CLINICAL REVIEW

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Division / Office	DPAP / ODEII / OND
Reviewer Name(s)	Peter Starke, MD
Review Completion Date	November 3, 2009
Established Name	Olopatadine Hydrochloride Nasal Spray 0.6%
(Proposed) Trade Name	Patanase® Nasal Spray
Therapeutic Class	Antihistamine
Applicant	Alcon Laboratories
Formulation(s)	Intranasal solution
Dosing Regimen	1 spray per nostril twice-daily
Indication(s)	Seasonal Allergic Rhinitis
Intended Population(s)	(b)(4)-11 years of age

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Products (HFD-570)

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
May 29, 2009	June 1, 2009	SE5-002, SDN-066/67	Efficacy supplement / Pediatric Exclusivity
June 23, 2009	June 24, 2009	SDN-072	Updated proposed labeling
July 9, 2009	July 10, 2009	SDN-072	Completed WR Exclusivity Determination Template
August 6, 2009	August 7, 2009	SDN-077	Response to Information Request of July 28, 2009
August 13, 2009	August 17, 2009	SDN-079	Annual Report
September 23, 2009	September 25, 2009	SDN-084	Proposed labeling incorporating changes from S-001 (b) (4)
October 5, 2009	October 7, 2009	SDN-085	Response to Information Request of September 23, 2009
October 16, 2009	October 20, 2009	SDN-088	Response to Clinical Pharmacology Request

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	**X**	**APPROVAL (AGES 6-11 YEARS)**
	X	(b) (4)
OTHER ACTION:		

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Referential Notation

References to source material are bracketed [ ] and follow a standard format: [submission: table, or figure; page number(s)]; for example, [ISE, T51, p499-501]. References assume the original submission, otherwise they show the submission and date. References to hard copy material outside the submission (e.g., FDA reviews, correspondence, meeting minutes) are descriptive; for example, [NDA XX-XXX, Medical Officer's Review, December 12, 1998].

Naming Conventions

The terminology for what is called a 'clinical study' and what is called a 'clinical trial' has changed in recent years. A 'Clinical Trial' is now defined as any prospective investigation in which the sponsor or investigator determines the method of assigning the investigational product or other interventions to one or more human subjects. This includes any investigation in which an investigator decides how the drug will be administered. 'Studies' are now defined as all investigations other than those defined above, including animal studies and investigations in humans such as observational or pharmacoepidemiologic studies. However, in the past, the term 'study' was more inclusive than the term 'trial', and therefore encompassed both of the new definitions. Furthermore, the old terminology is embedded everywhere. For example, study protocols continue to use this terminology (i.e., 'study number XXXX', or 'study drug', or 'study visit'). Additionally, FDAAA (2007) uses the term 'pediatric studies' to describe what would now be considered both clinical trials and studies under the new terminology. As a result, the terminology is confusing to a reader. Although this review attempts to follow the new naming format, it also retains the older terminology when referring to pediatric studies performed under PREA/BPCA and when referring to protocol-defined study events and treatments.

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend taking an Approval action for patients 6-11 years of age (b) (4)

1.2 Risk Benefit Assessment

Patients 6-11 years of age

The risk/benefit assessment of Patanase Nasal Spray supports extension of the approved treatment of [nasal symptoms of] seasonal allergic rhinitis (SAR) indication from adults and adolescents 12 years of age and older to children 6-11 years of age. In the clinical trial in this age group (**C-07-01**), the primary endpoint of change from baseline in reflective total nasal symptoms scores (rTNSS) showed that Patanase has efficacy at the proposed dose of 1 spray per nostril twice daily. Supportive evidence comes from dosing with 2 sprays per nostril twice daily and from most secondary endpoints, including instantaneous total nasal symptoms scores (iTNSS) and individual reflective scores for 3 of the 4 nasal symptoms (exception is nasal congestion). The clinical program was also supportive of its safety in this age group. With minor differences that are not considered clinically meaningful, the systemic exposure to olopatadine and its metabolites in children 6-11 years of age with the proposed 1-spray dose is similar to that seen in adults and adolescents 12 years of age and older with the 2-spray dose.

Safety issues with Patanase Nasal Spray have been primarily limited to local nasal events. Patanase was irritating to the nasal mucosa resulting in a number of patients in the adult/adolescent clinical trials reporting epistaxis and nasal ulcerations. These are probably related to the formulation itself, and specifically the low pH (3.7) of the product. The initial safety concern of nasal septal perforation with olopatadine nasal spray was resolved with reformulation to eliminate povidone and submission of a subsequent 12-month safety study that showed no perforations. As a result, the label carries WARNING AND PRECAUTION statements (section 5.1) stating that Patanase Nasal Spray should not be used in patients with nasal diseases other than allergic rhinitis, and patients should be monitored for local nasal adverse events while being treated with Patanase. Results from the pediatric trials in children 6-11 years of age using the povidone-free formulation also show events of irritation and epistaxis, but no nasal perforations and no other safety issues in this population. The rate of epistaxis reported in this age range with the povidone-free formulation at the proposed dose of 1 spray per nostril twice daily was 5.7% and 3.7% for Patanase and vehicle, respectively. This rate is approximately double the reported rate in adults and adolescents (3.2% for Patanase, 1.7% for vehicle) after 2 weeks of treatment. Targeted nasal examinations after 2

weeks of treatment at the proposed dose of 1 spray per nostril twice daily showed the rates of nasal ulceration in children 6-11 years of age to be 0.5% and 0.6% for Patanase and vehicle, respectively. Most nasal ulcerations were superficial in depth, although the short length of exposure would not be expected to be associated with more significant ulcerations. However, the time to healing varied significantly in this age group.

The pediatric dataset is limited by the fact the trials were only of 2 weeks duration, and no long-term trials were performed. Given the fact that cumulative rates for local nasal adverse events increased with long-term use in the adult/adolescent safety trials and the treatment for SAR may extend for up to several months at a time, the actual rates for AEs with longer term use are likely to be higher. While of concern, it is possible to extend the current WARNINGS AND PRECAUTIONS section of the labeling for local nasal effects to the 6-11 year old age range because the short-term safety dataset in children 6-11 years of age did not present any new safety signals for this age group.

Although 3 trials were performed in patients 6-11 years of age, I recommend that the ADVERSE EVENTS table for this age group be populated by the events from **C-07-01**, the single trial that evaluated the povidone-free Patanase formulation at the dose to be approved, 1 spray per nostril twice daily. Implementing this will provide a table that includes local nasal events with the proposed dose and approved formulation for this age group, which is not the case for the adult AE table in the PI (AE table populated by events from the clinical trials performed with the povidone-containing formulation).

Patients 2-5 years of age

(b) (4)

One safety and PK trial, **C-07-02**, was performed in patients 2-5 years of age (b) (4) PK from this trial demonstrated that systemic exposure in children 2-5 years of age with the proposed 1-spray dose is similar to that seen in adults and adolescents 12 years of age and older with the 2-spray dose and to children 6-11 years of age at the proposed 1 spray dose. (b) (4)

The safety dataset for this age range is quite limited (65 patients who received olopatadine for at least 1 week and the total duration of exposure was limited to 2 weeks) and is of particular concern for this age range because both nasal and non-nasal adverse events were noted. The rate of epistaxis with the povidone-free formulation in this age range was 6.1% for Patanase, double that seen with two weeks of treatment in patients 12 years of age and older and similar to that seen in patients 6-11 years o f age. Other adverse events of note included diarrhea (Patanase 9.1%, vehicle 0), rhinorrhea (Patanase 4.5%, vehicle 3.0%), dysgeusia (Patanase 3.0%, vehicle 0), wheeze (Patanase 3.0%, vehicle 1.5%), cough (Patanase 9.1%, vehicle 10.6%), and vomiting (Patanase 4.5%, vehicle 6.1%). Cough and vomiting, seen about equally in both treatment groups, are likely related to excess of the spray dripping down the posterior nasopharynx. The high incidence of diarrhea may also reflect local GI effects of excess swallowed olopatadine. Although the AEs reported likely give a reasonable estimate of the risks with short-term exposure in this age group, the same limitations apply for this age group as discussed above for the 6-11 year old age group. However, there are differences. The safety dataset for 6-11 years of age is much larger, and efficacy was demonstrated for that population. Furthermore, the safety dataset in children 6-11 years of age did not present any new non-nasal safety signals; for this reason, a longer-term safety trial is considered unnecessary. This is not the case for patients 2-5 years of age, in whom the incidence of non-nasal adverse events represent new safety signals that need further exploration. (b) (4)

Given the incidence of local and non-local AEs in this population, and the fact that efficacy was not evaluated in this trial (and therefore, the appropriate dose for this age range is unknown (b) (4)

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

(b) (4)

(b) (4)

2 Introduction and Regulatory Background

This is a pediatric efficacy supplement, S-002, submitted by Alcon Laboratories for Patanase® (Olopatadine Hydrochloride) Nasal Spray, 665 micrograms (mcg). Patanase is approved for treatment of the symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older, at a dose of two sprays per nostril twice-daily. This supplement seeks to extend the indication to patients (b) (4) through 11 (b) (4) years of age, at a dose of one spray per nostril twice-daily. With the NDA approval [April 15, 2008], studies in children 2-11 years of age were deferred, and studies in children below 2 years of age were waived for this indication.

This supplement contains the pediatric assessment for patients 2-11 years of age that was deferred with the original approval. The pediatric studies submitted with this supplement were performed in response to a Written Request (WR) issued by the Agency on July 19, 2007. The supplement was submitted June 1, 2009, and receives a 6-month priority review because it is contains the pediatric studies in response to the Written Request. The PDUFA goal date is December 1, 2009.

(b) (4)

The supplement consists of 244 volumes in paper CTD format, with 1 Module 1 volume, 2 Module 2 volumes, 1 Module 3 volume, 0 Module 4 volumes, and 240 Module 5 volumes.

2.1 Product Information

Patanase Nasal Spray contains a nonsterile aqueous solution of olopatadine, a histamine H_1 receptor antagonist, along with the following excipients: benzalkonium chloride 0.01%, dibasic sodium phosphate, edetate disodium, and sodium chloride in purified water, adjusted to a pH of approximately 3.7 by hydrochloric acid or sodium hydroxide. Each 100 microliter spray delivers 665 mg of olopatadine hydrochloride (600 mcg of olopatadine base). It is supplied in a white plastic HDPE spray bottle crimp-sealed with a manual metered dose spray pump and fitted with a white plastic nasal actuator and blue overcap. Alcon also produces a sample bottle meant to deliver 40 sprays. The drug substance is manufactured in (b) (4) The final drug product is manufactured in an Alcon facility in Barcelona, Spain.

(b) (4)

2.2 Currently Available Treatments for Proposed Indications

Numerous products are available for seasonal allergic rhinitis either over-the-counter or by prescription. Orally administered antihistamines are the first-line pharmacologic treatment of the symptoms of allergic rhinitis. Treatment options for SAR include intranasal sprays formulated with corticosteroids and with antihistamines. The two approved antihistamine nasal sprays in the US are Patanase and Astelin® (Azelastine HCl).

2.3 Availability of Proposed Active Ingredient in the United States

Antihistamines are used for symptomatic treatment of various allergic diseases, such as allergic rhinitis, allergic conjunctivitis, and urticaria. The applicant has two ophthalmic formulations of olopatadine marketed in the United States under the trade names Patanol and Pataday for the treatment of signs and symptoms of allergic conjunctivitis. Many antihistamines are currently marketed in the US in various dosage forms, including one as a nasal spray. Patanase provides patients with SAR another choice of an antihistamine nasal spray.

2.4 Important Safety Issues With Consideration to Related Drugs

Older antihistamines, such as diphenhydramine, hydroxyzine, and chlorpheniramine, have anticholinergic effects that may include dry mouth, tachycardia, and urinary retention. Somnolence also may occur with these antihistamines at greater frequencies than with the newer antihistamines. Epistaxis has been noted with other intranasal spray products with the seasonal allergic rhinitis and perennial allergic rhinitis indications, with incidences of 2% to 11%. Nasal septal perforation is very rare among non-corticosteroid nasal sprays for allergic rhinitis and has only been reported in postmarketing adverse events. Even among corticosteroid nasal sprays with allergic rhinitis indications, nasal septal perforation is uncommon.

2.5 Pertinent Regulatory History

The NDA for Patanase Nasal Spray was approved on April 15, 2008, for treatment of the symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older, at a dose of two sprays per nostril twice-daily.

The drug product has undergone multiple reformulations as clinical development progressed. (b) (4)

Between 2001 and 2003 the applicant conducted a number of clinical trials with two strengths of the

povidone-containing formulation of olopatadine, 0.4% and 0.6%, and these formed the basis of the original NDA. Review of the original NDA concluded that the 0.6% dosage strength was effective in the symptomatic treatment of SAR, and the results from the two pivotal efficacy trials, **C-02-37** and **C-02-10**, conducted for the NDA are depicted in the CLINICAL TRIALS section of the product insert as Studies 1 and 2.

However, the povidone containing formulation was found to be markedly irritating to the nasal mucosa in pre-clinical animal studies and there were unacceptably high frequencies of nasal septal perforation, nasal ulceration, and epistaxis in the clinical trials. In particular, nasal septal perforations were noted in the long-term (1-year) safety trial, **C-01-92**. The NDA was not approved and the applicant was asked to reformulate the product to either eliminate povidone from the formulation or reduce the concentration of povidone, and conduct clinical studies to show that the reformulated product is safe for use. The applicant reformulated the product by removing povidone (b) (4), the pH was reduced from (b) (4) to 3.7. Additionally the nasal spray pump was redesigned (b) (4)

The non-povidone containing Patanase formulation also is associated with nasal irritation and epistaxis, but is not associated with nasal septal perforations as was the povidone-containing formulation. NDA approval was based on efficacy provided by the original trials using the original povidone-containing formulation, bridging *in vitro* drug characterization data, a single-dose EEU pharmacodynamic trial (**C-05-64**) to link the old and new formulations, a 2-week efficacy and safety trial comparing the povidone-containing 0.6% formulation with Azelastine 0.1% and vehicle controls (**C-04-70**), and safety information coming from the 6-month interim results of a 12-month safety trial (**C-05-69**) with the reformulated product. An abbreviated clinical program was adequate because *in vitro* drug product characterization studies showed that the formulation used in the original NDA and the proposed to-be-marketed formulation performed similarly, and the product is a solution (b) (4) For a nasal solution formulation for location action, *in vitro* tests can be relied upon entirely to predict release of the drug substance from the drug product and availability at the local site of action. Similar *in vitro* characteristics of two nasal solution formulations ensure comparable delivery to the nasal mucosa and comparable efficacy.[1]

C-05-69 was a 12-month safety trial with the reformulated product in patients with perennial allergic rhinitis (PAR). Final results of that trial were submitted August, 13, 2008, as a labeling supplement (S-001). This was a randomized, double-blind, safety trial in 890 patients with PAR. Patients were randomized 1:1 to Patanase Nasal Spray (n=445) or vehicle control (n=445), with detailed nasal examinations performed at each trial visit. The 12-month local nasal safety results did not differ substantially from the 6-month results. There were no cases of nasal septal perforations. Epistaxis and discontinuations due to epistaxis occurred in 25% and 0.9% of patients who received

1 An Agency Draft Guidance titled "Bioavailability and Bioequivalence Studies for Nasal Aerosol and Nasal Spray for Local Action" is relevant to this point of discussion.

Patanase, and 28% and 0.2% of patients who received vehicle control, respectively. Nasal ulcerations and discontinuations due to nasal ulcerations occurred in 10% and 0.4% of patients who received Patanase, and 9% and 0.2% of patients who received vehicle control, respectively. The incidence of the adverse event of depression was greater in the Patanase-treatment group compared to vehicle control, 9 and 5, respectively; three patients, two of whom had preexisting histories of depression, treated with Patanase were hospitalized for depression or worsening of depression compared to none who received vehicle nasal spray. Somnolence was reported in one patient in each treatment group, and weight increase was reported in 6 patients who received Patanase and one who received vehicle. This information was added to the CLINICAL TRIALS section, and revised labeling was approved on June 17, 2009. The final labeling will be incorporated into the proposed labeling for this supplement.

With approval of the NDA in 2008, the applicant committed to conduct a required post-marketing safety study (PMR) issued under FDAAA Title IX for a 1 year safety trial to further assess the local nasal safety of Patanase Nasal Spray. In addition to Patanase and vehicle control, the study includes a third vehicle control arm with a normal pH formulation to assess whether the low pH of Patanase Nasal Spray is responsible for the local nasal irritation. The PMR carries the following required timelines: the protocol to be submitted by July 2008, the study to start by November 2008, and submission of the final clinical study by November 2012.

2.5.1 Pediatric studies (BPCA and PREA)

Clinical trials performed for the original NDA and Complete Response resubmission included children 12 years and older. The lower age cut-off is typical of an allergic rhinitis program for a new drug product or for a new formulation. During review of the original NDA the applicant submitted summary results of a clinical trial conducted in children 6 to 11 years of age with the povidone-containing formulation, showing that children were more susceptible to nasal adverse events that were seen in the adult and adolescent studies. In view of this finding and overall safety concern with the formulation, the Division advised the applicant during the review of the original NDA that no additional studies should be conducted in pediatric subjects until safety could be assured in older populations.

After reformulation of the product, the applicant submitted a revised pediatric development plan in January of 2007, discussed the plan with the Division in February, and submitted a PPSR in March of 2007, requesting that the Agency issue a pediatric Written Request to study children below 12 years of age. The Division concluded that removal of povidone was adequate to assure reasonable safety so that pediatric studies could be conducted. A Written Request was issued on July 19, 2007, asking for two studies with Patanase in patients 2 through 11 years of age. The decision to issue the Written Request for Patanase was made with concurrence of the CDER Pediatric Implementation Team (PdIT) [reviewed the Written Request] and the Division of Anti-Infective Ophthalmology Products [because of the ophthalmologic formulation of olopatadine]. In the end, the Written Request only contained the two Patanase studies that are submitted with this supplement, a 2-week safety and efficacy trial in patients 6-

11 years of age, and a 2-week safety and pharmacokinetics trial in patients 2-5 years of age. The Written Request is attached as an Appendix to this Review.

Comment: The studies requested/conducted for the Patanase Written Request are reasonably typical of studies that were being requested for intranasal drug products for treatment of SAR at the time the Written Request was issued. However, it is notable that the pediatric assessments for several of the intranasal corticosteroid products have included an evaluation of efficacy in patients down to 2 years of age (Nasacort AQ and Veramyst). These more recent examples have advanced the understanding that, in addition to safety, efficacy may be assessed in children 2-5 years of age.

The CDER Pediatric Exclusivity Board met to consider pediatric exclusivity of Patanase on August 11, 2009, and pediatric exclusivity was granted as of that date.

With NDA approval on April 15, 2008, SAR studies in children 12 through 16 years of age were considered completed, SAR studies in children 2 through 11 years of age were deferred, and SAR studies in children below 2 years of age were waived. The reason for deferral of the pediatric assessment in children 2-11 years of age was because the application was ready for approval for use in adults and the pediatric studies had not been completed. A waiver of pediatric study requirement for ages 0 to less than 2 years was granted because necessary studies would be impossible to conduct in light of the fact that seasonal allergic rhinitis does not occur in children under 2 years of age. The Division has taken the position that SAR occurs in children 2 years of age and older and PAR occurs in children 6 months of age and older. Although the lower age cut-off is somewhat arbitrary, there is literature support on the lower age bound (J Allergy Clin Immunol 2000; 106:832).

The NDA approval letter contains the PMR for pediatric studies with a submission date of July 1, 2009, without specifics for the studies because the Division had previously discussed the pediatric development plan with Alcon and the Division was aware that the first of the pediatric studies was being already performed in response to the Written Request. The Division set the PREA date for these studies to match the BPCA date, July 1, 2009. With this submission, the PREA PMR is considered fulfilled.

3 Ethics and Good Clinical Practices

There were no ethics or good clinical practices issues with this supplement.

3.1 Submission Quality and Integrity

No data quality or integrity issues were raised during the review of this supplement.

3.2 Compliance with Good Clinical Practices

Alcon states that all of the studies/clinical trials were performed in compliance with good clinical practices.

3.3 Financial Disclosures

Alcon submitted acceptable financial disclosure statements and certified that no investigator entered into any financial arrangements that could affect the outcome of the studies/clinical trials.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

None

4.2 Clinical Microbiology

None

4.3 Preclinical Pharmacology/Toxicology

No new pharmacology and toxicology studies were submitted with this supplement. The pharmacology and toxicology data were reviewed in the original NDA. In the original NDA review the major preclinical concern was local nasal toxicity, possibly from povidone in the formulation. Since the commercial formulation does not contain povidone, the local nasal toxicity findings seen in animals are not relevant, other than for historical purposes. The summary of preclinical data presented below comes from the Division Director's review of March 27, 2008, for Approval of the NDA.

> *"The applicant's initial human studies were conducted with a formulation containing 0.1% and 0.2% olopatadine and did not contain povidone. Pre-clinical support for the early human studies was primarily based on existing data on the ophthalmic formulation and limited data with the nasal formulation. The applicant's plan was to support systemic toxicity of olopatadine based on oral studies submitted with the ophthalmic formulation, and conduct limited bridging studies to support local nasal toxicity of the nasal formulation. This is a standard approach and was acceptable to the Division. As the clinical development program was progressing, the applicant changed the formulation to increase the olopatadine concentration to 0.4% and 0.6% and added povidone to enhance solubility of olopatadine. Since povidone is not contained in any nasal or inhalation formulation for long term use, the Division required that the applicant qualify the safety of nasal use of povidone by conducting long-term animal studies. There were three long term animal studies relevant to povidone. The first study was a 9-month intranasal study in dogs where an olopatadine formulation containing povidone was used for the full duration. The second study was a 6-month intranasal rat study where an olopatadine formulation containing povidone was used for the first 2 months and an olopatadine formulation*

without povidone was used for the subsequent 4 months. In these studies no local nasal toxicities were observed. The third study was a 6-month intranasal rat study with (b) (4) *and* (b) (4) *povidone. The rat was chosen as the most appropriate species based on 2-week studies in two species – rats and dogs. In this study olfactory epithelial degeneration and turbinate epithelial vacuolation were observed at high incidence with marked severity in a dose-dependent manner at both doses tested (2.7 mg/day and 6.8 mg/day). As no NOAEL was identified for povidone in the rat, there was no safety margin for the original proposed commercial formulation with the human exposure to povidone of 14.4 mg/day.*

Other than local nasal findings described above there were no toxicological findings of concern. Olopatadine was not genotoxic in the standard battery of assays and was not tumorigenic in oral carcinogenicity studies in mice and rats. Olopatadine was not teratogenic in rats and rabbits. However, olopatadine decreased the fertility index and reduced implantation rate in rats. It also decreased the number of live fetuses in rabbits and decreased the viability and body weights of pups in rats."

With approval of this supplement for children 6-11 years of age, several sections of the labeling will be updated to reflect the relationship of the preclinical toxicology data to this age group (Overdosage section; Carcinogenesis, Mutagenesis, and Impairment of Fertility section).

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

This is an approved drug, with the mechanism of action already evaluated and labeled.

4.4.2 Pharmacodynamics

This is an approved drug, with the pharmacodynamics already evaluated.

4.4.3 Pharmacokinetics

PK data in children 2-5 and 6-11 years comes from two trials, **C-07-02** in children 2-5 years of age using the povidone-free formulation, and **C-03-51** in children 6-11 years of age using the povidone-containing formulation. Results from those trials are summarized in Table 1 and Table 2.

In patients 6 through 11 years of age at a dose of 1 spray per nostril twice daily, the mean Cmax of olopatadine was about 2-fold less than that observed in adults while the mean $AUC_{0-12}$was comparable to that in adults. The Cmax and AUC_{0-12} of olopatadine N-oxide was comparable to that observed in adults, and the Cmax and AUC_{0-12} of N-desmethyl olopatadine is approximately 18% and 37% higher than that observed in adults, respectively. Somewhat similar results were noted in children 2-5 years of age,

as shown in the tables below. These differences are not considered clinically meaningful.

Table 1. PK of olopatadine and metabolites in pediatric PK trials

	Children 2-5 years C-07-02 (N=66) (1 spray dose)			Children 6-11 years C-03-51 (N=42) (1 spray dose)			≥12 years (2 spray dose)	
	Tmax h	Cmax ng/mL	AUC_{0-12} ng*h/mL	Tmax h	Cmax ng/mL	AUC_{0-12} ng*h/mL	Cmax ng/mL	AUC_{0-12} ng*h/mL
Olopatadine	0.92 (0.29)	13.4 (4.6)	75.0 (26.4)	1.25 (0.81)	15.4 (7.3)	62.3 (23.7)	23.2 (6.2)	78.0 (13.9)
M1	2.51 (0.25)	0.22 (0.08)	1.56 (0.54)	1.84 (0.86)	0.22 (0.11)	1.37 (0.50)	0.18 (0.06)	1.00 (0.41)
M3	1.50 (0.22)	0.34 (0.15)	2.03 (0.92)	1.50 (0.73)	0.39 (0.21)	1.80 (0.76)	0.63 (0.24)	2.42 (0.78)

Source: T13.1.-1, M5, V1, p134; Data for patients ≥12 years comes FDA Clinical Pharmacology Reviewer

Table 2. Comparison of olopatadine PK doses in pediatric and adult/adolescent populations

	2-5 years*	6-11 years**		≥12 years**
Dose (per nostril BID)	1 spray	1 spray	2 sprays	2 sprays
Cmax (ng/mL)	13.4 (4.6)	15.4 (7.3)	38.1 (19.4)	23.3 (6.2)
Tmax (h)	0.92 (0.29)	1.25 (0.81)	1.10 (0.67)	0.97 (0.52)
AUC_{0-12} (ng*h/mL)	75.0 (26.4)	62.3 (23.7)	137 (56.6)	78.0 (13.9)
T1/2 (h)	3.7	2.8 (1.1)	2.3 (0.5)	10.4 (5.1)
* From Pop-PK analysis ** From clinical trials in patients using povidone-containing 0.6% formulation.				

Source: M2, V1, T 2.7.2.3.-2, p16; T2.7.2.2.-4, p8

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Two clinical trials, **C-07-01** and **C-07-02** (Table 3), were submitted (b) (4) **C-07-01** was performed children 6 through 11 years of age, and **C-07-02** was performed in children 2 through 5 years of age. These two trials used the approved povidone-free Patanase Nasal Spray and were performed in response to a Written Request from the Agency, dated July 19, 2007, for studies in patients 2-11 years of age.

Two other pediatric clinical trials, **C-03-51** and **C-04-20** (Table 4), had been performed earlier in drug development and prior to issuing the WR. These trials were performed in patients 6-11 years of age, and used previous povidone-containing formulations (0.4% and 0.6%) of olopatadine nasal spray that were not approved because it was associated with (nasal irritation, mucosal ulcerations, and) septal perforations.

Table 3. Efficacy and safety studies with Patanase Nasal Spray in patients 2-11 years of age

Trial	Description	Treatments	Patients	Endpoints
C-07-01 US: 173 centers	2-week, R, double-masked, vehicle-controlled, MC efficacy and safety trial in SAR patients 6-11 years of age	BID dosing: Patanase, 1 spray/nostril Veh, 1 spray/nostril Patanase, 2 sprays/nostril Veh, 2 sprays/nostril	Total: 1188 298 297 296 297	1°: % change in average rTNSS Key 2°: % change in average rTOSS
C-07-02	14-day, R, double-masked safety and PK trial in allergic rhinitis patients 2-5 years of age	BID dosing: Patanase, 1 spray/nostril Veh, 1 spray/nostril	Total: 132 66 (37 2-3y, 29 4-5y) 66 (34 2-3y, 32 4-5y)	Safety and PK
Studies used currently approved Patanase formulation that does not contain povidone. Veh = Vehicle control				

Table 4. Pediatric (<12 y) studies with previous unapproved formulations of olopatadine

Trial	Description	Treatments*	Patients	Endpoints
C-03-51	Phase 1, 2-week, safety and PK trial in SAR patients 6-11 years of age	BID dosing: Olo 0.4%, 1 spray/nostril Olo 0.6%, 1 spray/nostril Olo 0.6%, 2 sprays/nostril Veh, 1 spray/nostril Veh, 2 sprays/nostril	257	Safety and PK
C-04-20 US: 52 centers	Phase 3, 2-week R, double-masked, PC efficacy and safety trial in SAR patients 6-11 years of age	BID dosing: Olo 0.4%, 1 spray/nostril Olo 0.6%, 1 spray/nostril Veh, 1 spray/nostril	Total: 525 176 173 176	1°: % change in average rTNSS
* These studies used the unapproved Patanase formulation that contains povidone. For this reason, the established name is used in the table. Veh = Vehicle control				

5.2 Review Strategy

Two clinical trials provide efficacy information in patients 6-11 years of age, only one of which was successful. **C-07-01** provides the pivotal efficacy information to support extension of the SAR indication to patients 6-11 years of age. This trial was reviewed for its contribution to efficacy and to safety. **C-04-20**, which had been performed in patients 6-11 years of age using the previous povidone-containing formulation, was a failed efficacy trial. However, it was reviewed for its contribution to safety in children 6-11 years of age. **C-03-51** provides PK information to support systemic exposure safety for the proposed dose of 1 spray per nostril twice daily in children 6-11 years of age.

None of the trials provide efficacy information for patients 2-5 years of age. Only one trial was performed in this age group. **C-07-02** provides both safety and PK information (b) (4)

All four trials were reviewed for their contribution to safety. Because several were performed using the previous povidone-containing formulation (Table 4), it was possible to compare intranasal safety in children 6-11 year of age across trials.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Brief summaries of pediatric studies/clinical trials performed with previous olopatadine formulations

5.3.2.1 C-03-51

C-03-51 was a randomized, multicenter (7 sites in the US), double-masked, vehicle-controlled, 5-arm, 2-week safety and PK trial comparing two dosage strengths and several dosages of povidone-containing olopatadine nasal spray with vehicle placebo in 257 patients 6-11 years of age with seasonal allergic rhinitis (SAR). The trial was conducted between September and December of 2004. After a 2-week vehicle control run-in period, patients were randomized to olopatadine 0.4% one spray/nostril twice daily (n=52), olopatadine 0.6% one (n=51) or two (n=52) sprays/nostril twice daily, or vehicle placebo one (n=51) or two (n=51) sprays/nostril twice daily administered by the patient or caretaker as 1 spray per nostril twice daily for 2 weeks. Safety assessments included PK of olopatadine and metabolites (only performed in the 155 olopatadine-exposed patients) and pharmacodynamic (6 ECGs each on Days 1 [pre-dose] and 15 [1.5 hours post-dose]) measurements, extent of exposure, nasal and physical examinations, cardiovascular parameters (pulse, systolic and diastolic BP), clinical labs, and adverse events.

This trial provides the PK information to support the proposed dose of Patanase Nasal Spray, one spray per nostril twice daily, in the 6-11 year age range. See Section 4.4.3 of this review for the top-line results, which shows that systemic exposure in this age group with 1 spray per nostril twice daily is comparable to that in adults and adolescents receiving 2 sprays per nostril twice daily.

No significant effect on QTc interval was noted. No patients had a QTcF value ≥500 msec or a change from baseline in maximum QTcF of >60 msec. Mean changes from baseline in QTcF were 3.7, 2.7, 2.0, 1.0 and -0.3 msec for olopatadine 0.6% 2 sprays, olopatadine 0.6% 1 spray, olopatadine 0.4% 1 spray, vehicle 2 sprays, and vehicle 1 spray, respectively. There was a difference in mean change in QTcF by gender, with females showing a larger numerical effect. For males, the mean changes from baseline in QTcF were 1.6, 0.2, 3.2, 1.0 and -2.2 msec for olopatadine 0.6% 2 sprays, olopatadine 0.6% 1 spray, olopatadine 0.4% 1 spray, vehicle 2 sprays, and vehicle 1 spray, respectively. For females, the mean changes from baseline in QTcF were 5.8, 5.1, 0.5, 1.0 and 1.1 msec for olopatadine 0.6% 2 sprays, olopatadine 0.6% 1 spray, olopatadine 0.4% 1 spray, vehicle 2 sprays, and vehicle 1 spray, respectively.

There were no deaths, and no SAEs. The most frequently reported AE was epistaxis. Five patients experienced a nasal ulcer, 1 in the olopatadine 0.6% 2 spray group, 2 in the olopatadine 0.6% 1 spray group, and 3 in the vehicle 1 spray group.

5.3.1.2 C-04-20

C-04-20 was a randomized, multicenter (52 sites in the US), double-masked, vehicle-controlled, 2-week efficacy and safety trial comparing two dosage strengths of povidone-containing olopatadine nasal spray with vehicle placebo in 525 patients 6-11 years of age with seasonal allergic rhinitis (SAR). The trial was conducted between March and August of 2005. After a 2-week vehicle control run-in period, patients were randomized to olopatadine 0.4% (n=176), olopatadine 0.6% (173), or vehicle placebo (n=176) administered by the patient or caretaker as one spray per nostril twice daily for 2 weeks. The primary efficacy endpoint was the percent change from baseline in combined AM+PM reflective Total Nasal Symptom Score (rTNSS) averaged across the trial. Safety assessments included the extent of exposure, nasal and physical examinations, cardiovascular parameters (pulse, systolic and diastolic BP) and adverse events.

Primary efficacy results (Table 5) showed numerical but not statistical superiority for both doses vs vehicle control. As a result, the trial was a failed efficacy trial.

There were no deaths, and the one SAE (1 patient on olopatadine 0.4% was hospitalized due to a urinary tract infection) was judged not to be related to study drug. Epistaxis was the most common AE, experienced in 5.7% (n=10), 4.6% (n=8), and 4.5% (n=8) of patients on olopatadine 0.4%, olopatadine 0.6%, and vehicle control, respectively. A total of 9 patients experienced a nasal ulcer, 1 on olopatadine 0.4%, 3 on olopatadine 0.6%, 4 on vehicle control, and 1 on vehicle during the run-in period [T14.3.1.8.-1, p342-8].

Table 5. C-04-20, Primary efficacy endpoint, ITT

	N	Baseline	Treatment period		p-value vs vehicle*
			Mean (SD)	Mean (%) change	
Olopatadine 0.4%, 1 BID	176	8.1 (1.7)	6.4 (2.2)	-1.7 (-20.9)	0.2910
Olopatadine 0.6%, 1 BID	173	8.3 (1.6)	6.5 (2.5)	-1.8 (-20.9)	0.2821
Vehicle, 1 BID	176	8.2 (1.5)	6.7 (2.2)	-1.5 (-17.2)	--
* P value from Dunnett's T test (without adjustment for age group)					

Source: M5, V59, T11.4.1.1.-1, p 120

5.3.2 C-07-01

5.3.2.1 Description of the Study and Study Population

C-07-01 was the pivotal efficacy and safety trial in patients 6-11 years of age. This was a randomized, multicenter (180 sites in the US), double-masked, vehicle-controlled, 2-week efficacy and safety trial comparing Patanase Nasal Spray with vehicle placebo in 1188 patients 6-11 years of age with seasonal allergic rhinitis (SAR). The trial compared two doses of Patanase against the corresponding dose of vehicle control, 1 and 2 sprays per nostril twice daily. The trial was conducted between September 2007 and November 2008.

There were 3 Protocol amendments. The first was on August 23, 2007, prior to enrollment of any patients, to include a RAST test and to delete the requirement of allergic rhinitis symptoms as part of the enrollment criteria. A second amendment on November 30, 2007, was proposed but never implemented, and was withdrawn on January 8, 2008. This amendment would have allowed inclusion of patients previously exposed to olopatadine or vehicle placebo in prior olopatadine clinical trials. A third amendment was implemented on July 15, 2008, with 825 patients enrolled in the trial. The amendment increased the number of trial sites from 120 to 180, moved PRQLQ from a key secondary to a secondary variable, added percent change from baseline in iTOSS and mean change from baseline in rTOSS as secondary variables, and revised the SAP to incorporate an ANCOVA with the randomization stratification and baseline TNSS as covariates as requested by FDA in March 2008. [Submission 8/7/08, p28-9] None of the amendments are judged to have affected the trial outcomes.

Inclusion criteria included: at least a 2 year history of SAR; positive skin prick, intradermal, or RAST test within 5 years to current seasonal allergen prevalent in the area; negative nasal examination; non-pregnant with appropriate contraception if sexually active; current seasonal symptoms with a minimum AM plus PM reflective Total Nasal Symptom Score (rTNSS) of 36 over the 3 calendar days; and willing/able to follow study instructions. Patients were excluded if they had systemic disorders or concurrent disease that could interfere with study evaluations; anatomic deformities; a diagnosis of chronic rhinosinusitis, or a diagnosis of sinusitis within 30 days, upper or lower respiratory infection within 14 days; asthma, except mild intermittent asthma; congestion that would interfere with study drug administration; use of prohibited medications, including all prescription or OTC nasal sprays, ocular allergy medications, all forms of corticosteroids, decongestants, systemic antibiotics and antifungal agents, ASA and NSAIDS, antihistamines, antiarrhythmic agents, antidepressants, inhaled ipratropium, nedocromil, and cromolyn, leukotriene pathway modifiers, and drugs that might prolong the QT interval; known non-responder to antihistamines for symptoms of SAR; ocular disorders other than allergic conjunctivitis, including nasolacrimal drainage malfunction, and clinically relevant abnormal vital signs.

The trial consisted of a 4-16 day single-masked vehicle (1 spray per nostril twice daily) run-in phase followed by randomization to 2 weeks of treatment with one of the following 4 treatment groups: Patanase (olopatadine 0.6%) Nasal Spray or vehicle nasal spray, administered by the patient's caregiver either as 1 or 2 sprays per nostril twice daily approximately 12 hours apart. Masking with regard to the dosing regimen (1 vs 2 sprays per nostril) was achieved by sealing the patient's dosing instructions in an envelope for the parent/caretaker to open after leaving the trial site on the day of randomization so that site personnel were not aware of the dosing assignment. Visits were at: screening (Visit 1), randomization (Visit 2), phone contact at 7 ±1 days (Visit 3), and 16 +7 days (Visit 4). Randomization was 1:1:1:1, and stratified by age groups of 6-8 and 9-11 years of age. Caregivers completed phone diaries prior to each dose throughout the study. Treatment compliance was assessed by measurement of study medication bottle weights and recording daily study medication use in the phone diary. Reflective (previous 12 hours) and instantaneous symptom scores for runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes were scored on a 0-4 severity

scale where 0=none, 1=mild, 2=moderate, 3=severe, and captured in a telephone diary twice daily (AM and PM) prior to dosing.

The primary efficacy endpoint was the percent change from baseline in reflective Total Nasal Symptom Score (rTNSS). rTNSS was defined as the, the average AM+PM severity scores for the sum of the four symptoms of runny nose, stuffy nose, itchy nose, and sneezing, averaged across days. Statistical analysis used an ANCOVA with factors for treatment, age stratification category, and baseline, with imputed values for all missing data with LOCF, to compare percent changes from baseline between Patanase and vehicle for each dosage. Sample size was based on at least 250 evaluable patients per group, which was calculated to provide 91% power to detect a treatment difference of 8.33% in percent change from baseline in rTNSS with an SD of 28.11% using a 2-sided test with an alpha of 0.05. Baseline was defined as the average of the 3 complete diary days prior to randomization with the highest combined AM+PM rTNSS out of the 4 complete diary days prior to randomization. Adjustment for multiplicity between doses was not made, as the primary objective was to demonstrate efficacy with the adult dose of 2 sprays per nostril twice daily, with efficacy for the lower dose of one spray per nostril considered as supportive of the adult dose. This is acceptable.

The key secondary efficacy endpoint was the percent change from baseline in reflective Total Ocular Symptom Score (rTOSS), defined as the average of AM+PM scores for the sum of the two symptoms of itchy eyes and watery eyes, averaged across days. Other secondary efficacy endpoints included the percent change from baseline in instantaneous TNSS (iTNSS) and TOSS (iTOSS), percent change from baseline in the 6 individual (average AM+PM) reflective and instantaneous symptom scores, mean change from baseline in (average AM+PM rTNSS), mean change from baseline in (average AM+PM) rTOSS, and the mean change from baseline in the overall Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ), averaged across days. The SAP states that no adjustment was made for multiplicity between the primary endpoint of rTNSS and all secondary endpoints, including rTOSS and individual treatment scores. The rationale given in the Statistical Analysis Plan is the same as for lack of a multiplicity adjustment between the two doses.

Caregiver Treatment Satisfaction Questionnaire (CGTSQ) and patient global assessments were also collected. Safety assessments included the extent of exposure, nasal and physical examinations, cardiovascular parameters (pulse, systolic and diastolic BP) and adverse events.

A total of 1188 patients were randomized and received at least one dose of study medication, 485 patients 6-8 years of age and 703 patients 9-11 years of age. Patient disposition is shown in Table 6 and demographics (ITT pop) in Table 7. Treatment groups appear to have been balanced at baseline, with no imbalances in discontinuations that might have affected the results.

The ITT population included 14 patients who had baseline data and were randomized but provided little or no on-treatment diary data. These patients were not included in the ITT efficacy analyses because, in order to be included and allow LOCF methodology to account for missing data, the SAP defined that a patient had to have at least one full day (AM and PM) of on-treatment diary data. This is the same methodology used in the

adult clinical trials, and is an acceptable approach. [Submission of 8/7/09, p19] Results including all ITT patients did not differ substantively from those in the tables below.

Table 6. C-07-01, Patient disposition

Disposition	Pat 1 BID	Veh 1 BID	Pat 2 BID	Veh 2 BID	Total
Randomized (ITT and Safety)	298	297	296	297	1188
Excluded from ITT and PP pops*	4	4	3	3	14
ITT population with sufficient on-treatment data to apply LOCF methodology for missing data	294	293	293	294	1174
Discontinued	~~17~~ 16	14	8	14	53
Adverse Event	~~7~~ 6†	4	5	4	20
Lost to FU	2	1	1	0	4
Patient/parent request	1	2	0	1	4
Treatment failure	3	4	2	8	17
Protocol violation	1	3	0	0	4
Other	3	0	0	1	4
Per Protocol (PP)*	281	283	288	283	1135

*Patients were excluded from the ITT pop if insufficient diary data were available to allow application of LOCF methodology. PP pop = patients who completed the trial and had 2 weeks of treatment.

†Response to IR of 9/23/09 shows correction to table for number of AEs causing discontinuation. Note that the total number of patients discontinued from Patanase 1 BID group should now read 16.

Source: M5, V18, T10.1.1 to 10.1.4 and T10.1.6, p53-7. Response to IR of Sept 23, 2009, T2, p2.

Table 7. C-07-01, Demographics, ITT

Demographics, ITT N (%)	Pat 1 BID N=298	Veh 1 BID N=297	Pat 2 BID N=296	Veh 2 BID N=297
Age, Mean (range)	8.8 (6-11)	8.8 (6-11)	8.8 (6-11)	8.8 (6-11)
6-8y	121 (40.6)	121 (40.7)	121 (40.9)	122 (41.1)
9-11y	177 (59.4)	176 (59.3)	175 (59.1)	175 (58.9)
Sex Male	168 (56.4)	172 (57.9)	174 (58.8)	173 (58.2)
Female	130 (43.6)	125 (42.1)	122 (41.2)	124 (41.8)
Race				
White	218 (73.2)	208 (70.0)	221 (74.7)	217 (73.1)
Black	48 (16.1)	62 (20.9)	50 (16.9)	57 (19.2)
Asian	6 (2.0)	6 (2.0)	6 (2.0)	10 (3.4)
Native Hawaiian / Pacific Islander	0	0	1 (0.3)	2 (0.7)
American Indian / Alaska Native	1 (0.3)	0	0	0
Other	20 (6.7)	14 (4.7)	10 (3.4)	9 (3.0)
Multi-racial	5 (1.7)	7 (2.4)	8 (2.7)	2 (0.7)
Ethnicity				
Hispanic, Latino, or Spanish	59 (19.8)	54 (18.2)	59 (19.9)	49 (16.5)
Not Hispanic, Latino, or Spanish	239 (80.2)	243 (81.8)	237 (80.1)	248 (83.5)

Source: M5, V18, T11.2.1-1, T11.2.1-4, p115, 118,

5.3.2.2 Efficacy

Results for the primary efficacy endpoints of percent change from baseline in reflective total nasal symptom scores (rTNSS) are shown in Table 8. Both treatment comparisons

won. Although there were four treatment groups with two treatment comparisons and two chances of success, no adjustment was made for multiplicity. The applicant's argument is that 2 sprays twice daily is the approved dose and was expected to win, whereas the 1 spray twice daily dose was included to explore a lower dose. That said, the 1 spray twice daily dose is the dose the applicant seeks for approval in this age range, and the results were statistically significant enough that an adjustment for multiplicity would still have rendered the results as statistically significant.

The applicant performed subgroup analyses on the primary endpoint for effects of sex, race, and ethnicity, and reported no significant differences between groups. There were too few Asians, Native Hawaiians, and American Indians enrolled to provide meaningful results for these subgroups. [T11.4.2.8.2.-1, T11.4.2.8.3.-1, and T11.4.2.8.4.-1, M5, V19, p244-254]

The FDA statistician was able to confirm the applicant's primary and secondary analyses. FDA also performed subgroup analyses of the primary endpoint by sex, age stratification (6-8y, 9-11y), race, and ethnicity. Except for a lack of difference between treatment groups for the higher dose in Blacks, the results were consistent with those for the primary analysis.

Table 8. C-07-01, Change in rTNSS, ITT

rTNSS	**Patanase, 1 BID 298 n=294**	**Vehicle, 1 BID 297 n=294**	**Patanase, 2 BID 296 n=293**	**Vehicle, 2 BID 297 n=293**
Baseline (SD)	8.99 (1.76)	9.09 (1.68)	9.18 (1.60)	8.83 (1.79)
Treatment period (SD)	6.75 (2.63)	7.39 (2.30)	6.73 (2.54)	6.93 (2.44)
Change from baseline	-2.24	-1.70	-2.45	-1.90
Percent change from baseline (SD)	**-24.7 (25.5)**	**-17.9 (24.1)**	**-26.5 (24.9)**	**-20.8 (24.4)**
Treatment differences				
LS Mean (95% CI), (Percent)	0.58 (0.22, 0.94) (**6.9%**)		0.43 (0.07, 0.80) (**5.1%**)	
p-value	p=0.0015 **(p=0.0007)**		p=0.0206 **(p=0.0120)**	
Mean and percent change from baseline in combined AM+PM reflective TNSS are shown. Results the primary endpoint of percent change from baseline are shown in **bold** font. Treatment differences and P-value are based on ANCOVA model with factors for treatment, age category, and baseline, including only patients with non-missing data, with no adjustment for multiplicity. 95% confidence intervals for LS mean treatment differences supplied by FDA statistical reviewer.				

Source: M5, V18, T11.4.1.1.1.-1, p64; V19, T11.4.1.1.-1 and T11.4.1.1.1.-1,p185-6

Results for secondary endpoints are shown in the tables below. Summary results of ANCOVA analyses are shown in Table 9, with more detailed results in the following tables. Changes in reflective and instantaneous TNSS and TOSS are shown in Table 10, and changes in all 6 individual reflective nasal and ocular symptom scores are shown in Table 11. The more detailed tables show baseline and treatment values, mean and percent change from baseline, numerical treatment differences in mean and % change for each dose comparison, and results of ANCOVA analyses for each dose comparison expressed as LS mean % change and the p=value.

Results for secondary endpoints are supportive of the primary efficacy measure for both doses studied. The results for the 1 spray per nostril twice daily dose were numerically

larger than those for the 2 sprays per nostril twice daily dose for the primary measure and all secondary measures, including mean change in reflective TNSS, percent change in instantaneous TNSS, and percent change individual reflective nasal symptom scores. In several instances the differences between treatments for the 2 sprays twice daily dose were numerically small and likely were not clinically meaningful, including results for iTNSS and individual symptom scores for stuffy nose and sneeze. In contrast, treatment differences for the 1 spray twice daily dose were likely clinically meaningful for all results except stuffy nose. Lack of a significant effect on nasal congestion [stuff nose] scores is not surprising for an antihistamine.

(b) (4)

), and therefore will not be discussed in this review.

Table 9. C-07-01, Summary of ANCOVA analyses of primary and secondary endpoints*, ITT

	Pat 1 BID N=298	Veh 1 BID N=297	Treatment Difference	Pat 2 BID N=296	Veh 2 BID N=297	Treatment Difference
rTNSS (mean change)	-2.28	-1.70	0.58	-2.40	-1.97	0.43
rTNSS (% change)	**-25.1%**	**-18.2%**	**6.9%**	**-26.4%**	**-21.2%**	**5.1%**
Runny nose	-23.6%	-16.7%	7.0%	-24.7%	-20.3%	4.4%
Itchy nose	-27.3%	-16.3%	11.0%	-27.7%	-19.7%	8.1%
Stuffy nose	-18.2%	-15.5%	2.7%	-22.1%	-19.1%	3.0%
Sneeze	-31.0%	-17.8%	13.2%	-26.0%	-22.7%	3.3%
iTNSS (% change)	-21.6%	-13.8%	7.8%	-22.0%	-18.9%	3.1%
PRQLQ	-0.67	-0.40	0.27	-0.63	-0.57	0.06
rTOSS (mean change)	-0.96	-0.61	0.34	-0.96	-0.71	0.25
rTOSS (% change)	-25.0%	-6.1%	18.9%	-25.0%	-9.5%	15.6%
Itchy eyes	-26.8%	-8.2%	18.6%	-25.4%	-6.9%	18.5%
Watery eyes	-27.0%	-14.3%	12.8%	-26.3%	-20.0%	6.3%
iTOSS (% change)	-28.1%	-5.5%	22.6%	-21.0%	-10.3%	10.6%

*LS means for change from baseline from ANCOVA model with factors for treatment, age category and baseline, including only patients with non-missing data at both visits. Primary endpoints shown **bolded**. Significant treatment differences are highlighted in yellow.

Table 10. C-07-01, Change in rTNSS, rTOSS, iTNSS, and iTOSS, ITT

	N	Baseline (SD)	Treatment (SD)	Change from baseline Mean (%)	Treatment Differences	
					Raw Mean or %	LS mean* p-value*
Reflective symptoms						
rTNSS						
Patanase, 1 BID	294	8.99 (1.8)	6.75 (2.6)	-2.24 (**-24.7%**)	0.54 (6.8%)	**6.9% p=0.0007**
Vehicle, 1 BID	294	9.09 (1.7)	7.39 (2.3)	-1.70 (**-17.9%**)		
Patanase, 2 BID	293	9.18 (1.6)	6.73 (2.5)	-2.45 (**-26.5%**)	0.55 (5.7%)	**5.1% p=0.0120**
Vehicle, 2 BID	293	8.83 (1.8)	6.93 (2.4)	-1.90 (**-20.8%**)		
rTOSS (means)						
Patanase, 1 BID	294	3.46 (1.6)	2.51 (1.6)	-0.95	0.34	p=0.0002
Vehicle, 1 BID	294	3.52 (1.6)	2.91 (1.6)	-0.61		
Patanase, 2 BID	293	3.59 (1.5)	2.57 (1.5)	-1.02	0.36	p=0.0091
Vehicle, 2 BID	293	3.28 (1.7)	2.62 (1.6)	-0.66		

	N	Baseline (SD)	Treatment (SD)	Change from baseline Mean (%)	Treatment Differences	
					Raw Mean or %	LS mean* p-value*
rTOSS (percents)						
Patanase, 1 BID	287	3.54 (1.5)	2.56 (1.6)	-24.5%	18.4%	18.9% p=0.0084
Vehicle, 1 BID	288	3.59 (1.6)	2.96 (1.5)	-6.1%		
Patanase, 2 BID	289	3.64 (1.4)	2.60 (1.5)	-26.3%	18.1%	15.6% p=0.0010
Vehicle, 2 BID	283	3.40 (1.6)	2.71 (1.6)	-8.2%		
Instantaneous symptoms						
iTNSS						
Patanase, 1 BID	294	8.41 (2.0)	6.54 (2.6)	-1.87 (-21.4%)	0.55 (7.6%)	7.8% p=0.0003
Vehicle, 1 BID	294	8.48 (2.2)	7.16 (2.4)	-1.32 (-13.8%)		
Patanase, 2 BID	293	8.62 (2.1)	6.54 (2.6)	-2.08 (-22.2%)	0.46 (3.7%)	3.1% p=0.2168
Vehicle, 2 BID	293	8.38 (2.2)	6.76 (2.6)	-1.62 (-18.5%)		
iTOSS						
Patanase, 1 BID	287	3.43 (1.5)	2.50 (1.6)	-0.93 (-27.0%)	0.37 (22.1%)	22.6% p<0.0001
Vehicle, 1 BID	284	3.49 (1.6)	2.93 (1.6)	-0.56 (-4.9%)		
Patanase, 2 BID	287	3.56 (1.5)	2.62 (1.5)	-0.94 (-22.5%)	0.31 (13.1%)	10.6% p=0.0237
Vehicle, 2 BID	286	3.28 (1.7)	2.65 (1.6)	-0.63 (-9.4%)		

For rTOSS, means and percents are presented separately, since the applicant used different data for each. Mean data includes patients who had non-missing data at both visits. Percent data includes patients who had non-missing data at both visits and non-zero data at baseline.

*From ANCOVA model with factors for treatment, age category and baseline.

Primary endpoints are shown **bolded**.

Sources: M5, V19, T11.4.1.1.-1 and T11.4.1.1.1.-1, p185-6; M5, V19, T11.4.1.2.1.-1 and T11.4.1.2.-2, p187-8; M5, V18, T11.4.1.2.-2, p67; M5, V18, T11.4.1.2.-1, p70; M5, V18, T11.4.1.3.-2, p72; M5, V19, T11.4.1.3.-1 and T11.4.1.3.-2, p189-90

Table 11. C-07-01, Change in individual reflective symptom scores, ITT

	N	Baseline (SD)	Treatment (SD)	Change from baseline Mean (%)	Treatment Differences	
					Mean (%)	LS mean* p-value*
Runny nose						
Patanase, 1 BID	293	2.3 (0.6)	1.7 (0.8)	-0.6 (-23.2%)	0.2 (6.8%)	7.0% p=0039
Vehicle, 1 BID	292	2.3 (0.5)	1.9 (0.6)	-0.4 (-16.4%)		
Patanase, 2 BID	293	2.3 (0.6)	1.7 (0.7)	-0.6 (-24.9%)	0.2 (5.2%)	4.4% p=0.0824
Vehicle, 2 BID	293	2.2 (0.6)	1.8 (0.7)	-0.4 (-19.7%)		
Itchy nose						
Patanase, 1 BID	292	2.2 (0.6)	1.6 (0.8)	-0.6 (-26.8%)	0.2 (11.0%)	11.0% p=0.0012
Vehicle, 1 BID	293	2.2 (0.6)	1.8 (0.7)	-0.4 (-15.8%)		
Patanase, 2 BID	293	2.2 (0.6)	1.6 (0.7)	-0.6 (-27.7%)	0.1 (8.5%)	8.0% p=0.0048
Vehicle, 2 BID	289	2.2 (0.6)	1.7 (0.7)	-0.5 (-19.2%)		
Stuffy nose						
Patanase, 1 BID	293	2.5 (0.5)	2.1 (0.7)	-0.4 (-17.6%)	0 (3.7%)	2.7% p=0.2505
Vehicle, 1 BID	293	2.5 (0.5)	2.1 (0.6)	-0.4 (-14.9%)		
Patanase, 2 BID	293	2.5 (0.5)	2.0 (0.7)	-0.5 (-22.1%)	0 (3.2%)	3.0% p=0.1762
Vehicle, 2 BID	292	2.5 (0.5)	2.0 (0.7)	-0.5 (-18.9%)		
Sneeze						
Patanase, 1 BID	290	2.0 (0.7)	1.4 (0.8)	-0.6 (-30.3%)	0.1 (12.6%)	13.2% p=0.0003
Vehicle, 1 BID	292	2.1 (0.7)	1.6 (0.8)	-0.5 (-17.7%)		
Patanase, 2 BID	292	2.1 (0.7)	1.5 (0.7)	-0.6 (-26.4%)	0.1 (5.1%)	3.3% p=0.2828
Vehicle, 2 BID	289	2.0 (0.7)	1.5 (0.8)	-0.5 (-21.3%)		

	N	Baseline (SD)	Treatment (SD)	Change from baseline Mean (%)	Treatment Differences	
					Mean (%)	LS mean* p-value*
Itchy eyes						
Patanase, 1 BID	286	2.0 (0.7)	1.4 (0.8)	-0.6 (-26.6%)	0.2 (18.6%)	18.6% p=0.0004
Vehicle, 1 BID	282	2.0 (0.7)	1.6 (0.8)	-0.4 (-8.0%)		
Patanase, 2 BID	288	2.0 (0.7)	1.4 (0.8)	-0.6 (-26.7%)	0.3 (21.3%)	18.5% p=0.0003
Vehicle, 2 BID	280	1.9 (0.8)	1.6 (0.8)	-0.3 (-5.4%)		
Watery eyes						
Patanase, 1 BID	261	1.7 (0.8)	1.2 (0.8)	-0.5 (-25.9%)	0.1 (12.1%)	12.8% p=0.0313
Vehicle, 1 BID	269	1.8 (0.8)	1.4 (0.8)	-0.4 (-13.8%)		
Patanase, 2 BID	266	1.8 (0.7)	1.3 (0.8)	-0.5 (-27.2%)	0.1 (7.1%)	6.3% p=0.1300
Vehicle, 2 BID	257	1.7 (0.8)	1.3 (0.8)	-0.4 (-20.1%)		
*From ANCOVA model with factors for treatment, age category and baseline, including only patients with non-missing data.						

Source: M5, V19, T11.4.1.3.-3, p191-6

5.3.2.3 Safety

The trial included 2 phases, a 4-16 day run-in period during which patients were treated with 1 spray of vehicle twice daily, and a 2-week randomized treatment period. Because vehicle was used during run-in and because there is some concern for local effects from the vehicle, this section and the accompanying AE tables contain information regarding exposure and events during the vehicle run-in phase in addition to that for the randomized treatment period.

A total of 2388 patients were dosed during the run-in period, of whom 1200 did not qualify for randomization and 1188 were randomized. Mean exposure to vehicle during run-in was 10.3 (SD 4.6) days.

Study drug exposure, total adverse events (AEs), serious AEs, and AEs leading to discontinuation from randomized treatment are shown in Table 12. Exposure after randomization was similar among treatment groups and sufficient to adequately assess efficacy.

There were no SAEs and no deaths. A total of 53 patients discontinued due to an adverse event, 34 during vehicle run-in, and 19 after randomization [see Table 26 for listing]. Discontinuations during the run-in period are significant for 12 patients discontinued due to epistaxis, and 3 patients discontinued due to nasal ulcers. [M5, V25, L14.3.2.-1, p260-74] Active treatment groups had slightly higher incidence of AEs leading to discontinuation, but there were no clear trends in the types of adverse events reported.

Common adverse events with an incidence ≥1% in any treatment group (including vehicle run-in) are shown in Table 13. This trial was the only trial in patients 6-11 years of age that used the approved Patanase formulation. As a result, Table 13 represents the only table in the submission that contains common AEs using the approved Patanase formulation in this age group. Since the incidence of local AEs may be different for the povidone-containing and povidone-free formulations and the other two trials in patients 6-11 years of age used the povidone-containing formulation, I

recommend that the AEs from this table be used to populate the AE table in the Adverse Events section for this age group. The appropriate columns to include would be columns 2 and 3 for Patanase and vehicle, corresponding to the proposed dose of Patanase of 1 spray per nostril twice daily dose.

Active treatment groups had slightly higher incidence of upper respiratory tract infections, dysgeusia, epistaxis, and rash, but no higher incidence of nasal discomfort or ulcerations. The incidence of bitter taste (dysgeusia) with Patanase use (1.0%) in this trial is low compared to the rate reported with Patanase use adults (12.3%). As a result, bitter taste will not be a significant deterrent to use in this population, as it is in older patients.

Epistaxis was the most frequent AE, and occurred in all treatment groups although slightly higher in the Patanase than in vehicle control groups, suggesting that this is at least in part due to the vehicle. The rate of epistaxis with Patanase treatment (5.7%) in this age group is somewhat concerning, since it is approximately double the rate seen with Patanase treatment in patients 12 years of age and older (who were treated with double the proposed dose in this age group: 2 sprays instead of the proposed 1 spray per nostril twice daily). Six patients (0.3%) experienced a nasal ulceration during vehicle run-in and seven patients (0.6%) experienced a nasal ulceration during the treatment phase, about half at each dose. Note that if a cutoff of AEs at a 1% rate is used, the incidence of nasal ulcerations will not appear in the AE table.

The higher rate of epistaxis with only 2 weeks of treatment is of some concern. Actual rates with longer-term use are likely to be higher, since cumulative rates increased with long-term use in the adult/adolescent safety trials. That said, the labeling for Patanase includes a statement in the WARNINGS AND PRECAUTIONS section (5.1) for local nasal effects, and this is reasonable to apply to this age group as long as the higher incidence of epistaxis is described in the ADVERSE EVENTS section (6.1).

Table 12. C-07-01, Summary of exposure and adverse events, Safety

Summary of Study Drug Exposure and Adverse Events, N (%)	Pat 1 BID N=298	Veh 1 BID N=297	Pat 2 BID N=296	Veh 2 BID N=297
Exposure in days, Mean (SD)	17.7 (23.0)	17.5 (2.9)	17.5 (2.7)	17.5 (3.1)
Total AEs	75 (25.2)	65 (21.9)	80 (27.0)	72 (24.2)
SAEs	0	0	0	0
AEs leading to discontinuation	6 (2.0)*	4 (1.3)	5 (1.7)	4 (1.3)
*Listing (V25, p 255-9) shows 6 patients in this grouping discontinued due to an AE. Response to IR of 9/23/09 shows correction to the original table in the study report for number of AEs causing discontinuation, which showed 7 patients discontinued from the Patanase 1 BID group due to an AE.				

Source: M5, V18, T12.1.-3 and T12.1.-1, p87-8. Response to IR of Sept 23, 2009, T2, p2.

Table 13. C-07-01, Common adverse events ≥1% in any treatment group, Safety

SOC / PT N (%)	Pat 1 BID N=298	Veh 1 BID N=297	Pat 2 BID N=296	Veh 2 BID N=297	Veh Run-in n=2388
GI					
Upper abdominal pain	1 (0.3)	1 (0.3)	2 (0.7)	3 (1.0)	16 (0.7)
Vomiting	1 (0.3)	3 (1.0)	2 (0.7)	2 (0.7)	5 (0.2)

SOC / PT N (%)	Pat 1 BID N=298	Veh 1 BID N=297	Pat 2 BID N=296	Veh 2 BID N=297	Veh Run-in n=2388
General & administration site					
Pyrexia	4 (1.3)	3 (1.0)	5 (1.7)	3 (1.0)	25 (1.0)
Infections & Infestations					
Pharyngitis streptococcal	1 (0.3)	0	4 (1.4)	1 (0.3)	8 (0.3)
Rhinitis	3 (1.0)	4 (1.3)		4 (1.3)	13 (0.5)
Upper respiratory tract infection	4 (1.3)	0	4 (1.4)	2 (0.7)	4 (0.2)
Viral upper respiratory tract infection	4 (1.3)	0	0	1 (0.3)	1 (0.0)
Injury, Poisonings, & Procedural					
Injury	3 (1.0)	4 (1.3)	6 (2.0)	4 (1.3)	16 (2.8)
Nervous system					
Dysgeusia	3 (1.0)	0	4 (1.4)	1 (0.3)	2 (0.1)
Headache	13 (4.4)	11 (3.7)	9 (3.0)	16 (5.4)	68 (2.8)
Respiratory, Thoracic, & Mediastinal					
Cough	2 (0.7)	3 (1.0)	4 (1.4)	3 (1.0)	16 (0.7)
Epistaxis	17 (5.7)	11 (3.7)	18 (6.1)	16 (5.4)	42 (1.8)
Nasal congestion	0	2 (0.7)	1 (0.3)	3 (1.0)	2 (.01)
Nasal discomfort	0	1 (0.3)	4 (1.4)	2 (0.7)	5 (0.2)
Nasal ulcer	2 (0.7)	1 (0.3)	1 (0.3)	3 (1.0)	6 (0.3)
Pharyngeolayrngeal pain	5 (1.7)	7 (2.4)	2 (0.7)	4 (1.3)	13 (0.5)
Rhinitis seasonal	1 (0.3)	4 (1.3)	0	1 (0.3)	3 (0.1)
Throat irritation	1 (0.3)	1 (0.3)	3 (1.0)	0	2 (0.1)
Skin & Subcutaneous					
Rash	4 (1.3)	0	1 (0.3)	2 (0.7)	11 (0.5)

AEs occurring with a frequency of 1.0% or more and more frequently in the Patanase 1 spray per nostril dose than in the corresponding vehicle dose, are highlighted in yellow. Since the 1-spray dose is to be the approved dose, I recommend that the AEs for this dose be placed in the labeling.

Source: M5, V18, T12.2.3.2.-1, p94; V24, T14.3.1.5.-1, p114-5

Nasal Examinations

Nasal examinations were conducted at the screening, randomization, and last trial visits, looking for significant anatomic abnormalities, evidence of infection, bleeding, and ulceration of the mucosa, with a more detailed examination using a grading scale (Figure 1) for patients with any positive findings. An adverse event was required to be recorded for any change (no to yes) in a nasal examination parameter.

Events with changes from baseline, broken down by screening exams, detailed examinations, and age group, are shown in Table 14. There were no events of significant anatomic abnormalities, intranasal mass, Grade 3 mucosal ulcerations, or nasal perforations. The 2-spray dose was associated with slightly more events of nasal irritation than the 1-spray dose. When the two active groups are compared to vehicle control groups, there were no differences between active and control in nasal irritation, although here were slightly more frequent events of blood in the nose and epistaxis in the two active groups. However, the only group with Grade 2 epithelial erosions was the vehicle 2 spray treatment group. Taken together, the results suggest that the vehicle nasal spray is somewhat irritating to the nose regardless of dose; the addition of olopatadine to vehicle did not result in significantly higher frequencies of intranasal examination events than vehicle alone.

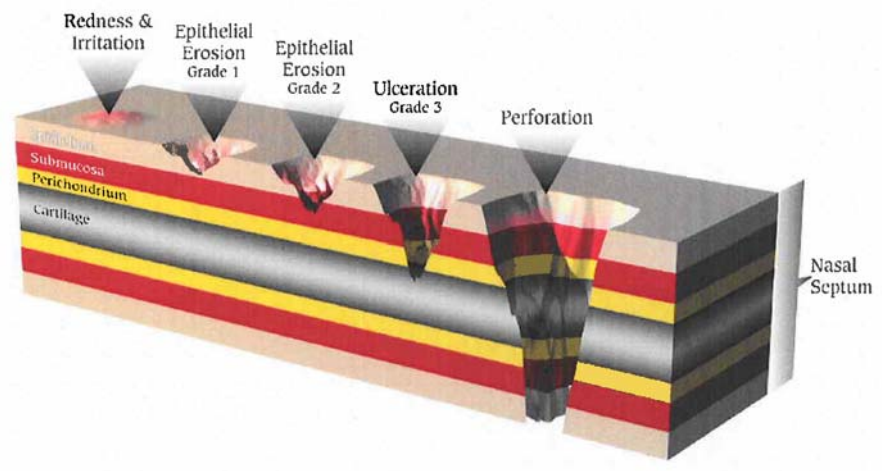

Figure 1. Nasal Examination Grading Scale

Note: Figure comes from C-07-02, which used the same grading scale for nasal examinations
Source: C-07-02, F12.5.1.-1, M5, V1, p107

Table 14. C-07-01, Nasal examinations

Change from baseline in Nasal Examinations	Pat 1 BID N=298	Veh 1 BID N=297	Pat 2 BID N=296	Veh 2 BID N=297
Screening examination				
Significant anatomic abnormalities	0	0	0	0
Infection	2 (0.7)	2 (0.7)	3 (1.0)	1 (0.3)
6-8y	1	0	2	1
9-11y	1	2	1	0
Possible mucosal ulceration	3 (1.0)	4 (1.4)	3 (1.0)	7 (2.4)
6-8y	1	2	3	1
9-11y	2	2	0	6
Blood in nose	7 (2.4)	3 (1.0)	7 (2.4)	5 (1.7)
6-8y	1	1	4	1
9-11y	6	2	3	4
Detailed examination (for patients with a positive screening examination)				
Intranasal mass	0	0	0	0
Redness, Irritation	1 (0.3)	3 (1.0)	4 (1.4)	4 (1.4)
6-8y	0	2	4	0
9-11y	1	1	0	4
Epithelial erosion, Grade 1	2 (0.7)	1 (0.3)	1 (0.3)	1 (0.3)
6-8y	1	0	1	0
9-11y	1	1	0	1
Epithelial erosion, Grade 2	0	0	0	2 (0.7)
6-8y	0	0	0	1
9-11y	0	0	0	1
Mucosal ulceration, Grade 3	0	0	0	0
Nasal perforation	0	0	0	0
Nasal Bleeding	7 (2.4)	3 (1.0)	6 (2.0)	5 (1.7)
6-8y	1	1	3	1
9-11y	6	2	3	4

Source: M5, V18, T12.5.1.-1 and T12.5.1.-2, p104-5

Physical Examinations and Vital Signs

There were no clinically relevant differences between treatment groups for physical examination or vital sign parameters.

5.3.4 C-07-02

5.3.3.1 Description of the Trial and Study Population

C-07-02 was the only trial performed in patients 2-5 years of age. This was a randomized, multicenter (9 sites in the US), double-masked, vehicle-controlled, 2-week safety and PK trial comparing Patanase Nasal Spray with vehicle placebo, 1 spray per nostril twice daily, in 132 patients 2-5 years of age with a history of allergic rhinitis (AR). The trial was conducted between October and December 2008. There were no protocol amendments or changes to planned analyses. The primary objective was to describe the safety of Patanase Nasal Spray administered twice daily in patients 2-5 years of age with a history of allergic rhinitis, and the secondary objective was to describe the pharmacokinetics of olopatadine and its 3 active metabolites in these patients.

Inclusion criteria included written permission from parent/legal guardian, history of allergic rhinitis symptoms and at least one documented positive skin test (prick ≥3mm, intradermal ≥7mm, or RAST 2+) for an allergen, and a normal nasal examination. Patients were excluded for need for a chronic or intermittent nasal spray during the study period, use of Patanase within 7 days of randomization; current or recent use (w/in 14 days) of a drug that may prolong the QT interval; history or evidence of nasolacrimal discharge system malfunction, concurrent disease that could complicate or interfere with evaluation of study meds; midfacial or anatomic nasal deformity; acute sinusitis within 30 days of randomization; congestion that would interfere with study drug administration; asthma, except mild intermittent asthma; current or recent history of uncontrolled neurological, cardiovascular, gastrointestinal, hematological, hepatic, and/or renal disease or evidence of other diseases on physical examination, that would preclude safe participation; hypersensitivity to olopatadine, benzalkonium chloride, or any components; history or current HIV, hepatitis B or C or A infection; relative of study site staff; family member of a patient currently enrolled in the study; participated in another study within 30 days; or had clinically relevant abnormalities in vital signs at screening.

A vehicle run-in period was not employed. After screening, patients were seen at clinical trial sites on the day of randomization and after 1 and 2 weeks of treatment. Randomization was 1:1 to Patanase or vehicle placebo, administered as 1 spray per nostril twice daily for 14 days by the parent/caregiver. A population PK approach was used to characterize the PK of olopatadine and its active metabolites (M1, M2, and M3) after the first dose on Day 1 (blood samples obtained at 15-30 minutes, 1.5-2.5 hours, and 5-8 hours) and on Day 15 (pre-dose trough and 1.5-2.5 hours post-dose). No efficacy assessments were performed. Treatment compliance was assessed by treatment diaries and bottle weights. Safety assessments included the extent of

exposure, nasal and physical examinations, cardiovascular parameters (pulse, systolic and diastolic BP) and adverse events.

Patients could discontinue at any time for any reason, including Investigator discretion, adverse event, lost to follow-up, protocol violation, patient decision, or other reason. Patients discontinued due to symptoms of allergic rhinitis were treated as having discontinued due to an adverse event. Nasal sprays were not permitted except that saline and oxymetazoline could be utilized for nasal examinations. Claritin was permitted as a rescue medication for symptoms of allergic rhinitis that required concomitant therapy.

A total of 132 patients were randomized and received at least one dose of study medication. Treatment groups appear to have been balanced at baseline, with no imbalances in discontinuations that might have affected the results. The numbers of patients randomized within the 2-3 and 4-5 year age groups are shown in Table 15, patient disposition is shown in Table 16, and demographics and baseline characteristics are shown in Table 17.

Table 15. C-07-02, Randomized and completed patients

	Pat 1 BID		Veh 1 BID		Total	
	Randomized	Completed	Randomized	Completed	Randomized	Completed
All patients	66	63	66	63	132	126
2-3y	37	34	34	32	71	66
4-5y	29	29	32	31	61	60
PK population	66	63	--	--	66	63
2-3y	37	34	--	--	37	34
4-5y	29	29	--	--	29	29

Source: T M5, V1, 10.1.-1 and T10.1.-2, p60

Table 16. C-07-02, Patient disposition

	Pat 1 BID	Veh 1 BID	Total
Exclusions / protocol deviations	5 (7.6%)	12 (18.2%)	17 (12.9%)
Inadequate PK data *	2	6	8
Discontinued	3	2	5
Protocol violation	0	2	2
Other †	0	2	2
Exclusions / protocol deviations by age group			
2-3 years	3 (8.1%)	10 (29.4%)	13 (18.3%)
4-5 years	2 (6.9%)	2 (6.3%)	4 (6.6%)

* Inadequate PK data.
† Patients with two or more protocol violations.

Source: Response to IR of Sept 23, 2009, T4, p6 with corrections to M5, V1, T10.2.-1, p61. Response to IR of Sept 23, 2009, T6 and T7, p10.

Table 17. C-07-02, Demographics and baseline characteristics, Safety

Demographics and Baseline Characteristics	Pat 1 BID N=66			Veh 1 BID N=66
	All	2-3y	4-5y	
Age, Mean (range)	3.4 (2-5)	2.6 (2-3)	4.4 (4-5)	
2-3y	37 (56.1%)	--	--	34 (51.5%)
4-5y	29 (43.9%)	--	--	32 (48.5%)
Weight, kg, Mean (SD)	17.2 (3.9)	14.6 (2.1)	20.6 (2.9)	
Height, cm, Mean (SD)	101.5 (10.9)	94.3 (9.1)	110.5 (4.4)	
BSA, m^2, Mean (SD)	0.68 (0.11)	0.61 (0.07)	0.79 (0.06)	
Sex Male	38 (57.6%)	17	21	30 (45.%)
Female	28 (42.4%)	20	8	36 (54.5%)
Race				
White	44 (66.7%)	27	17	45 (68.2%)
Black	18 (27.3%)	9	9	20 (30.3%)
Asian	1 (1.5%)	0	1	0
Other	3 (4.5%)	1	2	1 (1.5%)
Ethnicity				
Hispanic, Latino, or Spanish	17 (25.8%)	12	5	12 (18.2%)
Not Hispanic, Latino, or Spanish	49 (74.2%)	25	24	54 (81.8%)

Source: T11.2.1-1, T11.2.1.2.-2, T11.2.1.2.-3, T11.2.2.-1, T11.2.2.-2, and T11.2.2.-3, M5, V1, p70, 72-5

5.3.3.2 Safety

Summaries of study drug exposure and adverse events are shown in Table 18, and common AEs with an incidence ≥1% in either treatment group are shown in Table 19.

There were no SAEs and no deaths.

Two patients were discontinued due to an adverse event (1 rhinitis, 1 pneumonia), both in the vehicle control group.

Study drug exposure and the overall number of patients with AEs were similar between treatment groups, although the frequency of nasal adverse events was slightly higher with Patanase treatment than with vehicle control.

Common AEs of note that were higher in Patanase than in vehicle control were diarrhea, dysgeusia, and epistaxis. The disproportionate number of patients with diarrhea (Patanase 9.1%, vehicle 0) and discolored feces (Patanase 1.5%, vehicle 0) in the active group is suggestive of a treatment effect of swallowed olopatadine on the GI tract in this age group. Surprisingly, and unlike in **C-07-01**, epistaxis was not common in patients treated with vehicle control, but the rate of epistaxis (6.1%) in patients treated with Patanase is significant, and approximately double the rate for Patanase in patients 12 years of age and older (who were treated with double the dose in this age group: 2 sprays instead of 1 spray per nostril twice daily), suggesting that this age group is particularly sensitive to olopatadine. Compared with adults, and similar to what was seen in **C-07-01**, bitter taste (dysgeusia) was reported with relatively low incidence (Patanase 3.0%, vehicle 0), and therefore will not be a significant deterrent to use in this population as it is in older patients. Other AEs of note in the vehicle control that could be considered related to study drug treatment were dysphonia (1), nasal turbinate

hypertrophy (2), and nasal ulcer (1), suggesting that the vehicle is responsible for part of the irritation-type AEs. Additionally, about 10% of both groups experienced cough, and 5-6% experienced vomiting as an AE. These AEs were not seen on older age ranges. They most likely represent effects of excess drug/vehicle dripping into the nasopharynx.

Table 18. C-07-02, Exposure and Adverse events, Safety

Exposure and AE Summary N (%)	Pat 1 BID N=66	Veh 1 BID N=66
Exposure in days, Mean (SD)	15.1 (2.1)	15.2 (2.1)
Total Patients with AEs	26 (39.4)	24 (36.4)
Patients with Nasal AEs	11 (16.7)	7 (10.6)
Patients with Non-Nasal AEs	22 (33.3)	20 (30.3)
SAEs	0	0
AEs leading to discontinuation	0	2 (3.0)

Source: T12.1.-2, M5, V1, p91 and T12.2.3.4.-1, M5, V1, p102

Table 19. C-07-02, Common adverse events >1% in either treatment group, Safety

SOC / PT N (%)	Pat 1 BID N=66	Veh 1 BID N=66
Ear and Labyrinth		
Ear pain	0	1 (1.5)
Eye		
Eye pain	0	1 (1.5)
GI		
Diarrhea	6 (9.1)	0
Vomiting	3 (4.5)	4 (6.1)
Feces discolored	1 (1.5)	0
General and Administration site		
Pyrexia	2 (3.0)	6 (9.1)
Injection site pain	1 (1.5)	0
Vessel puncture site pain	0	1 (1.5)
Immune System		
Seasonal allergy	1 (1.5)	0
Infections & Infestations		
Gastroenteritis	1 (1.5)	0
Nasopharyngitis	1 (1.5)	1 (1.5)
Otitis media	1 (1.5)	2 (3.0)
Rhinitis	1 (1.5)	2 (3.0)
Sinusitis	1 (1.5)	0
Upper respiratory tract infection	1 (1.5)	0
Conjunctivitis infective	0	1 (1.5)
Croup infectious	0	1 (1.5)
Pharyngitis	0	1 (1.5)
Pharyngitis streptococcal	0	1 (1.5)
Pneumonia	0	1 (1.5)
Injury, Poisonings, Procedural complications		
Injury	0	4 (6.1)
Metabolism & Nutrition		
Decreased appetite	1 (1.5)	0
Musculoskeletal & Connective tissue		
Muscle spasms	0	1 (1.5)

SOC / PT N (%)	Pat 1 BID N=66	Veh 1 BID N=66
Pain in extremity	0	1 (1.5)
Nervous system		
Dysgeusia	2 (3.0)	0
Headache	0	3 (4.5)
Respiratory, Thoracic & Mediastinal		
Cough	6 (9.1)	7 (10.6)
Epistaxis	4 (6.1)	1 (1.5)
Rhinorrhea	3 (4.5)	2 (3.0)
Wheezing	2 (3.0)	1 (1.5)
Asthma	1 (1.5)	0
Nasal discomfort	1 (1.5)	0
Tonsillar hypertrophy	1 (1.5)	0
Dysphonia	0	1 (1.5)
Nasal turbinate hypertrophy	0	2 (3.0)
Nasal ulcer	0	1 (1.5)
Postnasal drip	0	1 (1.5)
Upper respiratory tract congestion	0	1 (1.5)
Skin & Subcutaneous		
Skin irritation	1 (1.5)	0
Dry skin	0	1 (1.5)
Pruritus generalized	0	1 (1.5)

Common AE with an incidence >3% (2 patients) and more frequent in the Patanase than vehicle treatment group are shown highlighted in yellow. I recommend that these AEs be placed in the labeling.

Source: T14.3.1.5.-1, M5, V1, p174-5

Nasal Examinations

Nasal examinations were conducted at the screening, randomization, and last study visits, looking for significant anatomic abnormalities, evidence of infection, bleeding, and ulceration of the mucosa, with a more detailed examination using a grading scale (Figure 1) for patients with any positive findings. An adverse event was required to be recorded for any change (no to yes) in a nasal examination parameter. Redness/irritation was coded as rhinitis, while Grades I/II epithelial erosions and Grade III ulcerations were coded as nasal ulceration.

Events with changes from baseline, broken down by screening exams, detailed examinations, and age group, are shown in Table 20. There were few events, and no events of significant anatomic abnormalities, intranasal masses, Grade 2 erosions, Grade 3 ulcerations, or nasal perforations. Whereas the results for **C-07-01**, suggested that vehicle nasal spray is somewhat irritating to the nose, even at the same dose used in this trial, the results of this trial was less suggestive of an irritating effect from the vehicle control.

Table 20. C-07-02, Nasal examinations

Change from baseline in Nasal Examinations	Pat 1 BID			Veh 1 BID		
	All N=66	2-3y N=37	4-5y N=29	All N=66	2-3y N=34	4-5y N=32
Screening examination						
Significant anatomic abnormalities	0	0	0	0	0	0
Infection	1 (1.5)	1	0	1 (1.5)	1	0
Possible mucosal ulceration	0	0	0	1 (1.5)	1	0
Blood in nose	2 (3.0)	2	0	2 (3.0)	2	0
Detailed examination (for patients with a positive screening examination)						
Intranasal mass	0	0	0	0	0	0
Redness, Irritation	1 (1.5)	1	0	1 (1.5)	1	0
Epithelial erosion, Grade 1	0	0	0	1 (1.5)	1	0
Epithelial erosion, Grade 2	0	0	0	0	0	0
Mucosal ulceration, Grade 3	0	0	0	0	0	0
Nasal perforation	0	0	0	0	0	0
Nasal Bleeding	2 (3.0)	2	0	1 (1.5)	1	0

Source: T12.5.1.-1 and T12.5.1.-2, M5, V1, p109-110

Physical Examinations and Vital Signs

There were no clinically relevant differences between treatment groups for physical examination or vital sign (heart rate and BP) parameters.

Summary and Recommendations

C-07-02 was the only trial performed in patients 2-5 years of age. This was a randomized, multicenter (9 sites in the US), double-masked, vehicle-controlled, 2-week safety and PK trial comparing Patanase Nasal Spray with vehicle placebo, 1 spray per nostril twice daily, in 132 patients 2-5 years of age with a history of allergic rhinitis (AR).

There were no SAEs and no deaths. Two patients were discontinued due to an adverse event (1 rhinitis, 1 pneumonia), both in the vehicle control group. Common AEs of note that were higher in Patanase than in vehicle control were diarrhea, dysgeusia, and epistaxis. The disproportionate number of patients with diarrhea (Patanase 9.1%, vehicle 0) and discolored feces (Patanase 1.5%, vehicle 0) in the active group is suggestive of a treatment effect of swallowed olopatadine on the GI tract in this age group. Surprisingly, and unlike in **C-07-01**, epistaxis was not common in patients treated with vehicle control, but the rate of epistaxis (6.1%) in patients treated with Patanase is significant and concerning, since it is approximately double the rate for Patanase in adults and adolescent patients (who were treated with double the dose in this age group: 2 sprays instead of 1 spray per nostril twice daily). Compared with adults, and similar to what was seen in **C-07-01**, bitter taste (dysgeusia) was reported with relatively low incidence (Patanase 3.0%, vehicle 0), and therefore will not be a significant deterrent to use in this population as it is in older patients. Other AEs of note in the vehicle control that could be considered related to study drug treatment were dysphonia (1), nasal turbinate hypertrophy (2), and nasal ulcer (1), suggesting that the vehicle is responsible for part of the irritation-type AEs. Additionally, about 10% of both groups experienced cough, and 5-6% experienced vomiting as an AE. These AEs were

not seen on older age ranges. They most likely represent effects of excess drug/vehicle dripping into the nasopharynx.

The limited dataset is of particular concern for the 2-5 year old age range, in whom only one 2-week trial was performed, with the safety dataset including 65 patients who received olopatadine for at least 1 week and total exposure limited to 2 weeks duration. Although the exposure to Patanase from this single trial is limited, the AEs reported likely give a reasonable estimate of the risks with short-term exposure in this age group. Given the incidence of local and systemic AEs in this population, and the fact that efficacy was not evaluated in this trial (and therefore, the appropriate dose for this age range is unknown) (b) (4)

6 Review of Efficacy

Efficacy Summary

This pediatric supplement seeks to extend the approved indication for treatment of the symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older, to patients (b) (4) through 11 (b) (4) 11) years of age, at a dose of one spray per nostril twice-daily.

To support efficacy in children 6-11 years of age, two clinical trials were performed, **C-04-20** and **C-07-01**, only one of which was successful (Table 21 and Table 22). However, the results from **C-07-01** appear robust and support efficacy for treatment of the symptoms of SAR in this age range using the proposed dose of 1 spray per nostril twice daily. This dose is half the approved dose for treatment of SAR in patients 12 years of age and older, and provides similar PK/systemic exposure in this age group as in patients 12 years of age and older at the higher (approved) dose.

One safety and PK trial, **C-07-02**, was performed in patients 2-5 years of age (b) (4) . PK from this trial demonstrated that systemic exposure in children 2-5 years of age with the proposed 1-spray dose is similar to that seen in adults and adolescents 12 years of age and older with the 2-spray dose and to children 6-11 years of age at the proposed 1 spray dose. (b) (4) See the individual clinical trial results and the Risk/Benefit section for further details. The rest of this section is devoted to the efficacy results in patients 6-11 years of age.

Individual clinical trial results, including results for secondary endpoints in **C-07-01**, may be found in Section 5.3 of this review, and are not repeated here. Results of the FDA statistical analyses are shown in Table 21.

As in the adult/adolescent clinical trials, the primary efficacy measure in both **C-07-01** and **C-04-20** were the percent change from baseline in AM+PM reflective total nasal symptom scores (rTNSS). However, the Division considers mean change from baseline to be a key secondary endpoint, and labeling for most products [including that for Patanase] contains the efficacy results displayed in this fashion. In **C-07-01**, Patanase was efficacious using both the declared primary endpoint of percent change and the key secondary endpoint of mean change. Both doses were statistically significant, with no adjustment made for multiplicity. Both doses were supported by other secondary measures including percent change in instantaneous TNSS and percent change in most individual nasal symptom scores (not shown in this section – see results in Section 5.3 of this review). Results for the 1 spray per nostril twice daily dosage were numerically larger than those for the 2 sprays per nostril twice daily dosage for the primary measure and all secondary measures, with treatment differences for the 1 spray twice daily dosage supportive for all individual nasal symptom scores except stuffy nose. Change in PAQLQ, while statistically significant, was numerically small and below the minimum important difference (MID) of 0.5. Subgroup analyses of the primary endpoint were consistent with the primary analysis. The results thereby support a recommendation to use the lower dose of 1 spray per nostril twice daily in this age group rather than the 2 sprays dose currently approved for patients 12 years of age and older.

Table 21. Primary efficacy from clinical trials in patients 6-11 years of age

Study Treatment	Change from baseline in rTNSS			
	n	Mean change	% change	p-value
C-07-01				
Olo 0.6%, 1 spray	294	-2.4	-25	0.0007
Vehicle 1 spray	294	-1.7	-18	
Olo 0.6%, 2 sprays	293	-2.5	-26	0.012
Vehicle, 2 sprays	293	-1.9	-21	
C-04-20				
Olo 0.6%, 1 spray	172	-1.8	-21	0.28* (0.17**)
Olo 0.4%, 1 spray	176	-1.7	-21	0.29* (0.14**)
Vehicle, 1 spray	175	-1.5	-17	

- P value from Dunnett's T test (without adjustment for age group (6-8y and 9-11y)

** P value from ANCOVA model (with adjustment for age group (6-8y and 9-11y)

Source: FDA statistical analyses

Table 22 shows the pediatric efficacy results within the context of the results represented in the labeling for the 0.6% and 0.4% formulations used in the adult/adolescent trials at a dose of 2 sprays per nostril twice daily. The table includes failed trial **C-04-20** in addition to the results for **C-07-01** and the adult/adolescent clinical trials. Although efficacy was demonstrated statistically in **C-07-01**, it is important to note that to do so the applicant had to increase the sample size for each arm beyond what was needed to demonstrate efficacy in adults and adolescents. It is likely that this was undertaken based on the results of **C-04-20** that used a smaller sample size per arm.

Furthermore, treatment differences using the same endpoint [mean change from baseline in AM+PM rTNSS] in adults and adolescents were larger than those seen in this study. As a result, efficacy with Patanase in children 6-11 years of age has been demonstrated from a statistical perspective, although the efficacy in this age group is modest.

The percent change from baseline in reflective ocular symptoms (rTOSS) characterized as was a key secondary endpoint in **C-07-01**. (b) (4)

[redacted]

Table 22. Comparison of Patanase pediatric and adult/adolescent primary efficacy* results

Study	n	Baseline	Mean (%) Change from Baseline	Treatment Difference	
				LS Mean	p-value
Adults and adolescents					
C-02-10					
Olo 0.6%, 2 sprays	220	9.17	-2.90 (30.1%)	0.98 (0.59, 1.37)	p<0.0001
Olo 0.4%, 2 sprays	228	9.26	-2.63	0.72 (0.33, 1.11)	p<0.0001
Vehicle, 2 sprays	223	9.07	-1.92 (18.7%)		
C-02-37					
Olo 0.6%, 2 sprays	183	8.71	-3.63 (39.2%)	0.96 (0.51, 1.42)	p<0.0001
Olo 0.4%, 2 sprays	188	8.90	-3.38	0.71 (0.26, 1.17)	
Vehicle, 2 sprays	191	8.90	-2.67 (27.0%)		
6-11 years					
C-07-01					
Olo 0.6%, 1 spray	294	8.99	-2.24 (24.7%)	0.58 (0.22, 0.94)	p=0.0015
Vehicle, 1 spray	294	9.09	-1.70 (17.9%)		
Olo 0.6%, 2 sprays	293	9.18	-2.45 (26.5%)	0.43 (0.07, 0.80)	p=0.0206
Vehicle, 2 sprays	293	8.83	-1.90 (20.8%)		
C-04-20					
Olo 0.6%, 1 spray	172	8.1	-1.7 (20.9%)	NA	p=0.3343
Olo 0.4%, 1 spray	176	8.1	-1.7 (20.9%)	NA	p=0.3502
Vehicle, 1 spray	175	8.2	-1.4 (17.2%)		

*Adult data from PI. All treatments are expressed as the number of sprays per nostril twice daily. All p-values based on mean [not percent] change from baseline in AM+PM rTNSS over 2-weeks of treatment. LS means expressed as absolute value for Active minus vehicle. Note that the 0.4% formulation is not approved, but was used in several clinical trials and is in the PI.

7 Review of Safety

Safety Summary

Although this section is the Review of Safety, it follows the applicant's methodology in the submission in that it provides an integrated summary of safety for the entire age group of 2-11 years of age. The applicant did not break down safety into the two age groups, and as a result, this integrated summary does not either. There were 3 trials in patients 6-11 years of age, and one trial in patients 2-5 years of age. Since there is only one trial (**C-07-02**) in the lower age group, for details regarding this age group the reader is advised to look at the individual clinical trial review, which contains a separate discussion of safety for this age group, as well as the Risk/Benefit discussion at the beginning of this review. Further, of the 3 clinical trials in patients 6-11 years of age, only one (**C-07-01**) used the approved povidone-free formulation of Patanase. Because local nasal effects may differ by formulation, please see the individual trial review for further details regarding safety from this trial.

The pediatric clinical trials provide a safety dataset considered adequate to assess safety in patients 6-11 years of age, but not adequate for patients 2-5 years of age. For patients 6-11 years of age, there is extensive short-term safety out to 2 weeks of treatment. For patients 2-5 years of age, the safety dataset includes 65 patients who received olopatadine for at least 1 week. For both age groups, the safety dataset is limited by the fact all trials were of only 2 weeks duration, and no long-term trials were performed.

Nasal septal perforation, present in the long-term safety trial with the povidone-containing formulation, is no longer an issue for the povidone-free formulation (based on the long-term safety trial submitted in supplement S-001). However, nasal irritation with epistaxis and nasal ulcerations remains the major issue for this product in children 2-11 years of age as it is in adults and adolescents 12 years of age and older. Targeted nasal examinations after 2 weeks of treatment during the pediatric trials showed the rates of epistaxis and nasal ulceration with the povidone-free formulation at the proposed dose of 1 spray per nostril twice daily, to be 5.8% and 0.5% for Patanase and 3.3% and 0.6% for vehicle, respectively. Most nasal ulcerations were superficial in depth, although the time to healing varied significantly. Actual rates in practice are likely to be higher, since cumulative rates increased with long-term use in the adult/adolescent safety trials. While of concern, it is possible to label for these occurrences for patients 6-11 years of age because the safety dataset for this age group out to 2 weeks of treatment does not present any new safety signals for this age range. However, the safety dataset in children 2-5 years of age is limited, and both nasal and non-nasal adverse events occurred in this age group. As a result, the safety dataset for this age range is not sufficient.

For the combined 2-11 year age range, four pediatric AEs had an incidence of ≥1.0% and were more frequent with olopatadine than vehicle treatment. These included dysgeusia (bitter taste), epistaxis, upper respiratory tract infection, and diarrhea. In this combined age range, several AEs were more common in children than in adults and

deserve mention. These events include epistaxis, cough, and pyrexia (fever). Epistaxis, discussed elsewhere, was twice as frequent in children as in adults. Cough is likely related to excess of the spray dripping down the posterior nasopharynx. Fever is more common in this age group than in adults, and is not unexpected as an AE. Likewise, several AEs were less common in children than in adults and deserve mention. Reports of bitter taste were much lower in children, and therefore might not be expected to limit use as it might in adults.

In addition to epistaxis and/or nasal irritation, the Written Request made note of certain types of adverse events that may be of concern. These included paradoxical excitability, somnolence, fatigue, and hyperkinesia. No increased incidence was noted for these events. Somnolence was not noted as an AE in the pediatric trials, and reports of fatigue were less common than reported in adults.

Depression was noted in some patients enrolled in the 12 month adult/adolescent safety trial, and the labeling was recently updated with this information. Targeted analyses of adverse events using the standardized MedDRA query (SMQ) for depression and suicide/self injury, with addition of the term insomnia did not show any increase in events these age groups. Three patients who reported 3 adverse events were found, including one event each of psychomotor hyperactivity and mood swings in patients on olopatadine, and one event of insomnia in a patient on vehicle.

7.1 Methods

The pediatric development program for children 2-11 years of age included 4 clinical trials, 3 in patients 6-11 years of age, and 1 in patients 2-5 years of age (Table 3 and Table 4). All four trials were 2 weeks in duration, and all collected adverse events and coded events using MedDRA terminology. Although this could have allowed pooling of general adverse event data from the 3 trials in children 6-11 years of age, this was not carried out by the applicant, who chose to pool the data for all four trials together. Since 2 trials had previously been performed in children 6-11 years of age using the povidone-containing formulation, and data for each trial was presented in the applicant's tables, I was able to separate intranasal adverse events and examinations in the pediatric trials using the povidone-containing formulation from those using the povidone-free formulation. The applicant did provide a comparison between pediatric adverse events and intranasal safety and previous results in adults/adolescents in both the 2-week efficacy using the povidone-containing formulation and the two 1-year safety trials with the povidone-containing and povidone-free formulations.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The pediatric development program included 2102 patients, of whom 936 were exposed to olopatadine nasal spray 0.6%, with 276 children exposed to the povidone-containing

formulation and 660 children exposed to the marketed povidone-free formulation. Of these, 298 children 6-11 years of age were exposed to the proposed dose of 1 spray per nostril twice daily, 296 children 6-11 years of age were exposed at the adult/adolescent approved dose of 2 sprays per nostril twice daily, and 66 children 2-5 years of age were exposed to the proposed dose of 1 spray per nostril twice daily. Of the 2102 patients in the development program, 1192 (56.7%) were male, 1410 (67.1%) were Caucasian, 366 (17.4%) were Black, and 326 (15.5%) were characterized as 'Other' race. The breakdown of patients and exposure by product, dose, and age group is shown in Table 23.

The overall number of patients and duration of exposure was considered adequate for assessment of common adverse events and specific nasal events of concern in patients 6-11 year of age. The number of patients in the 2-5 year age group exposed to olopatadine for at least 1 week is relatively small, 65 patients, and is not considered adequate for a full assessment of safety in this age range.

A major deficiency with the pediatric program was lack of any safety data beyond 2 weeks of treatment. Safety data with chronic use is available from adult/adolescent safety trials, but is not available either for patients 2-5 years or 6-11 years of age. For patients with SAR, it is expected that treatment typically lasts the entire season, and for some patients who have multiple seasonal allergies, through several seasons. Therefore, the expectation is that patients with SAR will be exposed for at least several months at a time, and may have intermittent exposure for 6 or more months per year.

Table 23. Summary of the number of patients in the pediatric development program and duration of exposure, all studies, 2-11y

Safety Database	Total N	1 spray BID				2 sprays BID			
		N	1-6d	7-16d	>16d	N	1-6d	7-16d	>16d
Olopatadine 0.6%	**936**	588	4	278	302	348	1	142	204
6-11 years	870	522	3	220	295	348	1	142	204
Povidone	276	224	1	126	96	52	0	44	8
Povidone-free	594	298	2	94	199	296	1	98	196
2-5 years (povidone-free)	66	66	1	58	7	--	--	--	--
Total povidone-free	660	364	3	152	206	296	1	98	196
Olopatadine 0.4%	**228**	228	5	119	104	--	--	--	--
Vehicle	**938**	590	6	276	306	348	4	138	206
6-11 years	872	524	4	219	299	348	4	138	206
2-5 years	66	66	2	57	7	--	--	--	--
Total	**2102**								
Table omits patients with <1 day of exposure. Data for 2-5 year age group comes from one trial: C-07-02.									

Source: M2, V1, Summary of Clinical Safety, T2.7.4.1.1.-1 and T2.7.4.1.2.-1, p 1-3

7.2.2 Explorations for Dose Response

The overall incidence of adverse events based on treatment and dose are shown in Table 24. Differences in incidence were small and likely not significant. No differences were noted in the overall incidence of adverse events in any of the dosing subgroups based on sex or race [results not shown].

Table 24. Incidence of patients with adverse events, by treatment

	Total N	Patients with adverse events	
		N	%
Olopatadine 0.4%, 1 spray BID	228	51	22.4%
Olopatadine 0.6%, 1 spray BID	588	178	30.3%
Olopatadine 0.6%, 2 sprays BID	348	91	26.1%
Vehicle, 1 spray BID	590	148	25.1%
Vehicle, 2 sprays BID	348	84	24.1%
Total	2102	522	26.3%

Source: M2, V1, Summary of Clinical Safety, T2.7.4.1.3.1.-1, p4

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in the pediatric studies/clinical trials.

7.3.2 Nonfatal Serious Adverse Events

One non-fatal serious adverse event was reported. Patient 1834, a 9 year old female treated with olopatadine 0.4% (formulation containing povidone) in **C-04-20**, developed a urinary tract infection on Day 6 of treatment and was hospitalized. The adverse event resolved with treatment, was assessed as unrelated to study drug, and the patient continued to participate in the trial. [M5, V61, p198]

7.3.3 Dropouts and/or Discontinuations

In the four pediatric trials, a total of 26 patients experienced 34 adverse events and were discontinued due to an adverse event. The incidence of patients discontinued due to adverse events (DAEs) by treatment group, is shown in Table 25, the adverse events leading to discontinuation by treatment group are shown in Table 26, and a count of adverse events by event code is shown in Table 27.

No particular pattern of DAEs emerges, although AEs of note include: 5 patients discontinued due to epistaxis (3 on povidone-free olopatadine, 1 on povidone-free vehicle, and 1 on povidone-containing vehicle), 1 for urticaria (olopatadine 0.6%), 3 for sinusitis, 1 for dysgeusia, 1 for throat irritation, 2 for rhinitis, and 2 for seasonal rhinitis.

Table 25. Incidence of patients discontinued due to adverse events, by treatment

	Total N	Patients discontinued due to an adverse event	
		N	%
Olopatadine 0.4%, 1 spray BID	228	1	0.4%
Olopatadine 0.6%	936	12	1.3%
1 spray BID	588	7	1.2%

	Total N	Patients discontinued due to an adverse event	
		N	%
2 sprays BID	348	5	1.4%
Vehicle	938	13	1.4%
1 spray BID	590	9	1.5%
2 sprays BID	348	4	1.1%

Source: M2, V1, Adverse Events, T2.7.4.2.1.5.-1, p16

Table 26. Listing of adverse events leading to discontinuation, by treatment

Invest/Patient	Study	Age	Sex	Onset Day	Adverse Event
Olopatadine 0.4%, 1 spray BID					
4031/470	C-03-51	6	M	15	Cough; Dyspnea; Pyrexia; Rhinitis; Sinusitis
Olopatadine 0.6%, 1 spray BID					
4096/4685	C-04-20	8	M	3	Conjunctivitis
1161/9025	C-07-01	7	M	1	Dysgeusia
1113/9004	C-07-01	10	M	9	Epistaxis; Streptococcal pharyngitis
1045/9008	C-07-01	11	M	7 9	Rhinitis seasonal Headache
1035/9005	C-07-01	9	F	11	Sinusitis
1138/9010	C-07-01	10	F	2	Upper respiratory tract infection
1027/9001	C-07-01	11	M	8	Upper respiratory tract infection
Olopatadine 0.6%, 2 sprays BID					
1029/9007	C-07-01	11	F	1	Retching; Throat irritation
1122/9015	C-07-01	10	M	8 10	Conjunctivitis bacterial Epistaxis
1076/9023	C-07-01	9	M	3	Epistaxis
1054/9027	C-07-01	8	M	11	Upper respiratory tract infection
1089/9019	C-07-01	10	F	6	Urticaria
Vehicle, 1 spray BID					
2833/1395	C-04-20	7	M	7	Epistaxis
4078/1154	C-04-20	7	F	12	Streptococcal pharyngitis
3200/1237	C-04-20	11	M	2	Upper respiratory tract infection
1025/9015	C-07-01	8	M	10	Asthma
1064/9002	C-07-01	11	M	4	Dermatitis contact
1052/9043	C-07-01	10	F	3	Rhinitis seasonal
1108/9028	C-07-01	9	M	11	Sinusitis
3204/1703	C-07-02	4	M	7	Pneumonia
3208/1001	C-07-02	2	M	3	Rhinitis
Vehicle, 2 sprays BID					
1071/9006	C-07-01	9	M	2	Asthma
1114/9018	C-07-01	6	F	2	Epistaxis
1031/9026	C-07-01	9	F	3	Streptococcal pharyngitis
1108/9031	C-07-01	7	F	9	Sinusitis; Upper respiratory tract infection
Note: Some patients experienced more than one adverse event. The table shows discontinuations after randomization in the 4 clinical trials, and does not include discontinuations from run-in, during which patients were exposed to vehicle.					

Source: M2, V1, Adverse Events, T2.7.4.2.1.5.-2, p16-7;
Clinical trial reports: C-07-02: T14.3.2.-1, p195; C-07-01: M5, V25, L14.3.2.-1, p255-74; C-04-20: M5, V61, T14.3.2.-1, p 847; C-03-51: M5, V50, T14.3.1.8.-1 p342-8.

Table 27. Adverse events leading to discontinuation, cumulative by AE coding

Adverse Event	Number of Events
Asthma	2
Conjunctivitis	1
Conjunctivitis bacterial	1
Cough	1
Dermatitis contact	1
Dysgeusia	1
Dyspnea	1
Epistaxis	5
Headache	1
Pharyngitis streptococcal	3
Pneumonia	1
Pyrexia	1
Retching	1
Rhinitis	2
Rhinitis seasonal	2
Sinusitis	3
Throat irritation	1
Upper respiratory tract infection	5
Urticaria	1
Total number of events	34

Source: M2, V1, Adverse Events, T2.7.4.2.1.5.-2, p16-7

7.3.4 Significant Adverse Events

Significant adverse events were defined as those for which an intervention occurred, including patients who were withdrawn from treatment, had a dose reduction, or needed significant other treatment. Since all patients with significant adverse events were discontinued, please refer to the discontinuation section above for details.

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Nasal irritation and ulceration

Patanase Nasal Spray is irritating to the nasal mucosa. In the original adult/adolescent clinical trials using the povidone-containing formulation, a number of patients reported epistaxis, and nasal ulcerations were seen on nasal examinations in some patients. Additionally, nasal septal perforations were noted in the long-term safety trial, **C-01-92**, in patients 12 years of age and older. In the initial 2-week efficacy and safety trials in children 6-11 years of age using the povidone-containing formulation, epistaxis and nasal ulcerations were more common than in noted adults/adolescents, leading the Division to request that further pediatric studies be halted until the product was reformulated. Adverse events associated with nasal irritation, and nasal perforation in particular, were originally considered as likely related to the presence of povidone in the

formulation, a view supported by the preclinical animal data. However, the low pH of (b) (4) was also considered an issue with regard to nasal irritation.

With reformulation, povidone was eliminated, but the pH of the formulation was reduced (b) (4) to 3.7, thereby raising the second concern for the formulation with regard to the low pH causing local mucosal irritation. However, the initial safety concern of nasal septal perforation noted with the povidone-containing formulation was resolved with reformulation and submission of a 12-month safety trial, **C-05-69**, that showed no perforations in patients 12 years of age and older. Nevertheless, the frequency of nasal irritation and ulcerations were not reduced, and in fact are somewhat higher with the new formulation. Comparison of results from the two 1-year safety trials, **C-01-92** and **C-05-69**, are shown in Table 28 and Table 29. Table 28 compares the results after 6 months of treatment, and Table 29 compares the results over 1 year of treatment. For consistency, both tables use the COSTART coding terminology that was used for the first trial, whereas Table 30 shows the 1 year results using MedDRA terminology.

Although **C-05-69** was performed with the intent to show a reduction in nasal irritation with the new formulation local nasal adverse events other than septal perforation are actually more common. As noted, the difference is considered as likely to be related to the low pH of the reformulated product, an issue that may only be resolved with submission of a required 1-year post-marketing safety trial in adults and adolescents that will compare the intranasal safety with regular scheduled long-term use of Patanase, vehicle placebo, and normal pH vehicle placebo. Because of local irritation, the label carries Warning and Precaution statements stating that Patanase Nasal Spray should not be used in patients with nasal diseases other than [seasonal] allergic rhinitis, and patients should be monitored for local nasal adverse events when they are on Patanase Nasal Spray.

Results of **C-05-69** were recently added to the labeling. This trial included 890 patients, 445 patients each on Patanase or vehicle control. In the Patanase and vehicle nasal spray groups, 72% and 74% of patients, respectively, completed the trial, and 7% and 5%, respectively, discontinued due to an adverse event. Epistaxis occurred in 25% and 28% of patients, and resulted in discontinuation of 0.9% and 0.2% of patients treated with Patanase and vehicle nasal spray, respectively. Nasal ulcerations occurred in 10% and 9% of patients, and resulted in discontinuation of 0.4% and 0.2% of patients treated with Patanase and vehicle nasal spray, respectively. There were no patients with nasal septal perforation in either treatment group.

Table 28. Comparison of nasal AEs (%) in first 6 months of 1-year safety trials

Percent of Patients with AE (COSTART)	C-01-92 with povidone		C-05-69 without povidone	
	Olo 0.6% n=459	Vehicle n=465	Olo 0.6% n=445	Vehicle N=445
Epistaxis	13.1	6.7	19.3	23.4
Rhinitis	7.0	9.2	23.4	23.1
Sinusitis	8.1	8.4	10.6	10.6
Nasal ulcer (exam monthly)	2.8	3.4	8.8	5.8
Pharyngitis	5.0	6.7	7.9	6.7
Nasal discomfort	1.3	1.5	2.7	2.9

Percent of Patients with AE (COSTART)	C-01-92 with povidone		C-05-69 without povidone	
	Olo 0.6% n=459	Vehicle n=465	Olo 0.6% n=445	Vehicle N=445
Dry nose	1.7	0.2	1.6	0.4
Nasal septal perforation	0.2	0.4	0	0

From Dr. Jim Kaiser's medical officer review of Patanase NDA.

Table 29. Comparison of nasal AEs (%) over 1 year in 1-year trials

Percent of Patients with AE (COSTART)	C-01-92 with povidone		C-05-69 without povidone	
	Olo 0.6% n=459	Vehicle n=465	Olo 0.6% n=445	Vehicle n=445
Rhinitis	12.2	15.3	31.0	32.1
Epistaxis	19.2	12.0	24.9	28.3
Sinusitis	12.4	13.3	15.7	13.5
Pharyngitis	7.4	8.4	9.2	9.2
Nasal ulcer (exam monthly)	4.1	4.5	10.3	8.5
Nasal discomfort	1.5	1.9	2.7	3.6
Dry nose	2.0	1.3	2.0	1.1
Nasal septal perforation	0.2	0.4	0	0

From Dr. Charles Lee's and Dr. Jim Kaiser's medical officer reviews of Patanase NDA and supplement S-001.

Table 30. C-05-69, Patients with nasal events at ≥2% incidence in olopatadine group

Nasal AEs MedDRA term	Olopatadine 0.6%				Vehicle			
	Patients n (%) n=445	Events			Patients n (%) n=445	Events		
		Mild	Mod	Severe		Mild	Mod	Severe
Epistaxis	111 (24.9)	180	9	0	126 (28.3)	203	9	0
Rhinitis	87 (19.6)	119	7	0	73 (16.4)	106	2	0
Nasopharyngitis	72 (16.2)	55	41	2	67 (15.1)	55	32	3
Sinusitis	66 (14.8)	35	56	5	58 (13.0)	36	32	4
Nasal Ulcer	46 (10.3)	56	6	0	38 (8.5)	46	6	0
Rhinitis allergic	46 (10.3)	52	40	5	65 (14.6)	47	97	4
Nasal discomfort	15 (3.4)	12	3	1	18 (4.0)	20	1	0
Sinus headache	15 (3.4)	10	6	5	23 (5.2)	18	23	1
Nasal congestion	14 (3.1)	8	6	2	17 (3.8)	10	5	2
Nasal dryness	9 (2.0)	7	3	0	5 (1.1)	3	2	0

From Dr. Jim Kaiser's medical officer review of Patanase supplement S-001.

Results in the two 2-week pediatric trials with the povidone-free formulation suggest that the findings in children 6-11 years of age have not changed from those seen with the povidone-containing formulation in this age group, with epistaxis continuing to occur more frequently in this age group than in adult/adolescent counterparts.

It is of note that the rates for epistaxis and nasal ulcerations in the 1-year safety trial discussed above are cumulative with treatment, whereas the expectation is that for treatment of SAR the treatment period is of a shorter duration of exposure than 1 year but longer than the duration of exposure used in typical 2-week efficacy and safety trials. For this reason, the data from the full 1-year of treatment in the safety trial

represents the worst case scenario, but the data from 2-weeks of treatment in the pediatric trials may underestimate the risk as well. Data from the adult/adolescent 1-year safety trial suggests that the rates go up with an increase in exposure. Furthermore, the adult data suggest that the duration of time to healing of nasal ulcerations in some patients is quite significant, leading to the possibility that if younger children are exposed to Patanase children for similar a duration of time they too will experience significant frequency and duration of nasal ulcerations. Data and comparisons specific to epistaxis and nasal ulcerations are presented in the sections below.

Epistaxis

Epistaxis was a common adverse event, both in adult/adolescent and pediatric trials. Table 31 summarizes the incidence of epistaxis in all 2-week trials, including both 0.6% formulations and doses. For adults and adolescents, all the 2-week trials used the povidone-containing formulation at a dose of 2 sprays per nostril twice daily, whereas the trials in children 2-11 years of age used both formulations and evaluated two doses, 1 or 2 sprays per nostril twice daily. The table also shows the incidence of epistaxis in the subgroups of patients enrolled in the two pediatric clinical trials that used the povidone-containing and povidone-free formulations, including the results by dose for the povidone-free formulation. The overall incidence of epistaxis was higher in children than in adults and adolescents, with no change in the incidence of epistaxis in the subgroup of children exposed to the povidone-free formulation. The results suggest that children are at higher risk for nasal irritation and epistaxis than their adult and adolescent counterparts even when the lower dose and povidone-free formulation is used.

As discussed in the section above, Table 31 represents the epistaxis rates that may be expected with 2 weeks of use. Rates will be higher with longer durations of use.

Table 31. Overall incidence of epistaxis in all adult/adolescent and pediatric 2-week trials

Epistaxis in 2-week trials	Children			Adults/Adolescents		
	Total N	N	%	Total N	N	%
All 0.6% formulations, combined data						
Olopatadine 0.6%*	936	57	6.1%	587	19	3.2%
Vehicle*	938	42	4.5%	593	10	1.7%
Povidone-containing formulation						
Olopatadine 0.6%	276	18	6.5%	587	19	3.2%
Vehicle	278	14	5.0%	593	10	1.7%
Povidone-free formulation						
Olopatadine 0.6%	660	39	5.9%	--	--	--
1 spray BID	364	21	5.8%	--	--	--
2 sprays BID	296	18	6.1%	--	--	--
Vehicle	660	28	4.2%	--	--	--
1 spray BID	363	12	3.3%	--	--	--
2 sprays BID	297	16	5.4%	--	--	--

* Note that this table contains data from all 2-week clinical trials. Adult data is from PI and submission. For adults and adolescents, all 2-week trials used the povidone-containing formulation at a dose of 2 sprays twice daily, whereas the trials in children 2-11 years of age

Epistaxis in 2-week trials	Children			Adults/Adolescents		
	Total N	N	%	Total N	N	%
used both formulations and two doses, 1 or 2 sprays twice daily. The table also shows the incidence of epistaxis in the subgroups of patients enrolled in pediatric clinical trials using the povidone-containing and povidone-free formulations, with the povidone-free data broken down by dose.						

Sources: M2, V1, Adverse Events, T1 and T2, p21-2. Data for the pediatric povidone-containing and povidone-free clinical trials are extracted from tables in the individual pediatric clinical trial reports.

Nasal Ulcerations

Targeted nasal examinations were performed to evaluate for nasal ulcerations, and reported as an AE if found. In the pediatric clinical trials, the next targeted nasal examination after the day of randomization was on the last study visit after 2 weeks of treatment (*Note*: trials in 6-11yo used vehicle run-in, so the examination on the day of randomization could pick up nasal irritation and ulcers from vehicle during run-in), whereas in the 1-year safety trials in adults/adolescents the first targeted nasal examination was after 1 month of treatment. For this reason, the applicant chose to use data based on a cutoff of 35 days of treatment in the adult/adolescent trials to compare with data from the last study visit in the pediatric trials. Results are shown in Table 32. Just as for epistaxis, the table contains combined and separate data for the povidone-containing and povidone-free 0.6% formulations. Table 33 and Table 34 show the listings of patients with nasal ulcerations in the adult/adolescent [out to 35 days of treatment] and pediatric [out to 2 weeks of treatment] trials, with the listings for the povidone-free formulations highlighted in yellow. As a result of differences in the adult vs pediatric data used, exposure was about double in those patients 12 years of age and older than in patients 2-11 years of age, so caution should be used when making a direct comparison of the results.

Additionally it is difficult to interpret the data with regard to the duration of nasal ulceration. The applicant did not provide information with regard to how these data were derived. It is likely that the data came from follow-up nasal examinations, so the true duration may be obscured if the ulceration resolved in the interim period. Nevertheless, the duration of nasal ulceration appears to have been protracted for a number of patients, although more so in the adult/adolescent grouping than in the 2-11 year old group. In the adult/adolescent grouping, 23 patients developed a nasal ulceration within the first 35 days of treatment [Table 33]. Although all but 3 were classified as mild in intensity, the duration of ulcerations before full healing ranged from 1 hour [a questionable duration] to 94 days (1 patient listed as data Not Available i.e., NA), with the majority out to a month or longer, 6/23 out 85 days or longer, and 3 listed as continuing despite having stopped treatment. In the 4 pediatric 2-week trials [Table 34], 18 patients developed nasal ulcerations, with all but 1 event classified as mild in intensity. The range of duration for patients who developed an ulceration ranged from 12 hours [again, questionable] to 20 days, with 2 patients listed as NA. For all but 2 patients, the event is listed as resolved, but for 2 patients (both on vehicle, 1 with povidone and 1 without) the event is listed as continuing without treatment. One potential implication from these data is that, with increasing durations of exposure, pediatric patients might expect to experience [not only more cumulative events, but] a longer duration prior to full healing of an ulceration.

Because the pediatric clinical trials were limited to 2 weeks duration, the results from children 2-11 years of age underestimate the incidence of nasal ulcerations that may be expected with longer-term chronic or intermittent use. For example, the overall incidence of nasal ulcerations with long-term chronic use in the 1-year adult/adolescent safety trials was 5.8%, whereas when the data are restricted to use for up to 35 days the incidence was 1.0%. Given the higher incidence of epistaxis in children than in adults in the 2-week trials and the earlier onset of nasal ulcerations in children than in adults in the comparisons below, the expectation is that children may also experience more significant events of nasal ulceration than adults with longer chronic use.

Most of the pediatric data comes from the trials in children 6-11 years of age. Because of the paucity of data in patients 2-5 years of age, it is difficult to estimate the incidence of local mucosal irritation in this age group. This is a significant deficiency in the application that should be supported by further safety trials in this age range.

Table 32. Incidence of nasal ulcerations with povidone-containing and povidone-free olopatadine 0.6% formulation in adult/adolescent (within first 35 days) and pediatric trials

Nasal ulcerations	Children 2-11y 2-week trials			Adults/Adolescents ≤35 days in 1-year trials		
	Total N	N	%	Total N	N	%
All 0.6% formulations, combined data						
Olopatadine 0.6%	936	8	0.9%	904	9	1.0%
1 spray BID	588	5	0.9%	--	--	--
2 sprays BID	348	3	0.9%	904	9	1.0%
Vehicle	938	9	1.0%	910	14	1.5%
1 spray BID	590	6	1.0%	--	--	--
2 sprays BID	348	3	0.9%	910	14	1.5%
Povidone-containing formulation						
Olopatadine 0.6%	276	5	1.8%	459	2	0.4%
1 spray BID	224	3	1.3%	--	--	-
2 sprays BID	52	2	3.8%	459	2	0.4%
Vehicle	278	4	1.4%	465	6	1.3%
1 spray BID	227	4	1.8%	--	--	--
2 sprays BID	51	0	0	465	6	1.3%
Povidone-free formulation						
Olopatadine 0.6%	660	3	0.5%	445	7	1.6%
1 spray BID	364	2	0.5%	--	--	--
2 sprays BID	296	1	0.3%	445	7	1.6%
Vehicle	660	5	0.8%	445	8	1.8%
1 spray BID	363	2	0.6%	--	--	--
2 sprays BID	297	3	1.0%	445	8	1.6%

Table shows patients on both povidone-containing and povidone-free 0.6% formulations. Adult data reflects events with an onset of ≤35 days from start of treatment in long-term trials, C-01-92 and C-05-69. Pediatric data is from all 4 pediatric trials. Data for povidone-free formulation comes from 1-year adult/adolescent trial, C-05-69, and two 2- week pediatric trials, C-07-01 and C-07-02. Data for povidone-containing formulation comes from 1-year adult/adolescent trial, C-01-92, and two 2- week pediatric trials, C-03-51 and C-04-20. One pediatric patient with a nasal ulceration on olopatadine 0.4% in C-03-51 is not shown in the tables.

Source: M2, V1, Adverse Events. Combined data from T2.7.4.2.1.2.-2 and T2.7.4.2.1.2.-3, p 11; Individual formulation data extracted from T2.7.4.2.1.2.-4 and T2.7.4.2.1.2.-5, p 12-3

Table 33. Listing of patients with on-treatment nasal ulcerations within first 35 days in adult/adolescent long-term safety trials

Study	Inv/Patient	Age	Sex	Onset day	Intensity	Duration	Outcome	DC
Olopatadine 0.6%, 2 sprays BID								
C-01-92	3218/9616	41	F	8	Mild	85 days	Resolved w/o Tx	No
C-01-92	3220/9804	43	M	33*	Mild	31 days	Resolved w/o Tx	No
C-05-69	3207/5427	46	F	28*	Mild	92 days	Continuing w/o Tx	No
C-05-69	4842/5998	32	M	29	Mild	N/A	Continuing w/o Tx	No
C-05-69	4090/5817	14	F	29*	Mild	59 days	Resolved w/o Tx	No
C-05-69	4949/7373	23	M	29*	Mild	28 days	Resolved w/o Tx	No
C-05-69	2550/5189	65	F	30	Mild	32 days	Resolved w/o Tx	No
C-05-69	4855/6354	46	M	9	Mild	33 days	Resolved w/o Tx	No
C-05-69	4856/6381	26	M	35*	Mild	55 days	Continuing w/o Tx	No
Vehicle, 2 sprays BID								
C-01-92	818/8716	28	M	8	Mild	85 days	Resolved w Tx	No
C-01-92	2867/8616	34	F	26	Moderate	17 days	Resolved w Tx	Yes
C-01-92	3795/8503	37	F	28	Moderate	2 days	Resolved w/o Tx	Yes
C-01-92	1689/8018	29	F	30	Mild	4 days	Resolved w/o Tx	No
C-01-92	2867/8607	36	F	33*	Mild	1 day	Resolved w/o Tx	No
C-01-92	3653/9919	47	F	35	Moderate	12 days	Resolved w/o Tx	No
C-05-69	4854/6329	54	M	28*	Mild	90 days	Resolved w/o Tx	No
C-05-69	4090/5815	41	F	30	Mild	36 days	Resolved w/o Tx	No
C-05-69	4950/7013	26	M	34	Mild	40 days	Resolved w/o Tx	No
C-05-69	4856/6391	47	M	28	Mild	94 days	Resolved w/o Tx	No
C-05-69	4855/6353	29	F	29	Mild	35 days	Resolved w/o Tx	No
C-05-69	4962/7317	53	F	29	Mild	35 days	Resolved w/o Tx	No
C-05-69	4946/6932	44	F	32	Mild	N/A	Resolved w/o Tx	No
C-05-69	4948/6867	50	F	33	Mild	29 days	Resolved w/o Tx	No

* Starred events are noted to have occurred intermittently. It is unclear what this means, although it potentially implies that the patient had more than one event.

Patients with nasal ulcerations during the vehicle run-in period are not included. Patients in trials with povidone-free formulation are highlighted in yellow.

Source: M2, V1, Adverse Events, T2.7.4.2.1.2.-4, p12.

Table 34. Listing of patients with on-treatment nasal ulcerations in pediatric 2-week trials

Study	Inv/Patient	Age	Sex	Onset day	Intensity	Duration	Outcome
Olopatadine 0.4%, 1 spray BID							
C-03-51	4026/101	10	M	9	Mild	7 days	Resolved w/o Tx
Olopatadine 0.6%, 1 spray BID							
C-03-51	4026/141	11	M	15	Mild	12 hours	Resolved w/o Tx
C-03-51	4028/515	7	F	15	Mild	13 hours	Resolved w/o Tx
C-04-20	3210/2528	10	F	17	Mild	20 days	Resolved w/o Tx
C-07-01	1126/9019	11	M	17	Mild	8 days	Resolved w/o Tx
C-07-01	1089/9003	8	M	17	Mild	8 days	Resolved w/o Tx
Olopatadine 0.6%, 2 sprays BID							
C-03-51	4027/229	9	F	16	Mild	18 days	Resolved w/o Tx
C-03-51	4027/206	11	F	7	Mild	7 days	Resolved w/o Tx
C-07-01	1074/9009	8	F	17	Mild	8 days	Resolved w/o Tx

Study	Inv/Patient	Age	Sex	Onset day	Intensity	Duration	Outcome
Vehicle, 1 spray BID							
C-03-51	4026/114	7	F	15	Mild	NA	Continuing w/o Tx
C-03-51	4027/234	8	F	15	Mild	12 hours	Resolved w/o Tx
C-03-51	4027/233	10	F	16	Mild	12 hours	Resolved w/o Tx
C-03-51	4026/104	11	F	8	Mild	7 days	Resolved w/o Tx
C-07-01	1118/9021	11	M	16	Mild	15 days	Resolved w/o Tx
C-07-02	3208/1001	2	M	3	Mild	7 days	Resolved w/o Tx
Vehicle, 2 sprays BID							
C-07-01	1101/9004	9	F	17	Mild	NA	Continuing w/o Tx
C-07-01	1138/9004	8	M	17	Mild	5 days	Resolved w/o Tx
C-07-01	1138/9003	10	M	16	Moderate	5 days	Resolved w/o Tx
Note: none of the patients in the listing were discontinued due to a nasal ulceration. Patients with nasal ulcerations during the vehicle run-in period are not included. Patients in trials with povidone-free formulation are highlighted in yellow.							

Source: M2, V1, Adverse Events, T2.7.4.2.1.2.-5, p 13

7.3.5.2 Depression

Depression was noted in some patients enrolled in the 12 month adult/adolescent safety trial, and the labeling was recently updated with this information. Because of these findings, the Division requested that Alcon perform further safety analyses of the pediatric safety database looking for any adverse events consistent with or associated with depression. Of note, the pediatric clinical trials were designed prior to this new safety information, and were not designed to elicit information regarding symptoms of depression.

In response, the applicant performed analyses of adverse events reported in the four pediatric trials using the standardized MedDRA query (SMQ) for depression and suicide/self injury, with addition of the term insomnia. Utilizing this search methodology, 3 patients who reported 3 adverse events were found. These included one event each of psychomotor hyperactivity and mood swings in patients on olopatadine, and one event of insomnia in a patient on vehicle. [Submission 8/7/09, p25-6]

In addition to epistaxis and/or nasal irritation, the Written Request made note of certain types of adverse events that may be of concern. These included paradoxical excitability, somnolence, fatigue, and hyperkinesia. No increased incidence was noted for these events (see Table 35 comparing common AEs in adults/adolescents and children 2-11 years of age).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

For common AEs, data were pooled from all 4 pediatric trials with both formulations. Table 35 compares common AEs in children 2-11 years of age with adults/adolescents.

The table includes events labeled in the PI for adults, and other events with an incidence of 0.5% or more in either treatment group in the pediatric population. Please see the results of trials **C-07-01** and **C-07-02** for common AEs from those trials.

Four pediatric AEs had an incidence of ≥1.0% and were more frequent with olopatadine than vehicle treatment. These included dysgeusia (bitter taste), epistaxis, upper respiratory tract infection, and diarrhea.

Several AEs were more common in children than in adults and deserve mention. These events include epistaxis, cough, and pyrexia (fever). Epistaxis, discussed elsewhere, was twice as frequent in children as in adults. Cough is likely related to excess of the spray dripping down the posterior nasopharynx. Fever is more common in this age group than in adults, and is not unexpected as an AE.

Likewise, several AEs were less common in children than in adults and deserve mention. Reports of bitter taste were much lower in children, and therefore might not be expected to limit use as it might in adults. Somnolence was not noted as an AE in the pediatric trials, and reports of fatigue were less common than in adults.

Table 35. Comparison of common adverse events in adult/adolescent and pediatric patients

Adverse Event	Adults/adolescents		Children 2-11 years	
	Olo 0.6% N=587	Vehicle N=593	Olo 0.6% N=936	Vehicle N=938
Adult-labeled events				
Dysgeusia (Bitter taste)	75 (12.8%)	5 (0.8%)	14 (1.5%)	2 (0.2%)
Headache	26 (4.4%)	24 (4.0%)	28 (3.0%)	44 (4.7%)
Epistaxis	19 (3.2%)	10 (1.7%)	57 (6.1%)	42 (4.5%)
Pharyngolaryngeal Pain	13 (2.2%)	8 (1.3%)	10 (1.1%)	16 (1.7%)
Post-nasal drip	9 (1.5%)	5 (0.8%)	1 (0.1%)	1 (0.1%)
Cough	8 (1.4%)	3 (0.5%)	12 (1.3%)	16 (1.7%)
Urinary tract infection	7 (1.2%)	3 (0.5%)	0	0
CPK elevation	5 (0.9%)	2 (0.3%)	0	0
Dry mouth	5 (0.9%)	1 (0.2%)	0	1 (0.1%)
Fatigue	5 (0.9%)	4 (0.7%)	1 (0.1%)	1 (0.1%)
Influenza	5 (0.9%)	1 (0.2%)	2 (0.2%)	2 (0.2%)
Nasopharyngitis	5 (0.9%)	4 (0.7%)	6 (0.6%)	3 (0.3%)
Somnolence	5 (0.9%)	2 (0.3%)	0	0
Throat irritation	5 (0.9%)	0 (0.0%)	5 (0.5%)	1 (0.1%)
Other events occurring ≥0.5% in either pediatric treatment group				
Upper respiratory tract infection	3 (0.5%)	3 (0.5%)	10 (1.1%)	4 (0.4%)
Rhinitis	0	0	10 (1.1%)	10 (1.1%)
Injury	6 (1.0%)	6 (1.0%)	13 (1.4%)	14 (1.5%)
Pyrexia	4 (0.7%)	2 (0.3%)	13 (1.4%)	15 (1.6%)
Diarrhea	2 (0.3%)	3 (0.5%)	9 (1.0%)	0
Vomiting	0	1 (0.2%)	8 (0.9%)	11 (1.2%)
Nasal discomfort	10 (1.7%)	10 (1.7%)	8 (0.9%)	5 (0.5%)
Sinusitis	2 (0.3%)	5 (0.8%)	8 (0.9%)	5 (0.5%)
Abdominal pain upper	1 (0.2%)	3 (0.5%)	7 (0.7%)	6 (0.6%)
Lymphadenopathy	1 (0.2%)	1 (0.2%)	3 (0.3%)	6 (0.6%)
Nasal ulcer	1 (0.2%)	0	8 (0.9%)	9 (1.0%)

Adverse Event	Adults/adolescents		Children 2-11 years	
	Olo 0.6% N=587	Vehicle N=593	Olo 0.6% N=936	Vehicle N=938
Pharyngitis streptococcal	1 (0.2%)	0	5 (0.5%)	3 (0.3%)
Rash	1 (0.2%)	0	5 (0.5%)	2 (0.2%)
Nasal congestion	1 (0.2%)	2 (0.3%)	1 (0.1%)	5 (0.5%)
Pediatric events with an incidence of 1.0% and more frequent with olopatadine treatment are shown in red font.				

Source: M2, V1, Safety in Special Groups, T2.7.4.5.1.3.2.-2, p21-6

7.4.2 Laboratory Findings

Only one of the four trials included clinical laboratory evaluations, **C-03-51**. No safety issues were identified during the review.

7.4.3 Vital Signs

No clinically relevant differences were noted during the review of physical examination or vital sign parameters in the trials.

7.4.4 Electrocardiograms (ECGs)

A cardiac effect QT trial had been performed in adults for the NDA, and no signal was noted in that trial. Additionally, cardiac safety was evaluated in one of the 12-month long-term safety trials. Results for these both of these trials are described in the CLINICAL PHARMACOLOGY: Pharmacodynamics (12.2) section of the labeling. For the pediatric supplement, the effect of olopatadine on QT was evaluated in **C-03-51**, and the applicant is seeking to add information from this 2-week trial to the same section of the labeling. Although information with regard to the QT evaluations from this trial may be appropriate in the study description and safety database section for this age group within the ADVERSE EVENTS section, it will not be appropriate to add information from this short-term trial to this section of the labeling. The evaluations performed and the results are described below.

A 12-lead ECG was obtained at screening, and on Days 1 and 15 of treatment 6 sequential ECGs were obtained about 1 minute apart starting 1 hour and 20 minutes post dosing. No significant effect on QTc interval was noted. No patients had a QTcF value ≥500 msec or a change from baseline in maximum QTcF of >60 msec. Mean changes from baseline in QTcF were 3.7, 2.7, 2.0, 1.0 and -0.3 msec for olopatadine 0.6% 2 sprays, olopatadine 0.6% 1 spray, olopatadine 0.4% 1 spray, vehicle 2 sprays, and vehicle 1 spray, respectively. There was a difference in mean change in QTcF by gender, with females showing a larger numerical effect. For males, the mean changes from baseline in QTcF were 1.6, 0.2, 3.2, 1.0 and -2.2 msec for olopatadine 0.6% 2 sprays, olopatadine 0.6% 1 spray, olopatadine 0.4% 1 spray, vehicle 2 sprays, and vehicle 1 spray, respectively. For females, the mean changes from baseline in QTcF

were 5.8, 5.1, 0.5, 1.0 and 1.1 msec for olopatadine 0.6% 2 sprays, olopatadine 0.6% 1 spray, olopatadine 0.4% 1 spray, vehicle 2 sprays, and vehicle 1 spray, respectively.

7.4.5 Special Safety Trials/Clinical Trials

No special safety studies were performed.

7.5 Other Safety Explorations

The applicant evaluated the incidence of adverse events by gender and by race. Results were consistent with those for the overall safety population, with no conclusions that would negatively impact any of these subpopulations. Results by age were not performed, except in comparison with the results from adults (discussed above).

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Evaluated for the NDA. No new information with this supplement.

7.6.2 Human Reproduction and Pregnancy Data

Evaluated for the NDA. No new information with this supplement.

7.6.3 Pediatrics and Assessment of Effects on Growth

This supplement contains the pediatric assessment for Patanase. That said, the assessment did not contain any long-term safety trials, and did not contain an assessment of the effect of Patanase Nasal Spray on growth. Antihistamines typically are not considered to have any direct effect on growth, so a growth study was not necessary as part of the evaluation of safety in children.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Evaluated for the NDA. No new information with this supplement.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

Patanase Nasal Spray was approved for use in adults and adolescents 12 years of age and older on April 15, 2008. In the time period between April 2008 and March 31, 2009, Alcon reports having sold (b) (4) units of Patanase, and having received 54 spontaneous adverse event reports, of which 1 was considered serious. This event occurred in an 88 year old male who used Patanase for 12 days before experiencing recurrent nosebleeds over several days requiring several emergency room visits. Other concomitant medications included Plavix and aspirin.

The company reports that review of the non-serious AE reports revealed no pattern to the other AE reports, and proposes the changes to the ADVERSE EVENTS: Post-Marketing Experience section. Labeling for this section is proposed to be updated to reflect adverse events reported for Patanase Nasal Spray since marketing approval, and not for oral formulations of olopatadine in other countries. As a result, the listing of additional adverse reactions reported is being removed and replaced with the sentence: "The post-marketing adverse events reported post-approval are consistent with the adverse events reported during clinical trials." Review of the events shows no pattern, and is consistent with the above statement, except that one postmarketing case of anosmia was reported. [M2, V1, S2.7.4.6, p3]

9 Appendices

9.1 Literature Review/References

A literature review was not conducted as part of the review of this submission.

9.2 Labeling Recommendations

Labeling recommendations are provided throughout this review, and are not summarized separately here. Proposed labeling will be reviewed and compared with the last approved label (supplement S-001, approved June 17, 2009, submitted in SPL June 25, 2009). A brief outline of the new labeling for which the applicant is seeking with this supplement follows:

9.3 Advisory Committee Meeting

An Advisory Committee meeting will not be held for this pediatric supplement.

9.4 Pediatric Written Request

The pediatric studies submitted with this supplement were performed in response to a Written Request (WR) issued by the Agency on July 19, 2007. Text of the Written Request follows.

"Reference is made to your Proposed Pediatric Study Request submitted to IND 60,116 on March 22, 2007, for olopatadine.

To obtain needed pediatric information on olopatadine, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

Type of Study to be Performed

Study 1: Safety and efficacy study in patients 6 years to <12 years of age

Study 2: Safety and PK study in patients 2 years to <6 years of age

Objective/Rationale

Study 1: To assess the efficacy and safety of olopatadine nasal spray in patients 6 years to <12 years of age when administered at an age- and/or weight-appropriate dose.

Study 2: To assess the safety of olopatadine nasal spray in patients 2 years to <6 years of age. To assess the pharmacokinetics (i.e., Cmax and AUC) of olopatadine and its active metabolites in patients 2 years to <6 years of age and to compare to those seen in adolescents and adults given the dose of olopatadine proposed for use in adolescents and adults.

Indication to be Studied: Allergic rhinitis

Age Groups in Which Study Will Be Performed

Study 1: Patients from 6 years to <12 years of age. Enroll patients so that there will be approximately equal representation of the following two age groups at the time of randomization: 6 years to <9 years, 9 years to <12 years.

Study 2: Patients from 2 years to <6 years of age. Enroll patients so that there will be approximately equal representation of the following two age groups at the time of randomization: 2 years to <4 years and 4 years to <6 years.

Study Design

Study 1: Perform a randomized, placebo-controlled, parallel-group efficacy and safety study with a treatment duration of two weeks. Provide an assessment of compliance with study treatment.

Study 2: Perform a randomized, placebo-controlled, parallel-group safety study with a treatment duration of two weeks. Provide an assessment of compliance with study treatment. Assess the single- and multiple-dose pharmacokinetics of olopatadine and its active metabolites. For the PK assessments, obtain a minimal amount and limited number of blood samples at adequate sampling times to evaluate pharmacokinetics

appropriately. Sampling times may be selected based on an optimum sampling strategy for the best estimation of the pharmacokinetics of olopatadine and its active metabolites.

Number of Patients to be Studied

Study 1: Enroll a sufficient number of patients to ensure a minimum of 250 patients per treatment arm (i.e., a total of at least 500 patients for the study) will complete at least 2 weeks of the study treatment, with at least 150 patients in each of the two following age groups: 6 years to <9 years and 9 years to <12 years.

Study 2: Enroll a sufficient number of patients to ensure that a minimum of 50 patients complete at least two weeks of study treatment, with at least 20 patients in each of the two following age groups: 2 years to <4 years and 4 years to <6 years.

Entry Criteria

Study 1: Patients 6 years to <12 years of age who have symptoms of allergic rhinitis.

Study 2: Patients 2 years to <6 years of age who have symptoms of allergic rhinitis or who have had such symptoms in the past.

Clinical Endpoints

Study 1: Include symptom scores that are recorded by parents or caregivers as efficacy endpoints. Assess efficacy at the start of the study and daily for the duration of the study. Include percent change from baseline in Total Nasal Symptom Score (TNSS), based on parent or caregiver reflective symptom assessments as the primary efficacy endpoint. Include percent change from baseline in TNSS, based on parent or caregiver instantaneous assessments as a secondary efficacy endpoint.

Include evaluations of parent or caregiver assessed individual symptom scores as secondary efficacy endpoints. Include recordings of adverse events, vital signs, physical examinations, and nasal examinations as safety endpoints. Perform vital signs, physical examinations, and nasal examinations at screening or baseline and toward the end of the study while participants are still on study drug. Record adverse events in a diary record.

Study 2: Determine the plasma concentration of olopatadine and its active metabolites using the same validated assay method employed previously or using an adequately cross-validated assay method.

Include recordings of adverse events, vital signs, physical examinations, and nasal examinations as safety endpoints. Assess safety endpoints at screening or baseline and toward the end of the study while participants are still on study drug. Record adverse events in a diary record.

Study Evaluations

Study 1: Include assessment of reflective and instantaneous symptoms recorded by parents or caregivers as study evaluations. Assess efficacy at the start of the study and daily for the duration of the study. Conduct Study 1 before conducting Study 2.

Study 2: Report plasma concentrations and pharmacokinetic parameters such as Cmax, Tmax, AUC, CL/F, and t1/2 for olopatadine and its active metabolites. Explore the effects of covariates, such as age, weight, height, and body surface area on the pharmacokinetics of olopatadine and its active metabolites. Utilize appropriate prior pharmacokinetic data available in children and adults. Provide a descriptive comparison of the pharmacokinetics of olopatadine and its active metabolites in children and adults.

Include descriptive analyses of adverse reactions, vital signs, physical examinations, and nasal examinations as study evaluations.

Drug Information

Dosage form: Nasal spray solution

Route of administration: Intranasal

Regimen:

Study 1: Administration of an age- and/or weight-appropriate dose or doses, with dosing and dosing intervals as determined by pharmacokinetic and/or clinical data.

Study 2: Administration of one or more dose levels with the total daily dose provided based on age- and/or weight considerations. Use an age-appropriate formulation in the studies described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.

Development of a commercially-marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

The bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the current proposed drug product to the age appropriate formulation may be conducted in adults.

Drug-specific Safety Concerns

Safety concerns include unanticipated adverse reactions, particularly paradoxical excitability, somnolence, fatigue, hyperkinesia, epistaxis, and/or nasal irritation.

Statistical Information

Study 1: Provide analyses of efficacy based on parent or caregiver-assessed symptom scores using an appropriate statistical test for the data. Provide descriptive analyses of adverse events, vital signs, physical examinations, and nasal examinations, and provide pharmacokinetics parameters as noted above in ***Study Evaluations***.

Study 2: Provide descriptive analyses of the pharmacokinetics parameters, adverse events, vital signs, physical examinations, and nasal examinations.

Labeling That May Result from the Study

Appropriate sections of the label may be changed to incorporate the findings of the study.

Format of Reports to be Submitted

You must submit full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

Timeframe for Submitting Reports of the Study

Reports of the above study must be submitted to the Agency on or before July 1, 2009. Please keep in mind that pediatric exclusivity only attaches to existing patent protection or exclusivity that has not expired at the time you submit your reports of the study in response to this Written Request.

Response to Written Request

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request, then you must indicate when the pediatric study will be initiated.

Please submit protocols for the above study to an Investigational New Drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a Written Agreement by submitting a Proposed Written Agreement. Clearly mark your submission **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study should be submitted as a New Drug Application or as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from the study. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS—PEDIATRIC EXCLUSIVITY**

DETERMINATION REQUESTED" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. The type of response to the Written Request (complete or partial);
2. The status of the supplement (withdrawn after the supplement has been filed or pending);
3. The action taken (i.e. approval, approvable, not approvable); or
4. The exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Guidance for Industry, *Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions*, is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/."

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21861	ANRPT-1	ALCON INC	PATANASE NASAL SPRAY (OLOPATADINE HCL)
NDA-21861	GI-1	ALCON INC	PATANASE NASAL SPRAY (OLOPATADINE HCL)
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/

PETER R STARKE
11/03/2009

LYDIA I GILBERT MCCLAIN
11/03/2009
I conur with the regulatory recommendations. See CDTL memo