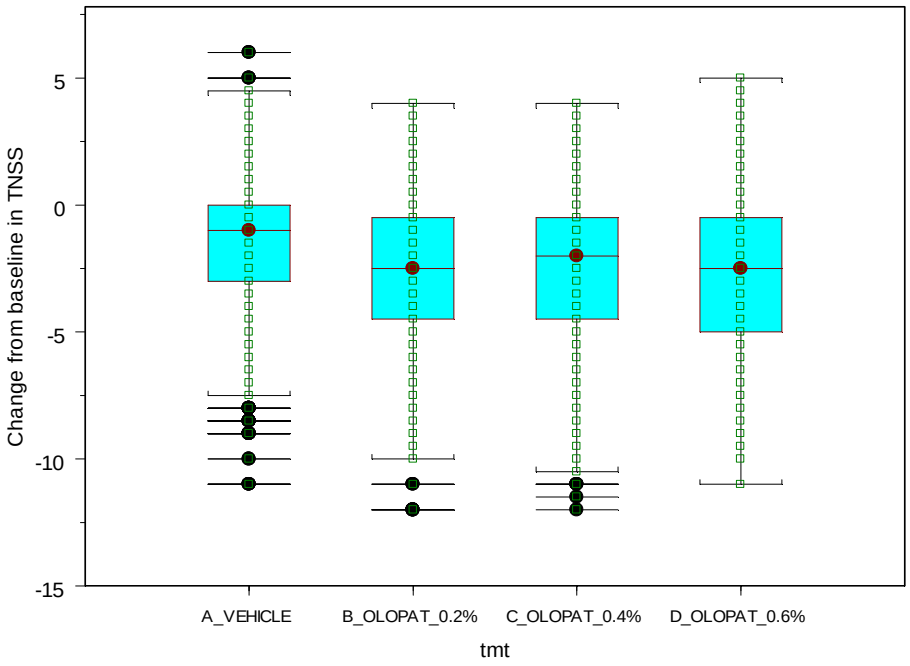



**Figure 2.2.4.1.1.** Change from baseline in TNSS following single nasal administration (2 sprays per nostril) of olopatadine 0.2-, 0.4-, and 0.6% nasal solution (Data from Study C-01-83).

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)

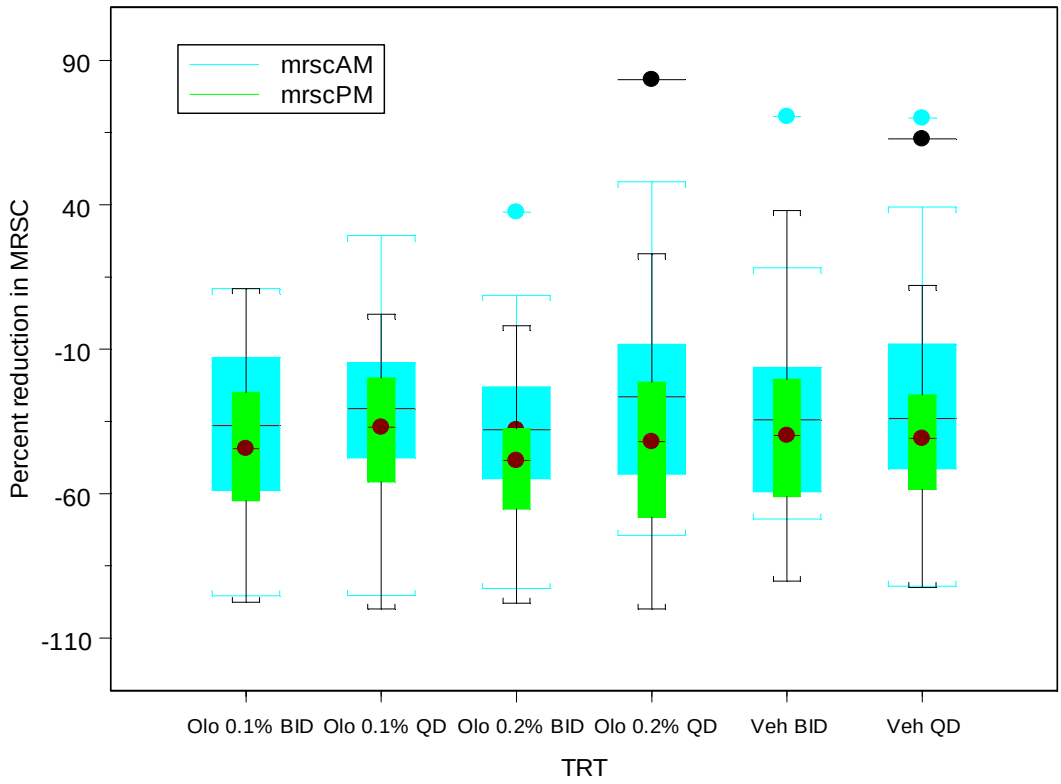



**Figure 2.2.4.1.2**. AM and PM percent reduction in MRSC (averaged across all visits) from the average AM and PM MRSC baselines following multiple administration of olopatadine 0.1 % and 0.2% nasal spray BID or QD (Data from Study C-00-10).

### 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.

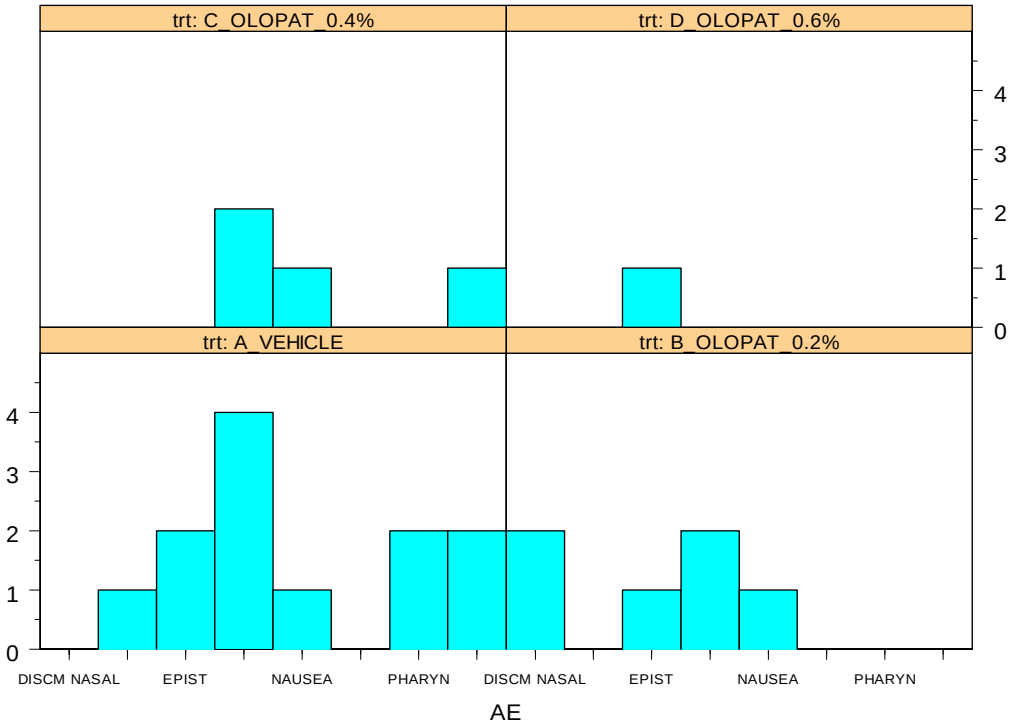



**Figure 2.2.4.2.1.** Adverse event frequency following single dose administration of olopatadine 0.2-, 0.4- and 0.6% to AR patients (Data from study C-01-83).

### 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 $\alpha$ value for each subject that provides a slope ~ zero from the regression of 1/RR $\alpha$ 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).

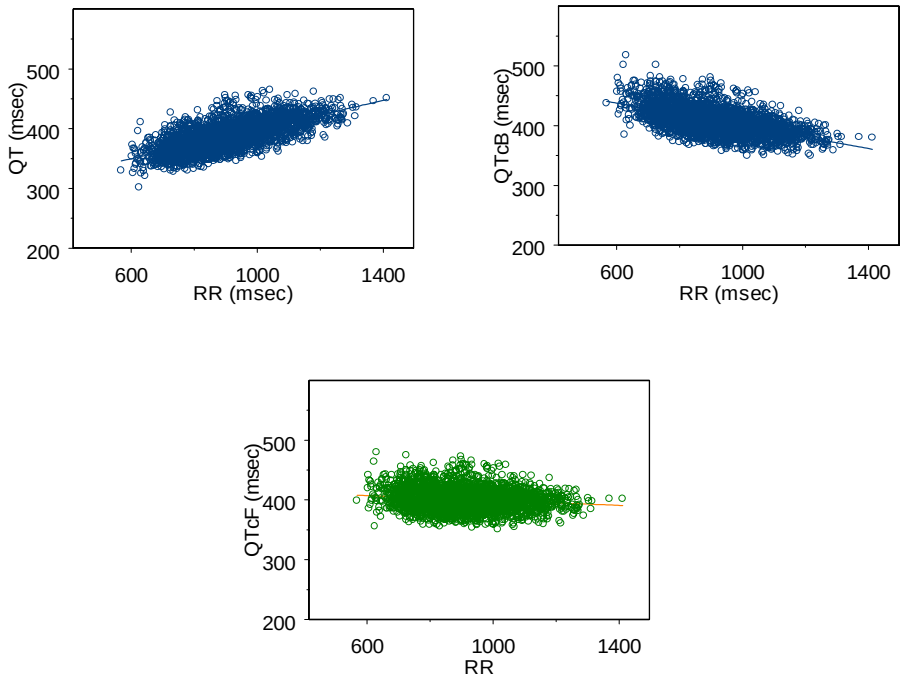



**Figure 2.2.4.3.1**. Individual QT, QTcB and QTcF as a function of RR following multiple administration of olopatadine 20 mg oral solution to male and female healthy volunteers.

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).

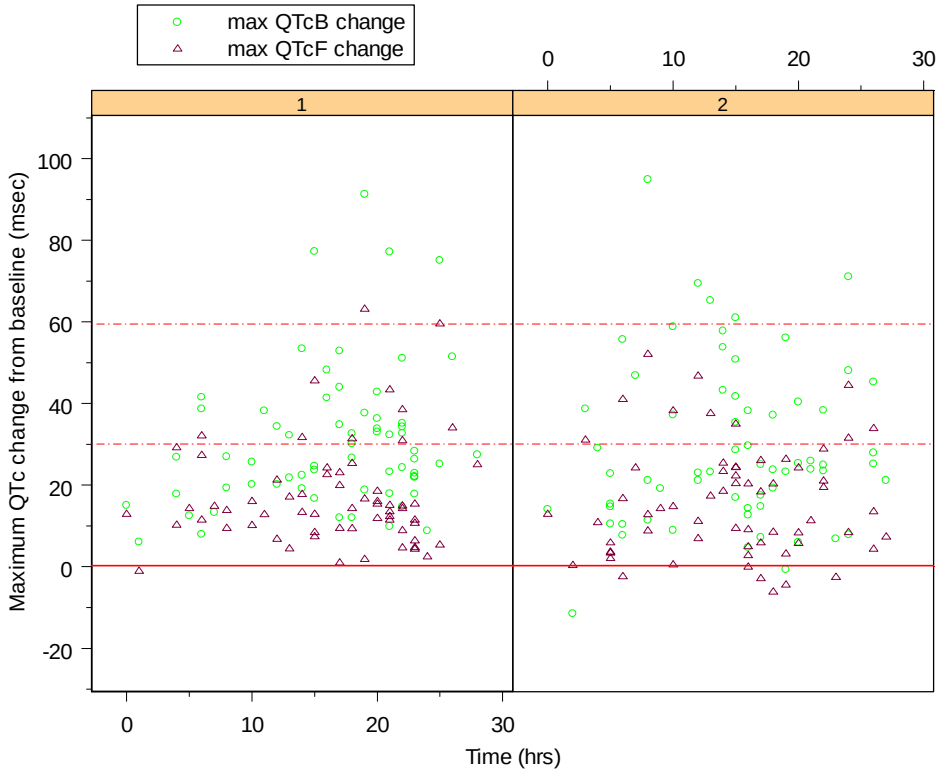



**Figure 2.2.4.3.2**. Individual maximum QTc change from baseline at steady state following multiple administration of the treatments (1=olopatadine and 2=placebo).

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 | 3636.5 | 73.3 | 634.7 | 2.8 | 86.1 |
| 102 | 3605.2 | 72.8 | 850.7 | 17.2 | 90.0 |
| 103 | 3556.6 | 71.4 | 762.1 | 15.3 | 86.7 |
| 104 | 3285.1 | 66.7 | 1025.8 | 20.8 | 87.6 |
| 105 | 3296.0 | 66.5 | 972.6 | 19.6 | 86.2 |
| 106 | 3498.7 | 70.2 | 567.7 | 11.4 | 81.6 |
| 107 | 3600.6 | 72.7 | 1374.8 | 27.8 | 100.4 |
| 108 | 3467.3 | 70.2 | 544.7 | 11.0 | 81.2 |
| Mean | 3493.3 | 70.5 | 841.7 | 17.0 | 87.5 |
| SD | 137.1 | 2.6 | 279.7 | 5.7 | 6.0 |
| Min | 3285.1 | 66.5 | 544.7 | 11.0 | 81.2 |

| | | | | | |
|---|---|---|---|---|---|
| Max | 3636.5 | 73 | 1375 | 27.8 | 100.4 |

**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.

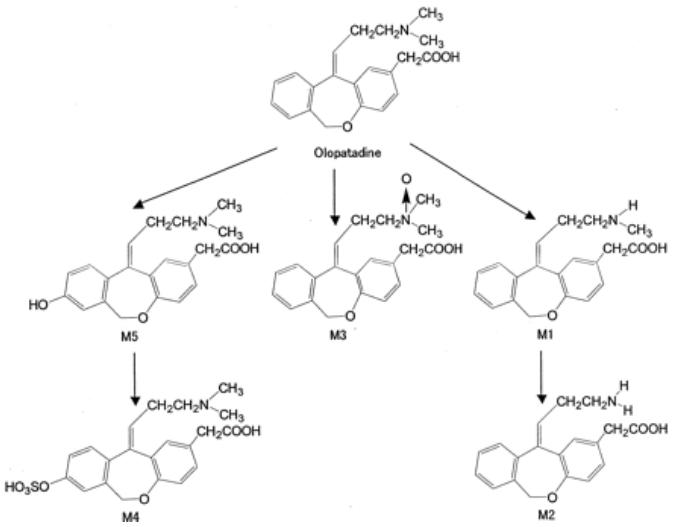



**Fig. 2.2.5.4.1.** Proposed metabolic pathway of olopatadine.

**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 [redacted] w/v povidone and [redacted] 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 [redacted] 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 103716 | **FID** 103717 | **FID** 103718 | **FID** 101688 | **FID** 105103 |
| Olopatadine Hydrochloride | 0.111 | 0.222 | 0.222 | 0.443 | 0.665 | 0.222 | 0.0111 |
| Olopatadine base | | | 0.2% | 0.4% | 0.6% | 0.2% | 0.01% |
| Benzalkonium Chloride | [redacted] | | 0.01 | 0.01 | 0.01 | None | None |
| Edetate Disodium | None | None | [redacted] | | | None | None |
| Povidone | None | None | | | | None | None |
| Sodium Chloride | [redacted] | | | | | - | - |
| Dibasic Sodium Phosphate | | | | | | - | - |
| Sodium Hydroxide and/or Hydrochloric Acid | | | | | | - | - |
| Purified Water | [redacted] | | | | | 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 [redacted] 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%<br>Inter-day l00-107%/RSD ≤l0.5% | C-00-58 Multiple dose-ranging PK (Alcon), Nasal, 0.1%, 0.2% BID<br><br>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%<br>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<br><br>Ml<br><br>M2<br><br>M3 | 0.050-5<br><br>0.050-5<br><br>0.250-25<br><br>0.050-5 | Intra-day 97.3-98.8%/RSD ≤5.6%<br>Inter-day 96-l0l%/RSD≤6.2%<br>Intra-day 108-1 12%/RSD ≤5.3%<br>Inter-day 110-11 1%/RSD≤4.9%<br>Intra-day 104-108%/RSD ≤6.2%<br>Inter-day 106-1 l0%/RSD≤6.3%<br>Intra-day 102-103%/RSD ≤4.4%<br>Inter-day 100-l04%/RSD≤5.7% | C-02-lO Phase III Efficacy/PK (Alcon), Nasal, Multiple dose 0.4%, 0.6% BID<br><br>C-02-54 Cardiovascular Safety/PK (Alcon), Oral Multiple dose 20 mg BID<br><br>C-02-46 Renal Impairment, Nasal, Single dose 0.6%<br><br>C-03-l 1 Absolute Bioavailability, Nasal/Intravenous |
| LC/MS/ MS | Human Urine | Olopatadine M3 | 3-1500<br><br>1-500 | Intra-day l00-10l%/RSD ≤4.9%<br>Inter-day 92-l00%/RSD≤9.5%<br>Intra-day l02-l04%/RSD≤4.8%<br>Inter-day 92-98%/RSD≤l 0.2% | C-02-46 Renal Impairment, Nasal, Single dose 0.6%<br><br>C-03-1l Absolute Bioavailability, Nasal/Intravenous |
| LC/MS/ MS | Human Urine | Ml<br><br>M2 | 0.50-250<br><br>0.50-250 | Intra-day l0l-104%/RSD ≤8.9%<br>Inter-day 9l-l03%/RSD≤5.7%<br>Intra-day 103-l09%/RSD ≤l4.3%<br>Inter-day 96-99%/RSD≤9.3% | C-02-46 Renal Impairment, Nasal, Single dose 0.6%<br><br>C-03-1 1 Absolute Bioavailability, Nasal/Intravenous |

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