CLINICAL PHARMACOLOGY REVIEW

NDA-21861 S-002	Submission Date(s): 1 June, 2009
Brand Name	PATANASE
Generic Name	Olopatadine Hydrochloride Nasal Spray 0.6%
Primary Clin Pharm Reviewer	Yun Xu, M.D. Ph.D.
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OND division	DPAP
Sponsor	Alcon
Submission Type	Original Submission
Priority Status	Priority
Formulation	Solution
Dosage and Administration	1 spray per nostril (1.2 mg) for patients (b) (4) through 11 years, twice daily
Indication	Relief of the symptoms of seasonal allergic rhinitis

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1 Executive Summary

Olopatadine Hydrochloride Nasal Spray 0.6% is approved as PATANASE Nasal Spray in the US for the relief of the symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older (NDA 21-861) with recommended dose of 2 sprays per nostril, twice daily. The objective of this NDA Supplement is to obtain a pediatric claim as well as pediatric exclusivity for PATANASE Nasal Spray. This NDA supplement provides supporting clinical safety and

efficacy information for registration of PATANASE Nasal Spray for treatment of allergic rhinitis in children 2 to 11 years of age. The recommended dose in patients (b) (4) through 11 years of age (1 spray per nostril, twice daily) is one-half the recommended dose in patients 12 years and older.

1.1 Recommendation

The Office of Clinical Pharmacology /Division 2 (OCP/DCP-2) has reviewed supplement of NDA 21861 submitted on 1 June, 2009 and finds it acceptable, provided that satisfactory agreement is reached between the sponsor and the Agency regarding language in the labeling text.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The recommended dose in patients (b) (4) through 11 years of age (0.6%, 1 spray per nostril, twice daily) is one-half the recommended dose in patients 12 years and older (0.6%, 2 spray per nostril). The steady-state systemic exposure (C_{max} and AUC_{0-12}) of olopatadine, metabolite N-desmethyl olopatadine (Ml), and metabolite olopatadine N-oxide (M3) are characterized in patients 6 through 11 years of age in study C-03-51. The results are compared to the steady-state systemic exposure in adult patients (from study C-02-10 in the original NDA submission). For both olopatadine and M3, steady-state systemic exposure in patients 6 through 11 years of age is lower than that in adults. For M1, steady-state systemic exposure in patients 6 through 11 years of age is higher than that in adults. The C_{max} and AUC_{0-12} of M1 in patients 6 through 11 years of age is approximately 18% and 37% higher than that observed in adult SAR patients, respectively. A sparse sampling approach was used to obtain PK information in patients 2 to <6 years of age. By directly comparing the concentrations at different time points (i.e. 2 hour post-dose and pre-dose) between patients 2 to <6 years of age (study C-07-02) and patients 6-11 years of age (study C-03-51), no apparent difference in olopatandie, M1 and M3 steady state exposure was identified between these two age groups following PATANASE Nasal Spray (0.6%) 1 spray per nostril, twice daily.

2 Pediatric Supplement Review

2.1 Regulatory Background and Clinical Development Plan

Olopatadine Hydrochloride Nasal Spray 0.6% is approved as PATANASE Nasal Spray in the US for the relief of the symptoms of SAR in patients 12 years of age and older (NDA 21-861). The objective of this NDA Supplement is to obtain a pediatric claim as well as pediatric exclusivity for PATANASE Nasal Spray. This NDA supplement provides supporting clinical safety and efficacy information for registration of PATANASE Nasal Spray for treatment of allergic rhinitis in children 2 to 11 years of age. The pediatric study requirement for children of ages 0 to 2 years was waived by FDA, because necessary studies would be difficult to conduct since SAR is not well characterized in children under 2 years of age.

The clinical development plan was specified by the FDA in a Written Request and consists of two clinical studies as follows:

Study #1(C-07-01): Phase III, US, safety and efficacy natural exposure study in patients 6 to 11 years of age. The objective of the study was to demonstrate the superiority of Olopatadine Hydrochloride Nasal Spray 0.6% relative to Nasal Spray Vehicle when given twice daily (BID) for the treatment of SAR for a 2 week period.

Study # 2 (C-07-02): Phase 1, US, safety and PK study in patients 2 years to less than 6 years of age who have a history of allergic rhinitis. The objectives of the study were to describe the safety and pharmacokinetics of Olopatadine Hydrochloride Nasal Spray 0.6% administered twice daily for two weeks in pediatric patients 2 to less than 6 years of age.

In addition to the two required studies listed above as stated in the written request, the following two studies (C-03-51 and C-04-20) were conducted in pediatric patients with PATANASE Nasal Spray containing povidone, which was not the commercially marketed formulation.

C-03-51: Phase 1, US, safety and PK study in pediatric SAR patients 6 to 11 years of age. The primary objectives of this study were to evaluate the safety and pharmacokinetics of olopatadine Nasal Spray 0.4% and 0.6% administered twice daily for 14.5 days in pediatric patients 6 to 11 years of age.

C-04-20: Phase III, US, safety and efficacy natural exposure study in pediatric SAR patients 6 to <12 years of age. The objective of the study was to evaluate 2 concentrations of olopatadine Nasal Spray (0.4% and 0.6%) administered as 1 spray per nostril, twice daily for two weeks.

Among these four studies, C-03-51 and C-07-02 collected pharmacokinetics data, and the study results are discussed below.

2.2 Study C-03-51

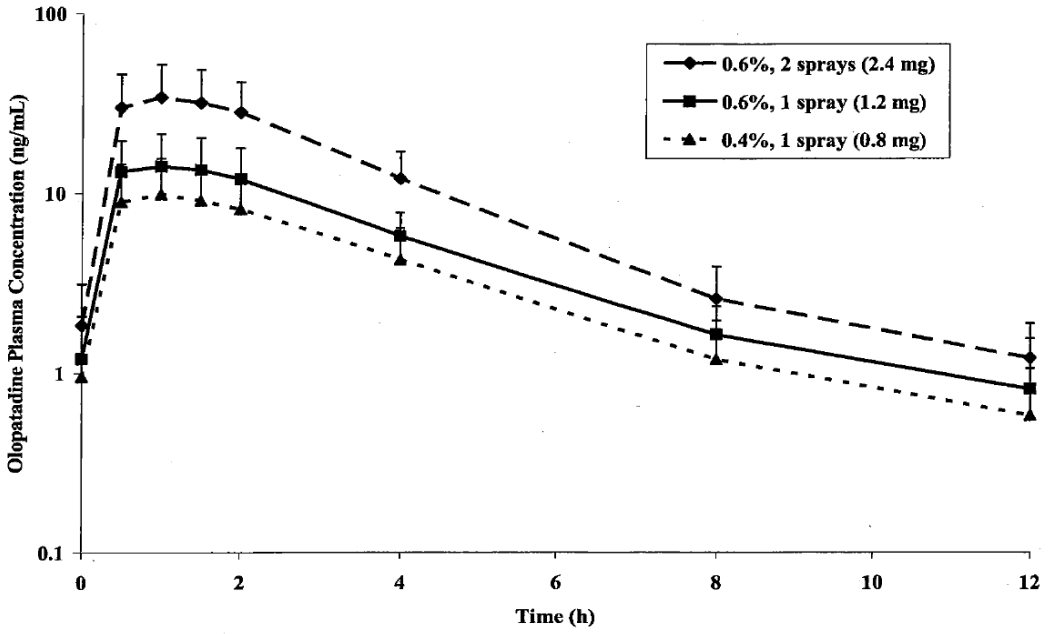
Study C-03-51 evaluated the safety and pharmacokinetics of olopatadine Nasal 0.4% and 0.6% administered as 1 spray per nostril, twice daily for 14.5 days in pediatric patients 6 to 11 years of age. The steady-state plasma pharmacokinetics of olopatadine and the two most abundant metabolites, N-desmethyl olopatadine (Ml) and olopatadine N-oxide (M3), were determined in pediatric SAR patients 6 to 11 years of age (n = 134) administered intranasal doses (total daily doses of 0.8 mg to 2.4 mg) of Olopatadine Hydrochloride Nasal Spray twice daily for 14 days with a final dose on the morning of Day 15. There were no measurable concentrations of N-didesmethyl olopatadine (M2).

Study C-03-51 used PATANASE Nasal Spray containing povidone, which is not the commercially marketed formulation. According to the original review of NDA 21861 by Dr. Sandra Suarez-Sharp dated July 22, 2005, the pharmacokinetics of olopatadine is similar between the commercially marketed formulation and the formulation containing povidone. Therefore, the pharmacokinetic results from the formulation containing povidone could be extrapolated to the commercially marketed formulation in pediatric patients.

As illustrated in Figure 1, olopatadine was rapidly absorbed with average peak plasma concentrations achieved within approximately one hour across the three active treatment groups (0.6% 2 sprays per nostril or 2.4 mg, 0.6% 1 spray per nostril or 1.2 mg; and 0.4% 1 spray per nostril or 0.8 mg). Plasma concentrations declined in a monophasic manner with the mean

elimination half-life of olopatadine ranging from 2.3 to 3.0 hours, up to 5-fold less than the half-life reported in adult SAR patients (8 to 10 hours) in Alcon Study C-02-10. The sponsor indicated the shorter half-lives observed in pediatric SAR patients may reflect incomplete characterization of the elimination phase due to the shorter sampling period (12 hours) in the current study compared to a 48-hour sampling schedule in adult SAR patients whose plasma concentrations declined in a biphasic manner, which is a reasonable explanation.

Figure 1. Mean (± SD) Steady-State (Day 15) Olopatadine Plasma Concentrations in Pediatric SAR Patients 6 to 11 Years of Age Administered Multiple Doses of Olopatadine Nasal Spray Twice-Daily



Across doses ranging from 0.8 mg to 2.4 mg, the mean steady-state olopatadine C_{max} and AUC_{0-12} increased linearly in a dose proportional manner (Table 1).

Table 1. Mean Steady-State (Day 15) Olopatadine Pharmacokinetic Parameters after Multiple Doses of Olopatadine Nasal Spray in Pediatric SAR Patients 6 to 11 Years of Age

Alcon Study C-03-51 (Pediatric SAR Patients)						
Treatment		**C_{max} (ng/mL)**	**T_{max} (h)**	**AUC_{0-12} (ng*h/mL)**	**CL/F (L/h)**	**$t_{½}$ (h)**
0.6% 2 sprays/nostril (2.4 mg)	**Mean**	38.1	1.10	137	22.5	2.3
	SD	19.4	0.67	56.6	15.7	0.5
	N	44	44	44	44	44
	Min	4.75	0.48	28.2	9.21	1.6
	Max	80.1	4.00	257	73.6	4.2
0.6% 1 spray/nostril (1.2 mg)	**Mean**	15.4	1.25	62.3	28.6	2.8
	SD	7.26	0.81	23.7	54.7	1.1
	N	42	42	42	42	42
	Min	0.464	0.45	1.41	8.4	1.8
	Max	29.0	4.00	87.5	371	7.6
0.4% 1 spray/nostril (0.8 mg)	**Mean**	10.8	1.06	44.3	27.2	3.0
	SD	6.18	0.55	20.6	39.0	1.9
	N	41	41	41	41	41
	Min	0.435	0.00*	2.39	8.45	1.9
	Max	24.9	2.00	91.5	252	12.2

*Olopatadine C_{max} for Patient 316 in the 0.8 mg treatment group occurred prior to the last dose on Day 15, i.e., T_{max} = 0 hr.

Metabolites Ml and M3 were rapidly formed with quantifiable levels observed in plasma as early as 30 minutes post-dose. At all doses (0.8, 1.2, and 2.4 mg), systemic exposure of both metabolites is markedly lower than that of olopatadine (see Table 2). Metabolite-to-parent ratios of C_{max}, AUC_{0-4} and AUC_{0-12} are less than 5% suggesting minimal conversion of olopatadine to its metabolites. These findings were nearly identical to results reported for adult SAR patients, who also exhibited minimal systemic exposure with ratios less than 1 % for Ml and less than 5% for M3.

Table 2. Metabolite/Parent Ratios of C_{max} and AUC at Steady-State (Day 15) After Multiple Doses of Olopatadine HCl Nasal Spray in Pediatric SAR Patients 6 to 11 Years of Age

Treatment	**Parameter**	**M1 Mean**	**M3 Mean**	**Parent Mean**	**M1/Parent (%)**	**M3/Parent (%)**
Olo 0.6% 2 Sprays	C_{max} (ng/mL)	0.447	1.05	38.1	1.21	2.79
	AUC_{0-4} (ng*h/mL)	1.53	3.08	95.1	1.45	3.23
	AUC_{0-12} (ng*h/mL)	2.70	4.33	137	1.75	3.14
Olo 0.6% 1 Spray	C_{max} (ng/mL)	0.216	0.389	15.4	1.39	2.42
	AUC_{0-4} (ng*h/mL)	0.721	1.19	41.0	1.57	2.76
	AUC_{0-12} (ng*h/mL)	1.37	1.80	62.3	1.99	2.77
Olo 0.4% 1 Spray	C_{max} (ng/mL)	0.128	0.270	10.8	1.21	2.53
	AUC_{0-4} (ng*h/mL)	0.444	0.870	28.8	1.57	2.94
	AUC_{0-12} (ng*h/mL)	0.950	1.39	44.3	1.95	2.88

Olo 0.6% 2 Sprays = Olopatadine Nasal 0.6% 2 Sprays
Olo 0.6% 1 Spray = Olopatadine Nasal 0.6% 1 Spray
Olo 0.4% 1 Spray = Olopatadine Nasal 0.4% 1 Spray

The recommended dose in patients 6 through 11 years of age (0.6%, 1 spray per nostril) is one-half the recommended dose in patients 12 years and old (0.6%, 2 spray per nostril), twice daily. The steady-state systemic exposure of olopatadine, metabolite N-desmethyl olopatadine (Ml), and metabolite olopatadine N-oxide (M3) are characterized in patients 6 through 11 years of age in study C-03-51. The results are compared to the steady-state systemic exposure in adult patients (from study C-02-10 in the original NDA submission), which are summarized in Table 3. For both olopatadine and M3, steady-state systemic exposure in patients 6 through 11 years of age is lower than that in adults. For M1, steady-state systemic exposure in patients 6 through 11 years of age is higher than that in adults. On average, the C_{max} and AUC_{0-12} values of M1 in patients 6 through 11 years of age are approximately 18% and 37% higher, respectively than that observed in adult SAR patients.

Table 3. Mean (± SD) Steady-State exposure of Olopatadine, N-desmethyl Olopatadine (Ml), and Olopatadine N-oxide (M3) after Multiple Doses of Olopatadine Nasal Spray in Patients among Different Age Groups

	Pediatric (6 through 11 years) patients 0.6%, 1 spray per nostril, twice daily with povidone	**Adult SAR pateints** 0.6%, 2 spray per nostril, twice daily
Olopatadine		
C_{max} (ng/mL)	15.4 ± 7.26	23.3 ± 6.2
AUC_{0-12} (ng*h/mL)	62.3 ± 23.7	78.0 ± 13.9
M1		
C_{max} (ng/mL)	0.216 ± 0.105	0.183 ± 0.062
AUC_{0-12} (ng*h/mL)	1.37 ± 0.5	1.00 ±0.405
M3		
C_{max} (ng/mL)	0.389 ± 0.212	0.629 ± 0.241
AUC_{0-12} (ng*h/mL)	1.80 ± 0.762	2.42 ±0.778

To assess the potential for QT-interval prolongation, 6 electrocardiograms (ECGs) were conducted at baseline (Day 1) and at 1.5 hours following the last intranasal dose on Day 15. There were no statistically significant or clinically relevant changes between patients treated with Olopatadine Hydrochloride Nasal Spray and patients treated with Olopatadine Hydrochloride Nasal Spray Vehicle in the maximum change from baseline for QTcF; heart rate; or changes from baseline in RR, PR or QRS intervals. Overall, Olopatadine Hydrochloride Nasal Spray did not negatively impact the cardiovascular safety in pediatric SAR patients 6 to 11 years old administered doses ranging from 0.8 mg to 2.4 mg twice daily.

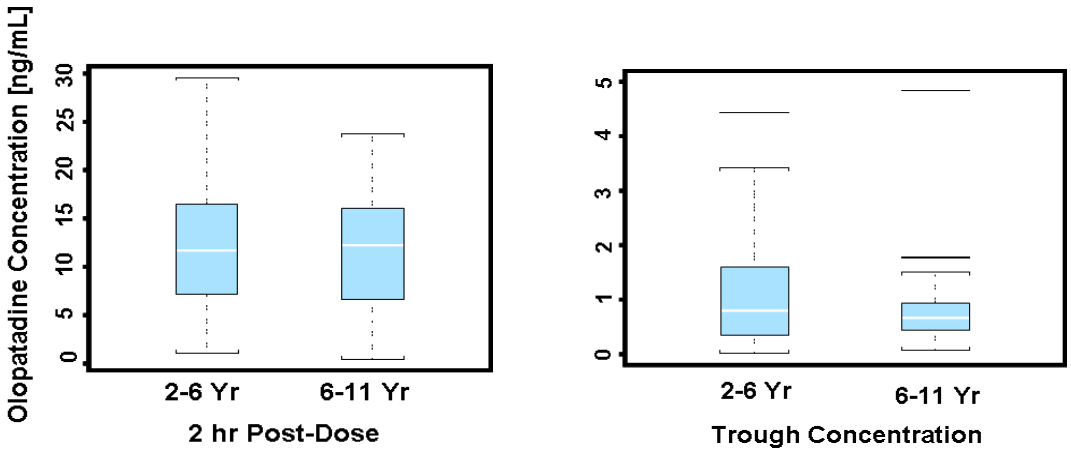
2.3 Study C-07-02

Study C-07 -02 was conducted to evaluate the safety and steady-state systemic pharmacokinetics of olopatadine and its major metabolites, N-desmethyl olopatadine (Ml), N-didesmethyl olopatadine (M2), and olopatadine N-oxide (M3) in pediatric patients 2 to less than 6 years of age administered one-half the recommended adult dose of Olopatadine Hydrochloride Nasal Spray 0.6%, (i.e., one spray per nostril (1.2 mg) twice daily equivalent to a total daily dose of 2.4 mg). Patients were treated for at least 14 days (BID) with a single dose on the morning of Day 15. Of the 132 enrolled patients, 71 patients were 2 to less than 4 years of age, and 61 patients

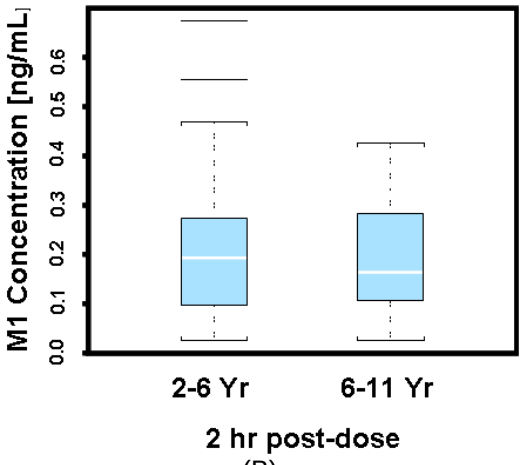
were 4 to less than 6 years of age. Of the 132 enrolled patients, 66 patients were randomized to receive Olopatadine Hydrochloride Nasal Spray 0.6% (37 patients were 2 to less than 4 years of age, and 29 patients were 4 to less than 6 years of age), and 66 patients were randomized to receive Olopatadine Hydrochloride Vehicle. A sparse sampling strategy was employed to limit the number of samples collected per patient. Plasma samples were collected on Day 1 after the first dose at three time intervals: 15 to 30 minutes, 1.5 to 2.5 hours; and 5 to 8 hours. On Day 15, a trough sample was collected prior to the final dose and a post-dose sample was collected between 1.5 and 2 hours. Samples were assayed for olopatadine, Ml, M2, and M3, using validated analytical methods for olopatadine, Ml and M3. However, there were no measurable plasma concentrations for M2 for further evaluation.

Because of the sparse sampling plan in this study, a pharmacometrics approach was used to analyze the data. Details of the analysis could be found in the pharmacometrics review. By directly comparing the concentrations at different time points (i.e. 2 hour post-dose and pre-dose) between patients 2-6 years of age and patients 6-11 years of age, no apparent difference in olopatandie, M1 and M3 steady state exposure after 14 days of administration was identified between these two age groups following PATANASE Nasal Spray (0.6%) 1 spray per nostril, twice daily (Figure 2 and Table 4),

Figure 2. Comparison of Steady State Olopatadine Concentration (A), M1 Concentration (B), and M3 Concentration (C) in Patients 6-11 Years of Age and in Patients 2-6 Years of Age



(A)



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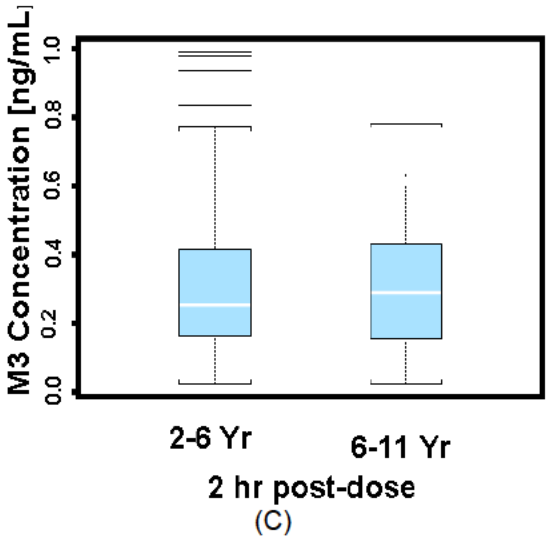


(C)

Note: most M1 and M3 trough concentrations were undetectable (Below LOQ).

Table 4. Summary Olopatadine, M1, and M3 Plasma Concentrations in Patients 6-11 Years of Age and in Patients 2 to <6 Years of Age

Compound	Day	Study C-03-51	Study C-07-02	Median Concentration (ng/mL)	
Age				2-<6 yr	6-11 yr
Olopatadine	15	2 hr	1.5 - 2.5 hr	11.7	12.25
		Trough	Trough	0.8	0.67
M1	15	2 hr	1.5 - 2.5 hr	0.19	0.16
		Trough	Trough	0.025	0.025
M3	15	2 hr	1.5 - 2.5 hr	0.25	0.29
		Trough	Trough	0.025	0.025

2.4 Analytical section

Analysis of olopatadine M1, and M2 and M3 were conducted using a previously validated HPLC/MS/MS method. Detailed review of the analytical methods could be found in the original review of NDA 21-861 by Dr Sandra Suarez-Sharp dated July 22, 2005. The limit of quantitation was 0.25 ng/mL for M2, and 0.05 ng/mL for olopatadine, M1 and M3. The results of sample analysis in individual study are acceptable as evidenced by QC sample precision and accuracy within ± 15%.

3 Detailed Labeling Recommendations

The labeling recommendation is based on the review for the original submission and the review for the re-submission. (b) (4)

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

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

4 Appendix

4.1 Pharmacometrics Review

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is the exposure of olopatadine similar for patients 2-6 years of age as compared to patients 6-11 years of age following 1200 µg q 12 hr?

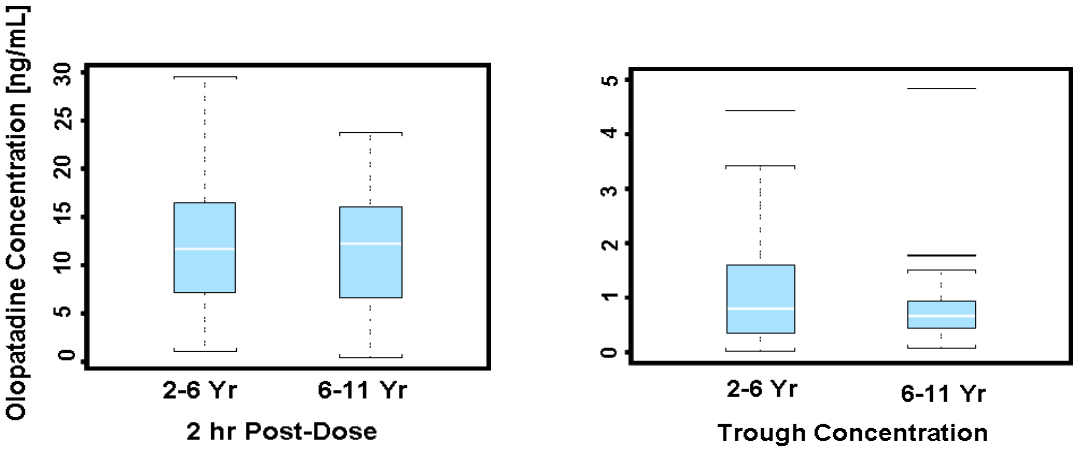
No apparent difference was identified in Olopatandie exposure in patients 2-6 years of age as compared to patients 6-11 years of age following 1200 µg q 12 hr.

In the current submission, the efficacy and safety information was collected in patients 6 – 11 years of age. In patients 2 - 6 years of age, only PK information was obtained and no efficacy and safety trial was conducted. Therefore, it is critical to understand if similar exposure can be achieved in patients 2-6 years of age and 6-11 years of age following the same dose (one spray per nostril twice daily or 1200 µg q 12 hr).

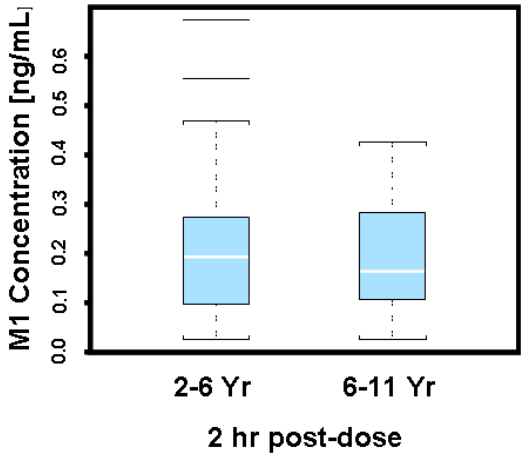
The sponsor collected PK samples in patients 2-6 years of age and 6-11 years of age from two separate trials (Study C-07-02 and Study C-03-51: Table 1). Age is not the only difference between the two trials. In fact, Study C-07-02 included patients 2-6 years of age using marketed formulation (with no povidone). However, Study C-03-51 was conducted in patients 6-11 years of age using non-commercially marketed formulation (with povidone). Previous review by Dr. Sandra Suarez-Sharp indicated that the formulation difference did not lead to meaningful change in Olopatadine pharmacokinetic profiles. Therefore, the concentrations for both Olopatadine and it metabolites (M1 and M3) collected in the two trials at steady state (i.e. Day 15) can be directly compared.

As indicated in Figure 1 and Table 2, no apparent difference in the steady state exposure of Olopatadine and its major metabolites were seen at various time points (i.e. 2 hour post-dose and pre-dose) in patients 2-6 years of age and 6-11 years of age following the same dose (one spray per nostril, twice daily or 1200 µg q 12 hr).

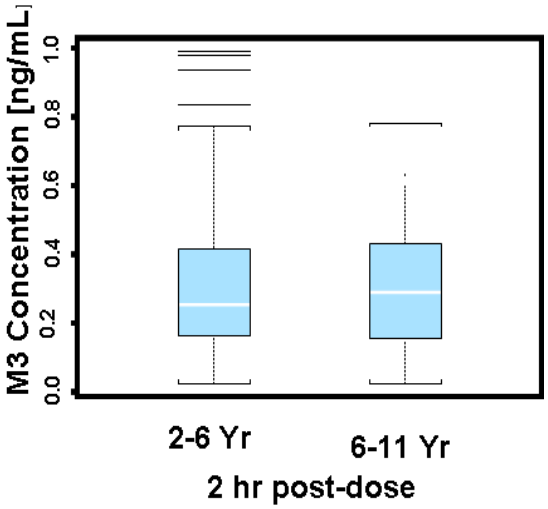
Figure 1 Comparison of Steady State Olopatadine Concentration (A), M1 Concentration (B), and M3 Concentration (C) in Patients 6-11 Years of Age and in Patients 2-6 Years of Age



(A)



(B)



(C)

Note: most M1 and M3 trough concentrations were undetectable (Below LOQ).

Table 1 Summary of PK Studies

Study	Age	Formulations	Sampling Day	Time Points
C-07-02	2-6 yr	Marketing Formulation (With No povidon)	Day 1	0.25-0.5, 1.5-2.5 and 5-8 hr
			Day 15	0, 1.5-2.5 hr
C-03-51	6-11 yr	None-Marketing-Formulation (With Povidon)	Day 15	0, 0.5, 1, 1.5, 2, 4, 8 and 12 hr

Table 2. Summary Olopatadine, M1, and M3 Accumulation

Compound	Day	Study C-03-51	Study C-07-02	Median Concentration (ng/mL)	
Age				2-6 yr	6-11 yr
Olopatadine	15	2 hr	1.5 - 2.5 hr	11.7	12.25
		Trough	Trough	0.8	0.67
M1	15	2 hr	1.5 - 2.5 hr	0.19	0.16
		Trough	Trough	0.025	0.025
M3	15	2 hr	1.5 - 2.5 hr	0.25	0.29
		Trough	Trough	0.025	0.025

1.2 Recommendations

None.

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

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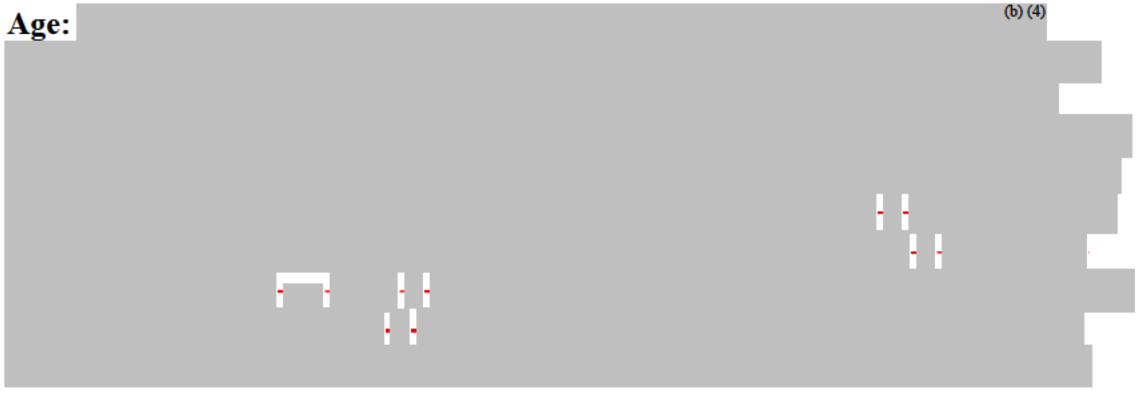
12.3 Pharmacokinetics

Age: (b) (4)



(b) (4)

(b) (4)

2 PERTINENT REGULATORY BACKGROUND

The submission dated on 29 May 2009 is a submission for pediatric study report. The sponsor is requesting an exclusivity determination from the Agency. The sponsor is also seeking the indication for the relief of the nasal (b) (4) symptoms of seasonal allergic rhinitis in adolescents, adults, and children (b) ( ) years.

Olopatadine hydrochloride (Patanase ® nasal spray) has been approved for the relief of the symptoms of seasonal allergic rhinitis in patients 12 years of age and older. The Agency issued a Written Request for pediatric studies on 29 June 2007. To fulfill the Written Request, the sponsor conducted two major clinical studies using the to-be-marketed formulation – Study Alcon C-07-01 (efficacy and safety study) for patients 6-12 years of age and Study Alcon C-07-02 (safety and pharmacokinetic study) for patients 2-6 years of age. Two additional studies were conducted by using the nasal spray formulation containing povidone (non-commercially marketed formulation). The clinical trials were summarized in Table 3.

Table 3 Summary of Clinical Trials

Trial	Type	Study Design	Patient	Treatment	Dosing	Duration	Sample Size
C-07-02	PK Study	Phase I, US, Randomized, vehicle-controlled, parallel group double-masked, multi-center safety and PK study	Pediatric patients 2-6 years of age with a history of allergic rhinitis	Olo 0.6% 1 spray per nostril, Olo Veh 1 spray per nostril	BID *	14 days	Total: 132, Olo 0.6% = 66, 2-4 yrs = 37 4-6 yrs = 29, Veh = 66, 2-4 yrs = 34, 4 - 6 yrs = 32
C-07-01	Pivotal Efficacy and Safety Study	Phase III, US, Natural exposure safety and efficacy, randomized, double-blind, vehicle-controlled, parallel group study	SAR patients 6 - 11 years of age	Olo 0.6% 1 spray per nostril, Veh 1 spray per nostril, Olo 0.6% 2 sprays per nostril Veh 2 sprays per nostril	BID	2 weeks	Vehicle run-in: 2388, Total randomized: 1188, Olo 0.6% 1 spray = 298, Veh 1 spray = 297, Olo 0.6% 2 sprays = 296, Veh 2 sprays = 297
Formulation: Commercial Formulation, Total Sample Size: Olopatadine 0.6% = 660 Vehicle = 660							
C-03-51	PK/PD Study	Phase I, US, Randomized, vehicle-controlled, parallel group double-masked, multi-center safety and PK study	Pediatric patients 6-11 years of age with a history of allergic rhinitis	Olo 0.4% 1 spray per nostril, Olo 0.6% 1 spray per nostril, Olo 0.6 % 2 sprays per nostril, Veh 1 spray per nostril, Veh 2 sprays per nostril	BID	2 weeks	Run-in: 271, Total randomized: 257, Olo 0.4% 1 spray = 52, Olo 0.6% 1 spray = 51, Olo 0.6% 2 sprays = 52, Veh 1 spray = 51, Veh 2 sprays = 51
C-04-20	Efficacy and Safety Study	Multi-center, double-masked, randomized, placebo-controlled, parallel group study	SAR patients 6 - 11 years of age	Olo 0.6% 1 spray per nostril, Olo 0.4% 1 spray per nostril, Veh 1 spray per nostril	BID	2 weeks	Vehicle run-in: 820, Total randomized: 525, Olo 0.6% = 173 Olo 0.4% = 176, Veh = 176
Formulation: Non-commercial Formulation, Total Sample Size: Olopatadine: 0.4% = 228, 0.6% = 278, Vehicle = 278							

3 RESULTS OF SPONSOR’S ANALYSIS

3.1 Population PK Analysis Results (Patients 2-6 years of Age)

The sponsor provided their population pharmacokinetic analysis results in a report entitled “Safety and Pharmacokinetics of PATANASE ® in Pediatric Patients 2 to < 6 Years of Age Who Have a History of Allergic Rhinitis: Report of Population Pharmacokinetic Analysis”.

The population pharmacokinetic analysis was conducted based on data collected from Study C-07-02. A total of 66 patients (2-5 years of age) were randomized to the olopatadine hydrochloride nasal spray 0.6% group. The medication was administered twice daily for at least 14 days with an additional single dose on the subsequent day. Each dose is equivalent to 1200 μg, resulting in a total dose of 2400 μg. Following the first dose on Day 1, three blood samples were collected at the following time intervals: 15 to 30 minutes, 1.5 to 2.5 hours, and 5 to 8 hours. On nominal Day 15, a trough blood sample was obtained prior to dosing. Plasma concentrations of Olopatadine and three metabolites N-desmethylolopatadine (M1), N, N-didesmethylolopatadine (M2), and olopatadine N-oxide (M3) were determined. Because M2 plasma concentrations were reported as less than LLOQ (0.25 ng/mL), no attempt was made to model M2.

The parent compound and two major metabolites (M1 and M3) were modeled simultaneously. Olopatadine and the two metabolites (M1 and M3) followed one-compartment model with first-order absorption and first-order elimination. The sponsor applied two different approaches to include body weight as a covariate for clearance and volume of distribution for both the parent compound and metabolites. In the first approach (Model 1), body weight was included as a covariate for clearance by using allometric scaling factor ($WT^{0.75}$). In the second approach (Model 2), body weight was included as a covariate for clearance directly (WT^{1}). The sponsor reported parameter estimates from the two models (Table 4). The sponsor also indicated that the model based on allometric scaling factor (Model 1) has an objective function value 12 units lower than the body weight normalized model (Model 2). It is to note that the fractions of olopatadine converted into M1 or M3 were arbitrarily selected and fixed (as 10%). No additional covariates were identified. The modeling process using body weight as allometric scaling factor was summarized in Table 5.

Table 4 Summary of the Parameter Estimates based on Population Pharmacokinetic Modeling

Model	Parameter	Typical Values	Standard Error	Interindividual Variability
	Olopatadine			

Model 1	Absorption Rate Constant (1/hr)	3.42	0.403	63.90%
	Apparent Clearance (L/hr)	49.5 (WT/70 kg) $^{0.75}$	2.58	37.40%
	Apparent Volume of Distribution (L)	375 (WT/70 kg)	30.3	54.10%
	M1 (metabolite 1)			
	Faction of Olopatadine metabolized to M1	0.1 (FIXED)		
	Apparent Clearance (L/hr)	239 (WT/70kg) $^{0.75}$	13.3	39.20%
	Apparent Volume of Distribution (L)	393 (WT/70kg)	32.4	39.20%
	M3 (metabolite 3)			
	Faction of Olopatadine metabolized to M3	0.1 (FIXED)		
	Apparent Clearance (L/hr)	191 (WT/70 kg) $^{0.75}$	11.8	49.90%
	Apparent Volume of Distribution (L)	100 (WT/70 kg)	11.3	49.90%
Model 2	Olopatadine			
	Absorption Rate Constant (1/hr)	3.41	0.594	62.60%
	Apparent Clearance (L/hr)	70.8 (WT/70 kg)	4.21	39.20%
	Apparent Volume of Distribution (L)	375 (WT/70 kg)	33.8	53.70%
	M1 (metabolite 1)			
	Fraction of Olopatadine metabolized to M1	0.1		
	Apparent Clearance (L/hr)	341 (WT/70 kg)	22	40.70%
	Apparent Volume of Distribution (L)	394 (WT/70 kg)	48.1	40.70%
	M3 (metabolite 3)			
	Fraction of Olopatadine metabolized to M3	0.1		
	Apparent Clearance (L/hr)	273 (WT/70 kg)	18.5	51.80%
	Apparent Volume of Distribution (L)	100 (WT/70 kg)	17.9	51.80%

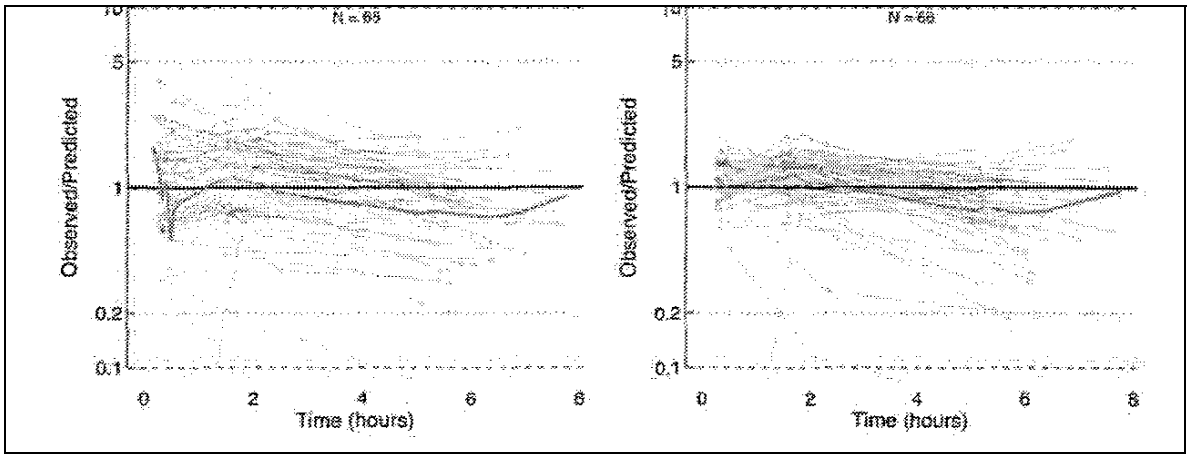
Model 1 = using allometric scaling factor for body weight effect

Model 2 = using body weight directly as a covariate.

The major diagnostic plots for Model 1 were shown in Figure 2. The visual predictive check results were presented in Figure 3.

Figure 2 Diagnostic Plots for Model 1

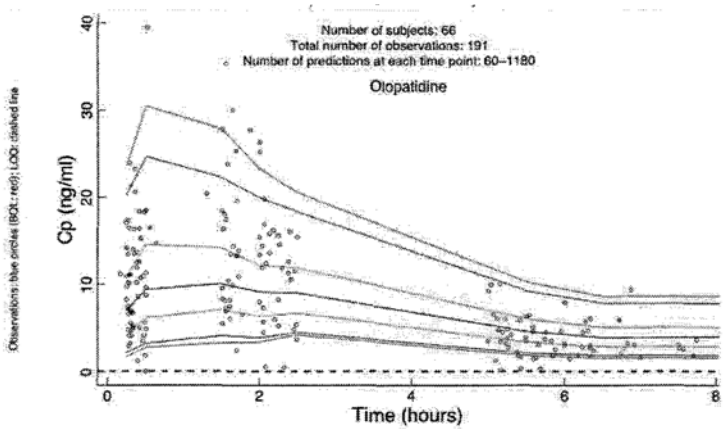
Population	Post Hoc
(N = 68)	(N=68)



Note: the plot represents the ratio of observed-to-predicted of olopatadine against time.

The left panel displays predicted values from the population fit; the right panel displays predicted values from the post hoc fit. The line of unity (black) and a smoother (superimposed) are displayed.

Figure 3 Visual Predictive Check Plots



Note: Values are displayed for olopatadine for Day 1 only. Circles represent observations; lines represent percentile bands for 20 simulations. The LLOQ is showed as a dashed line. Additional panels for Day 15 and for M1 and M3 are not presented but are available in the Appendix of the original report.

Table 5 Summary of Covariates Models Selected

C-07-02 Pharmacokinetic Analysis Report

Table 9. Allometric Models to Determine the Pharmacokinetic Characteristics of Olopatadine, M1, and M3.

Run #	Model	Comments	Objective Function
AL1	090414-175008	Base model with one absorption site	-1676.534
AL2	090414-175038	Model #1 with no absorption lag	-1676.242
AL3	090414-180442	Model A2 + Olopatadine CL differs between age groups	-1676.837
AL4	090414-185859	Model A2 + Olopatadine V_1 differs between age groups	-1677.750
AL5	090414-190041	Model A2 + M1 CL differs between age groups	-1677.410
AL6	090414-204836	Model A2 + M1 V_1 differs between age groups	-1677.086
AL7	090414-204923	Model A2 + M3 CL differs between age groups	-1680.301
AL8	090414-205016	Model A2 + M3 V_1 differs between age groups	-1676.269
AL9	090415-052811	Model A2 + Olopatadine CL varies as a function of age	-1677.602
AL10	090415-061943	Model A2 + Olopatadine V_1 varies as a function of age	-1676.501
AL11	090415-061423	Model A2 + M1 CL varies as a function of age	-1677.045
AL12	090415-063854	Model A2 + M1 V_1 varies as a function of age	-1677.548
AL13	090415-073229	Model A2 + M3 CL varies as a function of age	-1679.898
AL14	090415-072938	Model A2 + M3 V_1 differs between age groups	-1676.234
AL15	090415-073819	Model A2 minus two SIGMA terms	-1672.981
AL16	090415-083712	Model A15 with same OMEGA term for CL and V_1 for M1	-1672.902
AL17*	090415-084029	Model A16 with same OMEGA term for CL and V_1 for M3	-1668.957
AL18	090415-084248	Model A17 + OMEGA for V_1 for M3 scaled relative to that for Cl	-1672.902

* Optimal model

Reviewer's comments:

1. *The fractions of the major metabolites (M1 and M3) formed were arbitrarily selected and fixed to 0.1. The rationale of choosing the value of 0.1 for both M1 and M3 is unclear.*
2. *The sponsor assumed the same between-subject variability of V and CL for M1 (and M3). The rationale is unclear.*
3. *Diagnostic plots: The sponsor did not provide standard diagnostic plots such as: population predicted values vs. observed values, individual predicted values vs.*

observed values, weighted residual vs. population predicted values, and weighted residual vs. time. In stead, the sponsor used the log-transformed ratio of the observed-to-predicted value against time as a goodness-of-fit plot. Following a proportional error model, the ratio of the observed-to-predicted values supposed to be centered at one and symmetrically distributed. Taking additional log-transformation can be misleading.

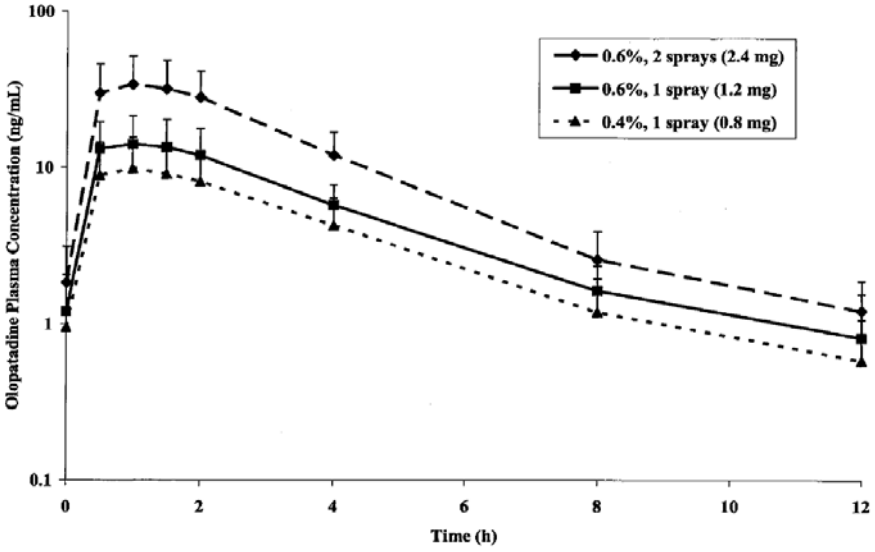
4. *Predictive Check: the sponsor's visual predictive check is based on only 20 simulations. The number of simulations conducted does not appear to be adequate.*

3.2 PK Analysis Results (Patients 6-12 years of Age)

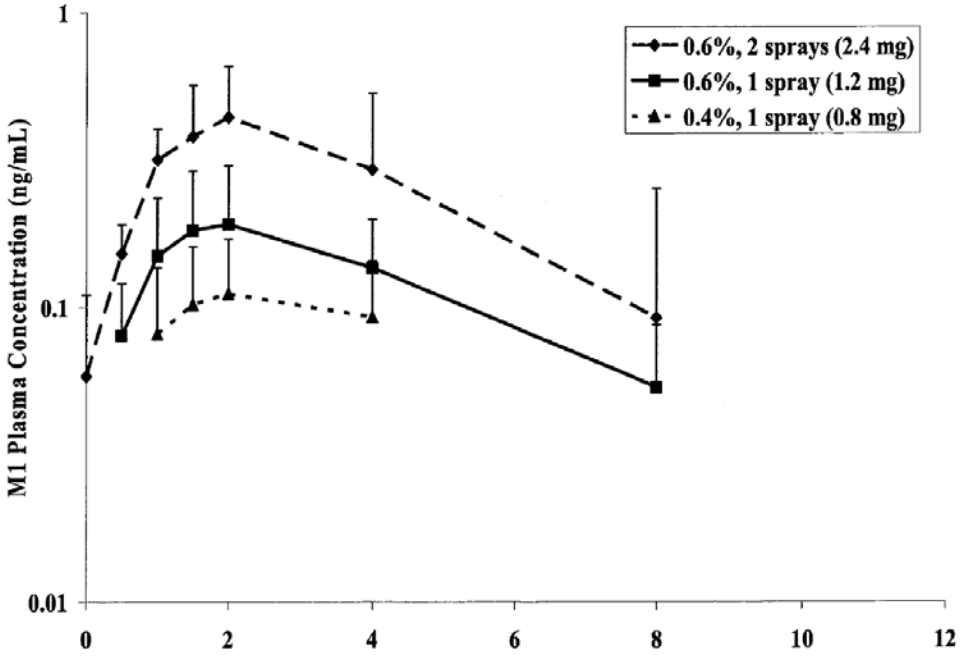
The sponsor conducted a separate PK study in patients 6-12 years of age by using the formulation with povidone. The study report entitled "A Double-Masked, Multiple-Dose, Five-Arm, Parallel-Design Safety and Pharmacokinetic Study of Olopatadine Following Administration of Olopatadine HCl Nasal Spray in Pediatric Patients 6 to 11 Years of Age" was submitted to the agency.

A total of 155 pediatric patients 6 to 11 years of age with history of seasonal allergic rhinitis was randomized to one of the three treatment groups administered Olopatadine Hydrochloride Nasal Spray: Olopatadine 0.4%, 1 spray / nostril (0.8 mg), Olopatadine 0.6% 1 spray / nostril (1.2 mg), Olopatadine 0.6% 2 spray / nostril (2.4 mg). Blood samples were taken at pre-dose, 0.5 hr, 1 hr, 1.5 hr, 2 hr, 4 hr, 8 hr, and 12 hr post-dose on Day 15 when the steady state was achieved. The pharmacokinetic profiles of the parent compound together with the two major metabolites (M1 and M3) were shown in Figure 4. The major pharmacokinetic parameters were summarized in Table 6. The metabolite and parent compound ratios of Cmax and AUC following multiple doses of Olopatadine Nasal Spray were demonstrated in Table 7.

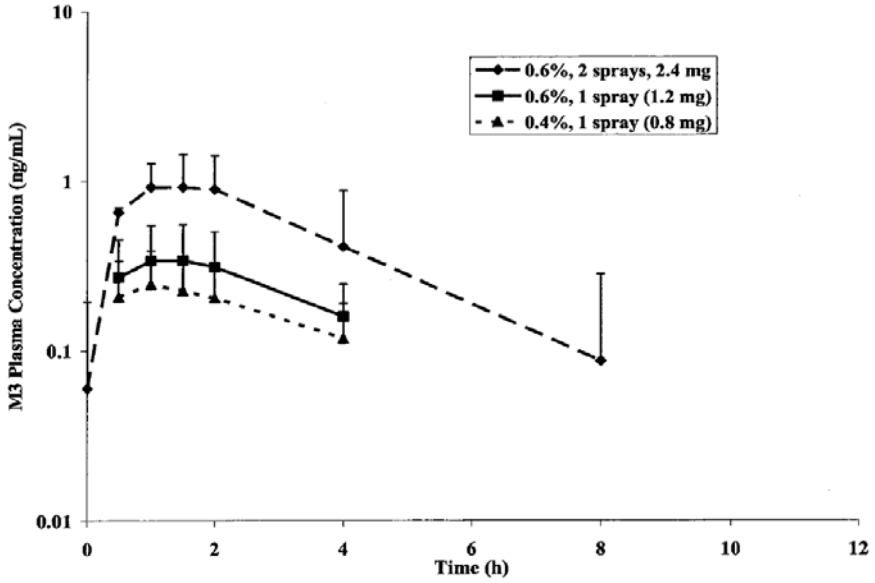
Figure 4 Pharmacokinetic Profiles for the Parent Compound (A) and Two other Major Metabolites M1 (B) and M3 (C)



(A)



(B)



(C)

Table 6 Summary of Major Pharmacokinetic Parameters

Alcon Study C-03-51 (Pediatric SAR Patients)						
Treatment		**C_{max} (ng/mL)**	**T_{max} (h)**	**AUC_{0-12} (ng*h/mL)**	**CL/F (L/h)**	**$t_{½}$ (h)**
0.6% 2 sprays/nostril (2.4 mg)	**Mean**	38.1	1.10	137	22.5	2.3
	SD	19.4	0.67	56.6	15.7	0.5
	N	44	44	44	44	44
	Min	4.75	0.48	28.2	9.21	1.6
	Max	80.1	4.00	257	73.6	4.2
0.6% 1 spray/nostril (1.2 mg)	**Mean**	15.4	1.25	62.3	28.6	2.8
	SD	7.26	0.81	23.7	54.7	1.1
	N	42	42	42	42	42
	Min	0.464	0.45	1.41	8.4	1.8
	Max	29.0	4.00	87.5	371	7.6
0.4% 1 spray/nostril (0.8 mg)	**Mean**	10.8	1.06	44.3	27.2	3.0
	SD	6.18	0.55	20.6	39.0	1.9
	N	41	41	41	41	41
	Min	0.435	0.00*	2.39	8.45	1.9
	Max	24.9	2.00	91.5	252	12.2

*Olopatadine C_{max} for Patient 316 in the 0.8 mg treatment group occurred prior to the last dose on Day 15, i.e., T_{max} = 0 hr.

Table 7 Metabolite / Parent Ratios of Cmax and AUC at Steady-State (Day 15) After Multiple Doses of Olopatadine HCl Nasal Spray in Pediatric SAR Patients 6 to 11 Years of Age

Treatment	Parameter	M1 Mean	M3 Mean	Parent Mean	M1/Parent (%)	M3/Parent (%)
Olo 0.6% 2 Sprays	C_{max} (ng/mL)	0.447	1.05	38.1	1.21	2.79
	AUC_{0-4} (ng*h/mL)	1.53	3.08	95.1	1.45	3.23
	AUC_{0-12} (ng*h/mL)	2.70	4.33	137	1.75	3.14
Olo 0.6% 1 Spray	C_{max} (ng/mL)	0.216	0.389	15.4	1.39	2.42
	AUC_{0-4} (ng*h/mL)	0.721	1.19	41.0	1.57	2.76
	AUC_{0-12} (ng*h/mL)	1.37	1.80	62.3	1.99	2.77
Olo 0.4% 1 Spray	C_{max} (ng/mL)	0.128	0.270	10.8	1.21	2.53
	AUC_{0-4} (ng*h/mL)	0.444	0.870	28.8	1.57	2.94
	AUC_{0-12} (ng*h/mL)	0.950	1.39	44.3	1.95	2.88

Olo 0.6% 2 Sprays = Olopatadine Nasal 0.6% 2 Sprays
Olo 0.6% 1 Spray = Olopatadine Nasal 0.6% 1 Spray
Olo 0.4% 1 Spray = Olopatadine Nasal 0.4% 1 Spray

4 REVIEWER'S ANALYSIS

4.1 Introduction

In the current submission, the efficacy and safety information was collected in patients 6 – 11 years of age. In patients 2 - 6 years of age, only PK information was obtained and no efficacy trial was conducted. The dose for patients in this age group is determined by matching exposure. Therefore, it is critical to determine if similar exposure was achieved in patients 2-6 years of age and 6-11 years of age following the recommended dose.

4.2 Objectives

The objective for the reviewer's analysis is:

- to determine whether similar exposure can be achieved in patients 2-6 years of age and 6-11 years of age following the recommended dose.

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 8.

Table 8. Analysis Data Sets

Study Number	Name	Link to EDR
Study C-07-02 (Population PK Dataset)	Data.090415-084029.csv	This is a paper-based submission. No EDR link is available. A CD was submitted with data.

Study C-07-02	c0702_metabolite1.sas7bdat c0702_metabolite2.sas7bdat c0702_metabolite3.sas7bdat c0702_olopatadine.sas7bdat	
Study C-03-51	c0351_metabolite1.sas7bdat c0351_metabolite2.sas7bdat c0351_metabolite3.sas7bdat c0351_olopatadine.sas7bdat	

4.3.2 Software

Software used in the analyses include NONMEM and S_Plus

4.4 Models and Results

4.4.1 Data Preview

We firstly investigated the pharmacokinetic data of Olopatadine and its metabolites (M1 and M3) in pediatric patients 2-6 years of age following multiple doses using the marketed formulation (with no pivodone). The data was derived from Study C-07-02. Blood samples were collected at the following time intervals: 15 to 30 minutes, 1.5 to 2.5 hours, and 5 to 8 hours on Day 1, pre-dose and 2 hours post-dose on Day 15. The mean concentration of the Olopantadien and its metabolites were summarized in Table 9. A direct comparison of Olopatadine concentrations 2 hours post-dose between Day 1 and Day 15 indicated no apparent accumulation (Table 9). Similar comparison for M1 and M3 concentrations also suggested no apparent accumulation (Table 9).

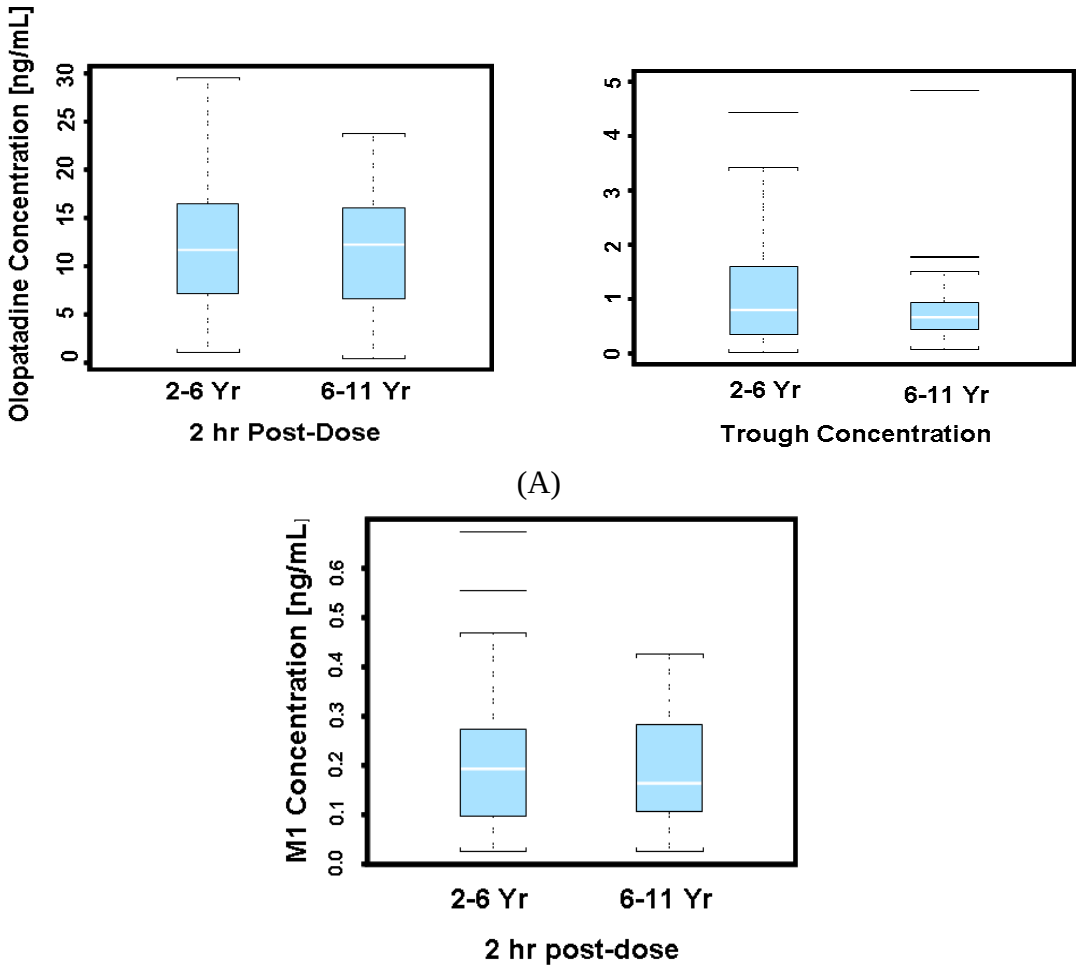
Table 9 Summary of Olopatadine and Its Metabolite Concentrations Following Multiple Doses of Olopatadine (1200 µg) at Various Time Points

Compound	Day	Nominal Time	Time Window	N	Mean	SD	Median	5-95 percentile
Olopatadine	1	0.375	15-30 min	63	10.66	6.6	10.2	3 - 20.4
	1	2	1.5 - 2.5 hr	64	13.1	7.4	12.5	3.8 - 27.5
	1	6.5	5 - 8 hr	64	3.88	2.2	3.375	1.3 - 9.0
	15	0	Pre-dose	54	1.85	3	1.04	0.11 - 6.6
	15	2	1.5-2.5 hr	62	12.5	6.6	11.7	2.8 - 25.5
M1	1	0.375	15-30 min	12	0.082	0.04	0.066	0.06 - 0.16
	1	2	1.5 - 2.5 hr	61	0.21	0.11	0.201	0.07 - 0.41
	1	6.5	5 - 8 hr	54	0.14	0.06	0.126	0.06 - 0.25
	15	0	Pre-dose	19	0.089	0.05	0.066	0.05 - 0.19
	15	2	1.5-2.5 hr	58	0.21	0.13	0.2	0.06 - 0.41
M3	1	0.375	15-30 min	45	0.16	0.09	0.14	0.06 - 0.34
	1	2	1.5 - 2.5 hr	60	0.32	0.21	0.27	0.10 - 0.68
	1	6.5	5 - 8 hr	54	0.15	0.08	0.14	0.06 - 0.31
	15	0	Pre-dose	20	0.12	0.12	0.08	0.05 - 0.84

	15	2	1.5-2.5 hr	60	0.34	0.23	0.26	0.09 - 0.84

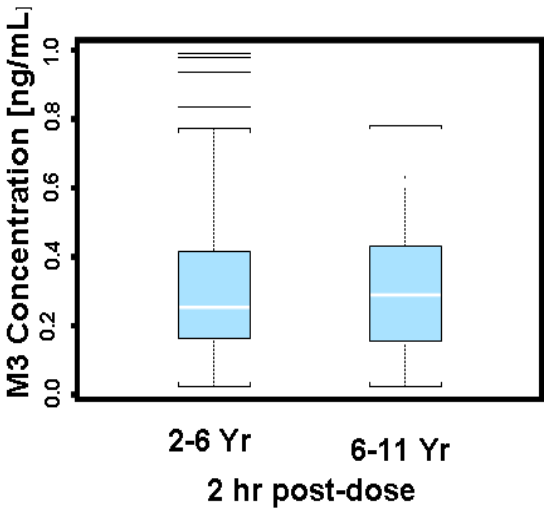
Secondly, we investigated the pharmacokinetic data obtained in pediatric patients 6-11 years of age using not-to-be-marketed formulation (with pivodone). The data was obtained from Study C03-51. The pharmacokinetic profiles of Olopatadine and its metabolites in patients 6-11 years of age are not expected to be affected by the formulation based on the PK comparison study in adults (Please refer to Dr. Sandra Suarez-Sharp's review). Blood samples were collected at pre-dose, 0.5 hr, 1 hr, 1.5 hr, 2 hr, 4 hr, 8 hr, and 12 hr post-dose on Day 15. PK observations at 2 hr and 12 hr post-dose on Day 15 were selected and compared with the concentrations collected at pre-dose and 1.5-2.5 hr post-dose on Day 15 in pediatric patients 2-6 years of age from Study C-07-02. The results were shown in Figure 5. Similar exposures of Olopatadine and its major metabolites were seen at various time points in patients 2-6 years of age and 6-11 years of age following the recommended dose (1200 µg q 12 hr).

Figure 5 Comparison of Olopatadine Concentration (A), M1 Concentration (B), and M3 Concentration (C) in Patients 6-11 Years of Age and in Patients 2-6 Years of Age using 1200 µg q 12 hr



(A)

(B)



(C)

Thirdly, we reviewed the population PK dataset collected from study C-07-02. About 320 PK observations from 66 subjects 2-6 years of age were included in the population PK analysis dataset (Data.090415-084029.csv). The main covariates include age, age group (defined as group 1=2-3 years, group 2 = 4 – 5 years), body weight. It is to note that the NONMEM datasets submitted to the agency do not contain additional demographic information such as: body surface area (BSA), race (RACE). The major demographic information is summarized in Table 10.

Table 10 Summary of Demographic Information

Demographic Information	Median (5-95 percentile)
Age	17 (12 - 23)
Body weight	3 (2-5)
Age group	Number of subjects
Group1 (2-3 yr)	37
Group2 (4-5 yr)	29

4.4.2 Population PK Modeling and Results

The sponsor simultaneously modeled the concentrations of Olopatadine and two major metabolites (M1 and M3) bearing several assumptions. However, the validity of the assumptions cannot be justified.

Our modeling approach, on the other side, focused on the concentration of Olopatadine itself. In the modeling preview process we identified the following data points (Table 11) were outliers probably due to error in dosing records. The three observations were excluded from the analysis. By using the updated datasets, the model building process was summarized in Table 12.

Table 11 Data Excluded from Population PK Analysis

Patient ID	Time	Reason
1003	335.07	The elapse time from the previous doing > 10 hours, the concentration values are too high
1318	337.35	
1603	382.92	

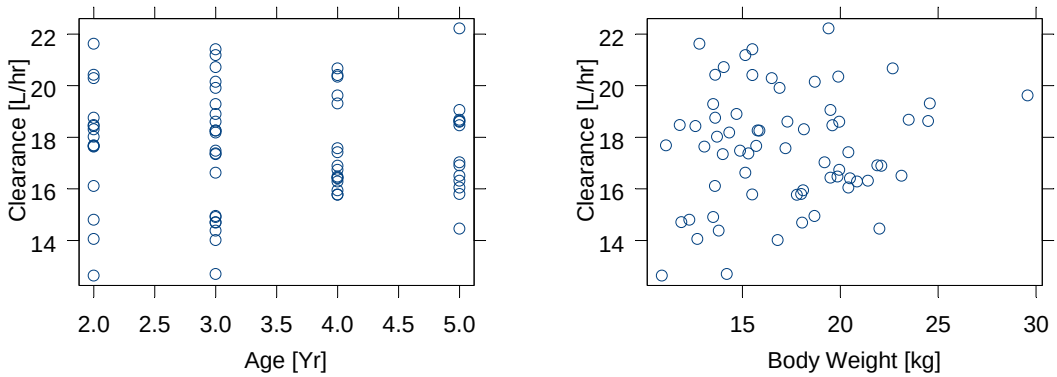
Table 12 Summary of the Population PK Modeling Process

No	Folder	Model	OFV
1	NM21	Using one compartment model	1092.058
2	NM31	Using two compartment model:	1132.542
3	NM41	Using one compartment model: CL ~ WT	1090.123
4	NM51	Using one compartment model: V~ WT	1092.044
5	NM61	Using one compartment model: CL ~ AGE	1091.955
6	NM71	Using one compartment model: CL ~ GROUP	1091.955
7	NM81	Using one compartment model: V~GROUP	1091.574
8	NM91	Using once compartment model: V ~ AGE	1088.539

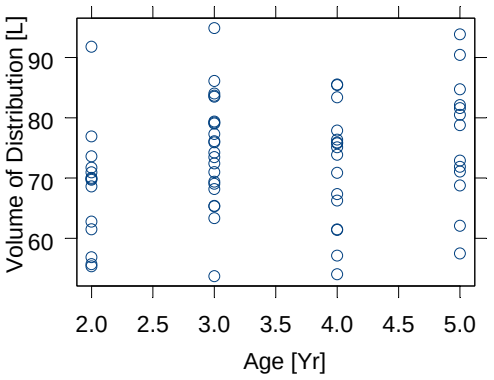
Note: GROUP is defined as Age =2, 3, Group=1, otherwise Group=2.

The one-compartment model with first-order absorption and first-order elimination adequately describes the PK observation for Olopatadine in patients 2-6 years of age. Two-compartment does not provide additional benefit in describing the PK observation. The interindividual variability of CL and V was plotted again body weight and age. A higher body weight appears to be associated with larger values in CL and V (Figure 6). However, population PK analysis did not indicate that body weight was a significant covariate within the observed age group (2-6 years of age) based on the observed data.

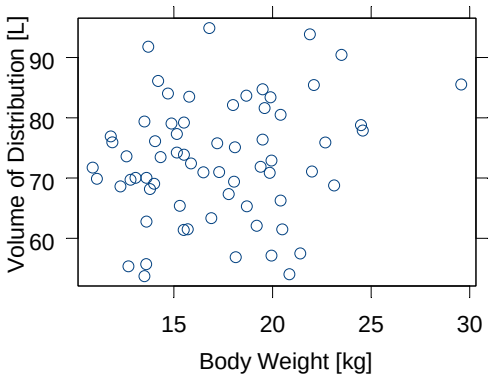
Figure 6 CL and V vs. Body Weight or Age



(A) (B)



(C)



(D)

Note: (A) = CL ~ Age

(B) = CL ~ Body Weight

(C) = V ~ Age

(D) = V ~ Body Weight

Based on the raw PK observation, the maximum concentration among the 3 time points following 1200 µg BID in patients 2-6 years of age at steady state was 12.4 ± 6.5 ng/mL. The estimated AUC over 12 hours at steady state can be calculated as: 69.4 ± 9.1 ng/mL*hr. The sponsor's modeling results indicated that Cmax for olopatadine is 13.4 ± 4.6 ng/mL and AUC_{0-12} is 75 ± 26.4 ng*h/mL. Even though, the sponsor's model has deficiencies, their estimated Cmax and AUC is still acceptable based on our evaluation using different modeling approach.

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	**Description**	**Location in \\cdsnas\pharmacometrics**
NM Folders		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21861	SUPPL-2	ALCON INC	PATANASE NASAL SPRAY (OLOPATADINE HCL)

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

/s/

YUN XU
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