CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-861s000

DIVISION DIRECTOR MEMO

DIVISION DIRECTOR'S MEMORANDUM

Date: July 27, 2005

To: NDA 21-861

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product: Patanase (olopatadine HCl) Nasal Spray, 665 mcg

Applicant: Alcon, Inc.

Administrative and Introduction

Alcon submitted a 505(b)(1) new drug application (NDA 21-861) on December 27, 2004 (CDER stamp date), for use of Patanase (olopatadine HCl) Nasal Spray for the treatment of symptoms of seasonal allergic rhinitis (SAR) (b) (4) in patients 12 years of age and older. The PDUFA due date for this application is October 27, 2005. Olopatadine belongs to a class of drug referred to as antihistamines, which exert their pharmacological effect by blocking the action of histamine on the H1 receptor. Many antihistamines are currently marketed in the United States in various dosage forms, including one as a nasal spray. Antihistamines are used for symptomatic treatment of various allergic diseases, such as allergic rhinitis, allergic conjunctivitis, and urticaria. Alcon has an ophthalmic formulation of olopatadine HCl marketed in the United States under the trade name Patanol for the treatment of the signs and symptoms of allergic conjunctivitis. The data submitted by Alcon in this NDA do not support approval of Patanase Nasal Spray as currently formulated because the product caused an unacceptably high frequency of nasal irritation and damage to the nasal mucosa in the clinical and preclinical studies. (b) (4)

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

The drug substance olopatadine HCl is a well known compound that is already approved in a commercial ophthalmic product. The drug substance is manufactured in (b) (4) The final drug product is a 0.6% solution of olopatadine and various excipients 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 HCl. 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 excipients contained in the Patanase Nasal Spray include povidone (b) (4) benzalkonium chloride, edetate disodium, sodium chloride, dibasic sodium phosphate, sodium hydroxide, hydrochloric acid, and purified water. The pH of the drug product is

targeted at (b) (4), which is in contrast to the ophthalmic formulation that has a pH of 7.0. Also the proposed commercial nasal formulation has 0.6% olopatadine, which is in contrast to the ophthalmic formulation that has 0.1% and 0.2% olopatadine. The applicant was initially developing 0.1% and 0.2% olopatadine nasal spray formulations, but because of clinical considerations later developed 0.4% and 0.6% formulations, and is proposing to market only the 0.6% formulation. To enhance solubility of olopatadine as the concentration increased, the solubility enhancer povidone at a concentration of (b) (4) was added. The low pH is not typical of a nasal spray product, and povidone is a novel excipient for a nasal formulation intended for long term use.

In addition to the formulation related issues mentioned above that have clinical ramifications (discussed in subsequent sections of this document), several CMC deficiencies were identified by the CMC review team, which were communicated to Alcon in a discipline review letter within the review cycle. Some of the deficiencies identified may be irrelevant since Alcon will likely need to reformulate the product. The major deficiencies that were identified relate to impurities generated on stability, design of the actuator, and spray content uniformity. Stability data showed that olopatadine is susceptible to degradation if the product was stored in the (b) (4), resulting in generation of impurities some of which are structural alerts. (b) (4) The impurities will either need to be reduced to an acceptable level or qualified. (b) (4) The spray content uniformity testing scheme submitted by Alcon is not adequate to test true dosing performance and suggests possible unacceptable dosing variability. In addition, the tail-off data suggest that the proposed label claim of 240 available actuations may not be supported.

Pharmacology and Toxicology

The main preclinical toxicological concern for Patanase Nasal Spray is the chronic nasal use of the proposed commercial product that contains (b) (4) povidone. Povidone caused olfactory epithelium degeneration and turbinate epithelial vacuolation in rats in a dose dependent fashion with no NOAEL being identified. Therefore, there is no safety margin for the proposed human use. This toxicity was identified during review of the preclinical studies submitted to the NDA as detailed in Dr. Gary Bond's review. The timelines of the availability of the various preclinical toxicity data and the relative timeline of the clinical studies are outlined in Dr. Gilbert-McClain's Clinical Team Leader summary review.

Alcon'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. Alcon'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. However, 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 Alcon qualify the safety of nasal use of povidone by conducting long-term animal studies. There are 3 long-term animal studies that are relevant to povidone. The first study was a 9-month intranasal study in dog 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 – rata and dogs. In this study olfactory epithelial degeneration and turbinate epithelial vaculation 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 is no safety margin for the proposed commercial formulation with the human exposure to povidone of 14.4 mg/day.

Olopatadine was not genotoxic in the standard battery of assays and was not tumorigenic in oral carcinogenicity studies in mice and rats. Olopatadine did not impair fertility in rats and was not teratogenic in rats and rabbits. However, olopatadine decreased the number of live fetuses in rabbits and decreased the viability and body weights of pups in rats.

Clinical and Statistical

Overview of the clinical program:

Alcon initially pursued development of 1% and 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, Alcon reformulated the product to increase the concentration of olopatadine to 0.4% and 0.6%, added povidone to increase the solubility of olopatadine as discussed in previous sections, and between 2001 and 2003 conducted a number of studies that form the basis of this application. Alcon proposes to commercially market only the 0.6% olopatadine formulation. The clinical studies that were conducted with these formulations and submitted with the NDA include two efficacy and safety studies in SAR patients lasting 2 weeks (C-02-10, C-02-37), one safety study in PAR patients lasting 1 year (C-01-92), and three EEU studies (C-01-83, C-03-48, C-03-52). All of these studies were conducted in patients 12 years of age and older. Alcon also submitted two high dose QT cardiac safety studies (C-00-23, C-02-54) using a solution formulation of olopatadine for oral administration. During the NDA review period Alcon submitted summary report of a 2-week efficacy and safety study in children ages 6 to 11 years with SAR (C-03-51). Detailed review of these studies and other supporting studies can be

found in Dr. Lee's clinical review and Dr. Gilbert-McClain's team leader memorandum, and in Dr. Guo's statistical review and Dr. Wang's secondary statistical review. Dr. Lee and Dr. Gilbert-McClain recommend a Not Approvable action on this application because they concluded that the proposed to-be-marketed formulation of olopatadine was toxic to the nasal mucosa (b) (4). I concur with that recommendation.

The pivotal studies mentioned above are briefly commented on in the following sections. The design and conduct of these studies are briefly described, followed by efficacy and safety findings and conclusions.

Design and conduct of the pivotal efficacy and safety 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 double-blind, multi-center, vehicle-controlled, parallel group in design, conducted in the United States in patients 12 years of age and older with SAR. The studies had 4-21 day placebo run-in periods followed by 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, such as (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. In study C-02-10 a total of 677 patients and in study C-02-37 a total of 565 patients were randomized approximately equally to the three treatment arms of which approximately 95% completed the study. There was no preferential dropout in any treatment arms.

Study C-03-51 was similar to studies C-02-10 and C-02-37, but with the notable 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 a 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 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, and 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 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 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 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 poprionate 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. In study C-01-83 a total of 320 patients, in study C-03-48 a total of 90 patients, and in study C-03-52 a total of 425 patients were enrolled.

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

The two high dose QT studies were 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/day was administered for 2.5 days. In study C-02-54 olopatadine oral solution 20 mg/day 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 current recommended in the ICH Guidance for such studies. Serial ECG and serial blood sampling for determination of plasma olopatadine concentration were done at baseline, after the first dose, 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.

Efficacy findings and conclusion:
The submitted studies support efficacy of olopatadine nasal spray 0.6% in patients with SAR 12 years of age and older (b) (4). In the two replicate 2-week studies conducted in SAR patients (C-02-10, and C-02-37), olopatadine nasal spray 0.6% and olopatadine 0.04% was statistically significantly superior to vehicle nasal spray for the primary efficacy endpoint (Tale 1). The effect sizes were quite robust and in the range expected for an antihistamine. Secondary endpoint results were also supportive of efficacy. There was a consistent numerical efficacy advantage for olopatadine 0.6%, the proposed commercial dose, over olopatadine 0.4%.

Table 1. Efficacy finding based on percent change from baseline*, Studies C-02-10 and C-02-37

Treatment Groups	n	Baseline Score Mean (SD)	Percent Change from Baseline Mean (SD)	Treatment Difference	
				Percent change Mean	P value
Study C-02-10					
Olopatadine NS 0.6%	220	9.2 (1.8)	- 30.1 (27.6)	- 11.4	<0.0001
Olopatadine NS 0.4%	228	9.3 (1.8)	- 27.6 (22.4)	- 8.9	0.0002
Vehicle NS	223	9.1 (1.8)	- 18.7 (22.3)		
Study C-02-37					
Olopatadine NS 0.6%	183	8.7 (1.8)	- 39.2 (26.9)	- 12.2	<0.0001
Olopatadine NS 0.4%	188	8.9 (1.7)	- 35.8 (28.1)	- 8.8	0.0037
Vehicle NS	191	8.8 (1.8)	- 27.0 (27.8)		

* 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 90 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 difference persists consistently after that time point. In study C-01-83 the difference between olopatadine 0.6% and olopatadine 0.4% from vehicle placebo for instantaneous TNSS started at 90 minutes and persisted consistently after that. In study C-01-83 the difference between olopatadine 0.6% (only dose studied) from vehicle placebo for instantaneous TNSS started at 30 minutes and persisted after that. Between the two studies the time point of 90 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 very different mechanism of action of these drugs.

Safety findings and conclusion:

The safety of olopatadine nasal spray is mainly assessed from the two 2-week studies in SAR patients (C-02-10 and C-02-37), and from the one 1-year study in PAR patients (study C-01-92). In these three studies a total of 866 subjects received the proposed commercial Patanase Nasal Spray at the proposed labeled dose. In the overall clinical development program a total of 1163 subjects received the proposed commercial Patanase Nasal Spray at the proposed labeled dose.

The safety assessment does not support approval because the data show that olopatadine nasal spray 0.6% is unsafe for use under labeled conditions (21 CFR 314.125 (b)(3)). In the clinical studies there were unacceptable high frequencies of nasal irritation and damage to the nasal mucosa at the proposed labeled dose. Adverse findings related to nasal irritation and damage to the nasal mucosa occurred with high frequencies in the olopatadine nasal spray group as well as the vehicle nasal spray group suggesting that the effects were not from the olopatadine drug substance but from the formulation. Preclinical data showed that povidone, an excipient used in the formulation, was markedly irritating to the nasal mucosa. Therefore, povidone in the proposed commercial formulation was partly responsible for the nasal adverse events seen in clinical studies.

In the clinical program the most common adverse event reported was epistaxis with frequencies of 9.1 % (106 out of 1163) with olopatadine nasal spray 0.6% and 7.3 % (64 out of 882) with vehicle nasal spray. The frequency of epistaxis was within the range reported by some other nasal spray products, particularly nasal corticosteroids. The product label of Nasonex Nasal Spray reports a 11% frequency of epistaxis. Two other related adverse events of concern were nasal ulceration and nasal septal perforation. Nasal ulceration was identified with frequencies of 1.6% (19 out of 1163) with

olopatadine nasal spray 0.6% and 2.1 % (21 out of 1008) with vehicle nasal spray. Nasal septal perforation was identified in one patient treated with olopatadine nasal spray 0.6% and in two patients treated with vehicle nasal spray, all from the 1-year study C-01-92. Nasal ulceration and nasal septal perforation are not typically seen with nasal spray products in relatively small pre-approval clinical studies, including those for nasal corticosteroids. Nasal perforation is often seen with nasal corticosteroids after marketing, but not in large numbers. The AERS database up to May 2005 had reports of 11 cases with Flonase and 8 cases with Nasonex. Compared to these numbers, the three cases seen in the olopatadine nasal spray program is a remarkable safety signal.

During review of the application Alcon 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 had a higher frequency of nasal adverse events, specifically epistaxis and ulceration, compared to adults and adolescents with same nominal dose of olopatadine nasal spray (Table 2). This further underscores the safety concern with olopatadine nasal spray.

Table 2. 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							
	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%)

Other than local nasal adverse events discussed above, olopatadine nasal spray appeared to be well tolerated. Vital signs, physical examination, clinical laboratory measures, and ECG did not show any findings of concerns. Interestingly somnolence was reported with a frequency of only 1.1% (13 out of 1163) with olopatadine nasal spray and 0.2 % (2 out of 1008), which is much lower than report of somnolence seen in other allergic rhinitis clinical studies. The reader is referred to Dr. Lee's comments on this finding.

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 essentially all the design features of a thorough QT study as currently recommended in the ICG Guidance on this topic with the exception that a positive control was not used. The study, along with the negative preclinical findings with olopatadine 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 CYP3A4 pathway.

Clinical Pharmacology and Biopharmaceutics
Alcon submitted results from a fairly comprehensive clinical pharmacology program with the NDA. The program addressed the key pharmacokinetic issues, such as pharmacokinetics after single dose and multiple dose 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. These studies are reviewed in detail in Dr. Suarez-Sharp's review and Dr. Fadiran's team leader memorandum and were found to be adequate to support approval.

The absolute bioavailability of olopatadine nasal spray is approximately 60% of nasally administered olopatadine was bioavailable. 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. Alcon conducted two cardiac safety QT studies, which are discussed under clinical section of this memorandum.

Data Quality, Integrity, and Financial Disclosure
DSI initially audited three sites during review of the application. 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 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. NDA review otherwise did not identify any irregularities that would raise concerns regarding data integrity. No ethical issues are present. All studies were conducted in accordance with accepted ethical standards. The applicant provided adequate disclosure of financial interest of the clinical investigators. There was one investigator who had a significant financial interest in Alcon. That investigator contributed a small number of patients to the whole clinical program. Review of the efficacy and safety data of the particular investigators' site did not show any suspicious trends.

Pediatric Considerations
Alcon included children 12 years and older in the studies that were submitted with the NDA. 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 NDA Alcon 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 Alcon was advised by the Division that no additional studies should be conducted in pediatric subjects until there were data to support safety of the product in older subjects. Alcon assured the Division that there were no ongoing or planned pediatric studies with the product. If Alcon is able to develop a viable olopatadine nasal spray product for the treatment of allergic rhinitis, the lower age bound would be largely limited by the suitability of the use of the device in young children. Given prior precedence with other similar drugs, the lower age bound could be as low as 2 years. As for the existence of the disease, 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).

Product Name
The trade name Patanase was reviewed by the DMETS of ODS and found to be acceptable. On October 5, 2005, a law firm submitted a petition to the Agency asking us to refrain from accepting the proposed trade name Patanase. They state the proposed trade name is confusingly similar to many other products and can lead to medication errors. Office of Regulatory Policy is reviewing the petition and will bring up the issue with DMETS. At this time the issue raised in the petition is not relevant because the application will not be approved.

Labeling
Detailed labeling review was not done because the application will not be approved.

Action
Alcon has not submitted adequate data to support approval on Patanase Nasal Spray for treatment of symptoms of SAR (b) (4). Submitted data show that the product is unsafe for use (b) (4). The action on this application will be NOT APPROVABLE.

The following sections expand on the deficiencies and lays out a path that Alcon may follow to support approval of the product.

Data submitted by Alcon show that Patanase Nasal Spray is unsafe for use under labeled conditions (21 CFR 314.125(b)(3)). Patanase Nasal Spray caused nasal irritation and damage to the nasal mucosa. In the clinical studies there were unacceptably high frequencies of nasal septal perforation, nasal ulceration, and epistaxis in the drug treated group as well as the vehicle nasal spray treated group. Preclinical data showed that povidone, an excipient in the formulation, was markedly irritating to the nasal mucosa, as manifested by olfactory epithelial degeneration and turbinate epithelial vaculation in rat studies. There is no NOAEL for the proposed human dose. Therefore, the use of

povidone in the proposed commercial formulation may be, in part or wholly, responsible for the nasal irritation and damage to the nasal mucosa. To support the approval of olopatadine as a nasal spray product for treatment of symptoms of SAR (b) (4), Alcon will need to reformulate the drug product to either eliminate povidone from the formulation or reduce the concentration of povidone, and conduct studies to show that the reformulated product is safe for use.

(b) (4)

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

/s/

Badrul Chowdhury
10/27/2005 12:14:20 PM
MEDICAL OFFICER