CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-861

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	March 27, 2008
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary and Allergy Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	21-861
Applicant Name:	Alcon Laboratories, Inc.
Date of Submission:	September 27, 2007
PDUFA Goal Date:	March 27, 2008
Proprietary Name:	Patanase Nasal Spray
Established Name:	Olopatadine hydrochloride
Dosage form:	Nasal Spray
Strength:	0.6% w/v (665 mcg olopatadine HCl in each 100 microliter spray)
Proposed Indications:	Seasonal Allergic Rhinitis
Action:	Approval

1. Introduction

Alcon Laboratories submitted a complete response to a previous not approvable action on this 505(b)(1) application for use of Patanase Nasal Spray for the relief of the symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older. The proposed dose is two sprays per nostril twice-daily. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

Olopatadine is an antagonist of the histamine H1 receptor. 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 will provide patients with SAR another choice of an antihistamine nasal spray.

3. Chemistry, Manufacturing, and Controls

The drug substance olopatadine hydrochloride is a well known compound that is already approved in a commercial ophthalmic product. Patanase Nasal Spray is a 0.6% solution of olopatadine hydrochloride, and excipients including benzalkonium chloride, dibasic sodium phosphase, edetate disodium, and sodium chloride in purified water, adjusted to a target pH 3.7 by hydrochloric acid or sodium hydroxide. The currently marketed ophthalmic formulations have 0.1% and 0.2% olopatadine and the target pH is 7.0. The

excipients in Patanase Nasal Spray are typical of nasal spray products. The relatively low pH is used to improve the solubility of olopatadine drug substance such that the concentration of 0.6% could be achieved without using any solubility enhancing agent. The formulation is contained in a plastic bottle (b) (4) with a metering spray pump and fitted with a plastic actuator and overcap. Each spray delivers 600 mcg of olopatadine base or 665 mg of olopatadine hydrochloride. The drug substance is manufactured in (b) (4) The final drug product is manufactured in an Alcon facility in Barcelona, Spain. The manufacturing and testing facilities associated with this drug product have acceptable EER status.

The drug product has undergone multiple reformulations as clinical development progressed. The applicant initially developed 0.1% and 0.2% olopatadine nasal spray formulations, but due to the lack of convincing efficacy later developed 0.4% and 0.6% formulations. To enhance solubility of the higher concentration, povidone (1-vinyl-2-pyrrolidinone polymer) at a concentration of (b) (4) % was added to the formulation. This formulation was the subject of the original NDA. The povidone containing formulation was found to be markedly irritating to the nasal mucosa in pre-clinical animal studies and clinical studies, therefore, the original NDA was not approved. The applicant reformulated the product by removing povidone, and to maintain solubility of olopatadine drug substance reduced the target pH from (b) (4) to 3.7. Additionally the nasal spray pump was redesigned to remove contact of the formulation with the (b) (4) portion of the pump. Contact with the (b) (4) was found to lead to the formation of degradants, some of which were suspected of being genotoxic. To link the formulation used in the original NDA and the proposed to-be-marketed formulation the applicant conducted extensive in vitro drug product characterization studies as required by the Agency. These studies showed that the two formulations performed similarly. An abbreviated clinical program with the new formulation was accepted as adequate because of this in vitro similarity, and also because of the fact that the product is a solution as opposed to a suspension (sees further discussion in Section 7.a).

4. Nonclinical Pharmacology and Toxicology

No new pharmacology and toxicology studies were submitted with this complete response. 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 proposed commercial formulation does not contain povidone, the local nasal toxicity findings seen in animals are not relevant, other than for historical purpose. The preclinical data are briefly summarized below.

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.

5. Clinical Pharmacology and Biopharmaceutics

The applicant submitted results from a fairly comprehensive clinical pharmacology program with the original NDA. The program addressed the key pharmacokinetic issues, such as pharmacokinetics after single dose and multiple doses in healthy subjects and patients with allergic rhinitis, in vitro and vivo metabolism, effect of renal impairment, effect of hepatic impairment, and drug-drug interaction.

The absolute bioavailability of olopatadine nasal spray is approximately 60% of nasally administered olopatadine. The bioavailability was similar in healthy subjects and subjects with SAR. Urinary excretion was the major route of elimination of absorbed drug (approximately 70%) with hepatic metabolism playing a minor role. In vitro studies suggest that hepatic cytochrome P450 (CYP) and flavin-containing monooxygenases (FMO) are involved in the minor hepatic metabolic pathway. Olopatadine did not inhibit the major CYP450 enzymes. Studies in patients with renal impairment showed no significant difference in systemic olopatadine exposure compared to subjects with normal renal function. Studies in patients with hepatic impairment were not done because hepatic metabolism is a minor route of elimination. Specific drug-drug interaction studies were not done because olopatadine did not inhibit major CYP enzymes in vitro.

The applicant conducted two cardiac safety QT studies, which are discussed in Section 8 of this review.

6. Clinical Microbiology

The final product is not sterile, which is acceptable for a nasal spray product. The manufacturing process is adequate from a microbiological perspective. During manufacturing the bulk drug solution is passed though a (b) (4) to reduce the microbial load.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

The applicant initially pursued development of 0.1% and 0.2% formulations of olopatadine, and between 1997 and 2000 conducted multiple studies including exploratory single-dose environmental exposure unit (EEU) studies (C-97-59, C-00-70), and phase 2 and 3 efficacy and safety studies lasting 2 weeks (C-00-10, C-00-33) and 8 weeks (C-01-05) with these formulations. These studies did not show robust and consistent efficacy. Therefore, the applicant reformulated the product to increase the concentration of olopatadine to 0.4% and 0.6%, and added povidone to increase the solubility of olopatadine as discussed in previous sections. Between 2001 and 2003 the applicant conducted a number of studies with the formulation containing olopatadine 0.4% and 0.6% that formed the basis of the original NDA. Review of the original NDA concluded that the product was effective in the symptomatic treatment of SAR. The safety evaluation, however, showed that the product caused irritation and damage to the nasal mucosa. There were unacceptably high frequencies of nasal septal perforation, nasal ulceration, and epistaxis in the clinical studies. 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 to eliminate povidone and made some other changes as described above in Section 3. With the reformulated product the applicant conducted one environmental exposure unit pharmacodynamic efficacy study and one long-term safety study. An abbreviated clinical program with the new formulation 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 solution as opposed to suspension. 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]

Some characteristics of the pivotal studies that form the basis of review and regulatory decision for this application are shown in Table 1. The design and conduct of these

[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.

studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 1. Pivotal Patanase clinical studies

ID	Study type	Study duration	Patient Age, yr	Treatment groups*	N (ITT)	Study Year#	Countries
Submitted with the original application [Patanase formulation containing (b) (4) povidone, pH (b) (4)							
C-02-10	Efficacy and safety SAR study	2 week	12 - 81	Op 0.4% 2 sp/nostril Op 0.6% 2 sp/nostril Vehicle placebo	228 220 223	2003	USA
C-02-37	Efficacy and safety SAR study	2 week	12 - 80	Op 0.4% 2 sp/nostril Op 0.6% 2 sp/nostril Vehicle placebo	188 183 191	2003	USA
C-01-92	Safety	52 week	12 - 79	Op 0.6% 2 sp/nostril Vehicle placebo	450 450	2004	USA, Canada
C-01-83	EEU Onset of Action	Single dose	17 - 65	Op 0.2% 2 sp/nostril Op 0.4% 2 sp/nostril Op 0.6% 2 sp/nostril Vehicle placebo	80 80 80 80	2002	Canada
C-03-48	EEU Onset of Action	Single dose	13 - 63	Op 0.6% 2 sp/nostril FP 2 sp/nostril Vehicle placebo	30 30 30	2003	Canada
C-03-52	EEU Onset of Action	Single dose	18 - 84	Op 0.6% 2 sp/nostril MF 2 sp/nostril Vehicle placebo	140 140 140	2004	Canada
C-02-54	High dose QT cardiac safety	2 week	18 - 75	OOS 20 mg BID Vehicle Placebo	34 34	2003	USA
Submitted with complete response [In studies C-05-64 and C-05-69 Patanase formulation containing no povidone, pH 3.7, was used; In study C-04-70 Patanase formulation containing (b) (4) povidone, pH (b) (4) was used]							
C-05-64	EEU PD efficacy	Single dose	16 - 64	O 0.6% 2 sp/nostril Vehicle placebo	204 202	2006	Canada
C-04-70	Efficacy and safety SAR study	2 week	12 - 64	Op 0.6% 2 sp/nostril Az 0.1% 2 sp/nostril Vehicle placebo	180 188 176	2005	USA
C-05-69	Safety	52 week (interim 26 wk)	12 - 85	O 0.6% 2 sp/nostril Vehicle placebo	445 445	2007	USA
* Op = Olopatadine in povidone containing formulation; O = Olopatadine in formulation not containing povidone; OOS = Olopatadine oral solution; FP = Flonase Nasal Spray; MF = Nasonex Nasal Spray; Az = Astelin Nasal Spray # Year study subject enrollment ended							

b. Design and conduct of the studies

2-week efficacy and safety studies (C-02-10, C-02-37, C-03-51):

Studies C-02-10 and C-02-37 were randomized, double-blind, multi-center, vehicle-controlled, parallel group in design, conducted in patients 12 years of age and older with SAR. The studies had a 4-21 day placebo run-in periods followed by a 2 weeks double blind treatment period. The treatment arms were olopatadine nasal spray 0.4%,

olopatadine nasal spray 0.6%, and vehicle nasal spray, all dosed twice daily. Efficacy was assessed by morning and evening reflective and instantaneous patient scoring of four nasal symptoms (runny nose, itchy nose, stuffy nose, and sneezing) and two eye symptoms (itchy eyes, and watery eyes) on a four point scale (0=none, 1=mild, 2=moderate, and 3=severe), and several other measures, (b) (4) the Allergy-Specific Work Productivity and Activity Impairment Questionnaire (WPAI-AS), and a life impact/health economic questionnaire. The primary efficacy endpoint was the change from baseline in the reflective Total Nasal Symptom Score (TNSS), which is the sum of four nasal symptoms, averaged over the 2 weeks of treatment. The studies were designed to have 240 patients per treatment arms to give a 90% power to detect 8.33 % difference (C-02-10) or 12.5% difference (Study C-02-37) in the primary efficacy endpoint at a two-sided alpha-level of 0.05. Safety assessment included recording of adverse events, vital signs, physical examinations, and clinical laboratory measure.

Study C-03-51 was similar to studies C-02-10 and C-02-37, but with the difference that patients 6-11 years with SAR were enrolled. A total of 271 patients were randomized equally to the three treatment arms of olopatadine nasal spray 0.4%, olopatadine nasal spray 0.6%, and placebo.

1-year safety study (C-01-92):

Study C-01-92 was randomized, double-blind, multi-center, vehicle-controlled, parallel group in design, conducted in the United States and Canada in patients 12 years of age and older with perennial allergic rhinitis (PAR). The study had a screening visit where eligibility was determined, followed by 12 months of double blind treatment with either olopatadine nasal spray 0.6% or vehicle nasal spray, dosed twice daily. Patients were seen in the clinic at monthly visits. The study was designed to primarily assess safety. Safety assessment included recording of adverse events, vital signs, physical examinations, ECG, and clinical laboratory measure. (b) (4) A total of 924 patients were randomized approximately equally to the two treatment arms of which approximately 70% completed the study. The frequency of discontinuation due to treatment failure, adverse events, and other reasons were similar in the two treatment arms. Treatment failure was the most common reason for discontinuation, accounting for approximately 8% of discontinuations.

EEU studies (C-01-83, C-03-48, C-03-52):

The three EEU studies were randomized, single-center (Ontario, Canada), single-dose, double-blind, vehicle- or active-controlled parallel group in design conducted in patients 16 years or 18 years of age and older with SAR. These studies were primarily designed

to get pharmacodynamic onset of action data for olopatadine. Eligible patients were primed with an allergen in the EEU for two days, and patients who met the eligibility criteria of a predefined minimum nasal symptom score were exposed to the allergen in the EEU on the test day and administered a single dose of study drug. Efficacy was primarily assessed by frequent instantaneous patient recording of four nasal symptoms (runny nose, itchy nose, stuffy nose, and sneezing) on a four point scale (0=none, 1=mild, 2=moderate, and 3=severe) over 12 hours after dosing. Treatment arms in study C-01-83 were olopatadine nasal spray 0.2%, olopatadine nasal spray 0.4%, olopatadine nasal spray 0.6%, and vehicle nasal spray. Treatments arms in study C-03-48 were olopatadine nasal spray 0.6%, fluticasone propionate nasal spray, and vehicle nasal spray. Treatment arms in study C-03-52 were olopatadine nasal spray 0.6%, mometasone furoate nasal spray, and vehicle nasal spray.

High dose QT cardiac safety studies (C-00-23, C-02-54):

The two high dose QT studies were randomized, single-center (Austin, Texas, for study C-00-23, and Phoenix, Arizona for study C-02-54), multi-dose, double-blind, placebo-controlled, two-period cross-over in design conducted in healthy male and female volunteers 18 years of age and older. In study C-00-23 olopatadine oral solution 5 mg twice-daily was administered for 2.5 days. In study C-02-54 olopatadine oral solution 20 mg twice-daily was administered for 14 days. The dose of olopatadine used in study C-00-23 was two times and in study C-02-54 was eight times the proposed dose for allergic rhinitis. Both studies used vehicle placebo control, but not active control as is currently recommended in the ICH Guidance for such studies. Serial ECG and serial blood sampling for determination of plasma olopatadine concentration were done at baseline, at day 12 post-administration, and after the last dose of study drug administration. ECGs were read in a central facility using appropriate methodologies. In study C-00-23 a total of 117 subjects were enrolled of whom 102 subjects completed the study, and in study C-02-54 a total of 32 subjects were enrolled of whom 32 subjects completed the study.

EEU study (C-05-64):

This was a randomized, single-center (Ontario, Canada), single-dose, double-blind, vehicle-controlled parallel group in design conducted in patients 16 years or 18 years of age and older with SAR. This study was primarily designed for pharmacodynamic assessment of efficacy of the reformulated olopatadine nasal spray not containing povidone. Eligible patients were primed with an allergen in the EEU for two days, and patients who met the eligibility criteria of a predefined minimum nasal symptom score were exposed to the allergen in the EEU on the test day and administered a single dose the study drug. Efficacy was primarily assessed by frequent instantaneous patient recording of four nasal symptoms (runny nose, itchy nose, stuffy nose, and sneezing) on a four point scale (0=none, 1=mild, 2=moderate, and 3=severe) over 12 hours after dosing. Treatment arms were olopatadine nasal spray 0.6%, and vehicle nasal spray.

2-week efficacy and safety studies (C-04-70):

Study C-04-70 was similar to studies C-02-10 and C-02-37 submitted with the original NDA with the exception that the treatment arms were olopatadine nasal spray 0.6%, Astelin Nasal Spray 0.1%, and vehicle nasal spray. Olopatadine formulation and the vehicle nasal spray used in this study were the old formulations that contained povidone. A total of 728 patients were randomized approximately equally to the three treatment groups.

1-year safety study (C-05-69):

This was a randomized, double-blind, multi-center, vehicle-controlled, parallel group in design, conducted in the United States in patients 12 years of age and older with PAR. The objective of the study was safety evaluation of the reformulated olopatadine nasal spray not containing povidone. With agreement with the FDA the applicant submitted 6 months results with the resubmission; results of the complete study were submitted towards the end of the review period. The study had a screening visit where eligibility was determined, followed by 52 weeks double blind treatment with either olopatadine nasal spray 0.6% or vehicle nasal spray, dosed twice daily. Screening visit included a detailed nasal examination, and subjects with findings suggestive of infection, anatomic abnormality, ulceration of the mucosa, or blood in the nose were disqualified from enrollment. Patients were seen in the clinic at monthly visits. Safety assessment included recording of adverse events, vital signs, and physical examinations. There were no laboratory measures and ECGs conducted because these safety issues were addressed before. Efficacy was assessed by the exact same measure used to assess efficacy in the previous 1year safety study C-01-92. Olopatadine blood levels were done as an additional check of compliance. Because of concerns of nasal septal perforation with the previous formulation, this study included a monthly thorough nasal examination that was made more detailed upon certain initial findings. A total of 890 patients were randomized equally to the two treatment arms of which approximately 85% stayed in the study at the 6-month interim analysis.

c. Efficacy findings and conclusions

The overall clinical program supports efficacy of Patanase Nasal Spray 0.6% at a dose of 2 sprays in each nostril twice daily for symptomatic relief of SAR. Primary support of efficacy is from studies submitted with the original NDA that used an olopatadine formulation containing povidone. Efficacy findings with the formulation used in the original NDA can be extrapolated to the proposed to-be-marketed formulation for reasons discussed above in Section 7.a. In addition, efficacy assessment with the proposed-to-be-marketed formulation showed efficacy. The EEU study C-05-64 showed consistent efficacy on all time points measured (16 time points over 12 hours) after dosing. The efficacy time profile curve for study C-05-64 was similar to those in two EEU studies C-01-83 and C-03-52 conducted with the olopatadine formulation containing povidone. Efficacy data from the 1-year safety study C-05-69 conducted with the proposed-to-be-marketed formulation was comparable to the efficacy data from the 1-year safety study C-01-92 conducted with the olopatadine formulation containing povidone.

Results of the primary efficacy variable for the two replicate 2-week studies conducted in SAR patients (C-02-10, and C-02-37) showed that olopatadine nasal spray 0.6% and 0.04% was statistically significantly superior to vehicle nasal spray (Table 2). Results of study C-04-70 also showed that olopatadine 0.6% was statistically significantly superior to vehicle nasal spray (data not shown). The effect sizes were in the range expected for an antihistamine. Secondary endpoint results were also supportive of efficacy. The applicant proposes to commercialize olopatadine 0.6% with the reasoning that there was a consistent numerical efficacy advantage for olopatadine 0.6% over olopatadine 0.4%. The reasoning is acceptable. (b) (4)

Table 2. Reflective total nasal symptom score averaged over 14 days of treatment*

Treatment Groups	n	Mean Baseline Score	Mean Change from Baseline	Treatment Difference	
				Point Estimate (95% CI)	P value
Study C-02-10					
Olopatadine NS 0.6%	220	9.17	- 2.90	- 0.98 (-1.37, -0.59)	<0.0001
Olopatadine NS 0.4%	228	9.26	- 263	- 0.72 (-1.11, -0.33)	0.0003
Vehicle NS	223	9.07	- 1.92		
Study C-02-37					
Olopatadine NS 0.6%	183	8.71	- 3.63	- 0.96 (-1.42, -0.51)	<0.0001
Olopatadine NS 0.4%	188	8.90	- 3.38	- 0.71 (-1.17, -0.26)	0.0023
Vehicle NS	191	8.75	- 2.67		

* Change from baseline in the morning and evening reflective total nasal symptom score (TNSS) averaged over 2-week period. TNSS comprised of scores of runny nose, itchy nose, stuffy nose, and sneezing, each scored by patients on 0-3 scale.

The EEU studies conducted in SAR patients would support a pharmacodynamic onset of action of 30 minutes. For regulatory purpose, onset of action is defined as the first time point, replicated in two studies, where the difference between the active treatment arm from placebo in efficacy measure is statistically significant and the significant difference persists consistently after that time point. In study C-01-83 the statistically significant differences between olopatadine 0.6% and olopatadine 0.4% from vehicle placebo for instantaneous TNSS were first observed at 90 minutes and persisted consistently after that. In study C-01-83 the statistically significant difference between olopatadine 0.6% (only dose studied) and vehicle placebo for instantaneous TNSS was first observed at 30 minutes and persisted after that. In study C-05-64 the statistically significant difference between olopatadine 0.6% (only dose studied) and vehicle placebo for instantaneous TNSS was first observed at 30 minutes and persisted after that. Among the three studies the onset time point of 30 minutes is replicated. In two onset of action studies mometasone furoate nasal spray (C-03-52) and fluticasone propionate nasal spray (C-03-

48) were included. The pharmacodynamic onset of action for olopatadine in these studies was numerically superior to the nasal corticosteroids. This apparent superiority of olopatadine is not unexpected given the different mechanism of action of these drugs.

(b) (4)

[redacted]

8. Safety

a. Safety database

The safety assessment for olopatadine 0.6% nasal spray for patients 12 years of age and older is primarily based on the three 2-week studies in SAR patients and two 52-week studies in PAR patients (Table 1). The 52-week study C-05-69 is important for this application because this is the only safety study conducted with the reformulated to-be-marketed olopatadine nasal spray.

b. Safety findings and conclusion

The Agency had previously concluded that the olopatadine formulation subject of original NDA was unsafe for use in allergic rhinitis patients because of nasal irritation and damage to the nasal mucosa resulting in unacceptably high frequencies of nasal septal perforation, nasal ulceration, and epistaxis. In study C-01-92 nasal septal perforation was identified in one patient treated with olopatadine nasal spray 0.6% and in two patients treated with vehicle nasal spray. Nasal septal perforation is extremely rare in controlled pre-marketing clinical studies with nasal spray products for allergic rhinitis. Nasal septal perforation is seen occasionally with corticosteroids after marketing, but even then they are rare. For example, up to March 2008 in the AERS database there were 17 cases with Flonase and 12 cases with Nasonex. Compared to these numbers the 3 cases seen in pre-marketing studies with olopatadine was a remarkable safety signal.

This complete response addressed safety concerns by reformulating the product as described in section 2 above, and submitting supporting safety data from 52-week safety study C-05-69 conducted with the reformulated product. The Agency agreed that 6 months data would be adequate because all cases of septal perforation with the previous formulation, the predominant safety concern with that formulation, occurred early during treatment.

In the safety study C-05-69 there were no deaths, and serious adverse events were rare and had no patterns that could raise safety concerns. There were no nasal septal perforations seen. Nasal ulceration occurred more in olopatadine treated patients compared to vehicle treated patients (8.8% vs 5.8%). Epistaxis was reported in 19.3% olopatadine treated patients compared to 23.4% in vehicle treated patients. These frequencies are higher than the previous one-year safety study. Results of the complete 12-month study period were submitted towards the end of the review period, and on preliminary review did not show any case of nasal septal perforation or findings substantially different than the results from the 6-month period.

Results of the new long-term safety study C-05-69 addresses the predominant safety concern of nasal septal perforation. Findings of the study supports the notion that povidone was responsible, in part or wholly, for the damage to the nasal mucosa. The safety concern of nasal septal perforation is addressed because none was seen in this study. Nasal septal ulcerations and epistaxis were commonly reported in this study in both treatment arms. The higher frequency may be due to increased scrutiny that the patients were subjected to in this study, or due to some other aspect of the formulation (discussed further below). Nasal ulcerations are rarely seen with other nasal spray products in controlled clinical studies. Of the commonly used nasal sprays for allergic rhinitis only the Veramyst product label reports a frequency of 1% with the drug.

Epistaxis was also seen in short-term (2-week) studies with frequencies of 3.2% (19 out of 587) in olopatadine nasal spray 0.6% group and 1.7% (10 out of 593) in vehicle nasal spray. The frequency of epistaxis with olopatadine nasal spray was within the range reported by some other nasal spray products, particularly nasal corticosteroids.

The findings of nasal ulcerations and epistaxis are further concerning because these appeared to be more frequent in children compared to adults with the formulation subject of the original NDA. During review of the original NDA the applicant submitted summary results of study C-03-51, a 2-week efficacy and safety study in children 6 to 11 years of age with SAR. Children 6 to 11 years of age had a higher frequency of nasal ulcerations and epistaxis compared to adults and adolescents with same nominal dose of olopatadine nasal spray (Table 3).

Table 3. Frequency of epistaxis and nasal ulceration in 2-week SAR studies

	Olo 0.6% 2 sp BID	Olo 0.6% 1 sp BID	Olo 0.4% 1 sp BID	Veh pbo 2 sp BID	Veh pbo 1 sp BID	Veh pbo Run in	Total
Adult and adolescent subjects, ages 12 years and older, Studies C-02-10 and C02-37							

	Olo 0.6% 2 sp BID	Olo 0.6% 1 sp BID	Olo 0.4% 1 sp BID	Veh pbo 2 sp BID	Veh pbo 1 sp BID	Veh pbo Run in	Total
	n = 407	n = 0	n = 418	n = 417	n = 0	n = 513	n = 1755
Epistaxis	14 (3.5%)	-	16 (3.8%)	8 (1.9%)	-	8 (1.6%)	46 (2.6%)
Ulceration	0 (0%)	-	0 (0%)	1 (0.2%)	1	1 (0.2%)	2 (0.1%)
Pediatric subjects, ages 6-11 years, Study C-03-51							
	n = 52	n = 51	n = 52	n = 51	n = 51	n = 514	n = 271
Epistaxis	5 (9.6%)	7 (13.7%)	5 (9.6%)	2 (3.9%)	5 (9.8%)	0 (0%)	24 (8.9%)
Ulceration	2 (3.8%)	2 (3.9%)	1 (1.9%)	0 (0%)	4 (7.8%)	1 (7.1%)	10 (3.7%)

Reformulation of the product with removal of povidone has addressed the major safety issue with nasal perforation, but the reformulated product still appears to be irritating with large numbers of patients having nasal ulcerations and epistaxis. Occurrences of these adverse reactions in both treatment arms, particularly in the long-term study, suggest that these are due to the formulation. One aspect of the formulation that may be responsible is the low pH of the product. The pH of the original formulation was already low at (b) (4) the new formulation has even a lower target pH of 3.7 with an allowable range of 3.5 to (b) (4) 3.95. This pH is substantially lower than other nasal spray products. The pH target or ranges for some other nasal products are as follows: Astelin is 5.0-5.4; Rhinocort is 4.5; Omnaris is 4.5; Nasonex is 4.3-4.9; Nasacort AQ is 5.0; Nasarel and Nasalide are 5.2; and Flonase and Veramyst are 6.0.

The findings of nasal ulcerations and epistaxis are concerning, but not to the extent that it would preclude approval of this product. The product label will have warning statement stating that this product should not be used in patients with nasal diseases other than allergic rhinitis, and patients should be monitored periodically for signs and symptoms of adverse effects on the nasal mucosa and consider stopping this product if patient develops epistaxis or nasal ulcerations. To further characterize these safety findings the applicant has agreed to conduct a 52-week safety study as post-marketing requirement. The study will be comparable in size to the previous 52-week safety studies, but will also include a vehicle placebo at normal pH arm in addition to vehicle placebo arm matching the pH of the product. This will help clarify if the low pH of the formulation is contributing to nasal adverse effects. Findings of this study will be included in the product label and can further inform the language of the warning and precaution section. This study will also address some limitations of the long-term safety study C-05-69 as discussed below.

The safety study C-05-69 included strict screening criteria that included a detailed nasal examination and subjects with findings suggestive of infection, anatomic abnormality, ulceration of the mucosa, or blood in the nose were disqualified from enrollment. The nasal evaluation was also detailed with monthly thorough nasal examination. While such a study may be sensitive in picking up nasal toxicity, particularly nasal septal perforation, it may not reflect real-life situation where patients with some nasal abnormalities may be given this drug product and the patients may not be followed thoroughly. The post-marketing required study will define the safety profile of olopatadine nasal spray in allergic rhinitis patients treated with no strict eligibility criteria to exclude patients with nasal abnormalities who otherwise may be prescribed this product, and not conduct

intense frequent nasal examination that could potentially remove patients early during treatment before manifesting serious nasal toxicity.

Safety findings other than local nasal findings are briefly described below. Formulation issues, such as povidone or pH, are unlikely to impact on any of these; therefore, data from all studies are relevant for the following discussion.

Vital signs, physical examination, clinical laboratory measures, and ECG did not show any findings of concern. The drug appeared to be sedating with somnolence reported by 0.9% patients with olopatadine 0.6% nasal spray and 0.3% in vehicle nasal spray in the three 2-week studies. The overall frequency of somnolence was lower than report of somnolence typically seen in other allergic rhinitis clinical studies; nevertheless the frequency was higher with olopatadine compared to vehicle nasal spray. In high dose cardiac safety and absolute bioavailability studies 7/166 subjects treated with olopatadine 5 mg or 20 mg twice daily by mouth or a single 1.5 mg intravenous dose reported somnolence. Also somnolence was the most common adverse event in the clinical development program in Japan with olopatadine 2.5 mg and 5 mg tablets, which are approved in Japan. Based on cross study comparison the AUC of olopatadine 0.6% nasal spray is about 16% of olopatadine tablet 5 mg. Overall data suggest that olopatadine can cause sedation and the label will reflect that. Other adverse events of note in the three 2-week studies that were more frequent with olopatadine 0.6% nasal spray were bitter taste, dry mouth, and fatigue.

The two high dose QT cardiac safety studies did not suggest a QT effect of olopatadine. Study C-00-23 was not very useful for assessing QT effect because a relatively small dose of olopatadine was used in this study and the subjects were dosed for only 2.5 days. Study C-02-54 was more thorough, used eight times the proposed dose of olopatadine, and dosed the subjects for 14 days. This study has the basic design features of a thorough QT study with the exception of including a positive control. In this study the mean change in QTcF from baseline was -2.9 msec and -3.5 msec for olopatadine and placebo group, respectively. There were no trends in QTcF outlier analyses using various QTcF thresholds. The study, along with negative findings from other clinical studies and preclinical findings assures QT cardiac safety of olopatadine. Pre-clinical studies did not show any QT effect in whole animal studies, and on hERG assay the IC50 of olopatadine was approximately 1000 times greater than terfenadine. Furthermore, olopatadine does not carry the burden of being significantly metabolized by the CYP major enzymes.

c. REMS/RiskMAP

REMS and RiskMAP were not deemed necessary for Patanase Nasal Spray. Other drugs of this class do not have REMS or RiskMAP.

9. Advisory Committee Meeting

An advisory committee was not convened for this application. Olopatadine is not a new molecular entity. Antihistamines, including nasal antihistamines, are a well studied drug class, and the clinical development program for this product was routine and typical for

similar drugs developed for allergic rhinitis. The nasal toxicity that was seen with previous formulation of olopatadine was obvious and fairly non controversial. There were no issues that warrant discussion at an advisory committee meeting.

10. Pediatric

There are no outstanding pediatric drug development issues at this time. The applicant included children 12 years and older in the studies that were submitted with the original NDA and this resubmission. The lower age cut-off used 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 study conducted in children 6 to 11 years of age as discussed above. The safety result of the study showed 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 applicant was advised by the Division during the review of the original NDA that no additional studies should be conducted in pediatric subjects until safety could be assured. After reformulation of the product, the applicant requested the Agency issue a pediatric written request to study children lower than 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 studies down to 2 years of age. The Pediatrics and Maternal Health Team of CDER reviewed the written request, and the Division of Anti-Infective Ophthalmology Products was contacted about the written request because of the ophthalmologic formulation of olopatadine. The results of the ongoing pediatric studies are due on July 1, 2009. The applicant has requested waiver of studies below 2 years of age, which is reasonable. 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).

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI initially audited three sites during review of the original NDA. These were routine inspections and the sites were recommended by the clinical review team based on large numbers of subjects enrolled at these sites. During review of the original NDA the clinical team identified some irregularities in the case report forms regarding the documentation for nasal septal perforation and suggested audit of two more sites. Audit of all five sites did not show any major irregularities. No DSI audit was conducted during review of the complete response. Review of the original NDA and complete response did not identify any irregularities that would raise concerns regarding data integrity. No ethical issues were present. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. The applicant certified that no investigator entered into any financial arrangements that could affect the outcome of the study. One investigator involved in studies submitted with the original NDA and two investigators involved in the long-term safety study submitted with the NDA complete response had significant equity interest in Alcon. The number of subjects that these investigators enrolled was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that equity interests could have influenced or biased the results of these studies.

c. Others

There are no outstanding issues with consults received from DDMAC, DMETS, DSRCS, or from other groups in CDER.

12. Labeling

a. Proprietary Name

The trade name Patanase was reviewed by the DMETS of ODS and found to be acceptable. On October 5, 2005, a Citizen's Petition was submitted asking the Agency to refrain from accepting the proposed trade name Patanase. The Petitions argues that the proposed trade name is confusingly similar to many other products and can lead to medication errors. DMETS re-evaluated the name based on the Petition and had no objection to the name. The name was also found to be acceptable to DDMAC from a promotional perspective.

b. Physician Labeling

The applicant submitted a label in the Physician's Labeling Rule format that generally contains information consistent with other products of this class. The label was reviewed by various disciplines of this Division, and by DDMAC, and DMETS. Various changes to different sections of the label were recommended to reflect the data accurately and truthfully and better communicate the findings to health care providers. The Division and the applicant have agreed to the final version of the label.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division, and DMETS, and the final version was found to be acceptable.

d. Patient Labeling and Medication Guide

The patient instructions for use was reviewed by various disciplines of this Division, and DSRCS, and found to be acceptable.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The applicant has submitted adequate data to support approval of Patanase Nasal Spray for the relief of the symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older. The action on this application will be Approval.

b. Risk Benefit Assessment

Overall the risk and benefit assessment of Patanase Nasal Spray support it approval without any specific restrictions. The drug was efficacious in the clinical studies at the proposed dose, and the overall clinical program is supportive of its safety. The initial safety concern of nasal septal perforation is resolved with reformulation of the product and subsequent 12-month safety study showing no perforation. Patanase Nasal Spray appears to be irritating to the nasal mucosa resulting in large number of patients reporting epistiaxis and nasal ulcerations in the clinical studies. These are probably related to the formulation, specifically low pH of the product. These findings are concerning, but not to the extent that it would preclude approval of this product. The label will have warning and precaution statements 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 when they are on Patanase Nasal Spray.

c. Post-marketing Risk Management Activities

No specific risk management activities are warranted.

d. Post-marketing Study Commitments

The applicant will conduct a required post-marketing safety study to further assess the local nasal safety of Patanase Nasal Spray. The study will be one-year in duration, similar in scope to the previously completed one-year safety study where nasal septal perforations were seen. The study will include an additional vehicle placebo arm with a normal pH formulation to assess whether the low pH of Patanase Nasal Spray is responsible for the local nasal irritation. Findings of the study will be included in the product label and can further inform the language of the warnings and precautions section. The study will be a required safety study because spontaneous adverse event reporting or other surveillance mechanism will not be able to discriminate if the low pH of the product is contributing to nasal irritation, and it will be difficult to sort through local nasal toxicities with background use of other drugs, such as nasal corticosteroids, in patients with allergic rhinitis.

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/s/

Badrul Chowdhury
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