CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-861s000

MEDICAL REVIEW(S)

CLINICAL TEAM LEADER REVIEW

Application Type	NDA
Submission Number	21-861
Submission Code	N-000 AZ
Letter Date	9/26/07
Stamp Date	9/26/07
PDUFA Goal Date	3/27/08
Reviewer Name	Charles E. Lee, M.D.
Review Completion Date	3/25/08
Established Name	Olopatadine HCl
(Proposed) Trade Name	Patanase® (olopatadine HCl) Nasal Spray
Therapeutic Class	H_1-receptor antagonist, antihistamine
Applicant	Alcon Research, Ltd.
Priority Designation	Standard
Formulation	Nasal spray solution
Dosing Regimen	2 sprays per nostril twice daily
Indication	(b) (4) treatment of the symptoms of seasonal allergic rhinitis
Intended Population	Adults and children 12 years of age and older

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1 EXECUTIVE SUMMARY

Study C-04-70 supports the efficacy and safety of olopatadine 0.6% nasal spray. Evidence of efficacy is provided by the primary efficacy endpoint and secondary efficacy endpoints. The study provides evidence of end-of-dosing interval efficacy. Data from the (b) (4). Adverse events are similar to those associated with non-corticosteroid intranasal sprays approved for the SAR indication. Other safety endpoints also do not identify a safety signal.

Onset of action was not replicated using an analysis of the percent change from baseline in instantaneous TNSS values at each time point in Studies C-02-10 and C-02-37. Both of these studies clearly showed that olopatadine 0.6% nasal spray was statistically superior to vehicle placebo for both percent change from baseline in reflective and instantaneous TNSS over the entire treatment period and for both absolute change from baseline in reflective and instantaneous TNSS over the entire treatment period. The sponsor's analysis of percent change from baseline in reflective TNSS with morning and evening scores averaged for each day of treatment resulted in an onset of action after one day of dosing, which was replicated in both studies. Of the two analyses, instantaneous TNSS and reflective TNSS, the onset of action based on the reflective TNSS provides a more accurate and informative description for the practitioner and should be the analysis reflected in the product label.

There were 1,491 patients 12 years of age and older exposed to olopatadine 0.6% nasal spray, which included 514 males and 978 females. Patients were largely female, Caucasian, and from 12 to less than 65 years of age. Adverse events occurring more commonly in olopatadine nasal spray than placebo and at a frequency greater than 2% in 2-week seasonal allergic rhinitis efficacy and safety studies included bitter taste, headache, epistaxis, pharyngolaryngeal pain, postnasal drip, cough, and urinary tract infection. Similar adverse events were noted in two long-term safety studies in adults and children 12 years of age and older with perennial allergic rhinitis. Overall 4.0% of patients treated with olopatadine 0.6% nasal spray discontinued because of adverse events compared with 3.3% of patients treated with vehicle placebo.

The frequency of depression was greater in the olopatadine 0.6% nasal spray treatment group than vehicle placebo only in Study C-01-92. However, Study C-01-92 was the longest study in the drug development program; C-02-10, C-02-37, C-04-70 were two-week studies and only six month data were available during the review cycle for C-05-69. Given these serious adverse event findings in C-05-69, postmarketing adverse event reports for depression should be monitored closely.

Somnolence is associated with olopatadine 0.6% nasal spray at the dose proposed for marketing. The label should include the standard class labeling for activities requiring mental alertness and warnings and precautions to avoid engaging in hazardous occupations requiring mental alertness when taking olopatadine nasal spray.

Waiver of pediatric studies is warranted for patients less than 2 years of age. It is appropriate to defer pediatric studies in patients 2 to less than 12 years of age as they currently are under way in response to a Written Request. The NDA submission includes studies in pediatric patients 12 to less than 18 years of age and therefore meets the pediatric study requirement for this group.

2 CONTENTS OF REVIEW

This review is intended to supplement Dr. James Kaiser's primary clinical review for Patanase (olopatadine HCl) Nasal Spray [Medical Officer Review, James Kaiser, M.D., NDA 21-861 N-000 AZ, 9/26/07]. It includes a review of 2-week clinical efficacy and safety study in adults and children 12 years of age and older with seasonal allergic rhinitis, addresses onset of action in clinical efficacy and safety studies, provides additional detail and clarification of safety information, and addresses the Pediatric Research Act requirements. The review provides support for efficacy and safety information in the drug label that was not addressed by the primary clinical review.

3 CLINICAL STUDY REVIEW

3.1 C-04-70: Safety and efficacy study of olopatadine hydrochloride nasal spray 665 mcg versus olopatadine nasal spray vehicle versus Astelin in treatment of seasonal allergic rhinitis.

Study initiated: May 11, 2005
Study completed: October 19, 2005
Study report dated: April 11, 2006
[Module 5, Volume 25, page 1; Module 5, Volume 28, page 1149]

3.1.1 Summary and reviewer's conclusion of study results

This study is a randomized, active- and vehicle-controlled, parallel group, three-arm, multicenter, Phase 3 clinical study of patients with seasonal allergic rhinitis. The study had a two-week double blind treatment period. The objectives of this study were to describe the efficacy and safety of olopatadine HCl 0.6% nasal spray when compared to olopatadine vehicle placebo nasal spray and azelastine HCl 0.1% nasal spray.

The primary efficacy endpoint was the percent change from baseline in the reflective TNSS. The difference from vehicle placebo in the percent change from baseline was -8.4% for olopatadine 0.6% and -11.5% for azelastine 0.1%. These values were statistically significant for olopatadine 0.6% (p 0.0026); a p value was not calculated for azelastine 0.1%. An additional primary analysis based on the mean change from baseline in the reflective TNSS also showed statistical superiority of olopatadine 0.6%. The effect size for the olopatadine 0.6% was 6.7% and the effect size for azelastine 0.1% was 8.3%, in the range expected for antihistamine drug products. Both olopatadine 0.6% and azelastine 0.1% were superior to vehicle placebo for percent change from baseline in the instantaneous TNSS, which provides evidence of end-of-dosing interval efficacy. Data

for individual symptom scores provides supportive evidence for the efficacy of olopatadine 0.6% and azelastine 0.1% for treatment of the seasonal allergic rhinitis symptoms of runny nose, stuffy nose, itchy nose, and sneezing. Both olopatadine 0.6% and azelastine 0.1% were superior to vehicle placebo for treatment of itchy eyes and watery eyes associated with seasonal allergic rhinitis. Patients treated with olopatadine 0.6% and patients treated with azelastine 0.1% had mean decreases of 0.4 and 0.3, respectively, in the (b) (4) Overall score compared to vehicle placebo. (b) (4)

Exposure to study drug was adequate to allow for assessment of safety. There were 30.0% (54/180) of patients treated with olopatadine 0.6% who had adverse events, compared with 40.4% (76/188) of patients treated with azelastine 0.1% and 21.6% (38/176) of patients treated with vehicle placebo. The most frequent adverse events for olopatadine 0.6% included taste perversion, headache, rhinitis, epistaxis, fatigue, and infection. There were no deaths in this study. One patient treated with azelastine 0.1% had a serious adverse event of appendicitis. There were no other serious adverse events in this study.

There were 12 patients (2.2%, 12/544) who withdrew from the study due to adverse events during the study treatment period. Of these 12 patients, five were treated with olopatadine 0.6%, two were treated with azelastine 0.1%, and five were treated with vehicle placebo. Taste perversion, headache, and pharyngitis resulted in the withdrawal of two patients each in the olopatadine 0.6% group; there were no withdrawals for these adverse events in the azelastine 0.1% and vehicle placebo groups. Safety data from vital signs, physical examinations, and nasal examinations did not identify a safety signal.

In summary, this study supports the efficacy and safety of olopatadine 0.6% nasal spray. Evidence of efficacy is provided by the primary efficacy endpoint and secondary efficacy endpoints. The study provides evidence of end-of-dosing interval efficacy. Data from the (b) (4) Adverse events are similar to those associated with non-corticosteroid intranasal sprays approved for the SAR indication. Other safety endpoints also do not identify a safety signal.

3.1.2 Objective

The objectives of this study were to describe the efficacy and safety of olopatadine HCl 0.6% nasal spray when compared to olopatadine vehicle placebo nasal spray and azelastine HCl 0.1% nasal spray [Module 5, Volume 25, page 76].

3.1.3 General study design

This study is a randomized, active- and vehicle-controlled, parallel group, three-arm, multicenter, Phase 3 clinical study of patients with seasonal allergic rhinitis. Approximately 850 patients were to be screened with approximately 480 patients to be randomized to study treatment. There were 728 patients actually screened and 544

patients were actually randomized. Approximately 20 study centers were to participate in the study. There were 20 study centers that actually participated [Module 5, Volume 25, page 72; Module 5, Volume 27, page 961].

3.1.4 Inclusion criteria

Inclusion criteria for enrollment included [Module 5, Volume 25, pages 82-85]:

1. At least a two-year history of non-recalcitrant seasonal allergic rhinitis during the fall or spring allergy season
2. Allergy to a current prevalent seasonal allergen that is present at the time of enrollment, defined by positive case history and positive skin prick test and/or intradermal test for a fall allergen within the one year prior to Visit 1
3. A sum of the AM and PM reflective scores of the TNSS for three of the four days prior to randomization must be least 36 out of the possible 72
4. The patient or guardian must be willing and able to give written informed consent.
5. Patients must be age 12 years or older.
6. Patients must be willing and able to attend required study visits.
7. Patients must be able to follow instructions.
8. Women of childbearing potential may participate only if they are not lactating, if they have a negative pregnancy test prior to study entry, and if they agree to use adequate birth control methods to prevent pregnancy.
9. Nasal examination must confirm the absence of significant anatomic abnormalities, infection, bleeding, and mucosal ulcerations.
10. Patients must observe the following drug washout times prior to enrollment (Table 1). Other drugs were only permitted if they are not expected to interfere with the ability of patients to participate in the study.

Table 1 Drug washout times [Module 5, Volume 25, pages 84-85]

Drug or treatment	Washout prior to Visit 1
Allergen immunotherapy	2 years
Systemic corticosteroids	30 days
Inhaled or ocular corticosteroids	30 days
Nasal corticosteroids	14 days
Nasal or inhaled ipratropium bromide, nedocromil, or cromolyn	14 days
Leukotriene pathway modifiers, systemic or topical anticholinergics	14 days
Oral or systemic antibiotics	14 days
Loratadine, desloratadine, levocabastine	14 days
Drugs that may prolong QT interval	14 days
Chlorpheniramine, clemastine, brompheniramine, hydroxyzine, azatadine, azelastine nasal spray	7 days
Ocular antiallergy medications	7 days
Topical nasal decongestants	7 days
Oral decongestants, diphenhydramine, cetirizine, fexofenadine, promethazine, cyproheptadine, triprolidine, acrivastine	3 days
NSAIDS, prn use	3 days
Aspirin, except low dose use of cardiac prophylaxis	3 days
Nasal saline and/or ocular saline	1 days

3.1.5 Exclusion criteria

Patients with the following exclusion criteria could not be enrolled [Module 5, Volume 25, pages 84-85]:

1. Rhinitis medicamentosa, obstructive nasal polyposis, or other aberration of nasal anatomy that could interfere with the investigation or evaluation of study medication or participation in the study
2. History of concurrent chronic sinusitis
3. Asthma, with the exception of mild intermittent asthma
4. Nasal congestion capable of interfering with successful nasal drug administration
5. Use of prohibited medications or inadequate washout of prohibited medications
6. Known non-responder to antihistamines for symptoms of seasonal allergic rhinitis
7. Chronic or intermittent use of inhaled, oral, intramuscular, intravenous, or potent or super-potent topical corticosteroids
8. Chronic use of long acting antihistamines and other concomitant medications (e.g., tricyclic antidepressants) that would affect assessment of the effectiveness of study drugs
9. Any systemic disorder that could interfere with the evaluation of study medications
10. History of or ongoing clinically relevant electrolyte abnormalities
11. Any ocular disorder other than allergic conjunctivitis which could interfere with evaluation of the study medication
12. Use of allergen immunotherapy within the past two years
13. Hypersensitivity to study drug or to any component of the test articles
14. History of drug or alcohol abuse
15. History of severe or uncontrolled cardiovascular, hepatic, renal, and/or other disease/illness that could be expected to interfere with the study
16. Clinically significant abnormal 12-lead ECG findings at Visit 1 as determined by the investigator
17. Upper or lower respiratory tract infection within 14 days of Visit 1
18. Diagnosis of acute sinusitis within 30 days of Visit 1
19. History, or evidence, of nasolacrimal drainage system malfunction
20. Planned travel outside of the study area for more than 48 hours of the study period
21. Study site staff or relatives of study site staff or other individuals who would have access to the clinical study protocol
22. Any patient that received test article treatment in any previous Alcon olopatadine nasal spray clinical trial
23. Participation in any other investigational study within 30 days before entry into this study or concomitantly with this study
24. The need for chronic or intermittent use of any nasal spray during the study period
25. Change in bottle weight outside the range stated in the protocol
26. Clinically abnormal vital signs

3.1.6 Protocol Amendments

There was one three protocol amendment, dated September 1, 2005. It allowed participation of patients with both fall and spring seasonal allergic rhinitis, changed the protocol-specified bottle weight ranges, and made minor editorial corrections. There were 71 patients enrolled in the study at the time of the amendment [Module 5, Volume 25, page 102].

Reviewer comment:
Ideally, the study should have been completed over one allergy season. The protocol amendment should not have a great impact the outcome of the study.

3.1.7 Study procedures

This was a randomized, active- and placebo-controlled, parallel group, three-arm, multicenter Phase 3 clinical study of patients with SAR. Approximately 850 patients were to be screened so that approximately 480 patients would complete that study at up to 20 centers. Patients were to have a positive case history and positive skin test to a prevalent fall or spring seasonal aeroallergen. There was a run-in period of four to 14 days during which patients received single blind vehicle placebo nasal spray. Patients were to have a minimum qualifying score for entry into the study. The sum of all AM and PM reflective TNSS for three of the four consecutive calendar days prior to randomization was to be at least 36 out of a maximum possible score of 72 [Module 5, Volume 25, pages 2, 77-79, 62].

Enrolled patients were randomized to either 0.6% olopatadine HCl nasal spray or azelastine HCl nasal spray 0.1%, or olopatadine vehicle nasal spray placebo for the 2-week treatment course. Patients evaluated the severity of symptoms of SAR twice daily during the study period. Symptoms assessed for severity are listed in Table 2. Patients were to assess the severity of their symptoms on the four-point, 0-3 scale, displayed in Table 3. Symptom assessments were both reflective of severity since their last symptom assessment and instantaneous. Patients recorded their assessments with an electronic personal digital assistant system (PDA). Symptoms were assessed twice daily prior to taking study medication—each morning upon awakening and each evening at bedtime. Patients also recorded study drug use in the PDA. Patients were required to attend four study visits (Screening, Randomization, Telephone Assessment, and Exit Visit) during the course of the study [Module 5, Volume 25, pages 77, 79, 91]. A Total Nasal Symptom Score (TNSS) was calculated based on the sum of scores for runny nose, itchy nose, stuffy nose and sneezing. Itchy eyes and watery eyes were not part of the TNSS. A reflective TNSS was calculated from patients' reflective diary recordings and an instantaneous TNSS was calculated from patients' instantaneous diary recordings. Patients were issued a Medical Problems Log to record any medical problems [Module 5, Volume 25, pages 80, 93, 167].

Table 2 Symptoms of allergic rhinitis assessed by patients, C-04-70 [Module 5, Volume 25, page 93]

Runny nose
Itchy nose
Stuffy nose
Sneezing
Itchy eyes
Watery eyes

Table 3 Scale for assessment of allergic rhinitis symptoms, C-04-70 [Module 5, Volume 25, page 93]

Score	Definition
0 = Absent	No sign/symptom is evident
1 = Mild	Sign/symptom clearly present, but minimal awareness; easily tolerated
2 = Moderate	Definite awareness of sign/symptom that is bothersome but tolerable
3 = Severe	Sign/symptom that is hard to tolerate; causes interference with activities or daily living and/or sleeping

This study used the following patient recorded outcome instruments: The (b) (4) the Treatment Satisfaction Questionnaire for Medication (TSQM), and the Allergy Visual Analog Scale (AVAS). The (b) (4) is described below; the TSQM and AVAS are not addressed in this review.

(b) (4)

The TSQM is a patient self-administered instrument for evaluating treatment satisfaction for medication. It was developed to permit comparisons across medication types and patient conditions. It is a 14-item questionnaire comprised of four domains, including Effectiveness, Side Effects, Convenience, and Global Satisfaction. (b) (4). holds the copyright for the TSQM [Module 5, Volume 25, page 256].[5]

The AVAS is a numeric indicator of health status in allergy. Patients indicate the state of their allergy problem on a 1 to 100 visual analog scale [Module 5, Volume 25, page 261].

Reviewer comments:

(b) (4)

The TSQM is reported to be validated but there has been no MID established.[6] *This instrument will not support a labeling claim and will not be reviewed. The AVAS is not validated and has no MID. It will also not be reviewed in this document.*

Adverse events were elicited by study staff and as observations by the study investigator. Adverse events were also recorded by patients in a Medical Problems Log [Module 5, Volume 25, pages 80, 94]. Physical exams were to be performed at baseline and at Visit 4. Vital signs and nasal examinations were to be performed at screening, baseline, and Visit 4 [Module 5, Volume 25, page 79].

An outline of the study procedures is displayed in Table 4.

Table 4 Study outline, C-02-37 [Module 5, Volume 25, page 7479

Activity	**Visit 1 Screening**	**Visit 2 Baseline**	**Visit 3 Phone**	**Visit 4 Exit**
	Clinic	**Clinic**	**Telephone call**	**Clinic**
	Day –14 to -4	**Day 0**	**Day 7**	**Day 16 or discontinuation**
Informed consent	X			
Inclusion/exclusion criteria	X	X		
Medical and medication history	X			
Skin test	X			
Nasal exam	X	X		X
Physical exam	X			X
Adverse events	X	X	X	X
Dispense study medications	X	X		
Vital signs	X	X[a]		Xa
Dispense diary card	X	X		
Symptom severity assessment	X		X[a, b]----------X[b]	
(b) (4)		X		X
AVAS				
TSQM				X
Collect and weigh study medication		X		X

[a]Prior to administration of study drug
[b]Twice daily during treatment period

3.1.8 Study medication

All patients received nasal spray vehicle placebo twice daily during the single blind, run-in period of the study. At Visit 2, patients were randomized to one of the following three study treatments in a 1:1:1 ratio for the double blind treatment period of the study [Module 5, Volume 25, pages 88-90]:

- Olopatadine 0.6% nasal spray twice daily (2.66 mg olopatadine HCl twice daily or 2.4 mg olopatadine free base twice daily)
- Azelastine 0.1% nasal spray twice daily (0.548 mg azelastine HCl twice daily)

- Nasal spray vehicle placebo twice daily

Patients were to take the study medication in the morning after they completed the symptom severity assessments [Module 5, Volume 25, page 93].

Olopatadine nasal spray and vehicle placebo study treatment were packaged in white, 30 mL HDPE plastic bottles with a white metered dose manual spray pump, white nasal adapter, and a blue dust cover. Each bottle contained a minimum fill of 30 mL of study treatment, providing 240 sprays. The nominal volume delivered was 0.1 mL/spray. Olopatadine nasal spray and vehicle placebo nasal spray were in physically identical bottles to preserve blinding. Azelastine nasal spray 0.1% was packaged in a white, 30 mL HDPE plastic bottle with a white plastic metered-dose spray tip and white nasal adapter. As delivered to the site, a foil overwrap covered the entire package to disguise the shape and appearance of the bottle, pump, and nasal adapter, and left only the applicator tip exposed. [Module 5, Volume 25, pages 88-90]. Lot numbers of study treatment are displayed in Table 5.

Olopatadine 0.6% nasal spray and vehicle placebo nasal spray drug products both contained povidone (b) (4). The to-be marketed formulation of olopatadine 0.6% nasal spray drug product does not include povidone.

Table 5 Study treatment lots used in C-02-37 [Module 2, Volume 2, page 2; Module 5, Volume 25, pages 88, 90]

Study treatment	Lot number	Formulation identification
Olopatadine 0.6% nasal spray	04-6001135-1	103718
Azelastine nasal spray 0.1%	05-500690-1 05-500731-1	100550 100550
Vehicle placebo	04-600133-1	103784

3.1.9 Assessment of compliance

Patients were required to enter the time of dosing in their PDA. Study centers weighed bottles of test medication at each visit. Patient bottles of study treatment were weighed at each visit. Bottle weight data from the randomization and exit visits were analyzed to assess compliance over the study period. The difference in bottle weights from screening to the randomization visit was used as a criterion for randomization. Patients whose bottle weights fell outside an expected range for duration of treatment during the 3- to 21-day run-in period were not randomized and discontinued from the study. In addition to PDA entries, bottle weight data were used to assess compliance over the treatment period [Module 5, Volume 25, pages 91-92].

3.1.10 Pollen counts

Pollen counts were performed daily by study staff or by a counting station in the community. Pollen counts were started one week before the first patient was screened until approximately one week after the last patient completed the study. The amount of daily rainfall was also recorded [Module 5, Volume 25, page 96].

3.1.11 Efficacy endpoints

Efficacy endpoints for this study are described below.

3.1.11.1 Primary efficacy endpoint

The primary efficacy endpoint was the percent change from baseline in the reflective TNSS, which was defined as the average of the AM and PM reflective severity scores for the patients' assessments of runny nose, stuffy nose, itchy nose, and sneezing, averaged across all days [Module 5, Volume 25, page 100].

3.1.11.2 Secondary efficacy endpoints

There were three secondary efficacy endpoints in this study [Module 5, Volume 25, page 100]. They were:

- Percent change from baseline in the AM and PM individual severity scores for patient diary symptoms (reflective) of itchy eyes averaged across all days
- Percent change from baseline in the AM and PM individual severity scores for patient diary symptoms (reflective) of watery eyes, averaged across all days
- (b) (4)

3.1.11.3 Exploratory efficacy endpoints

Exploratory efficacy endpoints and other patient-recorded outcomes are listed below [Module 5, Volume 25, pages 93, 101-102]

- The percent change from baseline in the instantaneous TNSS, defined as the average of the AM and PM instantaneous severity scores for the patients' assessments of runny nose, stuffy nose, itchy nose, and sneezing, averaged across all days
- Changes from baseline in the AM and PM individual severity scores for patient diary symptoms (reflective and instantaneous) of runny nose, stuffy nose, itchy nose, and sneezing, averaged across all days
- Changes from baseline in the AM and PM individual severity scores for patient diary symptoms (instantaneous) of itchy eyes and watery eyes, averaged across all days
- Mean TSQM scores
- Mean change from baseline in AVAS scores

3.1.12 Safety variables

Adverse events, both volunteered and elicited, were collected at study visits. ECGs were performed at the screening visit. Vital signs and a nasal examination were performed at the screening visit, the randomization visit, and at the final visit. Any clinically significant change from baseline in vital signs, physical examination, and nasal examination were reported as an adverse event [Module 5, Volume 25, pages 80, 93, 16].

3.1.13 Statistics

Statistical considerations in this study follow below.

3.1.13.1 Datasets analyzed

All patients who received study drug and had at least one on-therapy visit were included in the intent-to-treat (ITT) analysis. The ITT analysis was the primary statistical analysis. Last observation carried forward was used to fill incomplete data due to a missed diary entry. All patients who receive randomized drug and meet inclusion and exclusion criteria were evaluated in the per protocol (PP) analysis. All patients who received study drug were evaluated in the safety analysis [Module 5, Volume 25, pages 99, 110].

3.1.13.2 Statistical power

The applicant calculated that 160 evaluable patients per treatment group, for a total of 480 patients, would have a 90% power to detect a 10.0% difference in the TNSS change from baseline between the olopatadine and vehicle placebo treatment groups. The applicant assumes a standard deviation of 27.36% and a 0.05 level of significance with two-sided tests [Module 5, Volume 25, page 102].

3.1.13.3 Statistical analyses

The applicant used a two sample t-test to compare changes from baseline between treatment groups for the primary and secondary efficacy endpoints [Module 5, Volume 47, page 81]. Hommel's correction was used to address multiple comparisons among secondary efficacy endpoints [Module 5, Volume 25, page 271].

The primary comparison was olopatadine nasal spray and vehicle placebo using a superiority analysis. An active control, azelastine nasal spray 0.1%, was included to enable a comparison to an approved product. The study was not powered for formal non-inferiority analysis, but the sponsor specified that non-inferiority would require that the upper 95% confidence limit for the difference between olopatadine and azelastine nasal sprays would be less than 10%. The sponsor estimated that the 10% value represents approximately 50% of the difference between azelastine nasal spray and vehicle placebo nasal spray, based on data in the Astelin Nasal Spray summary basis of approval [Module 5, Volume 25, page 1010].

3.1.14 Results

Results of the study are reviewed below.

3.1.14.1 Patient disposition

The protocol called for 850 evaluable patients to be screened. A total of 728 patients were actually screened and 544 were enrolled and randomized to treatment. There were 544 patients in the ITT group. Table 6 summarizes patient disposition [Module 5, Volume 25, pages 103-106].

Table 6 Patient disposition, C-04-70 [Module 5, Volume 47, pages 103-108]

	Vehicle placebo n (%)	**Olopatadine NS, 0.6% n (%)**	**Azelastine NS, 0.1% n (%)**	**Total n (%)**
Patients screened	--	--	--	728
Patients failing screening	--	--	--	184
Patients randomized	176 (100)	180 (100)	188 (100)	544 (100)
Patients discontinued	13 (7.4)	12 (6.7)	8 (4.3)	33 (6.1)
Adverse event	5 (2.8)	5 (2.8)	2 (1.0)	12 (2.2)
Patient decision	1 (0.6)	1 (0.6)	0 (0.5)	2 (0.4)
Treatment failure	0 (1.6)	1 (0.6)	2 (1.0)	3 (0.6)
Protocol violation	4 (2.3)	5 (2.8)	3 (1.6)	12 (2.2)
Other	3 (1.7)	0 (0)	1 (0.5)	4 (0.7)
Patients in ITT analysis	176	180	188	544
Patients excluded from ITT analysis	0	0	0	0
Patients in PP analysis	161	167	166	504
Patients excluded from PP analysis	15	13	12	40
Patients in safety analysis	176	180	188	728*
Patients excluded from safety analysis	0	0	0	0

*includes 184 screening failures

There were 33 patients that discontinued from the study (Table 6). Adverse events and protocol violations were the most common reason for discontinuation from the study, however, the incidence of discontinuation was low. The incidence of discontinuations due to adverse events was similar among the treatment groups. The proportion of patients discontinuing for other reasons was also similar among the treatment groups [Module 5, Volume 25, page 108].

Protocol deviations occurred in 8.5% of vehicle placebo patients, 3.6% of olopatadine 0.6% patients, and 6.4% of azelastine 0.1% patients. The most common protocol deviation was use of excluded concomitant medication [Module 5, Volume 25, page 109]. The types of protocol deviations occurred were similarly distributed among treatment groups. These data are summarized in Table 7.

Table 7 Protocol deviations, C-04-70 [Module 5, Volume 47, page 91; NDA 21-861, N-000 BZ, 5/2/05, Biostatistics report C-02-37, page 6-9]

	Vehicle placebo N = 176 n (%)	**Olopatadine NS, 0.6% N = 180 n (%)**	**Azelastine NS, 0.1% N = 188 n (%)**	**Total N = 544 n (%)**
All protocol deviations	15 (8.5)	13 (3.6)	12 (6.4)	40 (7.4)
Inclusion criteria	2 (1.1)	3 (0.8)	1 (0.5)	8 (1.5)
Visit out of window	1 (0.6)	1 (0.3)	1 (0.5)	3 (0.6)
Exclusion criteria	11 (6.2)	9 (2.5)	7 (3.7)	5 (0.9)
Broken blind	1 (0.6)	0 (0)	1 (0.5)	1 (0.2)

3.1.14.2 Demographic and background characteristics

There were more females than males in the study. The population studied was largely of Caucasian race. Patients of Black and Hispanic races were represented at proportions fairly comparable to that of the general population. The mean age of patients in the study was 35.9 years. The large majority of patients ranged from 13-64 years of age. Patients greater than 64 years of age represented 1.3% of the total study population [Module 5, Volume 25, pages 95-96]. These data are displayed in Table 8.

Table 8 Demographics, C-02-37 [Module 5, Volume 47, pages 95-96]

Characteristic	Vehicle placebo N = 176	Olopatadine NS, 0.6% N = 180	Azelastine NS, 0.1% N = 188	Total N = 544
Gender	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Male	61 (34.7)	52 (28.9)	62 (33.0)	175 (32.2)
Female	115 (65.3)	128 (71.1)	126 (67.0)	369 (67.8)
Race	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Caucasian	133 (75.6)	136 (75.6)	141 (75.0)	410 (75.4)
Black	18 (10.2)	19 (10.6)	25 (13.3)	62 (11.4)
Asian	2 (1.1)	2 (1.1)	0 (0)	4 (0.7)
Hispanic	23 (13.1)	22 (12.2)	21 (11.2)	66 (12.1)
Other	0 (0)	1 (0.6)	1 (0.5)	2 (0.4)
Age, years				
Mean age	36.6	35.7	35.4	35.9
SD	13.1	12.8	12.9	12.9
Range	12-77	12-70	12-77	12-77
Age subgroups, years	**n (%)**	**n (%)**	**n (%)**	**n (%)**
0-12	5 (2.8)	5 (2.8)	3 (1.6)	13 (2.4)
13-64	169 (96.0)	172 (95.6)	183 (97.3)	524 (96.3)
>64	2 (1.1)	3 (1.7)	2 (1.1)	7 (1.3)

3.1.14.3 Compliance

The applicant assessed compliance based on bottle weights during the double blind treatment phase of the study. The applicant calculated a range of acceptable bottle weight ranges by days of therapy, assuming eight sprays per day, 0.101 g/spray, and 5 priming sprays per bottle. Compliance based on bottle weight data is provided in Table 9. The frequency of acceptable compliance ranged from approximately 75-80% overall. The frequency of acceptable compliance was similar among the individual treatment groups [Module 5, Volume 47, pages 73, 102-103].

Table 9 Compliance, bottle weight data, C-04-70 [Module 5, Volume 25, page 125]

Treatment	Total N	Below range n (%)	Acceptable n (%)	Above range n (%)
All patients	542	170 (31.4)	362 (66.8)	10 (1.8)
Olopatadine 0.6%	179	62 (34.6)	110 (61.5)	7 (3.9)
Azelastine 0.1%	187	61 (32.6)	124 (66.3)	2 (1.1)
Vehicle placebo	176	47 (26.7)	128 (72.7)	1 (0.6)

Two patients had missing bottle weights.

Reviewer comment:
The observed frequency of acceptable compliance with study treatment is less than ideal. There is an adequate degree of compliance to address efficacy and to provide safety information, however. It is interesting that there are more patients with bottle weights below the acceptable for the olopatadine and azelastine nasal spray treatment groups than for the vehicle placebo treatment group. It is possible that this may reflect the bad taste of the active treatment and active control drug products.

3.1.14.4 Pollen counts

Pollen counts were performed daily by study staff or by a counting station in the community. Pollen counts were started one week before the first patient was screened until approximately one week after the last patient completed the study. The amount of daily rainfall was also recorded [Module 5, Volume 25, page 96]. The vast majority of patients were dosed with study medication during times when fall seasonal aeroallergens were at a moderate to high level in the environment; only a few patients were dosed during the spring aeroallergen season Module 5, Volume 25, page 264-268].

Reviewer comment:
The pollen counts were at levels high enough to allow for an adequate assessment of efficacy.

3.1.14.5 Efficacy outcomes

Efficacy outcomes for this study are reviewed below.

3.1.14.5.1 Primary efficacy endpoint

The primary efficacy endpoint was the percent change from baseline in the reflective TNSS, which was defined as the average of the AM and PM reflective severity scores for the patients' assessments of runny nose, stuffy nose, itchy nose, and sneezing, averaged across all days [Module 5, Volume 25, page 100].

Results for the primary efficacy endpoint for the comparison of olopatadine 0.6% nasal spray and vehicle placebo nasal spray are summarized in Table 10. Baseline reflective TNSS values were similar among the treatment groups. There were two patients excluded because of missing data at study visits [Module 5, Volume 25, page 131-132]. The difference from vehicle placebo in the percent change from baseline was -8.4% for olopatadine 0.6%. This value was statistically significant for olopatadine 0.6% ($p < 0.0026$) [Module 5, Volume 25, page 129].

Table 10 Primary efficacy endpoint, percent change in reflective TNSS over treatment period, ITT group, C-04-70 [Module 5, Volume 25, pages 129, 145]

	Vehicle placebo **n = 175**	**Olopatadine NS, 0.6%** **n = 179**	**Azelastine NS, 0.1%** **n = 188**
Baseline (SD)	8.4 (1.6)	8.8 (1.7)	8.8 (1.7)
Treatment Period (SD)	6.7 (2.2)	6.4 (2.6)	6.2 (2.8)
Percent change from baseline (SD)	-18.4 (25.6)	-26.8 (26.9)	-29.9 (27.4)
Difference from vehicle placebo, percent change from baseline	--	-8.4	-11.5
p value	--	0.0026	Not calculated

The applicant also provided an additional primary analysis based on the mean change from baseline in the reflective TNSS. These data are summarized in Table 11. The difference from vehicle placebo in the change from baseline was -0.8 for olopatadine 0.6% and -1.0% for azelastine 0.1%. These values were statistically significant for olopatadine 0.6% (p = 0.0021) [Module 5, Volume 25, page 132].

Table 11 Additional analysis, mean change in reflective TNSS over treatment period, ITT group, C-04-70 [Module 5, Volume 25, pages 132, 245]

	Vehicle placebo **n = 175**	**Olopatadine NS, 0.6%** **n = 179**	**Azelastine NS, 0.1%** **n = 188**
Baseline (SD)	8.4 (1.6)	8.8 (1.7)	8.8 (1.7)
Treatment Period (SD)	6.7 (2.2)	6.4 (2.6)	6.2 (2.8)
Percent change from baseline (SD)	-1.6 (2.2)	-2.4 (2.4)	-2.6 (2.3)
Difference from vehicle placebo, change from baseline	--	-0.8	-1.0
Effect size	--	6.7%	8.3%
p value	--	0.0021	Not calculated

* Effect size = $\frac{\text{Difference from vehicle placebo, change from baseline} \times 100}{\text{Maximum change from baseline} = 12}$

Reviewer comment:
These data provide convincing evidence of efficacy for olopatadine 0.6%. This study was powered to detect a 10% difference in the percent change from baseline in reflective TNSS between the olopatadine and vehicle placebo treatment groups with 160 patients per treatment group. The applicant has demonstrated a highly statistically significant difference from placebo with a slightly smaller degree of efficacy and a slightly larger treatment group. The 6.7% effect size for the olopatadine 0.6% is in the range expected for antihistamine drug products. The additional analysis provides evidence that the degree of efficacy is clinically relevant. Azelastine 0.1% was numerically superior to olopatadine 0.6% in difference from placebo in both mean change from baseline and percent change from baseline. An inferential analysis of the comparison of azelastine 0.1% and placebo was not performed.

3.1.14.5.1.1 Subgroup analyses of primary efficacy endpoint

Patients 12 years of age and older were enrolled in the study. The difference from vehicle placebo in percent change from baseline in the reflective TNSS over the study treatment period for patients 12 to 17 years of age was similar to patients 13 to 64 years of age. Patients 12 to 17 years of age represented 2.4% (13/544) of the study population [Module

5, Volume 25, pages 95-96, 274]. The difference from vehicle placebo in percent change from baseline in the reflective TNSS over the study treatment period for patients greater than 64 years of age appeared to be greater than that for all patients, but there were few patients in the study who were greater than 64 years of age (7/544, 1.3%) [Module 5, Volume 25, pages 95-96 274].

The difference from vehicle placebo in percent change from baseline in the reflective TNSS over the study treatment period for olopatadine 0.6% in women was somewhat greater than that for men, however, olopatadine 0.6% was numerically superior to vehicle placebo for both genders [Module 5, Volume 25, page 277].

Olopatadine 0.6% was superior to vehicle placebo for patients of Caucasian, Black, Hispanic, and Asian races for difference from vehicle placebo in percent change from baseline in the reflective TNSS over the study treatment period. There were too few patients of other races to assess efficacy in these subgroups [Module 5, Volume 25, pages 279-280].

Reviewer comment:
There are too few patients in the racial subgroups to draw firm conclusions based on these data.

3.1.14.5.2 Secondary efficacy endpoints

There were three secondary efficacy endpoints in this study [Module 5, Volume 25, page 100]. They were:

- Percent change from baseline in the AM and PM individual severity scores for patient diary symptoms (reflective) of itchy eyes averaged across all days
- Percent change from baseline in the AM and PM individual severity scores for patient diary symptoms (reflective) of watery eyes, averaged across all days
- (b) (4)

These secondary efficacy endpoints are reviewed below.

3.1.14.5.2.1 Percent change from baseline for reflective itchy eye and watery eye scores

The percent change from baseline in the reflective individual severity scores for patient diary symptoms of itchy eyes and watery eyes, averaged across all days are summarized in Table 12 [Module 5, Volume 25, pages 135, 137, 139, 141]. Baseline individual symptom scores for each treatment group were comparable. There was a larger change from baseline for the PM scores than for the AM scores. In addition, there was a larger change from baseline for itchy eye scores than for watery eye scores.

Table 12 Secondary efficacy endpoints, percent change in reflective itchy eye and watery eye scores over treatment period, ITT group, C-04-70 [Module 5, Volume 25, pages 135, 137, 139, 141, 147, 149, 151, 153]

	Vehicle placebo	Olopatadine NS, 0.6%	Azelastine NS, 0.1%
Itchy eyes, AM score	**n = 172**	**n = 173**	**n = 178**
Baseline (SD)	1.9 (0.7)	2.0 (0.7)	2.0 (0.7)
Treatment Period (SD)	1.6 (0.7)	1.5 (0.8)	1.5 (0.8)
Percent change from baseline	-15.4 (38.6)	-23.3 (48.2)	-22.7 (46.7)
Difference from vehicle placebo, percent change from baseline	--	-7.9	-7.3
Itchy eyes, PM score	**n = 172**	**n = 174**	**n = 178**
Baseline (SD)	2.0 (0.7)	2.0 (0.7)	2.0 (0.7)
Treatment Period (SD)	1.6 (0.7)	1.4 (0.8)	1.5 (0.8)
Percent change from baseline	-16.6 (47.6)	-27.7 (41.6)	-27.3 (41.1)
Difference from vehicle placebo, percent change from baseline	--	-11.1	-10.7
Watery eyes, AM score	**n = 162**	**n = 170**	**n = 168**
Baseline (SD)	1.7 (0.8)	1.8 (0.8)	1.8 (0.7)
Treatment Period (SD)	1.3 (0.8)	1.3 (0.8)	1.3 (0.8)
Percent change from baseline	-18.2 (60.1)	-21.1 (63.0)	-23.9 (55.9)
Difference from vehicle placebo, percent change from baseline	--	-2.9	-5.7
Watery eyes, PM score	**n = 173**	**n = 173**	**n = 167**
Baseline (SD)	1.7 (0.7)	1.8 (0.8)	1.9 (0.8)
Treatment Period (SD)	1.3 (0.8)	1.3 (0.8)	1.3 (0.8)
Percent change from baseline	-24.2 (44.5)	-29.3 (40.8)	-28.5 (50.7)
Difference from vehicle placebo, percent change from baseline	--	-5.1	-4.3

<u>Reviewer comment:</u>
These data suggests that olopatadine 0.6% may have some effect on itchy eyes and watery eyes associated with seasonal allergic rhinitis. There is a smaller effect for watery eyes than for itchy eyes. A fairly similar effect was noted for azelastine 0.1%.

(b) (4)

(b) (4)

[redacted]

3.1.14.5.3.1 Percent change from baseline in the instantaneous TNSS

Results for the percent change from baseline in the instantaneous TNSS are summarized in Table 14. Baseline instantaneous TNSS values were similar among the treatment groups. The difference from vehicle placebo in the percent change from baseline was -

8.5% for olopatadine 0.6% and -10.6% for azelastine 0.1% [Module 5, Volume 25, page 161, 203].

Table 14 Secondary efficacy endpoint, percent change in instantaneous TNSS over treatment period, ITT group, C-04-70 [Module 5, Volume 25, pages 161, 203]

	Vehicle placebo **n = 175**	**Olopatadine NS, 0.6%** **n = 179**	**Azelastine NS, 0.1%** **n = 188**
Baseline (SD)	7.3 (2.2)	7.9 (2.1)	8.0 (2.1)
Treatment Period (SD)	6.0 (2.4)	6.0 (2.7)	6.0 (2.8)
Percent change from baseline	-14.9 (30.4)	-23.4 (29.7)	-25.5 (28.9)
Difference from vehicle placebo, percent change from baseline	--	-8.5	-10.6
Derived from above data:			
Change from baseline	-1.3	-1.9	-2.6
Difference from vehicle placebo, change from baseline	--	-0.6	-1.3
Effect size*	--	5.0%	10.8%

* Effect size = $\frac{\text{Difference from vehicle placebo, change from baseline} \times 100}{\text{Maximum change from baseline} = 12}$

Reviewer comment:
Numerically, both olopatadine 0.6% and azelastine 0.1% were superior to vehicle placebo. Azelastine 0.1% was superior to olopatadine 0.6%. These data support the end of dosing interval efficacy for both olopatadine 0.6% and azelastine 0.1%.

3.1.14.5.3.2 Percent change from baseline for reflective individual severity scores

The percent change from baseline in the reflective individual severity scores for patient diary symptoms of runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes, averaged across all days are summarized in Table 15 [Module 5, Volume 25, pages 163, 165, 167, 169, 171, 173, 175, 177, 205, 207, 209, 211, 213, 215, 217, 219]. Baseline individual symptom scores for each treatment group were comparable. For the applicant's proposed concentration, olopatadine 0.6%, the difference from vehicle placebo in percent change from baseline in reflective individual severity scores ranged from -13.2% for the PM score for runny nose to -2.5% for the PM scores for stuffy nose and itchy nose.

Table 15 Secondary efficacy endpoints, percent change in reflective individual severity scores over treatment period, ITT group, C-04-70 [Module 5, Volume 25, pages 163, 165, 167, 169, 171, 173, 175, 177, 205, 207, 209, 211, 213, 215, 217, 219

	Vehicle placebo	**Olopatadine NS, 0.6%**	**Azelastine NS, 0.1%**
Runny nose, AM score	**n = 174**	**n = 178**	**n = 187**
Baseline (SD)	2.1 (0.7)	2.2 (0.6)	2.2 (0.6)
Treatment Period (SD)	1.7 (0.7)	1.6 (0.8)	1.6 (0.8)
Percent change from baseline	-12.4 (40.6)	-25.6 (33.5)	-28.8 (33.8)
Difference from vehicle placebo, percent change from baseline	--	-13.2	-16.4
Runny nose, PM score	**n = 175**	**n = 178**	**n = 187**
Baseline (SD)	2.2 (0.6)	2.3 (0.6)	2.3 (0.5)
Treatment Period (SD)	1.7 (0.7)	1.6 (0.8)	1.6 (0.8)
Percent change from	-17.7 (32.2)	-24.8 (37.7)	-31.7 (32.4)

	Vehicle placebo	Olopatadine NS, 0.6%	Azelastine NS, 0.1%
baseline			
Difference from vehicle placebo, percent change from baseline	--	-7.1	-14.0
Stuffy nose, AM score	**n = 175**	**n = 179**	**n = 187**
Baseline (SD)	2.3 (0.5)	2.5 (0.5)	2.4 (0.5)
Treatment Period (SD)	2.0 (0.6)	2.0 (0.7)	1.9 (0.7)
Percent change from baseline	-12.0 (30.4)	-21.1 (27.4)	-21.7 (27.6)
Difference from vehicle placebo, percent change from baseline	--	-9.1	-4.0
Stuffy nose, PM score	**n = 174**	**n = 179**	**n = 187**
Baseline (SD)	2.4 (0.5)	2.4 (0.5)	2.5 (0.5)
Treatment Period (SD)	1.9 (0.6)	1.9 (0.7)	1.8 (0.8)
Percent change from baseline	-17.2 (29.8)	-19.7 (30.8)	-24.6 (28.6)
Difference from vehicle placebo, percent change from baseline	--	-2.5	-7.4
Itchy nose, AM score	**n = 175**	**n = 178**	**n = 186**
Baseline (SD)	2.0 (0.7)	2.1 (0.6)	2.2 (0.6)
Treatment Period (SD)	1.7 (0.7)	1.5 (0.8)	1.5 (0.8)
Percent change from baseline	-16.8 (38.8)	-25.6 (38.7)	-28.7 (36.3)
Difference from vehicle placebo, percent change from baseline	--	-8.8	-11.9
Itchy nose, PM score	**n = 175**	**n = 177**	**n = 186**
Baseline (SD)	2.1 (0.6)	2.4 (0.5)	2.3 (0.6)
Treatment Period (SD)	1.7 (0.7)	1.9 (0.7)	1.6 (0.8)
Percent change from baseline	-18.6 (37.5)	-19.7 (30.8)	-31.7 (31.8)
Difference from vehicle placebo, percent change from baseline	--	-2.5	-31.1
Sneezing, AM score	**n = 170**	**n = 178**	**n = 178**
Baseline (SD)	1.8 (0.7)	1.9 (0.7)	1.9 (0.8)
Treatment Period (SD)	1.3 (0.7)	1.3 (0.7)	1.2 (0.8)
Percent change from baseline	-17.0 (52.7)	-28.1 (40.8)	-31.0 (58.9)
Difference from vehicle placebo, percent change from baseline	--	-11.1	-14.0
Sneezing, PM score	**n = 174**	**n = 178**	**n = 179**
Baseline (SD)	1.9 (0.7)	2.0 (0.6)	2.0 (0.7)
Treatment Period (SD)	1.5 (0.7)	1.3 (0.7)	1.3 (0.8)
Percent change from baseline	-18.6 (38.2)	-31.7 (36.1)	-33.8 (42.4)
Difference from vehicle placebo, percent change from baseline	--	-13.1	-15.2

Reviewer comment:
These data provide additional supportive evidence for the efficacy of olopatadine 0.6% for the following symptoms of SAR: runny nose, stuffy nose, itchy nose, and sneezing. There appears to be less effect for stuffy nose.

3.1.14.6 Safety outcomes

Safety outcomes in the study are reviewed below.

3.1.14.6.1 Total drug exposure

Exposure to study treatment is summarized in Table 16. Of all patients treated with 0.6% olopatadine, 47.8% were treated for seven to 16 days, 51.7% were treated for more than 16 days, and 99.4% were treated for seven or more days.

Of all patients treated with 0.1% azelastine, 52.1% were treated for seven to 16 days, 47.3% were treated for more than 16 days, and 99.5% were treated for seven or more days.

Table 16 Exposure to study treatment, C-04-70 [Module 5, Volume 25, page 284]

Treatment	N	1 to 6 days		7-16 days		>16 days	
		n	(%)	n	(%)	n	(%)
Olopatadine NS 0.6%	180	1	(0.6)	86	(47.8)	93	(51.7)
Azelastine NS 0.1%	188	1	(0.5)	98	(52.1)	89	(47.3)
Vehicle placebo	176	3	(1.7)	84	(47.7)	89	(50.6)

Reviewer comment:
Exposure to study drug was adequate to allow for assessment of safety.

3.1.14.6.2 Adverse events

Adverse events were elicited by study staff and as observations by the study investigator. Adverse events were also recorded by patients in a Medical Problems Log [Module 5, Volume 25, pages 80, 94]. Adverse events occurring at a frequency of 1% or greater and more frequently in olopatadine 0.6% than vehicle placebo during the treatment period are summarized in Table 17. There were 30.0% (54/180) of patients treated with olopatadine 0.6% with adverse events, compared with 40.4% (76/188) of patients treated with azelastine 0.1%, and 21.6% (38/176) of patients treated with vehicle placebo. The most frequent adverse events for olopatadine 0.6% included taste perversion, headache, rhinitis, epistaxis, fatigue, and infection [Module 5, Volume 26, pages 627-638].

Table 17 Adverse events occurring at a frequency of 1.0% or greater and more frequently in olopatadine 0.6% than vehicle placebo during study treatment period, C-04-70 [Module 5, Volume 26, pages 627-638]

Adverse event	Olopatadine NS 0.6% N = 180		Azelastine NS 0.1% N = 188		Vehicle placebo N = 176	
Patients with adverse events	54	(30.0)	76	(40.4)	38	(21.6)
All adverse events	82	(45.6)	97	(51.6)	51	(29.0)
Taste perversion	22	(12.2)	38	(20.2)	3	(1.7)
Headache	7	(3.9)	9	(4.8)	6	(3.4)
Rhinitis	6	(3.3)	1	(0.5)	3	(1.7)

Adverse event	Olopatadine NS 0.6% N = 180	Azelastine NS 0.1% N = 188	Vehicle placebo N = 176
Epistaxis	4 (2.2)	4 (2.1)	2 (1.1)
Fatigue	3 (1.7)	3 (1.6)	2 (1.1)
Infection	3 (1.7)	5 (2.7)	1 (0.6)
Injury, accidental	2 (1.1)	1 (0.5)	1 (0.6)
Hypertension	2 (1.1)	0 (0)	1 (0.6)
Gastroenteritis	2 (1.1)	0 (0)	1 (0.6)
Pruritus	2 (1.1)	1 (0.5)	1 (0.6)
Dry mouth	2 (1.1)	1 (0.5)	0 (0)
Irritation throat	2 (1.1)	3 (1.6)	0 (0)

Fatigue was reported by three patients treated with olopatadine 0.6% (1.7%, 3/180) and three patients treated with azelastine 0.1% (1.6%, 3/188), compared to two in the vehicle placebo-treated patients (1.1%, 2/176). Somnolence was reported by one patient each in the olopatadine 0.6% group (0.6%, 1/180) and vehicle placebo group (0.6%, 1/176) and in no patients in the azelastine 0.1% group. Dry mouth and throat irritation were each reported by two patients treated with olopatadine 0.6% (1.1%, 2/180) and one patient treated with azelastine 0.1% (0.5%, 1/188) but none in vehicle placebo. For each of the study treatments, the majority of adverse events occurring during the treatment period were mild to moderate in severity and resolved without treatment [Module 5, Volume 26, pages 671-689].

Nasal adverse events occurring during this study are summarized in Table 18. Rhinitis, epistaxis, pharyngitis, and irritation of the throat were the most common nasal adverse events that occurred more frequently with olopatadine 0.6% than for vehicle placebo. There was one nasal ulcer in the study that occurred in a patient treated with azelastine 0.1%. There were no nasal septum perforations in the study [Module 5, Volume 25, pages 291, 295].

Table 18 Nasal adverse events occurring in C-04-70 [Module 5, Volume 25, pages 291, 295]

Adverse event MedDRA code	Olopatadine NS 0.6% N = 180	Azelastine NS 0.1% N = 188	Vehicle placebo N = 176
	n (%)	n (%)	n (%)
Rhinitis	6 (3.3)	1 (0.5)	3 (1.7)
Epistaxis	4 (2.2)	4 (2.1)	2 (1.1)
Nasal discomfort	3 (1.7)	7 (23.7)	3 (1.7)
Pharyngitis	3 (1.7)	0 (0)	2 (1.1)
Irritation throat	2 (1.1)	3 (1.6)	0 (0)
Sneezing	1 (0.6)	2 (1.1)	1 (0.6)
Dry nose	1 (0.6)	0 (0)	0 (0)
Nasal ulcer	0 (0)	1 (0.5)	10 (0)
Nasal pruritus	0 (0)	0 (0)	1 (0.6)

The incidence and character of adverse events in patients 12 to 17 years of age were similar to that of the general study population. There were too few patients 65 years of age and older (1.3%, 7/544) to analyze adverse events in this population. There were no clinically relevant differences in the proportions of patients with adverse events were similar to the proportion of patients without adverse events for male and female genders and for patients of Caucasian, Black, and other races [Module 5, Volume 25, page 302; Module 5, Volume 26, pages 692-693].

Reviewer comment:
The adverse event profile for olopatadine 0.6% and azelastine 0.1% were fairly similar. A low frequency of adverse events due to somnolence and anticholinergic symptoms were reported with olopatadine. Somnolence and fatigue occurred at similar frequencies in all treatment groups. There was no increase in the frequency of adverse events reported in subgroups.

3.1.14.6.3 Deaths and serious adverse events

There were no deaths in this study. There was one patient that had a serious adverse event in the study. This patient was in the azelastine 0.1% treatment group and was hospitalized due to appendicitis [Module 5, Volume 25, page 304].

3.1.14.6.4 Withdrawals due to adverse events

There were 12 patients (2.2%, 12/544) who withdrew from the study due to adverse events during the study treatment period. These data are summarized in Table 19. Of these 12 patients, five were treated with olopatadine 0.6%, two were treated with azelastine 0.1%, and five were treated with vehicle placebo. Taste perversion, headache, and pharyngitis resulted in the withdrawal of two patients each in the olopatadine 0.6% group; there were no withdrawals for these adverse events in the azelastine 0.1% and vehicle placebo groups. One patient in the olopatadine 0.6% group withdrew due to eight adverse events—taste perversion, pruritus, headache, pharyngitis, sneezing, cough increased, pain, and rhinitis [Module 5, Volume 25, page 306-307].

Table 19 Withdrawals due to adverse events, C-04-70 [Module 5, Volume 25, page 306-307]

Adverse event MedDRA code	**Olopatadine NS 0.6%** N = 180		**Azelastine NS 0.1%** N = 188		**Vehicle placebo** N = 176	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Patients withdrawing because of adverse events	5	(2.8)	2	(1.1)	5	(2.8)
All adverse events resulting in withdrawal	14	(7.8)	2	(1.1)	5	(2.8)
Taste perversion	2	(1.1)	0	(0)	0	(0)
Headache	2	(1.1)	0	(0)	0	(0)
Pharyngitis	2	(1.1)	0	(0)	0	(0)
Pruritus	1	(0.6)	0	(0)	0	(0)
Sneezing	1	(0.6)	0	(0)	0	(0)
Cough increased	1	(0.6)	0	(0)	0	(0)
Pain	1	(0.6)	0	(0)	0	(0)
Rhinitis	1	(0.6)	0	(0)	0	(0)
Nausea	1	(0.6)	0	(0)	0	(0)
Dyspepsia	1	(0.6)	0	(0)	0	(0)
Gastroenteritis	1	(0.6)	0	(0)	0	(0)
Appendicitis	0	(0)	1	(0.5)	0	(0)
Infection	0	(0)	1	(0.5)	0	(0)
Sinusitis	0	(0)	0	(0)	2	(1.1)
Dermatitis, contact	0	(0)	0	(0)	1	(0.6)
Arthopod bite	0	(0)	0	(0)	1	(0.6)

Reviewer comment:
The higher frequency of withdrawals in the olopatadine 0.6% group was largely due to one patient who had eight adverse events. The only withdrawals due to taste perversion, headache, and pharyngitis occurred in the olopatadine 0.6% group.

3.1.14.6.5 Vital signs

Pulse, systolic blood pressure, and diastolic blood pressure were measured at screening (Visit 1), randomization (Visit 2), and at exit (Visit 4). There were no clinically significant changes from baseline in mean values of vital signs for any of the treatment groups [Module 5, Volume 25, pages 322-330].

There were three patients who had clinically relevant changes in blood pressure that were reported as adverse events. Two patients were in the olopatadine 0.6% group; one had a systolic blood pressure of 141 at randomization and the other had a systolic blood pressure of 152 and a diastolic blood pressure of 103 at an unscheduled visit. One patient in the vehicle placebo group had a diastolic blood pressure of 97 at the exit visit. Each of the patients continued in the study [Module 5, Volume 25, pages 898, 903; Module 5, Volume 26, pages 696, 700]. Analysis of shift tables and scatter plots for the overall study population identified no safety concerns [Module 5, Volume 25, pages 334-351; Module 5, Volume 26, pages 906-924].

3.1.14.6.6 Physical examination

Physical examinations were performed at the screening visit (Visit 1) and at exit (Visit 4). Clinically relevant changes in physical examinations were reported as adverse events. Nasal and ocular findings were not required to be reported as adverse events unless the investigator assessed the finding as related to study drug or due to a cause other than seasonal allergic rhinitis. Adverse events have been reviewed earlier in this document in section 3.1.14.6.2. Overall, there were no differences among treatment groups in clinically relevant changes in physical examination findings from baseline [Module 5, Volume 25, pages 312-316].

3.1.14.6.7 Nasal examination

Nasal examinations were performed at the screening visit (Visit 1), randomization (Visit 2) and at exit (Visit 4). Clinically relevant changes in nasal examinations were reported as adverse events. Adverse events have been reviewed earlier in this document in section 3.1.14.6.2. Overall there were no differences among treatment groups in clinically relevant changes in nasal examination findings from baseline [Module 5, Volume 25, pages 317-320].

Reviewer comment:
Safety data from vital signs, physical examinations, and nasal examinations do not identify a safety signal.

4 ONSET OF ACTION IN CLINICAL EFFICACY AND SAFETY STUDIES

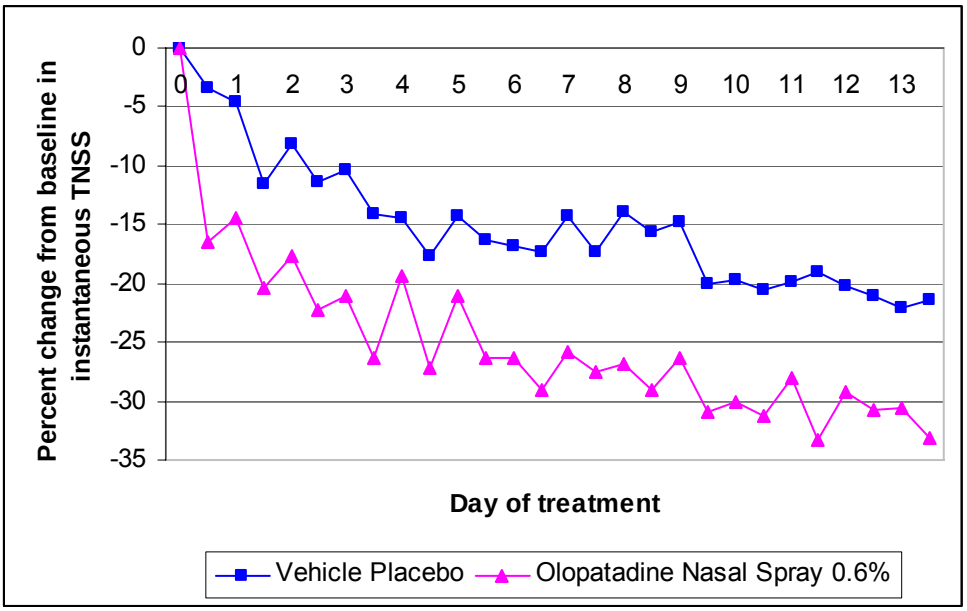
The applicant's initial proposed label included a claim that in studies C-02-10 and C-02-37, the percent reduction in reflective TNSS for patients treated with Patanase Nasal Spray was statistically superior to placebo on days one through 14 [Module 1, Volume 1, page 3.B.1]. The clinical review from the initial NDA addressed onset of action in these studies by assessing numerical superiority of olopatadine 0.6% compared with placebo. The review noted that the percent change from baseline in the AM and PM reflective and instantaneous TNSS values at each day showed a separation from vehicle placebo at Day 2 in Study C-02-10 and Day 1 in Study C-02-37. Numerical superiority over vehicle placebo for olopatadine 0.6% was maintained for each of the 14 study days for the AM and PM reflective TNSS values [Medical Officer Review, Charles E. Lee, M.D., NDA 21-861, N-000, 12/24/04, pages 131, 156]. It should be noted that such a claim should be supported by an inferential analysis of the instantaneous TNSS, however. The Division advised the applicant to submit this analysis to support their claim. The analysis was submitted by the applicant and is reviewed below [NDA 21-861, N-000C, 3/21/08].

4.1 Onset of action, Study C-02-10

Study C-02-10 was a randomized, vehicle-controlled, parallel group, three-arm, multicenter, phase 3 clinical study of patients with seasonal allergic rhinitis. The study had a two-week double blind treatment period. The objectives of this study were to demonstrate the superiority of olopatadine HCl nasal spray 0.4% and olopatadine 0.6% nasal spray nasal sprays compared with nasal spray vehicle placebo for the treatment of patients with seasonal allergic rhinitis. Percent change in instantaneous TNSS by treatment day was evaluated as a secondary efficacy endpoint. Assessments of symptom scores were made by patient twice daily. This endpoint was analyzed to assess the onset of action.

Results for olopatadine 0.6% and placebo are displayed in Figure 1 and are summarized in Table 20. Results for olopatadine 0.4% are not represented. Morning time points are Days 1, 2, 3, 4, and so forth. Evening time points are Days 0.5, 1.5, 2.5, and so forth. Olopatadine 0.6% was statistically superior to placebo at all time points except for the morning dose on Day 5.

Figure 1 Percent change in instantaneous TNSS by day of treatment, Study C-02-10 [NDA 21-861, N-000 C, 3/21/08]



0 **1** **2** **3** **4** 5 **6** **7** **8** **9** **10** **11** **12** **13**

0.5 **1.5** **2.5** **3.5** **4.5** **5.5** **6.5** **7.5** **8.5** **9.5** **10.5** **11.5** **12.5** **13.5**

$p < 0.05$ is **bold, underlined, and highlighted**

Table 20 Percent change in instantaneous TNSS by day of treatment, study C-02-10 [NDA 21-861, N-000 C, 3/21/08]

Study C-02-10	**Vehicle placebo**		**Olopatadine NS, 0.6%**	
Day 0.5	**n = 221**		**n = 216**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	7.9	(2.7)	7.1	(3.0)
Percent change from baseline	-3.4	(34.4)	-16.4	(32.3)
Difference from vehicle placebo, percent change from baseline	--		-13.0	
p value	--		<0.0001	
Day 1	**n = 221**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	7.9	(2.6)	17.3	(3.0)
Percent change from baseline	-4.6	(31.8)	-14.5	(31.9)
Difference from vehicle placebo, percent change from baseline	--		-9.9	
p value	--		0.0010	

Study C-02-10	Vehicle placebo		Olopatadine NS, 0.6%	
Day 1.5	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	7.4	(2.9)	6.8	(3.1)
Percent change from baseline	-11.5	(28.7)	-20.4	(33.2)
Difference from vehicle placebo, percent change from baseline	--		-8.9	
p value	--		0.0042	
Day 2	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	7.6	(2.8)	7.0	(3.1)
Percent change from baseline	-8.2	(29.7)	-17.7	(33.5)
Difference from vehicle placebo, percent change from baseline	--		-9.5	
p value	--		0.0024	
Day 2.5	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	7.4	(2.8)	6.7	(3.3)
Percent change from baseline	-11.3	(31.9)	-22.3	(34.2)
Difference from vehicle placebo, percent change from baseline	--		-10.0	
p value	--		0.0005	
Day 3	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	7.5	(2.9)	6.7	(3.2)
Percent change from baseline	-10.4	(34.5)	-21.0	(34.6)
Difference from vehicle placebo, percent change from baseline	--		-10.6	
p value	--		0.0017	
Day 3.5	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	7.1	(2.8)	6.3	(3.3)
Percent change from baseline	-14.1	(33.4)	-26.3	(34.4)
Difference from vehicle placebo, percent change from baseline	--		-12.2	
p value	--		0.0002	
Day 4	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	7.2	(2.8)	6.8	(3.2)
Percent change from baseline	-14.5	(28.8)	-19.4	(35.0)
Difference from vehicle placebo, percent change from baseline	--		-4.9	
p value	--		0.1957	
Day 4.5	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	6.9	(3.0)	6.2	(3.3)
Percent change from baseline	-17.6	(31.6)	-27.2	(35.3)
Difference from vehicle placebo, percent change from baseline	--		-9.6	
p value	--		0.0036	
Day 5	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	7.2	(3.0)	6.7	(3.4)
Percent change from baseline	-14.2	(32.7)	-21.1	(37.8)
Difference from vehicle placebo, percent change from baseline	--		-10.0	
p value	--		0.0056	
Day 5.5	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	7.0	(2.9)	6.3	(3.3)
Percent change from baseline	-16.3	(31.6)	-26.3	(37.9)
Difference from vehicle placebo, percent change from baseline	--		-12.2	
p value	--		0.0002	

Study C-02-10	Vehicle placebo		Olopatadine NS, 0.6%	
Day 6	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	6.9	(2.9)	6.3	(3.3)
Percent change from baseline	-16.9	(32.2)	-26.4	(37.2)
Difference from vehicle placebo, percent change from baseline	--		-9.5	
p value	--		0.0335	
Day 6.5	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	6.9	(3.0)	6.1	(3.3)
Percent change from baseline	-17.3	(34.5)	-29.0	(37.2)
Difference from vehicle placebo, percent change from baseline	--		-11.7	
p value	--		0.0010	
Day 7	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	7.1	(2.9)	6.3	(3.4)
Percent change from baseline	-14.3	(32.9)	-25.8	(38.4)
Difference from vehicle placebo, percent change from baseline	--		-11.5	
p value	--		0.0008	
Day 7.5	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	6.8	(3.0)	6.1	(3.3)
Percent change from baseline	-17.4	(37.7)	-27.5	(36.9)
Difference from vehicle placebo, percent change from baseline	--		-10.1	
p value	--		0.0060	
Day 8	**n = 221**		**n = 216**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	7.1	(2.9)	6.2	(3.4)
Percent change from baseline	-14.0	(35.3)	-26.9	(36.9)
Difference from vehicle placebo, percent change from baseline	--		-12.9	
p value	--		0.0002	
Day 8.5	**n = 221**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	6.9	(3.1)	6.0	(3.3)
Percent change from baseline	-15.7	(41.4)	-29.1	(35.1)
Difference from vehicle placebo, percent change from baseline	--		-13.4	
p value	--		0.0003	
Day 9	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	7.0	(2.9)	6.2	(3.3)
Percent change from baseline	-14.8	(38.0)	-26.4	(37.6)
Difference from vehicle placebo, percent change from baseline	--		-11.6	
p value	--		0.0014	
Day 9.5	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	6.6	(3.1)	5.9	(3.3)
Percent change from baseline	-20.1	(36.8)	-31.0	(37.2)
Difference from vehicle placebo, percent change from baseline	--		-10.9	
p value	--		0.0028	
Day 10	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	6.7	(3.1)	5.9	(3.4)
Percent change from baseline	-19.7	(37.2)	-30.1	(37.1)
Difference from vehicle placebo, percent change from baseline	--		-10.4	
p value	--		0.0044	

Study C-02-10	Vehicle placebo		Olopatadine NS, 0.6%	
Day 10.5	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	6.6	(3.0)	5.8	(3.4)
Percent change from baseline	-20.6	(38.6)	-31.2	(38.0)
Difference from vehicle placebo, percent change from baseline	--		-10.6	
p value	--		0.0048	
Day 11	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	6.7	(3.1)	6.1	(3.3)
Percent change from baseline	-19.9	(35.5)	-28.1	(37.6)
Difference from vehicle placebo, percent change from baseline	--		-8.2	
p value	--		0.0327	
Day 11.5	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	6.6	(3.0)	5.7	(3.4)
Percent change from baseline	-19.0	(39.7)	-33.3	(38.6)
Difference from vehicle placebo, percent change from baseline	--		-14.3	
p value	--		0.0002	
Day 12	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	6.6	(3.2)	6.0	(3.4)
Percent change from baseline	-20.2	(38.4)	-29.2	(36.7)
Difference from vehicle placebo, percent change from baseline	--		-9.6	
p value	--		0.0221	
Day 12.5	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	6.5	(3.1)	5.8	(3.3)
Percent change from baseline	-21.1	(44.1)	-30.7	(37.3)
Difference from vehicle placebo, percent change from baseline	--		-9.2	
p value	--		0.0211	
Day 13	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	6.5	(3.3)	5.9	(3.3)
Percent change from baseline	-22.1	(39.9)	-30.5	(36.8)
Difference from vehicle placebo, percent change from baseline	--		-8.4	
p value	--		0.0380	
Day 13.5	**n = 223**		**n = 220**	
Baseline (SD)	8.4	(2.2)	8.5	(2.2)
Treatment Period (SD)	6.5	(3.1)	5.7	(3.3)
Percent change from baseline	-21.4	(42.5)	-33.2	(36.7)
Difference from vehicle placebo, percent change from baseline	--		-11.8	
p value	--		0.0031	

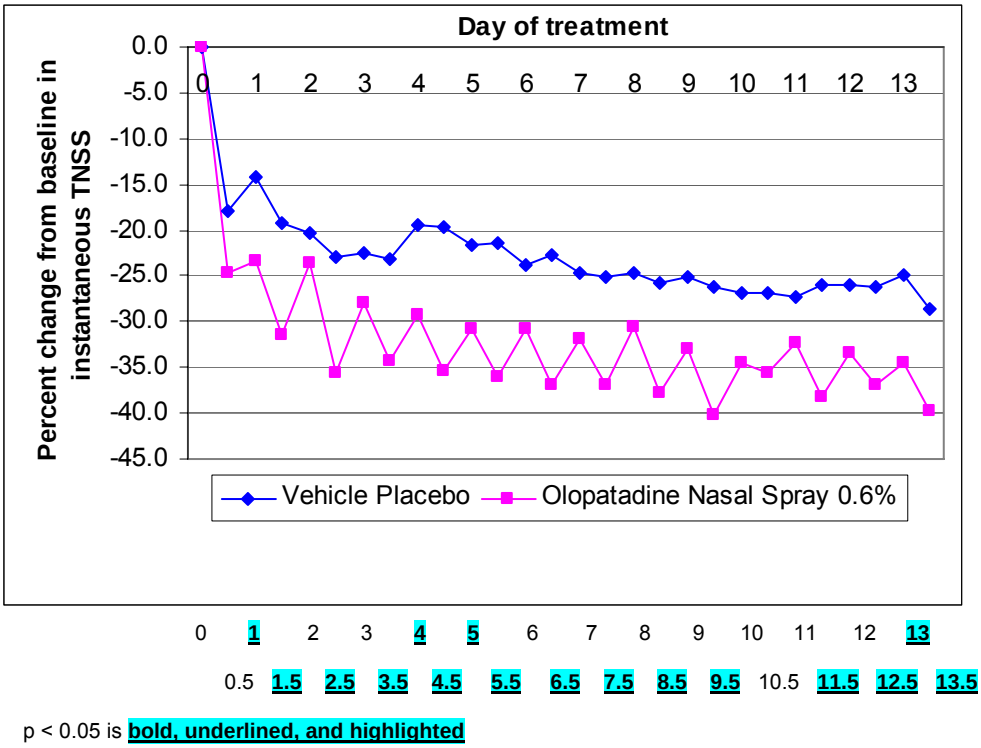
4.2 Onset of action, Study C-02-37

Study C-02-37 study was a randomized, vehicle-controlled, parallel group, three-arm, multicenter, phase 3 clinical study of patients with seasonal allergic rhinitis. The study had a two-week double blind treatment period. The objectives of this study were to demonstrate the superiority of olopatadine HCl nasal spray 0.4% and olopatadine 0.6% nasal spray nasal sprays compared with nasal spray vehicle placebo for the treatment of patients with seasonal allergic rhinitis. Percent change in instantaneous TNSS by treatment days evaluated as a secondary efficacy endpoint. Assessments of symptom

scores were made by patient twice daily. This endpoint was analyzed to assess the onset of action.

Results for olopatadine 0.6% and placebo are displayed in Figure 2 and are summarized in Table 21. Results for olopatadine 0.4% are not represented. Morning time points are Days 1, 2, 3, 4, and so forth. Evening time points are Days 0.5, 1.5, 2.5, and so forth. Olopatadine 0.6% was statistically superior to placebo at all evening time points except for 4.5 days after dosing. Olopatadine 0.6% was statistically superior to placebo for only morning time points on Days 1, 4, 5, 13.

Figure 2 Percent change in instantaneous TNSS by day of treatment, Study C-02-10 [NDA 21-861, N-000 C, 3/21/08]



p < 0.05 is **bold, underlined, and highlighted**

Table 21 Percent change in instantaneous TNSS by day of treatment, study C-02-37 [NDA 21-861, N-000 C, 3/21/08]

Study C-02-37	**Vehicle placebo**		**Olopatadine NS, 0.6%**	
Day 0.5	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	6.6	(2.7)	6.0	(2.6)
Percent change from baseline	-18.0	(32.3)	-24.7	(30.6)
Difference from vehicle placebo, percent change from baseline	--		-6.7	
p value	--		0.0884	

Study C-02-37	Vehicle placebo		Olopatadine NS, 0.6%	
Day 1	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	6.9	(2.6)	6.1	(2.8)
Percent change from baseline	-14.2	(30.4)	-23.4	(31.2)
Difference from vehicle placebo, percent change from baseline	--		-9.2	
p value	--		0.0053	
Day 1.5	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	6.5	(2.9)	5.4	(2.9)
Percent change from baseline	-19.2	(37.6)	-31.5	(36.1)
Difference from vehicle placebo, percent change from baseline	--		-12.3	
p value	--		0.0015	
Day 2	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	6.5	(2.9)	6.0	(2.8)
Percent change from baseline	-20.4	(33.4)	-23.6	(33.6)
Difference from vehicle placebo, percent change from baseline	--		-3.2	
p value	--		0.5264	
Day 2.5	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	6.2	(2.8)	5.2	(3.0)
Percent change from baseline	-22.9	(34.9)	-35.6	(33.0)
Difference from vehicle placebo, percent change from baseline	--		-12.7	
p value	--		0.0005	
Day 3	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	6.3	(2.9)	5.8	(3.0)
Percent change from baseline	-22.5	(33.9)	-27.9	(32.7)
Difference from vehicle placebo, percent change from baseline	--		-5.4	
p value	--		0.1995	
Day 3.5	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	6.2	(2.9)	5.3	(3.0)
Percent change from baseline	-23.1	(36.4)	-34.2	(33.7)
Difference from vehicle placebo, percent change from baseline	--		-11.1	
p value	--		0.0037	
Day 4	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	6.5	(3.1)	5.6	(3.0)
Percent change from baseline	-19.5	(36.4)	-29.2	(34.8)
Difference from vehicle placebo, percent change from baseline	--		-9.7	
p value	--		0.0148	
Day 4.5	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	6.5	(3.0)	5.2	(3.2)
Percent change from baseline	-19.6	(37.7)	-35.4	(36.5)
Difference from vehicle placebo, percent change from baseline	--		-15.8	
p value	--		<0.0001	
Day 5	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	6.4	(3.1)	5.5	(3.1)
Percent change from baseline	-21.6	(37.9)	-30.8	(36.1)
Difference from vehicle placebo, percent change from baseline	--		-9.2	
p value	--		0.0228	

Study C-02-37	Vehicle placebo		Olopatadine NS, 0.6%	
Day 5.5	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	6.4	(3.2)	5.2	(3.2)
Percent change from baseline	-21.4	(37.8)	-36.1	(35.3)
Difference from vehicle placebo, percent change from baseline	--		-14.7	
p value	--		0.0002	
Day 6	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	6.3	(3.2)	5.5	(3.1)
Percent change from baseline	-23.9	(36.8)	-30.7	(37.9)
Difference from vehicle placebo, percent change from baseline	--		-6.8	
p value	--		0.1292	
Day 6.5	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	6.2	(3.1)	5.1	(3.2)
Percent change from baseline	-22.8	(37.7)	-37.0	(35.8)
Difference from vehicle placebo, percent change from baseline	--		-14.2	
p value	--		0.0003	
Day 7	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	6.1	(3.1)	5.4	(3.2)
Percent change from baseline	-24.7	(37.1)	-31.9	(39.0)
Difference from vehicle placebo, percent change from baseline	--		-7.2	
p value	--		0.0991	
Day 7.5	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	6.0	(3.1)	5.1	(3.2)
Percent change from baseline	-25.2	(39.2)	-37.0	(38.3)
Difference from vehicle placebo, percent change from baseline	--		-11.8	
p value	--		0.0044	
Day 8	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	6.2	(3.2)	5.5	(3.1)
Percent change from baseline	-24.7	(39.9)	-30.6	(39.4)
Difference from vehicle placebo, percent change from baseline	--		-5.9	
p value	--		0.2202	
Day 8.5	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	6.0	(3.1)	5.0	(3.1)
Percent change from baseline	-25.8	(40.4)	-37.7	(36.7)
Difference from vehicle placebo, percent change from baseline	--		-11.9	
p value	--		0.0041	
Day 9	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	6.1	(3.2)	5.3	(3.1)
Percent change from baseline	-25.1	(39.7)	-32.9	(39.2)
Difference from vehicle placebo, percent change from baseline	--		-7.8	
p value	--		0.0870	
Day 9.5	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	6.0	(3.2)	4.9	(3.2)
Percent change from baseline	-26.3	(39.1)	-40.1	(35.7)
Difference from vehicle placebo, percent change from baseline	--		-13.8	
p value	--		0.0008	

Study C-02-37	Vehicle placebo		Olopatadine NS, 0.6%	
Day 10	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	5.9	(3.4)	5.3	(3.2)
Percent change from baseline	-26.9	(4.5)	-34.6	(35.0)
Difference from vehicle placebo, percent change from baseline	--		-7.7	
p value	--		0.0918	
Day 10.5	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	5.9	(3.4)	5.2	(3.2)
Percent change from baseline	-26.9	(43.6)	-35.5	(36.3)
Difference from vehicle placebo, percent change from baseline	--		-8.6	
p value	--		0.0572	
Day 11	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	5.8	(3.1)	5.3	(3.2)
Percent change from baseline	-27.2	(40.8)	-32.4	(37.1)
Difference from vehicle placebo, percent change from baseline	--		-5.2	
p value	--		0.3131	
Day 11.5	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	5.9	(3.3)	5.0	(3.1)
Percent change from baseline	-26.0	(42.9)	-38.3	(34.5)
Difference from vehicle placebo, percent change from baseline	--		-12.3	
p value	--		0.0047	
Day 12	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	6.0	(3.2)	5.4	(3.1)
Percent change from baseline	-26.0	(41.1)	-33.4	(35.5)
Difference from vehicle placebo, percent change from baseline	--		-7.4	
p value	--		0.1084	
Day 12.5	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	5.9	(3.2)	5.1	(3.3)
Percent change from baseline	-26.2	(42.8)	-37.0	(36.9)
Difference from vehicle placebo, percent change from baseline	--		-10.8	
p value	--		0.0155	
Day 13	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	5.9	(3.2)	5.3	(3.2)
Percent change from baseline	-24.9	(44.2)	-34.5	(35.8)
Difference from vehicle placebo, percent change from baseline	--		-9.6	
p value	--		0.0338	
Day 13.5	**n = 187**		**n = 177**	
Baseline (SD)	8.2	(2.0)	8.1	(2.3)
Treatment Period (SD)	5.7	(3.2)	4.8	(3.1)
Percent change from baseline	-28.7	(41.7)	-39.8	(35.8)
Difference from vehicle placebo, percent change from baseline	--		-11.1	
p value	--		0.0104	

The applicant provided an analysis of percent change from baseline in reflective TNSS with morning and evening scores averaged for each day of treatment. These data are displayed below in Figure 3 and Figure 4. Using this analysis onset of action was noted

after the first day of dosing in both studies [Module 1, Volume 1, Section 3.B, pages 1-11].

Figure 3 Percent change in reflective TNSS for Study C-02-37

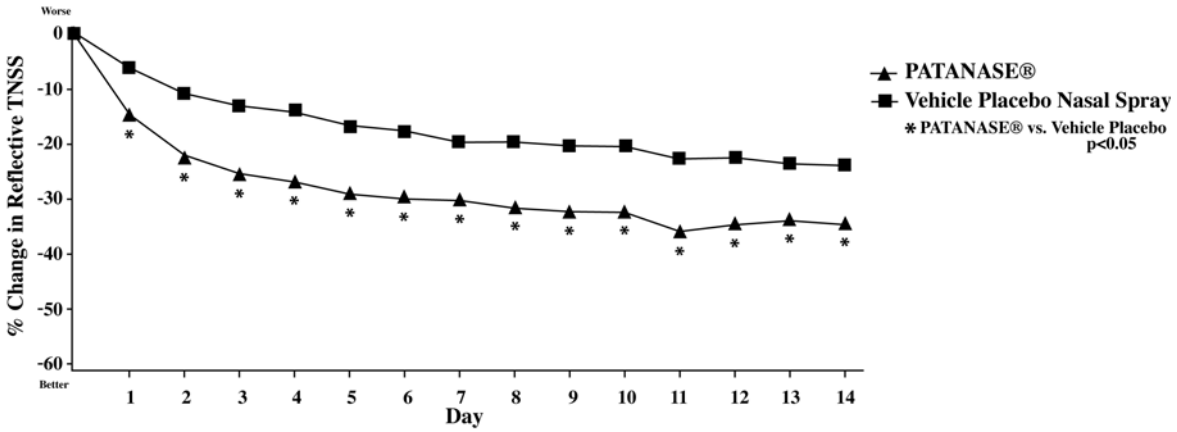
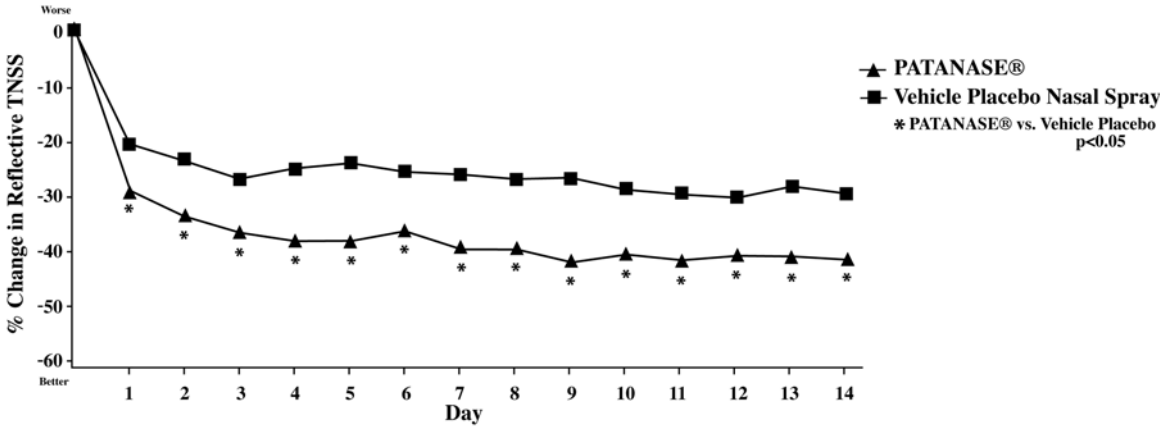


Figure 4 Percent change in reflective TNSS for Study C-02-10



<u>Reviewer comments</u>:
As noted above, an onset of action was not replicated using an analysis of the percent change from baseline in instantaneous TNSS values at each time point. This is likely due to the large placebo effect in study C-02-37, which was made more prominent because the analysis was based on percent change from baseline and not absolute change from baseline. In addition, these studies were powered to detect a significant difference from placebo for percent change from baseline the reflective TNSS; a larger sample size would be necessary to detect a difference in percent change from baseline in instantaneous TNSS. Both of these studies clearly showed the olopatadine 0.6% was statistically superior to placebo for both percent change from baseline in reflective and instantaneous TNSS over the entire treatment period and for both absolute change from baseline in reflective and instantaneous TNSS over the entire treatment period [Medical Officer Review, Charles E. Lee, M.D., NDA 21-861, N-000, 12/24/04].

The sponsor's analysis of percent change from baseline in reflective TNSS with morning and evening scores averaged for each day of treatment resulted in an onset of action after one day of dosing, which was replicated in both studies. The considerations noted above make establishing an onset of action from the instantaneous TNSS a very high hurdle. Of the two analyses, instantaneous TNSS and reflective TNSS, the onset of action based on the reflective TNSS provides a more accurate and informative description for the practitioner and should be the analysis reflected in the product label.

5 ADDITIONAL SAFETY INFORMATION

5.1 Exposure and demographics

Exposure to olopatadine 0.6% nasal spray and placebo are summarized below in Table 22 [Module 5, Volume 65, pages 99-100; Medical Officer Review, James Kaiser, M.D., NDA 21-861, N-000 AZ, 9/26/07; Medical Officer Review, Charles E. Lee, M.D., NDA 21-861, N-000, 12/24/04].

Table 22 Exposure to study treatment, olopatadine 0.6% nasal spray and placebo.

Overall exposure	
Total	2994
Males	1054
Females	1938
Olopatadine 0.6%	1491
Males	514
Females	977
Vehicle placebo	1503
Males	541
Females	961
Long term study C-01-92	
Total	924
Olopatadine 0.6%	459
Males	156
Females	303
Vehicle placebo	465
Males	165
Females	300
Long-term study C-05-69	
Total	890
Olopatadine 0.6%	445
Males	163
Females	282
Vehicle placebo	445
Males	149
Females	296
Two-week studies C-02-10, C-02-37, C-04-70 combined	
Total	1180
Olopatadine 0.6%	587
Males	194
Females	392
Vehicle placebo	593
Males	227
Females	365

Table 23 Demographics, Study C-01-92

	Vehicle placebo		Olopatadine 0.6%		Total	
	N		N		N	
	465		459		924	
	n	%	n	%	n	%
Gender						
Male	165	35.5	156	34.0	321	34.7
Female	300	64.5	303	66.0	603	65.3
Race						
Caucasian	368	79.1	360	78.4	728	78.8
Black	33	7.1	29	6.3	62	6.7
Asian	19	4.1	16	3.5	35	3.8
Hispanic	42	9.0	49	10.7	91	9.8
Other	3	0.6	5	1.1	8	0.9
Age						
0--11	7	1.5	7	1.5	14	1.5
12--64	447	96.1	445	96.9	892	96.5
≥65	11	2.4	7	1.5	18	1.9

Table 24 Demographics, C-05-69

	Vehicle placebo		Olopatadine 0.6%		Total	
	N		N		N	
	445		445		890	
	n	%	n	%	n	%
Gender						
Male	149	33.5	163	36.6	312	35.1
Female	296	66.5	282	63.4	578	64.9
Race						
Caucasian	361	81.1	359	80.7	720	80.9
Black	39	8.8	43	9.7	82	9.2
Asian	6	1.3	4	0.9	10	1.1
Hispanic	37	8.3	32	7.2	69	7.8
Other	2	0.4	7	1.6	9	1.0
Age						
0--11	0	0.0	0	0.0	0	0.0
12--64	436	98.0	434	97.5	892	100.2
≥65	9	2.0	11	2.5	18	2.0

Table 25 Demographics, C-02-10 plus C-02-37 plus C-04-70

	Vehicle placebo		Olopatadine 0.6%		Total	
	N		N		N	
	593		587		1180	
	n	%	n	%	n	%
Gender						
Male	227	38.3	194	33.0	421	35.7
Female	366	61.7	393	67.0	759	64.3
Race						
Caucasian	424	71.5	414	70.5	838	71.0

	Vehicle placebo		Olopatadine 0.6%		Total	
Black	47	7.9	51	8.7	98	8.3
Asian	5	0.8	11	1.9	16	1.4
Hispanic	114	19.2	105	17.9	219	18.6
Other	3	0.5	6	1.0	9	0.8
Age						
0--11	0	0.0	0	0.0	0	0.0
12--64	571	96.3	570	97.1	892	75.6
≥65	22	3.7	17	2.9	18	1.5

Reviewer comment:
These data form the basis of the figures in the ADVERSE REACTIONS section of the label.

5.2 Adverse events, Long-term study C-01-92

Adverse events reported in long-term study C-01-92 are summarized below in Table 26. Although not noted in the table, somnolence was reported by 3 patients (0.7%) in the olopatadine 0.6% treatment group and in 1 patient (0.2%) in the vehicle placebo group.

Table 26 Adverse events occurring at a frequency of 1.0% or greater and more frequently in olopatadine 0.6% than vehicle placebo during study treatment period, C-01-92 [NDA 21-861, N-000 BM, 2/27/08]

Adverse event MedDRA code	Olopatadine NS 0.6% N = 587		Vehicle placebo N = 593	
	n	(%)	n	(%)
All adverse events	1269	(216.2)	1244	(209.8)
Epistaxis	88	(19.2)	57	(12.3)
Nasopharyngitis	77	(16.8)	74	(15.9)
Injury	45	(9.8)	38	(8.2)
Dysgeusia	44	(9.6)	4	(0.9)
Seasonal allergy	31	(6.8)	31	(6.7)
Nasal congestion	29	(6.3)	29	(6.2)
Arthralgia	21	(4.6)	9	(1.9)
Cough	19	(4.1)	15	(3.2)
Otitis media	15	(3.3)	13	(2.8)
Diarrhea	13	(2.8)	6	(1.3)
Toothache	12	(2.6)	9	(1.9)
Rash	10	(2.2)	8	(1.7)
Depression	9	(2.0)	3	(0.6)
Nasal dryness	9	(2.0)	2	(0.4)
Contact dermatitis	8	(1.7)	3	(0.6)
Pain in extremity	8	(1.7)	7	(1.5)
Dizziness	7	(1.5)	6	(1.3)
Vomiting	7	(1.5)	4	(0.9)
Anxiety	6	(1.3)	3	(0.6)
Dysmenorrhea	6	(1.3)	2	(0.4)
Nausea	6	(1.3)	3	(0.6)
Seasonal rhinitis	6	(1.3)	3	(0.6)
Arthritis	5	(1.1)	1	(0.2)
Arthropod bite	5	(1.1)	4	(0.9)
Fatigue	5	(1.1)	1	(0.2)
Hypercholesterolemia	5	(1.1)	0	(0)
Muscle spasms	5	(1.1)	3	(0.6)
Tympanic membrane disorder	5	(1.1)	2	(0.4)

Reviewer comment:
Nasal adverse events were noted frequently in both treatment groups. The incidence of sedation among patients treated with olopatadine 0.6% was three times the rate of those treated with vehicle placebo.

5.3 Adverse events, Long-term study C-05-69

Adverse events reported in long-term study C-05-69 are summarized below in Table 27. Although not noted in the table, epistaxis was reported frequently in both treatment groups; epistaxis was reported by 23.4% (104/445) of patients treated with vehicle placebo and by 19.3% (86/445) of patients treated with olopatadine 0.6%. Somnolence was reported by 1 patient (0.2%) in the olopatadine 0.6% treatment group and in no patients (0%) in the vehicle placebo group.

Table 27 Adverse events occurring at a frequency of 0.9% or greater and more frequently in olopatadine 0.6% than vehicle placebo during study treatment period, C-01-92 [NDA 21-861, N-000 BM, 2/27/08]

Adverse event MedDRA code	Olopatadine NS 0.6% N = 445		Vehicle placebo N = 445	
	n	(%)	n	(%)
All adverse events	1043	(234.4)	1032	(231.9)
Rhinitis	65	(14.6)	55	(12.4)
Nasopharyngitis	52	(11.7)	51	(11.5)
Nasal ulcer	39	(8.8)	26	(5.8)
Dysgeusia	26	(6.5)	3	(0.7)
Asthma	18	(4.0)	15	(3.4)
Pharyngitis	17	(3.8)	10	(2.2)
Cough	16	(3.6)	14	(3.1)
Bronchitis	15	(3.4)	10	(2.2)
Diarrhea	11	(2.5)	5	(1.1)
Nasal congestion	11	(2.5)	9	(2.0)
Urinary tract infection	9	(2.0)	6	(1.3)
Toothache	8	(1.8)	6	(1.3)
Gastroenteritis	7	(1.6)	3	(0.7)
Nasal dryness	7	(1.6)	2	(0.4)
Dyspepsia	6	(1.3)	3	(0.7)
Herpes simplex	6	(1.3)	2	(0.4)
Neck pain	6	(1.3)	0	(0)
Viral infection	6	(1.3)	5	(1.1)
Anxiety	5	(1.1)	3	(0.7)
Conjunctivitis	5	(1.1)	2	(0.4)
Pruritus	5	(1.1)	0	(0)
Vomiting	5	(1.1)	2	(0.4)
Weight increased	5	(1.1)	0	(0)

Reviewer comment:
Nasal adverse events were noted frequently in both treatment groups in this study, also. One of the patients with weight gain discontinued the study because of the adverse event. The patient (2548-5155) was a 39 year-old woman with weight of 157 pounds at Day 1 of the study. She discontinued at Day 60; there was no weight at discontinuation noted. She was started on phenteramine 300 mg QD for weight gain the day before discontinuation [Module 5, Volume 11, Page 843; Module 5, Volume 39, pages 281-333].

5.4 Adverse events, Studies C-02-10, C-02-37, and C-04-70 combined

Adverse events reported in Studies C-02-10, C-02-37, and C-04-70 combined are summarized below in Table 28. Somnolence was reported by 5 patients (0.9%) in the olopatadine 0.6% treatment group and in 2 patients (2%) in the vehicle placebo group.

Table 28 Adverse events occurring at a frequency of 0.9% or greater and more frequently in olopatadine 0.6% than vehicle placebo during study treatment period, C-04-70, C-02-37, and C-04-70 combined [NDA 21-861, N-000 BM, 2/27/08]

Adverse event MedDRA code	Olopatadine NS 0.6% N = 587		Vehicle placebo N = 593	
	n	(%)	n	(%)
All adverse events	374	(63.7)	235	(39.6)
Dysgeusia	75	(12.8)	5	(0.8)
Headache	26	(4.4)	24	(4.0)
Epistaxis	19	(3.2)	10	(1.7)
Pharyngolaryngeal pain	13	(2.2)	8	(1.3)
Postnasal drip	9	(1.5)	5	(0.8)
Cough	8	(1.4)	3	(0.5)
Urinary tract infection	7	(1.2)	3	(0.5)
CPK increased	5	(0.9)	2	(0.3)
Dry mouth	5	(0.9)	1	(0.2)
Fatigue	5	(0.9)	4	(0.7)
Influenza	5	(0.9)	1	(0.2)
Nasopharyngitis	5	(0.9)	4	(0.7)
Somnolence	5	(0.9)	2	(0.3)
Throat irritation	5	(0.9)	0	(0)

Reviewer comment:
Nasal adverse events were noted frequently in both treatment groups. The incidence of sedation among patients treated with olopatadine 0.6% was three times the rate of those treated with vehicle placebo.

5.5 Discontinuations due to adverse events

The applicant based their analysis of discontinuations due to adverse events on those that were attributed to study drug. The applicant submitted their analyses based on COSTART terms initially. The applicant subsequently provided updated analyses based on all adverse events regardless of attribution and MedDRA terms for 2-week studies C-02-10, C-02-37, C-04-70, and Long-term studies C-01-92 and C-05-69 combined. These are summarized below in Table 29. Overall, 4.0% of the 1,491 patients across all five studies with exposure to olopatadine 0.6% nasal spray and 3.3% of patients treated with vehicle placebo nasal spray discontinued due to adverse events.

Table 29 Discontinuations due to adverse events, regardless of attribution, 2-week studies C-02-10, C-02-37, C-04-70, and Long-term studies C-01-92 and C-05-69 combined [NDA 21-861, N-000 C, 2/27/08].

	Olopatadine NS 0.6%		**Vehicle placebo**		**Total**	
	N		**N**		**N**	
	1491		1503		2994	
	n	**%**	**n**	**%**	**n**	**%**
Withdrawals due to adverse events	59	4.0	49	3.3	108	3.6

Reviewer comment:
These data are included in the ADVERSE REACTIONS, Clinical Trials Experience section of the label.

5.6 Severe adverse events for depression, Study C-05-69

There were two patients in Study C-05-69 who experienced severe adverse events for depression. Both were admitted to the hospital for their depression. The cases are outlined below [Medical Officer Review, James Kaiser, M.D., NDA 21-861, N-00 AZ, 9/26/07; Module 5, Volume 11, Page 843].

A 40 year-old woman (patient 38084-5371) with a history of depression, seasonal allergic rhinitis, tension headaches, and hypokalemia on no medications was hospitalized for depression (b) (4) days after randomization to the olopatadine treatment group. Daily medication for depression was later added. The patient discontinued from the trial 9 days after discharge from the hospital [Module 5, Volume 45, pages 2245-2278].

A 17 year-old woman (patient 4880-6477) with asthma, intermittent herpes simplex, overactive bladder, and history of allergy to sulfa had a nonserious adverse event of depression assessed as “moderate” in severity 4 days after randomization to olopatadine. She was hospitalized and treated for major depression on day (b) (4). Daily medication for depression was added. The subject continued in the trial [Module 5, Volume 46, pages 2797-2871].

Adverse events for depression were compared for 2-week studies C-02-10, C-02-37, C-04-70 combined, long-term study C-01-92, and long-term study C-05-69. Events for MedDRA terms “depression,” “postpartum depression,” and “bereavement reaction” are combined. These data are summarized below in Table 30.

Table 30 Adverse events for MedDRA terms for depression, 2-week studies C-02-10, C-02-37, C-04-70 combined, long-term study C-01-92, and long-term study C-05-69 [NDA 21-861, N-000 BM, 2/27/08].

Depression, combined MedDRA terms **Study**	**Olopatadine NS 0.6%** **n** **(%)**	**Vehicle placebo** **n** **(%)**
C-02-10, C-02-37, C-04-70 combined	N = 587	N = 593
	1 (0.2)	1 (0.2)
C-01-92	N = 459	N = 465
	9 (2.0)	3 (0.6)

Depression, combined MedDRA terms **Study**	**Olopatadine NS 0.6%** **n (%)**	**Vehicle placebo** **n (%)**
C-05-69	N = 445	N = 445
	4 (0.9)	5 (1.1)

Reviewer comment:
The frequency of depression was greater in the olopatadine 0.6% nasal spray treatment group than vehicle placebo only in Study C-01-92. However, Study C-01-92 was the longest study in the drug development program; C-02-10, C-02-37, C-04-70 were two-week studies and only six month data were available during the review cycle for C-05-69. Given the serious adverse event findings in C-05-69, postmarketing adverse event reports for depression should be monitored closely.

5.7 Somnolence

The clinical review for this application quotes the clinical review for the original NDA submission [Medical Officer Review, James Kaiser, M.D., NDA 21-861 N-000 AZ, 9/26/07; Medical Officer Review, Charles E. Lee, M.D., NDA 21-861 N-000, 12/24/04]:

> Somnolence was reported in the olopatadine clinical development program by 1.1% (13/1163) of patients treated with olopatadine 0.6% nasal spray and by 0.2% (2/1008) of those treated with vehicle placebo nasal spray twice daily.

These figures from the review of the original NDA submission included all studies of olopatadine 0.6% nasal spray in the drug development program. These studies comprised both the proposed dose, olopatadine 0.6% nasal spray, 2 sprays per nostril twice daily, and a dose that is not proposed for marketing, olopatadine 0.6% two sprays per nostril once daily.

The frequency of somnolence in studies of olopatadine 0.6% nasal spray, 2 sprays per nostril twice daily is summarized in Table 31. These figures include the 2-week studies C-02-10, C-02-37, C-04-70 combined, long-term study C-01-92, and long-term study C-05-69. At the dose and concentration propose for marketing, olopatadine 0.6% nasal spray appears to be associated with somnolence at a rate higher than vehicle placebo. The incidence of somnolence in patients treated with vehicle placebo twice daily ranged from 0% to 0.3%. This incidence of somnolence is lower than normally in placebo groups in seen seasonal and perennial allergic rhinitis trials in adults. The frequencies of somnolence in adults in the placebo groups in the clinical programs for Allegra (fexofenadine HCl), Astelin (azelastine HCl), Zyrtec (cetirizine HCl), and Claritin (loratadine) were from 0.9%, 5.4%, 6%, and 6.3%, respectively [Product Labels for Allegra, Astelin, and Zyrtec; Prior Prescription Product Label for Claritin]. The lower incidence of somnolence in the vehicle placebo twice daily group in the olopatadine nasal spray program suggests that these studies may have been less sensitive in picking up this adverse event.

Table 31 Adverse events for MedDRA terms for somnolence, 2-week studies C-02-10, C-02-37, C-04-70 combined, long-term study C-01-92, and long-term study C-05-69 [NDA 21-861, N-000 BM, 2/27/08].

Depression, combined MedDRA terms **Study**	**Olopatadine NS 0.6%** **n** **(%)**	**Vehicle placebo** **n** **(%)**
C-02-10, C-02-37, C-04-70 combined	N = 587	N = 593
	5 (0.9)	2 (0.3)
C-01-92	N = 459	N = 465
	3 (0.7)	1 (0.2)
C-05-69	N = 445	N = 445
	1 (0.2)	0 (0)

In the high dose cardiac safety studies submitted with the initial NDA application, somnolence was reported by 13.5% (7/166) of patients treated with olopatadine 5 mg or 20 mg twice daily by mouth or 1.5 mg given intravenously compared with 1.4% (2/140) of treated in the same studies with oral placebo. Olopatadine also clearly produces somnolence at higher doses when given orally or intravenously [Medical Officer Review, Charles E. Lee, M.D., NDA 21-861 N-000, 12/24/04; Office of Clinical Pharmacology Review, Sandra Suarez, Ph.D.., NDA 21-861 N-000, 12/24/04].

Somnolence was the most common adverse event in the clinical development program for olopatadine 2.5 mg and 5 mg tablets, which are approved in Japan. In addition, the adverse reactions section of the Japanese label for olopatadine 2.5 mg and 5.0 mg tablets states that somnolence has been reported to occur at a frequency of greater or equal to 5%. There is clearly less systemic exposure to olopatadine 0.6% nasal spray than to the oral product, however, the degree of systemic exposure is sufficient to provide additional support to the conclusion that the incidences of somnolence noted in the clinical development program are not due to chance.

Reviewer comment:
Somnolence is associated with olopatadine 0.6% nasal spray at the dose proposed for marketing. The label should include the standard class labeling for activities requiring mental alertness and warnings and precautions to avoid engaging in hazardous occupations requiring mental alertness when taking olopatadine nasal spray.

6 PEDIATRICS

6.1 Pediatric patients less than 2 years of age

The applicant requested a waiver of pediatric studies for children less than 2 years of age [Module 1, Volume 1, Section 3.A.8, page 1]. The applicant states that it is unlikely that the product would be used in a substantial number of patients less than 2 years of age that non-pharmacologic treatment, such as allergen avoidance, may be used. The applicant also notes that it is not practical to treat children less than 2 years of age with nasal spray formulations. This reviewer concurs with the applicant's rationale and supports the granting of a waiver studies in patients less than 2 years of age because the proposed indication, seasonal allergic rhinitis, does not occur in children less than 2 years of age.

6.2 Pediatric patients 6 to less than 12 years of age

The applicant submitted a Proposal for a Pediatric Study Request (PPSR) on December 20, 2004 [IND 60,116, N-060 PA, 12/20/04]. The Division declined to issue a Written Request for pediatric studies at that time because there was insufficient information at that time to determine if there are safety concerns for use of the product in younger children.

The sponsor chose to conduct two clinical studies of olopatadine 0.6% nasal spray (b) (4) povidone) in pediatric patients 6-11 years of age (Studies C-03-51 and C-04-20) even though a Written Request was not issued at that time in response to the PPSR. Olopatadine 0.6% nasal spray was numerically, but not statistically superior to placebo in both studies. In C-03-51, the frequency of epistaxis among the treatment groups ranged from 3.9% to 13.7%. The overall frequency was 8.9%. The frequency of epistaxis was higher than in the two pivotal seasonal allergic rhinitis efficacy and safety studies in adults that had been completed at that time, C-02-37 and C-02-10, where the frequency of epistaxis in active treatment groups ranged from 1.9% to 3.8% and the overall frequency was 2.6%. The frequency of nasal ulceration in this two-week study was also very high, and ranged from 1.9% to 14.3% among the active treatment groups and was 3.7% overall. The olopatadine formulation used in the pediatric study, C-03-51, and both the adult studies, C-02-37 and C-02-10, included (b) (4) povidone. It should be noted that the Studies C-03-51 and C-04-20 were not submitted to the NDA and are not relevant for approval of the product in adults and children 12 years and older, the proposed patient population.

The sponsor subsequently developed a povidone-free formulation of their product and submitted a second PPSR on March 20, 2006. Their PPSR included a protocol for a safety and efficacy study of olopatadine 0.6% nasal spray (0% povidone) in pediatric patients 6 to less than 12 years of age and a PK and safety study of olopatadine 0.6% nasal spray (0% povidone) in pediatric patients 2-5 years of age [Medical Officer Review, Charles E. Lee, M.D., IND 60,116, N-098 PA, 3/22/07].

C-07-01 was proposed to be an efficacy and safety study in pediatric patients six to less than 12 years of age. The study was to be a randomized, double blind, placebo controlled, two arm, parallel group study designed to demonstrate the superiority of olopatadine nasal spray (0% povidone) 0.6% to vehicle placebo (0% povidone) when given twice a day for a two week period. There were to be 1200 patients enrolled so that there are approximately 1,000 patients randomized. Double blind study treatments included(1) 0.6% olopatadine nasal spray (0% povidone), 1 spray each nostril twice daily, (2) 0.6% olopatadine nasal spray (0% povidone), 2 sprays each nostril twice daily, (3) nasal spray vehicle placebo (0% povidone), 1 spray each nostril twice daily, and (4) nasal spray vehicle placebo (0% povidone), 2 sprays each nostril twice daily. The primary efficacy endpoint was to be percent change from baseline in reflective TNSS. Analyses also

included percent change from baseline in instantaneous TNSS and (b) (4) Safety variables were to include adverse events, vital signs, and nasal examinations.

C-07-02 was to be a PK and safety study in pediatric patients two to less than 6 years of age. The study was to be a randomized, double blind, placebo controlled, two arm, parallel group, multiple dose, PK and safety study designed to describe the systemic exposure of olopatadine and its metabolites following intranasal administration of olopatadine 0.6% nasal spray (0% povidone) in 100 pediatric patients two to less than 6 years of age. There were to be 120 patients enrolled. Patients were to have a history of spring SAR or PAR. Double blind study treatments were to include olopatadine 0.6% (0% povidone) one spray each nostril twice daily (2.4 mg/day) and placebo nasal spray (0% povidone) one spray each nostril twice daily. The double blind treatment period was to be 14.5 days in duration. Blood samples for PK analysis were to be performed pre-dose and 0.5, 1, 1.5, 2, 6, and 12 hours post-dose. Sparse samples were to be taken. Each patient was to be assigned to three of the seven possible sampling times. Safety variables were to include adverse events, vital signs, physical and nasal examinations, laboratory studies, and ECGs.

The Division contacted the Division of Anti-Infective and Ophthalmic Products (DAIOP) to determine if additional information is needed on the use of olopatadine in the pediatric population. DAIOP replied that there have been pediatric studies completed for olopatadine ophthalmic drops, that there is no need for additional ophthalmology studies and that there are no issues with use of the drug in children. Patanol (olopatadine HCl ophthalmic solution) 0.1% (NDA 20-688) is indicated for the treatment of the signs and symptoms of allergic conjunctivitis in patients as young as 3 years of age. Pataday (olopatadine HCl ophthalmic solution) 0.2% (NDA 21-545) is indicated for the treatment of ocular itching associated with allergic conjunctivitis in patients as young as 3 years of age.

The Division’s Pediatric Exclusivity Working Group met on May 9, 2007 and May 30, 2007 to discuss a Written Request for pediatric studies. The resulting proposed Written Request was submitted to the Pediatric and Maternal Health Staff (PMHS) for comments. The Division advised PMHS that DAIOP does not need any additional information on the use of olopatadine in pediatrics, that the Division has been in close contact with the sponsor about their pediatric drug development plan, and the Written Request is similar in nature to those previously drafted for other antihistamines, both oral and intranasal. PMHS updated the language in the Written Request to conform to the most recent template and recommended that the Division ask the biometrics team to provide input regarding proposed sample sizes. PMHS did not feel that it was necessary to bring the Written Request to PdIT, as there were no issues that warranted discussion. The Division advised the sponsor that proposed pediatric trials C-07-01 and C-07-02, and completed pediatric studies C-03-51 and C-04-20 would be sufficient to allow the Agency to evaluate the proposed pediatric label claim for Patanase Nasal Spray. The Written Request for pediatric studies was issued on June 29, 2007. It is appropriate to defer pediatric studies in patients 6 to less than 12 years of age until July 1, 2009, the date specified by the Written Request.

6.3 Pediatric patients 12 years of age and older

The current submission includes studies in children from 12 to less than 18 years of age and the pediatric study requirement should be considered to be met in this patient population.

7 REFERENCES

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4 Juniper EF, et al. J Allergy Clin Immunol. 98(4):843-845, 1996

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/s/

Charles Lee
3/25/2008 05:36:30 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA 21-861
Submission Number	N-000
Submission Code	AZ
Letter Date	September 26, 2007
Stamp Date	September 27, 2007
PDUFA Goal Date	March 27, 2008
Reviewer Name	James Kaiser, M.D.
Review Completion Date	March 6, 2008
Established Name	Olopatadine Hydrochloride
(Proposed) Trade Name	PATANASE® (olopatadine hydrochloride) Nasal Spray
Therapeutic Class	H_1-receptor antagonist, antihistamine
Applicant	Alcon Research, Ltd.
Priority Designation	Standard
Formulation	Nasal spray
Dosing Regimen	Two sprays per nostril twice daily
Indication	(b) (4) treatment of symptoms of seasonal allergic rhinitis
Intended Population	Patients with seasonal allergic rhinitis 12 years old and older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

There are adequate efficacy and safety data to recommend approval of olopatadine 0.6% nasal spray for the treatment of patients with seasonal allergic rhinitis. The chief concern regarding the prior, povidone-containing formulation was the presence of nasal septal perforations occurring in the clinical trials. Alcon's newly-submitted single-dose pharmacodynamic study C-05-64 demonstrated a similar effect on nasal symptoms to that produced with the prior formulation, allowing a presumption that previously-generated efficacy information in seasonal allergic rhinitis would apply to the new product. No nasal septal perforations or other notable safety events occurred in the first 6 months of the 12-month safety trial C-05-69 that would preclude market approval.

A manufacturing site inspection has not been conducted by FDA at the time of this review. I recommend an "Approval" action if the site is found to be acceptable. I recommend an "Approvable" action if the site is found to be unacceptable.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

I do not recommend risk management activities for this application

1.2.2 Required Phase 4 Commitments

I do not recommend Phase 4 commitments for this application

1.2.3 Other Phase 4 Requests

I do not recommend Phase 4 requests for this application.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This is a review of newly submitted data. For review of Alcon's original, December 2004 NDA, see Dr. Charles Lee's Medical Officer review. The key clinical data included in the original NDA were two pivotal 2-week efficacy and safety trials in seasonal allergic rhinitis, a 12-month safety trial in subjects with perennial allergic rhinitis, and two single-dose environmental exposure unit trials. Clinical data also included three additional environmental

exposure unit studies, two 2-week trials and one 8-week clinical trial in subjects with seasonal allergic rhinitis, and 7 clinical pharmacology trials. The NDA was found not approvable. FDA stated in the nonapprovable letter of October 27, 2005, in part:

> Data submitted show that Patanase Nasal Spray has an unfavorable safety profile for use under labeled conditions given its benefits. Patanase Nasal Spray caused nasal irritation and serious damage to the nasal mucosa. In the clinical studies there were unacceptable high frequencies of nasal septal perforation, nasal ulceration, and epistaxis. Preclinical data showed that povidone, an excipient in the formulation, was markedly irritating to the nasal mucosa.

In addition, the NDA was found insufficient to (b) (4)

The current submission contains two trials whose data provide support for the proposed, povidone-free formulation (Table 1) in the treatment of patients with seasonal allergic rhinitis. (b) (4)

C-05-64, a study of the nasal effects of a single dose of olopatadine nasal spray, is a pharmacodynamic link to the older formulation. Its results allow a presumption that the 2-week efficacy in patients with seasonal allergic rhinitis demonstrated for the older, povidone-containing formulation would be the same with use of the current formulation. C-05-69's 6-month safety results show that the new formulation did not result in nasal septal perforations. It was designed to address the safety concerns from the previous formulation. The results of these two studies, in conjunction with the previously submitted clinical and nonclinical information, are sufficient to allow marketing approval of olopatadine 0.6% nasal spray.

Alcon has also conducted other trials of a povidone-containing formulation (Table 2) that are not important to the marketing approval decision about the proposed formulation. However, one of the trials (C-04-70) contains relevant safety information for labeling.

1.3.2 Efficacy

The original marketing submission contained replicate 2-week clinical trials conducted in subjects with seasonal allergic rhinitis. The clinical review of the original marketing submission by Dr. Charles Lee concluded that the data support efficacy of both a 0.4% and 0.6% olopatadine nasal spray formulation, but that there was an efficacy advantage for the 0.6% formulation. The review noted that improvements were noted for runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes and that the data also supported end-of-dosing-interval efficacy. Further efficacy information was not required for the marketing approval decision.

Clinical trial C-05-64, an environmental exposure unit trial, demonstrated that a single dose of the new formulation in symptomatic subjects with seasonal allergic rhinitis results in a similar effect, as measured by the total nasal symptom score at various times over 12 hours, as that produced with the former, povidone-containing formulation. Statistical differences from vehicle control were seen at each time point, including 30 minutes, over a 12-hour period. This finding is a critical link allowing the efficacy data from the prior formulation to support market approval. Olopatadine 0.6% nasal spray produced a statistical difference from placebo at 30 minutes. Because this replicates the finding of the previously-submitted single-dose

environmental unit trial C-03-52, it may now be concluded that symptoms, as recorded on the total nasal symptom score instrument, are improved after 30 minutes

(b) (4)

1.3.3 Safety

The primary evidence of safety of the new formulation comes from the 6-month results from C-05-69, a 12-month vehicle-controlled safety trial in 890 subjects with perennial allergic rhinitis. FDA had agreed, prior to the submission of the NDA, that the 6-month results would in principle be sufficient for a marketing approval decision. The trial collected adverse event information and the results of monthly nasal examinations; it did not collect detailed information on cardiovascular effects or clinical laboratory evaluations. No subject died, and serious adverse events did not form a notable pattern. The chief safety concern regarding the previous povidone-containing formulation of olopatadine nasal spray was the incidence of nasal septal perforations, which occurred in 1 subject on active drug and 2 vehicle control subjects in the clinical program before the drug was reformulated. Alcon reports no nasal septal perforations from either C-05-64 or C-05-69. Nasal ulceration occurred in more olopatadine-treated than vehicle-treated subjects (8.8% compared to 5.8%), but the events were mostly considered of "mild" severity. The adverse event "epistaxis" occurred in 19.3% of olopatadine-treated and 23.4% of vehicle-treated subjects. This is a notably higher than the incidence found in the first 6 months of the previous safety trial in perennial allergic rhinitis (C-01-92; incidence rates of 13.1% and 6.7%, respectively). The reason for the higher incidence is not clear, but this event is not a barrier to marketing approval.

There was no notable increase in somnolence as a reported adverse event in the newly submitted data. However, information previously reviewed regarding olopatadine nasal spray, and information from the use of Allelock (available in Japan as an oral tablet at 2.5 and 5 mg for allergic conditions including allergic rhinitis, urticaria, and itching due to cutaneous diseases and in Korea at 2.5 mg), suggest that a claim for non-sedation is not warranted. As Dr. Lee stated in his review of the original NDA submission:

> Somnolence was reported in the olopatadine clinical development program by 1.1% (13/1163) of patients treated with olopatadine nasal spray 0.6% and by 0.2% (2/1008) of those treated with vehicle placebo nasal spray twice daily. The incidence of somnolence in patients treated with vehicle placebo twice daily was lower than normally seen in SAR trials of antihistamines in adults. The low incidence of somnolence in the vehicle placebo group in the olopatadine program suggests that the study may have been less sensitive in picking up this adverse event. It is possible that

the design of the patient medical problem log may have led people to not record less severe adverse events such as somnolence.

Somnolence was noted in the high dose cardiac safety studies in this application by 13.5% (7/166) of patients treated with olopatadine 5 mg or 20 mg twice daily by mouth. Somnolence was the most common adverse event in the clinical development program for olopatadine 2.5 mg and 5 mg tablets, which are approved in Japan. A cross-study comparison shows that the C_{max} and AUC for olopatadine 0.6% are 16% and 18%, respectively, of those for olopatadine tablets 5 mg orally. There is clearly less systemic exposure to olopatadine 0.6% nasal spray than to the oral product, however, the degree of systemic exposure is sufficient to provide additional support to the conclusion that the incidences of somnolence noted in the clinical development program are not due to chance.

At the dose and concentration proposed for marketing, olopatadine 0.6% nasal spray appears to be associated with somnolence infrequently, but at a rate higher than vehicle placebo. The frequency of somnolence is sufficiently low to be excluded from the table of common adverse events in the ADVERSE REACTIONS section of the olopatadine 0.6% nasal spray label, but is different enough from vehicle placebo that a "non-sedating" claim would be not supported if the product were to be approved.

Safety results from C-05-64 do not add significantly to the understanding of safety. There was no pattern of notable toxicities, as expected from a single-dose trial.

By agreement with FDA, Alcon is to submit a summary of the data from the second 6 months of C-05-69 prior to the deadline for approval of olopatadine 0.6% nasal spray. As of the writing of this review, Alcon has not submitted the 12-month results of trial C-05-69.

The currently-submitted safety data show no nasal septal perforations.

There were no safety concerns specific to males or females, and analyses of adverse events did not reveal other concerning patterns related to age or race. However, there were relatively few subjects who were not "Caucasian" or in the age group 18-64 years, limiting the conclusiveness of these findings.

1.3.4 Dosing Regimen and Administration

The proposed dose and administration is two sprays per nostril twice daily in persons 12 years old and older. As one 100 µl spray contains 665 mcg of olopatadine HCl (600 mcg of olopatadine base) the total daily dose of olopatadine HCl is 5.32 grams; the daily dose of olopatadine base is 4.8 grams.

1.3.5 Drug-Drug Interactions

Alcon presents no analyses of drug-drug interactions. For the 6-month results of clinical trial C-05-69, Alcon states, "No drug interactions involving the test article were reported for patients experiencing adverse events."

1.3.6 Special Populations

The numbers of subjects in the trial C-05-69 or C-04-70 who were outside the 18-64 year age group or who were nonCaucasians were relatively small and minor differences in safety cannot be discerned reliably. There were no notable differences in safety between males and females, nor an unexpected pattern of safety events at the extremes of age.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Olopatadine is an antagonist at the histamine receptor type 1 (H1 receptor), a structural analog of doxepin whose chemical name is (Z)-11-[3-(dimethylamino) propylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid hydrochloride and whose molecular formula is $C_{21}H_{23}NO_3 \cdot HCl$.

The product is a plastic [redacted] (b) (4) spray bottle containing 30.5 grams of a nonsterile aqueous solution containing olopatadine hydrochloride, 6.66 mg/ml (equivalent to 600 mcg of olopatadine base), benzalkonium chloride [redacted] (b) (4)%, dibasic sodium phosphate, edetate sodium, sodium chloride, hydrochloric acid or sodium hydroxide or both, and purified water. The spray bottle has a manual metered-dose spray pump with a plastic applicator and overcap. The product is intended to be used after priming and is designed to supply 240 sprays of 100 µl, each containing 665 mcg olopatadine HCl. [redacted] (b) (4)

The product has been modified in a couple of important ways since it was proposed originally in 2004. Alcon has removed povidone from the formulation in order to address nasal toxicities seen in animals and the clinical trials. [redacted] (b) (4) In addition, the product pump was redesigned [redacted] (b) (4), which had led to the formation of degradants suspected of having carcinogenic potential.

2.2 Currently Available Treatment for Indication

Antihistamines are the first-line pharmacologic treatment of the symptoms of allergic rhinitis. Numerous products are available for seasonal allergic rhinitis either over-the-counter or by prescription. Azelastine HCl (Astelin®) is the only antihistamine nasal spray approved in the United States for the treatment of symptoms of seasonal allergic rhinitis.

2.3 Availability of Proposed Active Ingredient in the United States

Olopatadine is available in ophthalmic formulations for the treatment of signs and symptoms of allergic conjunctivitis as olopatadine HCl ophthalmic solution 0.1% (Patanol®) and 0.2% (Patanol® or PatadayTM).

Olopatadine is available in Japan and Korea as Allelock 2.5 mg tablets, and in Japan also as 5 mg tablets. The dosage approved in Japan for treatment of allergic rhinitis, urticaria and itching resulting from cutaneous diseases is 5 mg twice daily.

2.4 Important Issues With Pharmacologically Related Products

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 Presubmission Regulatory Activity

Alcon submitted NDA 21,861 on December 24, 2004 for olopatadine HCl for the (b) (4) treatment of (b) (4) seasonal allergic rhinitis. The NDA had CMC, nonclinical, and clinical deficiencies. The chief clinical issue was the occurrence of nasal septal perforations, ulcerations, and epistaxis. An increase in the incidence of concerning nasal adverse events in vehicle control subjects, and preclinical data, suggested that the presence of povidone was a critical contributor to the increased safety signal. FDA took a nonapprovable action in a letter to Alcon dated October 27, 2005, which made the following clinical points:

- To support approval of olopatadine as a nasal spray product for treatment of the symptoms of allergic rhinitis, Alcon must reformulate the product to lessen nasal toxicity and perform studies to confirm that the reformulation has the intended effects.
- To support efficacy in (b) (4), at least one trial would have to be conducted using a precise and reliable measure to assess efficacy, limiting the duration of efficacy assessment to a shorter time period than 1 year, such as 4 weeks, and conducting the study in a fashion that would minimize the contribution of seasonal allergens to the symptoms.

Alcon made changes to the product including elimination of povidone, (b) (4). FDA met with Alcon in January and June, 2006, regarding the clinical development plan. FDA stated that Alcon must submit a new long-term safety study. Alcon submitted two Special Protocol Assessments under IND 60116 for a long-term safety study, the latest in November, 2006.

Alcon submitted a Proposed Pediatric Study Request in March 2007, and FDA issued a Written Request on July 19, 2007 for two pediatric studies in patients with allergic rhinitis: 1) a 2-week safety and efficacy study in subjects 6-11 years old and 2) a 2-week safety and pharmacokinetics study in subjects 2-5 years old.

2.6 Other Relevant Background Information

There is no other important background information.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The CMC and microbiology review have concluded that the characteristics of the product are acceptable. Regarding levels of degradants (b) (4) previously seen in the product, the CMC reviewer concludes that no adjustment of the acceptance criteria would be necessary, depending on review of the toxicology reviewer. The toxicology review is summarized in the next section.

Alcon states that the two critical studies in this submission (C-05-64 and C-05-69) were "conducted using the PATANASE PVP-free formulation." Alcon also states that the device to be marketed was used in the critical safety trial C-05-69. The device used in the C-05-64 trial used a prior version of a pump in the device ((b) (4) as compared to the current (b) (4) . According to a CMC review memorandum (March 4, 2008), "no changes have been made to the components of the pump that would be expected to alter the delivery performance." The purpose of the C-05-64 trial was to establish a pharmacodynamic link to the older formulation. The safety findings were not remarkable. I find it reasonable to use the data from this trial in the marketing approval decision.

At the time of this review, FDA inspection of the manufacturing site had not been conducted. I recommend an "Approval" action if the site is found to be acceptable. I recommend an "Approvable" action if the site is found to be unacceptable.

3.2 Animal Pharmacology/Toxicology

Based upon review of the original NDA, FDA requested that Alcon tighten acceptance criteria for the degradants (b) (4) or conduct a carcinogenicity study. Alcon currently proposes acceptance criteria for (b) (4), of (b) (4) of the olopatadine level, respectively, and submits preclinical data related to (b) (4). Alcon has not submitted carcinogenicity data for (b) (4), but states that (b) (4) has not been observed in the current formulation to date.

Alcon's preclinical study for (b) (4) was entitled "26-Week Repeated Subcutaneous Dose Carcinogenicity Study In p53+/- Mice with A Toxicokinetic Study in C57BL/6 Mice with (b) (4)." The preclinical study for (b) (4) is entitled "26-Week Repeated Subcutaneous Dose Carcinogenicity Study In p53+/- Mice with A Toxicokinetic Study in C57BL/6 Mice with (b) (4) " The toxicology review concludes that pending Executive Carcinogenicity Assessment Committee concurrence, neither degradant is considered carcinogenic. The ECAC has concluded that the degradants are not carcinogenic. The review concludes that the acceptance criteria for (b) (4) are acceptable.

The pharmacology/toxicology review concludes that Alcon should lower the acceptance criterion for (b) (4) to no more than (b) (4).

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The submission contains reports of two trials using the proposed formulation. C-05-64 was a single-dose trial to establish a pharmacodynamic link to the older formulation to allow previously-established efficacy information to be applied. C-05-69 was a 12-month safety trial in patients with perennial allergic rhinitis whose 6-month results were submitted for a marketing approval decision upon agreement with FDA.

In addition, Alcon submits results from clinical trials of a povidone-containing formulation (Table 2). Of these trials, C-04-70 provides some safety data relevant to labeling. The data from the other trials is not necessary to support efficacy and safety, and these trials are not reviewed in detail.

4.2 Tables of Clinical Studies

Table 1 summarizes C-05-64, used to establish the pharmacodynamic link to the older formulation, and C-05-69, whose 6-month safety results were to address the issue of nasal toxicity.

Table 1. Clinical trials providing support for the current formulation in the current NDA resubmission

Study Number	Study Type	Treatment Groups	Treatment duration	Design	Number of subjects	Diagnosis, age of subjects
C-05-64	Efficacy of single dose in Environmental Exposure Unit	PVP-free olopatadine 0.6% single dose PVP-free vehicle single dose	single dose	Randomized, double-blind, vehicle controlled, parallel group	406 olopatadine: 204 vehicle: 202	SAR, at least 18 years
C-05-69	Safety	PVP-free olopatadine 0.6% twice daily PVP-free vehicle twice daily	up to 12 months; interim report submitted with data up to 6 months	Randomized, double-blind, vehicle controlled, parallel group	890, randomized equally to active and vehicle	PAR, at least 12 years

Table 2 summarizes submitted trials of a povidone-containing formulation. Trial C-04-70 contains safety information of importance to labeling.

Table 2. Clinical trials of PVP-containing formulations since NDA filing

Study Number	Study Type	Treatment Groups	Treatment duration	Design	Number of subjects	Diagnosis, age of subjects
						(b) (4)
C-04-70	Safety and efficacy	olopatadine 0.6%, PVP (b) (4) vehicle azelastine 0.1% twice daily dosing	16 days	Randomized, double-blind, parallel-group vehicle and active controlled	544: olopatadine 180 vehicle 176 azelastine 188	SAR, 12 to 77 years
						(b) (4)

4.3 Review Strategy

This review focuses on the two clinical trials using the proposed povidone-free formulation summarized above: C-05-64, a single-dose trial used to establish the pharmacodynamic link to the older formulation, and C-05-69, a 12-month safety trial. By agreement with FDA, Alcon submitted the first 6 months of data from C-05-69 for the marketing approval decision, with the 12-month results to be seen as supportive.

Alcon submitted reports of trials testing a povidone-containing formulation (Table 2). Trial C-04-70, since it was of a design similar to that of the critical efficacy trials submitted in the original NDA, contains additional safety information of relevance to labeling. The other trials are of limited usefulness (b) (4).

This review does not integrate the submitted studies for an evaluation of efficacy. Trial C-04-70's results are not considered important to the marketing approval decision. Trial C-05-64 had a primary endpoint that used the total nasal symptom score; however, this was a single-dose study whose purpose was to establish a pharmacodynamic link to the prior single-dose information.

The integrated summary of safety is primarily a comparison of the safety of the new formulation and the older formulation. It also contains a summary of the safety of olopatadine in the prior formulation, combining the results of C-02-10, C-02-37, and C-04-70.

4.4 Data Quality and Integrity

FDA conducted no audits for this resubmission. Alcon reported financial conflicts of interest for two investigators in (b) (4), the primary trial submitted to establish the safety of the

newly formulated product. The numbers of subjects involved (see the review of the trial appended) was not sufficient to merit an investigation.

4.5 Compliance with Good Clinical Practices

Alcon states that the clinical trials submitted were conducted in compliance with Good Clinical Practice. In addition, Alcon states that it did not and will not use in any capacity the services of any person debarred under section 306 of the federal FD&C Act in connection with this NDA application.

4.6 Financial Disclosures

Two investigators for trial (b) (4) reported financial conflicts of interest: (b) (4) reported expense, honorarium, and consulting fees totaling $31,223.46 and $31,742.50, respectively. The numbers of subjects studied by these investigators was too small to influence the judgment of safety substantially.

These investigators also reported financial conflicts of interest for (b) (4), which is not a critical or supportive trial for the approval of olopatadine nasal spray.

5 CLINICAL PHARMACOLOGY

The submission contains no new pharmacokinetic analyses. Alcon determined olopatadine concentrations in a subset of subjects from the safety trial C-05-69 to assist in determining that subjects were exposed to olopatadine.

Trial C-05-69 enrolled 890 subjects, of whom blood samples were collected from 159 in the olopatadine treatment group and 160 from the vehicle control group. Blood samples were collected at months 1 and 5 during treatment. Approximately 90% of the olopatadine subset had quantifiable olopatadine plasma concentrations.

The conclusion of the pharmacology review is that the olopatadine drug concentration data suggested a high degree of patient compliance among the tested subjects, and because of the randomized nature of treatment in the entire trial, among the entire trial population as well.

5.1 Pharmacokinetics

Alcon did not submit new information on the pharmacokinetics of olopatadine resulting from exposure to the proposed formulation.

5.2 Pharmacodynamics

Alcon submitted two high-dose cardiac safety studies in the original NDA submission. As Dr. Lee states in his review of these trials, study C-00-23 suggested that there is no QTc prolongation with olopatadine 5 mg solution twice daily by mouth. Study C-02-54 suggested that there is no QTc prolongation with olopatadine 20 mg twice daily by mouth for 14 days. A dose of 5 mg twice daily is approximately twice the proposed daily dose of olopatadine 0.6% nasal spray.

Alcon previously submitted C-02-54, a cardiovascular safety and pharmacokinetics study of twice-daily dosing of 20 mg olopatadine solution or placebo for 14 days in healthy adults. Dr. Sandra Suarez, the Office of Clinical Pharmacology reviewer, noted that some placebo corrected ΔQTc values (ΔΔQTc) were higher than 10 msec at some time points due to large negative ΔQTc values for placebo. Dr. Suarez concludes in her review of this trial that the lack of a positive control in the study makes differences from placebo in corrected QTc values uninterpretable. However, she concludes that "the lack of cardiovascular safety concerns from the phase 3 clinical trials, lack of postmarketing cardiovascular signal for the approved olopatadine tablet, no influence on the QT interval in hypokalemia-anesthetized dogs, and lack of potential for drug-drug interactions also suggest that olopatadine is unlikely to prolong QTc interval at the proposed therapeutic dose."

Alcon did not submit new information on the pharmacodynamics of olopatadine resulting from exposure to the proposed formulation.

5.3 Exposure-Response Relationships

Alcon did not submit new information on exposure-response relationships with olopatadine.

6 INTEGRATED REVIEW OF EFFICACY

The intent of the resubmission was to establish a pharmacodynamic link from the older, povidone-containing formulation to the proposed povidone-free formulation and to address safety findings from the original NDA. The pharmacodynamic link was established in trial C-05-64, which showed an effect on the total nasal symptom score over the 12 hours after a single dose given to symptomatic subjects with seasonal allergic rhinitis in an environmental exposure unit that was similar to that demonstrated in the single-dose trial C-01-83. This effect is discussed in the review of trial C-05-64. C-05-64 was not designed to establish clinical efficacy. Clinical trial C-05-69, the safety trial, was also not designed to evaluate efficacy in seasonal allergic rhinitis as its population was subjects with perennial allergic rhinitis, and it included as an effect measure a symptom score that is not adequate to measure efficacy.

6.1 Indication

Alcon proposes the following indication statement:

> Patanase® Nasal Spray is indicated for (b) (4) and treatment of the symptoms of seasonal allergic rhinitis such as (b) (4) in patients 12 years of age and older.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This section will focus on a comparison of the safety of the previously proposed formulation as determined in the long-term trial C-01-92 using the prior formulation and in C-05-69, using the current formulation, to discern the possible emergence of new safety issues as a result of administration of the new formulation. The comparison is appropriate because C-01-92 had a similar design and subject population to C-05-69. This comparison is conducted using findings up to 6 months (day 185 +5 days for the visit window). The final 12-month results of C-05-69 were not available for this comparison. In both C-01-92 and C-05-69 trials, subjects of either sex, aged 12 years and older, with perennial allergic rhinitis, were randomized equally to vehicle or olopatadine 0.6% nasal spray, two sprays twice a day in each nostril. Subjects, whose demographic characteristics were similar between the two trials, were seen monthly. Nasal examinations were conducted at clinic visits in C-01-92, but C-05-69 incorporated a detailed examination if necessary that was not a feature of C-01-92. Monitoring was otherwise similar enough to permit a comparison of safety between the two trials.

Rates of most adverse events were similar between the two trials. Two subjects in trial C-05-69 experienced serious depression, which is a concern. Postmarketing reports should be monitored for this adverse event. Other serious adverse events did not exhibit a concerning pattern in either trial.

The concerning event of nasal septal perforation did not occur in C-05-69. Epistaxis was reported more frequently in C-05-69 than in C-01-92 (Table 7). In trial C-05-69, epistaxis occurred in 19.3% of subjects as compared to 23.4% of vehicle control subjects; in trial C-01-92, the corresponding rates were 13.1% and 6.7%. The reason for this difference is unclear. It may be a result of differences in reporting during the trial, or the lowering of the pH of the formulation from (b) (4) to 3.7, or another factor. The frequency of epistaxis is not a barrier to approval; most of the events were judged of mild severity (122/129 in the olopatadine group and 147/152 in the vehicle control group); the rest were of moderate severity. The incidence of adverse events commonly associated with antihistamines was not notably different in C-05-69 (Table 11).

In addition, Alcon has submitted an analysis of adverse event rates combining data from trials C-02-10, C-02-37, and C-04-70. As described in the review of trial C-04-70 (see the appendix), these were all randomized, vehicle-controlled, 2-week double-blind trials in subjects 12 years old or older with seasonal allergic rhinitis. These three trials all studied the same povidone-containing formulation of olopatadine nasal spray. Demographics and exposure to trial medication in the trials were similar. In the pooled data (Table 10), taste perversion or dysgeusia was the most common adverse event that occurred more frequently than in vehicle control (12.8% as compared to 0.8%).

In the pooled data from trials C-02-10, C-02-37, and C-04-70, somnolence occurred in 5 (0.9%) of olopatadine-treated subjects and 2 (0.3%) of vehicle-treated subjects. As Dr. Charles Lee stated in his original NDA review:

> Somnolence was reported in the olopatadine clinical development program by 1.1% (13/1163) of patients treated with olopatadine nasal spray 0.6% and by 0.2% (2/1008)

of those treated with vehicle placebo nasal spray twice daily. The incidence of somnolence in patients treated with vehicle placebo twice daily was lower than normally seen in SAR trials of antihistamines in adults. The low incidence of somnolence in the vehicle placebo group in the olopatadine program suggests that the study may have been less sensitive in picking up this adverse event. It is possible that the design of the patient medical problem log may have led people to not record less severe adverse events such as somnolence.

Somnolence was noted in the high dose cardiac safety studies in this application by 13.5% (7/166) of patients treated with olopatadine 5 mg or 20 mg twice daily by mouth. Somnolence was the most common adverse event in the clinical development program for olopatadine 2.5 mg and 5 mg tablets, which are approved in Japan. A cross-study comparison shows that the Cmax and AUC for olopatadine 0.6% are 16% and 18%, respectively, of those for olopatadine tablets 5 mg orally. There is clearly less systemic exposure to olopatadine 0.6% nasal spray than to the oral product, however, the degree of systemic exposure is sufficient to provide additional support to the conclusion that the incidences of somnolence noted in the clinical development program are not due to chance.

At the dose and concentration proposed for marketing, olopatadine 0.6% nasal spray appears to be associated with somnolence infrequently, but at a rate higher than vehicle placebo. The frequency of somnolence is sufficiently low to be excluded from the table of common adverse events in the ADVERSE REACTIONS section of the olopatadine 0.6% nasal spray label, but is different enough from vehicle placebo that a “non-sedating” claim would be not supported if the product were to be approved.

The review of postmarketing and spontaneous adverse event reports for olopatadine ophthalmic solution 0.1% (Patanol®) for the original NDA did not identify a safety signal relevant to olopatadine nasal spray. The current update does not identify a new safety signal. The original NDA review noted that Japanese postmarketing adverse event reports for olopatadine 2.5 and 5 mg tablets suggested that olopatadine tablets may be associated with hepatic function abnormalities and noted that the Japanese regulatory agency had added hepatic function abnormal, liver disorder, acute hepatitis, and jaundice to the product label for olopatadine 2.5 mg and 5 mg tablets based these postmarketing reports. Updated information shows that liver-related adverse events continue to be reported. There was no signal for hepatic function abnormality in the olopatadine nasal spray program at the time of submission of the original NDA, and laboratory monitoring (including liver function testing) was not required in the submitted studies for the current proposed formulation. If approved, postmarketing adverse event reports for olopatadine nasal spray should be monitored for cases of hepatic function abnormalities.

The clinical trial adverse event data were presented as coded in COSTART terminology. Since this contained appropriate codes, it was adequate for an assessment of safety. Many of the tables in this integrated summary of safety are presented in COSTART. However, Alcon will

present its adverse event information for labeling in MedDRA terminology, which also contains appropriate terms.

7.1.1 Deaths

There have been no deaths in the clinical program for the new formulation of olopatadine nasal spray. There was one death in Alcon clinical trials of olopatadine nasal spray. A 41-year-old woman taking olopatadine 0.6% nasal spray in C-01-92 developed abdominal pain, perforated gastric ulcer, bacterial peritonitis, and sepsis and died of sepsis on study day (b) (4). This case is described in the original NDA review.

7.1.2 Other Serious Adverse Events

There were 15 subjects with 22 serious adverse events in the 12 months of C-01-92; the only event type that occurred more than once in the treatment group was medical/surgical procedure (hysterectomy and reconstruction of the bladder in one subject and gastric bypass surgery in another). In C-05-69, depression requiring hospitalization occurred in two subjects in the olopatadine treatment group. It is possible that these were chance events; however, depression should be monitored postmarketing if the product is approved. Surgical/medical procedure occurred in two subjects in the olopatadine treatment group (knee replacement and cholecystectomy) but not in the vehicle group. A serious abdominal adverse event (appendicitis and intestinal obstruction) occurred in one subject each in the olopatadine treatment group and one subject in the vehicle control group. Other events were various in nature (Table 41).

There was one serious adverse event in trial C-02-10 (syncope), which occurred in a subject on olopatadine and no serious adverse events in trial C-02-37 or in vehicle or olopatadine-treated subjects in C-04-70.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

See the next section.

7.1.3.2 Adverse events associated with dropouts

Safety trials C-01-92 and C-05-69

For the first 6 months of C-01-92 and C-05-69, similar numbers of subjects dropped out due to adverse events. In C-01-92, 3.5% of olopatadine and 4.1% of vehicle control subjects discontinued due to adverse events; in C-05-69, 4.9% of olopatadine and 3.4% of vehicle control subjects discontinued due to adverse events.

The numbers of subjects discontinuing due to adverse events was similar in the first 6 months of trials C-01-92 and C-05-69 (Table 3).

Table 3. Comparison of dropout rates due to adverse events in the first 6 months of C-01-92 and C-05-69

	N	n (%)
Olopatadine		
C-01-92*	459	16 (3.5)
C-05-69	445	22 (4.9)
Vehicle		
C-01-92*	465	19 (4.1)
C-05-69	445	15 (3.4)

*PVF (b) (4)-containing formulation
[Source: Alcon Table 4.3.-1]

Alcon did not provide a summary of numbers of subjects in C-01-92 who discontinued for adverse events (regardless of attribution of treatment causality) by adverse event type. Table 4, constructed by this reviewer, compares adverse events associated with withdrawal, using the events that occurred in 2 or more subjects in C-01-92 as the basis for comparison. The full table of events leading to discontinuation in C-05-69 is in Table 42. Adverse events not shown in Table 4 for C-05-69 did not occur at greater than 1 subject per treatment arm, except for rhinitis (3 events in the olopatadine treatment group and 1 in the vehicle treatment group). The proportions of subjects who have discontinued in the first 6 months of C-05-69 is similar to that in the 12 months of C-01-92. Sinusitis as a cause for discontinuation occurred more frequently in both treatment arms in C-05-69, and rhinitis (olopatadine 3 events, vehicle control, 1 event) occurred slightly more frequently. The numbers and nature of discontinuations is not a cause for concern for the new proposed formulation.

Table 4. Comparison of adverse events leading to discontinuation in the 12 months of C-01-92*; similar events used for comparison from the 6 months of C-05-69**

	C-01-92		C-05-69	
Adverse event (COSTART)	**Olopatadine 0.6% PVP (b) (4) N = 459**	**Vehicle PVP (b) (4) N = 465**	**Olopatadine 0.6% N =445**	**Vehicle N = 445**
Patients withdrawing because of adverse events	23 (5.0)	25 (5.4)	22 (4.9%)	16 (3.6%)
All adverse events resulting in withdrawal	29	28	30	20
Taste perversion	4	0	2	0
Nasal discomfort	3	1	0	2
Headache	2	4	1	2
Nasal ulcer	2	2	2	0
Epistaxis	2	1	3	1
Allergic reaction	1	1	**	**
Asthma	1	1	0	2
Sinusitis	1	1	4	4
Dizziness	0	3	0	2
Infection	0	2	-	-
Migraine	0	2	-	-
Nasal septum disorder	0	2***	0	1***

*Events listed for C-01-92 are those that occurred in 2 or more subject overall in the trial
** Adverse events not shown for C-05-69 did not occur at greater than 1 subject per treatment arm except rhinitis (3 olopatadine, 1 vehicle) (see Table 42 for the full table of events leading to discontinuation in C-05-69).
**1 event with Costart term "allergy" occurred in each treatment arm of C-05-69
***Events in C-01-92 were nasal septal perforations; in C-05-69, "Deviated septum at left naris"
[Sources: NDA original submission Medical Officer review and C-05-69 data set AE01.jmp]

Pooled 2-week trials in seasonal allergic rhinitis

Table 5 shows a pooled analysis of the rates of adverse events in the pooled seasonal allergic rhinitis trials (C-02-10, C-02-37, and C-04-70) leading to discontinuation.

Table 5. Summary of adverse events leading to discontinuation in combined trials C-02-10, C-02-37, and C-04-70 (povidone-containing formulation)

Adverse Event (COSTART)	Olopatadine 0.6% N = 587	Vehicle N = 593
	N (%)	N (%)
Headache	4 (0.7%)	1 (0.2%)
Flu syndrome	2 (0.3%)	
Pharyngitis	2 (0.3%)	
Taste perversion	2 (0.3%)	
Cough increased	1 (0.2%)	
Dizziness	1 (0.2%)	
Dyspepsia	1 (0.2%)	
Epistaxis	1 (0.2%)	1 (0.2%)
Gastroenteritis	1 (0.2%)	
Migraine	1 (0.2%)	
Nausea	1 (0.2%)	1 (0.2%)
Pain	1 (0.2%)	
Pneumonia	1 (0.2%)	
Pruritus	1 (0.2%)	
Rhinitis	1 (0.2%)	
Sinusitis	1 (0.2%)	3 (0.5%)
Sneezing	1 (0.2%)	
Syncope	1 (0.2%)	
Arthropod bite		1 (0.2%)
Bronchitis		
Contact dermatitis		1 (0.2%)
Vomiting		1 (0.2%)

[Source: Alcon response to FDA February 25, 2008 request, Table D-3]

In the pooled subject population, 2.4% of olopatadine-treated and 1.3% of vehicle-treated subjects discontinued (Table 6).

Table 6. Summary of subjects discontinuing due to adverse events in combined trials C-02-10, C-02-37, and C-04-70

Trial	Treatment group	Subjects discontinuing
C-02-10	Olopatadine 0.6% n=223	6 (2.7%)
	Vehicle n=225	1 (0.4%)
C-02-37	Olopatadine 0.6% n=184	3 (1.6%)
	Vehicle n=192	2 (1%)
C-04-70	Olopatadine 0.6% n=180	5 (2.8%)
	Vehicle n=176	5 (2.8%)
Total	Olopatadine 0.6% n=587	14 (2.4%)
	Vehicle n=593	8 (1.3%)

[Data from Alcon response to FDA February 25, 2008 request, Tables A-1, B-1, C-1, and D-1]

7.1.3.3 Other significant adverse events: nasal adverse events

Comparison of safety trials in perennial allergic rhinitis

Adverse events related to the nose are the most important aspect of the safety analysis of olopatadine identified in the review of the original NDA. Table 7 shows a comparison of the most frequent nasal adverse events occurring in the first 6 months of C-01-92 and C-05-69 (events that occurred at an incidence of at least 1% in either trial olopatadine group). These adverse events were reported generally more frequently in both treatment groups in C-05-69, the adverse events "nasal ulceration," "epistaxis," and, in particular, "rhinitis." The presence of olopatadine in the formulation was not associated with a remarkable increase over vehicle in events, except possibly in the case of nasal ulceration events (a 3% increase over vehicle control). The reason for this overall increase in nasal events is not clear. Two possible explanations are that the decrease in pH of the formulation (from (b) (4) to 3.7) results in a formulation that is more irritating to the nose, or that reporting was better in the later trial, C-05-69.

Table 7. Comparison of the most frequent* nasal adverse events in the first 6 months of C-01-92 and C-05-69

	C-01-92		C-05-69	
Coded AE (COSTART)	**Olopatadine 0.6% PVP** (b) (4)	**Vehicle PVP** (b) (4)	**Olopatadine 0.6%**	**Vehicle**
Epistaxis	60 (13.1)	31 (6.7)	86 (19.3)	104 (23.4)
Rhinitis	32 (7.0)	43 (9.2)	104 (23.4)	103 (23.1)
Sinusitis	37 (8.1)	39 (8.4)	47 (10.6)	47 (10.6)
Pharyngitis	23 (5.0)	31 (6.7)	35 (7.9)	30 (6.7)
Ulcer nasal	13 (2.8)	16 (3.4)	39 (8.8)	26 (5.8)
Discomfort nasal	6 (1.3)	7 (1.5)	12 (2.7)	13 (2.9)
Dry nose	8 (1.7)	1 (0.2)	7 (1.6)	2 (0.4)

*Occurring in either of the olopatadine groups at an incidence of ≥1%
[Source: Alcon Table 4.2.-3]

A crucial component of the evaluation of safety in these trials was the nasal examination. This aspect is discussed in section 7.1.7.5 (Special assessments: Nasal examination).

Pooled 2-week trials in seasonal allergic rhinitis

Nasal adverse events for the two-week seasonal allergic rhinitis trials C-02-10, C-02-37, and C-04-70 are shown in a combined table of all adverse events from these trials (Table 9, below). Epistaxis, pharyngitis, and rhinitis were nasal events whose incidence was greater than 1% and that occurred more frequently than in vehicle control.

7.1.4 Other Search Strategies

I used no alternative search strategies in the evaluation of this submission.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Clinical trials C-01-92 and C-05-69 called for subjects to attend clinic visits monthly during treatment. At this visit clinic personnel assessed the health history of the subjects, including the solicitation of adverse events, and reviewed a medical problem log on which subjects recorded changes in health between clinic visits. Adverse events were to be recorded as the result of a clinically significant change in vital signs, physical examination, and (in C-01-92) ECG. Importantly, clinically significant changes from baseline in the nasal examination, conducted monthly, were recorded as adverse events. In trial C-05-69 this was a two-step process, in which an initial examination (like the one in C-01-92) may have suggested the need for a more detailed assessment of the nature of the adverse event. This is one reason that the incidence and severity of nasal adverse events cannot be compared directly between the two trials.

The schedule of ascertainment of adverse events in the two-week seasonal allergic rhinitis trials was similar. Among the trials, C-02-37 did not provide for a medical problem log; the other trials did. Subjects were scheduled for a telephone call at a week after treatment and were seen in clinic at 2 weeks.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were categorized using conventional dictionaries. The categorization was adequate, based on a comparison of a selection of adverse event descriptions with COSTART terms.

7.1.5.3 Incidence of common adverse events

See the next section.

7.1.5.4 Common adverse event tables

Comparison of safety trials in perennial allergic rhinitis

Table 8 shows a comparison of the most frequent systemic (that is, non-nasal) adverse events occurring in the first 6 months of trials C-01-92 and C-05-69. The most notable difference between the two trials was the incidence of "infection" and headache, which were reported somewhat more frequently in C-05-69, but at a similar frequency in the two treatment groups in the trial. These data do not show a change in the systemic risk profile with the new formulation.

Table 8. Comparison of most frequent* nonnasal adverse events in the first 6 months of C-01-92 and C-05-69

	C-01-92		C-05-69	
Adverse event (COSTART)	**Olopatadine 0.6% PVP (b) (4) n=459**	**Vehicle PVP (b) (4) n=465**	**Olopatadine 0.6% n=445**	**Vehicle n=445**
Body as a Whole				
Infection	44 (9.6)	55 (11.8)	67 (15.1)	65 (14.6)
Headache	36 (7.8)	42 (9)	55 (12.4)	59 (13.3)
Cold Syndrome	55 (12)	46 (9.9)	52 (11.7)	52 (11.7)
Allergy	18 (3.9)	15 (3.2)	19 (4.3)	20 (4.5)
Injury Accidental	7 (1.5)	3 (0.6)	19 (4.3)	32 (7.2)
Flu Syndrome	16 (3.5)	14 (3)	13 (2.9)	19 (4.3)
Pain Back	16 (3.5)	23 (4.9)	12 (2.7)	12 (2.7)
Surg/Med Proc	8 (1.7)	9 (1.9)	11 (2.5)	14 (3.1)
Pain	12 (2.6)	14 (3.0)	6 (1.3)	6 (1.3)
Cardiovascular System				
Hypertension	3 (0.7)	5 (1.1)	13 (2.9)	15 (3.4)
Digestive System				
Diarrhea	10 (2.2)	5 (1.1)	11 (2.5)	6 (1.3)
Gastroenteritis	11 (2.4)	19 (4.1)	11 (2.5)	12 (2.7)
Musculoskeletal System				
Arthralgia	14 (3.1)	11 (2.4)	10 (2.2)	17 (3.8)
Respiratory System				
Asthma	12 (2.6)	14 (3.0)	19 (4.3)	17 (3.8)
Cough Increased	10 (2.2)	8 (1.7)	16 (3.6)	14 (3.1)
Bronchitis	19 (4.1)	18 (3.9)	15 (3.4)	10 (2.2)
Special Senses				
Taste Perversion	44 (9.6)	4 (0.9)	29 (6.5)	3 (0.7)

*Events occurring at an incidence of over 2.5%
[Source: Alcon Table 4.2.-7]

Pooled 2-week trials in seasonal allergic rhinitis

Table 9 is a summary of adverse events that occurred in 1% or greater in the olopatadine treatment group and at an incidence greater than in vehicle control.

Table 9. Summary of subjects with adverse events occurring at 1% or over in the olopatadine group and at a frequency greater than vehicle in combined C-02-10, C-02-37, and C-04-70

Adverse Event (COSTART)	Olopatadine Nasal 0.6% N = 587	Vehicle N = 593
	N (%)	N (%)
Nasal events		
Epistaxis	18 (3.1)	10 (1.7)
Pharyngitis	15 (2.6)	11 (1.9)
Rhinitis	16 (2.7)	7 (1.2)
Body as a Whole		
Headache	34 (5.8)	31 (5.2)
Respiratory System		
Cough Increased	7 (1.2)	3 (0.5)
Special Senses		
Taste Perversion	75 (12.8)	5 (0.8)
Hyperemia Eye	10 (1.7)	6 (1.0)
Urogenital System		
Urinary tract infection	7 (1.2)	3 (0.5)

[Data from Alcon response to FDA February 21, 2008 request, Table D-1]

Alcon also provided the analysis coded in MedDRA (Table 10). Alcon stated that the MedDRA terminology was applied to the adverse event descriptions, that is, it was not a translation from COSTART. This table is useful as MedDRA terms will be used for labeling. The difference in terminology does not change the reported incidence of events appreciably.

Table 10. Summary of subjects with adverse events occurring at 1% or over in the olopatadine group and at a frequency greater than vehicle in combined C-02-10, C-02-37, and C-04-70 (MedDRA terminology)

Adverse Event (MedDRA)	Olopatadine Nasal 0.6% N = 587	Vehicle N = 593
	N (%)	N (%)
Infections and Infestations		
Urinary Tract Infection	7 (1.2)	3 (0.5)
Nervous System Disorders		
Dysgeusia	75 (12.8)	5 (0.8)
Headache	26 (4.4)	24 (4.0)
Respiratory, thoracic, and mediastinal disorders		
Epistaxis	19 (3.2)	10 (1.7)
Pharyngolaryngeal pain	13 (2.2)	8 (1.3)
Postnasal drip	9 (1.5)	5 (0.8)
Cough	8 (1.4)	3 (0.5)

[Data fromAlcon response to FDA February 21, 2008 request, Table D-2]

Examination of adverse events with respect to age (12-17, 18-64, and ≥65), sex, and race, did not show any remarkable patterns. However, the numbers of nonCaucasians and subjects outside the 18-64-year age category were small, making comparative estimates of event rates problematic.

7.1.5.5 Identifying common and drug-related adverse events

Comparison of safety trials in perennial allergic rhinitis

Table 11 shows a comparison of the 12-month results from trial C-01-92 and the 6-month data from trial C-05-69 regarding adverse events associated with antihistamines and anticholinergic drugs. The data does not suggest that the change in formulation has changed the risk of any of these events notably.

Table 11. Comparison of C-01-92 12-month and C-05-69 6-month incidence of adverse events commonly associated with antihistamines and anticholinergic drugs

COSTART term	C-01-92 (12 months)		C-05-69 (6 months)	
	Olopatadine 0.6% PVP (b) (4) n=459	Vehicle PVP (b) (4) n=465	Olopatadine 0.6% n=445	Vehicle n=445
Dyspepsia	14 (3.1)	9 (1.9)	9 (2)	6 (1.3)
Nausea	6 (1.3)	4 (0.9)	5 (1.1)	9 (2)
Fatigue	5 (1.1)	1 (0.2)	4 (0.9)	4 (0.9)
Somnolence	3 (0.7)	1 (0.2)	1 (0.2)	0
Constipation	3 (0.7)	0	2 (0.4)	4 (0.9)
Dry mouth	2 (0.4)	2 (0.4)	4 (0.9)	3 (0.7)
Weight increase	1 (0.2)	0	5 (1.1)	0
Urinary retention	0	1 (0.2)	0	0

[Sources: Medical Officer original NDA review; Alcon Table 14.3.1.3.1.-1]

Pooled 2-week trials in seasonal allergic rhinitis

Table 12 shows the combined incidence of adverse events commonly associated with antihistamines and anticholinergic drugs in the 2-week controlled trials.

Table 12. Incidence of adverse events commonly associated with antihistamines and anticholinergic drugs in combined trials C-02-10, C-02-37, and C-04-70

COSTART term	Olopatadine 0.6% n= 587	Vehicle n= 593
Dyspepsia	5 (0.9)	1 (0.2)
Nausea	3 (0.5)	7 (1.2)
Fatigue	3 (0.5)	2 (0.3)
Somnolence	5 (0.9)	2 (0.3)
Constipation	2 (0.3)	1 (0.2)
Dry mouth	5 (0.9)	1 (0.2)
Weight increase	1 (0.2)	0
Urinary retention	0	1 (0.2)

[Data from Alcon response to FDA Request of February 21, 2008, Table D-1]

7.1.5.6 Additional analyses and explorations

I did not perform additional analyses and explorations.

7.1.6 Less Common Adverse Events

See section 7.1.5.5, adverse events associated with antihistamines and anticholinergic drugs. See section 7.1.3.3 for a review of the incidence of nasal ulcer and epistaxis, which are of concern in the use of a nasal spray.

7.1.7 Laboratory Findings

Laboratory evaluation was not included in the safety plan for the newly submitted trials of the proposed formulation. See the review of the original NDA for a discussion of all laboratory analyses.

7.1.7.1 Overview of laboratory testing in the development program

See Dr. Lee's review of the original NDA submission for an overview of laboratory evaluations in the development program.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

See section 7.1.7.

7.1.7.3 Standard analyses and explorations of laboratory data

See section 7.1.7.

7.1.7.4 Additional analyses and explorations

I did not perform additional analyses and explorations.

7.1.7.5 Special assessments: Nasal examination

The incorporation in C-05-69 of a second, more detailed examination in certain subjects provided additional information on the effects of olopatadine on the nose.

While three nasal septal perforations occurred in C-01-92 (two in the vehicle control group and one in the olopatadine treatment group), no nasal septal perforations occurred in C-05-69.

Table 13 shows a comparison of the nasal examination in C-01-92 with its counterpart, the initial examination in C-05-69. The data are expressed as the numbers of subjects with a change in the nasal examination from baseline to any visit. In C-05-69 there was a notable increase compared to C-01-92 in the incidence of "blood in the nose" and "possible ulcerations" that was present for both treatment groups. Epistaxis and nasal ulceration in trial C-05-69 were primarily graded as "mild," however. The second part of the nasal exam in C-05-69 showed that verified ulceration occurred in fewer subjects than had "possible ulceration" (41 olopatadine-treated subjects and 28 vehicle-treated subjects who had a second examination). One potential cause of the increase in these events is the lowering of the pH of the formulation from (b) (4) to 3.7. Another potential cause could be differences in monitoring.

Table 13. Subjects with change in nasal parameters from baseline - Baseline to Month 6 Data Set (Section A in C-05-69)

			Anatomic abnormality			Blood in the nose		
Olopatadine 0.6%		Total	N	n	%	N	n	%
	C-01-92*	459	451	2	0.4	451	43	9.5
	C-05-69	445	438	5	1.1	438	67	15.3
Vehicle								
	C-01-92*	465	451	4	0.9	451	23	5.1
	C-05-69	445	438	0	0	438	87	19.9
			Infection			Possible ulcerations		
Olopatadine 0.6%		Total	N	n	%	N	n	%
	C-01-92*	459	451	19	4.2	451	11	2.4
	C-05-69	445	438	18	4.1	438	67	15.3
Vehicle								
	C-01-92*	465	451	21	4.7	451	14	3.1
	C-05-69	445	438	12	2.7	438	61	13.9

**Povidone (b) (4)-containing formulation
[Source: ISS Table 4.4.4.-1]
Note: no nasal perforations occurred in C-05-69; one olopatadine- and two vehicle control-treated subjects experienced nasal perforations in C-01-92

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

See Dr. Lee's review of the original NDA submission for an overview of vital signs testing in the development program. Vital signs were tested in C-01-92 at baseline and at days 30, 90, 180, 270, and at end of trial participation; they were tested at baseline and monthly in C-05-69.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

This review discusses vital signs testing in the long-term trials C-05-69 and C-01-92.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Table 14 shows Alcon's analysis of mean changes in pulse and systolic and diastolic blood pressure changes from baseline to the 6 months in trials C-01-92 and C-05-69. The results show minor changes from baseline to exit in both groups.

Table 14. Comparison of cardiovascular determinations in C-01-92 and C-05-69: Mean changes from baseline to exit visit (6 months) in olopatadine treatment groups

			Overall population		12-17 yrs		18-64 yrs		≥65 yrs	
Parameter	Trial	Statistic	Olo 0.6%	Vehicle	Olo 0.6%	Vehicle	Olo 0.6%	Vehicle	Olo 0.6%	Vehicle
Pulse (bpm)	C-01-92*	*N*	*442*	*434*	*56*	*51*	*379*	*372*	*7*	*11*
		Mean	1.7	1.0	3.0	2.8	1.5	0.6	-1.7	7.0
	C-05-69	*N*	*439*	*438*	*46*	*53*	*382*	*376*	*11*	*9*
		Mean	-0.1	-0.7	-1.2	-2.4	-0.1	0.6	4.4	2.4
Systolic blood pressure (mmHg)	C-01-92*	*N*	*442*	*434*	*56*	*51*	*379*	*372*	*7*	*11*
		Mean	0.6	-0.7	0.3	1.1	0.8	-0.9	-8.2	-2.2
	C-05-69	*N*	*439*	*438*	*46*	*53*	*382*	*376*	*11*	*9*
		Mean	-2.2	-1.8	0.1	0.4	-2.3	-2.0	-8.3	-5.2
Diastolic blood pressure (mmHg)	C-01-92*	*N*	*442*	*434*	*56*	*51*	*379*	*372*	*7*	*11*
		Mean	-0.5	-0.8	-0.6	1.3	-0.4	-1.2	-6.0	-0.5
	C-05-69	*N*	*439*	*438*	*46*	*53*	*382*	*376*	*11*	*9*
		Mean	-1.3	-2.1	-0.3	-2.9	-1.4	-2.0	-2.3	-2.3

*Povidone (b) (4)-containing formulation
[Source: Alcon Tables 4.4.3.-1 and 4.4.3.-2]

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Alcon's integrated summary of safety does not include a comparison of outliers or shifts from normal. However, neither the original review of C-01-92 nor the current review of C-05-69 identified concerning patterns of toxicity based on shift analysis.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Alcon's integrated summary of safety does not include a comparison of outliers or dropouts or vital sign abnormalities. However, neither the original review of C-01-92 nor the current review of C-05-69 identified concerning patterns of toxicity based on vital sign abnormalities considered as adverse events.

7.1.8.4 Additional analyses and explorations

I performed no additional analyses and explorations of the vital sign data.

7.1.9 Electrocardiograms (ECGs)

Alcon did not perform electrocardiographic monitoring in C-05-69. FDA had told Alcon in a meeting of June 30, 2006 that further electrocardiographic data would not be needed provided that the new formulation stayed as a solution and that systemic exposure would not be expected to change. No comparison of the new formulation to the older formulation on potential electrocardiographic effects is possible.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Dr. Charles Lee's clinical review of the original NDA included a summary of the electrocardiographic testing in the development program:

> ECGs were performed as safety endpoints in 10 studies in this application: in three PK and safety studies with oral olopatadine (C-00-23, C-02-54, and C-03-10), two PK and safety studies with single dose exposure to olopatadine 0.6% nasal spray (C-02-46 and C-03-11), three non-pivotal SAR studies (C-00-10, C-00-33, and C-01-05), one PK study (C-00-58) with 0.1% and 0.2% concentrations of olopatadine, and one long-term pivotal PAR study (C-01-92). For each study, the effects of olopatadine on ECG parameters were analyzed, including an evaluation of mean changes in ECG intervals, categorical analysis of QT/QTc data, and evaluation of ECG abnormalities [Module 2, Volume 7, Section 2.7.4.4, page 76].

ECG evaluation was not performed as a safety parameter in the trials submitted in support of the new proposed formulation.

Dr. Lee summarized the preclinical cardiovascular and electrocardiographic preclinical results in his original NDA review:

> In non-clinical studies, olopatadine showed an antihypertensive effect in dogs in a dose dependent manner at 20, 50, & 100 mg/kg (59% decrease at high dose) with decreased total peripheral resistance. At <5mg/kg iv, no effects on heart rate, ECG & respiratory rate were observed. At <30mg/kg iv there were no effects on QTc. The IC50 for hERG channel is 1000X greater than for terfenadine. In studying the effect of the combination of olopatadine and itraconazole (to block CYP 3A4) on the ECG in conscious dogs, olopatadine alone causes a greater increase in heart rate and mean blood pressure (in contrast to an earlier experiment where olopatadine caused hypotension) than when administered along with itraconazole, while QT tended to be less affected. These data suggest that olopatadine may not elicit QT prolongation even when co-administered with the CYP 3A4-inhibitor itraconazole. In another study on the effects of olopatadine HCl on cloned hERG channels, olopatadine blocked hERG channels with an IC50 of 1.1 mM. This block showed no use or time dependence [Gary Bond, Ph.D., Pharmacology Review, NDA 21-861, N-000, 12/24/04].

Alcon previously submitted C-02-54, a cardiovascular safety and pharmacokinetics study of twice-daily dosing of 20 mg olopatadine solution or placebo for 14 days in healthy adults. Dr. Sandra Suarez, the Office of Clinical Pharmacology reviewer, found that some placebo corrected ΔQTc values (ΔΔQTc) were higher than 10 msec at some time points due to large negative ΔQTc values for placebo. Dr. Suarez concludes in her review of this trial that the lack of a positive control in the study makes differences from placebo in corrected QTc values uninterpretable. However, she concludes that "the lack of cardiovascular safety concerns from the phase 3 clinical trials, lack of postmarketing cardiovascular signal for the approved olopatadine tablet, no influence on the QT interval in hypokalemia-anesthetized dogs, and lack of potential for drug-drug interactions also suggest that olopatadine is unlikely to prolong QTc interval at the proposed therapeutic dose."

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

See section 7.1.9.

7.1.9.3 Standard analyses and explorations of ECG data

See section 7.1.9.1

7.1.9.4 Additional analyses and explorations

Alcon did not perform any special clinical studies for this submission. The original NDA review discusses two high-dose cardiac safety studies performed by Alcon.

7.1.10 Immunogenicity

Alcon did not test for the presence of olopatadine antibodies in the clinical program. Olopatadine, as a small molecule, is not expected to be immunogenic.

7.1.11 Human Carcinogenicity

Alcon did not perform human carcinogenicity studies in the clinical program.

7.1.12 Special Safety Studies

Alcon conducted two high-dose cardiac safety trials and submitted the results with the original NDA. These trials are discussed in the original clinical and pharmacology/biopharmaceutics reviews.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

In this submission Alcon has reported no withdrawal phenomena or abuse. There were no reports of withdrawal or rebound phenomena in the clinical development program described in the original NDA.

7.1.14 Human Reproduction and Pregnancy Data

The clinical trials in this submission, as well as the original submission, excluded pregnant females. Three subjects in trial C-05-69, one in the olopatadine treatment group and two in the vehicle group, discontinued participation as a result of becoming pregnant, but the outcome of pregnancy is not reported.

The original NDA review summarized product labeling for olopatadine 0.1% ophthalmic solution (Patanol). This information has not been revised, but is included here for ease of review:

> Olopatadine administered to male and female rats at oral doses of 62,500 times MROHD level resulted in a slight decrease in the fertility index and reduced implantation rate; no effects on reproductive function were observed at doses of 7,800 times the maximum recommended ocular human use level.

> Pregnancy: Pregnancy Category C. Olopatadine was found not to be teratogenic in rats and rabbits. However, rats treated at 600 mg/kg/day, or 93,750 times the MROHD and rabbits treated at 400 mg/kg/day, or 62,500 times the MROHD, during organogenesis showed a decrease in live fetuses. There are, however, no adequate and well controlled studies in pregnant women. Because animal studies are not always predictive of human responses, this drug should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the embryo or fetus.
>
> Nursing Mothers: Olopatadine has been identified in the milk of nursing rats following oral administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in the human breast milk. Nevertheless, caution should be exercised when PATANOL® (olopatadine hydrochloride ophthalmic solution) 0.1% is administered to a nursing mother.

Olopatadine is available in Japan and Korea as 2.5 mg tablets, and in Japan also as 5 mg tablets. In Japan it is approved for treatment of allergic rhinitis, urticaria and itching resulting from cutaneous diseases. Product labeling for Allelock, states,

> Allelock should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. Safety of the administration during pregnancy has not been established.
>
> Lactating women should not be given Allelock. If treatment with this drug is judged to be essential, breast feeding must be discontinued during treatment. Animal studies (rats) reported excretion of this drug in breast milk and weight increase inhibition of the neonates.

7.1.15 Assessment of Effect on Growth

Alcon has not conducted studies of the effect of olopatadine nasal spray on growth in the overall clinical development program. Labeling for Pataday and Patanol do not contain information on growth; nor does product labeling for Allelock. There were no reports of the effect on growth in Alcon's literature submission. A PubMed search using the terms "olopatadine" and "growth" as text words did not produce any published work on olopatadine and growth.

7.1.16 Overdose Experience

Alcon's postmarketing reports for the ophthalmic solution since the time of the original submission state that no one has reported an overdose as a postmarketing event. The December 18, 2006 to December 17, 2007 periodic update report for Allelock lists 5 cases of overdose:

- 61 year-old man took 35 mg and experienced somnolence, and "spontaneously recovered" after two days
- 16 year-old boy took 130 mg, had somnolence, and slept through the following day
- 3 year old who may have taken 22.5 mg, whose symptoms are not described, but who "spontaneously recovered" the following day

- 13 year-old boy took 40 mg and had no adverse reaction
- 89 year-old who took 40 mg along with other medications (epinastine, fluvoxamine maleate, and famotidine, who was found after 12 hours, and had "no abnormality such as sleepiness."

These reports do not point to a new safety concern with overdose.

7.1.17 Postmarketing Experience

Ophthalmic formulation

Olopatadine has been marketed by Alcon as an ophthalmic solution at 1 mg/ml and 2 mg/ml. Alcon provided postmarketing information regarding olopatadine ophthalmic formulations from December 1, 2004 through January 31, 2008. The great majority of the product was sold as the (b) (4). During this time period, about (b) (4) were sold (this includes sales of (b) (4) each); somewhat less than (b) (4) were sold. Sales of the 2 mg/ml solution are reported during the time period starting July 1, 2007; sales of the (b) (4) were about (b) (4). Sales figures cannot be used to determine the numbers of patients because of the intended episodic nature of the intended use (for symptoms). During the time period of the reports Alcon reports no regulatory actions taken for the product for safety reasons, no reports of drug interactions, overdose, or spontaneous reports of abuse or misuse. A total of 302 MedDRA terms were reported during the time period associated with use of the 1 mg/ml solution, of which about 62% were eye disorders. The rest were in various organ classes; somnolence was reported 3 times and abnormal hepatic function once. Of the 16 MedDRA terms reported with the 2 mg/ml solution, 4 were eye disorders, and the rest various, with no reports of somnolence or abnormal hepatic function). One case of use during pregnancy was reported, without outcome data. Four serious medically-confirmed cases were reported in different organ systems associated with the use of olopatadine ophthalmic preparations. The small number of cases and their varied nature do not suggest a pattern of toxicity.

Oral formulation

Olopatadine is available in Japan and Korea as Allelock 2.5 mg tablets, and in Japan also as 5 mg tablets. In Japan it is approved for treatment of allergic rhinitis, urticaria and itching resulting from cutaneous diseases. Alcon provided postmarketing summaries for Allelock for the time period December 18, 2004 to December 17, 2005 and December 18, 2006 to December 17, 2007. In the former time period (b) (4) 2.5-mg tablets and (b) (4) 5-mg tablets were sold; in the latter period, (b) (4) 2.5-mg tablets and (b) (4) 5-mg tablets were sold. Patient numbers are not reported.

The December 2004-December 2005 report contains an updated summary of a postmarketing clinical experience investigation involving cases actively collected. Among 7880 patients reviewed for safety, the incidences of events were not different from those reported from the review of this surveillance in the original NDA. The most common adverse events were somnolence (5.9%), malaise (0.33%), thirst (0.28%), aspartate aminotransferase increased (0.18%), alanine aminotransferase, blood LDH, and gamma glutamyltransferase increased (each 0.15%), eosinophil count increased and hemoglobin decreased (0.14% each) and dizziness and headache (each 0.13%). The outcomes of 3 pregnancies were reported: there was one miscarriage, and no problems were reported for the other two for either mother or child.

Between December 18, 2004 to December 17, 2005, 18 serious adverse reactions from 14 patients were reported. Liver disorder was reported in two patients and hepatic function abnormal and hepatitis in one patient each; other reactions were various. Between December 18, 2006 to December 17, 2007, 16 serious drug reactions occurred, of which three were liver-related: hepatic function abnormal, jaundice, and liver disorder.

In summary, the review of postmarketing and spontaneous adverse event reports for olopatadine ophthalmic solution 0.1% (Patanol®) in the original NDA did not identify a safety signal relevant to olopatadine nasal spray. The current update does not identify a new safety signal. The original NDA review noted that Japanese postmarketing adverse event reports for olopatadine 2.5 and 5 mg tablets suggested that olopatadine tablets may be associated with hepatic function abnormalities and noted that the Japanese regulatory agency had added hepatic function abnormal, liver disorder, acute hepatitis, and jaundice to the product label for olopatadine 2.5 mg and 5 mg tablets based these postmarketing reports. Updated information shows that liver-related adverse events continue to be reported. There has no signal for hepatic function abnormality in the olopatadine nasal spray program. However, if olopatadine 0.6% nasal spray is approved, postmarketing adverse event reports for olopatadine nasal spray should be monitored for cases of hepatic function abnormalities.

Reviewer comment

Postmarketing information reviewed here does not include Allelock information for the period December 18, 2005 to December 17, 2006. This information was requested from Alcon in February, 2008, but did not arrive in time for review. The current submission contains two of three years of data requested. In addition, information for the period December 200-2004 regarding Allelock, related to the use of over (b) (4) tablets, was reviewed in the original NDA submission. The missing information is very unlikely to change the understanding of the safety of olopatadine notably, and the decision on market approvability for olopatadine nasal spray can be made without it.

Review of the submitted postmarketing data does not suggest a safety concern that would preclude market approval.

7.2 Adequacy of Patient Exposure and Safety Assessments

The chief source of safety data in the current submission, C-05-69, exposed over 300 subjects to olopatadine 0.6% nasal spray at the proposed dose and frequency for over 6 months. FDA discussed the design of trial C-05-69 with Alcon prior to the NDA submission and stated that 6 months of data would be sufficient for a marketing approval decision.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The submission contains two trials studying the proposed formulation (Table 1). Trial C-05-69, the primary source of safety information, enrolled 890 subjects, of whom 445 received olopatadine 0.6% nasal spray. C-05-64 was a single-dose pharmacodynamic trial in an environmental exposure unit in symptomatic subjects with seasonal allergic rhinitis (C-05-64) that enrolled 406 subjects, of whom 204 received olopatadine 0.6% nasal spray. This single-dose trial provides very little safety information. It is reviewed in the appendix.

The results of trial C-04-70, a trial that studied the prior formulation of olopatadine, may be pooled with those of trials C-02-10 and C-02-37 to gain a better understanding of the rates of safety events with two weeks of exposure in subjects with seasonal allergic rhinitis. Trial C-04-70 enrolled 180 subjects in the olopatadine and 176 subjects in the vehicle control groups.

7.2.1.2 Demographics

Dr. Charles Lee's review of the original NDA describes the demographics of the overall clinical program for the povidone-containing formulation as fairly comparable to that of the general population. The demographics of currently submitted trials are similar to the ones previously submitted, as shown below.

Table 15 shows that the demographics of C-01-92 were similar to those of the currently-submitted safety trial, C-05-69 (see Table 31).

Table 15. Demographics of subjects in previously submitted safety trial C-01-92 ((b) (4) povidone-containing formulation)

Characteristic	Vehicle placebo N = 465		Olopatadine NS, 0.6% N = 459		Total N = 924	
Gender	n	(%)	n	(%)	n	(%)
Male	165	(35.5)	156	(34.0)	321	(34.7)
Female	300	(64.5)	303	(66.0)	603	(65.3)
Race	n	(%)	n	(%)	n	(%)
Caucasian	368	(79.1)	360	(78.4)	728	(78.8)
Black	33	(7.1)	29	(6.3)	62	(6.7)
Asian	19	(4.1)	16	(3.5)	35	(3.8)
Hispanic	42	(9.0)	49	(10.7)	91	(9.8)
Other	3	(0.6)	5	(1.1)	8	(0.9)
Age, years						
Mean age	35.2		36.9		36.1	
SD	13.9		13.9		13.9	
Range	12-79		12-78		12-79	
Age subgroups, years	n	(%)	n	(%)	n	(%)
0-12	7	(1.5)	7	(1.5)	14	(1.5)
13-64	447	(96.1)	445	(96.9)	892	(96.5)
>64	11	(2.4)	7	(1.5)	18	(1.9)

[Source: Medical Officer's review of original NDA, Table 91, based on original Alcon NDA, Module 5, volume 65, pp99-100]

Table 16 shows that the demographics of C-04-70 were similar to the demographics of the previously submitted efficacy and safety trials in seasonal allergic rhinitis, C-02-10 and C-02-37.

Table 16. Demographics of short-term trials of povidone-containing formulation in seasonal allergic rhinitis

	C-02-10		C-02-37		C-04-70	
	Olopatadine 0.6% n=223	**Vehicle n=225**	**Olopatadine 0.6% n=184**	**Vehicle n=192**	**Olopatadine 0.6% n=180**	**Vehicle n=176**
Age						
Mean (yrs)	37.2	40.3	35.6	35.5	35.7	36.6
Std dev. (yrs)	14.9	14.9	12.6	13.9	12.8	13.1
Min, max (yrs)	12, 75	12, 80	12, 71	12, 80	12, 70	12, 77
Ranges (yr) (n, %)						
12 - 64 years	211 (94.6)	209 (92.9)	181 (98.4)	187 (97.4)	177 (98.3)	174 (98.9)
≥65	11 (4.9)	15 (6.7)	3 (1.6)	5 (2.6)	3 (1.7)	2 (1.1)
Sex (n,%)						
Male	79 (35.6)	86 (38.4)	63 (34.2)	80 (41.7)	52 (28.9)	61 34.7)
Female	143 (64.4)	138 (61.6)	121 (65.8)	112 (58.3)	128 (71.1)	115 (65.3)
Race (n,%)						
Caucasian	140 (63.1)	149 (66.5)	138 (75.0)	142 (74.0)	136 (75.6)	133 (75.6)
Black	16 (7.2)	6 (2.7)	16 (8.7)	23 (12.0)	19 (10.6)	18 (10.2)
Asian	7 (3.2)	1 (0.4)	2 (1.1)	2 (1.0)	2 (1.1)	2 (1.1)
Hispanic	58 (26.1)	67 (29.9)	24 (13.0)	23 (12.0)	22 (12.2)	23 (13.1)
Other	1 (0.5)	1 (0.4)	4 (2.2)	2 (1.0)	1 (0.6)	0

[Sources: Alcon C-04-70 trial report Tables 11.2.1.-1 and 11.2.1.-2; Medical Officer's review of original NDA, Tables 34 and 60]

Table 17 shows a summary of the demographics from C-02-10, C-02-37, and C-04-70.

Table 17. Summary of demographics from combined C-02-10, C-02-37, and C-04-70

	Olopatadine 0.6% n=587	**Vehicle n=593**	**Combined n=1180**
Age			
Ranges (yr) (n, %)			
12-17	53 (9.0)	53 (8.9)	106 (9.0)
18 - 64 years	517 (88.1)	518 (87.3)	1035 (87.7)
≥65	17(2.9)	22 (3.7)	39 (3.3)
Sex (n,%)			
Male	194 (33.0)	227 (38.3)	421(35.7)
Female	393 (67.0)	366(61.7)	759 (64.3)
Race (n,%)			
Caucasian	414 (70.5)	424 (71.5)	838 (71.0)
Black	51 (8.7)	47 (7.9)	98 (8.3)
Asian	11 (1.9)	5 (0.8)	16 (1.4)
Hispanic	105(17.9)	114 (19.2)	219 (18.6)
Other	6 (1.0)	3 (0.5)	9 (0.8)

[Source: data from Alcon response to FDA February 27, 2008]

7.2.1.3 Extent of exposure (dose/duration)

Table 18 shows exposure to study drug up to the 6-month time point in trials C-01-92 and C-05-69. In C-01-92, exposure was slightly greater in the olopatadine group, a pattern that was

reversed in C-05-69, but the differences are slight. Between 77-81% of subjects stayed on treatment for at least 180 days in the two trials.

Table 18. Exposure up to 6 months in trials C-01-92 and C-05-69 (n, % of group or total)

Trial	Treatment	N	1-30 days	31-60 days	61-120 days	121-179 days	≥180 days
C-01-92	Olopatadine 0.6% PVP (b)	459	14 (3.1)	14 (3.1)	21 (4.6)	37 (8.1)	373 (81.3)
	Vehicle PVP (b)	465	26 (5.6)	24 (5.2)	25 (5.4)	33 (7.1)	357 (76.8)
	Total	*924*	*40 (4.3)*	*38 (4.1)*	*46 (5.0)*	*70 (7.6)*	*730 (79.0)*
C-05-69	Olopatadine 0.6%	445	26 (5.8)	8 (1.8)	34 (7.6)	41 (9.2)	336 (75.5)
	Vehicle	445	25 (5.6)	12 (2.7)	26 (5.8)	30 (6.7)	352 (79.1)
	Total	*890*	*51 (5.7)*	*20 (2.2)*	*60 (6.7)*	*71 (8.0)*	*688 (77.3)*

[Source: Alcon Table 4.1.-1]

Table 19 shows exposure data from the 2-week seasonal allergic rhinitis trials. Exposure was sufficiently similar among the trial to allow pooling the safety information from these trials.

Table 19. Exposure in 2-week seasonal allergic rhinitis trials

		1-6 days	7-16 days	>16 days	Mean (days)	Median (days)
C-02-10	Olopatadine 0.6% n=223	5 (2.2)	206 (92.4)	12 (5.4)	14.9	15
	Vehicle n=225	2 (0.9)	206 (91.6)	17 (7.6)	15.1	15
C-02-37	Olopatadine 0.6% n=184	5 (2.7)	113 (61.4)	66 (35.9)	15.7	16
	Vehicle n=192	2 (1.0)	119 (62.0)	71 (37.0)	16	16
C-04-70	Olopatadine 0.6% n=180	1 (0.6%)	86 (47.8%)	93 (51.7)	16.8	17
	Vehicle n=176	3 (1.7%)	84 (47.7%)	89 (50.6)	16.5	17

[Sources: Alcon C-04-70 trial report Tables 12.1.-4 and text; Medical Officer's review of original NDA, Tables 52 and 78]

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No clinical studies other than C-05-69 and C-05-64 provided data for safety of the proposed formulation.

7.2.2.2 Postmarketing experience

I review Alcon's submission of postmarketing data in section 7.1.17.

7.2.2.3 Literature

Alcon provided abstracts of laboratory studies, case reports, clinical trials, and reviews, of various formulations of olopatadine in response to a request for a summary of literature regarding olopatadine published since submission of the original NDA. This submission did not contain information affecting the judgment of safety and efficacy of the proposed product in the current NDA.

7.2.3 Adequacy of Overall Clinical Experience

The clinical data in the current submission, in conjunction with previously provided information related to safety, are adequate for an assessment of the safety of the proposed formulation.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Alcon submitted new animal studies to address the toxicology of potential degradants. These studies were deemed adequate by the toxicology reviewer.

7.2.5 Adequacy of Routine Clinical Testing

In trial C-05-69 subjects attended monthly visits at which adverse events are assessed and nasal exams conducted. This trial did not include evaluation of ECG or clinical laboratory determinations. However, the trial was intended primarily to address the issue of nasal toxicity, and included a more intensive evaluation of the nose in case initial examination indicated a clinically significant change from the baseline examination. In this sense C-05-69 provided a more intensive and potentially more accurate assessment of nasal toxicities than C-01-92.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The submission contains no new information about metabolism and clearance, nor a systematic exploration of drug interactions. However, the original NDA contained adequate information, and new information is not required.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Nasal septal perforations, which were noted with the previous formulation of olopatadine, are not expected for a nasal antihistamine, but have been seen with nasal corticosteroids. The toxicity that was addressed in the current submission was not thought to be a drug effect, but a byproduct of the formulation. C-05-69 was designed to look intensively at the effects of the product on the nose by incorporating a potentially two-part nasal examination. This examination was adequate to address the issue of nasal effects noted with the povidone-containing formulation. No special measures were taken to look for antihistamine class effects.

As pointed out in the review of the original NDA, the incidence of somnolence in subjects treated with placebo twice daily in the clinical development program for olopatadine nasal spray up to the time of the original NDA submission (2/1008) was lower than normally seen in seasonal allergic rhinitis trials of antihistamines in adults. This suggests that the sensitivity of the clinical trials to the detection of somnolence was lower than optimal.

I do not recommend special postmarketing studies of the expected incidence of somnolence in postmarketing studies. However, based on the overall data in the clinical program, I recommend (b) (4).

7.2.8 Assessment of Quality and Completeness of Data

The data were collected adequately to permit an assessment of safety.

7.2.9 Additional Submissions, Including Safety Update

By agreement with FDA, Alcon is to submit a summary of 12-month safety in trial C-05-69 for review prior to the marketing approval decision.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The important treatment-related adverse events seen in the review of the original NDA, as summarized by Dr. Charles Lee, were epistaxis, taste perversion, dry nose, somnolence, nasal ulcer, nasal septum disorder, and nasal septum perforation.

Table 43 shows events that occurred more frequently in olopatadine-treated subjects than in vehicle-treated subjects in trial C-05-69. Nasal ulcers (occurring in 8.8% of olopatadine-treated and 5.8% of vehicle treated subjects) and taste perversion (occurring in 6.5% of olopatadine-treated and 0.7% of vehicle treated subjects) were the most notable events. No nasal septal perforations occurred in trial C-05-69. Epistaxis occurred commonly in the trial as a whole (19.3% of olopatadine-treated and 23.4% of vehicle-treated subjects).

Trial C-05-69 was adequately designed to address the issue of nasal septal perforations. Safety findings in the current submission are not a bar to marketing approval of the proposed formulation.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

For the important events of local nasal toxicity, it is not appropriate to pool results from the long-term safety trials C-01-92 and C-05-69, as they studied different formulations. However, it is appropriate to pool safety results from trial C-04-70 with the safety data from the previously-submitted seasonal allergic rhinitis 20-week trials. The general features of these trials have been discussed in previous sections.

7.4.2 Explorations for Predictive Factors

Review of the adverse event data from C-05-69 did not reveal patterns according to the sex or race of the subject, although there were relatively few non-Caucasian subjects. There were too few subjects outside the age group 18-64 to associate greater risk with extremes of age. Alcon did not perform a study of a new dose level or frequency, for time dependency, or drug-disease interactions for this submission. For information on drug-demographic interactions, see section 7.4.2.

7.4.3 Causality Determination

The information in this submission is from trials that were vehicle-controlled. The comparison to an inactive treatment provides compelling evidence of treatment relationship.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The support for the dosing regimen for olopatadine 0.6% nasal spray is summarized in the review of the original NDA. Alcon proposes that the recommended dose of olopatadine 0.6% nasal spray is two sprays per nostril twice daily.

8.2 Drug-Drug Interactions

The current submission contains no new formal analysis of drug-drug interactions. This information was not required.

8.3 Special Populations

8.4 Pediatrics

Alcon's efficacy trials studied a population as young as 12 years old. As summarized in section 2.5 of this review, at Alcon's request, on July 19, 2007, FDA issued a Written Request for pediatric studies. Alcon has submitted two pediatric study protocols to IND 60116. In the current NDA submission, Alcon is requesting a deferral of submission of information regarding use of olopatadine 0.6% nasal spray in patients from the age of 2 to 12 years old. In the October 15, 2007 FDA letter of acknowledgement of receipt of NDA 21861, FDA deferred submission of pediatric studies until July 1, 2009. Alcon states that enrollment into the first of the pediatric trials has begun, and that all trials and data conducted in pediatric patients will be submitted to FDA on or before July 1, 2009.

Alcon also requests a waiver of any requirement to submit information on the use of olopatadine 0.6% nasal spray in patients below the age of 2 years. Alcon's reasons are 1) It is unlikely that the product would be used in a substantial number of patients because

nonpharmacologic treatments, such as avoidance of allergens, may be used first, and 2) it is "highly impractical" to treat children under 2 years of age with nasal sprays and studies would "pose a significant problem." FDA may grant a waiver of the requirement to perform studies below the age of 2 years because seasonal allergic rhinitis does not occur below the age of 2 years.

8.5 Advisory Committee Meeting

The submission does not require input from an advisory committee.

8.6 Literature Review

FDA asked Alcon to submit a summary of the literature regarding olopatadine published since the time of the original NDA submission until the cutoff date for the resubmission. Alcon provided abstracts of laboratory studies, case reports, clinical trials, and reviews, of various formulations of olopatadine. This information does not change the judgment of safety and efficacy of the proposed product in the current NDA.

8.7 Postmarketing Risk Management Plan

Because Alcon's olopatadine 0.6% nasal spray cannot be approved at this time, recommendations on risk management activity would be premature.

8.8 Other Relevant Materials

Alcon submitted labeling for Allelock. Allelock is available as 2.5 and 5 mg tablets. The Core Data sheet contains a summary of "Adverse Reactions" using data "from clinical trials before approval, drug use-results survey and special survey for long-term use include a total of 1,402 adverse reactions reported from 1,056 patients (11.0%) among 9,620 patients treated."

The report states that the most frequently observed adverse reactions included sleepiness in 674 patients (7.0%), ALT (GPT) increased in 68 (0.7%), malaise in 53 (0.6%), AST (GOT) increased in 46 (0.5%), and thirst in 36 (0.4%).

Labeling for Allelock states the following as "clinically significant adverse reactions:" "Hepatic function disorder with increases of AST (GOT), ALT (GTP), γ-GTP, LDH and Al-P, etc. and jaundice may occur."

Reactions occurring in ≥0.1% to <5% were:

- Rash, including erythema, etc., edema (face, extremities, etc.)
- Malaise, thirst, dizziness, headache,/dull headache
- Abdominal discomfort, abdominal pain, diarrhea, nausea
- Hepatic function abnormal [GOT, GPT, γ-GT, LDH, Al-P and T-Bil increased]
- Leukocytosis, leucopenia, eosinophilia, lymphopenia
- Occult blood in urine
- Serum cholesterol increased

Reactions occurring in <0.1% were:

- Itching, dyspnea
- Numbness, mental concentration decreased
- Constipation, stomatitis/angular stomatitis, tongue pain, heartburn, increased appetite
- BUN increased, blood creatinine increased, urinary protein positive, dysuria, pollakiuia
- Palpitation, blood pressure increased
- Urine sugar positive, chest discomfort, taste abnormality, weight increased, hot flushes

Other disorders whose incidence is unknown were "involuntary movement (face, extremities, etc.)," menstrual disorder, myalgia, and arthralgia.

The methods used to produce the summaries were not included in the labeling. In addition, potential population differences may complicate the understanding of these data, which do not come from the U.S. population. There was no signal for hepatic function abnormality in the olopatadine nasal spray clinical program. Nor did serious adverse events occur with any pattern to suggest toxicity. However, I concur with Dr. Charles Lee's recommendation from the review of the original NDA that postmarketing adverse event reports for olopatadine nasal spray should be monitored for cases of hepatic function abnormalities.

This review includes the adverse reactions summary as an indicator of potential safety issues that may occur with the use of olopatadine nasal spray.

9 OVERALL ASSESSMENT

9.1 Conclusions

The current resubmission provides data sufficient to judge that the efficacy measured in the pivotal 2-week trials in seasonal allergic rhinitis submitted with the original NDA would be applicable to the current formulation. Similarly, the 6-month results of the 12-month safety trial in subjects with perennial allergic rhinitis showed no findings that would preclude marketing approval of olopatadine 0.6% nasal spray. Specifically, there were no nasal septal perforations and other nasal findings were acceptable. No new systemic findings were apparent.

9.2 Recommendation on Regulatory Action

The submission contains information adequate to approve Alcon's olopatadine 0.6% nasal spray for its intended use. I recommend an "Approvable" action if the manufacturing site inspection cannot be completed during this review cycle.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

I do not recommend risk management activities for this application.

9.3.2 Required Phase 4 Commitments

I do not recommend Phase 4 commitments for this application

9.3.3 Other Phase 4 Requests

I do not recommend Phase 4 requests for this application.

9.4 Labeling Review

(b) (4)

9.5 Comments to Applicant

I recommend that the Division of Pulmonary and Allergy Products send comments based on the comments in the preceding section to Alcon.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 C-05-64: Olopatadine Nasal Spray 0.6% vs Vehicle in Treating Seasonal Allergic Rhinitis Patients in an Environmental Exposure Chamber

10.1.1.1 Protocol

10.1.1.1.1 Objective and overall design

Trial C-05-64 was a single-center, single-dose, vehicle-controlled, randomized, double-blind trial whose principal objective was the determination of efficacy of the newly-proposed, povidone-free olopatadine nasal spray formulation. The trial was designed to assess subjective responses in a population of allergen responders on a self-reported nasal symptom score questionnaire after exposure to allergen in an environmental exposure unit, and was intended to

provide crucial evidence supporting the clinical efficacy of the new formulation of olopatadine nasal spray. The trial in large part replicated the design of trial C-01-83, a single-dose, environmental unit trial submitted with the original NDA, except that in C-05-64 only one dose level was tested.

10.1.1.1.2 Procedures

This review will discuss protocol procedures first (Table 20 and Table 21), as this will give context to eligibility criteria, to be described subsequently.

During a qualifying phase candidates for randomization were to attend 4 visits: a Screening Visit (Visit 1), two Priming Visits (Visit 2a and 2b) and a Treatment Day Visit (Visit 3 pre-dose). Candidates were to be screened by medical history and nasal and skin prick tests at Visit 1. Qualifying candidates were to attend Visit 2a, at which medical histories and medications were reviewed for changes that could affect eligibility. At this visit they were to be exposed to short ragweed allergen for 3 hours in an environmental exposure unit (EEU), a room approximately 40 feet wide, 60 feet long, and 10feet high in which pollen is dispersed in HEPA-filtered air to an average pollen count of 3500±500 grains/m^3. Candidates recorded their nasal symptoms as a Total Nasal Symptom Score (TNSS): For each of the symptoms "runny nose," "itchy nose," "stuffy nose," and sneezing, the subject was to record a response on a scale from 0-3 (none, mild, moderate, and severe). Those who recorded a score of at least 6 out of a possible 12, with at least 2 for runny nose, on 2 consecutive diary cards were to proceed to a second priming visit (2b), at which the procedures were to be repeated. Candidates who recorded the same minimal score were to proceed to Visit 3 at least 24 hours but not more than 2 weeks after visit 2b. At Visit 3 candidates had to qualify again for receipt of the test article by recording 6 out of a possible 12 points on any of the 4 qualifying diary cards in the absence of unilateral or bilateral complete nasal blockage. Candidates who failed qualification at any visit prior to the final allergen exposure session (Visits 1, 2a, 2b, or 3a) were to be considered screening or priming failures. While continuing exposure to allergen at Visit 3, qualified subjects were randomized to self treatment (under observation) with either olopatadine nasal spray or vehicle, 2 sprays per nostril. Exposure to allergen continued for another 12 hours. Subjects recorded instantaneous symptom scores on the TNSS, which were the primary outcome determinations.

The trial did not require assessment of the effect of the trial drug on hematology, serum chemistry or electrocardiography.

Table 20. C-05-64: Procedures

Procedures	Visit 1 Screening	Visits 2a - 2b Priming-Baseline*	Visit 3 Treatment*
Informed Consent	X		
Inclusion/Exclusion Criteria	X	X	
Medical and medication history	X	X	X
Nasal Exam	X	X[1]	X
Vital Signs (pulse and blood pressure)	X	X[1]	X
Urine Pregnancy Test if applicable	X		X
Allergic diagnostic test (skin prick) if not in last 12 mo	X		
Review changes in med history and concomitant medications		X	X
Assess allergy symptoms to determine eligibility		X	X
Test article administration			X
Symptom diaries issued and collected		X	X
Medical Problems from first EEC exposure until randomization		X	X
Adverse Events reporting			X
Global Assessment Question (4-12 hrs after test article given)			X
Complete exit form			X

* Visits should not have been less than 24 hours or more than 2 weeks after prior visits.
[1] at Visit 2b
[Source: Alcon Table 9.1.-1]

Table 21. C-05-64: Procedures at Visit 3 (Qualifying and treatment visit)

Event	Time relative to treatment (hr:min)
Patients report to clinic	-3:00
Medical Problem Assessment	Prior to pollen exposure
Pollen exposure begins	-2:00
Qualifying diary cards	-1:30, -1:00, -0:45, -0:30
Medical Problem Assessment & Nasal Congestion Check	Prior to test article administration
Patient blows nose and then receives test article	0:00
Nasal symptom evaluations on diary card	Every 30 mins starting at 0:30-4:00, then every hour from 5:00-12:00
Obtain Vital Signs	1:00 - 3:00 (60-180 minutes)
Global Assessment Question	4:00 and 12:00
Nasal Exam	From 4-12 hrs post dose
Final adverse event assessment	12:00

[Source: Alcon Table 9.1.3.-1]

10.1.1.1.3 Subject eligibility

Subjects were to have seasonal allergic rhinitis and have skin test reactivity to short ragweed allergen. They were to fulfill eligibility criteria assessed during participation in the protocol. Specific medical eligibility criteria were:

Inclusion

- Age at least 18 years
- At least a two-year history of non-recalcitrant seasonal allergic rhinitis during the fall allergy season
- Positive case history and positive skin prick and/or intradermal test for short ragweed allergen (≥3-mm wheal greater than the diluent after skin prick testing, or ≥7-mm wheal greater than the diluent after intradermal testing) within the 12 months prior to Visit 1. If getting a skin test at Visit 1, specified washout times for antihistamines were to be followed
- "Priming" requirement: Fulfillment of the following criteria on each of two consecutive diary cards at a priming visit:

- a minimum TNSS of 6 out of 12, including a score of at least 2 for runny nose

--Patients must meet these same criteria at both priming visits of 3 hours chamber duration in order to proceed to the treatment visit (Visit 3).

- At the treatment visit (Visit 3), a minimum TNSS of 6 out of 12 (including a score of at least 2 for runny nose) on any one of four qualifying diary cards

- Observance of drug washout times, prior to Visit 2a and subsequent visits
- Absence of significant anatomic abnormalities, infection, bleeding, and mucosal ulcerations on nasal exam performed at screening, qualifying priming visit and prior to administration of test article

Exclusion

- Concurrent disease that might complicate or interfere with investigation or evaluation of the study medications such as:
    - Rhinitis medicamentosa
    - Large obstructive nasal polyps
    - Other anatomic nasal deformity that may interfere with the patient's participation in the study, as identified by nasal examination prior to administration of test article
    - Documented evidence of acute or significant chronic sinusitis, or upper respiratory tract infection as determined by the individual investigator
    - Asthma, with the exception of mild intermittent asthma as outlined in the National Asthma Education and Prevention Program Guidelines II, Step I
    - Congestion that would, in the opinion of the investigator, interfere with successful nasal drug administration/absorption (in either nostril)
- Use of prohibited medication
- Known non-responder to antihistamines for symptoms of SAR
- Chronic or intermittent use of inhaled, oral, intramuscular, intravenous, or potent or superpotent topical corticosteroids
- Chronic use of long acting antihistamines and other concomitant medications (e.g., tricyclic antidepressants) that would affect assessment of the effectiveness of study drug(s)
- Any systemic disorder that could interfere with the evaluation of the study medication(s)
- Upper or lower respiratory infection requiring antibiotics within 14 days of the first priming visit
- Diagnosis of sinusitis within 30 days of the initial priming visit
- Any ocular disorder (other than allergic conjunctivitis) including presumed infectious ocular disease (bacterial, fungal, viral, etc.), which could interfere with the evaluation of the study medication
- Hypersensitivity to the study drug(s) or any component of the test articles including benzalkonium chloride

- History of severe or uncontrolled cardiovascular, hepatic, renal and/or other disease/illness that could be expected to interfere with the study.
- History, or evidence, of nasolacrimal drainage system malfunction.
- The need for chronic or intermittent use of any nasal spray (prescription or over the counter) during the study period.

In addition, the protocol included criteria applied to women to avoid pregnancy, to avoid potential interference with participation due to drug use or knowledge of the study protocol, to exclude subjects who had participated in another investigational study within 30 days. The protocol allowed discretion for the investigator to enroll subjects with vital sign measurements outside specified ranges (systolic blood pressure 95 to 160 mmHg, diastolic blood pressure 55 to 90 mmHg, and pulse rate 50 to 100 beats/min) if these were not considered clinically relevant.

10.1.1.1.4 Trial treatment and its blinding

Subjects were to treat themselves with olopatadine or vehicle, 2 sprays per nostril.

The site was to provide trial treatment in white plastic bottles containing a minimal fill volume of 30 ml and delivering 100 µl per actuation once primed. Although olopatadine is known to have a bitter taste, Alcon took physical measures to blind the treatments. Bottles were to be masked with a label with the protocol number, subject number, and a statement that the treatment was to limited to nasal investigational use only.

10.1.1.1.5 Concomitant medications

Prospective patients were not to take specified medications for specified times prior to and after visit 2a. These medications were substantially the same as those for trial C-05-69 (see Concomitant medication section of the review for that trial), with the following additional prohibitions:

- Initiation of or change in immunotherapy
- Systemic, inhaled or ocular corticosteroids within 30 days
- Leukotriene pathway modifiers, systemic and topical anticholinergics, and systemic antifungal agents within 14 days
- Ocular anti-allergy medications within 7 days
- Oral decongestants, all over-the-counter cold and cough and sleep aids without components listed in other criteria (except saline), as-needed nonsteroidal anti-inflammatory agents, and aspirin (except low-dose for cardiac prophylaxis) within 3 days
- Nasal or ocular saline, or both, within 24 hours

Other drugs were permitted if they would not be expected to interfere with the ability of the subject to participate in the study, after review with the sponsor.

10.1.1.1.6 Analysis

The primary objective of the trial was to measure the superiority of olopatadine nasal spray compared to vehicle over 12 hours after administration as a single dose. The protocol states that differences between treatments at each time point would be used to evaluate the onset of action of each treatment arm.

<u>Populations</u>

The protocol defined the intent-to-treat and safety populations both as all subjects who received trial drug.

Primary effect measurement

The primary efficacy variable was the change from baseline in the TNSS, compared between treatment groups using 2-sample t-tests, with a 2-sided alpha of 0.05.

Secondary effect measurements

Secondary effect variables were 1) changes from baseline to each time point in each of the component scores of the TNSS measured using 2-sample t-tests and 2) the difference between treatment groups in the Patient's Global Rating Scale at each time point using a Cochran-Mantel Haenszel rank scores test. Tests used a 2-sided alpha of 0.05.

Sample size

The sample size of the trial was justified using an assumed treatment difference of 0.65 units in the TNSS change from baseline, with an approximate standard deviation of 2.0 units, and a 2-sided alpha of 0.05. Alcon calculated that this would give approximately 90% power to detect a significant treatment difference.

10.1.1.1.7 Protocol revisions

Alcon made no changes to the protocol or its analysis.

10.1.1.2 RESULTS

10.1.1.2.1 Trial initiation and completion

The trial was started on January 16, 2006 and was completed on March 11, 2006.

10.1.1.2.2 Identification of treatments used

The lot and formula identification numbers of the treatments are shown in Table 22.

Table 22. C-05-64: Identification of treatments

Treatment	Lot number	Formulation identification number
Olopatadine 0.6%	05-600187-1	109941 v.4
Vehicle	05-600188-1	109970 v.2

Alcon used the to-be-marketed olopatadine nasal spray formulation but not the to-be-marketed device for this trial. The device tested in this trial used a prior version of a pump (b) (4) as compared to the current (b) (4) According to a CMC review memorandum (March 4, 2008) regarding the current pump, "no changes have been made to the components of the pump that would be expected to alter the delivery performance." The device used in this trial would be expected to perform as the to-be-marketed device would.

10.1.1.2.3 Subjects

Enrollment and disposition

Four hundred six subjects were enrolled, randomized to treatment, and received trial treatment. No one discontinued.

Demographics and baseline total nasal symptom score

Demographics (Table 23) were balanced between the treatment groups and reflected a population that included very few in the geriatric age group, were balanced by sex, and were predominantly Caucasian.

Table 23. C-05-64: Demographics (ITT and safety population)

	Olopatadine 0.6% n=204	Vehicle n=202
Age		
Mean (yrs)	37.0	36.5
Std dev. (yrs)	12.0	11.5
Min, max (yrs)	18,79	18,76
Ranges (yr) (n, %)		
18 - 64 years	197 (96.6)	198 (98.0)
≥64	7 (3.4)	4 (2.0)
Sex (n,%)		
Male	107 (52.5)	100 (49.5)
Female	97 (47.5)	102 (50.5)
Race (n,%)		
Caucasian	96 (47.1)	106 (52.5)
Black	49 (24.0)	50 (24.8)
Asian	30 (14.7)	19 (9.4)
Hispanic	11 (5.4)	9 (4.5)
Other	18 (8.8)	18 (8.9)

[Source: Alcon Table 11.2.1.-2]

The baseline TNSS was the average of the last two diary cards collected during the allergen exposure prior to treatment (at Visit 3). The scores on each symptom could range from 0-3, so the total could be from 0-12. Scores indicated the presence of symptoms in the trial population, and were balanced between the treatment groups.

Table 24. C-05-64: Baseline instantaneous symptom scores*

		Olopatadine 0.6% n=204	Vehicle n=202
Total Nasal Symptom Score (TNSS)	Mean±std	9.8 ± 1.8	9.5 ± 1.8
	Min, max	4.5, 12.0	3.5, 12.0
Runny Nose	Mean±std	2.6 ± 0.5	2.5± 0.5
	Min, max	1.0, 3.0	1.0, 3.0
Itchy Nose	Mean±std	2.5 ± 0.6	2.5 ± 0.6
	Min, max	1.0, 3.0	0.5, 3.0
Stuffy Nose	Mean±std	2.5 ± 0.5	2.5± 0.6
	Min, max	1.0, 3.0	0.0, 3.0
Sneezing	Mean±std	2.1 ± 0.8	2.1 ± 0.8
	Min, max	0.0, 3.0	0.0, 3.0

*In the presence of allergen in an environmental exposure chamber; average of last 2 diary cards
[Source: Alcon Table 11.2.2.-1]

10.1.1.2.4 Protocol deviations

Protocol deviations occurred in a small number of subjects (22 vehicle, 28 olopatadine). Alcon identified three subjects (all in the olopatadine treatment group) who had what were considered deviations that might affect the efficacy assessment: Two subjects left the environmental chamber temporarily after dosing, and one inadequately washed out an excluded

medication. The most common deviation concerned the nasal examination; this deviation occurred equally in the treatment groups (14 olopatadine subjects, 12 vehicle subjects). The number and nature of the deviations would not be expected to have a notable impact on the effect conclusions of the trial.

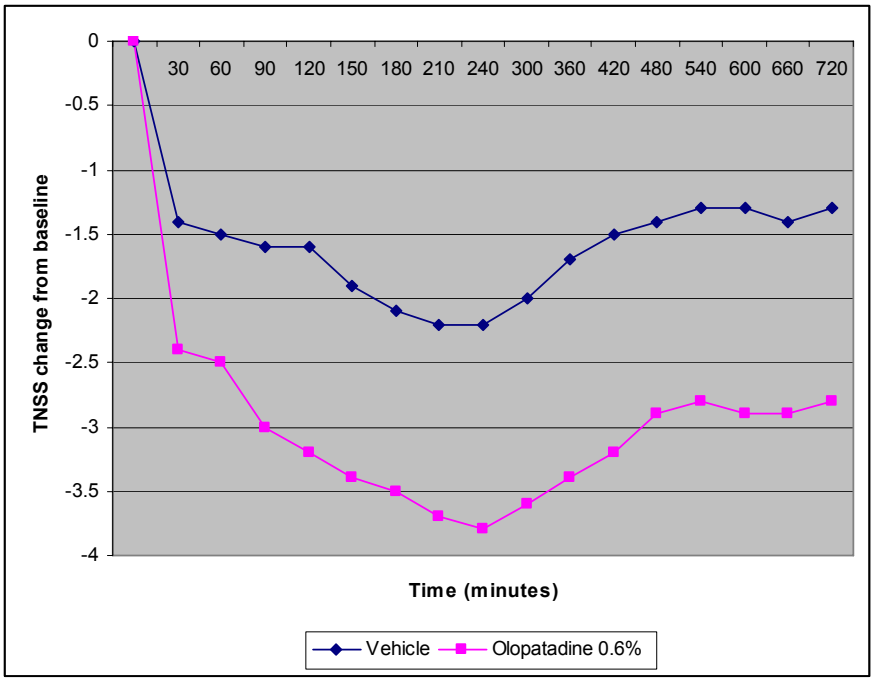
10.1.1.2.5 Compliance to trial treatment

Site personnel were to supervise the administration of the single dose of trial medication. All subjects received a single dose of trial medication.

10.1.1.2.6 Effect (12-hour symptoms)

Figure 1 illustrates the primary outcome, the total nasal symptom score analysis by treatment group expressed as mean change from baseline over the 12 hours after treatment. The analysis uses the last observation carried forward. The statistical test yielded a p-value less than 0.05 at each time point, a result that is corroborated by the analysis of the FDA statistical reviewer.

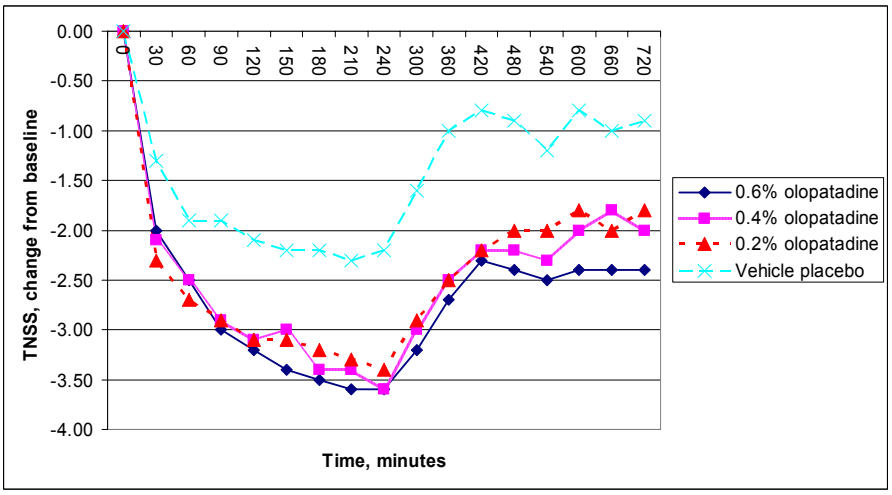
Figure 1. C-05-64: Mean change in Total Nasal Symptom Score at baseline and 12 hrs after treatment (Primary analysis, LOCF)



[Source: Data in Alcon Table 14.2.1.-1]

The treatment effect, including the effects at 30 minutes and 12 hours, is similar to that produced in the single-dose EEU trials C-01-83 and C-03-52, presented in the original NDA. For comparison, I reproduce here Dr. Charles Lee's figure representing the results of C-01-83 (Figure 2):

Figure 2. Data from previous formulation of olopatadine: Trial C-01-83 (Change from baseline TNSS after single dose of vehicle, olopatadine 0.2%, 0.4%, or 0.6%)



[Source: Medical Officer NDA21-861 review, Figure 1]

In C-01-83 and C-03-52, the comparison to placebo achieved a p-value of <0.05 at 90 and 30 minutes, respectively. Because Alcon has demonstrated a statistical difference between olopatadine 0.6% nasal spray in replicate trials at 30 minutes, the onset of action for a single dose may be assessed at 30 minutes.

Secondary outcomes

Individual component scores for the TNSS

The patterns of response from each of the component scores of the TNSS are similar to that of the TNSS, supporting the primary endpoint. For each component there is an early decline followed by persistent improvement compared to vehicle out to the last measurement. For runny nose, itchy nose, and sneezing, Alcon's statistical test yielded a p-value less than 0.05 at each time point throughout the measurement period. For stuffy nose, p-values were less than 0.05 for all time points except 60, 540, and 660 minutes. The FDA statistical review confirms that the components of the TNSS behaved similarly to the total.

Subject global rating scale

The results of the global 7-point rating scale were consistent with the TNSS. Scores overall were worse at 12 hours than at 4 hours in both treatment groups, but remained better than vehicle control overall in the olopatadine treatment group.

10.1.1.2.7 Safety

Adverse events were collected as solicited comments and as observations by the trial investigator and were coded using the COSTART system. Adverse events were coded when there were changes in health after initiation of trial treatment, including changes in concomitant medications due to a new medical diagnosis or a worsening illness. An adverse event was to be recorded for the emergence of a finding on the nasal examination. Changes in rhinitis symptoms recorded on diary cards for efficacy were not recorded as adverse events.

Exposure

All subjects received one dose of trial treatment.

Adverse events

There were no deaths or serious adverse events. No one discontinued due to an adverse event.

Table 25 shows that adverse events were rare, which is expected after a single dose of a nasal antihistamine. Headache was the most common adverse event, occurring more frequently in the vehicle control group.

Table 25. C-05-69: Adverse events occurring in at least 2 subjects in the trial (n,%)

Adverse event	Olopatadine 0.6% N =204	Vehicle N =202
Epistaxis	7 (3.4)	7 (3.5)
Rhinitis	0 (0)	2 (1)
Headache	8 (3.9)	19 (9.4)
Abdominal pain	1 (0.5)	1 (0.5)
Face edema	0	2 (1)
Vomit	1 (0.5)	2 (1)
Dyspepsia	1 (0.5)	1 (0.5)
Pruritus	1 (0.5)	1 (0.5)
Eye edema	0	2 (1)

[Source: Alcon Table 14.3.1.3.1.-1]

The frequency of epistaxis in this study was higher than the frequencies noted in Alcon's previously submitted single-dose environmental chamber studies C-03-52 (0% olopatadine 0.6%, 0.7% vehicle placebo) and C-01-83 (1.3% olopatadine 0.6%, 2.5% vehicle placebo). All the trials were conducted in Ontario, Canada. One possible reason for the discrepancy in epistaxis rates is that C-05-64 was conducted during the winter months, while C-03-52 was conducted during April through June and Study C01-83 was conducted during June and July. Winter weather conditions may have contributed to the increase in epistaxis rates.

Nasal examination

The nasal examination in 6 subjects in the olopatadine treatment group (3.0%) and 5 in the vehicle control group (2.5%) demonstrated bleeding. The nasal examination in 1 subject, in the vehicle control group, demonstrated infection. This review discusses bleeding immediately above. The nasal examination data do not suggest a concern for the safety of the product.

Concomitant medications

Information collected on concomitant medication use from a single-dose trial is of limited usefulness. Alcon recorded medications taken for adverse events. One subject in the olopatadine group took a medication for the adverse event "migraine and vomiting." Three subjects in the vehicle control group took medications for adverse events (headache; headache and vomiting; dizziness and headache). These data do not reveal any new safety concerns.

Cardiovascular findings

Vital signs were obtained at screening, baseline (visit 2b), and at 1-3 hours after the single dose at visit 3. Mean systolic and diastolic blood pressures (Table 26) were lower in the olopatadine treatment group at the exit vital sign determination, but by a clinically insignificant amount. Shift table analysis (Table 27) shows that this was accounted for by a small number of

subjects who had high baseline blood pressure that was normal at exit. Changes in pulse were not notably different between the treatment groups.

Table 26. C-05-64: Pulse and blood pressures at baseline and exit

			Baseline	Exit	Change from baseline
Pulse	Olopatadine 0.6%	N	204	204	204
		Mean±sdev (min, max)	73.1±12.4 (47, 126)	71.4±11.8 (45, 126)	-1.7±10.0 (-44, 28)
	Vehicle	N	202	202	202
		Mean±sdev (min, max)	73.1±10.8 (52,111)	71.7±10.9 (46, 105)	- 1.4±8.1 (-30, 22)
SBP	Olopatadine 0.6%	N Mean	204	204	204
		Mean±sdev (min, max)	126.8±18.0 (76,191)	123.0±16.7 (89, 179)	-3.9±12.2 (-37,37)
	Vehicle	N	202	202	202
		Mean±sdev (min, max)	124.8±16.4 (85,178)	123.7± 15.6 (85, 172)	- 1.1±15.1 (-76, 77)
DBP	Olopatadine 0.6%	N	204	204	204
		Mean±sdev (min, max)	76.6±10.5 (50, 113)	74.6±9.3 (51, 109)	-2.0±7.1 (-23, 17)
	Vehicle	N	202	202	202
		Mean±sdev (min, max)	74.7± 9.6 (50, 107)	73.8±8.9 (52, 100)	-0.9±8.1 (-25, 37)

[Source: Alcon Tables 12.5.2.2.-1, 12.5.2.2.-2, and 12.5.2.2.-3]

Table 27. C-05-64: Pulse and systolic and diastolic blood pressure: Comparison, baseline to exit

		Low Baseline			Normal Baseline			High Baseline		
Pulse	**N**	**Low**	**Normal**	**High**	**Low**	**Normal**	**High**	**Low**	**Normal**	**High**
Olopatadine 0.6%	204	12	11	0	16	152	2	0	9	2
Vehicle	202	10	11	0	15	162	1	0	1	2
SBP										
Olopatadine 0.6%	204	2	5	0	9	139	12	0	18	19
Vehicle	202	2	4	1	6	142	12	0	1	14
DBP										
Olopatadine 0.6%	204	1	3	0	4	171	3	0	13	9
Vehicle	202	2	2	0	5	177	5	0	6	5

* If an increase and decrease of the same magnitude occurred, the increase is reported.
[Source: Alcon Tables 12.5.2.2.-4, 12.5.2.3.-4, and 12.5.2.4.-4]

10.1.1.3 Summary of trial C-05-64

Trial C-05-64 was adequately conducted and demonstrated a similar treatment effect to the previously submitted single-dose environmental exposure unit study C01-83. No safety issues emerged from this single-dose study.

This trial provides an adequate pharmacodynamic link between the previous povidone-containing formulation and the current povidone-free formulation of olopatadine 0.6% nasal spray. It is reasonable to infer that the proposed povidone-free formulation would confer similar clinical efficacy to the povidone-containing previous formulation in SAR.

10.1.2 C-05-69: Safety Study of Olopatadine Nasal Spray

10.1.2.1 Protocol

10.1.2.1.1 Objective and overall design

Trial C-05-69 was a one-dose-level, randomized, double-blind, vehicle-controlled 12-month trial whose principal objective was the determination of safety of the newly-proposed, povidone-free olopatadine nasal spray formulation. As part of a prespecified plan, and with agreement of FDA, 6-month results have been submitted to FDA. The trial was intended to enroll at least 800 subjects with perennial allergic rhinitis with the aim of obtaining at least 300 subjects on active treatment evaluated for safety at 6 months. Visits, which include nasal examinations, occurred monthly. In order to support compliance with treatment, a subset of subjects were tested for blood olopatadine levels and the entire trial population answered a self-administered effectiveness question at one month.

The protocol used was version 3.0, effective November 28, 2006.

10.1.2.1.2 Procedures

This review will discuss protocol procedures (Table 28) first, as this will give context to eligibility criteria, to be described subsequently.

Informed consent was to be obtained at visit 1. Alcon selected a subset of sites at which to obtain consent for an addition set of blood draws for olopatadine concentrations (investigators were not to inform subjects at which visits the blood draws were to be performed). Olopatadine blood levels were to provide an additional measure of compliance. The subjects who agreed to have blood levels of olopatadine drawn also agreed to have some serologic testing. Subjects with antibody to hepatitis B surface antigen, hepatitis C, or with a positive test on an HIV ELISA screen were not to have their blood drawn for olopatadine blood levels. Investigators were to perform the first nasal examination (see below for more details), and determine other parameters as described in Table 28.

At recurring clinic visits the site was to give subjects two bottles of medication, which included a “back-up” bottle. The primary bottle was to be weighed, then primed (pumped 5 times or until a fine mist appeared) for the subject. The backup bottle was to be neither weighed nor primed. The subject was to receive a dosing diary upon which to record medication use. Subjects are to use the medication every 12 hours to the extent possible, and to store the medication upright at room temperature.

At subsequent visits, the sites weigh the bottles, dispense new primary bottles, and make other assessments according to Table 28. Blood was to be drawn for olopatadine concentrations in the subset of subjects who had agreed to have this test at day 30 and day 150.

Subjects are to be withdrawn for a nasal septal perforation and may be withdrawn at the discretion of the investigator for use of numerous medications or rescue medication (pseudoephedrine) for 7 days or more or a concerning nasal ulceration. The protocol specified that withdrawals would be classified under the categories adverse event, treatment failure, loss to follow-up, patient decision unrelated to an adverse event, protocol violation, or other.

The protocol included a crude measure of effect to assist in the determination that subjects were taking trial medication. At trial visits subjects placed the answer to a symptom question in the case report form (see "Analysis" below). This question is not a component of the TNSS, so the results cannot be compared directly.

The protocol did not require the assessment of hematology, chemistry or electrocardiographic data.

Table 28. C-05-69 Procedures

	Visit 1 Day 1	Visit 2 Day 30 ±5	Visit 3-5 Days 60, 90, 120 ±5	Visit 6 Day 150 ±5	Visit 7 Day 180 ±5	Visit 8-12 Days2 210,240, 270,300, 330 ±5	Visit 13 Day 365 (or Early Exit) ±10
Sign consent, verify inclusion/exclusion criteria	X						
Pregnancy test (if applicable)	X				X		X
Record medical and medication history	X						
Allergic diagnostic skin test if not performed in last year	X						
Subset of subjects (pk) - serology testing	X						
Dispense daily dosing diary	X	X	X	X	X	X	
Dispense medical problems log	X	X	X	X	X	X	
Nasal exam	X	X	X	X	X	X	X
Physical examination	X				X		X
Vital signs (blood pressure and pulse)	X	X	X	X	X	X	X
Patient effect questionnaire	X	X	X	X	X	X	X
Record changes in medical history and concomitant medications		X	X	X	X	X	X
Collect daily dosing diary		X	X	X	X	X	X
Review/emphasize dosing compliance		X	X	X	X	X	
Collect/review/issue medical problems page		X	X	X	X	X	X
Assess for adverse events (starts after first dose)	X	X	X	X	X	X	X
Weigh and dispense study medication	X	X	X	X	X	X	
Collect and weigh study medication		X	X	X	X	X	X
Subset of subjects - blood draw for plasma level analysis		X		X			
Complete exit form							X

[Source: Alcon C-05-69 protocol Table 17.-1]

10.1.2.1.3 Nasal examination

The long-term safety trial in PAR subjects submitted with the original NDA included a nasal examination at each visit. Because of the concerns over nasal septal perforation from the previous formulation, the current trial includes a nasal examination that can be made more detailed upon certain initial findings.

Alcon prepared investigators to perform the nasal examination with instructions delivered by Dr. Bradley Marple of Alcon and Dr. Robert Lanier, one of the trial investigators. The nasal examination was to be performed at each trial visit and was a component of eligibility (subjects with abnormalities on nasal examination were not to be permitted into the trial).

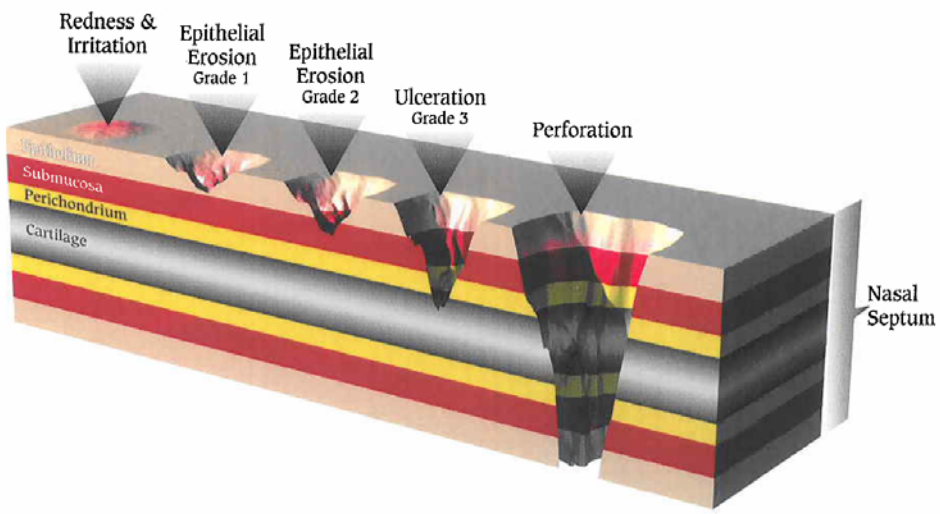
Baseline examination

The baseline examination was performed as one of the prerequisites of enrollment. It involves decongestion with oxymetazoline followed by flushing of the nasal cavities with saline, then inspection of the nose from 3 positions (head up 30 degrees, head neutral, and head down 30 degrees) using a nasal speculum with transilluminator. The finding of any "evidence of infection," "significant anatomic abnormality," ulceration of the mucosa, or blood in the nose found, would disqualify the person from enrollment.

Postrandomization examination

The postrandomization examination was a potentially two-step procedure (Sections A and B). Initially the investigator was to use a transilluminator and a nasal speculum for the examination, but not to decongest the nose. Findings in Section A are recorded as "evidence of infection," "significant anatomic abnormalities," possible ulceration of the mucosa," and "blood in the nose." Section A only was required if "evidence of infection" were found without other findings; an adverse event form must be filled out. Other findings require a Section B examination and an adverse event form that records the findings of that examination. Section B of the examination requires use of decongestant. Alcon referred examiners to an illustration of the various potential grades of damage to the nasal septum (from minimal damage through complete perforation of the septum, Figure 3). The finding of a nasal septal perforation requires confirmation with an otolaryngologist (or another otolaryngologist if the first examiner were one).

Figure 3. C-05-69: Illustration provided to guide detailed nasal examination Section B



[Source: Alcon Figure 12.5.1.-1]

Section B findings were to be recorded in relation to those in Section A as shown in Table 29.

Table 29. C-05-69: Reporting of nasal examination findings

Section A finding	Section B finding
Evidence of infection	(no examination required)
Significant anatomic abnormalities	Nasal perforation
	Intranasal mass
Possible ulceration of the mucosa	Redness, irritation
	Epithelial erosion Grade I
	Epithelial erosion Grade II
	Ulceration of the mucosa Grade III
Blood in the nose	Nasal Bleeding

[derived from C-05-69 case report form]

10.1.2.1.4 Subject eligibility

Subjects were to fulfill the following medical eligibility criteria:

Inclusion

1. One year history of non-recalcitrant perennial allergic rhinitis
2. Allergy to a perennial allergen, defined by positive case history and positive skin prick and/or intradermal test (≥3-mm wheal greater than the diluent after skin prick testing, or ≥7-mm wheal greater than the diluent after intradermal testing) within the 1 year prior to Visit 1.
3. Patient must be 12 years of age or older.
4. Nasal exam must confirm absence of significant anatomic abnormalities or evidence of infection, ulceration of the mucosa, and blood in the nose at Visit 1.

In addition, the protocol required washout times for specified medications (see section on concomitant medications) prior to Visit 1 and criteria applied to women to avoid pregnancy.

Exclusion

1. Concurrent disease or nasal exam finding that might complicate or interfere with investigation or evaluation of the study medications such as rhinitis medicamentosa, large obstructive nasal polyps, or other anatomic nasal deformity
2. A confirmed diagnosis of chronic rhinosinusitis within the last year
3. Congestion that would, in the opinion of the investigator, interfere with successful nasal drug administration/absorption (in either nostril)
4. Any systemic disorder that could interfere with the evaluation of the study medication(s)
5. Hypersensitivity to the study drug(s) or any component of the test articles, including benzalkonium chloride
6. History of severe, unstable or uncontrolled cardiovascular, hepatic, renal and/or other disease/illness that could be expected to interfere with the study.

In addition, the protocol excluded persons who had participated in any other Alcon olopatadine nasal spray trial and allowed the medical monitor discretion to declare any person ineligible for a sound medical reason.

10.1.2.1.5 Trial treatment and its blinding

Trial treatments are provided in masked white bottles as in trial C-05-64 (see above). Subjects are encouraged to follow an every-12 hour schedule and are given a medication diary in which to record medication use.

The protocol contains detailed instructions to investigators to convey to subjects regarding use of the trial medication. These instructions include washing hands with soap and

water, tilting the head forward, not spraying toward the nasal septum, breathing in gently while depressing the applicator and breathing out after each spray, and not blowing the nose for several minutes after using the spray.

Comment

As in trial C-05-64, the adequacy of the physical measures to blind the treatments was uncertain. Alcon did not administer a blinding questionnaire.

10.1.2.1.6 Concomitant medications

Prohibited

Prospective patients were not to take specified medications for specified times prior to visit 1:

- 14 days: nasal corticosteroids; nasal ipratropium bromide (or atropine), nedocromil or sodium cromolyn, loratadine (Claritin®), desloratadine (Clarinex®), or levocabastine; antiarrhythmic agents (disopyramide, procainamide HCl, quinidine sulfate, flecainide, propafenone, amiodarone, bretylium, dofetilide, ibutilide fumarate (Corvert), N-acetylprocainamide, Sotalol HCl (Betapace)
- 7 days: nasal sprays not specified above, topical nasal decongestants, herbal products used to relieve allergy symptoms, chlorpheniramine, clemastine fumarate, brompheniramine maleate, hydroxyzine, hydroxyzine pamoate, azatadine maleate, azelastine 0.1 % nasal spray (Astelin®), cetirizine HCl (Zyrtec®), fexofenadine HCl (Allegra®)
- 3 days: Diphenhydramine, promethazine HCl, cyproheptadine HCl (Periactin®), triprolidine HCl, and acrivastine
- Sleep aids containing any of the antihistamines were prohibited for the relevant time period

The protocol states that "limited intermittent use" of these treatments other than nasally administered medications and antiarrhythmic agents (for less than 7 consecutive days) was allowed at the discretion of the investigator.

Dispensed rescue medication

Investigators are to dispense small quantities of pseudoephedrine for subjects to use as rescue medication upon agreement of the investigator.

10.1.2.1.7 Analysis

Populations

The protocol defines four populations:

- Safety: those who receive drug
- Efficacy: intent-to-treat (ITT): those who receive drug and have at least one clinic visit while on trial treatment.
- Per protocol: ITT population, meeting eligibility criteria
- Pharmacokinetic ITT: safety population who have a "reported" bioanalytical result (concentration value or below the limit of quantification (BLQ)) for at least one post-dose pharmacokinetic blood draw

Primary effect measurement

The subject-assessed measure of treatment effect was a question on a 4-point scale:

I would rate the study medication's effectiveness for relieving my allergy symptoms since my last visit as:

1. Complete Relief
2. Moderate Relief
3. Mild Relief
4. No Relief

This question was used to assess effect on symptoms in Alcon's previous long-term safety trial, previously submitted to the NDA. A clinically important minimal difference has not been established for this question. However, the intent of this assessment was to ascertain if there was any treatment effect, as a measure of confirmation that subjects had been taking trial treatment, and not to demonstrate efficacy.

The primary effect analysis was to be a two-sample t-test on the comparison between treatment groups of the mean value of the patient questionnaire at day 30. Secondary efficacy analysis was to be performed on the average number of days of rescue medication use and the mean response to the patient questionnaire over the duration of the trial (average of visits 2-13 or last visit).

Safety

Safety was to be assessed through comparison of adverse events and results of the nasal examinations. Serious adverse events are defined as death or events that are life-threatening, result in an inpatient hospitalization or prolongation of an existing hospitalization, result in a persistent or significant disability or incapacity, or are a congenital anomaly or birth defect. They also include events that may jeopardize the subject and may require medical or surgical intervention to prevent one of these outcomes.

Compliance was to be assessed through examination of diary dosing records, the recording of bottle weights, and by olopatadine blood levels in a subset of patients.

The protocol specifies that an interim data base lock would occur after all subjects had completed the day 180 evaluation. Regarding maintenance of the blind, the protocol states, "only selected Alcon Biostatistics, Investigational Product Safety, and Pharmacokinetics/Drug Metabolism staff will be aware of treatment assignments at the patient level. Alcon Clinical Science personnel will have access only to the study results summarized by treatment group. All patients, investigators and Alcon staff who have contact with patients and investigators will remain masked with regard to patient-level treatment assignments during and after interim analysis."

10.1.2.1.8 Protocol revisions

All protocol revisions were made prior to the initiation of the trial. Notable revisions included:

- Change to a two-arm design testing povidone-free active and vehicle arms from a three-arm design comparing olopatadine nasal spray containing povidone 0.5% to povidone-free vehicle and povidone-free placebo.
- Addition of determination of blood levels of olopatadine in a subset of subjects as a measure of subject adherence to treatment
- Removal of the requirement for trained physicians to conduct the nasal examination
- Addition of a statistical test for superiority and a change in the primary endpoint measure to be at day 30 rather than an average of all on-treatment visits
- Addition of clinical sites so that less than 1/3 of the principal investigators would have been used in prior Alcon olopatadine nasal spray clinical trials

Since Alcon made these revisions to the trial prior to its initiation, they could not affect the integrity or interpretation of the trial.

10.1.2.2 RESULTS

10.1.2.2.1 Trial initiation and interim last visit dates

The trial was started on December 6, 2006. The last 6-month visit date for analysis was July 31, 2007.

10.1.2.2.2 Financial conflict of interest

Two investigators, (b) (4), reported financial conflicts of interest: (b) (4). (b) (4) (b) (4) The numbers of subjects enrolled by these two investigators was insufficient to alter the results of the trial substantially.

10.1.2.2.3 Identification of trial drug lots

The lot and formula identification numbers of the treatments are shown in Table 30. Alcon tested the to-be-marketed device and olopatadine nasal spray formulation.

Table 30. C-05-69: Identification of treatments

Treatment	Lot number	Formulation identification number
Olopatadine 0.6%	06-500834-1	FID 109941
	06-600215-1	
Vehicle	06-500816-1	FID 109970
	06-500835-1	
	07-500853-1	

10.1.2.2.4 Subjects

Enrollment

In pre-study discussions, FDA had told Alcon that not more than one third of the sites in the trial should have previously participated in studies in the NDA. In response, Alcon increased the number of sites and complied with that requirement.

Eighty sites, all in the U.S., enrolled 890 subjects. No site accounted for a notable preponderance of subjects, with enrollment ranging from 2-18 per site, and most sites enrolling around 12 subjects.

Demographics

Age, sex, and "race" were balanced between the treatment groups (Table 31). There were about twice as many women as men in the trial, and the great majority of subjects were Caucasian. The trial enrolled very few subjects in the geriatric age group.

Table 31. C-05-69: Demographics (ITT and safety population)

	Olopatadine 0.6% n=445	Vehicle n=445
Age		
mean (yrs)	36.5	37.0
median (yrs)	37.0	37.0
min, max (yrs)	12,73	12,76
Ranges (yr) (n, %)		
12 - 17	46 (10.3)	53 (11.9)
18 - 64 years	388 (87.2)	383 (86.1)
≥65 - <75 years	11 (2.5)	8 (1.8)
≥75 - <85 years	0	1 (0.2)
Sex (n,%)		
Male	163 (36.6)	149 (33.5)
Female	282 (63.4)	296 (66.5)
Race (n,%)		
Caucasian	359 (80.7)	361 (81.1)
Black	43 (9.7)	39 (8.8)
Asian	4 (0.9)	6 (1.3)
Hispanic	32 (7.2)	37 (8.3)
Other	7 (1.6)	2 (0.4)

[Sources: Alcon Tables 11.2.1.-1 and 11.2..-2]

Disposition

A slightly greater fraction of subjects discontinued in the olopatadine group for adverse events or for treatment failure (Table 32). See the safety review for a discussion of discontinuations for adverse events.

Table 32. C-05-69: Summary of reasons for discontinuation (ITT and safety population)

Reason	Olopatadine 0.6% n=445	Vehicle n=445
Adverse event	22 (4.9)	16 (3.6)
Lost to monitoring	16 (3.6)	15 (3.4)
Decision unrelated to adverse event	19 (4.3)	21 (4.7)
Treatment failure	20 (4.5)	16 (3.6)
Protocol violation	7 (1.6)	6 (1.3)
Other	8 (1.8)	9 (2)
TOTAL	92 (20.6)	83 (18.7)

[Source: Alcon Table 10.1.-7]

The numbers of subjects in each treatment group who had discontinued at each monthly visit was approximately equal (Table 33).

Table 33. C-05-69: Cumulative discontinuations by trial day (ITT and safety population)

	D1	D30	D60	D90	D120	D150	D180
Olopatadine 0.6% n=445	0	19	29	43	59	71	83
Vehicle n=445	0	14	28	41	54	64	72

[Source: Alcon Table 10.1.-1]

10.1.2.2.5 Protocol deviations

Visit time window violation was fairly common in both treatment groups but would not be expected to have a notable effect on the interpretation of the trial. Cardiovascular protocol

deviations were generally related to the taking of blood pressure. Table 34 shows that in general other protocol deviations were not common and were fairly balanced between treatment groups. Because of their importance to the trial, deviations in the nasal examination were examined. The great majority of violations of the nasal examination pertained to decongestant either being used or not being used. Protocol deviations overall in trial C-05-69 would not be expected to change the interpretation of the trial or cast doubt on the trial's integrity.

Table 34. C-05-69: Summary of subjects with protocol deviations

Protocol deviation	Olopatadine 0.6% n=445	Vehicle n=445
General		
Incorrect randomization	2 (0.4)	1 (0.2)
Visit window violation	122 (27.4)	120 (27.0)
Prohibited medication	17 (3.8)	22 (4.9)
Non-compliance with med	13 (2.9)	8 (1.8)
Visit		
Physical examination	4 (0.9)	9 (2)
Nasal examination	25 (5.6)	28 (6.3)
Cardiovascular	51 (11.5)	47 (10.6)
Study medication	39 (8.8)	42 (9.4)
Effect questionnaire	19 (4.3)	15 (3.4)
Dosing diary	10 (2.2)	13 (2.9)
Medical problem	5 (1.1)	12 (2.7)
Pregnancy	7 (1.6)	1 (0.2)
Other	11 (2.5)	15 (3.4)

[Source: Alcon data set DEVI01.jmp]

10.1.2.2.6 Compliance to trial treatment

Subjects filled out a dosing diary for each day on the trial, and Alcon analyzed these data as a proportion of the doses expected (Table 35). Subjects in each group took an average of approximately 81% of potential doses, with a median of 85%, according to the dosing diary.

Table 35. C-05-69: Dosing diary percent of doses taken compared to expected (ITT population)

	Olopatadine 0.6% n=440*	Vehicle n=439*
Mean ± std. deviation	81.2 ± 13.1	81.3 ± 13.1
Median	85.3	85.1
25th, 75th percentile	82.4, 86.3	83.1, 86.1
min, max	3,99	3,99

*Use data for 11 subjects were missing.
[Source: Alcon Table 11.4.1.3-1]

Bottles were to be weighed at each visit as a measure of compliance. The difference between dispensed weight and returned weight was to be calculated as bottle weight used. Alcon's analysis of bottle weight data, using observed data only, is shown in Table 36. This shows that there was notable variability in the determination of bottle weights (including some notable outlier values). However, the overall data suggest that treatments were approximately evenly taken by the two treatment groups.

Table 36. C-05-69: Analysis of bottle weight used (grams at each visit)

Visit	Treatment	N	Mean ± std. deviation	Median	25th, 75th percentile	min, max
Day 30	olo 0.6%	415	18.0 ± 5.9	19.10	14.0, 22.5	1.3, 36.0
	vehicle	422	19.0 ± 5.9	19.9	15.2, 22.6	2.1, 47.4
Day 60	olo 0.6%	409	18.0 ± 6.2	19.0	13.6, 22.2	0.5, 41.5
	vehicle	406	18.7 ± 5.8	19.3	14.7, 22.8	0.9, 37.5
Day 90	olo 0.6%	395	17.9 ± 6.0	18.3	13.7, 22.4	-6.0, 30.0
	vehicle	390	19.1 ± 6.6	20.1	15.5, 22.7	-0.3, 86.8
Day 120	olo 0.6%	378	18.2 ± 5.9	18.9	14.1, 22.8	0, 36.5
	vehicle	386	18.9 ± 5.8	20.1	15.1, 23.2	2.1, 33.1
Day 150	olo 0.6%	369	17.9 ± 5.7	18.4	14.3, 22.4	-0.2, 30.3
	vehicle	371	18.3 ± 5.8	19.1	14.9, 22.1	-13.7, 47.9
Day 180	olo 0.6%	354	20.1 ± 6.3	21.5	16.5, 24.9	-0.3, 32.9
	vehicle	363	19.9 ± 6.0	21.1	16.5, 24.5	-0.03, 30.3

[Source: Data from Alcon table 14.2.3.-2]

The pharmacology substudy was reviewed by FDA pharmacology reviewers (see separate review). This section is a summary of their review, which appears in a separate document.

Of the 890 subjects enrolled, blood samples were collected from 159 in the olopatadine treatment group and 160 from the vehicle control group. Blood samples were collected at months 1 and 5 during treatment and assessed for olopatadine concentrations using a validated method with a limit of quantitation of 0.05 ng/ml. Approximately 90% of the olopatadine subset had quantifiable olopatadine plasma concentrations.

The conclusion of the pharmacology review is that the olopatadine drug concentration data suggested a high degree of patient compliance among the tested subjects, and because of the randomized nature of treatment in the entire trial, among the entire trial population as well.

10.1.2.2.7 Effect on symptoms as assessed by questionnaire

This review will focus on the analysis of the ITT population to minimize potential biases introduced by the selection of other populations. All subjects who were randomized had an on-treatment visit, and are in the ITT population.

Scores on the subject-assessed questionnaire could range from 1-4, so potentially a difference in the groups of 3 points could occur. Treatment with olopatadine resulted in a difference from vehicle control of 0.2 points (Table 37). Questionnaire data for 29 subjects were missing. This small amount of data would not be expected to change the overall result notably.

Table 37. C-05-69: Primary analysis: Symptom questionnaire at 30 days*; ITT population, LOCF)

Statistic	Olopatadine 0.6% n=431*	Vehicle n=430**
Mean ± std. deviation	2.5 ± 0.9	2.7 ± 0.9
Median	2.0	3.0
25th, 75th percentile	2.0, 3.0	2.0, 3.0
min, max	1,4	1,4
p-value on means	0.001	

*Scores ranged from 1 (complete relief) to 4 (no relief)
**Questionnaire data for 29 subjects were missing.
[Source: Alcon Table 11.4.1.1-1]

The FDA statistician verified the results of Alcon's analysis. This difference, measured at 30 days, is the same treatment effect seen in Alcon's previously-submitted safety trial, in which the result was measured at 12 months.

Exploratory analyses of the primary outcome variable

Alcon's submitted an analysis of the per-protocol population (not shown in this review) which was consistent with the analysis of the ITT population.

Alcon explored the distribution of scores in the ITT population (Table 38). While the percents of subjects with complete relief were smaller than those with moderate and mild relief, the intertreatment group difference was greater in favor of olopatadine in the complete relief category, supporting the primary endpoint.

Table 38. C-05-69: Primary outcome analysis (LOCF)

Score on symptom questionnaire	Olopatadine 0.6% n=431*	Vehicle n=430*
Complete (=1)	67 (16%)	45 (11%)
Moderate (=2)	164 (38%)	153 (36%)
Mild (=3)	137 (32%)	134 (31%)
No relief (=4)	63 (15%)	98 (23%)
p-value (CMH rank scores test)	0.002	

*Questionnaire data for 29 subjects were missing.
[Source: Alcon Table 11.4.1.1.1.-2]

Alcon analyzed the percent of patients with complete relief, complete or moderate relief, and some relief. These do not contribute additional information to the analysis of the distribution of scores, and are not reported here.

Subset analyses of the primary outcome variable

The trend of primary outcome results was maintained for each sex. For males (n=304), mean scores for treatment with olopatadine and vehicle were 2.5 and 2.8, respectively, and for females (n=557), 2.4 and 2.6, respectively. Median scores for males and females were 2.0 and 3.0 for treatment with olopatadine and vehicle, respectively.

Mean and median scores in the 18-64 year age subgroup (n=743) were the same as the overall trial population. In the geriatric subgroup (n=20) mean and median scores on the symptom questionnaire were consistent with the pattern in the 18-64 year-old subgroup (olopatadine mean 2.3, vehicle mean 3.0; medians 2.0 and 3.0, respectively); however, mean scores on the questionnaire in the adolescent subjects (n=98) trended in the opposite direction (olopatadine 2.5, vehicle, 2.4) while the median scores were equal in the adolescent subjects (2.0). These results must be interpreted with caution, as the numbers of subjects in the adolescent and geriatric age groups is small.

Mean and median scores among Caucasians (n= 701) were the same as the overall trial population. Scores among "blacks" (n= 80) trended in the opposite direction to those of the Caucasians (olopatadine mean 2.5, vehicle mean 2.3; medians 3.0 and 2.0, respectively) while those among Hispanics (overall n= 62) were more consistent with Caucasians (olopatadine mean 2.4, vehicle mean 2.7; median 3.0 for both treatment groups). These results, as well as the results (not summarized in this review) among Asians (n=10) and "others" (n=8) must be interpreted with caution, as the numbers of subjects in the nonCaucasians groups is small.

<u>Secondary outcomes</u>

- *Response to patient questionnaire over 6 months of the trial.* These scores were nearly the same as those in the primary analysis.

- Rescue medication use (Table 39). For the purposes of the interim analysis, the analysis of rescue medication use was to be the average use from visits 2 through 7. The discrepancy between the mean use and median use indicates that a minority of subjects with greater use "drove" the mean use data. These results do not substantially alter the assessment of efficacy as established for patients with seasonal allergic rhinitis.

Table 39. C-05-69: Days of rescue medication use to day 30 (LOCF)

	Olopatadine 0.6% n=440*	Vehicle n=439*
Mean ± std. deviation	6.5 ± 14.6	5.7 ± 12.1
Median	0	1.0
25th, 75th percentile	0.0, 6.0	0.0, 6.0
min, max	0, 138	0, 155
p-value (2-sample t-test on means)	0.33	

*Use data for 11 subjects were missing.
[Source: Alcon Table 11.4.1.2-2]

10.1.2.2.8 Safety

Adverse events were coded using the COSTART system. Adverse events were recorded when there were changes in health, changes in concomitant medications due to a new medical diagnosis or worsening illness, for nasal or physical examination findings, or a cardiovascular parameter. Adverse events were collected as solicited comments and as observations by the trial investigator.

Exposure

Exposure was similar between the treatment groups, and adequate to allow for an assessment of safety (Table 40).

Table 40. C-05-69: Exposure (Safety population)

	1-30 days	31-60 days	61-120 days	121-179 days	≥180 days	Mean ±sdev	Median (min, max)
Olopatadine 0.6% n=445	26 (5.8%)	8 (1.8%)	34 (7.6%)	41 (9.2%)	336 (75.5%)	161 ± 48	182 (1,200)
Vehicle n=445	25 (5.6%)	12 (2.7%)	26 (5.8%)	30 (6.7%)	352 (79.1%)	162 ± 48	182 (1,191)

[Source: Alcon Tables 12.1.-2 and 12.1.-3]

Adverse events

Deaths

There were no deaths.

Serious adverse events

Twelve subjects in the olopatadine treatment arm and 7 subjects in the vehicle arm had serious adverse events (Table 41). Two subjects in the olopatadine treatment group were hospitalized for depression:

1) A 40 year-old woman with a history of depression, seasonal allergic rhinitis, tension headaches, and hypokalemia on no medications was hospitalized for depression (b) (4) after randomization to the olopatadine treatment group. Daily medication for depression was later added. The patient discontinued from the trial 9 days after discharge from the hospital.

2) A 17 year-old woman with asthma, intermittent herpes simplex, overactive bladder, and history of allergy to sulfa had a nonserious adverse event of depression assessed as

"moderate" in severity 4 days after randomization to olopatadine. She was hospitalized and treated for major depression on (b) (4). Daily medication for depression was added. The subject continued in the trial.

Surgical/medical procedure occurred in two subjects in the olopatadine treatment group (knee replacement and cholecystectomy) but not in the vehicle group. A serious abdominal adverse event (appendicitis and intestinal obstruction) occurred in one subject each in the olopatadine treatment group and one subject in the vehicle control group. Other events were various in nature.

Table 41. C-05-69: Serious adverse events

Treatment	Sex/Age	Coded AE	Onset day	Intensity	Duration	Outcome*	D/c due to AE
Olopatadine 0.6%	F/49	Uterine Fibroid Enlarge	110	Moderate	2d	Resolved w/Tx	N
	F/72	Carcinoma Lung	5	Severe	N/A	Continuing w/Tx	Y
	F/40	Depression	11	Moderate	4d	Resolved w/Tx	N
	F/17	Depression	20	Severe	3d	Resolved w/Tx	N
	M/42	Appendicitis	138	Severe	11h	Resolved w/Tx	N
	F/38	Obstruction Intestinal	103	Severe	4h	Resolved w/Tx	N
	F/40	Embolism	78	Severe	N/A	Continuing w/Tx	N
			86	Severe	N/A	Continuing w/Tx	N
			98	Severe	N/A	Continuing w/Tx	Y
	M/14	Injury Accidental	101	Severe	1d	Resolved w/Tx	N
	F/65	Surgical/Medical Proc [knee replacement]	82	Severe	4d	Resolved w/Tx	N
	M/59	Surgical/Medical Proc [cholecystectomy]	137	Moderate	6d	Resolved w/Tx	N
Vehicle	F/32	Uterine Disorder	153	Severe	57d	Resolved w/Tx	N
	F/43	Uterine Fibroid Enlarged	41	Moderate	34	Resolved w/Tx	N
	F/38	Pneumothorax	64**	Severe	6d	Resolved w/Tx	N
	M/47	Appendicitis	178	Severe	2d	Resolved w/Tx	N
	F/44	GI Disorder	113**	Severe	4d	Resolved w/Tx	N
	M/64	Headache	167	Severe	1d	Resolved w/Tx	N
	F/52	Injury Accidental	57**	Severe	12d	Resolved w/Tx	N

*Tx = Treatment; **Occurred intermittently
[Source: Alcon Table 12.3.1.2.-1]

Three subjects experienced serious adverse events subsequent to the data cutoff date for the submission. In the olopatadine treatment group two subjects experienced serious adverse events: 1) a subject had a bicycle accident and experienced multiple trauma, and 2) a subject experience dehydration. In the vehicle treatment group a subject experienced fecal impaction after surgery. These events do not contribute to a pattern of toxicity.

Reviewer comment: Two subjects in the trial, both in the olopatadine treatment group, experienced depression requiring hospitalization. One subject had a history of depression and the other did not. The incidence of depression overall was similar between the two treatment groups at 6 months (olopatadine group 4 subjects; vehicle control, 5 subjects) and it is possible that these serious events represent chance occurrences. Depression should be monitored postmarketing in patients exposed to olopatadine.

Discontinuations due to an adverse event

Table 42 is a summary of the adverse events resulting in discontinuation. Two subjects discontinued due to the occurrence of nasal ulceration, both in the olopatadine treatment group. The events were classified as mild and moderate in severity. Otherwise, discontinuations do not show a pattern of concern.

Table 42. C-05-69: Adverse events resulting in discontinuation

	Olopatadine 0.6% N =445	Vehicle N =445
Patients withdrawing because of adverse events	22 (4.9%)	16 (3.6%)
All adverse events resulting in withdrawal	30	20
Adverse event		
Rhinitis	3	1
Sinusitis	4	4
Epistaxis	3	1
Taste perversion	2	0
Ulcer nasal	2	0
Allergy	1	1
Carcinoma lung	1	0
Dermatitis	1	0
Dyspepsia	1	0
Embolism	1	0
Erythema multiforme	1	0
Headache	1	2
Laryngismus	1	0
Myalgia	1	0
Pain	1	0
Pneumonia	1	0
Pruritus	1	0
Multiple sclerosis	1	0
Surgical/medical procedure	1	0
Weight increase	1	0
Anxiety	0	1
Asthma	0	2
Discomfort nasal	0	2
Dizziness	0	2
Insomnia	0	1
Nasal septum disorder (deviated septum)	0	1
Nausea	0	1
Palpitations	0	1

[source: AE01.jmp]

Adverse events

Nasal ulceration and taste perversion (commonly described as a bitter taste) were adverse events that occurred notably more frequently among the active treatment group than the vehicle control group (Table 43). Rhinitis occurred frequently, and at a similar incidence and distribution of severity in both treatment groups. Nasal ulceration was coded as a result of the nasal examination, discussed in a subsequent section. The majority of the infections were upper respiratory tract illnesses; other infections were of various kinds.

Table 43. C-05-69: Subjects with events at 2% or greater and at an incidence greater than vehicle

COSTART term	Olopatadine 0.6% n=445	Vehicle n=445
Nasal		
Rhinitis	104 (23.4)	103 (23.1)
Ulcer nasal	39 (8.8)	26 (5.8)
Pharyngitis	35 (7.9)	30 (6.7)
Body as a whole		
Infection	67 (15.1)	65 (14.6)
Digestive system		
Diarrhea	11 (2.5)	6 (1.3)
Dyspepsia	9 (2)	6 (1.3)
GI disorder	9 (2)	7 (1.6)
Cough increased	16 (3.6)	14 (3.1)
Bronchitis	15 (3.4)	10 (2.2)
Special senses		
Taste perversion	29 (6.5)	3 (0.7)
Conjunctivitis	10 (2.2)	4 (0.9)
Urogenital system		
Urinary tract infection	9 (2)	6 (1.3)

[Source: Alcon Table 12.2.3.2.-2]

Nasal ulceration was graded as "mild" in 91% (42/46) events in the olopatadine group and 85% of the vehicle group events (28/30); the other events were graded "moderate." Nasal ulceration was an event that came from the objective evaluation (see discussion of the nasal examination below).

Among all adverse events, the following were also notable:

- Epistaxis occurred frequently, and at a higher rate in the vehicle control group (olopatadine, 86 subjects (19.3%); vehicle control, 104 subjects (23.4%)). In the previous 12-month safety trial C-01-92, the rates of epistaxis in the olopatadine and vehicle control groups were 19% and 12%, respectively. The reason for the increase in epistaxis in the vehicle group in the current trial is not clear. Most of the events of epistaxis in either treatment group in the current trial were of mild severity (122/129 events in the olopatadine group and 147/152 events in the vehicle control group); the others were of moderate severity.
- One subject in the olopatadine treatment group experienced a liver function abnormality (mild severity). Examination of adverse events showed no other liver adverse events.
- One subject in the olopatadine treatment group experienced somnolence as an adverse event. This event was not reported in the vehicle control group.

Adverse events generally did not show a concerning pattern with respect to sex. Comparison of adverse events by age is complicated by the small numbers of subjects 12-17, at least 65 year old compared to those 18-64 years old. Similarly, comparisons among the racial groups is complicated by the small numbers of subjects who were not Caucasians. There was no notable pattern of events occurring at the extremes of age, nor were patterns of events notably different among the racial subgroups.

One subject on olopatadine experienced an event called "anaphylaxis." The subject developed throat tightness after exposure to horseradish smell. The subject had a history of allergy to horseradish. The event was judged to be of moderate intensity, resolved with treatment with albuterol, and olopatadine administration was not interrupted.

Nasal examination

The nasal examination was conducted at each clinic visit. If an "anatomic abnormality," "blood in the nose," or "possible ulceration" were found on an initial examination (Section A), a second, more detailed examination (Section B) was performed. Findings in Section B were recorded in the case report form under Section A headings.

Table 44 shows results in Section A expressed as the number of subjects with the events listed during the 6 months of the trial. Bleeding and "possible ulceration" occurred in a moderate number of subjects.

Table 44. C-05-69: Section A nasal examination: Numbers of subjects with nasal examination findings on at least one occasion (n, % of subjects)

	Olopatadine 0.6% n=438	**Vehicle n=438**
Evidence of Infection*	18 (4.1)	12 (2.7)
Anatomic abnormalities**	5 (1.1)	0
Possible ulcerations	67 (15)	61 (13.9)
Bleeding	67 (15)	87 (20)

*Section B was not required to be done for this finding, but an adverse event form was filled out for it
**Swelling of the turbinates due to allergic rhinitis (n=2) and nasal polyps (n=3). See also Section B findings
[Source: Alcon Table 12.5.1.-3]

Table 45 shows Section B findings among the subjects with anatomic abnormalities, possible ulcerations, or bleeding on section A examination (note that the table shows percents of treatment groups who had a Section B evaluation, not percents of the overall treatment group). Epithelial erosions of Grades 1 and 2 occurred more frequently in active-treated subjects. There was no erosion of grade 3 nor were there any nasal septal perforations.

Table 45. C-05-69: Section B nasal examination: Numbers of subjects with nasal examination findings on at least one occasion (n, % of subjects with a Section B evaluation)

	Olopatadine 0.6% n=103	Vehicle n=110
Redness/irritation	70 (68)	57 (52)
Nasal bleeding	59 (57)	77 (70)
Epithelial erosion		
Grade 1	37 (36)	27 (25)
Grade 2	4[1] (4)	1[2] (1)
Grade 3	0	0
Nasal perforation	0	0
Intranasal mass[3]	4 (4)	1 (1)

[1] Severity: 3 mild, one moderate
[2] Severity: mild
[3] Described as polypoid changes (n=1, active group) or polyps
[Source: Alcon Tables 12.5.1.-4, 12.5.1.-5, 12.5.1.-7]

Alcon presented by-visit information regarding the nasal examinations among those subjects with Grade 2 erosions. Two subjects in the olopatadine treatment group had a Grade 2 erosion at two consecutive visits; in one of these subjects nasal examination at subsequent visits revealed Grade 1 erosion and in the other, subsequent evaluation showed no reportable finding on Section B examination. Two other subjects on olopatadine had a Grade 2 epithelial erosion that was followed by no reportable finding at the next visit. Upon request, Alcon submitted a

tabulation of selected olopatadine diary use information for subjects who had epithelial erosions. Subjects did not tend to discontinue medication upon the occurrence of these events.

Contribution of nasal examination to adverse event terms

The nasal examination was one source of adverse events. In response to a request from FDA, Alcon summarized the adverse events that resulted from the nasal examination Sections A and B (Table 46). The adverse event term nasal ulceration derived solely from the nasal examination; for the other events, the nasal examination was one component, but not the sole source, of recorded adverse events.

Table 46. C-05-69: Adverse event terms from the nasal examination

Adverse Event (Nasal exam finding)	Olopatadine 0.6% N = 445	Vehicle N = 445
Sinusitis (Evidence of Infection)	18 (4.1%)	12 (2.7%)
Neoplasm[1] (Significant Anatomic Abnormality)	4 (0.9%)	1 (0.2%)
Rhinitis (Possible Ulceration of the Mucosa)	65 (14.6%)	57 (12.8%)
Nasal ulceration (Possible Ulceration of the Mucosa)	39 (8.8%)	26 (5.8%)
Nasal septum perforation	0	0
Epistaxis (Blood in the Nose)	67 (15.1%)	88 (19.8%)

[1]Described as intranasal mass (n=1, active group) or polyps
[Source: Alcon January 10, 2008 response to FDA request]

Alcon performed a by-subject analysis (not shown here) of the occurrence over time of nasal irritation, epistaxis, and nasal ulceration. As epistaxis occurred in more subjects than did nasal ulceration, it is not surprising that the occurrence of epistaxis did not predict the subsequent occurrence of nasal ulceration. In addition, nasal ulceration occurred without the prior occurrence of epistaxis in some subjects.

Events that can occur with antihistamine and anticholinergic drugs

Table 47 shows the incidence of adverse events that are associated with antihistamine and anticholinergic drugs. They occurred infrequently in either treatment group.

Table 47. C-05-69: Incidence of adverse events associated with antihistamine and anticholinergic drugs

COSTART term	Olopatadine 0.6% n=445	Vehicle n=445
Dyspepsia	9 (2)	6 (1.3)
Nausea	5 (1.1)	9 (2)
Fatigue	4 (0.9)	4 (0.9)
Somnolence	1 (0.2)	0
Constipation	2 (0.4)	4 (0.9)
Dry mouth	4 (0.9)	3 (0.7)
Weight increase	5 (1.1)	0
Urinary retention	0	0

[Source: Alcon Table 14.3.1.3.1.-1]

Vital signs

Pulse and blood pressure were recorded at monthly visits after the subject had been seated quietly for 5 minutes. Three subjects in the active group and 1 in the vehicle control group experienced tachycardia as an adverse event, all of which were "mild" in severity and resolved without treatment. Review of group statistics by treatment visit, including shifts from baseline, did not show a notable pattern for either treatment group.

Thirteen subjects in the olopatadine treatment group and 15 in the vehicle control group experienced what was considered a clinically relevant increase in blood pressure. Most of the events were of mild severity and the overall severity was balanced between treatment groups. Review of the data tabulation did not reveal a notable difference in clinical features of the events. Group statistics showed slight decreases in systolic and diastolic blood pressure from baseline to the 6 month time point (for example, mean decreases in systolic blood pressure in the olopatadine and vehicle control groups of approximately 3 and 2 mm Hg, respectively, and mean decreases in diastolic blood pressure of 1.7 mm Hg, vehicle, 2.1 mm Hg, respectively) that were not clinically different between the treatment groups.

Concomitant medications

Review of changes in medications occurring during the trial did not reveal concerns in addition to those manifested by review of adverse events.

10.1.2.3 Summary of C-05-69

Clinical trial C-05-69 was adequately conducted for a reasonable interpretation of its results. In this randomized, double-blind trial of subjects with perennial allergic rhinitis the symptom questionnaire results, collected at 30 days of treatment, were substantially the same as the 12-month results from the previously submitted trial of the previous, povidone-containing formulation. This result, in combination with drug levels obtained in a subset of subjects, is sufficient evidence for exposure to allow an interpretation of safety. No death occurred, and serious adverse events did not occur in a concerning pattern. Discontinuations for adverse events were infrequent. There were no reports of nasal septal perforations. Nasal septal ulceration, which occurred in 8.8% of olopatadine and 5.8% of vehicle control subjects, was mostly of mild severity. Epistaxis occurred frequently in both groups (19.3% in the olopatadine group and

23.4% in the vehicle control group). The pattern of adverse events and results of the nasal examination conducted monthly over the course of the 6 months do not raise toxicity concerns that would be a barrier to approval.

10.1.3 Additional Reports of Clinical Trials (Povidone-containing Formulation)

Alcon submits reports of three clinical trials (see Table 2) of olopatadine 0.6% nasal spray containing povidone. This review will describe the notable features of the designs and findings of the trials briefly.

C-04-70

Alcon's "Safety and Efficacy Study of Olopatadine Hydrochloride Nasal Spray 665 mcg versus Olopatadine Hydrochloride Nasal Spray Vehicle versus Astelin in Treatment of Seasonal Allergic Rhinitis" was a multicenter trial of randomized, double-blind treatment for 16 days of subjects at least 12 years of age with seasonal allergic rhinitis. The design of the trial was similar to that of the pivotal efficacy trials C-02-10 and C-02-37 submitted in the original NDA. The objective of the trial was to assess efficacy and safety. It was conducted between May 11, 2005 and October 19, 2005.

Alcon attests that the trial was conducted according to Good Clinical Practice, and that no investigator reported a conflict of financial interest.

Procedures

Table 48 shows the procedures in the trial, which were similar to those in the prior seasonal allergic rhinitis efficacy trials.

Screening (Visit 1) procedures included assessment for eligibility, a medical and medication history, a physical and nasal examination, a skin prick test was followed by treatment with olopatadine vehicle during a 4-14-day run-in period. Eligibility for randomization at visit 2 included the presence of symptoms (with a total nasal symptom score of at least 36 from any 3 of the 4 calendar days immediately preceding visit 2) and an acceptable nasal examination. Trial personnel called the subject at 7 days after randomization to assess adherence to treatment and diary completion, medication changes, and adverse events. The final clinic visit was 16 days after randomization; notable procedures at this visit included assessment of adverse events, diary symptom information, and a nasal examination.

Blood tests (hematology and serum chemistry) were not required.

Table 48. C-04-70: Procedures

	Visit 1 Screening	Visit 2 Randomization	Visit 3 Telephone call	Visit 4 or Early Exit
	4-14 days		Day 7±1	Day 16 (+7)
Consent form	X			
Inclusion/Exclusion	X	X		
Pregnancy test (urine) if applicable	X	X		X
Medical and medication history	X			
Allergic Rhinitis Symptoms history	X			X
Skin prick or intradermal test if not done in last 5 yrs.	X			
Physical examination	X			X
Nasal examination	X	X		X
12-lead ECG	X			
Blood pressure and pulse	X	X		X
Review changes in medical history and concomitant medications		X	X	X
Adverse events	X	X	X	X
Weigh and dispense/Collect Study medication	X	X		X
Administer dose at study site	X	X		
Dispense diary/medical problems log with instructions	X	X		
(b) (4) and Allergy Visual Analog Scale		X		X
Treatment Satisfaction Questionnaire for Medications				X
Determine TNSS based on Daily Compliance Report		X		
Review Medical Problems Log		X	X	X
Review Status Summary report for subject compliance			X	X
Complete Screening Exit/Randomization form		X		
Complete Exit form				X

[Source: Alcon Table 9.1.-1]

Subjects

Subjects were to have seasonal allergic rhinitis and be without concurrent medical conditions that might interfere with evaluation of the medication. Notable medical eligibility criteria were:

Inclusion

- 2-year history of nonrecalcitrant spring or fall allergic rhinitis
- Allergy to a current prevalent seasonal allergen of the area (positive case history and positive skin prick or intradermal test or both)
- Washout of prohibited medications
- Sum of AM and PM reflective total nasal symptom scores of at least 36 for 3 complete calendar days out of the 4 prior to randomization
- Absence of significant anatomic abnormalities, infection, bleeding, and mucosal ulcerations on nasal examination prior to administration of test article at visits 1 and 2

Exclusion

- Concurrent disease such as rhinitis medicamentosa or large obstructive nasal polyps,
- Any other nasal anatomic deformity on nasal examination at visit 1 or 2 that would interfere with participation, or history or evidence of nasolacrimal drainage system dysfunction
- Systemic or ocular disorder (other than allergic conjunctivitis) that would interfere with evaluation of study medication

- History of severe, unstable, or uncontrolled cardiovascular, hepatic, renal, or other disease or illness that would interfere with the study
- Current chronic sinusitis or acute sinusitis within 30 days of visit 1
- Respiratory tract infection within 14 days of visit 1
- Asthma, except mild intermittent asthma
- Congestion that would interfere with administration of nasal drugs
- Use of prohibited medications
- Non-responsive to antihistamines for seasonal allergic rhinitis
- Chronic or intermittent use of oral, intramuscular, intravenous, or dermal potent or super-potent topical corticosteroids
- Chronic use of long-acting antihistamines (for reasons other than allergic rhinitis) or medications that would affect assessment of effectiveness
- History of or ongoing clinically relevant electrolyte abnormalities
- Use of anti-allergy immunotherapy within the past 2 years
- Hypersensitivity to study drug or any component
- Clinically relevant ECG abnormalities at visit 1, and QTcB values or >450 msec for males and 470 msec for females
- Current or use within 14 days of any drugs that may prolong the QT interval
- Planned travel outside the study area for more than 48 hours during the study period.
- Clinically relevant abnormal vital signs at visit 1 or visit 2 (normal ranges in protocol: systolic blood pressure 95-160 mm Hg, diastolic blood pressure 55-90 mm Hg, and pulse 50-100 bpm).
- Bottle weight at visit 2 outside the acceptable range

Prohibited medications and washout periods

Table 49 shows prohibited medications and their washout periods. They are similar to those in the pivotal efficacy trials.

Table 49. C-04-70: Prohibited medications

Drug	Washout prior to visit 1
Anti-allergy immunotherapy in the previous two years	Last 2 years
Systemic corticosteroids (oral, parenteral, intravenous, rectal)	30 days
Inhaled or ocular corticosteroids	30 days
Nasal corticosteriods	14 days
Nasal or inhaled ipratroprium bromide (or atropine) nedocromil or sodium cromolyn	14 days
Leukotriene pathway modifiers and systemic and topical anticholinergics	14 days
Systemic antibiotics (except those used to treat acne)	14 days
Systemic antifungal agents	14 days
Loratadine, desloratidine, and levocabastine	14 days
Chlorpheniramine, clemastine fumarate, brompheniramine maleate, hydroxyzine, hydroxyzine pamoate, azatadine maleate, azelastine 0.1 % nasal spray, cetirizine HCL, fexofenadine HCL	7 days
Ocular anti-allergy medications including lodoxamide, olopatadine	7 days
Topical nasal decongestants	7 days
Diphenhydramine, promethazine HCl, cyproheptadine HCl, triprolidine HCl, acrivastine	3 days
Oral decongestants, such as pseudoephedrine, all over-the-counter cold/cough and sleep aids without a component listed above	3 days
NSAIDS (as-needed use)	3 days
Aspirin (except low dose for cardiac prophylaxis)	3 days
Nasal and/or ocular saline	1 day
Antiarrhythmic agents	
Class IA: Disopyramide, procainamide HCl, Quinidine Sulfate	14 days
Class IC: Flecainide, Propafenone	14 days
Class III: Amiodarone, Bretylium, Dofetilide, Ibutilide Fumerate, N-acetylprocainamide, Sotalol HCl	14 days
Herbals	
St. Johns Wort, Ma Huang, Ginkgo Biloba and/or any herbal with the potential to relieve allergy symptoms	7 days

[Source: Alcon Table 9.3.1.-1]

Treatment

Treatment consisted of 2 sprays in each nostril twice daily of olopatadine HCl Nasal Spray 0.6% (formulation containing povidone (b) (4), olopatadine vehicle placebo (formulation containing povidone (b) (4)), or azelastine HCl nasal spray 0.1%.

Analysis

The primary efficacy test was the percent change from baseline in the Total Nasal Symptom Score, defined as the average of the morning and evening reflective severity scores.

Protocol modifications

Alcon made a protocol modification on September 1, 2005, after 71 subjects had entered into the screening phase of the trial. The amendment changed the wording of the eligibility criteria to include subjects with fall as well as spring allergic rhinitis, to expand the change in bottle weight ranges, to remove a reference to blue dust covers in the section on dosing compliance, and the change contact information. These changes would not have been expected to change the results of the trial, nor reflect on the overall conduct of the trial.

Results

The results of the azelastine treatment group are not relevant to the assessment of safety of olopatadine 0.6% nasal spray from this trial, and are not reported here.

Enrollment and trial subjects

Twenty-one sites enrolled 728 subjects, despite an original goal of 480 subjects. However, of the 728, 184 were judged screening failures and were not randomized, 120 of whom

were for insufficient symptoms on the diary. Of the 544 subjects analyzed for safety, 180 were in the olopatadine treatment group and 176 in the vehicle control group.

Demographics of the olopatadine and vehicle control groups were reasonably balanced and reflected a primarily Caucasian population with a majority of women, and a mean age in around 36 years old. These demographics are not notably different from those in the pivotal efficacy trials C-02-10 and C-02-37.

Table 50. C-04-70: Demographics (ITT population*)

	Olopatadine 0.6% (povidone (b) (4)) n=180	Vehicle n=176
Age		
Mean (yrs)	35.7	36.6
Std dev. (yrs)	12.8	13.1
Min, max (yrs)	12, 70	12, 77
Ranges (yr) (n, %)		
12 - 64 years	177 (98.3)	174 (98.9)
≥65	3 (1.7)	2 (1.1)
Sex (n,%)		
Male	52 (28.9)	61 34.7)
Female	128 (71.1)	115 (65.3)
Race (n,%)		
Caucasian	136 (75.6)	133 (75.6)
Black	19 (10.6)	18 (10.2)
Asian	2 (1.1)	2 (1.1)
Hispanic	22 (12.2)	23 (13.1)
Other	1 (0.6)	0

*Subjects who entered the treatment period
[Source: Alcon Tables 11.2.1.-1 and 11.2.1.-2]

Discontinuations and protocol deviations

Table 51 shows discontinuations for subjects from the olopatadine and vehicle control treatment groups. It shows that discontinuations from these groups were infrequent and reasonably balanced.

Table 51. C-04-70: Discontinuations

Reason for discontinuation	Olopatadine 0.6% (povidone (b) (4)) n=180	Vehicle n=176
Adverse event	5	5
Decision unrelated to adverse event	1	1
Treatment failure	1	-
Protocol violation	5	4
Other	-	3
Total	12	13

*Subjects who entered the treatment period
[Source: Alcon Tables 11.2.1.-1 and 11.2.1.-2]

Table 52 shows that violations of eligibility were infrequent. The number of these protocol violations in the azelastine treatment arm was similar. Review of listings of other violations indicates that their nature and number would not be expected to affect the ability of the trial to assess safety or efficacy or reflect on the integrity of the trial notably.

Table 52. C-04-70: Major protocol violations

Protocol deviation	Olopatadine 0.6% (povidone (b) (4)) n=180	Vehicle n=176
Inclusion criterion	3	2
Visit out of window	1	1
Exclusion criterion	9	11
Breaking of blind*	0	1
Total	13 (7.2%)	15 (8.5%)

[Source: Alcon Table 10.2.-1]
Note: Alcon Table 16.2.2.-1 notes that 1 other subject in the vehicle group had the blind broken

Trial treatment

The trial tested the same formulation of vehicle and active olopatadine nasal spray that were used in the pivotal seasonal allergic rhinitis efficacy trials C-02-10 and C-02-37.

Efficacy

FDA has not reviewed the efficacy analysis in trial C-04-70. The study is not considered to be a pivotal efficacy study in this drug development program. Results reported are consistent with Alcon's conclusion that olopatadine-treated subjects had more improvement in the reflective total nasal symptom score than vehicle-treated subjects. Based on Alcon's reported results, the difference between olopatadine and vehicle control in the percent change from baseline in reflective total nasal symptom scores in trial C-04-70 was -8.4, and the difference in the mean change in reflective TNSS scores was -0.8 points. In the previously-submitted trials C-02-37 and C-02-10, the difference from placebo for the percent change from baseline was -12.2 and -11.4, respectively, and the difference from placebo in the mean change in reflective TNSS was -1.0 and -1.1, respectively. A treatment effect supports the use of the safety information from the trial.

(b) (4)

Safety

Exposure to study treatment was a little over 2 weeks in both the olopatadine and vehicle control groups (Table 53). This exposure is comparable to the exposure in the pivotal seasonal allergic rhinitis trials (Table 19).

Table 53. C-04-70: Exposure (Treatment period population)

	1-6 days	7-16 days	>16 days	Mean (days)	Median (days)
Olopatadine 0.6% n=180	1 (0.6%)	86 (47.8%)	93 (51.7)	16.8	17
Vehicle n=176	3 (1.7%)	84 (47.7%)	89 (50.6)	16.5	17

[Source: Alcon Table 12.1.-4 and text]

No one died. No subject in the olopatadine or vehicle control group experienced a serious adverse event or a nasal ulcer.

Table 54 shows the adverse events resulting in discontinuation from the trial. The events did not form a concerning pattern. More than one event may have been listed as a reason for discontinuation. Five subjects discontinued for adverse events from each group shown.

Table 54. C-04-70:Adverse events resulting in discontinuation (Subjects and % of group)

Adverse events (COSTART)	Olopatadine 0.6% Povidone (b) (4) n=180	Vehicle n=176
Headache	2 (1.1%)	0
Pharyngitis	2 (1.1%)	0
Taste perversion	2 (1.1%)	0
Cough increased	1 (0.6%)	0
Dyspepsia	1 (0.6%)	0
Gastroenteritis	1 (0.6%)	0
Nausea	1 (0.6%)	0
Pain	1 (0.6%)	0
Pruritus	1 (0.6%)	0
Rhinitis	1 (0.6%)	0
Sneezing	1 (0.6%)	0
Sinusitis	0	2 (1.1%)
Dermatitis contact	0	1 (0.6%)
Epistaxis	0	1 (0.6%)
Arthropod bite	0	1 (0.6%)

[Source: Alcon Response to February 25, 2008 FDA Request,Table C-2]

Table 55 shows adverse events that occurred in at least 3 subjects and at an incidence greater than vehicle. Taste perversion was the most common adverse event in the olopatadine treatment group. Somnolence was reported by one subject in each treatment group.

Table 55. C-04-70: Adverse events occurring in 3 or more subjects and at an incidence greater than vehicle

Adverse events (COSTART)	Olopatadine 0.6% Povidone (b) (4) n=180	Vehicle n=176
Nasal		
Rhinitis	6 (3.3)	3 (1.7)
Epistaxis	4 (2.2)	2 (1.1)
Pharyngitis	3 (1.7)	2 (1.1)
Body as a whole		
Headache	7 (3.9)	6 (3.4)
Infection	3 (1.7)	1 (0.6)
Fatigue	3 (1.7)	2 (1.1)
Special senses		
Taste perversion	22 (12.2)	3 (1.7)

[Source: Alcon Table 14.3.1.3.1.-1]

Review of all adverse events with respect to subgroups of sex, age category (12-17, 18-64, and at least 65), and race showed no remarkable patterns. However, the relatively small numbers of males and the small numbers of nonCaucasians and subjects at the extremes of age of the enrolled population make comparisons problematic.

Nasal examination

Nasal examination results were reported as clinically relevant increases from baseline in nasal parameters as assessed at the final visit. In neither group were anatomic abnormalities or mucosal ulcerations reported. Infection was noted in 2 subjects in both the olopatadine and vehicle treatment groups, and bleeding was noted in 1 subject in the olopatadine and 1 in the vehicle treatment group.

Vital signs

Based on shifts from baseline to the any visit, there were no notable differences between olopatadine- and vehicle-treated subjects in pulse or systolic or diastolic blood pressure. Hypertension as an adverse event was reported for two subjects in the olopatadine group and one in the vehicle group.

Summary of the results of trial C-04-70

C-04-70 was similarly designed to the pivotal efficacy trials in seasonal allergic rhinitis and the data are adequate for an assessment of safety. Efficacy was not reviewed by FDA. No deaths or other serious adverse events occurred in the olopatadine or vehicle control groups. Taste perversion was the most common adverse event, occurring notably more frequently in the olopatadine group. The safety results of this trial add to the existing data on two-week safety for the povidone-containing formulation of olopatadine.

C-04-45

Alcon's "A Double-Masked, Vehicle-Controlled, Multiple-Dose, Safety and Pharmacokinetic Study of Olopatadine Nasal Spray 0.6% and Olopatadine Nasal Spray 0.6% Plus Degradation Products of Olopatadine, Following Intranasal Administration in Healthy Subjects" was a single-center, randomized, double-blind, 5-parallel-arm trial in healthy subjects at least 20 years old whose objective was to determine plasma pharmacokinetics and safety of olopatadine and the degradation product (b) (4) Twelve subjects were enrolled into each of 5 treatment arms (see Table 2). In each arm the dose was two 100 µl sprays per nostril twice daily for 5 days, with a single administration on day 6. Randomized treatments were olopatadine vehicle, olopatadine 0.6%, olopatadine 0.6% with (b) (4) olopatadine 0.6% with (b) (4) or olopatadine 0.6% with (b) (4) (concentrations of (b) (4) are expressed as percents of the olopatadine concentration). The trial was conducted between March 21, 2005 and April 8, 2005. Alcon attests that the trial was conducted according to Good Clinical Practice.

Qualified subjects were to be domiciled for up to 8 days and were to be dosed every 12 hours. Safety evaluations were to include daily evaluation of blood pressure and pulse, a nasal examination, and a review of adverse events and concomitant medications. An ECG was to be done for screening and at discharge; clinical laboratory tests were to be done at screening, the day before the first dose, and at discharge.

Sixty subjects were enrolled, with an age range of 20-77 (mean ages of the groups were from 36 to 49 years of age). Males and females were randomized approximately equally (the largest disparity in the numbers of males and females randomized to a group was 2). Approximately 43% of the trial population was Caucasian and 48% Hispanic, without remarkable disparities among the groups. Five "Blacks" were enrolled, of whom 1 was enrolled in the vehicle group, and none in the olopatadine 0.6% group.

The analytical plan called for pharmacokinetic analysis only of the 12 subjects receiving olopatadine with the (b) (4) degradants, with analysis of other groups to clarify the results if needed. The pharmacokinetic analysis of this study has not been evaluated at FDA. Alcon reports that Day 6 plasma determinations showed quantifiable concentrations of olopatadine (≥0.050 ng/ml).

All 60 subjects were evaluable for the safety analysis. All subjects received 6 days of dosing. No deaths or other serious adverse events were reported in any subject in the trial. Nasal septal disorder (characterized as septal erythema) was reported for 4/12 subjects in the

olopatadine 0.6%-only group, 3/12 in the olopatadine+ (b) (4) group, 2/12 in the olopatadine+ (b) (4) and vehicle groups, and in none of the subjects in the olopatadine+ (b) (4) group. One clinically relevant change from baseline occurred upon nasal examination and was reported as an adverse event. Nasal bleeding was observed in a subject in the olopatadine+ (b) (4) treatment group. Regarding cardiovascular events, one subject, in the olopatadine+ (b) (4) group, experienced "tachycardia" graded as "mild" as an adverse event. Nonnasal adverse events occurred sporadically, usually in no more than 1 subject per treatment group, and in no particularly informative pattern.

The safety results from this trial do not change the understanding of the safety of olopatadine 0.6% nasal spray.

Trial C-03-49

Alcon's "Randomized, Multicenter, Crossover Study to Evaluate Sensory Attributes of Olopatadine 0.6% Nasal Spray and Astelin® in Patients with Allergic Rhinitis" was a 6-center trial of randomized, double-blind single-dose treatment of 110 subjects at least 18 years of age with seasonal allergic rhinitis, followed after a washout period of 24 hours by crossover to the alternative treatment. Treatments were 2 sprays in each nostril of olopatadine HCl Nasal Spray 0.6% (formulation containing povidone (b) (4)) and Astelin (azelastine HCl) Nasal Spray 137 mcg. The objective of the trial was to assess "sensory attributes including taste and aftertaste." The trial was conducted between August 29, 2005 and November 17, 2005. Alcon attests that the trial was conducted according to Good Clinical Practice.

Screening procedures included assessment of eligibility, including a nasal examination. Eligibility for randomization at visit 2 included a history of seasonal allergic rhinitis, the presence of at least one nasal allergy symptom recorded on a Symptom Severity Rating Scale (runny, itchy, or stuffy nose or sneezing), the absence of disorders that would complicate the evaluations, and an acceptable nasal examination. Changes in concomitant medications and adverse events were collected at each treatment visit and at the end of the trial, 24 hours after the second treatment was administered. Vital signs were collected for eligibility and prior to the first dose, for screening purposes. The protocol did not include the collection of laboratory test determinations or ECGs.

Six sites enrolled 110 subjects, all of whom were evaluated for safety. Subjects were predominantly Caucasian (88%), female (67%), and below the age of 65 (95%).

All subjects were exposed to both drugs. No one died, there were no other serious adverse events, and no one discontinued due to an adverse event. The adverse event that occurred at the greatest frequency in the olopatadine treatment group was headache, which occurred in 3 subjects.

The results of this trial do not signal a new safety concern for the proposed, povidone-free formulation.

Reviewer comment

FDA does not condone a clinical study to qualify potentially toxic degradants. The trial was started shortly after submitting the protocol. When the Division of Pulmonary and Allergy Products called Alcon about the trial, Alcon informed DPAP that the last of the subjects were to complete in a few days.

10.2 Line-by-Line Labeling Review

(b) (4)

REFERENCES

None

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/s/

James Kaiser
3/6/2008 03:53:52 PM
MEDICAL OFFICER

Charles Lee
3/6/2008 03:57:53 PM
MEDICAL OFFICER
I concur.

MEDICAL OFFICER FILING REVIEW

Division Of Pulmonary and Allergy Products

APPLICATION:	NDA 21, 861	**PRODUCT NAME:**	Olopatadine HCl
APPLICANT:	Alcon Research, Ltd.	**TRADE NAME:**	Patanase® Nasal Spray
MEDICAL OFFICER:	James Kaiser, M.D.	**CATEGORY:**	Antihistamine (H_1 receptor antagonist)
TEAM LEADER:	Charles E. Lee, M.D.	**ROUTE:**	Nasal
DATE OF REVIEW:	November 13, 2007		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
September 26, 2007	September 27, 2007	N-000	Resubmission, new formulation

RELATED APPLICATIONS

IND 60,116 (Alcon): olopatadine for rhinoconjunctivitis

REVIEW SUMMARY: Alcon has submitted a response to a nonapprovable action taken by FDA in October 2005 regarding the original submission of NDA 21-861. Safety, preclinical, and CMC issues led to this action. Administration of the original formulation of olopatadine HCl nasal spray was associated with unacceptable levels of epistaxis, nasal ulceration, and nasal septal perforation.

The submission may be filed. The principle clinical component is the 6-month results from clinical trial C-05-69, which is a 12-month controlled safety study with nasal examinations. In addition, there is a single dose, placebo controlled environmental exposure unit (EEU) study intended to provide a "bridge" to efficacy data from previously completed EEU studies and efficacy and safety studies.

The submitted label has potential issues in the indication statement and the presentation of safety and efficacy.

OUTSTANDING ISSUES: See the review for comments to Alcon.

RECOMMENDED REGULATORY ACTION

X **FILEABLE** **NOT FILEABLE**

Table of contents

1. Regulatory background

Alcon submitted NDA 21,861 on December 24, 2004 for olopatadine HCl for the (b) (4) treatment of (b) (4) seasonal allergic rhinitis. The NDA had CMC, nonclinical, and clinical deficiencies; the chief clinical issue was the occurrence of nasal septal perforations, ulcerations, and epistaxis. An increase in the incidence of concerning nasal adverse events in vehicle control subjects, and preclinical data, suggested that the presence of (b) (4) povidone was a critical contributor to the increased safety signal. FDA took a nonapprovable action in a letter to Alcon dated October 27, 2005, which made the following clinical points:

- To support approval of olopatadine as a nasal spray product for treatment of the symptoms of allergic rhinitis, Alcon (b) (4)
- To support efficacy in (b) (4), at least one trial would have to be conducted with a design as outlined in the letter.

(b) (4) FDA met with Alcon in January and June, 2006, regarding the clinical development plan. FDA stated that Alcon must submit a new long-term safety study. Alcon has submitted two Special Protocol Assessments for a long-term safety study, the latest in November, 2006. Alcon submitted a Proposed Pediatric Study Request in March 2007, and FDA issued a Written Request for pediatric studies in July 2007.

2. Summary of the contents of the submission

The submission is entirely paper except for the package insert, which is also submitted electronically. The patient's instructions for use are submitted in paper only.

The clinical data included in the submission are

- C-05-69: 6-month results of this 12-month safety study. FDA told Alcon that submission of the 6-month results would be acceptable, with 12-month results to be seen as supportive. In addition, FDA told Alcon that the trial should have a measure of efficacy. This clinical trial, which is pivotal to the submission, has required elements for review (text of the report, tables, listings, relevant case report forms).
- C-05-64: Single-dose environmental exposure unit study of the new formulation. Based on results submitted for the June, 2006 meeting between FDA and Alcon, FDA stated that pending review in the NDA, further efficacy trials in SAR might not be needed.
- Three trials using a povidone-containing formulation. These are not important to the judgment of safety and efficacy of the new formulation.

The submission contains substantial CMC data and preclinical data, neither of which are considered in this clinical filing review.

3. Proposed labeling

Alcon has submitted carton labeling, labeling in format consistent with the Physician Labeling Rule (PLR), and submitted a document entitled "Patient Information." Alcon claims an indication for the (b) (4) treatment of the symptoms of seasonal allergic rhinitis (b) (4) in patients 12 years of age and older." Potential problematic issues include 1) (b) (4), 2) (b) (4)

(b) (4) and 3) (b) (4)

t

4. Clinical information in newly submitted trials

The critical clinical information for the new submission is the 6-month safety results from trial C-05-69, which also includes results from nasal examinations.

5. Filing decision

The application may be filed.

6. Comments to the applicant

The Division of Pulmonary Products will send the following comments to Alcon:

1. Provide a comparison of the safety of long-term trials C-01-92 (povidone-containing formulation) and C-05-69 (new proposed formulation) with respect to subgroups of age, gender, and race. This comparison should only be performed for similar periods of exposure.

2. Provide an updated summary of the literature regarding olopatadine. The update should cover the time between the original submission of NDA 21-861 and the cut-off date for the current submission.

3. Provide an update of foreign marketing information for all forms of olopatadine. The update should cover the time between the original submission of NDA 21-861 and the cut-off date for the current submission.

4. Submit any information provided to investigators in trial C-05-69 instructing them on physical examinations of the nose and solicitation and evaluation of nasal adverse events.

5. Provide a by-subject table of contents for the case report forms for each trial for which they were submitted.

6. Clarify when you intend to submit the 12-month data from trial C-05-69.

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/s/

James Kaiser
11/13/2007 02:20:44 PM
MEDICAL OFFICER

Charles Lee
11/13/2007 02:38:46 PM
MEDICAL OFFICER
I concur.

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Products (HFD-570)

APPLICATION:	NDA 21-861	**TRADE NAME:**	Patanase® Nasal Spray
APPLICANT/SPONSOR:	Alcon, Inc.	**USAN NAME:**	Olopatadine HCl
MEDICAL OFFICER:	Charles E. Lee, M.D.		
TEAM LEADER:	Lydia Gilbert-McClain, M.D.	**CATEGORY:**	H_1-antihistamine
DATE:	6/21/06	**ROUTE:**	Intranasal, solution

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
5/31/06	6/1/06	NDA 21-861, N-000 MP	Meeting package, path forward

RELATED APPLICATIONS

Document Date	Application Type	Comments
12/24/05	NDA 21-861, N-000	NDA submission
3/31/00	IND 60,116, N-000	Opening IND

REVIEW SUMMARY:

Alcon, Inc. submitted an NDA for nasal spray solution formulation of olopatadine 0.6% on December 24, 2004. The proposed indication was (b) (4) treatment of the symptoms of SAR (b) (4) in adults and children 12 years of age and older. The proposed dose was two sprays per nostril twice daily. The Division took a "Not Approvable" action on October 27, 2005. The NDA had clinical, non-clinical, and CMC deficiencies. Data submitted showed that the product had an unacceptable safety profile. The formulation caused nasal irritation and damage to the nasal mucosa in non-clinical and clinical studies. Epistaxis, nasal ulceration, and nasal septum perforation were noted in clinical studies in patients treated with active drug product and vehicle placebo. These findings appeared to be related to the product formulation, and possibly to the povidone excipient. The applicant plans to amend the application to respond to the deficiencies in the action letter and has asked for a meeting with the Division to address issues related to the safety profile of the product. The applicant proposes to remove povidone from the formulation. They plan to demonstrate that removal of povidone from the formulation does not impact the quality of the product, and propose using bioequivalence data from in vitro tests to show that the reformulated product is comparable to pivotal clinical trial batches and to primary stability batches. They also plan to (b) (4) The applicant's plan to (b) (4) will not be sufficient to support the safety of the reformulated product. Clinical data will be required to support the safety of the reformulated product.

OUTSTANDING ISSUES: Clinical studies will be necessary

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	____ **FILEABLE**	____ **NOT FILEABLE**	
	APPROVAL	**APPROVABLE**	**NOT APPROVABLE**
OTHER ACTION:	**X—NO ACTION INDICATED**		

1. BACKGROUND

Alcon, Inc. submitted an NDA for nasal spray solution formulation of 0.6% olopatadine on December 24, 2004. The proposed indication is (b) (4) and treatment of the symptoms of seasonal allergic rhinitis (SAR) (b) (4) in adults and children 12 years of age and older. The proposed dose was two sprays per nostril twice daily.

The Division took a "Not Approvable" action on October 27, 2005. The NDA had clinical, non-clinical, and CMC deficiencies. Data submitted showed that the product had an unacceptable safety profile. The formulation caused nasal irritation and damage to the nasal mucosa in non-clinical and clinical studies. Epistaxis, nasal ulceration, and nasal septum perforation were noted in clinical studies in patients treated with active drug product and vehicle placebo. These findings appeared to be related to the product formulation, and possibly to the povidone excipient.

The applicant plans to amend the application to respond to the deficiencies in the action letter and has reformulated their product to contain (b) (4) The previous formulation contained (b) (4) povidone, and there was concern that nasal adverse events noted in the development program were related to the povidone.

The sponsor has submitted a briefing package that addresses their plan to respond to the deficiencies in the NDA. The package includes a list of study reports to be provided in the response, a synopsis of an environmental exposure chamber (EEC) study of 0.6% povidone-free olopatadine in the treatment of symptoms of SAR, a discussion of safety findings from the clinical studies submitted with the NDA, a draft protocol for a safety study of 0.6% olopatadine nasal spray containing (b) (4) povidone in the treatment of symptoms of (b) (4), and clinical and nonclinical toxicology questions for Division comment.

This review addresses the proposed contents of the response, the EEC study synopsis, the discussion of safety findings, the draft protocol for the safety study, and the clinical questions for Division comment.

2. PROPOSED CONTENTS OF RESPONSE

The sponsor proposes to submit a CMC amendment and results of various nonclinical toxicology studies. The sponsor proposes to submit a report of a clinical pharmacology study of their drug product containing various levels of (b) (4) and (b) (4) degradation products (b) (4) a report of a completed EEC study of povidone-free 0.6% olopatadine nasal spray and povidone-free nasal spray vehicle in the treatment of symptoms of SAR (Study C-05-64), and a the results of a clinical safety study (b) (4) [page 2].

<u>Reviewer comment</u>:
The types of clinical studies to be submitted to the NDA are acceptable. Details regarding the design of the safety study are addressed later in this review.

3. EEC STUDY C-05-64

Study C-05-64 was a single center, randomized, double blind, placebo controlled, two-arm, parallel group EEC study designed to demonstrate the superiority of 0.6% olopatadine nasal spray (povidone-free) relative to vehicle (povidone-free) in treatment of symptoms of SAR over a 12-hour period. The sponsor states that the study had the same design as Studies C-01-83 and C-03-52, which were reviewed in the original NDA submission [page 3].

Reviewer comment:
These studies had similar designs, but were not of identical designs. Study C-01-83 studied 0.2%, 0.4%, and 0.6% concentrations of olopatadine nasal spray as well as olopatadine nasal spray vehicle. Study C-03-52 studied 0.6% olopatadine nasal spray, olopatadine nasal spray vehicle, and Nasonex Nasal Spray [Medical Officer Review, Charles E. Lee, M.D., NDA 21-861, N-000, 12/24/04].

There were 406 patients randomized to treatment. Those randomized were 18 years of age and older with a history of SAR to short ragweed pollen, as defined by history and skin test, and were successfully primed.

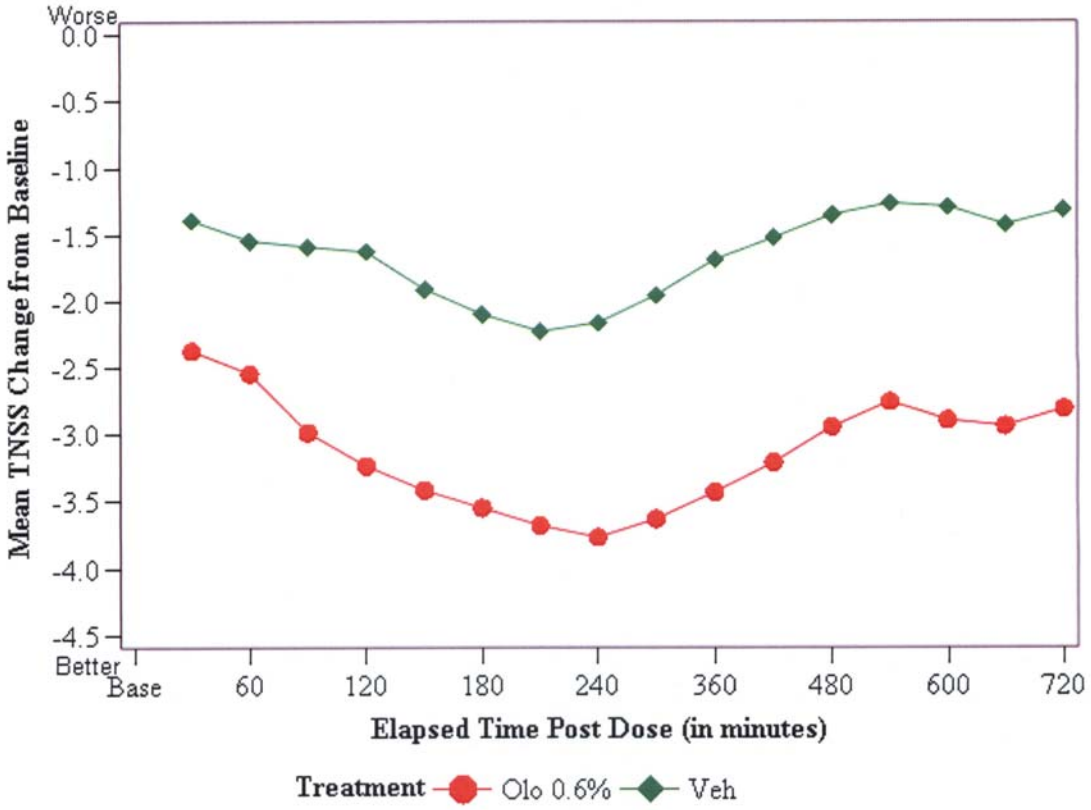
The primary efficacy variable was the change from baseline in the instantaneous Total Nasal Symptom Score (TNSS). Secondary efficacy variables included changes from baseline in individual allergic rhinitis symptom scores and the Patient Global Rating Scale, a seven-point scale used to assess allergic rhinitis symptoms at four hours post dose and the end of the dosing interval, compared to that before dosing. Of the 406 patients randomized to treatment, 395 were 13 to 64 years of age, and 11 were older than 64 years of age. There were 207 males and 199 females. There were 202 patients of Caucasian race, 49 of Asian race, 46 of Hispanic or other race [pages 20-21].

Reviewer comment:
It is unclear if patients were 13 years of age or older or 18 years of age or older.

Olopatadine 0.6% was statistically superior to vehicle placebo and TNSS at all time points post-dose. For olopatadine 0.6%, onset of action was noted at 30 minutes post-dose and the therapeutic effect was maintained until the final assessment, at 720 minutes post-dose [pages 21-23]. These data are displayed in Figure A below.

Reviewer comment:
Olopatadine is statistically superior to placebo at all time points. The effect size at all time points is clinically relevant and similar to the effect size noted in the previous EEC studies, Study C-01-83, and Study C-03-52.

Figure A. Mean change in TNSS from baseline, Study C-05-64 [page 23].



Safety variables included adverse events and nasal examinations. There were a small number of adverse events in this single dose study. The most common adverse event noted was headache, which was reported by 3.9% (8/204) of patients treated with olopatadine 0.6% and 9.4% (19/202) of patients treated with vehicle placebo. Epistaxis was present in 3.4% (7/204) of patients treated with olopatadine 0.6% and 3.5% (7/202) of patients treated with vehicle placebo. All other adverse events occurred at a frequency of 1.0% or less (2 or fewer patients). There were no deaths, serious adverse events, or withdrawals due to adverse events in this study.

The frequency of epistaxis in this study (3.4% olopatadine 0.6%, 3.5% vehicle placebo) was higher than the frequencies noted in Study C-03-52 (0% olopatadine 0.6%, 0.7% vehicle placebo) and Study C-01-83 (1.3% olopatadine 0.6%, 2.5% vehicle placebo) [pages 38-39]. The sponsor notes that the study was performed during January through March in Ontario, Canada, and that a higher incidence of epistaxis might be likely due to lower indoor humidity and cold and windy outdoor air. Study C-03-52 was conducted during April through June and Study C01-83 was conducted during June and July; these studies were conducted in Ontario, Canada also.

Reviewer comments:
This reviewer concurs that winter weather conditions may have been a contributing factor to the higher rates of epistaxis in this study.

These studies provide evidence that povidone does not have an effect on the efficacy of 0.6% olopatadine nasal spray. The sponsor will not need to provide any addition evidence to establish efficacy of their reformulated product.

4. APPLICANT'S DISCUSSION OF SAFETY FINDINGS

The sponsor's safety discussion focuses on three topics: (1) the duration of the proposed safety study, C-05-69, (2) adverse event guidance to be provided to the investigator, and (3) a scale to be used in documenting nasal examinations. These are reviewed below.

1.1. Duration of safety study

The sponsor believes that a three-month safety study will be sufficient to support the safety of their reformulated product. The sponsor states that there is no evidence to suggest that there is a progression from one event (epistaxis, nasal ulceration, and nasal septum perforation) to the next [page 43]. The sponsor summarized their data by plotting onset and duration of these events by patient. These data are presented below in Figures B and C [pages 46, 47].

Figure B [page 46]

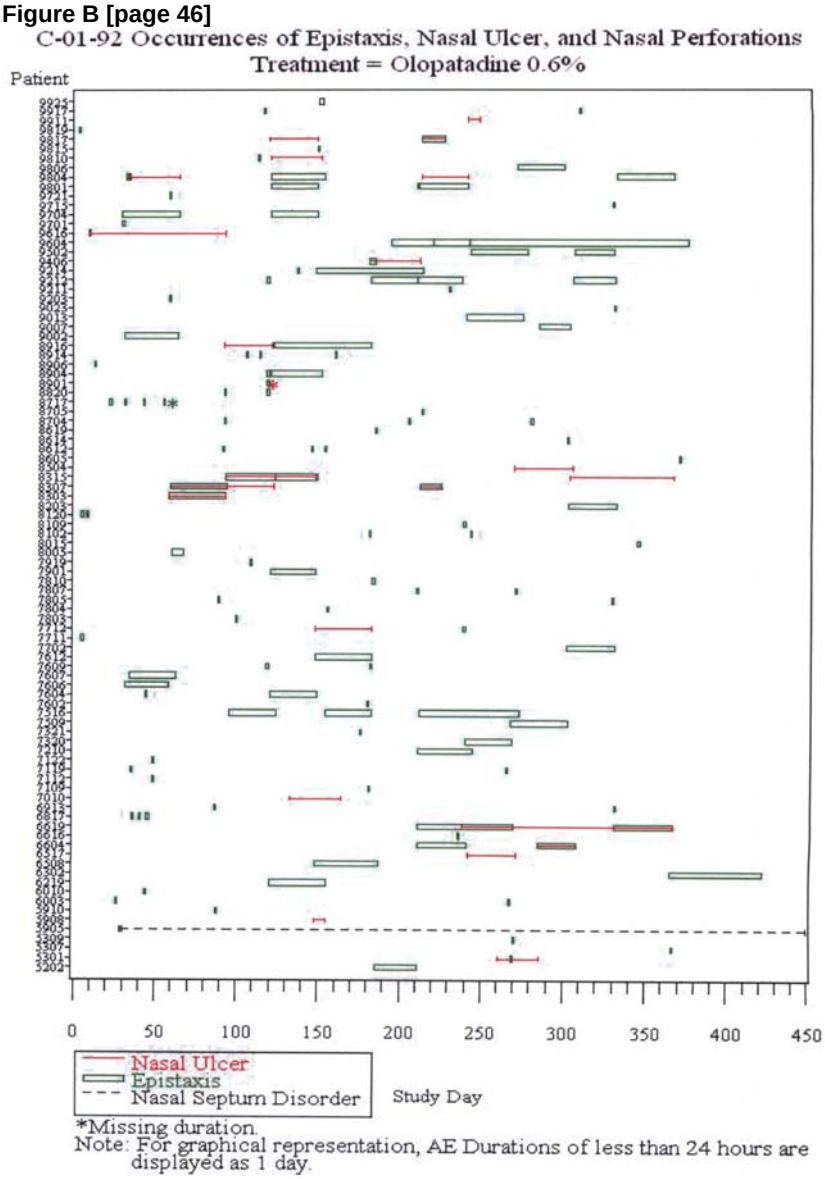
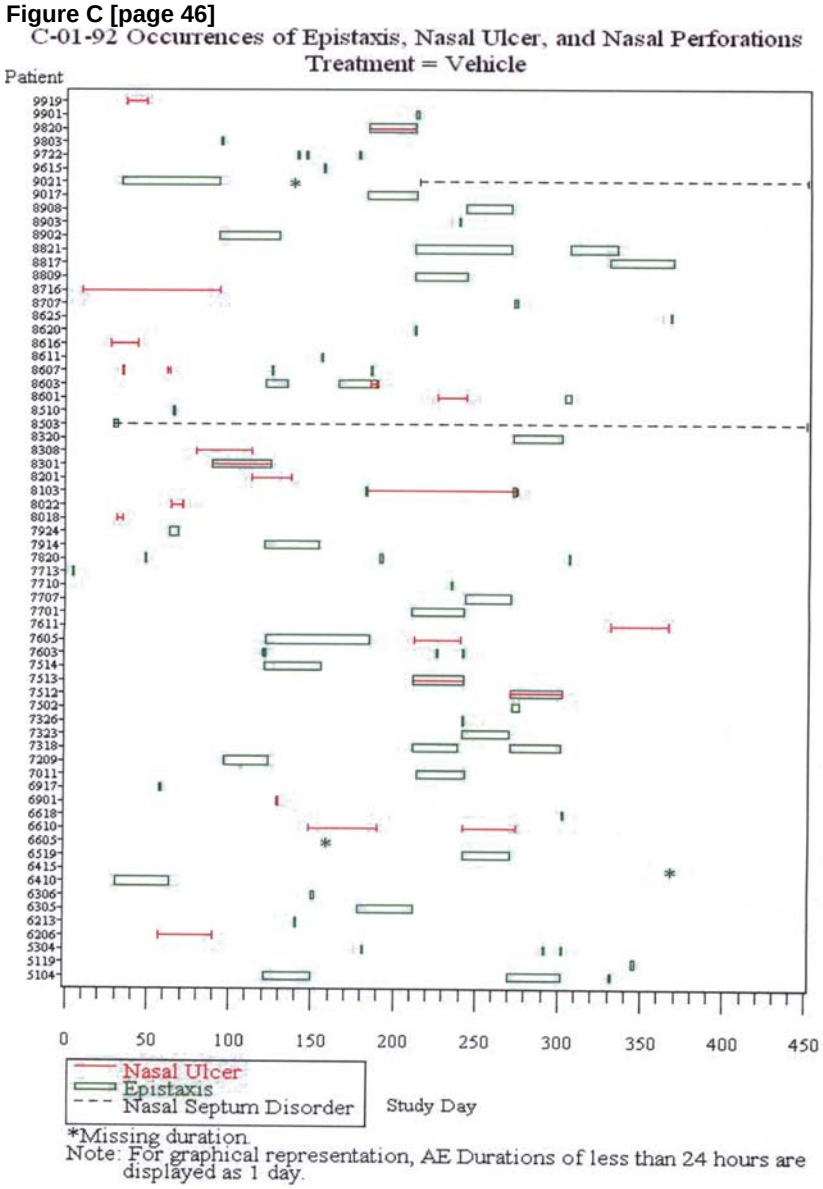


Figure C [page 46]



<u>Reviewer comment</u>:
This reviewer concurs that the data show no apparent progression from epistaxis to nasal ulceration or vice versa. There are too few patients to determine if there is a progression to nasal septal perforation.

The sponsor also states that there is no relationship between the duration of exposure and the onset of epistaxis, nasal ulceration, and nasal septum perforation [page 43].

The sponsor summarized their data on epistaxis by presenting the (1) number of adverse events of epistaxis based on onset day, and (2) plotting the cumulative number of patients with a report of epistaxis against the earliest day of onset. These data are displayed in Table 1 and Figure D below [page 50].

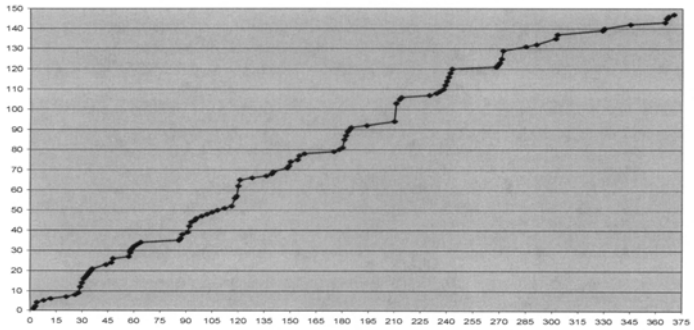
Table 1 and Figure D [page 50].

Summary of Overall Frequency of Epistaxis Adverse Events by Onset Day
Related and Not Related Adverse Events Combined (C-01-92 only)

Number of Events by 30 Day Periods				Number of Events by 3 Month Periods			
Time of Onset (Day)	Olopatadine 0.6%	Vehicle	Combined	Olopatadine 0.6%	Vehicle	Combined	Time of Onset (Period)
1 to 30	11	3	**14**	28	10	**38***	1st 3 months
31 to 60	14	4	**18**				
61 to 90	3	3	**6**				
91 to 120	17	7	**24**	26	17	**43***	2nd 3 months
121 to 150	6	6	**12**				
151 to 180	3	4	**7**				
181 to 210	8	5	**13**	23	19	**42**	3rd 3 months
211 to 240	11	9	**20**				
241 to 270	4	5	**9**				
271 to 300	2	4	**6**	9	8	**17**	Final 3 months
301 to 330	5	3	**8**				
331 to 365	2	1	**3**				
> 365	2	2	**4**	2	2	**4**	> 365
Total	**88**	**56**	**144**	**88**	**56**	**144**	**Total**

* 7 events occurred in the Day 91 to 95 time range

Cumulative Number of Patients with an Adverse Event of Epistaxis
(Olopatadine 0.6% and Vehicle groups combined)
(x-axis = onset day; y-axis = number of events)



Please note: patients 5304, 6604, 7318 (1 Olopatadine 0.6%; 2 Vehicle) each experienced 2 occurrences of nasal ulcer (1 assessed as related, the other not related). This patient is only counted once (the earliest occurrence in Table 2); however, both the related and not related occurrences are presented in this graph.

<u>Reviewer comment</u>:
The number of patients with epistaxis increase at a fairly even rate over time.

The sponsor summarized their data on nasal ulceration by presenting the (1) number of adverse events of nasal ulceration based on onset day, and (2) plotting the cumulative number of patients with a report of nasal ulceration against the earliest day of onset. These data are displayed in Table 2 and Figure E below [page 50].

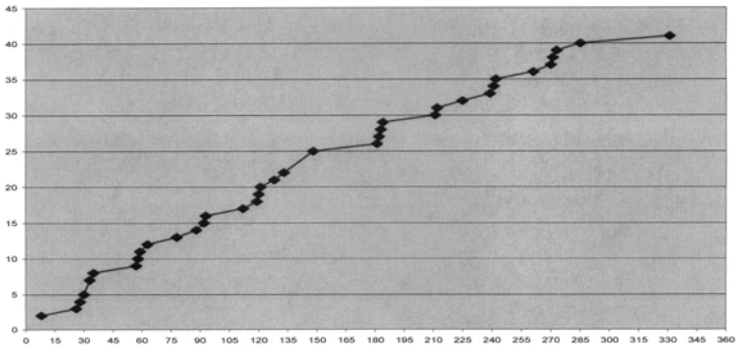
Table 2 and Figure E [page 50].

Summary of Overall Frequency of Nasal Ulceration Adverse Events by Onset Day Related and Not Related Adverse Events Combined (C-01-92 only)

Number of Events by 30 Day Periods				Number of Events by 3 Month Periods			
Time of Onset (Day)	Olopatadine 0.6%	Vehicle	Combined	Olopatadine 0.6%	Vehicle	Combined	Time of Onset (Period)
1 to 30	1	4	**5**	4	10	**14***	1st 3 months
31 to 60	3	3	**6**				
61 to 90	0	3	**3**				
91 to 120	4	1	**5**	8	3	**11***	2nd 3 months
121 to 150	4	2	**6**				
151 to 180	0	0	**0**				
181 to 210	1	3	**4**	6	6	**12**	3rd 3 months
211 to 240	1	3	**4**				
241 to 270	4	0	**4**				
271 to 300	1	1	**2**	1	2	**3**	Final 3 months
301 to 330	0	0	**0**				
331 to 365	0	1	**1**				
> 365	0	0	**0**	0	0	**0**	> 365
Total	**19**	**21**	**40**	**19**	**21**	**40**	**Total**

* 2 events occurred in the Day 92 to 93 time range

Cumulative Number of Patients with an Adverse Event of Nasal Ulceration (Olopatadine 0.6% and Vehicle groups combined) (x-axis = onset day; y-axis = number of events)



Please note: patient 8103 experienced 2 occurrences of nasal ulcer (1 assessed as related, the other not related). This patient is only counted once (the earliest occurrence in Table 1); however, both occurrences are presented in this graph.

<u>Reviewer comment</u>:
The number of patients with nasal ulceration increase at a fairly even rate over time.

Based on these data, the sponsor argues that since there is no relationship suggestive of a progression from one of these nasal adverse events to another and since there is no relationship between the duration of exposure and the onset of the events, that a three-month safety study would be adequate in duration to assess the safety of the revised formulation of the product [page 43].

<u>Reviewer comment</u>:
This reviewer concurs that the data suggest a three-month safety study might be of adequate duration to assess the risk of epistaxis and nasal ulceration associated with this product. However there is insufficient data to draw this conclusion for nasal septum perforation, the most serious of these three events. As noted in the NDA action letter, it appears that these events may be related to the povidone excipient in the formulation. We do not know if the (b) (4)

concentration of povidone in the revised formulation is low enough to eliminate the risk of nasal septum perforation. There does not be any progression from epistaxis and/or nasal ulceration to nasal septum perforation, and these events may not be used as a surrogate signal for the future development of nasal septum perforation. In addition, one patient (#9021) in the long-term safety study C-01-92 was noted to have a nasal septum perforation at day 210. In light of these points, and given that the occurrence of nasal septum perforation is infrequent, an exposure of an additional 300 patients to the new formulation in a three month study is not sufficient to support safety. Twelve months of safety data will be necessary to support the safety of the reformulated product. Alternatively, the sponsor may provide six months of safety data for a larger number of patients exposed to the reformulated product.

1.2. Adverse event guidance

The sponsor states that the method of defining adverse events occurring in the clinical studies in the NDA was conservative in that an assessment of clinical relevance by the study investigator was not part of the evaluation. The sponsor proposes to define an adverse event as a clinically relevant change in nasal examination, physical examination, or vital signs [pages 55-56].

Reviewer comment:
This is not acceptable. Any change in nasal examination, physical examination, or vital signs should be reported as an adverse event. The sponsor should provide an analysis of adverse events due changes in nasal examination, physical examination, and vital signs as well as an analysis of clinically relevant changes in nasal examination, physical examination, and vital signs.

1.3. Scale for assessment of nasal examination findings

Nasal examinations are to be conducted with a standardized procedure and using oxymetazoline 0.05% topically as a decongestant, a nasal speculum, and a transilluminator light source [pages 61-62].

The scale to be used at the baseline examination is displayed in Table 3 below. Any patient with any of the findings present at baseline examination is not to be enrolled or randomized [page 59].

Table 3. Baseline nasal examination scale [page 59].

Examination	Score
Evidence of transient process	
Purulent drainage	0 = absent 1 = present
Nasal septal bleeding	0 = absent 1 = present
Nasal septal crusting	0 = absent 1 = present
Turbinate bleeding or blood in mucus	0 = absent 1 = present
External nasal process	0 = absent 1 = present
Significant anatomic abnormalities	
Nasal septum perforation	0 = absent 1 = present
Nasal septal ulceration	0 = absent 1 = present
Intranasal mass	0 = absent 1 = present
Nasal septal deviation	0 = absent

Examination	Score
	1 = present

The scale to be used at post-baseline examinations is displayed in Table 3 below. Any patient with any of the findings present at post-baseline examination is to have an assessment of clinical relevance. Adverse event forms will only be filled out for patients who have clinically relevant findings [page 60].

Table 4. Post-baseline nasal examination scale [page 60].

Examination	Score	Clinically relevant*
Evidence of transient process		
Purulent drainage	0 = absent 1 = present	1 = No 2 = Yes
Nasal septal bleeding	0 = absent 1 = present	1 = No 2 = Yes
Nasal septal crusting	0 = absent 1 = present	1 = No 2 = Yes
Turbinate bleeding or blood in mucus	0 = absent 1 = present	1 = No 2 = Yes
External nasal process	0 = absent 1 = present	1 = No 2 = Yes
Significant anatomic abnormalities		
Nasal septum perforation	0 = absent 1 = present	1 = No 2 = Yes
Nasal septal ulceration	0 = absent 1 = present	1 = No 2 = Yes
Intranasal mass	0 = absent 1 = present	1 = No 2 = Yes
Nasal septal deviation	0 = absent 1 = present	1 = No 2 = Yes

*If clinically relevant, an adverse event form is to be completed.

Reviewer comments:
The proposed nasal exam is acceptable. However, any change in nasal examination must be reported as an adverse event. The sponsor may also provide additional analyses of these nasal events using the proposed classification.

It is unclear to this reviewer how a nasal septum perforation occurring in this study in a patient with a normal nasal examination at baseline would not be "clinically relevant." That said, the post-baseline nasal examination scale is acceptable, and it is acceptable for the sponsor to assess the clinical relevance of the nasal examination findings. What is not acceptable is that the sponsor plans to complete an adverse event form only for "clinically relevant" findings at the post-baseline exam. The sponsor must report all changes in nasal examination as adverse events and provide an analysis of these events. To insure that the safety data from the proposed study may be compared to your previously conducted studies, the sponsor must provide an analysis of all epistaxis, all nasal ulcerations, and all nasal septal perforations. A separate analysis of "clinically relevant" changes should also be provided.

As an aside, the number of patients with a change from nasal septum deviation absent at baseline exam to nasal septum deviation present at post-baseline exam will give an indication of the quality and validity of the nasal examinations. A change in nasal septum deviation would not be expected in the absence of a history of facial trauma occurring during the course of the study.

5. SAFETY STUDY C-05-64

The sponsor provided a draft protocol for a safety study C-05-64. It is reviewed below.

1.4. Title: C-05-69: Long-term safety study of olopatadine nasal spray

1.5. Objective

The objective of this study is to describe and compare the safety of olopatadine 0.6% nasal spray versus vehicle placebo and Astelin Nasal Spray 0.1% when given as two sprays per nostril twice daily for three months in patients with perennial allergic rhinitis (PAR) [pages 67, 74].

1.6. General study design

This study is a randomized, vehicle- and active-controlled, parallel group, double blind, three-arm, three-month, multicenter safety study of patients with PAR. There are to be up to 55 study centers. After meeting inclusion and exclusion criteria, patients are to receive olopatadine nasal spray 0.06%, olopatadine nasal spray vehicle, or Astelin Nasal Spray for use twice daily [pages 67, 81]. Patients are to come for four monthly office visits [page 81]. Adverse events are to be volunteered by patients and are to be recorded in a medical problems log [page 83]. Study staff will also elicit adverse events at office visits [pages 68, 82, 83].

Reviewer comment:
As noted earlier in this review, a three-month treatment duration is insufficient to assess the safety of the product.

1.7. Patient population

Approximately 1200 patients are to be screened and 1000 randomized to obtain at least 300 evaluable olopatadine-treated patients per group at 3 months [pages 81, 91]. Patients are to be randomized at a 1:1:1 ratio [page 80]. Patients are to be ages 12 years and older, and are to have a one-year history of history of non-recalcitrant PAR and a positive skin test to a PAR allergen within one year prior to Visit 1 [page 77].

Reviewer comment:
History of ulcers of medical treatment for epistaxis must not be an exclusion criterion for this study. This exclusion criterion would make it impossible to compare the results of this study with results of completed studies. Furthermore, the product is likely to be used by patients who have a history of these conditions.

The sponsor plans to use some of the same study centers at C-02-92 and to enroll some of the same patients. Sites previously used in the NDA may not participate in this study. Enrollment of the same patients will compromise blinding.

1.8. Study treatment

Study treatments will include olopatadine nasal spray 0.6%, vehicle placebo, and Astelin Nasal Spray 0.1% [page 75]. Study treatment is to be administered at the dose of 2 sprays each nostril twice daily, morning and evening. Patients will be encouraged to maintain a 12-hour dosing frequency [pages 68, 76]. Study treatment will be delivered to the site in a foil overwrap that will cover the entire package to disguise the shape and appearance of the bottle, pump, and nasal adapter, and leave the applicator tip exposed [page 75]. At study visits, patients are to return their bottle of study medication and will be dispensed a new bottle. The site staff will prime the new bottle [page 83].

Reviewer comment:
The sponsor should add a treatment arm with vehicle placebo containing 0% povidone in place of the Astelin Nasal Spray treatment arm. The Astelin Nasal Spray treatment arm will not provide much useful information. The study is not designed or powered to draw conclusions on the relative safety of olopatadine 0.6% and Astelin. In addition, the results from the Astelin Nasal Spray treatment arm would not be suitable for the label because they would not be replicated. Use of Astelin will also compromise blinding. It is unlikely that use of a foil overwrap` will be sufficient to adequately blind study treatment since the bottles different shapes and sizes and the tips are of different appearances, especially since study staff are to prime the bottles.

There is insufficient nonclinical data to support a study of 6 months duration or longer. The sponsor will need to provide nonclinical support for the proposed dose and duration of treatment with the revised formulation prior to conducting the clinical study.

Study staff is to review dosing compliance with patients, but there are to be no patient daily dosing diaries [pages 65, 85]. There appear to be no plans for bottle weights for use as an assessment of compliance.

Reviewer comment:
The study must have an assessment of compliance to provide a measure of validity to the safety findings. Patients should record use of study treatment in a daily diary. Bottle weights should be performed by study staff to provide an assessment of compliance. The sponsor will be encouraged to add pharmacokinetic sampling as an additional measure of compliance.

Pseudoephedrine may be used as a rescue medication. Patients will be allowed to use pseudoephedrine only if instructed to do so by the study site. Patients will not record use of rescue medication but are to be asked about use of rescue medication use at each office visit [pages 87-88].

Reviewer comment:
Use of rescue medication should be recorded by patients in a daily diary.

1.9. Efficacy variables

There is to be no assessment of efficacy [page 65].

Reviewer comment:
There must be some assessment of efficacy to provide a measure of validity to the safety findings. The sponsor could use the patient-related relief assessment question used in Study C-01-92. Alternatively, the sponsor could also consider powering the study for assessment of efficacy using patient self-rated instantaneous and reflective total symptom scores for the first four weeks of the study. Demonstration of efficacy (b) (4) *of the product for treatment of symptoms of SAR.*

1.10. Safety variables

The primary safety variables are adverse events and nasal examination. Adverse events will be presented descriptively by treatment. Adverse events, both volunteered and elicited, are to be recorded in patient medical problems pages and at clinic visits. A table containing the number and percentage, by treatment, of patients with a change in any nasal examination parameter will be presented. Secondary safety variables include physical examination and vital sign [pages 83, 90].

Predefined scales will be used to assess presence and clinical relevance of abnormalities on nasal and physical examination [pages 86, 101-103; Table 3 and Table 4 of this review, above] Clinically relevant change in nasal examination, physical examination, or vital signs will be considered to be adverse events [pages 94, 101-103].

Nasal examinations are to be conducted with a standardized procedure and using oxymetazoline 0.05% topically as a decongestant, a nasal speculum, and a transilluminator light source [page 86].

Reviewer comment:
Any change in nasal examination, physical examination, or vital signs should be reported as an adverse event. The sponsor should provide an analysis of adverse events due changes in nasal examination, physical examination, and vital signs as well as an analysis of clinically relevant changes in nasal examination, physical examination, and vital signs.

Some epistaxis is to be expected with use of a nasal spray for the treatment of allergic rhinitis. Incidences of epistaxis from previous studies of olopatadine and for other nasal sprays for the treatment of allergic rhinitis may be considered to be a benchmark. The validity of the study will be questioned and the product may not be approvable if the results of this study show an incidence of epistaxis that is substantially lower than in other studies of olopatadine or in other products.

1.11. Statistics

All patients who receive study drug are to be evaluated for the safety analysis [page 90]. The sponsor's goal is to have at least 300 patients on olopatadine 0.06% nasal spray complete three months of study treatment. The sponsor estimates that approximately 1200 patients will need to be screened and 1000 patients randomized to achieve the desired number of patients completing the study [page 91].

1.12. Summary

The sponsor has provided a protocol for a three-month safety study of olopatadine nasal spray 0.6%, vehicle placebo, and Astelin Nasal Spray 0.1% in patients with PAR. There are to be no patient daily dosing diaries and there are no plans for bottle weights for use as an assessment of compliance. Patients will not record use of rescue medication but are to be asked about use of rescue medication use at each office visit. There is to be no assessment of efficacy. The primary safety variables are adverse events and nasal examination. Adverse events will be presented descriptively by treatment. Adverse events, both volunteered and elicited, are to be recorded in patient medical problems pages and at clinic visits. Predefined scales will be used to assess

presence and clinical relevance of abnormalities on nasal and physical examination. Clinically relevant change in nasal examination, physical examination, or vital signs will be considered to be adverse events.

The three month treatment duration is insufficient to assess the safety of the product. The Astelin Nasal Spray treatment arm will not provide much useful information and will detract from the number of patients treated with olopatadine 0.6% and vehicle placebo. Use of Astelin Nasal Spray will also compromise blinding. The study must have an assessment of compliance to provide a measure of validity to the safety findings. Patients should record use of study treatment and rescue medication in a daily diary. Bottle weights should be performed by study staff to provide an assessment of compliance.

There must be some assessment of efficacy to provide a measure of validity to the safety findings. Any change in nasal examination, physical examination, or vital signs should be reported as an adverse event. The sponsor should provide an analysis of adverse events due changes in nasal examination, physical examination, and vital signs as well as an analysis of clinically relevant changes in nasal examination, physical examination, and vital signs. The sponsor will be provided with comments on the protocol.

6. CLINICAL QUESTIONS FROM THE SPONSOR

1. The results of a recently completed environmental chamber clinical trial, C-05-64, compared to results from previous studies of the same design, C-01-83 and C-03-52 (previously submitted in NDA 21-861), demonstrate for both onset and duration of action clinically equivalent reductions in the total nasal symptom scores for Patanase containing (b) (4) PVP (C-01-83 and C-03-52) and Patanase containing 0% PVP (C-05-64) (Figure 1; details in Tab 1). These clinical results demonstrate that the pharmacological efficacy of olopatadine is not affected by the presence or absence of PVP in the formulation. Because our reformulation is only a (b) (4) we propose to utilize (a) the results of this study along with (b) spray characterization testing (requirements to be confirmed with the FDA chemists and data to be included in the CMC amendment) to bridge to the efficacy results from our pivotal studies. Does the Agency agree that this approach provides a sufficient bridge to the pivotal efficacy data that an additional SAR study would not be necessary?

   <u>Division response</u>:
   Yes, this approach is acceptable. An additional SAR study will not be necessary if review of the complete study report for C-05-64 demonstrates similar efficacy to studies C-01-83 and C-03-52.

2. Since efficacy is unaffected by the presence or absence of PVP, likewise, if follows that the pharmacokinetic profile of the revised formulation is comparable to that used in previous clinical trials. Therefore Alcon proposes to rely on clinical pharmacokinetic data previously submitted in NDA 21-861 for our final label. Does the Agency agree?

   <u>Division response</u>:

We disagree that the pharmacokinetic profile is a valid measure of efficacy for your product. The product is a topical nasal spray and it is unclear to what extent systemic exposure and topical exposure contribute to its efficacy.

We agree that you may rely on previously submitted clinical pharmacokinetic data, as long as the efficacy and safety data obtained from the revised formulation is comparable to that obtained from the original formulation and the revised formulation is considered stable from the CMC perspective (e.g., stay as a solution/no precipitation).

3. The results from a one-year clinical trial (Study C-01-92, NDA 21-861) demonstrated that the long-term safety of Patanase including cardiovascular effects (e.g., no prolongation of QTc interval). The safety effects that the FDA questioned at our January 12, 2006 meeting were local nasal: epistaxis, nasal ulceration, and septal perforation. Alcon proposes to conduct a new clinical trial, C-05-69, to establish nasal safety for Patanase containing (b) (4) PVP and rely on the original NDA 21-861 for safety aspects in our final label, other than local nasal effects. Does the Agency agree?

   <u>Division response</u>:
   We disagree. Safety data (nasal and non-nasal adverse events, nasal and physical examinations, and vital signs) from the new clinical trial will provide the long-term safety information needed to support approval and labeling of your product.

   It is acceptable to rely on the original NDA for cardiovascular safety, and it will not be necessary to include ECGs or laboratory studies as safety endpoints in your new clinical trial.

4. The FDA raised concerns over the incidence of local nasal effects (epistaxis, ulceration, and septal perforation) (b) (4) The FDA required Alcon to (b) (4) A comprehensive analysis of safety data from C-01-92 demonstrates that the rates of epistaxis, ulceration, and septal perforation were constant throughout the long-term study, indicating that the rates of these events are independent of duration of exposure to test article (see discussion in Tab 2). In order to (b) (4)

(b) (4)

[redacted]

5. Due to the safety concerns arising from the previous Patanase clinical studies, some of which may have been attributed to how data and information was collected and subsequently classified, Alcon has worked with medical experts to design improved patient dosing instructions (see protocol C-05-69, Section 9.4.6, page 23), a more extensive and clinically meaningful nasal examination (see protocol C-05-69, Section 9.4.3.1, page 21), and clinically relevant classification of observed nasal changes (see protocol C-05-69, Section 18.1, pages 36-38). The exam and classification have been developed both as a means to provide a comparison to data from previous studies as well as to characterize a realistic nasal adverse event profile for Patanase containing [redacted] (b) (4) PVP (see safety discussion in Tab 2). Does the Agency agree that the proposed nasal exam and classification are acceptable?

   Division response:
   We disagree that the safety concerns arising from the previous clinical studies were a result of data collection and classification. In fact, the data collection and classification were similar to that used in comparable development programs for intranasal sprays with indications for allergic rhinitis.

   Your proposed nasal exam and the nasal classification are acceptable. However, any change in nasal examination must be reported as an adverse event. You may also provide additional analyses of these nasal events using your proposed classification.

   To insure that the safety data from the proposed study may be compared to your previously conducted studies, you must provide an analysis of all epistaxis, all nasal ulcerations, and all nasal septal perforations.

   We have the following additional comments on the protocol for C-05-69:
   - *We strongly recommend that you add a treatment arm with vehicle placebo containing 0% povidone in place of the Astelin Nasal Spray treatment arm. The Astelin Nasal Spray treatment arm will not provide much useful information. The study is not designed or powered to draw conclusions on the relative safety of olopatadine 0.6% and Astelin. In addition, the results from the Astelin Nasal Spray treatment arm would not be suitable for the label because they would not be replicated. Use of Astelin will also compromise blinding. It is unlikely that use of a foil overwrap will be sufficient to adequately blind study treatment since the bottles*

different shapes and sizes and the tips are of different appearances, especially since study staff are to prime the bottles.

- *History of ulcers of medical treatment for epistaxis must not be an exclusion criterion for this study. This exclusion criterion would make it impossible to compare the results of this study with results of completed studies. Furthermore, the product is likely to be used by patients who have a history of these conditions.*
- *The study must have an assessment of compliance to provide a measure of validity to the safety findings. Patients should record use of study treatment in a daily diary. Bottle weights should be performed by study staff to provide an assessment of compliance. We also strongly encourage you to add pharmacokinetic sampling as an additional measure of compliance.*
- *Use of rescue medication should be recorded by patients in a daily diary.*
- *There must be some assessment of efficacy to provide a measure of validity to the safety findings. You could use the patient-related relief assessment question used in Study C-01-92. Alternatively, you could also consider powering the study for assessment of efficacy using patient self-rated instantaneous and reflective total symptom scores for the first four weeks of the study. Demonstration of efficacy* (b) (4) *of the product for treatment of symptoms of SAR.*
- *Any change in physical examination or vital signs should be reported as an adverse event. Provide an analysis of adverse events due changes in physical examination and vital signs as well as an analysis of clinically relevant changes in physical examination and vital signs.*
- *Some epistaxis is to be expected with use of a nasal spray for the treatment of allergic rhinitis. Incidences of epistaxis from previous studies of olopatadine and for other nasal sprays for the treatment of allergic rhinitis may be considered to be a benchmark. The validity of the study will be questioned and the product may not be approvable if the results of this study show an incidence of epistaxis that is substantially lower than in other studies of olopatadine or in other products.*
- *There are additional pharmacology/toxicology requirements to be met prior to beginning this study. See responses to Toxicology Questions 1 and 3.*

6. Alcon proposes to rely on (b) (4) other that local nasal safety data, previously submitted in NDA 21-861 for our final label. Doe the Agency agree?

   <u>Division response</u>:
   We disagree. Safety data (nasal and non-nasal adverse events, nasal and physical examinations, and vital signs) from the new clinical trial will be the basis for the long-term safety of your product.

   It is acceptable to rely on the original NDA for cardiovascular safety, and it will not be necessary to include ECGs or laboratory studies as safety endpoints in your new clinical trial. You may rely on previously submitted data on renal impairment, ADME, mass balance, and dose response.

7. There are a limited number of sites that are qualified to participate in this study. Because the size and scope of this study, Alcon proposes to use some of the same clinical sites previously used in NDA 21-861 to facilitate enrollment. Does the Agency agree that this is acceptable?

   Division response:
   We disagree. Sites previously used in the NDA may not participate in this study.

   Special qualifications will not be required to prescribe your product, if approved. Likewise, special qualifications are not necessary for participation in this study.

8. Alcon anticipates the enrollment of some of the same patients previously used in NDA 21-861. Is this acceptable to the Agency?

   Division response:
   No. This is not acceptable. Enrollment of the same patients will compromise blinding.

Reviewed by:

_____
Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Products

_____
Lydia Gilbert-McClain, M.D.
Medical Team Leader, Division of Pulmonary and Allergy Products

cc: Original NDA
IND 60,116
HFD-570/Division File
HFD-570/McClain/Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-570/Bond/Pharmacology-Toxicology Reviewer
HFD-570/Sun/Pharmacology-Toxicology Team Leader
HFD-570/Fadiran/Clinical Pharmacology and Biopharmaceutics Team Leader
HFD-570/Zeccola/CSO

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/s/

Charles Lee
8/2/2006 02:28:24 PM
MEDICAL OFFICER

Lydia McClain
8/2/2006 02:33:51 PM
MEDICAL OFFICER
I concur

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 21-861	**TRADE NAME:**	Patanase® Nasal Spray
APPLICANT/SPONSOR:	Alcon, Inc.	**USAN NAME:**	Olopatadine HCl
MEDICAL OFFICER:	Charles E. Lee, M.D.		
TEAM LEADER:	Lydia Gilbert-McClain, M.D.	**CATEGORY:**	H_1-antihistamine
DATE:	10/28/05	**ROUTE:**	Intranasal, solution

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
10/6/05	10/7/05	NDA 21-861, N-000, BM	IR, nasal ulceration and epistaxis in pediatric study C-03-51
3/11/05	3/14/05	IND 60,116, N-063, IM, PN	Phase 3 protocol, ages 6-11 years

RELATED APPLICATIONS

Document Date	Application Type	Comments
12/24/05	NDA 21-861, N-000	NDA submission
3/31/00	IND 60,116, N-000	Opening IND

REVIEW SUMMARY:

The applicant, Alcon, Inc., submitted an NDA for nasal spray solution formulation of olopatadine 0.6% on December 24, 2004. The proposed indication ia (b) (4) treatment of the symptoms of SAR (b) (4) such as (b) (4) in adults and children 12 years of age and older. The proposed dose was two sprays per nostril twice daily. The Division took a "Not Approvable" action on October 27, 2005. The NDA had clinical, non-clinical, and CMC deficiencies. Data submitted showed that the product had an unacceptable safety profile. The formulation caused nasal irritation and damage to the nasal mucosa in non-clinical and clinical studies. Epistaxis, nasal ulceration, and nasal septum perforation were noted in clinical studies in patients treated with active drug product and vehicle placebo. These findings appeared to be related to the product formulation, and possibly to the povidone excipient. Children appear to be more sensitive to epistaxis and nasal ulceration from the formulation than adults. The Division had a teleconference with the applicant on August 12, 2005 and asked them to submit case report forms for patients in study C-03-51 who had adverse events for epistaxis and nasal ulceration, the informed consent section dealing with nasal adverse events, and a copy of the Clinical Investigator Brochure. The current submission includes these items. The sponsor contends that the incidences of epistaxis in various reports from the literature were similar to, and in most cases higher than, those observed in C-03-51 with olopatadine or vehicle placebo nasal sprays. The applicant also contends that the incidence of nasal ulceration for olopatadine in C-03-51 was similar to the incidence of nasal ulceration in the large scale, multidose studies in patients 12 years of age and older that were submitted in the original NDA. These data do not support the applicant's contentions. It is not appropriate to compare the incidences of these events in C-03-51 with the incidences in the entire development program, which includes a one-year safety study. The appropriate comparison for the incidences of these events is the two-week SAR studies in adults. These data show that children have a higher incidence of epistaxis and nasal ulceration from the product than adults, and appear to be more sensitive to the irritative effects of the product formulation.

OUTSTANDING ISSUES:

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	____ **FILEABLE**	____ **NOT FILEABLE**	
	APPROVAL	**APPROVABLE**	**NOT APPROVABLE**
OTHER ACTION:	**NO ACTION INDICATED**		

1. BACKGROUND

The applicant, Alcon, Inc., submitted an NDA for nasal spray solution formulation of 0.6% olopatadine on December 24, 2004. The proposed indication is (b) (4) treatment of the symptoms of SAR (b) (4) in adults and children 12 years of age and older. The proposed dose was two sprays per nostril twice daily.

The Division took a "Not Approvable" action on October 27, 2005. The NDA had clinical, non-clinical, and CMC deficiencies. Data submitted showed that the product had an unacceptable safety profile. The formulation caused nasal irritation and damage to the nasal mucosa in non-clinical and clinical studies. Epistaxis, nasal ulceration, and nasal septum perforation were noted in clinical studies in patients treated with active drug product and vehicle placebo. These findings appeared to be related to the product formulation, and possibly to the povidone excipient.

Children appear to be more sensitive to epistaxis and nasal ulceration from the formulation than adults. The applicant completed study C-03-51 after submission of the NDA, and submitted a study summary with the 120-day safety update [NDA 21-861, N-000 SU, Volume 1, Section 1, pages 9-10]. The study was a multicenter, double blind, parallel group, PK, efficacy, and safety study of olopatadine nasal spray in pediatric patients 6 to 11 years of age. There were 271 patients enrolled. There was a 4- to 14-day run-in period in which patients received vehicle placebo 2 sprays each nostril twice daily. Patients were then randomized to two weeks of treatment with one or two sprays twice daily of olopatadine 0.6%, one spray twice daily of olopatadine 0.4%, or one or two sprays twice daily of vehicle placebo. In C-03-51, the frequency of epistaxis among the treatment groups ranged from 3.9% to 13.7%. The overall frequency was 8.9%. The frequency of epistaxis was higher than in the two pivotal SAR efficacy and safety studies in adults, C-02-37 and C-02-10, where the frequency of epistaxis in active treatment groups ranged from 1.9% to 3.8% and the overall frequency was 2.6%. The frequency of nasal ulceration in this two-week study ranged from 1.9% to 14.3% among the active treatment groups and was 3.7% overall. The frequency of nasal ulceration in the two pivotal SAR efficacy and safety studies in adults was quite low; there were only two cases of nasal ulceration with an overall frequency of 0.1%. Adverse events for epistaxis and nasal ulceration from this two-week study are summarized and compared in Table 1 with the two pivotal two-week SAR efficacy and safety studies in adults.

Table 1. Adverse events for epistaxis and nasal ulceration, pediatric study C-03-51 and adult SAR studies C-02-37 and C-02-10 [NDA 21-861, N-000 SU, Volume 1, Section 1, pages 9-10; NDA 21-861, N-000, 12/24/05, Module 5, Volume 49, pages 731-732; NDA 21-861, N-000, 12/24/05, Module 5, Volume 57, pages 637-638]

C-03-51														
Adverse event	**Olopatadine 0.6% 2 spr BID N = 52**		**Olopatadine 0.6% 1 spr BID N = 51**		**Olopatadine 0.4% 1 spr BID N = 52**		**Veh pbo 2 spr BID N = 51**		**Veh pbo 1 spr BID N = 51**		**Veh pbo Run-in BID N = 14**		**Total N = 271**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Epistaxis	5	(9.6)	7	(13.7)	5	(9.6)	2	(3.9)	5	(9.8)	0	(0)	24	(8.9)
Nasal ulceration	2	(3.8)	2	(3.9)	1	(1.9)	0	(0)	4	(7.8)	1	(7.1)	10	(3.7)
C-02-37 and C-02-10 combined														
Adverse event	**Olopatadine 0.6% 2 spr BID N = 407**		**Olopatadine 0.6% 1 spr BID N = 0**		**Olopatadine 0.4% 2 spr BID N = 418**		**Veh pbo 2 spr BID N = 417**		**Veh pbo 1 spr BID N = 0**		**Veh pbo Screen BID N = 513**		**Total N = 1755**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Epistaxis	14	(3.4)	--		16	(3.8)	8	(1.9)	--		8	(1.6)	46	(2.6)
Nasal ulceration	0	(0)	--		0	(0)	1	(0.2)	--		1	(0.2)	2	(0.1)

The Division had a teleconference with the applicant on August 12, 2005 to discuss these adverse events in C-03-51 and to place the pediatric study on clinical hold. However, all patients had completed dosing and no additional pediatric studies were ongoing, therefore a clinical hold action was not taken. The applicant stated that they would not be initiating new clinical studies in the pediatric population in the immediate future. The applicant was asked to submit case report forms for patients in C-03-51 who had adverse events for epistaxis and nasal ulceration, the informed consent section dealing with nasal adverse events, and a copy of the Clinical Investigator Brochure. The current submission includes these items. They are reviewed below.

2. ADVERSE EVENTS FOR EPISTAXIS

The applicant notes that there were 24 patients with adverse events for epistaxis in C-03-51. The incidence of epistaxis ranged from 0% to 14% in the treatment groups. The applicant notes that the incidence of epistaxis in patients with allergic rhinitis and in allergic rhinitis patients treated with nasal sprays is as high as 27.5% and similar to, and in most cases higher than, those observed with either active test article or vehicle placebo nasal spray. The sponsor noted that poor delivery technique may have caused physical trauma that resulted in epistaxis [Volume 1, Epistaxis and Nasal Irritation Comparison to Literature Review, pages 1-4].

Reviewer comment:
Regardless of whether the epistaxis noted in this study is related to dosing technique and regardless of the incidence of epistaxis with other products, the incidence of epistaxis in

children in this two-week study was higher than those noted in adults treated with the same product in two-week studies (see Table 1). Children have a higher incidence of epistaxis from the product than adults, and appear to be more sensitive to the irritative effects of the product formulation.

3. ADVERSE EVENTS FOR NASAL ULCERATION

The applicant notes that there were 10 patients in C-03-51 who had adverse events for nasal ulceration. The sponsor states that three of the adverse events were due to trauma, and that only seven of the events could have a potential association with study treatment, with an incidence of 2.6%. All of the events were considered to be mild in severity. None resulted in discontinuation of the study post-randomization. Eight of the events resolved without treatment; two were continuing. The applicant stated that the incidence of nasal ulceration for the olopatadine 0.4% and 0.6% treatment groups (1.9% to 3.9%) was similar to the incidence of nasal ulceration in the large scale, multidose studies in patients 12 years of age and older that were submitted in the original NDA [Volume 1, Review of Nasal Ulceration, pages 1-9].

Reviewer comment:
The incidence of nasal ulceration in children in this two-week study was higher than those noted in adults treated with the same product in two-week studies (see Table 1). The applicant's comparison of the incidence of nasal ulceration in C-03-51 with the incidences noted in the large scale, multidose studies is not appropriate because most of the cases of nasal ulceration in the large scale, multidose studies were in long-term safety study C-01-92. The appropriate comparison is with the two-week SAR studies in adults (see Table 1). Children have a higher incidence of nasal ulceration from the product than adults, and appear to be more sensitive to the irritative effects of the product formulation.

4. INFORMED CONSENT AND CLINICAL INVESTIGATOR BROCHURE

The informed consent for this study notes that nasal discomfort, nose bleeds, and nasal symptoms are possible side effects and risks of study medication [Volume 5, Informed Consent approved 11/5/04, page 3].

Reviewer comment:
Interestingly, an earlier version of the informed consent states that "no significant local or systemic toxicity was seen following the administration of olopatadine as a nasal spray" [Volume 5, Informed Consent version 9/17/04, page 6]. This statement is not found in the more recent version of the informed consent.

The Clinical Investigator Brochure states that olopatadine was well tolerated in both six-month rat and nine-month dog intranasal toxicity studies and that no in-life or histological signs of test-article related toxicity were observed during either of these chronic studies [Volume 5, Clinical Investigator Brochure, page 14]. The brochure lists epistaxis, nasal discomfort, nasal irritation, nasal ulcer as occurring in clinical studies with olopatadine nasal spray [Volume 5, Clinical Investigator Brochure, pages 36-39].

Reviewer comment:
The sections of the informed consent, which has been approved by the applicant's IRB, and the Investigator Brochure dealing with the epistaxis and nasal ulceration in clinical studies are acceptable.

Reviewed by:

_____
Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

_____
Lydia Gilbert-McClain, M.D.
Medical Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original NDA
IND 60,116, N-063, IM, PN, 3/11/05
HFD-570/Division File
HFD-570/McClain/Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-570/Zeccola/CSO

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

/s/

Charles Lee
11/2/2005 01:39:59 PM
MEDICAL OFFICER

Lydia McClain
11/3/2005 09:21:53 AM
MEDICAL OFFICER
I concur

Medical Team Leader Review

NDA 21-861
Drug Product: Patanase® (olopatadine HCl) nasal spray, 665 mcg
Applicant: Alcon, Inc
Review Date: September 22, 2005
Review by: Lydia I. Gilbert-McClain, MD, FCCP, Medical Team Leader

Background/Administrative

A new drug application for olopatadine hydrochloride 665 mcg nasal spray (Patanase®) was submitted to the Agency on December 24, 2004 and the CDER stamp date on the application is December 27, 2004. The PDUFA date for this application is October 27, 2005. The application was submitted under 505(b)(1) of the Food Drug and Cosmetic Act. The proposed indication is for the (b) (4) treatment of the symptoms of seasonal (b) (4) allergic rhinitis. (b) (4) in adults and children 12 years of age and older.

The Applicant has an ophthalmic formulation of olopatadine hydrochloride 0.1% and 0.2% (Patanol®) approved and marketed in the U.S. The Applicant's initial plan was to conduct a limited toxicology program and to bridge intranasal toxicology data to the existing systemic toxicology studies conducted for the ophthalmic formulation. However, during development the Applicant changed the formulation to add (b) (4) (b) (4) to the formulation. Because (b) (4) is not contained in any intranasal or oral inhalation product the Applicant needed to conduct more extensive pharm/tox studies than they originally intended (*see Pharm/Tox section*). The drug development program for olopatadine nasal spray was carried out under IND 60,116 which was first opened on March 31, 2000. An EOP2 meeting was held on October 11, 2001 and a preNDA meeting was held on September 30, 2003. At the EOP2 meeting, the Applicant was advised to establish the cardiac safety of the product and the Applicant was advised that one pivotal SAR (b) (4) study along with the phase 2 studies already completed could support (b) (4) the proposed indications.

Chemistry, Manufacturing and Controls and Establishment Evaluation

Olopatadine hydrochloride is an antihistamine with selective and specific H1 antagonist activity. Olopatadine hydrochloride has a molecular weight of 373.88 and the molecular formula $C_{21}H_{23}NO_3.HCl$. Initially, the Applicant was developing a (b) (4) spray but later changed the formulation to develop a 0.4% and 0.6% solution but the Applicant only intends to market the 0.6% formulation. This change required the addition of (b) (4) to the formulation and lowering of the target pH to (b) (4) [in contrast to the pH 7.0 for the ophthalmic preparations] to enhance the solubility of the product.

Olopatadine nasal spray (Patanase®) 0.6% is formulated as a metered-spray solution for intranasal administration only. The nasal spray contains 0.6% w/v olopatadine (base) in a non-sterile aqueous solution with a pH of approximately (b) (4). Each spray is designed to deliver 665 mcg of olopatadine hydrochloride in (b) (4) of spray. The formulation

contains benzalkonium chloride (0.01%), dibasic sodium phosphate, edetate disodium, povidone, sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust pH) and purified water. The formulation is packaged in a plastic (HDPE) bottle with a (b) (4) metered-dose spray pump that is fitted with a plastic actuator and overcap.

Several approvable CMC issues were identified during the review cycle. Stability studies revealed that olopatadine is more susceptible to degradation if the product (b) (4) Some of the degradants identified have structural alert moieties (b) (4) and the levels of (b) (4) are higher than what is acceptable from a Pharmacology/toxicology standpoint. The data on spray content uniformity (SCU) is unreliable because of the procedure used for collecting these data. Additionally, tail-off raises the question as to whether the current label claim of 240 actuations is supported. Finally, the design of the actuator is such that is very difficult to replace it onto the pump. The CMC reviewer sent a Discipline Review letter to the Applicant during the review cycle with several of these issues. These issues have not been resolved during this review cycle and the CMC review has recommended an approvable action on the application.

Clinical Development Program

A total of 18 studies were completed as part of the drug development program for olopatadine nasal spray. Of these, 6 studies (1 dose response study, 1 PK, 2 efficacy and safety studies, and 2 EEU studies) were conducted using the initial formulation. Three (3) PK studies were conducted with olopatadine oral solution - one phase 1 mass balance study and 2 cardiac safety and PK studies. A total of 9 studies were completed with the to-be-marketed povidone-containing formulation. Of these studies, 3 were PK and dose-ranging studies, 3 were the pivotal efficacy and safety studies comprised of 2 two-week efficacy and safety studies and 1 long-term (1 year) safety study, and 3 were environmental exposure unit studies (EEU) designed to assess dose response and onset of action.

Approximately 4,071 patients participated in the olopatadine nasal spray development program. Of these ~ 1,177 patients were exposed to treatment with olopatadine nasal spray 0.6%. Duration of exposure to olopatadine nasal spray 0.6% was for one day in ~ 314 patients in EEU and single-dose PK studies, for 2 weeks in ~ 404 patients in the pivotal efficacy studies and for 1 year in ~ 459 patients in the long-term safety study. The remainder of the patients were exposed to treatment with olopatadine 0.4%, the initial formulation of olopatadine nasal spray, olopatadine oral solution, or placebo.

There were 3 EEU studies with the proposed formulation (C-01-83, C-03-52, and C-03-48). These studies were single center randomized placebo and active (C-03-48 and C-03-52) controlled single- dose studies. Mometasone (Nasonex®) and fluticasone propionate (Flonase®) were used as active controls in the active controlled studies C-03-52 and C-03-48 respectively. The primary endpoint in these studies was the change from baseline in the instantaneous total nasal symptom score (TNSS). Studies C-01-83 and C-03-52 confirmed an onset of action for olopatadine 0.6% nasal spray of 90 minutes. Although

in study C-03-52, the onset of action was at 30 minutes, the timepoint of 90 minutes is supported since this is the earliest time point of the other study and results need to be replicated to support an onset of action claim. (b) (4)

Efficacy

The pivotal efficacy studies were conducted with olopatadine nasal spray 0.6% and 0.4%. These were randomized double-blind placebo-controlled studies conducted in patients 12 years of age and older with seasonal allergic rhinitis. A total of 1,242 patients were enrolled in these studies. Study C-02-37 was conducted during the late summer and fall season (Late August – November) , and study C-02-10 was conducted during early December – March in patients with mountain cedar pollen allergy. The studies were designed with a single-blind run-in period of 3 -21 days during which the patients received placebo nasal spray and recorded their nasal symptoms in diary cards. The single-blind period was followed by a 2-week double-blind randomized treatment period where patients were treated with olopatadine nasal spray 0.6%, olopatadine nasal spray 0.4%, or placebo 2 sprays per nostril twice daily. Patients recorded the severity of their SAR symptoms twice daily on diary cards prior to taking study medication. Compliance to study medication was assessed by direct patient query, weighing of medication bottles, and by review of patient diary cards. The primary efficacy variable was based on the TNSS calculated based on the sum of scores for runny nose, itchy nose, stuffy nose, and sneezing. Eye symptoms were not part of the TNSS. The primary efficacy endpoint was the percent change from baseline in the reflective AM and PM TNSS averaged over the 2-week treatment period. Several secondary endpoints were evaluated including instantaneous TNSS, daily reflective and instantaneous TNSS, " (b) (4) health resource utilization, and treatment differences between groups out to 180 minutes post dose to evaluate an onset of action.

Results

Study C-02-37

A total of 192 patients were randomized to placebo, 189 to olopatadine 0.4% and 184 patients to olopatadine 0.6%. The majority of patients (96.7%) completed the study and the number of discontinuations was equal (n = 8) in each of the treatment groups. Females represented a higher percentage (62%) of patients and the predominate race in the patient population was Caucasian. Compliance was ~ 77% across treatment groups – not the best but acceptable enough for assessment of efficacy and short-term safety. Both olopatadine 0.6% and olopatadine 0.4% had a statistically significant improvement in the reflective TNSS over the 2-week treatment period compared to placebo. Numerically, olopatadine 0.6% had a more robust effect than olopatadine 0.4%. (*see table below*) The secondary efficacy endpoints included the individual nasal symptoms which favored olopatadine over placebo with nasal congestion showing the lest numerical improvement. (b) (4) .

Study C-02-10

A total of 677 patients were randomized;225 in the placebo group, 229 in the olopatadine 0.4% group and 223 in the olopatadine 0.6% treatment group. A similar percentage of patients as in study C-02-37 (~97%) completed the study. The population demographics was similar to that of the study C-02-37 with two-thirds of the patients being female and the majority of the patient population being Caucasian. The primary efficacy results seen in study C-02-37 were replicated in this study (see results table below) and the secondary endpoints (individual nasal symptoms, instantaneous scores, daily reflective and instantaneous scores) favored olopatadine over placebo.

	Study C-02-37		
	Placebo (n = 191)	**Olopatadine 0.4% (n =188)**	**Olopatadine 0.6% (n = 183)**
Baseline TNSS (SD)	8.8 (1.8)	8.9 (1.7)	8.7 (1.8)
Treatment period (SD)	6.3 (2.5)	5.7 (2.6)	5.3 (2.6)
Mean change from baseline (SD)	-2.4 (2.5)	-3.2 (2.5)	-3.4 (2.5)
Mean % change from baseline (SD)	-27 (27.8)	-35.8 (28.1)	-39.2 (26.9)
Olopatadine - placebo	--	- 0.8 (8.8) $p \leq 0.0037$	(12.2) $p \leq 0.0002$
	C-02-10		
	Placebo (n=223)	**Olopatadine 0.4% (n =228)**	**Olopatadine 0.6% (n=220)**
Baseline TNSS (SD)	9.1 (1.8)	9.3 (1.8)	9.2 (1.8)
Treatment period (SD)	7.3 (2.3)	6.7 (2.4)	6.4 (2.7)
Mean change from baseline (SD)	-1.7 (2.0)	-2.6 (2.1)	-2.8 (2.5)
Mean % change from baseline (SD)	-18.7 (22.3)	-27.6 (22.4)	-30.1 (27.6)
Olopatadine – placebo Mean change (% change)	-	-0.9 (8.9%) $p = 0.0002$	-1.1 (11.4%) $p < 0.0001$

In subset analyses, olopatadine appeared to be less efficacious in patients 12- 17 year-old age however, the total number of subjects in this age group is small (61/1240 [~ 5%]) and there is no scientific reason to expect that olopatadine will not work in this age group. The discrepant results may be the effect of poor compliance in this subgroup given that the compliance in the overall patient population was not great to begin with. The finding of efficacy in the overall population should provide assurance of efficacy in the 12- 17 year old age group.

Study C-01-92

This was a one-year safety study designed primarily to assess the long term safety of olopatadine 0.6% nasal spray in patients with perennial allergic rhinitis (PAR). (b) (4)

Safety

Safety data were obtained from the 2-week and the one-year long term safety study in adults by collecting adverse events (volunteered or solicited), vital signs, physical

examinations, nasal examinations, and laboratory studies. Safety information was also obtained from a 2-week study in pediatric patients (C-03-51) submitted in the 120-safety update to the NDA. In preclinical studies the excipient povidone caused nasal toxicity in the 6-month rat studies. Therefore, nasal adverse events noted in both the active treatment groups and in the placebo groups were carefully reviewed. Nasal events occurring in both the placebo and treatment groups provided clinical support for the concern of nasal toxicity from povidone in the formulation.

There were no safety signals in the vital signs or laboratory studies. The most common adverse event noted in the development program was taste perversion and was drug-related and dose-related. A total of 53/407 (13%) patients in the olopatadine 0.6% treatment group reported taste perversion compared to 31/418 (8%) patients in the olopatadine 0.4% treatment group and 2/417 (< 0.5%) patients in the placebo group in the 2-week efficacy and safety studies. In the one-year safety study (C-01-92), taste perversion was reported in 44/459 (9.6%) patients in the olopatadine 0.6% treatment group compared to 4/465 (<1%) patients on placebo.

Although in the adult 2-week efficacy/safety studies the nasal adverse events did not raise undue safety concerns, the findings in the one-year safety study, as well as the findings in the 2-week pediatric study provide strong support for the conclusion that the excipient povidone in the formulation is a serious safety concern. The most common nasal AE in the 2-week adult studies was epistaxis occurring in 3.4% (14/407), 3.8% (16/418), and 2% (8/417) of the patients in the olopatadine 0.6%, olopatadine 0.4%, and placebo groups respectively. Nasal irritation was reported in only 4 patients (~1%) in the olopatadine 0.6% treatment group, 1 patient in the olopatadine 0.4% treatment group, and 3 patients (~1%) in the placebo group. There was one report of a nasal ulcer in a patient in the placebo group. In a 2-week study in pediatric patients 6 to 11 years of age (study C-03-51) randomized to olopatadine 0.6%, olopatadine 0.4%, or placebo, epistaxis was reported in 9% (24/271) of the patients and 10 patients (4%) reported nasal ulceration. These findings were reported in both the placebo and the active treatment groups raising the safety concern about the formulation.

In the one-year safety study (C-01-92) epistaxis was the most common adverse event reported with an incidence of 19% (88/367) of patients in the olopatadine 0.6% treatment group and 12% (56/465) in the placebo group. Cold syndrome was the second most common adverse event (16% in olopatadine and placebo treatment groups) followed by taste perversion (9.6% olopatadine vs < 1% placebo). Other nasal AEs of concern reported in the long-term study were nasal ulcer and nasal septum perforation. Nasal ulcer was reported in 19 patients (4.1%) in the olopatadine treatment group and in 21 patients (4.5%) in the placebo group. There were 3 cases of nasal septum perforation – 1 in the olopatadine group and 2 in placebo. These findings are concerning and support the conclusion that the formulation is toxic to the nasal mucosa. While epistaxis has been described in other development programs for allergic rhinitis with nasal sprays, the additional finding of nasal ulcers and septal perforation in the one year study as well as the finding of nasal ulceration in the 2-week study in patients 6 to 11 years of age has not

been seen in other nasal spray for this indication and provide strong evidence against approving this drug product.

Cardiac Safety

In preclinical studies the effect of olopatadine on cloned hERG channels was evaluated. Olopatadine blocks hERG channels with an IC_{50} of 1.1mM. Two clinical studies (C-00-23 and C-02-54) evaluating the effect on QT of olopatadine were conducted and submitted with the NDA. Study C-00-23 evaluated the cardiovascular effect of 5 mg olopatadine oral solution twice daily in healthy volunteers for 2 days, whereas study C-02-54 studied 20 mg olopatadine oral solution administered twice daily for 14 days and was a more thorough QT study in terms of design and analyses than study C-00-23. Therefore, study C-02-54 provided the most useful information about olopatadine and cardiac safety. Study C-02-54 was conducted with 32 healthy male and female volunteers aged 18 to 75 years. The study was designed as a double-blind, randomized two-way crossover study with a washout period of 6 days between treatment groups. The 20 mg dose was chosen so that levels 8 to 10 fold higher than what would be achieved with the proposed dose of the nasal spray could be studied. Multiple-dose PK studies with olopatadine nasal spray 0.6% revealed an AUC_{0-12} of 78 ± 13.9 (range 54.4 -103) ng*h/mL and the AUC_{0-12} with olopatadine 20 mg oral solution was 997 ±152 (range 689 -1280) ng*h/ml. Serial ECGs were performed over a 24-hour period at baseline, on Day 12, and after the last dose on Day 14 for each treatment period. ECGs were manually read at a central reading center and ECG readers were blinded to study treatments. Both Bazett's and Fridericia's correction formulae were used to analyze the QT interval. There was no effect of olopatadine on QT. Additionally, there was no linear correlation between QTc change from baseline and olopatadine systemic exposure (*See Biopharm Primary review*).

Clinical pharmacology and Biopharmaceutics

The Applicant conducted 7 biopharm studies and these are reviewed in depth in Dr. Sandra Suarez-Sharp's review. The clinical pharmacology studies included dose ranging studies, PK and bioavailability studies, one mass balance study and 2 cardiac safety studies. Three minor active metabolites (M1 [N-desmethyl olopatadine], M2, and M3[olopatadine-N-oxide] have been identified however, metabolism of olopatadine is only a minor route of elimination with urinary excretion being the major pathway (70%) of elimination and excretion via the feces accounting for ~ 17%. Olopatadine did not affect the activity of the major cytochrome P450 enzyme family. The single dose and multiple-dose PK studies demonstrated that the AUC_{0-12} was 78 ± 13.9 (range 54.4 -103) in multiple dose studies with a $t_{1/2}$ of 10.4 ± 5.1 hours (range = 4.0 -21.8).

Preclinical pharmacology/toxicology

The initial IND study for this development program was conducted with a formulation that did not contain povidone. The initial formulation was a topical aqueous nasal solution with benzalkonium chloride (0.01%), dibasic sodium phosphate, sodium chloride, and hydrochloric acid/sodium hydroxide (to adjust pH). There were no preclinical data to support the initial clinical study, however the IND was allowed to proceed because of prior clinical experience with olopatadine hydrochloride ophthalmic

solution (0.1%) an approved product under the trade name Patanol® for the treatment of the symptoms of allergic conjunctivitis. Subsequent review of preclinical studies (13-week and 8 week interim sacrifice from a 6-month toxicity study) in rats dosed intranasally supported a NOAEL of 0.2 mg/day intranasally for 8 weeks. Initially, the Applicant intended to bridge the intranasal toxicology data to the existing systemic toxicology studies conducted for the ophthalmic formulation. Therefore, with this in mind, the Division indicated that the Applicant did not need to conduct chronic toxicology studies in two species for the intranasal program. However, the Applicant later changed the formulation to increase the concentration of the active ingredient, add (b) (4), decrease the concentration of (b) (4), and reduce the pH of the formulation to (b) (4) Although (b) (4) had been used in oral formulations it is not contained in any approved inhalation or intranasal formulation therefore, the pharmacology/toxicology team noted that the Applicant would need to test povidone via the intranasal route (*Pharm/tox review Dr. Jui Shah December 2002).* The Applicant had already conducted a 14-day intranasal toxicity study in rats with the new formulation of olopatadine containing povidone and had submitted a summary to the Division in April 2002. The Applicant was asked to submit all data including histopathology for the 14-day rat study (*FAX Jan 16, 2003*) to support the completed 2-week pivotal study C-02-37 and the ongoing 2-week SAR mountain cedar study C-02-10. In that FAX, the Applicant was also informed that prior to using the povidone-containing formulation in longer term clinical trials they must conduct a 6-month bridging study in the most appropriate species using the new formulation. The Division also stated that the selection of species for the 6-month study should be based on two 2-week studies in two species of which at least one should be a non-rodent. The Applicant conducted a 6-month rat and 9-month dog intranasal study with olopatadine, however, the Applicant did not submit histopathology data for these studies prior to the submission of the NDA. From the brief summaries submitted it appeared at the time that the studies supported use of olopatadine nasal spray 0.6% for 14 days (*Pharm/Tox Review Dr. Jui Shah June 2003*).

Full histopathology data for the 6- and 9-month toxicology studies as well as the 6-month bridging study were submitted with the NDA. The formulation containing the excipient povidone was only tested for the first 2 months of the 6-month rat study. In the 6-month intranasal bridging study in rats for the excipient povidone, olfactory epithelial degeneration and respiratory turbinate epithelial vacuolation were observed at high incidence with some marked severity in povidone-treated groups in a dose-dependent manner at both doses tested (2.7 and 6.8 mg/day). As a result, there is no NOAEL for the povidone in the formulation. (*Pharm/tox Review Dr. Gary Bond*). The concern that the chronic use of this povidone-containing formulation of olopatadine is toxic to the nasal mucosa was conveyed to the Applicant during this review cycle via a teleconference (*T-con minutes May 25, 05*).

The *in vitro* gentoxicity test was positive and the SHE-cell assay was equivocal for the degradants (b) (4) and (b) (4) and as such these degradants are considered to be genotoxic. During the review cycle, the Applicant was informed that their concentrations must be controlled at specifications of no more than (b) (4) of the active drug substance.

Data Quality, Integrity, and Financial Disclosure
Three sites were selected for routine DSI audit for a general survey of the trial conduct at these sites. Three investigators – 2 from study C-02-37 and 1 from study C-02-10 were selected for routine DSI audit. These sites were chosen because they enrolled the largest number of patients in these studies. The result of the DSI audit of these sites was favorable and there were no irregularities observed. During the review cycle, the primary reviewer was concerned about irregularities in some Case Report Forms regarding the documentation of nasal septum perforations and DSI was contacted to conduct a for-cause inspection at 2 study centers. That inspection is still ongoing at the time of this review.

Pediatric Considerations
The Applicant included children 12 years of age and older in the adult development program and submitted protocols to the IND for studies in children 4 to 11 years of age and children 2 to 5 years of age during the NDA review cycle. During the NDA review cycle, the Applicant also completed one 2-week PK safety and tolerability study in patients 4 to 11 years of age (C-03-51). The safety results from this study was submitted in the 120-day safety update to the NDA and reported a high incidence of epistaxis (9%) and nasal ulcers (4%) in this patient population. In view of the nasal findings and the safety concerns with the formulation, during the review cycle the Applicant was advised that no additional studies should be conducted in pediatric patients under 12 years of age until their were data to support the long-term safety of the product in patients over 12 years of age.

Product Name
A trade name consult was sent to the Office of Drug Safety Division of Medication Errors and technical support (DMETS) on March 23, 05 and is pending at this time.

Labeling
Labeling has been deferred because the recommended action on this application is "Not Approvable"

Conclusions
The Applicant has adequately established the efficacy of olopatadine nasal spray 0.6% for the treatment of the symptoms of SAR (b) (4) Additionally, the nasal adverse events in the one-year safety study along with the pre-clinical findings support the conclusion that the povidone-containing olopatadine formulation is toxic to the nasal mucosa with chronic administration. These findings represent a significant safety signal for this product given that similar findings have not been reported in development programs for other nasal spray products for similar indications. For example, there were no reports of nasal septal perforations in the clinical development programs with Astelin, Atrovent, Flonase, or Nasonex. Nasal ulcers were reported with the clinical development program for Atrovent nasal spray 0.03% but the AE reports were included with "nasal irritation" and no percentages were given for nasal ulcers. The Nasonex label reports "rare cases" of nasal ulcers and the labels for the other nasal spray products do not report any cases of nasal

ulcers. Considering the prior experience with other nasal sprays, the AEs seen with the olopatadine development program are unusually high and given the disease being treated, constitutes an unacceptable risk/benefit ratio. This application should be given a "Not Approvable" action because there are substantial development issues with this program that would require changes to the formulation, and the conduct of efficacy and safety studies. In the first place, the Applicant will need to reformulate the drug product in order to reduce the risk of nasal pathology in humans and will have to provide data to support the efficacy and long-term safety of the reformulated product. (b) (4) [redacted] The primary medical officer has recommended a "Not Approvable" action and I concur with his recommendation.

Recommended Regulatory Action

I recommend that this application be given a "Not Approvable" action. I concur with the comments to the Applicant in the primary medical officer review.

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

/s/

Lydia McClain
10/7/2005 11:17:05 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-861
Submission Code	N-000
Letter Date	12/24/04
Stamp Date	12/27/04
PDUFA Goal Date	10/27/05
Reviewer Name	Charles E. Lee, M.D.
Review Completion Date	8/24/05
Established Name	Olopatadine HCl
(Proposed) Trade Name	Patanase® (olopatadine HCl) Nasal Spray, 665 mcg
Therapeutic Class	H_1-receptor antagonist, antihistamine
Applicant	Alcon, Inc.
Priority Designation	S
Formulation	Nasal spray solution
Dosing Regimen	2 sprays per nostril twice daily
Indication	(b) (4) treatment of the symptoms of seasonal (b) (4) allergic rhinitis, (b) (4)
Intended Population	Adults and children 12 years of age and older

Submissions reviewed in this document:

NDA 21-861, N-000, 12/24/04
NDA 21-861, N-000 BZ, 4/11/05
NDA 21-861, N-000 BB, 4/11/05
NDA 21-861, N-000 BZ, 5/2/05
NDA 21-861, N-000 BM, 6/27/05
NDA 21-861, N-000 SU, 7/7/05
NDA 21-861, N-000 BM, 7/11/05
NDA 21-861, N-000 BZ, 7/14/05
NDA 21-861, N-000 BM, 7/14/05
NDA 21-861, N-000 BM, 7/18/05
NDA 21-861, N-000 BP, 7/22/05

Referenced IND:
IND 60,116, N-000, 3/31/00

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends a "Not Approvable" action.

The applicant's data support the efficacy of olopatadine 0.6% nasal spray for the treatment of symptoms of seasonal allergic rhinitis (SAR), (b) (4) The applicant's data do not support the safety of olopatadine 0.6% nasal spray.

The applicant must develop a formulation that is not toxic to the nasal mucosa, demonstrate its clinical safety, and provide evidence to support its efficacy before the product may be considered for approval.

Given the safety signal for nasal ulceration and nasal septum perforation, pediatric studies in children 2 to 11 years of age should be deferred until the applicant has developed a formulation that is not toxic to the nasal mucosa and confirmed its clinical safety in older patients.

1.2 Recommendation on Postmarketing Actions

No postmarketing actions are indicated because the product is not recommended for approval.

1.2.1 Risk Management Activity

No risk management activity is indicated because the product is not recommended for approval.

1.2.2 Required Phase 4 Commitments

There are no required phase 4 commitments because the product is not recommended for approval.

1.2.3 Other Phase 4 Requests

There are no other phase 4 requests because the product is not recommended for approval.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This NDA is for olopatadine 0.6% nasal spray. The product is a selective H_1-histamine receptor antagonist and a structural analog of doxepin.

The proposed indication is the (b) (4) treatment of the symptoms of SAR (b) (4) in adults and children 12 years of age and older. The proposed dose is two sprays per nostril twice daily, or a total dose of 2.4 mg of olopatadine base twice daily.

There were three pivotal efficacy and safety studies in this application.

1. C-02-37, a randomized, double blind, active and placebo controlled, parallel group, pivotal phase 3, natural exposure, efficacy and safety study of olopatadine 0.4% and 0.6% nasal spray administered twice daily in patients with SAR

2. C-02-10, a randomized, double blind, active and placebo controlled, parallel group, pivotal phase 3, natural exposure, efficacy and safety study of olopatadine 0.4% and 0.6% nasal spray administered twice daily in patients with SAR

3. C-01-92, a randomized, double blind, active and placebo controlled, parallel group, pivotal phase 3, natural exposure, long-term (b) (4) safety study of olopatadine 0.6% nasal spray administered twice daily in patients with PAR

There were two pivotal clinical studies to provide dose-ranging and/or onset of action information:

1. C-01-83, a randomized, double blind, placebo controlled, parallel group, phase 2, single dose, dose response and onset of action environmental exposure unit (EEU) study of olopatadine 0.2%, 0.4%, and 0.6% nasal spray in patients with SAR [Module 2, Volume 20, C-01-83 Synopsis, page 1]

2. C-03-52, a randomized, double blind, active and placebo controlled, parallel group, phase 2, single dose, onset of action EEU study of olopatadine 0.6% nasal spray and mometasone furoate nasal spray 50 mcg (MFNS) in patients with SAR [Module 2, Volume 20, C-03-52 Synopsis, page 1]

In addition, there were six supportive clinical studies, which included pilot EEU studies, phase 2 and phase 2/3 dose response studies, and a nasal challenge study.

There were seven pharmacokinetic (PK) and pharmacodynamic (PD) studies in this application, including three single dose PK studies, one multiple dose PK study, one mass balance study, and two high dose cardiac safety PK/PD studies.

Safety information in this application consisted of integrated safety information from clinical studies in the applicant's drug development program. This safety information included adverse events, laboratory studies, physical examinations, nasal examinations, and ECGs. The applicant also provided a review of worldwide postmarketing adverse event reports for olopatadine HCl ophthalmic solution 0.1%, a review of postmarketing adverse event reports from Japan for

olopatadine HCl 2.5 mg and 5 mg tablets, and a review of the published medical literature for safety information relevant to use of olopatadine.

1.3.2 Efficacy

The applicant's data support the efficacy of olopatadine 0.6% nasal spray and olopatadine 0.4% nasal spray for the treatment of symptoms of SAR. (b) (4) The applicant is only seeking approval of olopatadine 0.6%.

There was a statistically significant difference from vehicle placebo in the percent change and mean change from baseline in reflective total nasal symptoms score (TNSS) compared to vehicle placebo for olopatadine 0.6% in the pivotal SAR efficacy and safety studies. The differences from vehicle placebo in both these endpoints were less for olopatadine 0.4%, but were also statistically significant. These data provide convincing evidence of efficacy for the SAR indication, in replicate, for olopatadine 0.6%, the applicant's proposed concentration, and for olopatadine 0.4%. There is an efficacy advantage for olopatadine 0.6% over olopatadine 0.4%. The efficacy advantage provides support for the applicant's choice to seek approval of olopatadine 0.6% and not olopatadine 0.4%.

The applicant's data support end of dosing interval efficacy for olopatadine 0.6% and olopatadine 0.4%. The difference from vehicle placebo in the percent change from baseline in instantaneous TNSS was similar for olopatadine 0.6% and olopatadine 0.4% in the pivotal SAR efficacy and safety studies.

Improvements in individual symptom scores were noted for runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes for olopatadine 0.6% and olopatadine 0.4%. Improvements in these individual symptoms were less for olopatadine 0.4%. Of all the individual symptoms, stuffy nose showed the least improvement in both treatment groups. Evidence of dose response effect in each of the studies was noted for all symptoms except stuffy nose. The data suggest that olopatadine 0.6% has an efficacy advantage over olopatadine 0.4% in degree of effect and the number and types of individual symptoms for which there is evidence of efficacy. The dose response effect noted for each of the symptoms provides support for the applicant's choice to seek approval of the olopatadine 0.6% over olopatadine 0.4%.

(b) (4)

The results of the applicant's EEU studies support an onset of action claim. The data demonstrate, in replicate, an onset of action at 90 minutes post-dose for olopatadine 0.6%. A statistically significant difference from vehicle placebo in TNSS was noted at 90 minutes post-dose for olopatadine 0.6% in study C-01-83 and at 30 minutes in study C-03-52, and these

differences were maintained at each of the remaining time points in the studies. The difference from vehicle placebo in TNSS for olopatadine 0.6% at 90 minutes in these studies was similar to the difference from vehicle placebo in TNSS over the treatment period noted in the two pivotal SAR efficacy and safety studies, approximately 1 point. This finding suggests that the effect noted at onset of action is clinically relevant.

The applicant's proposed labeling contains a claim that olopatadine 0.6% is (b) (4)

The applicant's data do not support a labeling or advertising claim (b) (4) The olopatadine product used in the study to support these claims was not the to-be-marketed product and the study was primarily an observational study. The design of this study is not adequate to support these claims. In addition, the clinical relevance of these effects is uncertain and it is unclear how this information would guide or instruct the practitioner to use this medication more knowledgeably.

(b) (4)

1.3.3 Safety

The overall exposure in the olopatadine nasal spray clinical development program meets ICH and FDA guidelines and is sufficient to allow for assessment of safety. The exposure and the duration of exposure to olopatadine 0.6% nasal spray, the concentration proposed for marketing, are also sufficient to allow for assessment of safety. The demographics of patients in the clinical program and exposure of subpopulations to olopatadine 0.6% nasal spray are adequate to provide an assessment of safety.

There was one death in the drug development program for olopatadine nasal spray. A 41-year old woman who was treated with olopatadine 0.6% in long-term safety study C-01-92 underwent elective gastric bypass surgery to treat obesity. She developed abdominal pain, a perforated gastric ulcer, bacterial peritonitis, and sepsis and died on Study Day (b) (6) This death does not identify a safety signal for olopatadine.

The incidence of non-fatal serious adverse events was similar in the olopatadine 0.6% (0.9%, 11/1163) and vehicle placebo BID (1.1%, 11/1008) groups. Surgical/medical procedure was the only non-fatal serious adverse event that occurred in more than one patient in any group. Serious adverse events did not identify a safety signal for olopatadine.

Epistaxis was the most common nasal adverse event that was reported at a frequency of ≥2% for olopatadine and more frequently than vehicle placebo in the pivotal efficacy and safety studies. Epistaxis was also common in the vehicle placebo group. The most common non-nasal adverse events at a frequency of ≥2% were taste perversion, cold syndrome, cough increased, flu syndrome, arthralgia, and dyspepsia. A dose response effect was noted for taste perversion and dyspepsia.

Both olopatadine 0.6% nasal spray and vehicle placebo appear to be irritating to the nose. Epistaxis, dry nose, and irritation of the throat were noted for olopatadine 0.6% at frequencies of greater than 1% and more commonly than in vehicle placebo. Rhinitis, sinusitis, and pharyngitis were noted at frequencies of 4% or greater in both olopatadine 0.6% and vehicle placebo groups. Epistaxis, dry nose, throat irritation, rhinitis, and pharyngitis, by themselves and at these frequencies, are not a serious safety concern. However more serious nasal adverse events, nasal ulceration and nasal septum perforation, were noted in the olopatadine drug development program.

Nasal ulceration was reported frequently in the olopatadine 0.6% group (1.6%, 19/1163) and the vehicle placebo twice daily group (2.1%, 21/1008) in the overall clinical development program. Nasal septum perforation was noted in one patient treated with olopatadine 0.6% (0.1%, 1/1163) and in two patients treated with vehicle placebo (0.2%, 2/1008) in the overall clinical development program. All of the patients who had nasal septum perforation were enrolled in study C-01-92, the one-year, long term efficacy and safety study. Non-clinical data suggest that the product is toxic to the nasal mucosa and that the toxicity may be related to the povidone excipient in the formulation. Nasal septum perforation has never been seen during the development programs for non-steroid or corticosteroid nasal sprays for allergic rhinitis. As a postmarketing adverse event, it is extremely rare for non-steroid nasal sprays and is uncommonly reported for corticosteroid nasal sprays with allergic rhinitis indications. Nasal ulceration and nasal septum perforation represent a major safety signal for olopatadine 0.6% nasal spray and are sufficient to affect the approvability of the application.

Children appear to be more sensitive to epistaxis and nasal ulceration from the formulation than adults, based on data from a study in children 6 to 11 years of age that was completed after submission of the NDA and summarized in the 120-day safety update.

Events reported at a frequency of 1% to <2% were dry nose and irritation of the throat in both the olopatadine and vehicle placebo groups. Non-nasal adverse events reported at this frequency were otitis media, diarrhea, hyperemia of the eye, dermatitis, toothache, accidental injury, ear pain, myalgia, extremity pain, dizziness, hypertension, and depression. A dose response effect was not noted for these adverse events. The frequencies of these less common adverse events were fairly similar for the olopatadine 0.6% and vehicle placebo groups.

Adverse events related to anticholinergic effects of antihistamines include dry mouth, tachycardia, and urinary retention. These adverse events were infrequently seen in the clinical development program, and occurred at similar frequencies in the active and vehicle placebo treatment groups.

Somnolence was reported in the olopatadine clinical development program by 1.1% (13/1163) of patients treated with olopatadine nasal spray 0.6% and by 0.2% (2/1008) of those treated with vehicle placebo nasal spray twice daily. The incidence of somnolence in patients treated with vehicle placebo twice daily was lower than normally seen in SAR trials of antihistamines in adults. The low incidence of somnolence in the vehicle placebo group in the olopatadine program suggests that the study may have been less sensitive in picking up this adverse event. It is possible that the design of the patient medical problem log may have led people to not record less severe adverse events such as somnolence.

Somnolence was noted in the high dose cardiac safety studies in this application by 13.5% (7/166) of patients treated with olopatadine 5 mg or 20 mg twice daily by mouth. Somnolence was the most common adverse event in the clinical development program for olopatadine 2.5 mg and 5 mg tablets, which are approved in Japan. A cross-study comparison shows that the C_{max} and AUC for olopatadine 0.6% are 16% and 18%, respectively, of those for olopatadine tablets 5 mg orally. There is clearly less systemic exposure to olopatadine 0.6% nasal spray than to the oral product, however, the degree of systemic exposure is sufficient to provide additional support to the conclusion that the incidences of somnolence noted in the clinical development program are not due to chance.

At the dose and concentration proposed for marketing, olopatadine 0.6% nasal spray appears to be associated with somnolence infrequently, but at a rate higher than vehicle placebo. The frequency of somnolence is sufficiently low to be excluded from the table of common adverse events in the ADVERSE REACTIONS section of the olopatadine 0.6% nasal spray label, but is different enough from vehicle placebo that a “non-sedating” claim would be not supported if the product were to be approved.

There were no safety concerns specific to patients 12-17 years of age, 18-64 years of age, or 65 years of age or older noted in the adverse event data from the pivotal efficacy and safety studies for olopatadine 0.6%, although there were relatively few patients in the studies 65 years of age or older. The types and frequencies of common adverse events were similar among these populations. There were no safety concerns specific to patients of female or male gender noted in adverse event data from the pivotal efficacy and safety studies for olopatadine 0.6%. The types and frequencies of common adverse events were similar in both genders. There were no safety concerns specific to patients of Caucasian, Black, Hispanic, Asian, or Other races noted in adverse event data from the pivotal efficacy and safety studies for olopatadine 0.6%. There were relatively few patients in the studies of Asian and Other races. The types and frequencies of common adverse events were similar among patients of these races.

Review of hematology, blood chemistry, and urinalysis data from the studies in the application revealed no safety signal. Vital signs data from six natural exposure SAR and PAR studies in this application and shift table and scatter plot analyses of vital signs data from the three pivotal SAR and PAR (b) (4) safety studies did not reveal safety concerns.

An integrated analysis of ECG data from the supportive SAR studies in this application and an analysis of ECG data from the pivotal, one-year PAR study showed no evidence of a safety signal. There were two high dose cardiac safety studies in this application. Data from these studies suggest that there is no QTc prolongation with doses of olopatadine up to 20 mg twice daily by mouth for 14 days. The applicant's summary of patients with ECG abnormalities in studies C-00-10, C-00-33, and C-01-05 was incomplete.

A review of postmarketing and spontaneous adverse event reports for olopatadine ophthalmic solution 0.1%, (b) (4) did not identify a safety signal relevant to olopatadine nasal spray. Japanese postmarketing adverse event reports for olopatadine 2.5 and 5 mg tablets suggest that olopatadine tablets may be associated with hepatic function abnormalities. The Japanese regulatory agency added hepatic function abnormal, liver disorder, acute hepatitis, and jaundice to the product label for olopatadine 2.5 mg and 5 mg tablets based these postmarketing reports. There was no signal for hepatic function abnormality in the olopatadine nasal spray program. If approved, postmarketing adverse event reports for olopatadine nasal spray should be monitored for cases of hepatic function abnormalities.

In summary, the applicant has not established the safety of olopatadine 0.6% nasal spray. The product appears to be toxic to the nasal mucosa and is associated with nasal ulceration and nasal septum perforation. The preclinical findings suggest that the toxicity is related to the product formulation and not to olopatadine drug substance and the clinical data supports this conclusion because the nasal events were present in patients treated with olopatadine 0.6% nasal spray and vehicle placebo nasal spray. The safety data do not support approval of this application. Although the nasal septum perforations occurred only in the one-year PAR study and not in the two-week SAR studies, an attempt to manage the risk of this adverse event by limiting its use to a short period of treatment would not be an option. The duration of treatment with the product in the general population would be longer than two weeks. Patients with seasonal allergic rhinitis commonly have symptoms that last through more than one season of symptoms, and it is reasonable that many practitioners might use the product for PAR, even if the product was approved only for treatment of symptoms of SAR. The applicant will need to develop a formulation that is not toxic to the nasal mucosa, demonstrate its clinical safety, and provide evidence to support its efficacy before the product may be considered for approval.

Given the safety signal for nasal ulceration and nasal septum perforation, pediatric studies in children 2 to 11 years of age should be deferred until the applicant has developed a formulation that is not toxic to the nasal mucosa and confirmed its clinical safety in older patients.

1.3.4 Dosing Regimen and Administration

The proposed dose of olopatadine 0.6% nasal spray in adults and children 12 years of age and older is two sprays per nostril twice daily (2.66 mg olopatadine HCl twice daily or 2.4 mg olopatadine free base twice daily). The studies in this application support the proposed concentration and dose of the product for the SAR indication. (b) (4)

Phase 2 and 2/3 dose ranging studies failed to demonstrate efficacy for (b) (4) and (b) (4) concentrations of olopatadine. The pivotal SAR efficacy and safety studies showed efficacy for both 0.4% and 0.6% concentrations of olopatadine, but there was an efficacy advantage for the 0.6% concentration. The twice daily dosing interval is supported by the pivotal SAR efficacy and safety studies and the onset of action studies, which showed evidence of efficacy at the end of the dosing interval.

Dose related adverse events for olopatadine nasal spray included taste perversion and dyspepsia. Taste perversion is may affect patient acceptance of the product but would not be expected to create safety concerns. The incidence of dyspepsia was low (2.1% for olopatadine 0.6%) and is not likely to cause major safety concerns. At the dose and concentration proposed for marketing, olopatadine 0.6% nasal spray appears to be associated with somnolence infrequently, but at a rate higher than vehicle placebo. There was no evidence for a dose response effect for somnolence for the nasal spray formulation of olopatadine. Higher oral doses of olopatadine are associated with somnolence. Epistaxis, nasal ulceration, and nasal septum perforation were not dose related. Nasal ulceration and nasal septum perforation were related to the formulation and occurred both in olopatadine 0.6% nasal spray and vehicle placebo.

1.3.5 Drug-Drug Interactions

Data from the in-vitro metabolism of ^{14}C-olopatadine showed that metabolism of olopatadine is a minor route of elimination. In addition, olopatadine did not affect the activity of the major CYP P450 enzymes such as 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. It is unlikely that substrates, inhibitors or inducers of these enzymes may affect the PK of olopatadine and its metabolites. No major effects of olopatadine should be expected on the PK of other drugs.

The applicant also performed an analysis of adverse events occurring in patients taking concomitant medications. The baseline medications included analgesics and antipyretics, antidiabetic agents, antihistamine drugs, anti-infective agents, antilipemic agents, antitussives and expectorants, cardiovascular drugs, CNS agents, eye, ear, nose and throat preparations, gastrointestinal drugs, hormones and synthetic substitutes, NSAIDS, psychotherapeutic agents, serums, toxoids, and vaccines, sympathomimetic agents, and thyroid and antithyroid agents. No safety concerns were identified by this analysis of patients taking concomitant medications.

1.3.6 Special Populations

Decreased efficacy in patients 12-17 years of age was noted in the pivotal SAR efficacy and safety studies, but the number of patients in this age group was small and the finding is probably not relevant given the overall efficacy findings among the other age groups. There were no differences in efficacy among other special populations. There were no differences in the safety profile among patients of 12-17 years of age, 18-64 years, 65 years of age or greater, or among patients of different genders or races. Children 6 to 11 years of age appear to be more sensitive to epistaxis and nasal ulceration from the formulation than adults.

An examination of the frequency of adverse events, laboratory studies, vital signs, physical examinations, nasal examinations, and ECGs in patients with varying severities of renal disease of did not identify a drug-disease interaction. The applicant performed an analysis of adverse events occurring in patients with baseline concomitant diseases. These diseases included arthritis, asthma, diabetes mellitus, gastrointestinal disorders, hyperlipidemia, hypertension, musculoskeletal disorders, nervous system disorders, and thyroid disorders. No safety concerns were identified with this analysis.

Non-clinical data suggest that olopatadine is not teratogenic. The clinical study protocols in the olopatadine nasal spray drug development program excluded the participation of pregnant females. No adequate and controlled clinical studies of olopatadine have been conducted in pregnant women. The applicant's proposed labeling states that the product should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the fetus.

The applicant's proposed labeling states that olopatadine has been identified in the milk of nursing rats and that it is not known if topical nasal administration could result in sufficient systemic absorption to produce detectable quantities in human breast milk. The labeling states that the product should be used by nursing mothers only if the potential benefit to the patient outweighs the potential risk to the infant.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

This NDA is for olopatadine 0.6% nasal spray. The applicant is Alcon, Inc. The product is a selective H_1-histamine receptor antagonist and a structural analog of doxepin [Module 2, Volume 2, Section 2.3P, page 1]. The applicant seeks approval of the product for seasonal allergic rhinitis (SAR) (b) (4)

The product is a nonsterile, multiple dose, nasal spray solution containing 600 mcg/spray (0.6%) of olopatadine base or 665 mcg/spray (0.665%) of olopatadine HCl. It contains the following excipients: benzalkonium chloride, edentate disodium, (b) (4) sodium chloride, dibasic sodium phosphate, sodium hydroxide, hydrochloric acid, and purified water. The product is packaged in a plastic bottle (b) (4) with a metered dose spray pump and fitted with a plastic actuator and overcap [Module 2, Volume 2, Section 2.3.P, pages 2-3].

The proposed indication is the (b) (4) treatment of the symptoms of SAR (b) (4) in adults and children 12 years of age and older [Module 1, Volume 1, Section 3.B, page 8]. The proposed dose is two sprays per nostril twice daily, or a total dose of 2.4 mg of olopatadine base twice daily [Module 1, Volume 1, Sections 3.B and 3.C].

Olopatadine HCl ophthalmic solution, 0.1%, Patanol®, is approved in the United States for the treatment of the signs and symptoms of allergic conjunctivitis. A 0.2% concentration of olopatadine HCl ophthalmic solution is approved for the treatment of ocular itching associated with allergic conjunctivitis. An oral dosage form, olopatadine 2.5 mg and 5 mg tablets, is approved in Japan for the treatment of allergic conditions, including allergic rhinitis, urticaria, and itching resulting from skin diseases [Module 2, Volume 4, Section 2.5, Clinical Overview, page 5].

2.2 Currently Available Treatment for Indications

Antihistamines are the first-line drugs for pharmacologic therapy of allergic rhinitis. Multiple oral antihistamines are available as OTC products, as specified by the OTC monograph for Antihistamine Drug Products [21 CFR 341.72]. Many oral antihistamines are approved as prescription drug products under NDAs and ANDAs for the SAR indication.

Currently marketed prescription oral antihistamines with a PAR indication include Clarinex® (desloratadine), Phenergan (promethazine HCl), and Zyrtec® (cetirizine HCl).

Astelin Nasal Spray is the only antihistamine nasal spray approved in the United States for treatment of symptoms of SAR.

Other classes of medications that are approved as prescription products for treatment of symptoms of SAR and/or PAR include oral, parenteral, and intranasal corticosteroids. Atrovent Nasal Spray 0.03% is approved as a prescription product for the symptomatic relief of rhinorrhea associated with allergic rhinitis and Atrovent Nasal Spray 0.06% is approved as a prescription product for the symptomatic relief of rhinorrhea associated with SAR. NasalCrom (cromolyn sodium) Nasal Spray is approved as an OTC product for treatment and prevention of allergic rhinitis.

If approved, the applicant's product would be the second prescription antihistamine nasal spray in the United States with an indication for treatment of symptoms of SAR (b) (4)

2.3 Availability of Proposed Active Ingredient in the United States

Olopatadine HCl ophthalmic solution, 0.1% (Patanol®), is approved in the United States for the treatment of the signs and symptoms of allergic conjunctivitis (NDA 20-688). It was approved on December 18, 1996. The product label states that headaches were reported at an incidence of 7%. Adverse experiences that were reported in less than 5% of patients included asthenia, blurred vision, burning or stinging, cold syndrome, dry eye, foreign body sensation, hyperemia, hypersensitivity, keratitis, lid edema, nausea, pharyngitis, pruritus, rhinitis, sinusitis, and taste perversion. The label notes that some of these events were similar to the underlying disease being studied [Patanol Product Label].

A 0.2% concentration of olopatadine HCl ophthalmic solution was approved for the treatment of ocular itching associated with allergic conjunctivitis (NDA 21-545) on December 22, 2004. The product label states that symptoms similar to cold syndrome and pharyngitis were reported at an incidence of 10%. Adverse experiences that were reported in 5% or less of patients included blurred vision, burning or stinging, conjunctivitis, dry eye, foreign body sensation, hyperemia, hypersensitivity, keratitis, lid edema, pain and ocular pruritus, asthenia, back pain, flu syndrome, headache, increased cough, infection, nausea, rhinitis, sinusitis, and taste perversion. The label notes that some of these adverse events were similar to the underlying disease being studied [Olopatadine HCl Ophthalmic Solution 0.2% Product Label].

2.4 Important Issues with Pharmacologically Related Products

Adverse events related to anticholinergic effects of antihistamines include dry mouth, tachycardia, and urinary retention. Somnolence is associated with many older antihistamines, such as diphenhydramine, hydroxyzine, and chlorpheniramine. Some of the newer antihistamines are also associated with somnolence as well, but at lower frequencies or at doses higher than those recommended in the label. Somnolence was noted in the controlled clinical trials for Zyrtec® (cetirizine HCl) at a frequency of 13.7%, compared with 6.3% for placebo [Zyrtec® Product Label]. Claritin® (loratadine) may be associated with somnolence at doses greater than the labeled dose [Claritin® OTC Product Label].

Epistaxis has been noted with other intranasal spray products with the SAR and/or PAR indications, with incidences of 2% to 11%. Nasal septum perforation is an extremely rare adverse event among non-steroid nasal sprays with allergic rhinitis indications and has only reported in postmarketing adverse events. Even among corticosteroid nasal sprays with allergic rhinitis indications, nasal septum perforation is uncommon.

Taste perversion has been noted in the clinical development programs for Astelin Nasal Spray and Atrovent Nasal Spray 0.03% and 0.06% [Product Labels, Astelin Nasal Spray, Atrovent Nasal Spray 0.03%, Atrovent Nasal Spray 0.06%].

2.5 Presubmission Regulatory Activity

The applicant's opening IND was submitted on March 31, 2000 [IND 60,116, N-000, 3/31/00]. An End-of-Phase 2 meeting was held on October 11, 2001. At that time, the applicant was pursuing (b) (4) SAR (b) (4) indications, and had completed two phase 2 nasal allergen challenge studies and two phase 2 natural exposure SAR studies with 0.1% and 0.2% olopatadine, and had submitted protocols for phase 3 studies with 0.1% olopatadine. The Division advised the applicant that they must establish the cardiac safety of the product, that one SAR study and one (b) (4) study could support approval of (b) (4) indications, and that long-term safety data would also be required. The Division also recommended that the applicant firmly establish the correct dose prior to conducting phase 3 studies [Meeting Minutes and Medical Officer Review, IND 60,116, N-019, 9/5/01]. The applicant chose to reformulate their product and to conduct additional dose ranging studies with 0.2%, 0.4%, and 0.6% olopatadine nasal spray. Following the completion of additional dose ranging studies, the applicant conducted their pivotal phase 3 efficacy and safety studies (C-02-37 and C-02-10) and their long-term safety study (C-01-92). A Pre-NDA meeting was held on September 30, 2003. Points of discussion included data necessary to support onset of action and patient-reported outcome claims, and patient exposure necessary to support the safety of the product [Meeting Minutes and Medical Officer Review, IND 60,116, N-039 MR, 7/2/03].

Assessment of (b) (4) was added as an additional objective for the long-term PAR study C-01-92 after the Pre-NDA meeting was held. (b) (4) This endpoint does not provide support for the (b) (4) but is acceptable to support the validity of safety conclusions from this study [Medical Officer Review, Charles E. Lee, M.D., IND 60,116, N-032, PN, 2/4/03]. Additional information on the efficacy endpoint for study C-01-92 may be found in Section 10.1.3.15.5.1 of this review.

2.6 Other Relevant Background Information

The applicant is also pursuing approval of olopatadine 0.6% nasal spray in the European Union. The applicant has met with the EMA, the Irish Medicines Agency, and the Danish Medicines Agency regarding olopatadine 0.6% nasal spray. Ireland and Denmark were chosen because they were Rapporteur and Co-rapporteur Member States for the European Union application for olopatadine 0.1% ophthalmic drops. Both the Irish Medicines Agency and the Danish Medicines have asked the applicant to conduct a study that includes a marketed comparator in addition to olopatadine 0.6% and vehicle placebo [Module 2, Volume 4, Section 2.5, pages 26-27].

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The product is a nonsterile, multiple dose, nasal spray solution containing 600 mcg/spray (0.6%) of olopatadine base or 665 mcg/spray (0.665%) of olopatadine HCl. It contains the following excipients: benzalkonium chloride, edetate disodium, povidone, sodium chloride, dibasic sodium phosphate, sodium hydroxide, hydrochloric acid, and purified water. (b) (4) The pH was chosen, in combination with a (b) (4) concentration of the solubility enhancer povidone, to achieve the desired concentration of 0.6% olopatadine [Module 2, Volume 3, Section 2.3.P, pages 5, 7]. The product is packaged in a plastic bottle (b) (4) with a metered dose spray pump and fitted with a plastic actuator and overcap [Module 2, Volume 2, Section 2.3.P, pages 2-3].

The to-be-marketed formulation of drug product was used in the pivotal studies in this application [Module 2, Volume 3, Section 2.3.P, pages 3-5].

Olopatadine HCl drug substance is manufactured for the applicant by (b) (4) [Module 2, Volume 3, Section 2.3.S, page 3]. Olopatadine 0.6% nasal spray will be manufactured by (b) (4)

Major CMC deficiencies in the application relate to drug substance-related impurities, dose delivery data, data supporting the label claim number of actuations, and acceptance criteria for drug substance and drug product. (b) (4) (structural alerts for mutagenicity), are formed from the drug substance in the product when stored in a horizontal position. In that orientation, levels of the (b) (4) impurity are beyond those that are acceptable to the Division's Pharmacology/Toxicology team. This issue is also addressed in Section 3.2 of this review. There is also a serious question about the representative nature of the dose delivery data collected to assess uniformity of dosing. In addition, the applicant's tail-off data do not appear to support the label claim number of actuations (240). The design of the actuator is such that replacement after cleaning is quite difficult. Finally, acceptance criteria for the drug substance and drug product specifications are in need of tightening to reflect the data obtained.

More detailed information may be found in Dr. Craig Bertha's CMC review [CMC Review, C. Bertha, Ph.D., NDA 21-861, N-000, 12/24/04].

The product quality microbiology review found no deficiencies and recommended approval of the application based on microbiological product quality [J. Barletta, Ph.D., Product Quality Microbiology Review, NDA 21-861, N-000, 12/24/04].

3.2 Animal Pharmacology/Toxicology

The pharmacology-toxicology team has safety concerns about the chronic intranasal use of the to-be-marketed product, which contains (b) (4) povidone. There was olfactory epithelium degeneration and turbinate epithelium vacuolation observed in the applicant's six-month rat study with intranasal povidone at both doses tested with no NOAEL identified. These effects were observed to be dose responsive in incidence and severity [Communication to Applicant dated 5/25/05; Pharmacology-Toxicology Review, Gary Bond, Ph.D., NDA 21-861, N-000, 12/24/04]. The non-clinical data suggest that the product is toxic to the nasal mucosa. Based on these non-clinical assessments, the safety of the proposed clinical formulation cannot be determined.

Data in this applicant suggests that the (b) (4) degradants in the product are genotoxic and that the (b) (4) degradant is a genotoxic structural alert. The applicant has been asked to provide documentation that the levels of these impurities are at comparable or higher levels in the applicant's rat or mouse carcinogenicity studies with olopatadine. The applicant was advised that if this is not the case, it will be necessary to limit these impurities to (b) (4)% in the drug product or to conduct a carcinogenicity assay with the isolated impurities [Communication to Applicant dated 5/25/05].

In non-clinical studies, olopatadine showed an antihypertensive effect in dogs in a dose dependent manner at 20, 50, & 100 mg/kg (59% decrease at high dose) with decreased total peripheral resistance. At <5 mg/kg iv, no effects on heart rate, ECG & respiratory rate were observed. At <30 mg/kg iv there were no effects on QTc. The IC_{50} for hERG channel is 1000X greater than for terfenadine. In studying the effect of the combination of olopatadine and itraconazole (to block CYP 3A4) on the ECG in conscious dogs, olopatadine alone causes a greater increase in heart rate and mean blood pressure (in contrast to an earlier experiment where olopatadine caused hypotension) than when administered along with itraconazole, while QT tended to be less affected. These data suggest that olopatadine may not elicit QT prolongation even when co-administered with the CYP 3A4-inhibitor itraconazole. In another study on the effects of olopatadine HCl on cloned hERG channels, olopatadine blocked hERG channels with an IC_{50} of 1.1 mM. This block showed no use or time dependence [Pharmacology Review, Gary Bond, Ph.D., NDA 21-861, N-000, 12/24/04].

More detailed information may be found in Dr. Gary Bond's Pharmacology/Toxicology review [Pharmacology/Toxicology Review, G. Bond, Ph.D., NDA 21-861, N-000, 12/24/04].

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

There were five clinical studies considered by the applicant to be pivotal, six supportive clinical studies, and seven pharmacokinetic (PK) and pharmacodynamic (PD) studies in the applicant's drug development program [Module 2, Volume 4, Section 2.5, pages 7-11, 42, 44]. Other sources of clinical data in this application included worldwide postmarketing adverse event reports for olopatadine 0.1% ophthalmic solution and Japanese postmarketing adverse event reports for olopatadine 2.5 mg and 5 mg tablets. The applicant also completed a review of the published medical literature for safety information relevant to olopatadine.

The clinical review of this application focuses on the five pivotal clinical studies, which were reviewed in depth. The supporting clinical studies received an abbreviated review. The cardiac safety studies, C-02-54 and C-02-23, and a PK study in healthy subjects and subjects with renal impairment, C-02-46, received a focused review. The safety data for the other four PK and PD studies were reviewed with the applicant's Integrated Summary of Safety.

The pivotal and supportive clinical studies and the clinical pharmacology studies in this application are summarized in Table 1. More detailed descriptions of the pivotal clinical studies follow below.

Study C-02-37 was a randomized, double blind, placebo controlled, parallel group, pivotal phase 3, natural exposure, efficacy and safety study of olopatadine 0.4% and 0.6% nasal spray administered twice daily in patients with SAR [Module 2, Volume 20, C-02-37 Synopsis, page 1]. There were 565 male and female patients with fall seasonal allergic rhinitis, 12 years of age and older who were randomized. There was a three to 21 day placebo run-in period. The primary efficacy endpoint was percent change from baseline in reflective Total Nasal Symptoms Score over the two week double blind treatment period. Secondary efficacy endpoints included percent change from baseline in instantaneous Total Nasal Symptoms Score over the two week double blind treatment period, percent change from baseline in reflective and instantaneous individual symptom scores, (b) (4) and Work Productivity and Activity Improvement (WPAI-AS) among others. Safety endpoints included adverse events, vital signs, physical examinations, nasal examinations, and clinical laboratory studies. Eleven of the 565 patients who were exposed to study treatment withdrew from the study because of adverse events. There were no deaths or serious adverse events in the study [Module 2, Volume 20, C-02-37 Synopsis, pages 1-6]. The detailed review of this study is found in Section 10.1.1 of this document.

Study C-02-10 was a randomized, double blind, placebo controlled, parallel group, pivotal phase 3, natural exposure, efficacy and safety study of olopatadine 0.4% and 0.6% nasal spray administered twice daily in patients with SAR. There were 677 male and female patients with seasonal allergic rhinitis to mountain cedar pollen, 12 years of age and older who were randomized. There was a three to 21 day placebo run-in period. The primary efficacy endpoint

was percent change from baseline in reflective Total Nasal Symptoms Score over the two week double blind treatment period. Secondary efficacy endpoints included percent change from baseline in instantaneous Total Nasal Symptoms Score over the two week double blind treatment period, percent change from baseline in reflective and instantaneous individual symptom scores, (b) (4) and health economics (WPAI-AS) assessments. A subset of patients had blood samples taken for PK analysis. Safety endpoints included adverse events, vital signs, physical examinations, nasal examinations, and clinical laboratory studies. Eight of the 677 patients who were exposed to study treatment withdrew from the study because of adverse events. There were no deaths in this study. There was one serious adverse event (syncope) in the study [Module 2, Volume 20, C-02-10 Synopsis, pages 1-7; Module 5, Volume 56, page 220]. The detailed review of this study is found in Section 10.1.2 of this document.

Study C-01-92 was a randomized, double blind, placebo controlled, parallel group, pivotal phase 3, natural exposure, long-term (b) (4) safety study of olopatadine 0.6% nasal spray administered twice daily in patients with PAR. There were 924 male and female patients with PAR, 12 years of age and older who were randomized. There was a three to 21 day placebo run-in period. The treatment period was one year. (b) (4) Safety endpoints included adverse events, vital signs, physical examinations, nasal examinations, and ECGs. Forty-eight of the 924 patients who were exposed to study treatment withdrew from the study because of adverse events. Of the 48 patients who withdrew from the study, 23 were treated with olopatadine 0.6% and 25 were treated with vehicle placebo. There was one death in the study, a patient treated with olopatadine 0.6% who died of sepsis after a gastric bypass operation. There were 15 serious adverse events in the study, with seven treated with olopatadine 0.6% and eight treated with vehicle placebo [Module 2, Volume 20, C-01-92 Synopsis, pages 1-5; Module 2, Volume 65, pages 198-202]. The detailed review of this study is found in Section 10.1.3 of this document.

Study C-01-83 was a randomized, double blind, placebo controlled, parallel group, pivotal phase 2, single dose, dose response and onset of action EEU study of olopatadine 0.2%, 0.4%, and 0.6% nasal spray in patients with SAR. There were 320 male and female patients with seasonal allergic rhinitis to short ragweed pollen, 16 years of age and older who were randomized. Patients that met minimum total nasal symptom scores on each of two priming visits were enrolled in the study. Patients were exposed to pollen in the EEU and diary cards were completed and peak nasal inspiratory flow rates were measured at various intervals during the study period. The primary efficacy endpoint was percent change from baseline in reflective Total Nasal Symptom Score over the treatment period. Secondary efficacy endpoints included percent change from baseline in individual symptom scores over the treatment period, change from baseline in nasal inspiratory flow rate, and patient global rating over the treatment period. Safety endpoints included adverse events, vital signs, and nasal examinations. There were no patients who withdrew from the study because of adverse events. There were no deaths or serious adverse events in the study [Module 2, Volume 20, C-01-83 Synopsis, pages 1-4; Module 2, Volume 37, pages 90]. The detailed review of this study is found in Section 10.1.4 of this document.

C-03-52 was a randomized, double blind, active and placebo controlled, parallel group, pivotal phase 2, single dose, onset of action EEU study of olopatadine 0.6% nasal spray and mometasone furoate 50 mcg nasal spray in patients with SAR. There were 425 male and female patients with seasonal allergic rhinitis to short ragweed pollen, 18 years of age and older who were randomized. Patients that met minimum total nasal symptom scores at two priming visits and predose were enrolled and entered the treatment phase of the study. Patients were exposed to pollen in the EEU and diary cards were completed and peak nasal inspiratory flow rates were measured at various intervals during the study period. The primary efficacy endpoint was percent change from baseline in reflective Total Nasal Symptoms Score over the treatment period. Secondary efficacy endpoints included percent change from baseline in individual symptom scores over the treatment period and patient global rating over the treatment period. Safety endpoints included adverse events, vital signs, and nasal examinations. There were no patients who withdrew from the study because of adverse events. There were no deaths or serious adverse events in the study [Module 2, Volume 20, C-03-52 Synopsis, pages 1-5]. The detailed review of this study is found in Section 10.1.5 of this document.

4.2 Tables of Clinical Studies

The pivotal and supportive clinical studies and clinical pharmacology studies in this application are summarized in Table 1.

Table 1 Summary of studies NDA 21-861 [Module 5, Volume 20, Section 2.7.6, pages 1-9; Module 5, Volume 20, Section 2.7.6, Study Synopses]

Pivotal Clinical Studies						
Study Number	**Study Type**	**Treatment Groups**	**Treatment duration**	**Design**	**Number of subjects**	**Diagnosis, age of subjects**
C-02-37	Pivotal efficacy and safety study	Olopatadine NS 0.4%, 2 sp ea nostril BID Olopatadine NS 0.6%, 2 sp ea nostril BID Vehicle placebo, 2 sp ea nostril BID	2 weeks	Multicenter, randomized, double blind, active and placebo controlled, parallel group	565	Patients with SAR, men and women, ≥12 years
C-02-10	Pivotal efficacy and safety study	Olopatadine NS 0.4%, 2 sp ea nostril BID Olopatadine NS 0.6%, 2 sp ea nostril BID Vehicle placebo, 2 sp ea nostril BID	2 weeks	Multicenter, randomized, double blind, active and placebo controlled, parallel group	677	Patients with SAR, men and women, ≥12 years
C-01-92	Long-term safety study	Olopatadine NS 0.6%, 2 sp ea nostril BID Vehicle placebo, 2 sp ea nostril BID	1 year	Multiple center, randomized, double blind, placebo controlled, parallel group	924	Patients with PAR, men and women, ≥12 years
C-01-83	Pivotal dose response EEU study	Olopatadine NS 0.2%, 2 sp ea nostril Olopatadine NS 0.4%, 2 sp ea nostril Olopatadine NS 0.6%, 2 sp ea nostril Vehicle placebo, 2 sp ea nostril	1 day	Single center, randomized, double blind, placebo controlled, parallel group	320	Patients with SAR, men and women, ≥16 years
C-03-52	Pivotal onset of action EEU study	Olopatadine NS 0.6%, 2 sp ea nostril Mometasone furoate 50 mcg, 2 sp ea nostril Vehicle placebo, 2 sp ea nostril	1 day	Single center, randomized, double blind, active and placebo controlled, parallel group	425	Patients with SAR, men and women, ≥18 years

Table 1, continued. Summary of studies NDA 21-861 [Module 5, Volume 20, Section 2.7.6, pages 1-9; Module 5, Volume 20, Section 2.7.6, Study Synopses]

Supportive Clinical Studies						
Study Number	**Study Type**	**Treatment Groups**	**Treatment duration**	**Design**	**Number of subjects**	**Diagnosis, age of subjects**
C-97-59	Pilot phase 2 EEU study	Olopatadine NS 0.1%, 1 sp ea nostril Azelastine NS 0.1%, 1 sp ea nostril Emedastine NS 0.05%, 1 sp ea nostril Vehicle placebo, 1 sp ea nostril	1 day	Single center, randomized, double blind, active and placebo controlled, four-way crossover	12	Patients with SAR, men and women, ≥16 years
C-00-10	Phase 2 dose response efficacy and safety study	Olopatadine NS 0.1%, 2 sp ea nostril QD Olopatadine NS 0.1%, 2 sp ea nostril BID Olopatadine NS 0.2%, 2 sp ea nostril QD Olopatadine NS 0.2%, 2 sp ea nostril BID Vehicle placebo, 2 sp ea nostril QD Placebo, 2 sp ea nostril BID	2 weeks	Multicenter, randomized, double blind, active and placebo controlled, parallel group	192	Patients with SAR, men and women, ≥12 years
C-00-33	Phase 2-3 efficacy and safety study	Olopatadine NS 0.1%, 2 sp ea nostril BID Azelastine NS 0.1%, 2 sp ea nostril BID Vehicle placebo, 2 sp ea nostril BID	2 weeks	Multicenter, randomized, double blind, active and placebo controlled, parallel group	166	Patients with SAR, men and women, ≥12 years
C-00-70	Phase 2 EEU study	Olopatadine NS 0.1%, 2 sp ea nostril Olopatadine NS 0.2%, 2 sp ea nostril Azelastine NS 0.1%, 2 sp ea nostril Vehicle placebo, 2 sp ea nostril	1 day	Single center, randomized, single blind, active and placebo controlled, three-phase, two-way crossover	20	Patients with SAR, men and women, ≥16 years
C-01-05	Phase 2-3 efficacy and safety study	Olopatadine NS 0.1%, 2 sp ea nostril QD Olopatadine NS 0.1%, 2 sp ea nostril BID Azelastine NS 0.1%, 2 sp ea nostril BID Vehicle placebo, 2 sp ea nostril QD Vehicle placebo, 2 sp ea nostril BID	8 weeks	Multicenter, randomized, double blind, active and placebo controlled, parallel group	397	Patients with SAR, men and women, ≥12 years
C-03-48	Phase 3 pilot onset of action EEU study	Olopatadine NS 0.6%, 2 sp ea nostril Fluticasone propionate 0.05%, 2 sp ea nostril Vehicle placebo, 2 sp ea nostril	1 day	Single center, randomized, double blind, active and placebo controlled, parallel group	90	Patients with SAR, men and women, ≥12 years

Table 1, continued. Summary of studies NDA 21-861 [Module 5, Volume 20, Section 2.7.6, pages 1-9; Module 5, Volume 20, Section 2.7.6, Study Synopses]

Clinical Pharmacology Studies						
Study Number	**Study Type**	**Treatment Groups**	**Treatment duration**	**Design**	**Number of subjects**	**Diagnosis, age of subjects**
C-00-58	Phase 1 PK study	Olopatadine NS 0.1%, 2 sp ea nostril QD Olopatadine NS 0.1%, 2 sp ea nostril BID Olopatadine NS 0.2%, 2 sp ea nostril QD	2.5 days	Single center, randomized, open label, multiple dose, parallel group	36	Healthy men and women, 18-75 years
C-02-21	Phase 1 PK study	Olopatadine NS 0.6%, 2 sp ea nostril Vehicle placebo NS, 2 sp ea nostril	1 day	Single center, randomized, double blind, single dose, parallel group	36	Healthy men and women, ≥18 years
C-03-11	Phase 1 BA study	Olopatadine NS 0.4%, 2 sp ea nostril Olopatadine NS 0.6%, 2 sp ea nostril Olopatadine iv solution 0.01%, 1.5 mg	1 day	Single center, randomized, open label, single dose, three way crossover	12	Healthy men and women, 18-45 years
C-02-46	Phase 1 PK study	Olopatadine NS 0.6%, 2 sp ea nostril	1 day	Single center, randomized, open label, single dose	25	Adult men and women with renal impairment, ≥18 years
C-03-10	Phase 1 mass balance excretion study	Olopatadine oral solution 0.67%, 5 mg/200 µCi ^{14}C olopatadine	1 day	Single center, open label, single dose	8	Healthy men and women, 19-45 years
C-02-54	Phase 1 cardiac safety and PK study	Olopatadine oral solution, 0.2%, 20 mg BID Placebo solution BID	2 weeks	Single center, randomized, double blind, placebo controlled, multiple dose, 2-way crossover	34	Healthy men and women, 18-75 years
C-00-23	Phase 1 cardiac safety and PK study	Olopatadine oral solution, 5 mg BID Placebo solution BID	2.5 days	Single center, randomized, double blind, placebo controlled, multiple dose, 2-way crossover	117	Healthy men and women, 18-75 years

4.3 Review Strategy

The clinical review of this application focuses on the five pivotal clinical studies, which were reviewed in depth. Three of these studies, C-02-37, C-02-10, and C-01-92, were intended to support the proposed SAR (b) (4) indications. The other two pivotal studies, C-01-83 and C-03-52, were EEU studies intended to provide information on onset of action and/or dose response and efficacy of the product compared with Nasonex® (mometasone furoate) Nasal Spray (MFNS). Six supporting clinical studies received an abbreviated review. Cardiac safety studies, C-02-54 and C-02-23, and a PK study in healthy and subjects and subjects with renal impairment, C-02-46, received a focused review. The safety data for the other four PK and PD studies were reviewed with the applicant's Integrated Summary of Safety.

The Integrated Review of Efficacy in this review focuses mainly on the two pivotal SAR efficacy and safety studies, C-02-37 and C-02-10, the pivotal PAR study, C-01-92, and the two studies conducted to provide information on onset of action and/or dose response and efficacy of the product compared with (MFNS).

The Integrated Review of Safety in this review focused on the safety information in the applicant's Integrated Summary of Safety. The safety information included adverse events, laboratory studies, physical examinations, nasal examinations, and ECGs from clinical studies in the applicant's drug development program. Changes in physical examinations and nasal examinations were recorded as adverse events and are addressed in the review of adverse events. The applicant's safety data also included a review of worldwide postmarketing adverse event reports for olopatadine HCl ophthalmic solution 0.1%, a review of postmarketing adverse event reports from Japan for olopatadine HCl 2.5 mg and 5 mg tablets, and a review of the published medical literature for safety information relevant to use of olopatadine.

4.4 Data Quality and Integrity

There were routine and for-cause audits by the Division of Scientific Investigations (DSI) in this application.

A general survey of the trial conduct at the site, IRB approval process, and conduct of internal auditing by the applicant were suggested for the routine DSI audits. There were three investigators selected for routine DSI audit:

1. Sandra Gawchik, D.O. (3203)
   Asthma & Allergy Research Associates
   President's House
   One Medical Center
   Upland, PA 19013
   Phone: (610) 876-2103
   Fax: (210) 876-6565

Subinvestigators:
(b) (4)

This center was one of the centers that randomized the greatest number of patients in pivotal study C-02-37 [Module 5, Volume 51, page 1514]. DSI audit identified minor protocol deviations and a FDA Form 483 was issued, but the data was considered to be acceptable by DSI [DSI Consultation, NDA 21-861, N-000, 12/24/04].

2. Paul Ratner, MD (3619)
   Sylvana Research
   7711 Louis Pasteur Dr., Suite 406
   San Antonio, TX 78229
   Phone: (210) 614-6673
   Fax: (210) 614-5340

   Subinvestigators:
   (b) (4)

   This center was one of the centers that randomized the greatest number of patients in pivotal study C-02-37 and one of the centers that randomized the greatest number of patients in pivotal study C-02-10 [Module 5, Volume 51, page 1517; Module 5, Volume 60, page 1444]. There was no action indicated by the DSI audit at this site. No FDA Form 483 was issued. The data were considered to be acceptable by DSI [DSI Consultation, NDA 21-861, N-000, 12/24/04].

3. Niran J. Amar, M.D. (3642)
   Allergy and Asthma Center
   405 Londonderry Drive, Suite 100
   Waco, TX 76712
   Phone: (254) 751-1144

   Subinvestigators:
   (b) (4)

   This center was one of the centers that randomized the greatest number of patients in pivotal study C-02-10 [Module 5, Volume 60, page 1443]. There was no action indicated by the DSI audit at this site. No FDA Form 483 was issued. The data were considered to be acceptable by DSI [DSI Consultation, NDA 21-861, N-000, 12/24/04].

There were for-cause audits of two study centers because of irregularities in Case Report Forms regarding the documentation of nasal septum perforations. The results of these for-cause audits are pending at the time of this review. The two study centers identified for for-cause audit were:

4. Kenneth T. Kim, MD (3795)
   2600 Redondo Avenue
   Fourth Floor
   Suite 401
   Long Beach, CA 90806
   Phone: 562-997-7888
   Fax: 562-997-8884

   Regarding Case Report Form for Patient #3795-8503
   [Module 5, Volume 71, page 2435]

5. John A. Zora, MD (3812)
   Rx Research
   1990 Riverside Parkway
   Lawrenceville, GA 30043
   Phone: Not provided in submission
   Fax: Not provided in submission

   Regarding Case Report Form for Patient #3812-5905
   [Module 5, Volume 71, page 2451]

4.5 Compliance with Good Clinical Practices

The applicant stated that the studies in this application were performed in compliance with good clinical practice. [Module 5, Volume 1, page 5; Module 5, Volume 5, page 2; Module 5, Volume 8, page 1; Module 5, Volume 11, page 1; Module 5, Volume 16, page 1; Module 5, Volume 20, page 1; Module 5, Volume 25, page 2; Module 5, Volume 37, page 1; Module 5, Volume 42, page 2; Module 5, Volume 47, page 1; Module 5, Volume 56, page 1; Module 5, Volume 65, page 1 ; Module 5, Volume 77, page 1; Module 5, Volume 78, page 1; Module 5, Volume 83, page 2; Module 5, Volume 87, page 1; Module 5, Volume 90, page 2; Module 5, Volume 96, page 1].

The applicant stated that they did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with the application [Module 1, Volume 1, Section 3.A.3, page 1].

4.6 Financial Disclosures

The applicant stated that there was one investigator that participated in one of the studies that had financial interests or arrangements to disclose. (b) (4) received consulting, travel and expense reimbursement,

and honorarium fees in the total of $45,215.74 [Module 1, Volume 1, Section 3.A.6, pages 1-2, Section 3.A.6.2, page 13]. The applicant certified that they did not enter into any other financial arrangement with any of the other clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study. The applicant also certified that the other clinical investigators did not have a proprietary interest in the proposed product or a significant equity in the applicant. The applicant also certified that no other investigator was the recipient of significant payments [Module 1, Section 3.A.6.3, Forms FDA 3454].

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Single-dose pharmacokinetics were assessed following single intranasal administration of olopatadine 0.4% or olopatadine 0.6% in SAR patients and olopatadine 0.1%, 0.2%, 0.4%, or 0.6% in healthy subjects. The mean PK parameters resulting from these studies are shown in Table 2. The mean and range in the olopatadine C_{max} and AUC values in SAR patients following single intranasal doses (two sprays/nostril) of either olopatadine 0.4% nasal spray (1.6 mg) or olopatadine 0.6% nasal spray (2.4 mg) were comparable to those in healthy subjects [S. Suarez, Ph.D., Clinical Pharmacology and Biopharmaceutics Review, NDA 21-861, N-000, 12/24/05].

Table 2 Mean pharmacokinetic parameters of olopatadine after single Intranasal doses [S. Suarez, Ph.D., Clinical Pharmacology and Biopharmaceutics Review, NDA 21-861, N-000, 12/24/05]

Study	Dose	C_{max} (ng/mL)	T_{max} (h)	AUC (ng*h/mL)	$t_{1/2}$ (h)
Study C-02-10 SAR patients	0.4% (N=14)	14.4 ± 4.4 (5.97 -21.9)	0.86 ± 0.41 (0.25 - 1.50)	48.9 ± 12.5 (23.3 - 67.4)	ND
	0.6% (N=13)	21.7 ± 8.7 (7.11 - 36.4)	1.00 ± 0.50 (0.25 - 2.00)	67.7 ± 21.1 (24.0 - 98.0)	ND
Study C-02-21 Healthy volunteers	0.6% (N=8)	29.3 ± 15.1 (13.6-58.4)	0.97 ± 0.54 (0.50 -2.00)	75.1 ± 29.4 (31.8 - 126)	ND
Study C-03-11 Healthy volunteers	0.4% (N=11)	12.5 ± 6.1 (1.98 -20.7)	1.04 ± 0.24 (0.75-1.50)	42.5 ± 16.0 (17.0-66.4)	8.6 ± 5.7 (1.75-17.9)
	0.6% (N=11)	17.5 ± 6.7 (6.37 -27.6)	1.05 ± 0.31 (0.75 - 1.50)	60.3 ± 20.3 (20.2 - 98.0)	10.0 ± 5.7 (3.2 -22.2)
Study C-02-46 Healthy volunteers	0.6% (N=6)	18.1±10.9 (3.80 - 29.9)	1.17±0.52 (0.50 - 2.00)	77.0±51.3 (17.0 - 139)	11.5±3.0 (7.2 - 14.5)

ND = not determined, sampling only out to 12 hours post-dose

The multiple-dose PK of olopatadine was examined in two studies following intranasal administration (study C-02-10 and study C-00-58) (two sprays/nostril) from 0.1%, 0.2%, 0.4%, and 0.6%. Comparison of the systemic exposure (C_{max} and AUC_{0-12}) of olopatadine after single and multiple intranasal doses in SAR patients (C-02-10) indicate minimal accumulation (<1.3-fold) with twice-daily administration. Mean T_{max} and $t_{1/2}$ values were similar in healthy subjects and SAR patients [S. Suarez, Ph.D., Clinical Pharmacology and Biopharmaceutics Review, NDA 21-861, N-000, 12/24/05].

Table 3 Mean pharmacokinetic parameters of olopatadine after multiple QD or BID intranasal doses [S. Suarez, Ph.D., Clinical Pharmacology and Biopharmaceutics Review, NDA 21-861, N-000, 12/24/05]

Study	Dose/Regimen (N)	C_{max} (ng/mL)	T_{max} (h)	AUC0-12 (ng*h/mL)	$t_{1/2}$ (h)
Study C-02-10 SAR patients	0.4%O BID x 14 days (N = 14)	15.9 ± 6.4 (3.65-29.0)	1.00 ± 0.55 (0.25-2.00)	57.3 ± 24.5 (10.4-114)	8.3 ± 4.9 (2.1-21.3)
	0.6%O BID x 14 days (N = 13)	23.3 ± 6.2 (14.4-35.3)	0.97 ± 0.52 (0.08 - 1.50)	78.0 ± 13.9 (54.4- 103)	10.4 ± 5.1 (4.0-21.8)
Study C-00-58 Healthy Subjects	0.1% QD x 3 days (N = 12)	4.36 ± 2.27 (0.41 -7.92)	1.23 ± 0.59 (0.50 -2.00)	13.92± 5.90 (1.40 -20.67)	6.3 ± 4.1 (1.96 - 13.5)
	0.1% BID x 3 days (N = 12)	3.42 ± 1.31 (0.97 — 5.05)	1.06 ± 0.42 (0.50 - 1.50)	12.03 ± 3.66 (4.80 - 16.54)	8.3 ± 3.5 (3.06 - 13.3)
	0.2% BID x 3 days (N = 12)	8.48 ± 3.12 (2.77- 15.0)	1.25 ± 0.38 (0.75-2.00)	28.33 ± 9.88 (11.09- 14.03)	15.0 ± 9.6 (3.16-29.9)

Dose-proportionality following single and multiple intranasal administration of olopatadine 0.4% nasal spray or olopatadine 0.6% nasal spray in SAR patients and olopatadine nasal spray 0.2% or 0.6% in healthy subjects was evaluated in Studies C-03-10 and C-03-11, respectively. Olopatadine peak plasma concentrations increased in proportion to the intranasal dose averaging 12.5 ± 6.1 ng/mL and 17.5 ± 6.7 ng/mL for olopatadine 0.4% nasal spray and olopatadine 0.6% nasal spray, respectively (study C-03-11). Similar dose-proportional increases were seen in mean AUC values (an increase in 1.5 in dose resulted in a 1.4 increase in the olopatadine C_{max} and AUC) [S. Suarez, Ph.D., Clinical Pharmacology and Biopharmaceutics Review, NDA 21-861, N-000, 12/24/05].

Three minor active metabolites (M1, M2, and M3) were identified in PK studies, but only N-desmethyl olopatadine (Ml) and olopatadine N-oxide (M3) were quantified in plasma samples following single intranasal doses of olopatadine nasal 0.4% or olopatadine nasal 0.6%. The C_{max} and AUC values for these metabolites did not appear to be markedly different between SAR patients and healthy subjects. Following single intranasal doses of olopatadine 0.4% and 0.6% plasma concentrations of M1 and M3 increased roughly in proportion to the olopatadine dose in both healthy subjects and SAR patients [S. Suarez, Ph.D., Clinical Pharmacology and Biopharmaceutics Review, NDA 21-861, N-000, 12/24/05].

Data from the in-vitro metabolism of ^{14}C-olopatadine showed that metabolism of olopatadine is a minor route of elimination. Two different metabolites, M1 and M3, were formed when olopatadine was incubated with human liver microsomes. After a one-hour incubation, M1 and M3 accounted for 5.2 and 30.5% of the initial olopatadine concentration, respectively. M1 formation was catalyzed primarily by CYP2A4, while M3 formation is catalyzed by FMO1 and FMO3. Therefore, it is unlikely that substrates, inhibitors or inducers of these enzymes may affect the PK of olopatadine and its metabolites. In addition, olopatadine did not affect the activity of the major CYP P450 enzymes such as 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. Therefore, no major effects of olopatadine should be expected on the PK of other drugs [S.

Suarez, Ph.D., Clinical Pharmacology and Biopharmaceutics Review, NDA 21-861, N-000, 12/24/05].

After single intranasal administration of olopatadine 0.6% nasal spray to 25 subjects/patients (6 subjects with normal renal function, 7 patients with mild renal impairment, 6 patients with moderate renal impairment, and 6 patients with severe renal impairment), no clinically significant differences were observed in the systemic exposure. The plasma C_{max} and AUC values in patients with severe renal impairment were approximately 2.6- and 5.6-fold higher than those in healthy subjects. Higher plasma concentrations of the minor, active Ml and M3 metabolites were seen with increasing renal impairment particularly those in severely-impaired patients with 2.6- and 3.6-fold higher mean C_{max} values, respectively. Urinary excretion of parent and metabolites was reduced in renally impaired patients. Despite the higher systemic exposure of parent drug and metabolites, the extent of exposure is still 10- to 250-fold lower than that observed following oral doses of 20 mg to 400 mg, which were safe and well-tolerated. Therefore, dosage adjustment of olopatadine based on renal impairment is not necessary [S. Suarez, Ph.D., Clinical Pharmacology and Biopharmaceutics Review, NDA 21-861, N-000, 12/24/05].

The effect of liver impairment on the PK of olopatadine and its metabolites was not evaluated. The rationale provided by the applicant is that olopatadine (and its metabolites) are mainly eliminated by the kidney. In a mass balance study, total radioactivity was predominantly excreted in urine (70% of total administered dose) suggesting that liver metabolism is not an important route of elimination [S. Suarez, Ph.D., Clinical Pharmacology and Biopharmaceutics Review, NDA 21-861, N-000, 12/24/05].

5.2 Pharmacodynamics

There were two high dose cardiac safety studies in this application, Studies C-00-23 and C-02-54.

Study C-00-23 was a randomized, double blind, placebo controlled, crossover, multiple dose, phase 1, PK/PD study of cardiovascular safety of olopatadine solution, 5 mg orally or placebo in healthy subjects. Data from this study suggest that there is no QTc prolongation with olopatadine 5 mg twice daily by mouth, approximately twice the dose administered by the labeled dose for the proposed nasal spray product. Details may be found in Section 7.1.12 and Section 10.1.12 of this review.

Study C-02-54 was a randomized, double blind, placebo controlled, crossover, multiple dose, phase 1, PK/PD study of cardiovascular safety of olopatadine solution, 20 mg orally or placebo in healthy subjects. Data from this study suggest that there is no QTc prolongation with olopatadine 20 mg twice daily by mouth for 14 days. This dose is approximately eight times the dose administered by the proposed nasal spray product. Details may be found in Section 7.1.12 and Section 10.1.13 of this review and in Dr. Sandra Suarez's Clinical Pharmacology and Biopharmaceutics Review [S. Suarez, Ph.D., Clinical Pharmacology and Biopharmaceutics Review NDA 21-861, N-000, 12/24/04].

5.3 Exposure-Response Relationships

Since systemic absorption of intranasally administered drugs is the result of nasal and gastrointestinal absorption, plasma concentrations cannot be correlated to efficacy. The appropriate dose and dosing regimen must therefore be based on dose-response relationships rather than exposure-response relationships.

Dose response relationships for efficacy are addressed in this document in the Integrated Review of Efficacy (Section 6). Safety data in this application showed dose response effects for taste perversion and dyspepsia. Somnolence is noted frequently (13.5%) for oral olopatadine at high oral doses (5 mg and 20 mg twice daily). Somnolence was noted in the pivotal clinical studies at frequencies of 1.1% and 1.6% for the olopatadine 0.6% and 0.4% groups, respectively, and at higher frequencies than the vehicle placebo (0.2%), as noted in Table 16 of this review. Dose response relationships for safety are addressed in this document in the Integrated Review of Safety (Section 7).

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The applicant's proposed indication follows below [Module 1, Volume 1, 3.B., Prescribing Information, page 8]:

> PATANASE® Nasal Spray is indicated in patients 12 years of age and older for the (b) (4) treatment of the symptoms of seasonal (b) (4) allergic rhinitis (b) (4)

6.1.1 Methods

The following key studies are addressed in this section. These studies were either pivotal efficacy and safety studies supporting the efficacy of the product or were studies supporting proposed labeling claims for efficacy.

6.1.1.1 Pivotal efficacy and safety studies

The pivotal efficacy and safety studies were:

1. C-02-37, a randomized, double blind, active and placebo controlled, parallel group, pivotal phase 3, natural exposure, efficacy and safety study of olopatadine 0.4% and 0.6% nasal spray administered twice daily in patients with SAR [Module 2, Volume 20, C-02-37 Synopsis, page 1]

2. C-02-10, a randomized, double blind, active and placebo controlled, parallel group, pivotal phase 3, natural exposure, efficacy and safety study of olopatadine 0.4% and 0.6% nasal spray administered twice daily in patients with SAR [Module 2, Volume 20, C-02-10 Synopsis, page 1]

3. C-01-92, a randomized, double blind, active and placebo controlled, parallel group, pivotal phase 3, natural exposure, long-term (b) (4) safety study of olopatadine 0.6% nasal spray administered twice daily in patients with PAR [Module 2, Volume 20, C-01-92 Synopsis, page 1]

Studies C-02-37 and C-02-10 are the pivotal studies supporting the proposed SAR indication. In Section 6.1.4 of this review, efficacy results for the primary efficacy endpoints and major secondary efficacy endpoints of these studies will be compared. Study C-01-92 is the pivotal study supporting the proposed (b) (4) and will be discussed separately in Section 6.1.4 because it utilized a different primary efficacy endpoint.

6.1.1.2 Studies supporting other labeling claims

Studies addressed in this section include:

1. C-01-83, a randomized, double blind, placebo controlled, parallel group, phase 2, single dose, dose response and onset of action environmental exposure unit (EEU) study of olopatadine 0.2%, 0.4%, and 0.6% nasal spray in patients with SAR [Module 2, Volume 20, C-01-83 Synopsis, page 1]

2. C-03-52, a randomized, double blind, active and placebo controlled, parallel group, phase 2, single dose, onset of action EEU study of olopatadine 0.6% nasal spray and mometasone furoate nasal spray 50 mcg (MFNS) in patients with SAR [Module 2, Volume 20, C-03-52 Synopsis, page 1]

3. C-00-70, a randomized, single blind, active and placebo controlled, crossover, single dose, phase 2, nasal allergen challenge study of olopatadine 0.1% and 0.2% nasal spray and azelastine 0.1% nasal spray in patients with SAR [Module 2, Volume 20, C-00-70 Synopsis, page 1]

Studies C-01-83 and C-03-52 are pivotal EEU studies intended to support an onset of action and comparative superiority claim for the SAR indication. Onset of action results for these studies will be compared in Section 6.1.4 of this review. Study C-00-70 is a supportive study intended to support claims relevant to possible (b) (4) of olopatadine nasal spray and will be discussed separately because of its different design and efficacy endpoints.

6.1.1.3 Other clinical studies

Other clinical studies, studies C-97-59, C-00-10, C-00-33, C-01-05, and C-03-48, were either phase 2 pilot studies or phase 2 dose response and/or efficacy and safety studies. Studies C-97-

59, C-00-10, C-00-33, and C-01-05 provided evidence that olopatadine 0.1% and 0.2% nasal sprays were not effective, and based on these data, the applicant chose olopatadine 0.4% and 0.6% nasal spray concentrations for further development. Results of these phase 2 studies are discussed individually in Section 10.1 of this review.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint for the pivotal efficacy and safety studies for the SAR indication was the percent change from baseline in the reflective total nasal symptom score (TNSS). The reflective TNSS was defined as the average of the AM and PM reflective severity scores for the patients' assessments of runny nose, stuffy nose, itchy nose, and sneezing, averaged across all days [Module 5, Volume 47, pages 77, 79]. The applicant also provided an additional analysis of the absolute change from baseline in the reflective TNSS, defined as the average of the AM and PM reflective severity scores for the patients' assessments of runny nose, stuffy nose, itchy nose, and sneezing, averaged across all days [Module 5, Volume 47, pages 77, 109].

There were three key secondary efficacy endpoints in the SAR studies [Module 5, Volume 47, pages 77, 79, 81, 160-164]. They were:

- The percent change from baseline in the instantaneous TNSS, defined as the average of the AM and PM instantaneous severity scores for the patients' assessments of runny nose, stuffy nose, itchy nose, and sneezing, averaged across all days
- Changes from baseline in the AM and PM individual severity scores for patient diary symptoms of runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes, averaged across all days
- (b) (4)

Other secondary efficacy endpoints in these studies will not be discussed because they were of lesser importance or, in the case of the WPAI-AS and health economics instruments, are not validated or are incompletely validated instruments and will not support labeling claims.

The primary efficacy endpoint for the PAR study was the mean response to the patient-related relief assessment question over the duration of the study [Module 5, Volume 65, pages 76, 79].

(b) (4)
(b) (4)
. This
recommendation of the Division to provide additional support for the validity of safety assessments [Medical Officer Review, Charles E. Lee, M.D., IND 60,116, N-024, MR, 7/9/02]. This study was not powered to detect a difference between treatment groups for this endpoint. The instrument is a blunt and crude measure of efficacy, and although acceptable to support the validity of safety conclusions, does not provide support for the (b) (4) [Medical Officer Review, Charles E. Lee, M.D., IND 60,116, N-032, PN, 2/4/03]. Accordingly, the discussion of these data in Section 6.1.4 is brief.

Studies C-01-83 and C-03-52 are intended to support an onset of action and comparative superiority claim for the SAR indication. The primary efficacy variable for these EEU studies was the change from baseline in the instantaneous TNSS. The TNSS was defined as the sum of the severity scores for the patients' assessments of runny nose, stuffy nose, itchy nose, and sneezing. Patients made assessments of their symptoms after study treatment administration at 30 minute intervals for four hours, then at 60 minute intervals until 12 hours post-treatment [Module 5, Volume 37, page 45].

Study C-00-70 is a study supporting claims relevant to possible (b) (4) of olopatadine nasal spray. The primary efficacy variables included allergen-induced sneezes, allergen-induced changes in the levels of mast cell tryptase, albumin, and lysozyme in nasal lavage fluids. Secondary efficacy variables included allergen-induced changes in the levels of immunoreactive LTC_4 and histamine in nasal lavage fluids, and patient-assessed SAR symptom severity. These data will not support a labeling or advertising claim. Accordingly, discussion of the results of this study in Section 6.1.4 is brief.

6.1.3 Study Design

6.1.3.1 Pivotal SAR efficacy and safety studies, C-02-37 and C-02-10

These studies were randomized, vehicle-controlled, parallel group, three-arm, multicenter, phase 3 clinical studies in patients with seasonal allergic rhinitis (SAR). The patient population included adults and children, 12 years of age and older, with at least a two-year history of non-recalcitrant SAR and allergy to a prevalent allergen that is present at the time of enrollment. The diagnosis of SAR was defined by positive case history and positive skin prick test and/or intradermal test for a fall allergen within the one year prior to the screening visit. These studies were adequately controlled to assess efficacy. The two week duration of study treatment, patient population, inclusion and exclusion criteria, and demographics were adequate to allow for results to be generalized to the population of SAR patients in the proposed labeling.

6.1.3.2 Pivotal PAR (b) (4) safety study, C-01-92

This study was a randomized, vehicle-controlled, parallel group, two arm, multicenter, phase 3, clinical study of patients with PAR. The patient population included adults and children, 12 years

of age and older, with at least a two-year history of non-recalcitrant PAR and allergy to a perennial allergen. The diagnosis of PAR was defined by positive case history and positive skin prick test and/or intradermal test for a perennial allergen within the one year prior to the screening visit. (b) (4) Although the study was adequate for these aspects of study design, (b) (4)

6.1.3.3 Pivotal SAR EEU studies C-01-83 and C-03-52, SAR onset of action claim

These studies were single center, randomized, vehicle-controlled, double blind, parallel group, single dose, clinical studies utilizing an EEU. The patient populations included males and females, 16 years of age or older in study C-01-83, and 18 years of age and older in study C-03-52. Patients had at least a 2-year history of non-recalcitrant seasonal allergic rhinitis during the fall pollen season. Patients had to have allergy to short ragweed pollen, as defined by a positive history and skin test. These studies were adequately controlled to assess efficacy. The design of the study, with frequent patient self-assessment of symptom severity after administration of study treatment, and 12-hour duration of symptom assessments, were adequate to assess onset of action for the SAR indication. Inclusion and exclusion criteria and study demographics were adequate to allow for results to be generalized to the population of SAR patients in the proposed labeling.

6.1.3.4 Supportive study C-00-70, possible (b) (4) of olopatadine

This was a single center, randomized, active and vehicle-controlled, single blind, three phase, two way crossover, single dose, nasal challenge study. Patients were adult volunteers, 18-65 years of age, with a history of SAR to short ragweed or Timothy grass pollen. The product used in the study was not the to-be-marketed product. This study was primarily an observational study and was not formally powered to identify a difference between treatments. There was no correction for multiplicity and no primary comparison was specified. Study treatment was administered to asymptomatic SAR patients immediately prior to allergen challenge and not to patients who were experiencing symptoms of SAR. The allergen challenges were also performed with single doses of allergen extracts; quite different than the manner and amount of exposure that SAR patients receive during the natural pollen season. The clinical relevance of this information is uncertain and it is unclear how this information would guide or instruct the practitioner to use this medication more knowledgeably. (b) (4)

6.1.4 Efficacy Findings

6.1.4.1 Pivotal SAR studies, C-02-37 and C-02-10

6.1.4.1.1 Primary efficacy endpoint

Results for the primary efficacy endpoint, percent change from baseline in the reflective TNSS, are summarized in Table 4. There was a statistically significant difference from vehicle placebo for olopatadine 0.6% and olopatadine 0.4% in both studies. The difference from vehicle placebo for olopatadine 0.6% was -12.2% in study C-02-37 and -11.4 in study C-02-10. The difference from vehicle placebo for olopatadine 0.4% was -8.8% in study C-02-37 and -8.8% in study C-02-10. A dose response effect was noted in both studies, with olopatadine 0.6% showing a greater difference from vehicle placebo than olopatadine 0.4%.

Table 4 Primary efficacy endpoint, difference from vehicle placebo in percent change in reflective TNSS over treatment period, ITT group, pivotal SAR efficacy and safety studies C-02-37 and C-02-10 [Module 5, Volume 47, page 106; Module 5, Volume 56, page 108]

	Difference from vehicle placebo in percent change in reflective TNSS			
	Olopatadine 0.4%		**Olopatadine 0.6%**	
	Study C-02-37	**Study C-02-10**	**Study C-02-37**	**Study C-02-10**
Difference from vehicle placebo, percent change from baseline	-8.8	-8.9	-12.2	-11.4
p value	0.0037	0.0002	<0.0001	<0.0001

Mean change from baseline in the reflective TNSS is summarized in Table 5. There was a statistically significant difference from vehicle placebo for olopatadine 0.6% and olopatadine 0.4% in both studies. The difference from vehicle placebo for olopatadine 0.6% was -1.0 in study C-02-37 and -1.1 in study C-02-10, with effect sizes of 8.3% and 9.2%, respectively. The difference from vehicle placebo for olopatadine 0.4% in both studies was less than that for olopatadine 0.6% (-0.8 in study C-02-37 and -0.9 in study C-02-10, with effect sizes of 6.7% and 7.5%, respectively), consistent with a dose response effect.

Table 5 Mean change in reflective TNSS over treatment period, ITT group, C-02-37 and C-02-10 [Module 5, Volume 47, page 109; Module 5, Volume 56, page 111]

	Difference from vehicle placebo in change in reflective TNSS			
	Olopatadine 0.4%		**Olopatadine 0.6%**	
	Study C-02-37	**Study C-02-10**	**Study C-02-37**	**Study C-02-10**
Difference from vehicle placebo, change from baseline	-0.8	-0.9	-1.0	-1.1
Effect size*	6.7%	7.5%	8.3%	9.2%
p value	0.0031	0.0002	0.0002	<0.0001

* Effect size = $\frac{\text{Difference from vehicle placebo, change from baseline} \times 100}{\text{Maximum change from baseline} = 12}$

These data provide convincing evidence of efficacy in replicate for olopatadine 0.6% and 0.4%. There is an efficacy advantage for olopatadine 0.6%, the applicant's proposed dose, over olopatadine 0.4%. The additional analysis provides evidence that the degree of efficacy is clinically relevant. The effect sizes for olopatadine 0.6% and 0.4% were in the range expected

for antihistamine drug products. The dose response effect noted provides support for the applicant's choice to seek approval of the olopatadine 0.6% over olopatadine 0.4%.

Decreased efficacy in patients 12-17 years of age was noted in the pivotal SAR efficacy and safety studies, but the number of patients in this age group was small and the finding is probably not relevant given the overall efficacy findings among the other age groups. There was no difference in efficacy among patients 18-64 years of age or among patients of different genders or races. There were few patients 65 years of age or greater.

6.1.4.1.2 Secondary efficacy endpoints

6.1.4.1.2.1 Instantaneous TNSS

The difference from vehicle placebo in the percent change from baseline in the instantaneous TNSS was similar in studies C-02-37 and C-02-10 for olopatadine 0.6% and olopatadine 0.4%. The difference from vehicle placebo was -9.7% in study C-02-37 and -10.4 in study C-02-10 for olopatadine 0.6% and the difference from vehicle placebo was -8.0% in study C-02-37 and -8.5% in study C-02-10 for olopatadine 0.4% [Module 5, Volume 47, page 112; Module 5, Volume 56, page 114]. These values are comparable, but smaller than those for the primary efficacy endpoint and support the end of dosing interval efficacy for olopatadine 0.6% and olopatadine 0.4%.

Table 6 Percent change in instantaneous TNSS over treatment period, ITT group, C-02-37 and C-02-10 [Module 5, Volume 47, pages 112, 171; Module 5, Volume 56, pages 114, 175]

	Difference from vehicle placebo in percent change in instantaneous TNSS			
	Olopatadine 0.4%		**Olopatadine 0.6%**	
	Study C-02-37	**Study C-02-10**	**Study C-02-37**	**Study C-02-10**
Difference from vehicle placebo, percent change from baseline	-8.0	-8.5	-9.7	-10.4

6.1.4.1.2.2 Percent change from baseline for reflective individual severity scores

The percent change from baseline in the reflective individual severity scores for patient diary symptoms of runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes, averaged across all days for Studies C-02-37 and C-02-10 are summarized in Table 7.

Table 7 Percent change in reflective individual severity scores over treatment period, ITT group, C-02-37 and C-02-10 [Module 5, Volume 47, pages 116, 120, 124, 128, 132, 136; Module 5, Volume 56, pages 118, 122, 126, 130, 134, 140]

Individual Symptom	Difference from vehicle placebo in percent change in reflective individual severity scores			
	Olopatadine 0.4%		Olopatadine 0.6%	
	Study C-02-37	Study C-02-10	Study C-02-37	Study C-02-10
Runny nose	-8.1	-3.9	-13.6	-11.6
Stuffy nose	-3.7	-8.1	-2.5	-8.5
Itchy nose	-10.3	-11.4	-11.7	-13.0
Sneezing	-20.5	-14.6	-22.7	-16.9
Itchy eyes	-5.0	-13.0	-11.2	-18.4
Watery eyes	-7.2	-11.9	-9.6	-13.9

For the applicant's proposed concentration, olopatadine 0.6%, the difference from vehicle placebo in percent change from baseline in reflective individual severity scores was greatest for sneezing and smallest for stuffy nose. Improvements in individual symptom scores were noted for runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes. Improvements in stuffy nose scores were smaller than those for the other individual symptoms. Except for stuffy nose scores in study C-02-37, effect sizes were similar to, or greater than, those noted for the percent change from baseline for the reflective TNSS, the primary efficacy endpoint in these studies.

For olopatadine 0.4%, the difference from vehicle placebo in percent change from baseline in reflective individual severity scores was greatest for sneezing and smallest for runny nose and stuffy nose. Improvements in individual symptom scores were noted for runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes. Improvements in runny nose and stuffy nose scores were smaller than those for the other individual symptoms. Except for runny nose scores in study C-02-10, stuffy nose scores in study C-02-37, and itchy eyes scores in C-02-37, effect sizes were similar to, or greater than, those noted for the percent change from baseline for the reflective TNSS, the primary efficacy endpoint in these studies. Evidence of dose response effect in each of the studies was noted for all symptoms except stuffy nose.

The data suggest that olopatadine 0.6% has an efficacy advantage over olopatadine 0.4% in degree of effect and the number and types of individual symptoms for which there is evidence of efficacy. The dose response effect noted for each of the symptoms provides support for the applicant's choice to seek approval of the olopatadine 0.6% over olopatadine 0.4%.

(b) (4)

(b) (4)

6.1.4.2 Pivotal PAR study, C-01-92

(b) (4)

6.1.4.3 Pivotal EEU studies C-01-83 and C-03-52, SAR onset of action claim

The primary efficacy variable in these EEU studies was the change from baseline in the instantaneous TNSS [Module 5, Volume 37, page 45]. Results of the primary efficacy variable at each of the time points in Studies C-01-83 and C-03-52 are displayed in Figure 1 and Figure 2, respectively. In study C-01-83, a statistically significant difference from vehicle placebo in TNSS was noted at 90 minutes post-dose for olopatadine 0.6%. In study C-03-52, a statistically significant difference from vehicle placebo in TNSS was noted at 30 minutes post-dose for olopatadine 0.6%. The statistically significant differences were maintained at each of the remaining time points in the studies. The difference from vehicle placebo in TNSS for

olopatadine 0.6% at 90 minutes in these two studies was similar to the difference from vehicle placebo in TNSS over the treatment period noted in the two pivotal SAR efficacy and safety studies (approximately 1). This finding suggests that the effect noted at onset of action is clinically relevant. These data demonstrate, in replicate, an onset of action at 90 minutes post-dose for olopatadine 0.6%.

Based on these data, the applicant's proposed labeling contains a claim that (b) (4) The findings are not replicated. More importantly, the mechanisms of action of these drugs are quite different, and a comparison of their effect will not support a (b) (4), even if replicated.

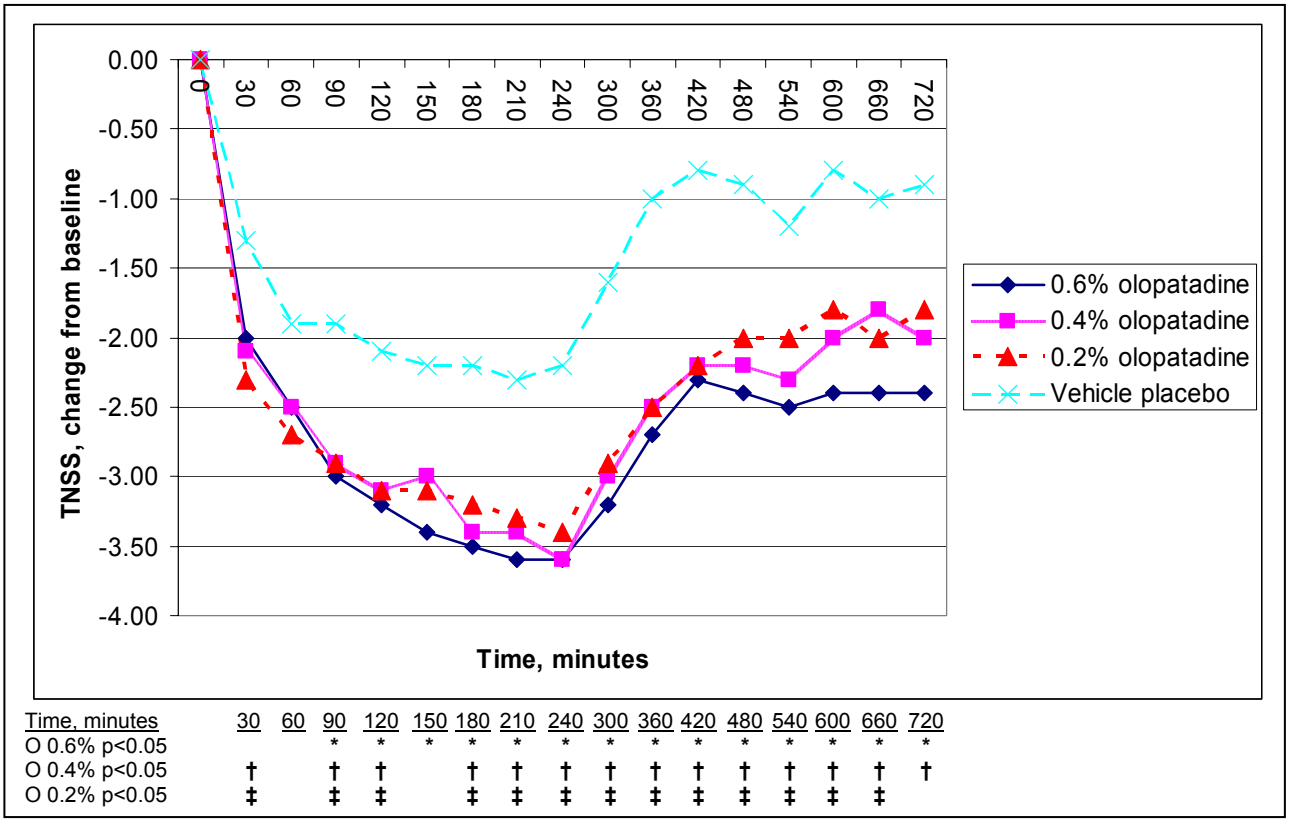

Figure 1 Change in baseline in TNSS, C-01-83 [plotted from data, Module 5, Volume 37, page 153]

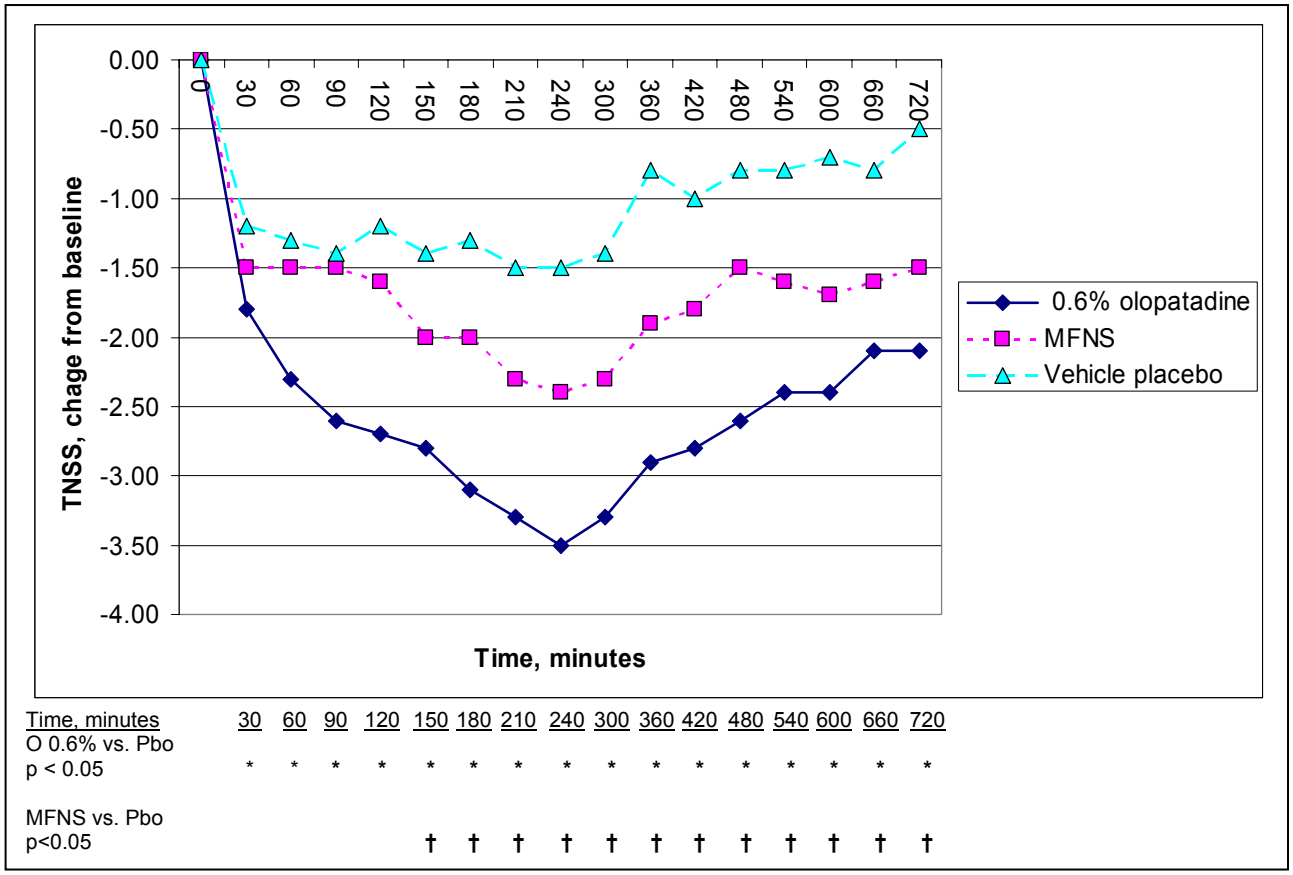

Figure 2 Change in baseline in TNSS, C-03-52 [plotted from data, Module 5, Volume 42, pages 209-211, 219-221]

6.1.4.4 Supportive study C-00-70, possible (b) (4) of olopatadine

The primary efficacy variables in this study included allergen-induced sneezes, allergen-induced changes in the levels of mast cell tryptase, albumin, and lysozyme in nasal lavage fluids. Secondary efficacy variables included allergen-induced changes in the levels of immunoreactive LTC_4 and histamine in nasal lavage fluids, and patient-assessed SAR symptom severity. The severity of SAR symptoms was measured using visual analog scales [Module 5, Volume 87, pages 1-6, 39-40, 52, 62]. Results from this study cannot be used to support a labeling or advertising claim. The olopatadine product used in the study was not the to-be-marketed product and the study was primarily an observational study, not powered to identify a difference between treatments. There was no correction for multiplicity and no primary comparison was specified. Although the applicant makes non-inferiority conclusions, these conclusions are not appropriate because the study was not designed as a non-inferiority study and no delta was specified. Other drawbacks of the study are that study treatment was administered to asymptomatic SAR patients immediately prior to allergen challenge; not to SAR patients who were experiencing symptoms. The allergen challenges were performed with single doses of allergen extracts; quite different from the manner and amount of exposure that SAR patients receive during the natural pollen season. Therefore, the clinical relevance of this information is uncertain and it is unclear how

this information would guide or instruct the practitioner to use this medication more knowledgeably.

6.1.5 Clinical Microbiology

This section is not relevant. There was no clinical microbiology review and the product is not an antimicrobial.

6.1.6 Efficacy Conclusions

The applicant's data support the efficacy of olopatadine 0.6% nasal spray and olopatadine 0.4% nasal spray for the treatment of symptoms of SAR. (b) (4) The applicant is only seeking approval of olopatadine 0.6%.

There was a statistically significant difference from vehicle placebo in the percent change from baseline in reflective TNSS and difference from vehicle placebo in mean change from baseline in reflective TNSS for olopatadine 0.6% in the pivotal SAR efficacy and safety studies. The differences from vehicle placebo in the percent change from baseline in reflective TNSS and mean change from baseline in reflective TNSS for olopatadine 0.4% in both studies were less than that for olopatadine 0.6%, but were statistically significant. These data provide convincing evidence of efficacy, in replicate, for olopatadine 0.6%, the applicant's proposed concentration and for olopatadine 0.4%. There is an efficacy advantage for olopatadine 0.6% over olopatadine 0.4%. The efficacy advantage provides support for the applicant's choice to seek approval of olopatadine 0.6% and not olopatadine 0.4%.

Decreased efficacy in patients 12-17 years of age was noted in the pivotal SAR efficacy and safety studies, but the number of patients in this age group was small and the finding is probably not relevant give the overall efficacy findings among the other age groups. There was no difference in efficacy among patients 18-64 years of age or among patients of different genders or races. There were few patients 65 years of age or greater.

The applicant's data support end of dosing interval efficacy for olopatadine 0.6% and olopatadine 0.4%. The difference from vehicle placebo in the percent change from baseline in instantaneous TNSS was similar for olopatadine 0.6% and olopatadine 0.4% in the pivotal SAR efficacy and safety studies.

Improvements in individual symptom scores were noted for runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes for olopatadine 0.6% and olopatadine 0.4%. Improvements in these individual symptoms were less for olopatadine 0.4%. Of all the individual symptoms, stuffy nose showed the least improvement in both treatment groups. Evidence of dose response effect in each of the studies was noted for all symptoms except stuffy nose. The data suggest that olopatadine 0.6% has an efficacy advantage over olopatadine 0.4% in degree of effect and the number and types of individual symptoms for which there is evidence of efficacy. The dose response effect noted for each of the symptoms provides support for the applicant's choice to seek approval of the olopatadine 0.6% over olopatadine 0.4%.

The results from the (b) (4) instrument do not support labeling or marketing claims. (b) (4)

(b) (4)

The results of the applicant's EEU studies support an onset of action claim. The data demonstrate, in replicate, an onset of action at 90 minutes post-dose for olopatadine 0.6%. A statistically significant difference from vehicle placebo in TNSS was noted at 90 minutes post-dose for olopatadine 0.6% in study C-01-83 and at 30 minutes in study C-03-52, and these differences were maintained at each of the remaining time points in the studies. The difference from vehicle placebo in TNSS for olopatadine 0.6% at 90 minutes was similar to the difference from vehicle placebo in TNSS over the treatment period noted in the two pivotal SAR efficacy and safety studies (approximately 1). This finding suggests that the effect noted at onset of action is clinically relevant.

The applicant's proposed labeling contains a claim that olopatadine 0.6% is (b) (4) The applicant's claim that olopatadine 0.6% is (b) (4) is not supported. The findings are not replicated, and more importantly, the mechanisms of action of these drugs are quite different. A comparison of their effect would not support a (b) (4) even if replicated.

The applicant's data do not support a labeling or advertising claim for (b) (4) The olopatadine product used in the study to support these claims was not the to-be-marketed product and the study was primarily an observational study. The design of this study is not adequate to support these claims. In addition, the clinical relevance of these effects is uncertain and it is unclear how this information would guide or instruct the practitioner to use this medication more knowledgeably.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The applicant's Integrated Summary of Safety consisted of integrated safety information from clinical studies in the applicant's drug development program. This safety information included adverse events, laboratory studies, physical examinations, nasal examinations, and ECGs. The applicant's Integrated Summary of Safety also included a review of worldwide postmarketing

adverse event reports for olopatadine HCl ophthalmic solution 0.1%, a review of postmarketing adverse event reports from Japan for olopatadine HCl 2.5 mg and 5 mg tablets, and a review of the published medical literature for safety information relevant to use of olopatadine. Safety findings are summarized immediately below and are addressed in depth in subsequent sections of this review.

The overall exposure to olopatadine nasal spray meets ICH and FDA guidelines and is sufficient to allow for assessment of safety. The exposure and the duration of exposure to olopatadine 0.6% nasal spray are also sufficient to allow for assessment of safety. The demographics of patients in the clinical program and exposure of subpopulations to olopatadine 0.6% nasal spray are adequate to provide an assessment of safety.

There was one death in the drug development program. A 41-year old woman who was treated with olopatadine 0.6% in long-term safety study C-01-92 underwent elective gastric bypass surgery to treat obesity. She developed abdominal pain, perforated gastric ulcer, bacterial peritonitis, and sepsis and died on Study Day (b) (6) This death does not identify a safety signal for olopatadine.

The incidence of non-fatal serious adverse events was similar in the olopatadine 0.6% (0.9%, 11/1163) and vehicle placebo BID (1.1%, 11/1008) groups. Surgical/medical procedure was the only non-fatal serious adverse event that occurred in more than one patient in any group. Serious adverse events did not identify a safety signal for olopatadine.

Epistaxis was the most common nasal adverse event that was reported at a frequency of ≥2% for olopatadine and more frequently than vehicle placebo in the pivotal efficacy and safety studies. Epistaxis was also common in the vehicle placebo group.

Both olopatadine 0.6% nasal spray and vehicle placebo appear to be irritating to the nose. Epistaxis, dry nose, and irritation of the throat were noted for olopatadine 0.6% at frequencies of greater than 1% and more commonly than in vehicle placebo. Rhinitis, sinusitis, and pharyngitis were noted at frequencies of 4% or greater in both olopatadine 0.6% and vehicle placebo groups. Epistaxis, dry nose, throat irritation, rhinitis, and pharyngitis, by themselves and at these frequencies, are not a serious safety concern. However more serious nasal adverse events, nasal ulceration and nasal septum perforation, were noted in the olopatadine drug development program.

Nasal ulceration was reported frequently in 19/1163 patients in the olopatadine 0.6% group (1.6%) and in 21/1008 patients in the vehicle placebo twice daily group (2.1%) in the overall clinical development program. Nasal septum perforation was noted in one patient treated with olopatadine 0.6% (0.1%, 1/1163) and in two patients treated with vehicle placebo (0.2%, 2/1008) in the overall clinical development program. All of the patients who had nasal septum perforation were enrolled in study C-01-92, the one-year, long term (b) (4) safety study. Non-clinical data suggest that the product is toxic to the nasal mucosa and that the toxicity may be related to the povidone excipient in the formulation. Nasal septum perforation has never been seen during the development programs for non-steroid or corticosteroid nasal sprays for allergic

rhinitis. As a postmarketing adverse event, it is extremely rare for non-steroid nasal sprays and is uncommonly reported for corticosteroid nasal sprays with allergic rhinitis indications. Nasal ulceration and nasal septum perforation represent a major safety signal for olopatadine 0.6% nasal spray and are sufficient to affect the approvability of the application.

Children appear to be more sensitive to epistaxis and nasal ulceration from the formulation than adults, based on data from a study in children 6 to 11 years of age that was completed after submission of the NDA and summarized in the 120-day safety update.

Non-nasal adverse events reported at a frequency of ≥2% were taste perversion, cold syndrome, cough increased, flu syndrome, arthralgia, and dyspepsia. A dose response effect was noted for taste perversion and dyspepsia.

Events reported at a frequency of 1% to <2% were dry nose and irritation of the throat and were reported more frequently for olopatadine and more frequently than vehicle placebo in the pivotal efficacy and safety studies. Irritation of the throat was also common in the vehicle placebo group. Non-nasal adverse events reported at a frequency of 1 to <2% were otitis media, diarrhea, hyperemia of the eye, dermatitis, toothache, accidental injury, ear pain, myalgia, extremity pain, dizziness, hypertension, and depression and were similar in the olopatadine 0.6% and vehicle placebo groups. A dose response effect was not noted for these adverse events.

Adverse events related to anticholinergic effects of antihistamines include dry mouth, tachycardia, and urinary retention. These adverse events were infrequently seen in the clinical development program and occurred at similar frequencies in the active and vehicle placebo treatment groups.

Somnolence was reported in the olopatadine clinical development program by 1.1% (13/1163) of patients treated with olopatadine nasal spray 0.6% and by 0.2% (2/1008) of those treated with vehicle placebo nasal spray twice daily. The incidence of somnolence in patients treated with vehicle placebo twice daily was lower than normally seen in SAR trials of antihistamines in adults. The low incidence of somnolence in the vehicle placebo group in the olopatadine program suggests that the study may have been less sensitive in picking up this adverse event. It is possible that the design of the patient medical problem log may have led people to not record less severe adverse events such as somnolence.

Somnolence was noted in the high dose cardiac safety studies in this application by 13.5% (7/166) of patients treated with olopatadine 5 mg or 20 mg twice daily by mouth. Somnolence was the most common adverse event in the clinical development program for olopatadine 2.5 mg and 5 mg tablets, which are approved in Japan. A cross-study comparison shows that the C_{max} and AUC for olopatadine 0.6% are 16% and 18%, respectively, of that for olopatadine tablets 5 mg orally. There is clearly less systemic exposure to olopatadine 0.6% nasal spray than to the oral product, however, the degree of systemic exposure is sufficient to provide additional support to the conclusion that the incidences of somnolence noted in the clinical development program are not due to chance.

At the dose and concentration proposed for marketing, olopatadine 0.6% nasal spray appears to be associated with somnolence infrequently, but at a rate higher than vehicle placebo. The frequency of somnolence is sufficiently low to be excluded from the table of common adverse events in the ADVERSE REACTIONS section of the olopatadine 0.6% nasal spray label, but is different enough from vehicle placebo that a "non-sedating" claim would be not supported if the product were to be approved.

There were no safety concerns specific to patients 12-17 years of age, 18-64 years of age, or 65 years of age or older, although there were relatively few patients in the studies 65 years of age or older. The types and frequencies of common adverse events were similar among these populations. There were no safety concerns specific to patients of female or male gender. The types and frequencies of common adverse events were similar in both genders. There were no safety concerns specific to patients of Caucasian, Black, Hispanic, Asian, or Other races noted. There were relatively few patients in the studies of Asian and Other races. The types and frequencies of common adverse events were similar among patients of these races.

Review of hematology, blood chemistry, and urinalysis data from the studies in the application revealed no safety signal. Vital signs data from six natural exposure SAR and PAR studies in this application and shift table and scatter plot analyses of vital signs data from the three pivotal SAR and PAR (b) (4) safety studies did not reveal safety concerns.

An integrated analysis of ECG data from the supportive SAR studies in this application and a analysis of ECG data from the pivotal, one-year PAR study showed no evidence of a safety signal. There were two high dose cardiac safety studies in this application. Data from these studies suggest that there is no QTc prolongation with doses of olopatadine up to 20 mg twice daily by mouth for 14 days. The applicant's summary of patients with ECG abnormalities in studies C-00-10, C-00-33, and C-01-05 was incomplete.

A review of postmarketing and spontaneous adverse event reports for olopatadine ophthalmic solution 0.1%, Patanol®, did not identify a safety signal relevant to olopatadine nasal spray. Japanese postmarketing adverse event reports for olopatadine 2.5 and 5 mg tablets suggest that olopatadine tablets may be associated with hepatic function abnormalities. The Japanese regulatory agency added hepatic function abnormal, liver disorder, acute hepatitis, and jaundice to the product label for olopatadine 2.5 mg and 5 mg tablets based on these postmarketing reports. There was no signal for hepatic function abnormality in the olopatadine nasal spray program. If the product were to be approved, postmarketing adverse event reports for olopatadine nasal spray should be monitored for cases of hepatic function abnormalities.

In summary, the applicant has not established the safety of olopatadine 0.6% nasal spray. The product appears to be toxic to the nasal mucosa and it is associated with nasal ulceration and nasal septum perforation. The preclinical data suggest that the toxicity is related to the product formulation and not to olopatadine drug substance. The clinical findings support this assessment because the nasal events were present in patients treated both with olopatadine 0.6% nasal spray and vehicle placebo nasal spray. The safety data do not support approval of this application. Although the nasal septum perforations occurred only in the one-year PAR study and not in the

two-week SAR studies, an attempt to manage the risk of this adverse event by limiting its use to a short period of treatment would not be an option. The duration of treatment with the product in the general population would be longer than in the two-week studies in the development program. Patients with seasonal allergic rhinitis commonly have symptoms that last through more than one season of symptoms, and it is reasonable that many practitioners might use the product for PAR, even if the product was approved only for treatment of symptoms of SAR. The applicant will need to develop a formulation that is not toxic to the nasal mucosa, demonstrate its clinical safety, and provide evidence to support its efficacy before the product may be considered for approval.

Given the safety signal for nasal ulceration and nasal septum perforation, pediatric studies in children 2 to 11 years of age should be deferred until the applicant has developed a formulation that is not toxic to the nasal mucosa and demonstrated its clinical safety in older patients.

7.1.1 Deaths

There was one death in the drug development program for olopatadine nasal spray. Patient #3206-7818 was a 41-year old woman with carpal tunnel syndrome, sinus headaches, gastric reflux, SAR, obesity, and menstrual cramps who was treated with olopatadine 0.6% in long-term safety study C-01-92. She underwent elective gastric bypass surgery on Study Day (b) (6) to treat obesity. She developed abdominal pain, perforated gastric ulcer, bacterial peritonitis, and sepsis on Study Day (b) (6). Sepsis resulted in death of the patient on Study Day (b) (6). This adverse event was considered not to be related to study treatment [Module 2, Volume 7, Section 2.7.4.2, page 75; Module 5, Volume 65, page 198; Module 5, Volume 69, page 1417; Module 5, Volume 143, pages 28, 84].

There was one death among the postmarketing adverse reports from Japan for olopatadine tablets. The patient (Report No. A20030225) was a 44 year-old male who was treated with a daily dose of 10 mg of olopatadine tablets for allergic rhinitis. He was found to be dead in bed on the morning of his (b) (6) treatment day. He was diagnosed as having a myocardial infarction. He had a prior history of cardiovascular disease, including PR interval prolongation and right bundle branch block and ST elevation in leads V2 and V3. The event was not attributed to olopatadine [NDA 21-861 BB, 4/11/05, Volume 1, Section Dec 2002/Dec 2003, page 23 and Appendix 2-2, page 6].

There were no deaths identified in the applicant's review of the published medical literature for safety information relevant to use of olopatadine [NDA 21-861, N-000 BB, 4/11/05, Volume 3, Question 2 Response, page 1].

Deaths did not identify a safety signal for olopatadine.

7.1.2 Other Serious Adverse Events

There were 23 non-fatal serious adverse events in 17 patients in clinical studies in the drug development program for olopatadine nasal spray. These data are summarized in Table 10. Twenty-one of these non-fatal serious adverse events occurred in long-term safety study C-01-92, one occurred in study C-01-05, and one occurred in study C-02-10. The incidence of these adverse events was low in the drug development program. The incidence was similar in the olopatadine 0.6% (0.9%, 11/1163) and vehicle placebo BID (1.1%, 11/1008) groups. Surgical/medical procedure was the only non-fatal serious adverse event that occurred in more than one patient in any group.

Table 10 Serious adverse events in clinical development program of olopatadine nasal spray [Module 2, Volume 6, Section 2.7.4, pages 11-14; Module 2, Volume 7, Section 2.7.4.2, pages 77-78]

Serious adverse event	Olopatadine 0.6% N = 1163		Vehicle placebo BID N = 1008		Azelastine 0.1% BID N = 147	
	n	(%)	n	(%)	n	(%)
All serious adverse events	11	(0.9)	11	(1.1)	1	(0.7)
Patients with serious adverse events	8	(0.7)	8	(0.8)	1	(0.7)
Surgical/medical procedure	2	(0.2)	1	(0.1)	0	(0)
Appendicitis	1	(0.1)	1	(0.1)	0	(0)
Biliary pain	1	(0.1)	1	(0.1)	0	(0)
Syncope	1	(0.1)	1	(0.1)	0	(0)
Heart failure	1	(0.1)	0	(0)	0	(0)
Supraventricular tachycardia	1	(0.1)	0	(0)	0	(0)
Hernia	1	(0.1)	0	(0)	0	(0)
Gastritis	1	(0.1)	0	(0)	0	(0)
GI disorder	1	(0.1)	0	(0)	0	(0)
Abdominal pain	1	(0.1)	0	(0)	0	(0)
Myocardial infarction	0	(0)	1	(0.1)	0	(0)
Bone fracture	0	(0)	1	(0.1)	0	(0)
Overdose	0	(0)	1	(0.1)	0	(0)
Heart block	0	(0)	1	(0.1)	0	(0)
Tachycardia	0	(0)	1	(0.1)	0	(0)
Endometrial disorder	0	(0)	1	(0.1)	0	(0)
Hypesthesia	0	(0)	1	(0.1)	0	(0)
Angina pectoris	0	(0)	0	(0)	1	(0.7)

There was one serious adverse event identified in the applicant's review of the published medical literature for safety information relevant to use of olopatadine. A patient in a clinical study of olopatadine ophthalmic solution developed ocular discomfort in the eye upon installation of the medication. The patient withdrew from the study. The publication did not state which criteria made the event serious, however [NDA 21-861, N-000 BB, 4/11/05, Volume 3, Question 2 Response, page 1].

Serious adverse events did not identify a safety signal for olopatadine.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The applicant provided a summary of dropouts from the three pivotal efficacy and safety studies, studies C-02-37, C-02-10, and C-01-92. These data are summarized in Table 11. There was a higher percentage of dropouts in the olopatadine 0.6% and the vehicle placebo groups than the olopatadine 0.4% group because the olopatadine 0.6% and vehicle placebo groups included data from study C-01-92, a one-year study. Olopatadine 0.4% was used only in studies C-02-37 and C-02-10, which were two-week studies. Treatment failure was the most common reason for dropouts in the olopatadine 0.6% and vehicle placebo groups.

Table 11 Dropouts from pivotal efficacy and safety studies, C-02-37, C-02-10, and C-01-92 [Module 2, Volume 6, Section 2.7.3, pages 62-65]

Reason for dropout	Olopatadine 0.6% N = 866		Olopatadine 0.4% N = 418		Vehicle placebo N = 882	
	n	(%)	n	(%)	n	(%)
Total	142	(16.4)	13	(3.1)	169	(19.2)
Treatment failure	37	(4.3)	1	(0.2)	46	(5.2)
Adverse event	32	(3.7)	7	(1.7)	28	(3.2)
Lost to follow-up	31	(3.6)	2	(0.5)	35	(4.0)
Patient decision	21	(2.4)	2	(0.5)	27	(3.1)
Protocol violation	12	(1.4)	0	(0)	12	(1.3)
Other	9	(1.0)	1	(0.2)	20	(2.3)

7.1.3.2 Adverse events associated with dropouts

Adverse events resulting in dropouts in the clinical development program for olopatadine nasal spray and occurring in two or more patients in any group are summarized in Table 12. Data in the table are entered as numbers of patients because the frequencies of these events were low. The most frequent adverse events resulting in dropout for olopatadine 0.6% was headache, taste perversion, nasal discomfort, and epistaxis. Nasal discomfort also resulted in dropouts in the vehicle placebo group. There were two patients in the olopatadine 0.6% group and two patients in the vehicle placebo group that dropped out due to nasal ulceration. There also were two patients in the vehicle placebo group that dropped out because of nasal septum disorder. Both of these patients had nasal septum perforations and were enrolled in the long-term (b) (4) safety study C-01-92. These adverse events are discussed in detail in Section 7.1.6, Section 10.1.3.15.6.2, and Section 10.1.3.15.6.4 of this review. These data suggest that olopatadine 0.6% is associated with taste perversion and indicate that olopatadine 0.6% and vehicle placebo are irritating to the nasal mucosa. The occurrences of nasal ulcerations and nasal septum perforations are important and significant safety signals for this product.

There were two patients with short non-sustained episodes of ventricular tachycardia lasting a few seconds in the olopatadine group in the cardiac safety study, C-00-23. One of the patients had a ventricular triplet prior to receiving treatment with olopatadine, suggesting a pre-existing condition. One patient in the vehicle placebo group experienced a short, non-sustained episode of

ventricular tachycardia. These episodes were detected during Holter monitoring [Module 5, Volume 25, pages 65, 68, 69, 72]. It is likely that the short non-sustained episodes of ventricular tachycardia would not have been detected if Holter monitoring was not performed and it is likely that they do not represent a safety signal. More information may be found in Section 10.1.12 of this review.

Table 12 Adverse events resulting in dropouts and occurring in two or more patients in any treatment group, clinical development program for olopatadine nasal spray [Module 2, Volume 7, Section 2.7.4.2, pages 79-86]

Adverse event resulting in dropout	Olopatadine 0.6% N = 1163 n	Olopatadine 0.4% N = 510 n	Olopatadine 0.2% N = 130 n	Olopatadine 0.1% N = 360 n	Olopatadine oral or iv N = 166 n	Azelastine 0.1% N = 147 n	Vehicle placebo* N = 1923 n
Headache	4	1		2		3	9
Taste perversion	4		1				
Nasal discomfort	3						2
Epistaxis	3			2			4
Sinusitis	2	2		1		1	8
Nasal ulcer	2						3
Flu syndrome	2						
Dizziness	1	1	1	1			3
Nausea	1		1				2
Vomiting	1						2
Asthma	1					2	1
Migraine	1						3
Infection		1		2		1	5
Pharyngitis		1		2			1
Bronchitis		1					3
Asthenia				1			2
Tachycardia ventricular					2		1
Nasal septum disorder							2
Abdominal pain							2
Urticaria							2

7.1.3.3 Other significant adverse events

Other than dropouts due to adverse events, which are discussed in Section 7.1.3.2 above, there were no events or laboratory abnormalities that led to any other intervention such as dose reduction or significant additional concomitant therapy.

7.1.4 Other Search Strategies

There were two high dose cardiac safety studies in this application, Studies C-00-23 and C-02-54.

Study C-00-23 was a randomized, double blind, placebo controlled, crossover, multiple dose, phase 1, PK/PD study of cardiovascular safety of olopatadine solution, 5 mg orally or placebo in healthy subjects. Data from this study suggest that there is no QTc prolongation with olopatadine 5 mg twice daily by mouth, approximately twice the dose administered by the labeled dose for

the proposed nasal spray product. Details may be found in Section 7.1.12 and Section 10.1.12 of this review.

Study C-02-54 was a randomized, double blind, placebo controlled, crossover, multiple dose, phase 1, PK/PD study of cardiovascular safety of olopatadine solution, 20 mg orally or placebo in healthy subjects. Data from this study suggest that there is no QTc prolongation with olopatadine 20 mg twice daily by mouth for 14 days. This dose is approximately eight times the dose administered by the proposed nasal spray product. Details may be found in Section 7.1.12 and Section 10.1.13 of this review and in Dr. Sandra Suarez's Clinical Pharmacology and Biopharmaceutics Review [S. Suarez, Ph.D., Clinical Pharmacology and Biopharmaceutics Review NDA 21-861, N-000, 12/24/04].

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

The bulk of the safety data in this application comes from pivotal efficacy and safety studies C-02-37, C-02-10, and C-01-92. Adverse events, both volunteered and elicited, were collected at study visits in these studies. Adverse events were not recorded by patients in patient medical problem logs in study C-02-37. Adverse events were recorded by patients in patient medical problem logs in Studies C-02-10 and 01-92 [Module 5, Volume 47, pages 74, 75, 195; Module 5, Volume 56, pages 76-78, 194; [Module 5, Volume 65, pages 3, 62, 66-67, 76-78].

The patient medical problem logs used in these studies instructed patients to list new medical problems and medications that they took since their last visit and gave "sprained ankle treated with Tylenol" as an example [NDA 21-861, N-000 BZ, 7/14/05, page not numbered]. The example could have led some patients to record only more severe medical problems or medical problems that required treatment with medications. If so, it is possible that some milder adverse events may not have been reported or recorded by patients.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded using a modified COSTART dictionary [Module 2, Volume 7, Section 2.7.4.2, page 2]. In the course of the review, no discrepancies were noted between literal terms for adverse events and the COSTART terms. Categorization and coding of adverse events was adequate.

7.1.5.3 Incidence of common adverse events

Adverse events occurring in the clinical development program for olopatadine at a frequency of ≥2.0% for olopatadine 0.6% nasal spray are summarized in Table 13 [Module 2, Volume 7, Section 2.7.4.2, pages 55-58]. Epistaxis and taste perversion were the most common adverse events for olopatadine nasal spray 0.6%. Epistaxis was also noted in other concentrations of olopatadine, in azelastine nasal spray 0.1% twice daily, and in vehicle placebo. Infection, cold

syndrome, rhinitis, sinusitis, and pharyngitis were also common adverse events for olopatadine nasal spray 0.6% and were noted in other concentrations of olopatadine nasal spray and in vehicle placebo. Frequencies of these events were fairly similar in the olopatadine 0.6% and vehicle placebo groups. These events are common in the general population and in patients with allergic rhinitis. In addition, these figures include data from approximately 450 patients in olopatadine 0.6% and vehicle placebo groups in the one year efficacy and safety study C-01-92. One would expect a fair number of patients to report symptoms associated with upper respiratory tract infections in a study of this duration. There was no clear dose relationship in this cross-study comparison of adverse event frequencies. It should be noted however, that dose-response effects were noted for taste perversion, cold syndrome, and cough increased in study C-02-37 and for taste perversion, rhinitis, and urinary tract infection in study C-02-10 (Section 10.1.1.14.7.2 and Section 10.1.2.15.7.2 of this review).

Epistaxis is associated with other nasal sprays approved for allergic rhinitis indications. The incidence of epistaxis noted in labeling of nasal sprays approved in adults for allergic rhinitis indications range from 2.0% for Astelin Nasal Spray 2 sprays each nostril twice daily to 11% for Nasonex 200 mcg once daily. Incidences of epistaxis in vehicle placebo in adults with these approved products range from 1.4% for Astelin vehicle placebo to 6% for Nasonex vehicle [Astelin Product Label, Nasonex Product Label]. Epistaxis, by itself, is not a safety concern unless associated with more serious nasal adverse events such as nasal ulceration and nasal septum perforation.

Taste perversion or bitter taste is also associated with other non-corticosteroid nasal sprays approved for rhinitis indications. Bitter taste was reported by 19.7% of patients in the pivotal SAR studies for the Astelin Nasal Spray drug development program. Bitter taste was noted in the Atrovent 0.03% and 0.06% Nasal Spray 0.06% programs, but at incidences of less than 2% and 1%, respectively [Astelin Product Label, Atrovent Nasal Spray Product Label]. Taste perversion is not a safety concern, but could result in poor patient acceptance of the product.

Somnolence and anticholinergic effects, such as dry mouth and urinary retention were not among adverse events reported in 2% or more of patients treated with olopatadine 0.6% nasal spray. These adverse events will be addressed below in Section 7.1.6 of this review.

Table 13 Adverse events occurring in the clinical development program for olopatadine at a frequency of ≥2.0% for olopatadine 0.6% nasal spray [Module 2, Volume 7, Section 2.7.4.2, pages 55-58]

Adverse event	O 0.6% BID/QD N = 1163 n (%)	O 0.4% BID/QD N = 510 n (%)	O 0.2% BID N = 43 n (%)	O 0.2% QD N = 130 n (%)	O 0.1% BID N = 186 n (%)	O 0.1% QD N = 174 n (%)	O iv/po N = 166 n (%)	E 0.05% QD N = 12 n (%)	Az 0.1% BID N = 147 n (%)	Az 0.1% QD N = 30 n (%)	MFNA 50 mcg QD N = 142 n (%)	Veh Pbo BID N = 1008 n (%)	Veh Pbo QD N = 369 n (%)	Veh screen BID N = 546 n (%)	V po N = 140 n (%)
Epistaxis	106 (9.1)	16 (3.1)		3 (2.3)	13 (7.0)	9 (5.2)			12 (8.2)			68 (6.7)	11 (3.0)	8 (1.5)	
Taste perversion	102 (8.8)	31 (6.1)	4 (9.3)	4 (3.1)	13 (7.0)	5 (2.9)			39 (26.5)			7 (0.7)			
Infection	88 (7.6)	4 (0.8)			8 (4.3)	5 (2.9)			8 (5.4)			93 (9.2)	5 (1.4)	3 (0.5)	
Cold syndrome	80 (6.9)	4 (0.8)	1 (2.3)			2 (1.1)			2 (1.4)			78 (7.7)		1 (0.2)	
Headache	80 (6.9)	27 (5.3)	2 (4.7)	5 (3.8)	19 (10.2)	10 (5.7)	6 (3.6)		13 (8.8)	1 (3.3)	2 (1.4)	94 (9.3)	16 (4.3)	17 (3.1)	4 (2.9)
Rhinitis	66 (5.7)	5 (1.0)		1 (0.8)	5 (2.7)	6 (3.4)	3 (1.8)		3 (2.0)			76 (7.5)	6 (1.6)		
Sinusitis	58 (5.0)	3 (0.6)			2 (1.1)				3 (2.0)	1 (3.3)		65 (6.4)	1 (0.3)	6 (1.1)	
Pharyngitis	46 (4.0)	9 (1.8)			7 (3.8)	5 (2.9)			6 (4.1)			52 (5.2)	5 (1.4)	1 (0.2)	
Pain back	29 (2.5)	1 (0.2)	1 (2.3)		4 (2.2)	2 (1.1)	1 (0.6)					35 (3.5)	1 (0.3)	2 (0.4)	2 (1.4)
Cough increased	28 (2.4)	4 (0.8)			1 (0.5)	4 (2.3)						19 (1.9)	5 (1.4)	1 (0.2)	
Flu syndrome	27 (2.3)											24 (2.4)	1 (0.3)	1 (0.2)	
Bronchitis	27 (2.3)	2 (0.4)							2 (1.4)			32 (3.2)		3 (0.5)	
Allergy	25 (2.1)					1 (0.6)						30 (3.0)			
Arthralgia	25 (2.1)				1 (0.5)							13 (1.3)			
Pain	23 (2.0)	5 (1.0)			3 (1.6)	4 (2.3)	4 (2.4)		4 (2.7)			30 (3.0)	1 (0.3)	1 (0.2)	

O: Olopatadine E: Emedastine Az: Azelastine MFNA: Mometasone furoate nasal spray Veh pbo: Vehicle placebo

7.1.5.4 Common adverse event tables

Adverse events occurring in pivotal efficacy and safety studies C-02-37, C-02-10, and C-02-92 were integrated to arrive at the table to be used in the ADVERSE REACTIONS section in the applicant's proposed labeling [Module 1, Volume 1, Section 3.B. Prescribing Information, page 10]. The proposed labeling includes adverse events for olopatadine 0.6% and vehicle placebo, but not olopatadine 0.4%.

Adverse events occurring at a frequency of ≥2% and more frequently in olopatadine 0.6% than in vehicle placebo in the pivotal efficacy and safety studies are summarized in Table 14. Epistaxis was the most common nasal adverse event for olopatadine 0.6% in this analysis. Epistaxis was also common in the vehicle placebo group. The most common non-nasal adverse events for olopatadine 0.6% in this analysis were taste perversion, cold syndrome, cough increased, flu syndrome, arthralgia, and dyspepsia. A dose response effect was noted for taste perversion and dyspepsia. The frequencies of cold syndrome and flu syndrome were fairly similar for the olopatadine 0.6% and vehicle placebo groups.

Table 14 Adverse events occurring at a frequency of ≥2% and more frequently in olopatadine 0.6% than in vehicle placebo in pivotal efficacy and safety studies, C-02-37, C-02-10, and C-01-92 [Module 2, Volume 6, Section 2.7.4.2, pages 92-94]

Adverse event	Olopatadine 0.6% N = 866		Olopatadine 0.4% N = 418		Vehicle placebo N = 882	
	n	(%)	n	(%)	n	(%)
Nasal adverse events						
Epistaxis	102	(11.8)	16	(3.8)	64	(7.3)
Non-nasal adverse events						
Taste perversion	97	(11.2)	31	(7.4)	6	(0.7)
Cold syndrome	80	(9.2)	4	(1.0)	76	(8.6)
Cough increased	28	(3.2)	4	(1.0)	17	(1.9)
Flu syndrome	27	(3.1)	0	(0)	24	(2.7)
Arthralgia	25	(2.9)	0	(0)	13	(1.5)
Dyspepsia	18	(2.1)	6	(1.4)	10	(1.0)

Adverse events occurring at a frequency of 1% to <2% and more frequently in olopatadine 0.6% than in vehicle placebo in the pivotal efficacy and safety studies are summarized in Table 15. Dry nose and irritation of the throat were the most common adverse events for olopatadine 0.6% in this analysis. Irritation of the throat was also common in the vehicle placebo group. The most common non-nasal adverse events for olopatadine 0.6% in this analysis were otitis media, diarrhea, hyperemia of the eye, dermatitis, toothache, accidental injury, ear pain, myalgia, extremity pain, dizziness, hypertension, and depression. A dose response effect was not noted for these adverse events. The frequencies of these less common adverse events were fairly similar for the olopatadine 0.6% and vehicle placebo groups.

Table 15 Adverse events occurring at a frequency of 1% to <2% and more frequently in olopatadine 0.6% than in vehicle placebo in pivotal efficacy and safety studies, C-02-37, C-02-10, and C-01-92 [Module 2, Volume 6, Section 2.7.3, pages 92-94]

Adverse event	Olopatadine 0.6% N = 866		Olopatadine 0.4% N = 418		Vehicle placebo N = 882	
	n	(%)	n	(%)	n	(%)
Nasal adverse events						
Dry nose	12	(1.4)	1	(0.2)	2	(0.2)
Irritation throat	11	(1.3)	1	(0.2)	9	(1.0)
Non-nasal adverse events						
Otitis media	17	(2.0)	0	(0)	14	(1.6)
Diarrhea	15	(1.7)	0	(0)	9	(1.0)
Hyperemia eye	14	(1.6)	9	(2.2)	9	(1.0)
Dermatitis	13	(1.5)	0	(0)	9	(1.0)
Toothache	13	(1.5)	0	(0)	7	(0.8)
Injury accidental	12	(1.4)	5	(1.2)	11	(1.2)
Pain ear	12	(1.4)	3	(0.7)	8	(0.9)
Myalgia	11	(1.3)	2	(0.5)	11	(1.2)
Pain extremity	11	(1.3)	0	(0)	7	(0.8)
Dizziness	11	(1.3)	6	(1.4)	7	(0.8)
Hypertension	10	(1.2)	1	(0.2)	8	(0.9)
Depression	9	(1.0)	1	(0.2)	4	(0.5)

7.1.5.5 Identifying common and drug-related adverse events

Of the common adverse events noted in the pivotal studies, epistaxis, taste perversion, dyspepsia, and dry nose appear to be drug related. The frequencies of these adverse events for olopatadine 0.6% were sufficiently different from vehicle placebo to suggest causality. In addition, dose response effects were noted for taste perversion and dyspepsia. Epistaxis and dry nose are not unexpected adverse events for a topical antihistamine nasal spray. Epistaxis was also frequently reported in the vehicle placebo group, which suggests that the formulation may be irritating to the nasal mucosa. As previously noted, epistaxis is noted in labeling for nasal spray products approved for allergic rhinitis indications, both for active drug and vehicle placebo. Epistaxis, by itself, is not a safety concern unless associated with more serious nasal adverse events such as nasal ulceration and nasal septum perforation.

7.1.5.6 Additional analyses and explorations

There were no safety concerns specific to patients 12-17 years of age, 18-64 years of age, or 65 years of age or older noted in the adverse event data from the pivotal efficacy and safety studies for olopatadine 0.6%, although there were relatively few patients in the studies 65 years of age or older. The types and frequencies of common adverse events were similar among these populations [Module 2, Volume 8, Section 2.7.4.5, pages 2-17].

There were no safety concerns specific to patients of female or male gender noted in adverse event data from the pivotal efficacy and safety studies for olopatadine 0.6%. The types and frequencies of common adverse events were similar in both genders [Module 2, Volume 8, Section 2.7.4.5, pages 18-28].

There were no safety concerns specific to patients of Caucasian, Black, Hispanic, Asian, or Other races noted in adverse event data from the pivotal efficacy and safety studies for olopatadine 0.6%. There were relatively few patients in the studies of Asian and Other races. The types and frequencies of common adverse events were similar among patients of these races [Module 2, Volume 8, Section 2.7.4.5, pages 29-39].

7.1.6 Less Common Adverse Events

Infrequent adverse events of note occurring in the clinical development program for olopatadine nasal spray are summarized in Table 16.

Adverse events related to anticholinergic effects of antihistamines include dry mouth, tachycardia, and urinary retention. These adverse events were infrequently seen in the clinical development program, and occurred at similar frequencies in the active and vehicle placebo treatment groups.

Somnolence is associated with many older antihistamines, such as diphenhydramine, hydroxyzine, and chlorpheniramine. Some of the newer antihistamines are also associated with somnolence as well, but at lower frequencies or at doses higher than those recommended in the label. Somnolence was noted in the controlled clinical trials for Zyrtec® (cetirizine HCl) at a frequency of 13.7%, compared with 6.3% for placebo [Zyrtec® Product Label]. Claritin® (loratadine) may be associated with somnolence at doses greater than the labeled dose [Claritin® OTC Product Label].

Somnolence was reported in the olopatadine clinical development program by 1.1% (13/1163) of patients treated with olopatadine nasal spray 0.6% and by 0.2% (2/1008) of those treated with vehicle placebo nasal spray twice daily. Somnolence was noted in the high dose cardiac safety studies in this application by 13.5% (7/166) of patients treated with olopatadine 5 mg or 20 mg twice daily by mouth. Olopatadine clearly produces somnolence at high doses. At the dose and concentration propose for marketing, olopatadine 0.6% nasal spray appears to be associated with somnolence infrequently, but at a rate higher than vehicle placebo.

The applicant's review of the published medical literature for safety information relevant to use of olopatadine identified two studies of 10 mg oral doses of olopatadine on psychomotor function in relation to other antihistamines. Results of these studies showed that olopatadine was more sedating than chlorpheniramine, cetirizine, fexofenadine or bepotastine [5,6] [NDA 21-861, N-000 BB, 4/11/05, Volume 3, Question 2 Response, page 1].

Somnolence was the most common adverse event in the clinical development program for olopatadine 2.5 mg and 5 mg tablets, which are approved in Japan. In the drug development program for olopatadine 2.5 mg and 5 mg tablets, somnolence was reported by 11.6% (203/1746) of patients [NDA 21-861, N-000 BB, 4/11/05, Volume 1, Question 1, page 1; NDA 21-861, N-000 BB, 4/11/05, Volume 2, Allelock Tablets Product Label, page 3]. Somnolence was the most common adverse event noted in Japanese postmarketing clinical experience investigation for olopatadine 2.5 and 5.0 mg tablets, with frequencies in periodic safety updates

ranging from 3.8% to 7.6% [NDA 21-861, N-000 BB, 4/11/05, Volume 1, Dec 2003/Dec 2004 Periodic Safety Report, Appendix I, pages 1-3, Appendix II, page 1]. The dosage approved in Japan for treatment of allergic rhinitis, urticaria and itching resulting from cutaneous diseases is 5 mg twice daily [NDA 21-861, N-000 BB, 4/11/05, Volume 2, Allelock Tablets Product Label, page 2]. The proposed dose of olopatadine nasal spray 0.6%, two sprays each nostril twice daily or 2.4 mg twice daily, is 48% of the approved oral dose in Japan. The single dose mean C_{max} values for olopatadine 5 mg orally was 107.7 ng/mL and the mean AUC value was 326 ng.h/mL [NDA 21-861, N-000 BB, 4/11/05, Volume 2, Allelock Tablets Product Label, page 5]. For olopatadine 0.6% nasal spray, the mean C_{max} value was 17.5 ng/mL and the mean AUC value was 60.3 ng.h/mL [Clinical Pharmacology and Biopharmaceutics Review, S. Suarez, Ph.D., NDA 21-861, N-000, 12/24/04]. A cross-study comparison of these values shows that the C_{max} and AUC for olopatadine 0.6% are 16% and 18%, respectively, of those for olopatadine tablets 5 mg orally. There is clearly less systemic exposure to olopatadine 0.6% nasal spray than to the oral product, however, the degree of systemic exposure is sufficient to provide additional support to the conclusion that the incidences of somnolence noted in the clinical development program are not due to chance.

In addition, in Studies C-02-10 and C-01-92, patients were instructed by the Patient Problem Log to record medical problems and medications that were taken during the study. A sprained ankle treated with Tylenol was given as an example of such a problem [NDA 21-861, N-000 BZ, 7/14/05, page 3 and attachments]. It is possible that the example given by the form may have led people to not record less severe adverse events such as somnolence. The incidence of somnolence in patients treated with vehicle placebo twice daily was 0.2%. This incidence is lower than normally seen in SAR trials in adults. The frequencies of somnolence in adults in the placebo groups in the clinical programs for Allegra (fexofenadine HCl), Astelin (azelastine HCl), Zyrtec (cetirizine HCl), and Claritin (loratadine) were from 0.9%, 5.4%, 6%, and 6.3%, respectively [Product Labels for Allegra, Astelin, and Zyrtec; Prior Prescription Product Label for Claritin]. The lower incidence of somnolence in the vehicle placebo twice daily group in the olopatadine program suggests that the study may have been less sensitive in picking up this adverse event.

Table 16 Infrequent adverse events of note occurring in the clinical development program for olopatadine nasal spray [Module 2, Volume 9, Section 2.7.4.7, pages 67-269; Module 5, Volume 67, pages 779, 1042, 1073, 1083]

Adverse event	O 0.6% BID/QD N = 1163 n (%)	O 0.4% BID/QD N = 510 n (%)	O 0.2% BID N = 43 n (%)	O 0.2% QD N = 130 n (%)	O 0.1% BID N = 186 n (%)	O 0.1% QD N = 174 n (%)	O iv/po N = 166 n (%)	E 0.05% QD N = 12 n (%)	Az 0.1% BID N = 147 n (%)	Az 0.1% QD N = 30 n (%)	MFNA 50 mcg QD N = 142 n (%)	Veh Pbo BID N = 1008 n (%)	Veh Pbo QD N = 369 n (%)	Veh screen BID N = 546 n (%)	V po N = 140 n (%)
Anti-cholinergic adverse events															
Dry mouth	5 (0.4)	2 (0.4)			1 (0.5)	1 (0.6)			2 (1.4)			3 (0.3)		1 (0.2)	
Tachycardia	2 (0.2)			1 (0.8)								3 (0.3)		2 (0.4)	
Urinary retention												1 (0.1)			
Other adverse events of note															
Somnolence	13 (1.1)	8 (1.6)		1 (0.8)	2 (1.1)		7 (13.5)		2 (1.4)		1 (0.7)	2 (0.2)	2 (0.5)		
Other nasal adverse events															
Nasal ulcer	19 (1.6)				1 (0.5)	2 (1.1)			1 (0.7)			21 (2.1)	1 (0.3)	1 (0.2)	
Nasal septum disorder	5 (0.4)				4 (2.2)	2 (1.1)	1 (0.6)					6 (0.6)			
Nasal septum perforation*	1 (0.1)											2 (0.2)			

O: Olopatadine E: Emedastine Az: Azelastine MFNA: Mometasone furoate nasal spray Veh pbo: Vehicle placebo

*Nasal septum perforation is a subset of nasal septum disorder

The frequency of somnolence is sufficiently low to be excluded from the table of common adverse events in the ADVERSE REACTIONS section of the olopatadine 0.6% nasal spray label, but is different enough from vehicle placebo that a "non-sedating" claim would not be supported if the product were to be approved.

Other less common nasal adverse events of note in the clinical development program for olopatadine included nasal ulcer, nasal septum disorder, and nasal septum perforation.

Both olopatadine 0.6% and the vehicle placebo appear to be irritating to the nose. Epistaxis, dry nose, and irritation of the throat were noted for olopatadine 0.6% at frequencies of greater than 1% and more commonly than in vehicle placebo (Table 14 and Table 15). Rhinitis, sinusitis, and pharyngitis were noted at frequencies of 4% or greater in both olopatadine 0.6% and vehicle placebo groups (Table 13). Epistaxis, dry nose, throat irritation, rhinitis, and pharyngitis, by themselves and at these frequencies, are not a serious safety concern. However more serious nasal adverse events, nasal ulceration and nasal septum perforation, were noted in the drug development program.

Nasal ulceration was reported frequently in the olopatadine 0.6% group (1.6%, 19/1163) and the vehicle placebo twice daily group (2.1%, 21/1008) in the overall clinical development program. Nasal septum perforation was noted in one patient treated with olopatadine 0.6% (0.1%, 1/1163) and in two patients treated with vehicle placebo (0.2%, 2/1008) in the overall clinical development program.

All of the patients who had nasal septum perforations were enrolled in study C-01-92, the one-year, long term (b) (4) safety study. In C-01-92, nasal ulceration was reported in 4.1% of the olopatadine 0.6% group (19/459) and 4.5% of the vehicle placebo group (21/465). Nasal septum perforation was noted in one patient treated with olopatadine 0.6% (0.2%, 1/459) and in two patients treated with vehicle placebo (0.4%, 2/465). The incidences of nasal ulceration and nasal septum perforation in the long-term safety study would be more likely to represent what might be seen in the general population of patients with allergic rhinitis. Patients with seasonal allergic rhinitis commonly have symptoms that last through more than one season of symptoms, and it is reasonable that many practitioners might use the product for PAR, even if the product was approved only for treatment of symptoms of SAR. The duration of treatment with the product in the general population would be likely to be longer than the exposures in the two-week or shorter studies in the development program, where there were fewer cases of nasal ulceration and no cases of nasal septum perforation.

The applicant provided additional information about the three patients with nasal septum perforations, patients #3812-5905, #3795-8503, and #3652-9021, all in study C-01-92.

The applicant stated that patient #3812-5905 in study C-01-92 had a nasal septum perforation at baseline and had been enrolled in violation of the protocol. This patient was treated with olopatadine 0.6% "Nasal septal perforation" was added to the patient's baseline history in the Case Report Form (CRF) and the Exit Form in the CRF accurately reflected that the patient

exited the study with a protocol violation [NDA 21-861, N-000 BM, 7/18/05, Nasal Perforation Safety Information, page not numbered].

Reviewer comment:
This patient was enrolled at the study center of (b) (4) *The screening medical history, physical examination, and nasal examination performed on* (b) (6) *did not note a history of presence of nasal septum perforation. At Visit 3, on* (b) (6)*, the nasal examination "revealed nasal septal perforation was present at Visit #1 but inadvertently not recorded." Bleeding was initially marked as being absent but the CRF was changed to reflect that bleeding was present. There was no Data Clarification Form for this CRF change. At Visit 4, the nasal examination noted "Small perforation nasal septum. This was missed on initial PE. May have been secondary to trauma in past but not drug." The CRF originally noted that significant nasal abnormalities were absent, but the CRF was changed to state that significant nasal abnormalities were present. There was no Data Clarification Form for this CRF change. Other Data Clarification Forms were generated on June 21, 2004 and September 20, 2004, approximately* (b) (6) *after the original data was entered on the CRF. The Data Clarification Forms for June 21, 2004 change the response of inclusion/exclusion criteria met from "Yes" to "No" and add a comment that the nasal exam at Visit 3 revealed the nasal septum perforation was present at Visit 1, but was missed. Data Clarification Forms for September 20, 2004 add nasal septal perforation to the medical history page, and add that the nasal septal perforation was due to trauma prior to baseline [NDA 21-861, N-000 BM, 7/18/05, Nasal Perforation Safety Information, CRF 3812-5905, pages 1-39].*

The changes in the CRFs are irregular and it is concerning that the Data Clarification Forms were not completed until one year after the data was entered into the CRF. In addition, there are no Data Clarification Forms for some of the other changes to the CRF. It is concerning that the abnormality was not picked up by the screening history or nasal examination, and was associated with bleeding when noted at Visit 4, as one would expect a new nasal septum perforation to present. DSI is performing a for-cause audit of this site because of these irregularities.

In a teleconference with the Division on May 26, 2005, the applicant suggested that pre-existing nasal disease was a factor in one of the nasal septal perforations [NDA 21-861, Teleconference Minutes, 5/26/05]. Additional information was submitted by the applicant [NDA 21-861, N-000 BM, 7/18/05, Nasal Perforation Safety Information, page not numbered]. The applicant stated that patient #3795-8503 in study C-01-92 had several pertinent nasal baseline history conditions that were not reported to the investigator until the patient was informed that a nasal septum perforation was present. This patient was treated with vehicle placebo. The applicant notes that the patient had a history of a "thin septal wall", daily epistaxis, a history of nasal cauterization, and nasal saline irrigation three to four times a week. The applicant notes that had the investigator been aware of the nasal history at screening, it is unlikely that the patient would have been enrolled in the study.

Reviewer comment:
This patient was enrolled at the study center of (b) (4) *The case report form for patient #3796-8503 indicates that this patient had a history of a "thin septal wall" and "epistaxis QD" [Module 5, Volume 142, page 1981]. The entries for these conditions on the screening medical history are in clearly different handwriting than entries higher up on the page. No correction marks or initials are present on the page. The date of the screening history was* (b) (6) *Adverse Event Forms for "significant nasal abnormality" were changed to "anterior bilateral ulcerations (nasal septum)" and "ulcerations of mucosa" were changed to "septal hole" on* (b) (6) *[Module 5, Volume 142, pages 1992, 1994]. These changes are in the same handwriting as the entries on the screening medical history for thin septal wall and epistaxis. The CRF indicates that there were no anatomic abnormalities at the screening visit on physical or nasal examinations, however.*

Concurrent nasal disease that might complicate or interfere with investigation or evaluation of the study medication was an exclusion criterion for this study. Strictly speaking, based on the medical history, the patient should have been excluded from the study. The development of nasal ulceration and nasal septum perforation in this patient is an important safety finding regardless of whether there was a pre-existing "thin septal wall." DSI is also performing a for-cause audit of this site because of irregularities in the CRF.

The applicant stated that patient #3652-9021 in study C-01-92 was observed to have a nasal septum perforation at Visit 9, on (b) (6) This patient was treated with vehicle placebo. The patient was withdrawn from the study on February 11, 2004. The applicant notes that the patient was subsequently diagnosed with fibromyalgia syndrome and systemic lupus erythematosus as a result of the work-up initiated when the nasal septum perforation was discovered. The investigator notes that autoimmune diseases are a common cause for nasal septum perforations and that the autoimmune condition was the most likely cause of the perforation.

Reviewer comment:
This patient was enrolled at the study center of (b) (4) *The case report form for patient #3652-9021 indicates that the patient was noted to have a nasal septum perforation with bleeding margins at Visit 9 and that after consulting with the applicant, the patient was withdrawn from the study.*

Nasal septum perforations may occur in systemic lupus erythematosus, as the applicant notes.[7,8] *However, given that the non-clinical data suggest that the formulation is toxic to the nasal mucosa and that there were two other cases of nasal septum perforations in the drug development program, one must also consider the possibility that this event is attributable to study treatment.*

Even if one accepts the nasal septum perforation in patient #3812-5905 as being pre-existing, and in #3652-9021 because of previously undiagnosed autoimmune disease, the third case remains a problem. It is difficult to accept the diagnosis of "thin nasal septum" as a predisposing factor for this event, even without the irregularities in the CRF. The development of

nasal ulceration and nasal septal perforation in this patient is an important safety finding regardless of whether there was a pre-existing "thin septal wall." A single nasal septal perforation in a drug development program of this size for a non-corticosteroid nasal spray product is sufficient to affect the approvability of the product.

Children appear to be more sensitive to epistaxis and nasal ulceration from the formulation than adults. The applicant completed study C-03-51 after submission of the NDA, and submitted a study summary with the 120-day safety update [NDA 21-861, N-000 SU, Volume 1, Section 1, pages 9-10]. The study was a multicenter, double blind, parallel group, PK, efficacy, and safety study of olopatadine nasal spray in pediatric patients 6 to 11 years of age. There were 271 patients enrolled. There was a 4- to 14-day run-in period in which patients received vehicle placebo 2 sprays each nostril twice daily. Patients were then randomized to two weeks of treatment with one or two sprays twice daily of olopatadine 0.6%, one spray twice daily of olopatadine 0.4%, or one or two sprays twice daily of vehicle placebo.

Adverse events for epistaxis and nasal ulceration from this two-week study are summarized and compared in Table 17 with the two pivotal two-week SAR efficacy and safety studies in adults. In C-03-51, the frequency of epistaxis among the treatment groups ranged from 3.9% to 13.7%. The overall frequency was 8.9%. The frequency of epistaxis was higher than in the two pivotal SAR efficacy and safety studies in adults, C-02-37 and C-02-10, where the frequency of epistaxis in active treatment groups ranged from 1.9% to 3.8% and the overall frequency was 2.6%.

The frequency of nasal ulceration in this two-week study was also very high, and ranged from 1.9% to 14.3% among the active treatment groups and was 3.7% overall. The frequency of nasal ulceration in the two pivotal SAR efficacy and safety studies in adults was quite low; there were only two cases of nasal ulceration with an overall frequency of 0.1%.

Table 17 Adverse events for epistaxis and nasal ulceration, pediatric study C-03-51 and adult SAR studies C-02-37 and C-02-10 [NDA 21-861, N-000 SU, Volume 1, Section 1, pages 9-10; Module 5, Volume 49, pages 731-732; Module 5, Volume 57, pages 637-638]

C-03-51														
Adverse event	**Olopatadine 0.6% 2 spr BID N = 52**		**Olopatadine 0.6% 1 spr BID N = 51**		**Olopatadine 0.4% 1 spr BID N = 52**		**Veh pbo 2 spr BID N = 51**		**Veh pbo 1 spr BID N = 51**		**Veh pbo Run-in BID N = 14**		**Total N = 271**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Epistaxis	5	(9.6)	7	(13.7)	5	(9.6)	2	(3.9)	5	(9.8)	0	(0)	24	(8.9)
Nasal ulceration	2	(3.8)	2	(3.9)	1	(1.9)	0	(0)	4	(7.8)	1	(7.1)	10	(3.7)
C-02-37 and C-02-10 combined														
Adverse event	**Olopatadine 0.6% 2 spr BID N = 407**		**Olopatadine 0.6% 1 spr BID N = 0**		**Olopatadine 0.4% 2 spr BID N = 418**		**Veh pbo 2 spr BID N = 417**		**Veh pbo 1 spr BID N = 0**		**Veh pbo Screen BID N = 513**		**Total N = 1755**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Epistaxis	14	(3.4)	--		16	(3.8)	8	(1.9)	--		8	(1.6)	46	(2.6)
Nasal ulceration	0	(0)	--		0	(0)	1	(0.2)	--		1	(0.2)	2	(0.1)

Nasal septum perforation is associated with use of intranasal corticosteroids, as well as abuse of intranasal cocaine. In a 12-month, open label, long term safety study of triamcinolone acetate aqueous nasal spray in 172 patients with perennial allergic rhinitis, there was one patient with nasal septum perforation [Module 5, Volume 73, pages 304-3053]. The labels for Flonase and Nasonex Nasal Sprays advise the prescriber that nasal septum perforations were noted in postmarketing adverse event reports. Labels for these drugs do not note nasal septum perforations occurring in the clinical development program. There is also no mention of nasal septum perforations in the labels for Astelin Nasal Spray and Atrovent Nasal Sprays 0.03% and 0.06%, non-corticosteroid nasal spray products with SAR indications.

Searches of AERS using the DataMart application were performed on May 18 and 25, 2005 to identify postmarketing cases of nasal septum perforation associated with intranasal spray medications with SAR and PAR indications. The search term was "nasal septum perforation." These searches identified 11 cases of nasal septum perforation associated with Flonase and eight cases associated with Nasonex. There were no cases associated with the use of Atrovent Nasal Spray 0.03% and 0.06% and NasalCrom Nasal Spray. There was one case associated with the use of Astelin Nasal Spray. This patient was also using Flonase and Astelin was not the primary suspect drug, however.

It should also be noted that the pharmacology-toxicology team has safety concerns about the chronic intranasal use of the to-be-marketed product, which contains (b) (4) povidone. There was olfactory epithelium degeneration and turbinate epithelium vacuolation observed in the applicant's six-month rat study with intranasal povidone. These effects were observed to be dose responsive in incidence and severity [Communication to Applicant dated 5/25/05;

Pharmacology-Toxicology Review, Gary Bond, Ph.D., NDA 21-861, N-000, 12/24/04]. The non-clinical data suggest that the product is toxic to the nasal mucosa.

In support of their product formulation, the applicant notes that povidone is used in various Afrin Nasal Spray products at concentrations up to approximately 2.7% w/v. As noted above, the concentration of povidone in the to-be marketed product and the vehicle placebo is (b) (4) [Module 2, Section 2.3.P, page 7]. However, it should be noted that Afrin is not intended for chronic use, and that the language specified by the OTC monograph for decongestant drug products warns the consumer not to use the product for more than three days [21 CFR 341.80(c)(2)(iii)]. The fact that Afrin Nasal Spray contains povidone at a concentration of 2.7% w/v does not provide support for the proposed product, which will be used for periods much longer than three days. Interestingly, there was one report in the AERS database of nasal septum perforation associated with the use of Afrin Nasal Spray. The report for this case, which was not confounded with use of other intranasal medications, indicates that the patient used Afrin daily for eight years, which provides additional concern regarding chronic intranasal exposure to the povidone excipient.

In summary, the formulation for the proposed product appears to be toxic to the nasal mucosa, and is associated with epistaxis and nasal ulcer. With chronic use, it is associated with a significant risk of nasal septum perforation. Non-clinical data suggest that the signal may be related to the povidone excipient. The three cases noted in the one-year study of 924 patients are particularly remarkable, given that the AERS database contains only 11 cases of nasal septum perforation for Flonase Nasal Spray and eight cases for Nasonex Nasal Spray. Both Flonase and Nasonex are products known to be associated with nasal septum perforation and both products have had extensive postmarketing exposures. Even accounting for underreporting, these data suggest that the frequency of this adverse event is much higher for the applicant's product than for Flonase and Nasonex.

Based on AERS data, it appears that nasal septum perforation is extremely rare among non-steroid nasal sprays with allergic rhinitis indications. Even among corticosteroid nasal sprays with allergic rhinitis indications, nasal septum perforation appears to be uncommon. These findings represent a major safety signal and are sufficient to affect the approvability of the application.

7.1.7 Laboratory Findings

Review of hematology, blood chemistry, and urinalysis data from the pivotal SAR efficacy and safety studies in this application, C-02-37 and C-02-10, revealed no safety signal. Laboratory findings are reviewed in greater depth below.

7.1.7.1 Overview of laboratory testing in the development program

Clinical laboratory studies were performed in the two pivotal efficacy and safety SAR studies (C-02-37 and C-02-10), two supportive SAR studies with lower concentrations of olopatadine, and in six pharmacokinetic studies. This summary of laboratory findings focuses on the laboratory data from the two pivotal efficacy and safety SAR studies, where patients were dosed with olopatadine 0.6% and olopatadine 0.4% nasal sprays dosed twice daily for two weeks. Patients in those studies had hematology, blood chemistry, and urinalysis studies at baseline and at the exit or final visit [Module 2, Volume 7, Section 2.7.4.3, page 1]. Laboratory data for other studies did not identify safety concerns and are discussed individually in the individual study reports section of this review, Section 10.1.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The two pivotal efficacy and safety studies were that were selected for review in this section were placebo controlled SAR studies with olopatadine 0.6%, the concentration proposed for marketing, and olopatadine 0.4% as the active treatment arms.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Mean changes in hematology parameters in the two pivotal SAR efficacy and safety studies were small, not clinically relevant, and were similar among the treatment groups [Module 2, Volume 7, Section 2.7.4.3, pages 5-11].

Among the pivotal SAR efficacy and safety studies, there was an increase in mean CPK levels for all groups but olopatadine 0.6% for study C-02-37. These values are displayed in Table 18. There was a greater increase in mean CPK levels in patients treated with olopatadine 0.6% in study C-02-10 and in patients treated with vehicle placebo in study C-02-37. The degree of variability and range of these values was great, however, and the changes in values were not dose-related. Many of the patients with elevated CPK values had concomitant physical activity or medications known to be associated with increased CPK levels. These changes in CPK levels were not clinically relevant [Module 2, Volume 7, Section 2.7.4.3, pages 18-29, 38-45].

Table 18 Mean change in CPK levels, Studies C-02-37 and C-02-10 [Module 2, Volume 7, Section 2.7.4.3, pages 18-29]

Study	Olopatadine 0.6% Change, IU/mL (SD) Maximum, Minimum	Olopatadine 0.4% Change, IU/mL (SD) Maximum, Minimum	Vehicle placebo Change, IU/mL (SD) Maximum, Minimum
C-02-37	-7.3 (123.7) -806.0, 672.0	10.3 (93.4) -641.0, 495.0	20.4 (192.0) (-585.0, 2093.0)
C-02-10	42.8 (285.5) -293.0, 2820.0	13.8 (199.1) -2857.0, 205.0	7.5 (191.1) -585.0, 2093.0

Mean changes in other blood chemistry parameters in the two pivotal SAR efficacy and safety studies were also not clinically relevant [Module 2, Volume 7, Section 2.7.4.3, pages 12-29].

Mean changes in urinalysis parameters in the two pivotal SAR efficacy and safety studies were small, not clinically relevant, and were similar among the treatment groups [Module 2, Volume 7, Section 2.7.4.3, pages 32-35].

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Shift table analysis showed no clinically relevant shifts in hematology values in the two pivotal SAR efficacy and safety studies [Module 2, Volume 7, Section 2.7.4.3, pages 2-4].

Shift table analysis for CPK values is summarized in Table 19. Shift table analysis showed that the percentage of patients with increases in CPK values was 4.3% (17/402) for olopatadine 0.6%, 2.6% (11/413) for olopatadine 0.4%, and 4.4% (18/411) for vehicle placebo. The percentage of patients with decreases in CPK values was 6.2% (25/402) for olopatadine 0.6%, 24.8% (20/413) for olopatadine 0.4%, and 4.9% (20/411) for vehicle placebo. The percentage of patients with increases in CPK values in each of the treatment groups was similar to the percentage of patients with decreases in CPK values. In addition, the percentage of patients with increases and decreases were similar within each treatment group. The shift table analysis of CPK values showed no clinically relevant shifts in the two pivotal SAR efficacy and safety studies [Module 2, Volume 7, Section 2.7.4.3, pages 14-16, 38-45].

Table 19 Shift table for CPK values, C-02-37 and C-02-10 combined [Module 7, Volume 7, Section 2.7.4.3, pages 14-16]

Treatment	Baseline	Final Visit	
		Normal	High
Olopatadine 0.6%	Normal	341	17
N = 402	High	25	19
Olopatadine 0.4%	Normal	372	11
N = 413	High	20	10
Vehicle placebo	Normal	354	18
N = 411	High	20	19

Normal values ranged from 0-235 for men and 0-190 for women. It was therefore impossible to have a “low” CPK value.

Shift table analysis showed no clinically relevant shifts in urinalysis values in the two pivotal SAR efficacy and safety studies [Module 2, Volume 7, Section 2.7.4.3, pages 30-35].

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Laboratory abnormalities reported as adverse events in C-02-37 and C-02-10 are summarized in Table 20. There were no dropouts due to clinically relevant laboratory anomalies. Except for the patient with a kidney calculus, all clinically relevant abnormalities were nonserious, and mild or moderate in severity. [Module 2, Volume 7, Section 2.7.4.2, pages 92; Module 2, Volume 7, Section 2.7.4.3, pages 36-38]. More information on individual cases may be found in the reviews of the individual studies, Section 10.1.1.14.7.8 and Section 10.1.2.15.7.8.

Table 20 Laboratory abnormalities reported as adverse events in C-02-37 and C-02-10 [Module 2, Volume 7, Section 2.7.4.2, pages 92; Module 2, Volume 7, Section 2.7.4.3, pages 36-38]

Laboratory abnormality reported as adverse event	Olopatadine 0.6% N = 407		Olopatadine 0.4% N = 418		Vehicle placebo N = 417	
	n	(%)	n	(%)	n	(%)
Urinary tract infection	5	(1.2)	3	(0.7)	2	(0.5)
CPK increased	2	(0.5)	0	(0)	1	(0.2)
Pyuria	1	(0.2)	0	(0)	1	(0.2)
Hematuria	0	(0)	1	(0.2)	0	(0)
Thrombocytopenia	0	(0)	1	(0.2)	0	(0)
Hyperglycemia	0	(0)	1	(0.2)	0	(0)
Hypercholesterolemia	0	(0)	1	(0.2)	0	(0)
Hyperlipemia	0	(0)	2	(0.5)	0	(0)
Eosinophilia	0	(0)	1	(0.2)	0	(0)
SGPT increased	0	(0)	1	(0.2)	1	(0.2)
GGTP increased	0	(0)	0	(0)	1	(0.2)
Kidney calculus	0	(0)	0	(0)	1	(0.2)

7.1.7.4 Additional analyses and explorations

The applicant performed an additional analysis of SGOT (ASAT) and SGPT (ALAT) levels because increases in serum transaminase levels have been reported for Astelin 0.1% Nasal Spray, another intranasal antihistamine. There were no clinically relevant increases in mean transaminase levels in the pivotal SAR efficacy and safety studies. Although the distribution of patients with shifts from normal to high in SGOT and SGPT was higher in the olopatadine 0.6% group (8 patients and 9 patients, respectively) compared with the olopatadine 0.4% (3 patients and 6 patients, respectively) and vehicle placebo groups (3 patients and 7 patients respectively), most shifts were small and not clinically relevant. There were two patients in the olopatadine 0.6% group, no patients in the olopatadine 0.4% group, and one patient in the vehicle placebo group with an increase in SGOT greater than twice the upper limit of normal. There was one patient in the olopatadine 0.6% group and no patients in the olopatadine 0.4% and vehicle placebo groups with increases in SGPT greater than twice the upper limit of normal. Patients with these increases are summarized below [Module 2, Volume 7, Section 2.7.4.3, pages 46-49].

Patient #3207-2606 in study C-02-10 was a 36 year-old Caucasian woman who was treated with olopatadine 0.6% nasal spray and had an increase in SGOT from 17 IU/L at baseline to 97 IU/L at the exit visit. The patient's SGPT level increased from 18 IU/L at baseline to 129 IU/L at the exit visit. At the time of the exit visit the GGT was 65 IU/L, LDH 154 IU/L, total bilirubin of 0.3 mg/dL, and alkaline phosphatase of 80 IU/L. A retest 16 days later showed the SGOT and SGPT returned to normal levels of 12 IU/L and 10 IU/L, respectively.

Patient #3207-1490 in study C-02-10 was a 16-year old Caucasian male who was treated with olopatadine 0.6% nasal spray who had an increase in SGOT from 25 IU/L at baseline to 107 IU/L at the exit visit. The patient's SGPT level increased from 14 IU/L at baseline to 43 IU/L at the exit visit. At the time of the exit visit the GGT was 13IU/L, LDH 168 IU/L, total bilirubin of 0.9 mg/dL, alkaline phosphatase of 98 IU/L, and CPK 3000 U/L. A retest 7 days later showed the SGOT and SGPT returned to 47 IU/L and 34 IU/L, respectively. The patient had a CPK of 820 U/L at retest. Increases in SGOT, SGPT, and CPK were attributed to exercise.

Patient #3203-1827 in study C-02-10 was a 38-year old Caucasian female treated with vehicle placebo who had an increase in SGOT from 46 IU/L at baseline to 326 IU/L at the exit visit. The patient's SGPT level increased from 41 IU/L at baseline to 138 IU/L at the exit visit. At the time of the exit visit the GGT was 515 U/L, LDH 301 IU/L, total bilirubin of 0.3 mg/dL, and alkaline phosphatase of 182 IU/L. The patient was taking cyclobenzaprine and controlled release oxycodone tablets at the time of the elevation.

The additional analysis of SGOT and SGPT levels does not reveal a safety signal for olopatadine 0.6% nasal spray.

7.1.7.5 Special assessments

No special laboratory assessments were performed in the pivotal SAR studies in this application.

7.1.8 Vital Signs

Vital signs data from six natural exposure SAR and PAR studies in this application did not reveal safety concerns. Shift table and scatter plot analyses of vital signs data from the three pivotal SAR and PAR efficacy and safety studies also did not reveal safety concerns. Vital signs data are reviewed in greater depth below.

7.1.8.1 Overview of vital signs testing in the development program

Vital signs testing was performed in seven PK and PD studies, one nasal allergen challenge study, three environmental exposure unit studies, and six natural exposure safety and efficacy studies in patients with SAR or PAR in the drug development program for olopatadine nasal spray.

This summary of vital signs mainly focuses on the data from the six natural exposure studies in patients with SAR or PAR, where patients were dosed with olopatadine spray at concentrations of 0.1% to 0.6% twice daily for two weeks to one year. In all but one of these six studies, patients had vital signs at the screening and exit or final visits only [Module 2, Volume 7, Section 2.7.4.4, pages 16-17]. Shift table and scatter plot analyses focus on the three pivotal SAR and PAR efficacy and safety studies, C-02-37, C-02-10, and C-01-92.

Vital signs data for other studies did not identify safety concerns and are discussed individually in the individual study reports section of this review, Section 10.1.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The six natural exposure SAR and PAR studies that were selected for review in this section were placebo controlled and included olopatadine 0.6% nasal spray, the concentration proposed for marketing, as well as concentrations of olopatadine nasal spray as low as 0.1%. These studies were also chosen for review in this section because the dose and durations used would be more reflective of the use of the product in clinical practice [Module 2, Volume 7, Section 2.7.4.4, pages 16-17].

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Mean changes in pulse among treatment groups in the six natural exposure SAR and PAR studies were small and less than 1.3 BPM. There were no clinically relevant differences among treatment groups in mean change in pulse for the overall, adolescent, adult, or elderly patient populations. There were no dose-related changes in pulse observed [Module 2, Volume 7, Section 2.7.4.4, pages 20-21].

Mean changes in systolic blood pressure among treatment groups in the six natural exposure SAR and PAR studies were small and less than 3.5 mm Hg. There were no clinically relevant differences among treatment groups in mean change in systolic blood pressure for the overall, adolescent, adult, or elderly patient populations. There were no dose-related changes in systolic blood pressure observed [Module 2, Volume 7, Section 2.7.4.4, pages 21-22].

Mean changes in diastolic blood pressure among treatment groups in the six natural exposure SAR and PAR studies were small and less than 1.3 mm Hg. There were no clinically relevant differences among treatment groups in mean change in diastolic blood pressure for the overall, adolescent, adult, or elderly patient populations. There were no dose-related changes in diastolic blood pressure observed [Module 2, Volume 7, Section 2.7.4.4, pages 23-24].

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Shift table and scatter plot analyses for change from baseline to exit visit demonstrated no clinically relevant differences between treatment groups in pulse rate, systolic blood pressure, and diastolic blood pressure. No safety concerns were identified [Module 2, Volume 7, Section 2.7.4.4, pages 25-33, 42-49, 59-67].

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Laboratory abnormalities reported as adverse events in the six natural exposure studies are summarized in Table 21. The incidences of vital signs abnormalities reported as adverse events were fairly similar in the natural exposure studies. There was no suggestion of a dose response effect.

Table 21 Vital signs abnormalities reported as adverse events in natural exposure studies C-00-10, C-00-33, C-01-05, C-02-37, C-02-10, and C-01-92 [Module 2, Volume 6, Section 2.7.4, pages 12-13, 41; Module 2, Volume 7, Section 2.7.4.4, page 19]

Pulse and blood pressure abnormalities reported as adverse event	Olopatadine 0.6% N = 866		Olopatadine 0.4% N = 418		Olopatadine 0.2% QD N = 31		Olopatadine 0.1% BID N = 33		Azelastine 0.1% BID N = 174		Vehicle placebo BID N = 1008	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Hypertension	10	(1.2)	1	(0.2)	0	(0)	0	(0)	1	(0.6)	8	(0.8)
Tachycardia	1	(0.1)	0	(0)	1	(3.2)	0	(0)	0	(0)	3	(0.3)
Bradycardia	0	(0)	0	(0)	0	(0)	1	(3.0)	1	(0.6)	0	(0)

One patient in study C-01-92 discontinued the study due to hypertension. Patient #3080-6614 was a 44 year-old Caucasian male who was treated with olopatadine 0.6% nasal spray who developed a blood pressure of 138/100 on Day 188, Visit 8 of the study. The event was not serious, was mild in intensity, and resolved with treatment with ramipril [Module 2, Volume 7, Section 2.7.4.4, page 17; Module 5, Volume 69, page 1504].

One patient in study C-01-92 experienced a serious adverse event for tachycardia, but did not discontinue from the study. Patient #3200-6312 was a 79 year-old Caucasian female with congestive heart failure, COPD, arthritis, and hypertension who was treated with vehicle placebo and who was noted to have a pulse of 133 at (b) (6) of the study. The date of onset was unknown and the event was assessed as serious because she needed hospitalization. She was treated with digoxin, and eventually required pacemaker installation. The event did not interrupt continuation in the study [Module 2, Volume 7, Section 2.7.4.4, page 18; Module 5, Volume 69, page 1652].

Outliers and dropouts for vital signs abnormalities did not suggest a safety signal.

7.1.8.4 Additional analyses and explorations

No additional analyses and explorations of vital signs data were performed.

7.1.9 Electrocardiograms (ECGs)

The applicant performed an integrated analysis of ECG data from the supportive SAR studies in this application (C-00-10, C-00-33, and C-01-05) and an individual analysis of ECG data from the pivotal, 1-year PAR study. These data showed no evidence of a safety signal. ECG findings are presented in greater depth below. Data from the two high dose cardiac safety studies in this application, Studies C-00-23 and C-02-54, are not reviewed in this section but are summarized in Section 7.1.12 and reviewed in greater depth in Section 10.1.12 and Section 10.1.13.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECGs were performed as safety endpoints in 10 studies in this application: in three PK and safety studies with oral olopatadine (C-00-23, C-02-54, and C-03-10), two PK and safety studies with single dose exposure to olopatadine 0.6% nasal spray (C-02-46 and C-03-11), three non-pivotal SAR studies (C-00-10, C-00-33, and C-01-05), one PK study (C-00-58) with 0.1% and 0.2% concentrations of olopatadine, and one long-term pivotal PAR study (C-01-92). For each study, the effects of olopatadine on ECG parameters were analyzed, including an evaluation of mean changes in ECG intervals, categorical analysis of QT/QTc data, and evaluation of ECG abnormalities [Module 2, Volume 7, Section 2.7.4.4, page 76].

Integrated analyses of ECG data from supportive SAR studies C-00-10, C-00-33, and C-01-05 were performed by the applicant. Treatments received by patients in these studies included olopatadine 0.2% BID, olopatadine 0.2% QD, olopatadine 0.1% BID, olopatadine 0.1% QD, azelastine 0.1% BID, vehicle placebo BID, and vehicle placebo QD. The applicant also performed a separate analysis of ECG data from the long-term PAR study C-01-92. Patients in this study received olopatadine 0.6% BID or vehicle placebo BID.

In non-clinical studies, olopatadine showed an antihypertensive effect in dogs in a dose dependent manner at 20, 50, & 100 mg/kg (59% decrease at high dose) with decreased total peripheral resistance. At <5mg/kg iv, no effects on heart rate, ECG & respiratory rate were observed. At <30mg/kg iv there were no effects on QTc. The IC_{50} for hERG channel is 1000X greater than for terfenadine. In studying the effect of the combination of olopatadine and itraconazole (to block CYP 3A4) on the ECG in conscious dogs, olopatadine alone causes a greater increase in heart rate and mean blood pressure (in contrast to an earlier experiment where olopatadine caused hypotension) than when administered along with itraconazole, while QT tended to be less affected. These data suggest that olopatadine may not elicit QT prolongation even when co-administered with the CYP 3A4-inhibitor itraconazole. In another study on the effects of olopatadine HCl on cloned hERG channels, olopatadine blocked hERG channels with an IC_{50} of 1.1 mM. This block showed no use or time dependence [Gary Bond, Ph.D., Pharmacology Review, NDA 21-861, N-000, 12/24/04].

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The applicant excluded the PK studies (C-00-58, C-02-54, C-03-10, and C-03-11) from the ECG analysis because ECG assessments included only an evaluation of whether the ECG was normal or abnormal [Module 2, Volume 7, Section 2.7.4.4, page 76]. ECG analyses from the high-dose cardiac safety studies (C-00-23 and C-02-54) are not included in this section because they are summarized in a different section of this review, Section 7.1.12, and are reviewed individually in Section 10.1.12 and Section 10.1.13 of this review.

Integrated analyses of ECG data from supportive SAR studies C-00-10, C-00-33, and C-01-05 and a separate analysis of ECG data from long-term PAR study C-01-92 follow below.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

7.1.9.3.1.1 Supportive SAR studies C-00-10, C-00-33, and C-01-05

ECG data from supportive SAR studies C-00-10, C-00-33, and C-01-05 showed no clinically relevant differences among treatment groups in mean change in PR interval. There was no dose related effect of olopatadine on PR interval or QRS interval.

RR interval was not collected in studies C-00-10 and C-00-33 and was not collected as specified in the protocol for study C-01-05. As a result there was little data for this ECG parameter. No clinically relevant differences in mean change in RR interval were noted [Module 2, Volume 7, Section 2.7.4.4, page 81].

No clinically relevant differences in mean QT interval were noted among treatment groups in these studies. Mean QTcB interval increased by approximately 4 msec in the olopatadine 0.2% groups and 2 to 3 msec in the olopatadine 0.1%, azelastine 0.1%, and vehicle placebo BID treatment groups in supportive SAR studies C-00-10, C-00-33, and C-01-05. The mean QTcB interval decreased by approximately 3 msec in the vehicle placebo QD group [Module 2, Volume 7, Section 2.7.4.4, pages 82-83].

7.1.9.3.1.2 Pivotal PAR study C-01-92

Mean change from baseline to Visit 8 (180 days) and mean change from baseline to Exit visit in PR, QRS, QQ, QT, QTcB, an QTcF intervals were similar for olopatadine 0.6% and vehicle placebo and small differences were not clinically relevant [Module 2, Volume 7, Section 2.7.4.4, pages 89-91].

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.9.3.2.1 Supportive SAR studies C-00-10, C-00-33, and C-01-05

There were 10 occurrences of individuals with QTcB intervals greater than normal (>450 msec for men and >470 msec for women) among 721 patients in these studies. There were no meaningful differences between the treatment groups in the percentage of patients with QTcB intervals greater than normal. There was no dose related effect on percentage of patients with QTcB intervals greater than normal [Module 2, Volume 7, Section 2.7.4.4, pages 84-85].

There were nine occurrences of individuals with change from baseline in QTcB >60 msec for among a total of 720 patients in these studies. There were no meaningful differences between the treatment groups in percentage of patients with change from baseline in QTcB interval of <30 msec, ≥30 to ≤60 msec, and >60 msec. There was no dose related effect on percentage of patients for change from baseline in QTcB interval of <30 msec, ≥30 to ≤60 msec, and >60 msec [Module 2, Volume 7, Section 2.7.4.4, pages 84-85].

A similar incidence of patients with changes from normal to abnormal in ECG interpretation was observed among treatment groups in these studies. No U waves were noted in any of these studies [Module 2, Volume 7, Section 2.7.4.4, page 87].

7.1.9.3.2.2 Pivotal PAR study C-01-92

The percentage of patients with an increase in PR interval from normal to <200 msec (the upper limit of normal for the laboratory reading the ECGs) at any visit was similar in the olopatadine 0.6% and vehicle placebo groups [Module 2, Section 2.7.4.4, page 92].

The percentage of patients with an increase in QRS interval from normal to <98 msec (the upper limit of normal for the laboratory reading the ECGs) at any visit was slightly higher in the olopatadine 0.6% group (2.3%) than the vehicle placebo group (0.9%) [Module 2, Section 2.7.4.4, page 92].

The percentage of patients at any visit with an increase in RR interval from normal to <1200 msec (the upper limit of normal for the laboratory reading the ECGs) or from normal to <600 msec (the lower limit of normal for the laboratory reading the ECGs) was similar in the olopatadine 0.6% and vehicle placebo groups [Module 2, Section 2.7.4.4, pages 95-96].

There were two patients in each treatment group with a QTcB interval greater than normal at any visit. There were no patients in either treatment group with a QTcF interval greater than normal at any visit [Module 2, Volume 7, Section 2.7.4.4, pages 104-105].

The percentage of patients with changes in QTcB interval from baseline to any visit of ≥30 to ≤60 msec was similar for the olopatadine 0.6% (6.5%, 28/434) and the vehicle placebo group (8.8%, 38/432). There was one patient with a change in QTcB interval from baseline to any visit of >60 msec in the olopatadine 0.6% group (0.2%, 1/434) and the vehicle placebo group (0.2%, 1/432) [Module 2, Volume 7, Section 2.7.4.4, pages 103-108].

The percentage of patients with changes in QTcF interval from baseline to any visit of ≥30 to ≤60 msec was similar for the olopatadine 0.6% (3.7%, 16/434) and the vehicle placebo group (4.6%, 20/432). There were no patients in either group with a change in QTcB interval from baseline to any visit of >60 msec [Module 2, Volume 7, Section 2.7.4.4, pages 103-108].

No clinically relevant differences between treatment groups in the percentage of patients with a change from baseline to maximum QTcB or QTcF >60 msec [Module 2, Volume 7, Section 2.7.4.4, pages 107-108].

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

7.1.9.3.3.1 Supportive SAR studies C-00-10, C-00-33, and C-01-05

The applicant referred to their summary of vital signs [Module 2, Volume 7, Section 2.7.4.4.2] for discussion of adverse events due to ECG abnormalities [Module 2, Volume 7, Section 2.7.4.4, page 87]. This section identifies two patients with bradycardia reported from ECGs in study C-01-05. One patient was treated with olopatadine 0.1% nasal spray BID and one was

treated with azelastine 0.1% nasal spray BID. However, the report for this study indicates that there were two patients who discontinued the study due to prolonged QT. One of these patients was treated with olopatadine 0.1% BID and the other was treated with vehicle placebo BID.

Reviewer comment:
The summary of patients with ECG abnormalities in studies C-00-10, C-00-33, and C-01-05 appears to be incomplete [Module 2, Volume 7, Section 2.7.4.4, pages 19, 87].

7.1.9.3.3.2 Pivotal PAR study C-01-92

ECGs were interpreted in study C-01-02 by cardiologists at the ECG reading center and abnormalities were assessed for clinical relevance. The percentages of patients determined to have clinically relevant changes in ECGs were similar for both treatment groups [Module 2, Volume 7, Section 2.7.4.4, pages 109-110]. Adverse events associated with abnormal ECGs were noted in three patients in the olopatadine 0.6% group (0.6%, 3/459) and six patients in the vehicle placebo group (1.3%, 6/465). Review of these adverse events did not identify a safety concern [Module 2, Volume 7, Section 2.7.4.4, pages 111-113].

7.1.9.4 Additional analyses and explorations

There were two high dose cardiac safety studies in this application Studies C-00-23 and C-02-54 performed in the drug development program. They are summarized in Section 7.1.12 and reviewed in greater depth in Section 10.1.12 and Section 10.1.13 of this review.

No additional analyses and explorations of ECG data were performed by the applicant.

7.1.10 Immunogenicity

There were no clinical studies that assessed the immunogenicity of the product in this application.

7.1.11 Human Carcinogenicity

No human carcinogenicity studies were performed as part of this drug development program.

7.1.12 Special Safety Studies

There were two high dose cardiac safety studies in this application Studies C-00-23 and C-02-54.

Study C-00-23 was a randomized, double blind, placebo controlled, crossover, multiple dose, phase 1, PK/PD study of cardiovascular safety of olopatadine solution, 5 mg orally or placebo, twice daily for 2 ½ days, in healthy subjects. Maximum positive single dose and steady-state QTc interval change from baseline (Emax) values for olopatadine were less than or the same as those for placebo [Module 5, Volume 25, page 54]. The incidences of patients with QTcB Emax values <30 msec or ≥30 to ≤60 msec in the olopatadine group were comparable to those in the placebo group. The incidence of patient with QTcB values >60 seconds was lower in the

olopatadine group than in the placebo group. The incidences of patients with QTcF Emax values <30 msec or ≥30 to ≤60 msec was higher in the olopatadine group than in the placebo group. The incidence of patients with QTcB values >60 seconds was comparable in both treatment groups. These data suggest that there is no QTc prolongation with olopatadine 5 mg twice daily by mouth, approximately twice the dose administered by the labeled dose for the proposed nasal spray product. More details may be found in Section 10.1.12 of this review. This study was not reviewed by the Clinical Pharmacology and Biopharmaceutics reviewer, Dr. Sandra Suarez, because higher systemic exposures were achieved in Study 02-54.

Study C-02-54 was a randomized, double blind, placebo controlled, crossover, multiple dose, phase 1, PK/PD study of cardiovascular safety of olopatadine solution, 20 mg orally or placebo, twice daily for 14 days, in healthy subjects. In addition to analyzing QTcF, QTcB, and uncorrected QTc values, the applicant analyzed QTc data with a correction formula that renders a slope of zero when plotted versus RR by subject (QTcI). Median and mean QTcF, QTc, and QTcI values for olopatadine were less than that for placebo. QTcB values were similar to those for the other analyses [Module 5, Volume 20, pages 86, 91-93]. Maximum positive QTc interval change from baseline (Emax) was also analyzed. QTcF and QTcI Emax values for olopatadine were comparable with those for placebo. QTcB Emax values were similar to those for the other analyses [Module 5, Volume 20, pages 93-94]. The incidences of patients with changes in QTcF Emax and QTc I Emax values <30 msec, ≥30 to ≤60 msec, and >60 msec were comparable in the olopatadine and placebo groups. Results for incidence of change from baseline in QTcB Emax were similar QTcF Emax and QTcI Emax [Module 5, Volume 20, pages 95-96]. Morphologic assessment of ECG data did not reveal a safety signal [Module 5, Volume 20, page 105]. These data suggest that there is no QTc prolongation with olopatadine 20 mg twice daily by mouth for 14 days. This dose is approximately eight times the dose delivered by the nasal spray product. More details may be found in Section 10.1.13 of this review and in Dr. Sandra Suarez's Clinical Pharmacology and Biopharmaceutics Review [S. Suarez, Ph.D., Clinical Pharmacology and Biopharmaceutics Review NDA 21-861, N-000, 12/24/04].

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There were no reports of withdrawal or rebound phenomena in the clinical development program for olopatadine nasal spray [Module 2, Volume 8, Section 2.7.4.5, page 124].

There is no information on withdrawal phenomena or abuse potential in the product labeling for olopatadine 0.1% ophthalmic solution [Product Label, Patanol®]. There were no reports of withdrawal or rebound phenomena in worldwide postmarketing safety data for olopatadine 0.1% ophthalmic solution [Module 2, Volume 8, Section 2.7.4.6, pages 1-9].

There is no information on withdrawal phenomena or abuse potential in the Japanese product labeling for olopatadine 2.5 mg and 5 mg tablets [NDA 21-861, N-000 BB, Volume 1, Allelock Tablets Product Label, pages 1-11]. There were no reports of withdrawal or rebound phenomena in Japanese postmarketing safety data for olopatadine 2.5 mg and 5 mg tablets [NDA 21-861, N-000 BB, Volume 1, Dec 2003/Dec 2004 Periodic Safety Report, Appendix I, pages 1-3, Appendix II, pages 1-6].

There were no reports of withdrawal or rebound phenomena identified in the applicant's review of the published medical literature for safety information relevant to the use of olopatadine [NDA 21-861, N-000 BB, Volume 3, Question 2 Response, pages 1-3].

7.1.14 Human Reproduction and Pregnancy Data

The clinical study protocols in the olopatadine nasal spray drug development program excluded the participation of pregnant females and no information was obtained on its use in this population [Module 2, Volume 8, Section 2.7.4.5, page 123].

The product label for olopatadine 0.1% ophthalmic solution includes the following information relative to human reproduction and pregnancy [Product Label, Patanol®]:

> Olopatadine administered to male and female rats at oral doses of 62,500 times MROHD level resulted in a slight decrease in the fertility index and reduced implantation rate; no effects on reproductive function were observed at doses of 7,800 times the maximum recommended ocular human use level.
>
> Pregnancy: Pregnancy Category C. Olopatadine was found not to be teratogenic in rats and rabbits. However, rats treated at 600 mg/kg/day, or 93,750 times the MROHD and rabbits treated at 400 mg/kg/day, or 62,500 times the MROHD, during organogenesis showed a decrease in live fetuses. There are, however, no adequate and well controlled studies in pregnant women. Because animal studies are not always predictive of human responses, this drug should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the embryo or fetus.
>
> Nursing Mothers: Olopatadine has been identified in the milk of nursing rats following oral administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in the human breast milk. Nevertheless, caution should be exercised when PATANOL® (olopatadine hydrochloride ophthalmic solution) 0.1% is administered to a nursing mother.

The product labeling for olopatadine 2.5 mg and 5 mg tablets includes the following information [NDA 21-861, N-000 BB, Volume 1, Allelock Tablets Product Label, pages 1-11]:

> Allelock should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. Safety of the administration during pregnancy has not been established.
>
> Lactating women should not be given Allelock. If treatment with this drug is judged to be essential, breast feeding must be discontinued during treatment. Animal studies (rats) reported excretion of this drug in breast milk and weight increase inhibition of the neonates.

7.1.15 Assessment of Effect on Growth

No clinical studies to evaluate the effect on growth were performed as part of the drug development program for olopatadine nasal spray.

There is no information on effects on growth in the product labeling for olopatadine 0.1% ophthalmic solution [Product Label, Patanol®]. There were no reports of effects on growth in worldwide postmarketing safety data for olopatadine 0.1% ophthalmic solution [Module 2, Volume 8, Section 2.7.4.6, pages 1-9].

There is no information on effects on growth in the Japanese product labeling for olopatadine 2.5 mg and 5 mg tablets. The label states that the safety of the product in small for date babies, neonates, infants, or children has not been established (no clinical experience) [NDA 21-861, N-000 BB, Volume 1, Allelock Tablets Product Label, pages 1-11]. There were no reports of effects on growth in Japanese postmarketing safety data for olopatadine 2.5 mg and 5 mg tablets [NDA 21-861, N-000 BB, Volume 1, Dec 2003/Dec 2004 Periodic Safety Report, Appendix I, pages 1-3, Appendix II, pages 1-6].

There were no reports of effects on growth identified in the applicant's review of the published medical literature for safety information relevant to the use of olopatadine [NDA 21-861, N-000 BB, Volume 3, Question 2 Response, pages 1-3].

7.1.16 Overdose Experience

No information is available on overdosage in humans in the clinical studies in this application [Module 2, Volume 8, Section 2.7.4.5, page 124].

There is no information on overdose in the product labeling for olopatadine 0.1% ophthalmic solution [Product Label, Patanol®]. There were no reports of overdose in worldwide postmarketing safety data for olopatadine 0.1% ophthalmic solution [Module 2, Volume 8, Section 2.7.4.6, pages 1-9].

There is no information on overdose in the Japanese product labeling for olopatadine 2.5 mg and 5 mg tablets [NDA 21-861, N-000 BB, Volume 1, Allelock Tablets Product Label, pages 1-11]. There were no reports of overdose in Japanese postmarketing safety data for olopatadine 2.5 mg and 5 mg tablets [NDA 21-861, N-000 BB, Volume 1, Dec 2003/Dec 2004 Periodic Safety Report, Appendix I, pages 1-3, Appendix II, pages 1-6].

There were no reports of overdose identified in the applicant's review of the published medical literature for safety information relevant to the use of olopatadine [NDA 21-861, N-000 BB, Volume 3, Question 2 Response, pages 1-3].

7.1.17 Postmarketing Experience

The applicant provided a review of postmarketing and spontaneous adverse event reports for olopatadine ophthalmic solution 0.1%. Olopatadine ophthalmic solution 0.1%, Patanol®, was approved in the United States on December 18, 1996. The review included worldwide spontaneous event reports over the period between January 1, 1997 and August 31, 2004 [Module 2, Volume 8, Section 2.7.4., pages 1-9]. Over this period, total sales of the product were (b) (4) units. The most common ocular adverse event was eye irritation (71 reports). The mon non-ocular adverse events were drug ineffective (198 reports), headache (45 reports), nausea (14 reports) dizziness (12 reports), and dermatitis (11 reports) [Module 2, Volume 8, Section 2.7.4., pages 1-9].

The applicant also provided a review of postmarketing adverse event reports for olopatadine tablets, which were approved in Japan on December 22, 2000. The review included adverse event reports from Japan for the period between December 18, 2000 and December 17, 2004 [NDA 21-861, N-000 BB, 4/11/05, Volume 1, Question 1 Response, page 1]. Over this period total sales of 2.5 mg tablets were (b) (4) tablets and total sales of 5.0 mg tablets were (b) (4) tablets. There were a total of 139 spontaneous adverse events reported to the Japanese Ministry of Health, Labor, and Welfare over this period. The most common spontaneous adverse events reported were eosinophil count increased (18 reports), white blood cell count increased (16 reports), hepatic function abnormal (16 reports), dizziness (9 reports), liver disorder (8 reports), and face edema (6 reports). There was one case of acute hepatitis and one case of jaundice. Based on the postmarketing data, in December 2002, the Japanese regulatory agency added hepatic function abnormal, liver disorder, acute hepatitis, and jaundice to the product label. There were also 7785 patients evaluable in a Japanese postmarketing clinical experience investigation. In this postmarketing investigation, there were 767 adverse events reported. The most common adverse events in the postmarketing investigation were somnolence (459 reports, 5.9%), malaise (26 reports, 0.3%), thirst (23 reports, 0.3%), SGOT increased (13 reports, 0.2%), LDH increased (11 reports, 0.1%), SGPT increased (10 reports, 0.1%), and GGT increased (10 reports, 0.1%) [NDA 21-861, N-000 BB, 4/11/05, Volume 1, Question 1 Response, pages 1, Appendix I, pages 1-3, Appendix II, pages 1-6].

There were no postmarketing spontaneous adverse event reports included in the applicant's safety update [NDA 21-861, N-000 SU, 7/7/05, Volume 1, Clinical Safety, pages 2-18].

The Japanese postmarketing data suggest that olopatadine tablets may be associated with hepatic function abnormalities. There was no signal for hepatic function abnormality in the safety data from clinical studies in the olopatadine nasal spray program. If approved, postmarketing adverse event reports for olopatadine nasal spray should be monitored for cases of hepatic function abnormalities.

7.2 Adequacy of Patient Exposure and Safety Assessments

The designs of the studies in this application, patient demographics, exposure of subpopulations, and duration of exposure to olopatadine 0.6% nasal spray are sufficient to allow for assessment of safety. Adequacy of patient exposure and safety assessments are reviewed in depth below.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

There were five clinical efficacy and safety studies considered by the applicant to be pivotal in their drug development program [Module 2, Volume 4, Section 2.5, pages 10-11, 44]. There were six supportive clinical efficacy and safety studies in the applicant's drug development program [Module 2, Volume 4, Section 2.5, pages 8-9]. There were seven pharmacokinetic (PK) and pharmacodynamic (PD) studies in the applicant's drug development program [Module 2, Volume 4, Section 2.5, pages 7-8, 42]. The designs of studies in this application were adequate to allow for assessment of safety.

The clinical efficacy and safety, PK, and PD studies in the olopatadine drug development program are summarized in Table 22.

Table 22 Summary of studies NDA 21-861 [Module 5, Volume 20, Section 2.7.6, pages 1-9; Module 5, Volume 20, Section 2.7.6, Study Synopses]

Pivotal Clinical Studies						
Study Number	**Study Type**	**Treatment Groups**	**Treatment duration**	**Design**	**Number of subjects**	**Diagnosis, age of subjects**
C-02-37	Pivotal efficacy and safety study	Olopatadine NS 0.4%, 2 sp ea nostril BID Olopatadine NS 0.6%, 2 sp ea nostril BID Vehicle placebo, 2 sp ea nostril BID	2 weeks	Multicenter, randomized, double blind, active and placebo controlled, parallel group	565	Patients with SAR, men and women, ≥12 years
C-02-10	Pivotal efficacy and safety study	Olopatadine NS 0.4%, 2 sp ea nostril BID Olopatadine NS 0.6%, 2 sp ea nostril BID Vehicle placebo, 2 sp ea nostril BID	2 weeks	Multicenter, randomized, double blind, active and placebo controlled, parallel group	677	Patients with SAR, men and women, ≥12 years
C-01-92	Long-term safety study	Olopatadine NS 0.6%, 2 sp ea nostril BID Vehicle placebo, 2 sp ea nostril BID	1 year	Multiple center, randomized, double blind, placebo controlled, parallel group	924	Patients with PAR, men and women, ≥12 years
C-01-83	Pivotal dose response EEU study	Olopatadine NS 0.2%, 2 sp ea nostril Olopatadine NS 0.4%, 2 sp ea nostril Olopatadine NS 0.6%, 2 sp ea nostril Vehicle placebo, 2 sp ea nostril	1 day	Single center, randomized, double blind, placebo controlled, parallel group	320	Patients with SAR, men and women, ≥16 years
C-03-52	Pivotal onset of action EEU study	Olopatadine NS 0.6%, 2 sp ea nostril Mometasone furoate 50 mcg, 2 sp ea nostril Vehicle placebo, 2 sp ea nostril	1 day	Single center, randomized, double blind, active and placebo controlled, parallel group	425	Patients with SAR, men and women, ≥18 years

Table 22, continued. Summary of studies NDA 21-861 [Module 5, Volume 20, Section 2.7.6, pages 1-9; Module 5, Volume 20, Section 2.7.6, Study Synopses]

Supportive Clinical Studies						
Study Number	**Study Type**	**Treatment Groups**	**Treatment duration**	**Design**	**Number of subjects**	**Diagnosis, age of subjects**
C-97-59	Pilot phase 2 EEU study	Olopatadine NS 0.1%, 1 sp ea nostril Azelastine NS 0.1%, 1 sp ea nostril Emedastine NS 0.05%, 1 sp ea nostril Vehicle placebo, 1 sp ea nostril	1 day	Single center, randomized, double blind, active and placebo controlled, four-way crossover	12	Patients with SAR, men and women, ≥16 years
C-00-10	Phase 2 dose response efficacy and safety study	Olopatadine NS 0.1%, 2 sp ea nostril QD Olopatadine NS 0.1%, 2 sp ea nostril BID Olopatadine NS 0.2%, 2 sp ea nostril QD Olopatadine NS 0.2%, 2 sp ea nostril BID Vehicle placebo, 2 sp ea nostril QD Vehicle placebo, 2 sp ea nostril BID	2 weeks	Multicenter, randomized, double blind, active and placebo controlled, parallel group	192	Patients with SAR, men and women, ≥12 years
C-00-33	Phase 2-3 efficacy and safety study	Olopatadine NS 0.1%, 2 sp ea nostril BID Azelastine NS 0.1%, 2 sp ea nostril BID Vehicle placebo, 2 sp ea nostril BID	2 weeks	Multicenter, randomized, double blind, active and placebo controlled, parallel group	166	Patients with SAR, men and women, ≥12 years
C-00-70	Phase 2 EEU study	Olopatadine NS 0.1%, 2 sp ea nostril Olopatadine NS 0.2%, 2 sp ea nostril Azelastine NS 0.1%, 2 sp ea nostril Vehicle placebo, 2 sp ea nostril	1 day	Single center, randomized, single blind, active and placebo controlled, three-phase, two-way crossover	20	Patients with SAR, men and women, ≥16 years
C-01-05	Phase 2-3 efficacy and safety study	Olopatadine NS 0.1%, 2 sp ea nostril QD Olopatadine NS 0.1%, 2 sp ea nostril BID Azelastine NS 0.1%, 2 sp ea nostril BID Vehicle placebo, 2 sp ea nostril QD Vehicle placebo, 2 sp ea nostril BID	8 weeks	Multicenter, randomized, double blind, active and placebo controlled, parallel group	397	Patients with SAR, men and women, ≥12 years
C-03-48	Phase 3 pilot onset of action EEU study	Olopatadine NS 0.6%, 2 sp ea nostril Fluticasone propionate 0.05%, 2 sp ea nostril Vehicle placebo, 2 sp ea nostril	1 day	Single center, randomized, double blind, active and placebo controlled, parallel group	90	Patients with SAR, men and women, ≥12 years

Table 22, continued. Summary of studies NDA 21-861 [Module 5, Volume 20, Section 2.7.6, pages 1-9; Module 5, Volume 20, Section 2.7.6, Study Synopses]

Clinical Pharmacology Studies						
Study Number	**Study Type**	**Treatment Groups**	**Treatment duration**	**Design**	**Number of subjects**	**Diagnosis, age of subjects**
C-00-58	Phase 1 PK study	Olopatadine NS 0.1%, 2 sp ea nostril QD Olopatadine NS 0.1%, 2 sp ea nostril BID Olopatadine NS 0.2%, 2 sp ea nostril QD	2.5 days	Single center, randomized, open label, multiple dose, parallel group	36	Healthy men and women, 18-75 years
C-02-21	Phase 1 PK study	Olopatadine NS 0.6%, 2 sp ea nostril Vehicle placebo NS, 2 sp ea nostril	1 day	Single center, randomized, double blind, single dose, parallel group	36	Healthy men and women, ≥18 years
C-03-11	Phase 1 BA study	Olopatadine NS 0.4%, 2 sp ea nostril Olopatadine NS 0.6%, 2 sp ea nostril Olopatadine iv solution 0.01%, 1.5 mg	1 day	Single center, randomized, open label, single dose, three way crossover	12	Healthy men and women, 18-45 years
C-02-46	Phase 1 PK study	Olopatadine NS 0.6%, 2 sp ea nostril	1 day	Single center, randomized, open label, single dose	25	Adult men and women with renal impairment, ≥18 years
C-03-10	Phase 1 mass balance excretion study	Olopatadine oral solution 0.67%, 5 mg/200 µCi ^{14}C olopatadine	1 day	Single center, open label, single dose	8	Healthy men and women, 19-45 years
C-02-54	Phase 1 cardiac safety and PK study	Olopatadine oral solution, 0.2%, 20 mg BID Placebo solution BID	2 weeks	Single center, randomized, double blind, placebo controlled, multiple dose, 2-way crossover	34	Healthy men and women, 18-75 years
C-00-23	Phase 1 cardiac safety and PK study	Olopatadine oral solution, 5 mg BID Placebo solution BID	2.5 days	Single center, randomized, double blind, placebo controlled, multiple dose, 2-way crossover	117	Healthy men and women, 18-75 years

7.2.1.2 Demographics

The demographics of patients in all clinical studies in the olopatadine nasal spray drug development program are summarized in Table 23. The large majority of patients in the clinical studies ranged between 12-64 years of age. Patients 65 years of age and older represented 2.7% of the population. There were more females than males in the studies in the drug development program. Patients of Caucasian race represented the largest racial population in the drug development program, but patients of Black and Hispanic races were represented at proportions fairly comparable to that of the general population.

For the concentration of olopatadine proposed for marketing, 0.6%, the majority of patients were also from 18-64 years of age. There were fairly few patients 65 years of age and older exposed to olopatadine 0.6%. Racial subgroups were represented at proportions fairly comparable to that of the general population [Module 2, Volume 9, Section 2.7.4.7, pages 3-12].

The demographics of patients in the clinical program and exposure of subpopulations to olopatadine 0.6% nasal spray are adequate to provide an assessment of safety.

Table 23 Demographics, all clinical studies, olopatadine nasal spray drug development program [Module 2, Volume 9, Section 2.7.4.7, pages 3-12]

	Age, yr			**Gender**		**Race**				
Treatment	**12-17**	**18-64**	**>65**	**Male**	**Female**	**Caucasian**	**Black**	**Asian**	**Hispanic**	**Other**
	N	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**
Total (%)	341 (8.0)	3795 (89.3)	114 (2.7)	1707 (40.2)	2543 (59.8)	2999 (42.5)	497 (11.7)	177 (4.2)	503 (11.9)	74 (1.7)
	n	**n**	**n**	**n**	**n**	**n**	**n**	**n**	**n**	**n**
O 0.6% BID/QD	101	1026	36	446	717	812	123	65	152	11
O 0.4% BID/QD	32	464	14	177	333	353	48	11	96	2
O 0.2% BID	1	42	0	20	23	33	8	0	0	2
O 0.2% QD	6	123	1	59	71	77	22	22	7	2
O 0.1% BID	24	160	2	87	99	146	30	5	0	5
O 0.1% QD	18	155	1	75	99	132	32	3	0	7
O oral, iv BID/QD	0	157	9	86	80	103	4	2	50	7
E 0.05% QD	0	12	0	7	5	12	0	0	0	0
Az 0.1% BID	23	119	5	58	89	123	18	2	0	4
Az 0.1% QD	0	30	0	14	16	22	6	0	0	2
FP 0.05% QD	3	27	0	9	21	15	11	0	0	4
MFNA 50 mcg QD	0	140	2	71	71	74	47	7	9	5
Veh pbo BID	105	869	34	374	634	766	76	23	133	10
Veh pbo QD	28	339	2	156	213	246	68	35	14	6

Veh oral BID	0	132	8	68	72	85	4	2	42	7

O: Olopatadine E: Emedastine Az: Azelastine MFNA: Mometasone furoate nasal spray Veh pbo: Vehicle placebo

7.2.1.3 Extent of exposure (dose/duration)

The extent of exposure in all clinical studies in the olopatadine nasal spray drug development program is summarized in Table 24. Overall, there were 4250 patients exposed to study treatment in the drug development program. Overall exposure to olopatadine nasal spray, from 0.1% to 0.6% concentrations, was 2206 patients. The overall exposure to olopatadine nasal spray is greater than the 1500 patients recommended in ICH and FDA guidances [International Conference on Harmonisation (ICH) Guideline for Industry E1A, Extent of Population Exposure Required to Assess Clinical Safety: For Drugs Intended For Long-Term Treatment of Non-Life-Threatening, March 1995, and FDA Draft Guidance for Industry, Allergic Rhinitis: Clinical Development Programs for Drug Products, June 2000].

Table 24 Extent of exposure, all clinical studies, olopatadine nasal spray drug development program [Module 2, Volume 7, Section 2.7.4.7, pages 1-2]

Treatment	Total N	1 day n (%)	2-10 days n (%)	11-20 days n (%)	21-40 days n (%)	41-70 days n (%)	71-160 days n (%)	161-250 days n (%)	251-340 days n (%)	341-368 days n (%)	≥369 days n (%)
Total	4250	1027 (24.2)	344 (8.1)	1602 (37.7)	63 (1.5)	386 (9.1)	57 (1.3)	63 (1.5)	53 (1.2)	479 (11.3)	176 (4.1)
O 0.6% BID/QD	1163	305 (26.2)	15 (1.3)	394 (33.9)	14 (1.2)	11 (0.9)	29 (2.5)	34 (2.9)	24 (2.1)	245 (21.1)	92 (7.9)
O 0.4% BID/QD	510	92 (18.0)	7 (1.4)	407 (79.8)	4 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
O 0.2% BID	43	0 (0)	12 (27.9)	37 (72.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
O 0.2% QD	130	99 (76.2)	2 (1.5)	29 (22.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
O 0.1% BID	186	0 (0)	15 (8.1)	78 (41.9)	4 (2.2)	89 (47.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
O 0.1% QD	174	14 (8.0)	34 (19.5)	32 (18.4)	3 (1.7)	91 (52.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
O oral, iv BID/QD	166	22 (13.3)	112 (67.5)	32 (19.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
E 0.05% QD	12	12 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Az 0.1% BID	147	1 (0.7)	5 (3.4)	47 (32.0)	4 (2.7)	90 (61.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Az 0.1% QD	30	30 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
FP 0.05% QD	30	30 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
MFNA 50 mcg QD	142	142 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Veh pbo BID	1008	11 (11.1)	16 (1.6)	482 (47.8)	33 (3.3)	62 (6.2)	28 (2.8)	29 (2.9)	29 (2.9)	234 (23.2)	84 (8.3)
Veh pbo QD	369	269 (72.9)	19 (5.1)	37 (10.0)	1 (0.3)	43 (11.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Veh oral BID	140	0 (0)	107 (76.4)	33 (23.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

O: Olopatadine E: Emedastine Az: Azelastine MFNA: Mometasone furoate nasal spray Veh pbo: Vehicle placebo

Cumulative duration of exposure to the olopatadine 0.6% nasal spray, the concentration proposed for marketing, is summarized in Table 25. Exposures to olopatadine 0.6% nasal spray approximate the 300 patients evaluated for 6 months and 100 patients evaluated for 1 year recommended in ICH and FDA guidances [International Conference on Harmonisation (ICH) Guideline for Industry E1A, Extent of Population Exposure Required to Assess Clinical Safety: For Drugs Intended For Long-Term Treatment of Non-Life-Threatening, March 1995, and FDA Draft Guidance for Industry, Allergic Rhinitis: Clinical Development Programs for Drug Products, June 2000].

Table 25 Cumulative duration of exposure to olopatadine 0.6% nasal spray, olopatadine nasal spray drug development program [Module 2, Volume 7, Section 2.7.4.7, pages 1-2]

Treatment	Total N	1 day n (%)	≥2 days n (%)	≥11 days n (%)	≥21 days n (%)	≥41 days n (%)	≥71 days n (%)	≥161 days n (%)	≥251 days n (%)	≥341 days n (%)	≥369 days n (%)
O 0.6% BID/QD	1163	1163 (100.0)	858 (73.8)	843 (72.5)	449 (38.6)	435 (37.4)	424 (36.5)	395 (34.0)	361 (31.0)	337 (29.0)	92 (7.9)

O: Olopatadine

The overall exposure and duration of exposure to olopatadine 0.6% nasal spray are sufficient to allow for assessment of safety.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No other clinical studies provided data for evaluation of safety.

7.2.2.2 Postmarketing experience

The applicant provided a review of postmarketing and spontaneous adverse event reports for olopatadine ophthalmic solution 0.1%. Olopatadine ophthalmic solution 0.1%, Patanol®, was approved in the United States on December 18, 1996. The review included worldwide spontaneous event reports over the period between January 1, 1997 and August 31, 2004 [Module 2, Volume 8, Section 2.7.4., pages 1-9].

The applicant also provided a review of postmarketing adverse event reports for olopatadine tablets, which were approved in Japan on December 22, 2000. The review included adverse event reports from Japan for the period between December 18, 2000 and December 17, 2004 [NDA 21-861, N-000 BB, 4/11/05, Volume 1, Question 1 Response, page 1].

7.2.2.3 Literature

The applicant provided a review of the medical literature for safety information relevant to the use of olopatadine. The review was based on a search of Medline for published clinical trials that included olopatadine. The search was limited to clinical trials published in English and excluded studies reported only in abstracts. The search identified 33 studies, including 30 studies with ophthalmic formulations of olopatadine and three studies with oral administration of olopatadine. The applicant provided a summary of each of the studies and an analysis of the safety information included in them [NDA 21-861, N-000 BB, 4/11/05, Volume 3, Question 2 Response, page 1].

7.2.3 Adequacy of Overall Clinical Experience

The designs of studies in this application, as described in Section 7.2.1.1, were adequate to allow for assessment of safety.

As noted above in Section 7.2.1.2 and Section 7.2.1.3, there was an adequate number of subjects exposed to the drug, and adequate numbers within demographic subsets to allow for an assessment of safety. In addition, as noted in Section 7.2.1.3, the doses and duration of exposure were also adequate to allow for an assessment of safety.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Non-clinical data showed that olopatadine did not cause QT prolongation, even when co-administered with the CYP 3A4-inhibitor itraconazole. Olopatadine blocked hERG channels, but only at a high IC50 of 1.1 mM [Gary Bond, Ph.D., Pharmacology Review, NDA 21-861, N-000, 12/24/04]. The applicant performed integrated analyses of ECG data from supportive SAR studies C-00-10, C-00-33, and C-01-05 and a separate analysis of ECG data from long-term PAR study C-01-92. In addition, the applicant performed two high dose cardiac safety studies with oral olopatadine at the doses of 5 mg twice daily for 2 ½ days (C-00-23) and 20 mg twice daily for 14 days (C-02-54). The studies in the applicant's clinical drug development program were sufficient to assess the cardiac safety of olopatadine.

7.2.5 Adequacy of Routine Clinical Testing

The bulk of the safety data in this application comes from pivotal efficacy and safety studies C-02-37, C-02-10, and C-01-92. Adverse events, both volunteered and elicited, were collected at study visits in these studies. Adverse events were not recorded by patients in patient logs in study C-02-37. Adverse events were recorded by patients in patient logs in Studies C-02-10 and 01-92 [Module 5, Volume 47, pages 74, 75, 195; Module 5, Volume 56, pages 76-78, 194; [Module 5, Volume 65, pages 3, 62, 66-67, 76-78]. The patient logs used in these studies instructed patients to list new medical problems and medications that they took since their last visit and gave "sprained ankle treated with Tylenol" as an example [NDA 21-861, N-000 BZ, 7/14/05, page not numbered]. The example could have led some patients to record only more severe medical

problems or medical problems that required treatment with medications. If so, it is possible that some milder adverse events may not have been reported or recorded by patients.

Otherwise, the methods of monitoring laboratory parameters, vital signs, physical examinations, nasal examinations, and ECGs were adequate to allow for assessment of safety.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Data from the in-vitro metabolism of ^{14}C-olopatadine showed that metabolism of olopatadine is a minor route of elimination. In addition, olopatadine did not affect the activity of the major CYP P450 enzymes such as 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. It is unlikely that substrates, inhibitors or inducers of these enzymes may affect the PK of olopatadine and its metabolites. No major effects of olopatadine should be expected on the PK of other drugs [S. Suarez, Ph.D., Clinical Pharmacology and Biopharmaceutics Review, NDA 21-861, N-000, 12/24/04]. The applicant's evaluation of the metabolism of olopatadine and its potential for drug interaction was adequate.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Evaluation of the potential for somnolence and anticholinergic effects, which are associated with older antihistamines, may have been less than ideal. Adverse events, both volunteered and elicited, were collected at study visits in pivotal efficacy and safety studies C-02-37, C-02-10, and C-01-92. Adverse events were not recorded by patients in patient logs in study C-02-37. Adverse events were recorded by patients in patient logs in Studies C-02-10 and 01-92 [Module 5, Volume 47, pages 74, 75, 195; Module 5, Volume 56, pages 76-78, 194; [Module 5, Volume 65, pages 3, 62, 66-67, 76-78]. The patient logs used in these studies instructed patients to list new medical problems and medications that they took since their last visit and gave "sprained ankle treated with Tylenol" as an example [NDA 21-861, N-000 BZ, 7/14/05, page not numbered]. The example could have led some patients to record only more severe medical problems or medical problems that required treatment with medications. If so, it is possible that some milder adverse events such as somnolence and dry mouth may not have been reported or recorded by patients. Despite this limitation, studies in the application were able to detect a signal for somnolence, which was reported by 1.1% (13/1163) of patients treated with olopatadine nasal spray 0.6% and by 0.2% (2/1008) of those treated with vehicle placebo nasal spray twice daily. Urinary retention, another anticholinergic effect, would have been less likely to be overlooked because of its severity.

Two antihistamines previously approved in the United States were withdrawn from the market because of QT prolongation associated with higher than recommended doses and drug-drug interactions. The applicant's evaluation of the cardiac safety of olopatadine and its potential for drug interaction was acceptable, as noted previously.

7.2.8 Assessment of Quality and Completeness of Data

As noted above, the applicant's safety assessments were adequate to conduct an appropriate safety review.

7.2.9 Additional Submissions, Including Safety Update

The applicant submitted the required 120-day safety update, dated July 7, 2005 [NDA 21-861, N-000 SU, 7/7/05]. The clinical portion of the safety update includes information on one completed clinical study of olopatadine nasal spray, 0.6% and 0.4%. The safety update also notes that there is safety information on three ongoing clinical studies. The information from these three studies is limited, however. The applicant states that there have been no serious adverse events and no patients who have discontinued because of adverse events in two of the three ongoing studies, and that no patients have been enrolled in the third ongoing study [NDA 21-861, N-000 SU, 7/7/05, Volume 1, Section 1, pages 16-17]. Safety information regarding adverse events of epistaxis and nasal ulceration occurring in the completed study, C-03-51, is addressed in Section 7.1.6 of this review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The following are considered to be important, treatment-related adverse events. Discussions of the adverse events are found in the corresponding referenced sections of this review.

- Epistaxis — Section 7.1.5.3, Section 7.1.5.4, Section 7.1.6
- Taste perversion — Section 7.1.5.3, Section 7.1.5.4
- Dry nose — Section 7.1.5.4
- Somnolence — Section 7.1.6
- Nasal ulcer — Section 7.1.6
- Nasal septum disorder — Section 7.1.6
- Nasal septum perforation — Section 7.1.6

Common, less important adverse events included cold syndrome, cough increased, flu syndrome, arthralgia, and dyspepsia. These events occurred at a frequency of greater than 2% and more commonly in olopatadine 0.6% than in vehicle placebo and are addressed in Section 7.1.5.4 of this review. A dose response effect was noted for taste perversion and dyspepsia. The frequencies of cold syndrome and flu syndrome were fairly similar for the olopatadine 0.6% and vehicle placebo groups.

In conclusion, the formulation for the proposed product appears to be toxic to the nasal mucosa, and is associated with epistaxis, nasal ulcer, and with chronic use is associated with a significant risk of nasal septum perforation. As noted previously, non-clinical data suggest that the signal may be related to the povidone excipient. Based on AERS data, it appears that nasal septum perforation is extremely rare among non-steroid nasal sprays with allergic rhinitis indications. Even among corticosteroid nasal sprays with allergic rhinitis indications, nasal septum

perforation appears to be less frequent than with olopatadine nasal spray uncommon. These findings represent a major safety signal and are sufficient to affect the approvability of the application.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Pooling of data is discussed in the following sections of this review.

7.4.1.1 Pooled data vs. individual study data

Adverse events occurring in all studies for olopatadine at a frequency of ≥2.0% were summarized by treatment group by the applicant to obtain a comprehensive listing of adverse events noted with the various formulations of olopatadine, active controls, and vehicle placebo controls used in the clinical development program.

Adverse events occurring in pivotal efficacy and safety studies for SAR and PAR (C-02-37, C-02-10, and C-02-92) were integrated to arrive at a comprehensive listing of adverse events associated with olopatadine 0.6% nasal spray, the concentration proposed for marketing.

Clinical laboratory studies were performed in the two pivotal SAR efficacy and safety studies (C-02-37 and C-02-10), two supportive SAR studies with lower concentrations of olopatadine, and in six pharmacokinetic studies. This summary of laboratory findings focused on the laboratory data from the two pivotal SAR efficacy and safety studies, where patients were dosed with olopatadine 0.6% and olopatadine 0.4% nasal sprays dosed twice daily for two weeks.

Vital signs testing was performed in seven PK and PD studies, one nasal allergen challenge study, three environmental exposure unit studies, and six natural exposure safety and efficacy studies in patients with SAR or PAR in the drug development program for olopatadine nasal spray. The summary of vital signs mainly focused on the data from the six natural exposure studies in patients with SAR or PAR, where patients were dosed with olopatadine spray at concentrations of 0.1% to 0.6% twice daily for two weeks to one year.

ECGs were performed as safety endpoints in 10 studies in this application. ECGs were performed in three PK and safety studies with oral olopatadine (C-00-23, C-02-54, and C-03-10), two PK and safety studies with single dose exposure to olopatadine 0.6% nasal spray (C-02-46 and C-03-11), three non-pivotal SAR studies (C-00-10, C-00-33, and C-01-05) and one PK study (C-00-58) with 0.1% and 0.2% concentrations of olopatadine, and one long-term pivotal PAR study (C-01-92).

Integrated analyses of ECG data from supportive SAR studies C-00-10, C-00-33, and C-01-05 were performed by the applicant. The applicant also performed a separate analysis of ECG data from the long-term PAR study C-01-92. The applicant excluded the PK studies (C-00-58, C-02-

54, C-03-10, and C-03-11) from the ECG analysis because ECG assessments included only an evaluation of whether the ECG was normal or abnormal.

7.4.1.2 Combining data

The rationale for combining data by pooling is addressed in the previous section of this review, Section 7.4.1.1.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Dose-response effects were noted for taste perversion and dyspepsia in the pivotal efficacy and safety studies, C-02-37, C-02-10, and C-01-92. Somnolence was noted frequently in studies using 5 mg and 20 mg olopatadine orally twice daily, but at much lower frequencies with olopatadine nasal spray, 0.1%, 0.2%, 0.4%, and 0.6%. Dose dependency of adverse findings was suggested by a dose-response relationship between the frequency of an adverse event and the dose of study treatment taken.

7.4.2.2 Explorations for time dependency for adverse findings

Nasal septum perforations were noted only in the one-year (b) (4) safety study for PAR, C-01-92.

The applicant sorted adverse events by onset day for all clinical studies and for multiple dose studies with olopatadine 0.6% nasal spray. A review of adverse events by onset day revealed no clinically relevant differences between treatment groups [Module 2, Volume 8, Section 2.7.4.5, page 123].

No other clinical explorations for time dependency for adverse findings were performed.

7.4.2.3 Explorations for drug-demographic interactions

The frequency of epistaxis in children 6 to 11 years of age was higher than the frequency of epistaxis in adults, when comparing two-week SAR studies. The frequency of nasal ulceration in children 6 to 11 years of age was much higher than the frequency of nasal ulceration in adults, when comparing these studies.

An examination of the frequency of adverse events associated with olopatadine and demographic characteristics did not suggest any other drug-demographic interactions.

7.4.2.4 Explorations for drug-disease interactions

An examination of the frequency of adverse events, laboratory studies, vital signs, physical examinations, nasal examinations, and ECGs in patients with varying severities of renal disease did not identify a drug-disease interaction, as noted in Section 10.1.14 of this review.

The applicant performed an analysis of adverse events occurring in patients with baseline concomitant diseases. The baseline concomitant diseases included arthritis, asthma, diabetes mellitus, gastrointestinal disorders, hyperlipidemia, hypertension, musculoskeletal disorders, nervous system disorders, and thyroid disorders. No safety concerns were identified by this analysis of patients with these baseline concomitant diseases [Module 2, Volume 8, Section 2.7.4.5, pages 40-66]. There were no other explorations of drug-disease interactions performed in this application.

7.4.2.5 Explorations for drug-drug interactions

The applicant performed an analysis of adverse events occurring in patients taking concomitant medications. The baseline medications included analgesics and antipyretics, antidiabetic agents, antihistamine drugs, anti-infective agents, antilipemic agents, antitussives and expectorants, cardiovascular drugs, CNS agents, eye, ear, nose and throat preparations, gastrointestinal drugs, hormones and synthetic substitutes, NSAIDS, psychotherapeutic agents, serums, toxoids, and vaccines, sympathomimetic agents, and thyroid and antithyroid agents. No safety concerns were identified by this analysis of patients taking concomitant medications [Module 2, Volume 8, Section 2.7.4.5, pages 67-122]. There were no other explorations of drug-disease interactions performed in this application. No other clinical explorations for drug-drug interactions were performed.

7.4.3 Causality Determination

Epistaxis, nasal ulcer, and nasal septum disorder were attributed to olopatadine nasal spray and olopatadine nasal spray vehicle placebo. These nasal adverse events are likely to be related to topical administration of this nasal spray product.

Nasal septum perforation was associated with olopatadine 0.6% nasal spray and olopatadine nasal spray vehicle. The formulation appears to be irritating to the nasal mucosa, and non-clinical data suggest that the formulation is toxic to the nasal mucosa [Communication to Applicant dated 5/25/05; Pharmacology-Toxicology Review, Gary Bond, Ph.D., NDA 21-861, N-000, 12/24/04].

Taste perversion was attributed to olopatadine nasal spray. There was a dose response relationship with the frequency of taste perversion. In addition, azelastine, an antihistamine nasal spray approved for treatment of symptoms of SAR is also associated with taste perversion.

Dry nose was attributed to olopatadine nasal spray 0.6%. The incidence of dry nose for olopatadine 0.6% (1.4%, 12/866) was higher than for olopatadine 0.4% (0.2%, 1/418) or vehicle placebo (0.2%, 2/882), as noted in Section 7.1.5.4 of this review.

Somnolence was attributed to olopatadine, although it was infrequently noted. Somnolence was reported in the olopatadine clinical development program by 1.1% (13/1163) of patients treated with olopatadine nasal spray 0.6% and by 0.2% (2/1008) of those treated with vehicle placebo nasal spray twice daily. Somnolence was noted in the high dose cardiac safety studies in this application by 13.5% (7/166) of patients treated with olopatadine 5 mg or 20 mg twice daily by mouth. Olopatadine clearly produces somnolence at high doses. At the dose and concentration propose for marketing, olopatadine 0.6% nasal spray appears to be associated with somnolence infrequently, but at a rate higher than vehicle placebo. Somnolence was the most common adverse event in the clinical development program for olopatadine 2.5 mg and 5 mg tablets, which are approved in Japan.

The frequency of somnolence is sufficiently low to be excluded from the table of common adverse events in the ADVERSE REACTIONS section of the olopatadine 0.6% nasal spray label, but is different enough from vehicle placebo that a “non-sedating” claim would not be supported if this product were to be approved.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dose of olopatadine 0.6% nasal spray in adults and children 12 years of age and older is two sprays per nostril twice daily (2.66 mg olopatadine HCl twice daily or 2.4 mg olopatadine free base twice daily). The studies in this application support the proposed concentration and dose of the product for the SAR indication.

Phase 2 and 2/3 dose ranging studies C-01-83, C-97-59, C-00-10, C-00-33, and C-01-05 failed to demonstrate efficacy for 0.1% and 0.2% concentrations of olopatadine. These studies are reviewed in Section 10.1 of this document.

Pivotal SAR efficacy and safety studies C-02-37 and C-02-10 showed efficacy for both 0.4% and 0.6% concentrations of olopatadine, but there was an efficacy advantage for the 0.6% concentration. Effect sizes were larger for olopatadine 0.6% than for olopatadine 0.4%. These studies are reviewed in Sections 10.1.1 and 10.1.2 of this document. Onset of action studies C-01-83 showed efficacy sufficient to support an onset of action claim for olopatadine 0.6% but not for olopatadine 0.2% or 0.4%. The onset of action of olopatadine 0.6% was replicated in study C-03-52. These studies are reviewed in Sections 10.1.4 and 10.1.5 of this document.

Twice daily dosing is supported by pivotal SAR efficacy and safety studies C-02-37 and C-02-10 and onset of action studies C-01-83 and C-03-52, which showed evidence of efficacy at the end

of the dosing interval. These studies are reviewed in Sections 10.1.1 , 10.1.2, 10.1.4, and 10.1.5 of this document.

Dose related adverse events for olopatadine nasal spray included taste perversion and dyspepsia. Taste perversion may affect patient acceptance of the product but would not be expected to create safety concerns. The incidence of dyspepsia was low (2.1% for olopatadine 0.6%) and is not likely to cause major safety concerns.

At the dose and concentration proposed for marketing, olopatadine 0.6% nasal spray appears to be associated with somnolence infrequently, but at a rate higher than vehicle placebo. There was no evidence for a dose response effect for somnolence with the nasal spray formulation of olopatadine. Higher oral doses of olopatadine are associated with somnolence.

Epistaxis, nasal ulceration, and nasal septum perforation were not dose related. Nasal ulceration and nasal septum perforation were related to the formulation and occurred both in olopatadine 0.6% nasal spray and vehicle placebo.

No modification of the proposed dose is necessary for special populations. Decreased efficacy in patients 12-17 years of age was noted in the pivotal SAR efficacy and safety studies, but the number of patients in this age group was small and the finding is probably not relevant given the overall efficacy findings among the other age groups. There was no difference in efficacy among other special populations. There were no differences in the safety profile among patients 12-17 years of age, 18-64 years, 65 years of age or greater, or among patients of different genders or races.

(b) (4)

8.2 Drug-Drug Interactions

Data from the in-vitro metabolism of ^{14}C-olopatadine showed that metabolism of olopatadine is a minor route of elimination. In addition, olopatadine did not affect the activity of the major CYP P450 enzymes such as 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. It is unlikely that substrates, inhibitors or inducers of these enzymes may affect the PK of olopatadine and its metabolites. No major effects of olopatadine should be expected on the PK of other drugs [S. Suarez, Ph.D., Clinical Pharmacology and Biopharmaceutics Review, NDA 21-861, N-000, 12/24/04].

The applicant also performed an analysis of adverse events occurring in patients taking concomitant medications. The baseline medications included analgesics and antipyretics, antidiabetic agents, antihistamine drugs, anti-infective agents, antilipemic agents, antitussives and expectorants, cardiovascular drugs, CNS agents, eye, ear, nose and throat preparations, gastrointestinal drugs, hormones and synthetic substitutes, NSAIDS, psychotherapeutic agents, serums, toxoids, and vaccines, sympathomimetic agents, and thyroid and antithyroid agents. No safety concerns were identified by this analysis of patients taking concomitant medications.

8.3 Special Populations

No modification of the proposed dose is necessary for special populations. Decreased efficacy in patients 12 to 17 years of age was noted in the pivotal SAR efficacy and safety studies, but the number of patients in this age group was small and the finding is probably not relevant given the overall efficacy findings among the other age groups. This is discussed in Sections 10.1.1 and 10.1.2 of this document. There was no difference in efficacy among other special populations. There were no differences in the safety profile among patients 12 to 17 years of age, 18 to 64 years, 65 years of age or greater, or among patients of different genders or races.

Children 6 to 11 years of age appear to be more sensitive to epistaxis and nasal ulceration from the formulation than adults. The applicant completed study C-03-51 after submission of the NDA, and submitted a study summary with the 120-day safety update. The frequency of epistaxis in children 6 to 11 years of age was higher than the frequency of epistaxis in adults, when comparing two-week SAR studies. The frequency of nasal ulceration in children 6 to 11 years of age was much higher than the frequency of nasal ulceration in adults, when comparing these studies. These findings are discussed in Section 7.1.6 of this document.

An examination of the frequency of adverse events, laboratory studies, vital signs, physical examinations, nasal examinations, and ECGs in patients with varying severities of renal disease did not identify a drug-disease interaction, as noted in Section 10.1.14 of this review. The applicant performed an analysis of adverse events occurring in patients with baseline concomitant diseases. The baseline concomitant diseases included arthritis, asthma, diabetes mellitus, gastrointestinal disorders, hyperlipidemia, hypertension, musculoskeletal disorders, nervous system disorders, and thyroid disorders. No safety concerns were identified by this analysis of patients with these baseline concomitant diseases.

Non-clinical data suggest that olopatadine is not teratogenic. The clinical study protocols in the olopatadine nasal spray drug development program excluded the participation of pregnant females. No adequate and controlled clinical studies of olopatadine have been conducted in pregnant women. The applicant's proposed labeling states that the product should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the fetus.

The applicant's proposed labeling states that olopatadine has been identified in the milk of nursing rats and that it is not known if topical nasal administration could result in sufficient systemic absorption to produce detectable quantities in human breast milk. The labeling states that the product should be used by nursing mothers only if the potential benefit to the patient outweighs the potential risk to the infant.

8.4 Pediatrics

The applicant requested a waiver of pediatric studies for children less than 2 years of age [Module 1, Volume 1, Section 3.A.8, page 1]. The applicant states that it is unlikely that the product would be used in a substantial number of patients less than 2 years of age that non-pharmacologic treatment, such as allergen avoidance, may be used. The applicant also notes that

it is not practical to treat children less than 2 years of age with nasal spray formulations. This reviewer concurs with the applicant's rationale and supports the granting of a waiver at the time of the NDA action for studies in patients less than two years of age.

During the review cycle for the NDA, the applicant submitted a Proposal for a Pediatric Study Request (PPSR) [IND 60,116, N-060 PA, 12/20/04]. The Division declined to issue a Written Request for pediatric studies because there was insufficient information at that time to determine if there are safety concerns for use of the product in younger children. Given the safety signal noted for nasal ulceration nasal septum perforation, it still is not appropriate to issue a Written Request of pediatric studies.

During the NDA review cycle, the applicant completed a two-week dose-ranging, efficacy, PK, and safety study in SAR in patients 6 to 11 years of age [NDA 21-861, N-000 SU, Volume 1, Section 1, pages 9-10]. There are no data on the pharmacokinetics or safety of the product in children from 2 to less than 6 years of age. Ultimately, any Written Request for pediatric studies for this drug must address not only children from 6 to 11 years of age, but also children from 2 to less than 6 years of age.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. NDA acknowledgement letters are required to address waiver or deferral of the pediatric study requirement. There was no NDA acknowledgment letter for this application, however. The pediatric study requirement should be addressed in the action letter for this application. Given the safety signal for nasal ulceration and nasal septum perforation, pediatric studies in children 2 to 11 years of age should be deferred until the applicant has developed a formulation that is not toxic to the nasal mucosa and demonstrated its clinical safety in older patients.

8.5 Advisory Committee Meeting

There was no advisory committee meeting held regarding this application.

8.6 Literature Review

The applicant provided a review of the medical literature for safety information relevant to use of olopatadine as part of their Integrated Summary of Safety. The review was based on a search of Medline for published clinical trials that included olopatadine. The search was limited to clinical trials published in English and excluded studies reported only in abstracts. The search identified 33 studies, including 30 studies with ophthalmic formulations of olopatadine and three studies with oral administration of olopatadine. The applicant provided a summary of each of the studies an analysis of the safety information included in them [NDA 21-861, N-000 BB, 4/11/05, Volume 3, Question 2 Response, page 1]. Safety information relevant to the applicant's review of the medical literature is addressed in Sections 7.1.1, 7.1.2, 7.1.6, 7.1.13, 7.1.15, and 7.1.16 of this review.

8.7 Postmarketing Risk Management Plan

The applicant did not submit a postmarketing risk management plan.

8.8 Other Relevant Materials

The Division of Medication and Technical Support was consulted to review the applicant's proposed trade name, "Patanase® (olopatadine HCl) Nasal Spray, 665 mcg" and proposed labeling. The consultation is pending at the time of this review.

DSI audits are addressed in Section 4.4 of this review.

There were no actual use or label comprehension studies in this application.

9 OVERALL ASSESSMENT

9.1 Conclusions

The applicant's data support the efficacy of olopatadine 0.6% nasal spray and olopatadine 0.4% nasal spray for the treatment of symptoms of SAR, (b) (4) The applicant is only seeking approval of olopatadine 0.6%.

Data for the primary efficacy endpoint in the pivotal SAR efficacy and safety studies provide convincing evidence of efficacy, in replicate, for olopatadine 0.6%, the applicant's proposed concentration, and for olopatadine 0.4% for SAR. There is an efficacy advantage of olopatadine 0.6% over olopatadine 0.4%. The efficacy advantage provides support for the applicant's choice to seek approval of olopatadine 0.6% and not olopatadine 0.4%. The applicant's data support end of dosing interval efficacy for olopatadine 0.6% and olopatadine 0.4%. Improvements in individual symptom scores were noted for runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes for olopatadine 0.6% and olopatadine 0.4%. Improvements in stuffy nose scores were smaller than those for the other individual symptoms for olopatadine 0.6%. Evidence of dose response effect in each of the studies was noted for all symptoms except stuffy nose. The data suggest that olopatadine 0.6% has an efficacy advantage over olopatadine 0.4% in degree of effect and the number and types of individual symptoms for which there is evidence of efficacy. The dose response effect noted for each of the symptoms provides support for the applicant's choice to seek approval of the olopatadine 0.6% over olopatadine 0.4%.

(b) (4)

The applicant has provided adequate data to assess the safety of olopatadine 0.6% nasal spray. The product appears to be toxic to the nasal mucosa and is associated with nasal ulceration and nasal septum perforation. The preclinical findings suggest that the toxicity is related to the product formulation and not to olopatadine drug substance and the clinical data supports this conclusion because the nasal events were present in patients treated with olopatadine 0.6% nasal spray and vehicle placebo nasal spray. The safety data do not support approval of this application. Although the nasal septum perforations occurred only in the one-year PAR study and not in the two-week SAR studies, an attempt to manage the risk of this adverse event by limiting its use to a short period of treatment would not be an option. The duration of treatment with the product in the general population would be longer than two weeks. Patients with seasonal allergic rhinitis commonly have symptoms that last through more than one season of symptoms, and it is reasonable that many practitioners might use the product for PAR, even if the product was approved only for treatment of symptoms of SAR. Furthermore, the finding of nasal ulcerations (3.7%) in the two-week SAR study in patients 6 to 11 years of age supports the concern of unacceptable nasal toxicity with this formulation. The applicant will need to develop a formulation that is not toxic to the nasal mucosa, demonstrate its clinical safety, and provide evidence to support its efficacy before the product may be considered for approval.

Given the safety signal for nasal ulceration and nasal septum perforation, pediatric studies in children 2 to 11 years of age should be deferred until the applicant has developed a formulation that is not toxic to the nasal mucosa and demonstrated its clinical safety in older patients.

9.2 Recommendation on Regulatory Action

This reviewer recommends a “Not Approvable” action.

9.3 Recommendation on Postmarketing Actions

No postmarketing actions are indicated because the product is not recommended for approval.

9.3.1 Risk Management Activity

No risk management activity is indicated because the product is not recommended for approval.

9.3.2 Required Phase 4 Commitments

There are no required phase 4 commitments because the product is not recommended for approval.

9.3.3 Other Phase 4 Requests

There are no other phase 4 requests because the product is not recommended for approval.

9.4 Labeling Review

Labeling review is not necessary at this time because the product is not recommended for approval.

9.5 Comments to Applicant

Division comments:

1. *The submitted data from your clinical program do not support your proposed indication of the* (b) (4) *treatment of the symptoms of SAR* (b) (4) *in adults and children 12 years of age and older. The data do not support the efficacy of olopatadine 0.6% nasal spray for the* (b) (4)

2. *The safety data from your clinical program indicate that your drug product is toxic to the nasal mucosa. Clinical and preclinical data suggest that the toxicity is related to the inactive ingredient povidone in the formulation.*

3. *These deficiencies may be addressed by the following:*

   a. (b) (4)

   b. *Reformulate the drug product in order to reduce the risk of nasal pathology in humans*

   c. *Provide data to support the safety and efficacy of the reformulated product in patients 12 years of age and older for the management and treatment of the symptoms of SAR* (b) (4).

10 APPENDICES

10.1 Review of Individual Study Reports

Reviews of individual study reports in this NDA follow below.

10.1.1 C-02-37: A placebo controlled, efficacy and safety study of olopatadine nasal spray for the treatment of seasonal allergic rhinitis.

Study initiated: August 19, 2002
Study completed: November 27, 2002
Study report dated: August 30, 2004
[Module 5, Volume 47, page 56; Module 5, Volume 55, page 3160]

10.1.1.1 Summary and reviewer's conclusion of study results

This study is a randomized, vehicle-controlled, parallel group, three-arm, multicenter, phase 3 clinical study of patients with seasonal allergic rhinitis (SAR). The study had a two-week double blind treatment period. The objectives of this study were to demonstrate the superiority of olopatadine HCl nasal spray 0.4% and olopatadine nasal spray 0.6% nasal sprays compared with olopatadine HCl nasal spray vehicle placebo for the treatment of patients with SAR.

The primary efficacy endpoint was the percent change from baseline in the reflective TNSS. The difference from vehicle placebo in the percent change from baseline was -12.2% for olopatadine 0.6% and -8.8% for olopatadine 0.4%. These values were statistically significant for olopatadine 0.6% ($p < 0.0001$) and olopatadine 0.4% ($p = 0.0037$). An additional primary analysis based on the mean change from baseline in the reflective TNSS also showed statistical superiority of olopatadine 0.6% and olopatadine 0.4%. The effect size for the olopatadine 0.6% was 8.3%, in the range expected for antihistamine drug products. Both olopatadine 0.6% and olopatadine 0.4% were superior to vehicle placebo for percent change from baseline in the instantaneous TNSS, which provides evidence of end-of-dosing interval efficacy. Data for individual symptom scores provides supportive evidence for the efficacy of olopatadine 0.6% and olopatadine 0.4% for treatment of the SAR symptoms of runny nose, itchy nose, sneezing, itchy eyes, and watery eyes, but not for stuffy nose. Percent change from baseline in the reflective and instantaneous TNSS scores provide evidence of efficacy throughout the two-week treatment period for olopatadine 0.6% and olopatadine 0.4%. The percent change from baseline in the reflective TNSS over the study treatment period for patients 12 to 17 years of age (approximately 10% of the study population) was less than that for the general study population and the results of the study suggest that olopatadine 0.6% and olopatadine 0.4% were not effective in this age group. The significance of this finding is unclear since the disease characteristics are the same in this age group and these patients are old enough to administer a nasal spray and record symptoms. There were too few patients 65 years of age and older (1.9% of the study population) to provide a subgroup analysis of efficacy in this population.

Patients treated with olopatadine 0.6% had a mean change of (b) (4) These data may provide additional support for the efficacy of olopatadine 0.6%, if replicated. (b) (4) The Allergy-Specific Work Productivity and Activity Impairment Questionnaire (WPAI-AS) provides indirect supporting evidence for the symptom score and (b) (4) results. Differences between treatment groups in the percentage of patients missing time from daily, leisure, and volunteer activities may be additional support for the efficacy of olopatadine 0.6% and olopatadine 0.4% in the treatment of symptoms of SAR. These endpoints will not support a labeling claim, however, because the WPAI-AS is incompletely validated, there has been no MID established, and the missed time instrument is not validated.

Exposure to study drug was adequate to allow for assessment of safety. There was a dose-response effect noted for patients with adverse events. There were 39.7% (73/184) of patients treated with olopatadine 0.6% who had adverse events, compared with 30.7% (58/189) of patients treated with olopatadine 0.4% and 26.6% (51/192) of patients treated with vehicle placebo. The most frequent adverse events for olopatadine 0.6% included taste perversion, hyperemia of eye, epistaxis, pharyngitis, back pain, cold syndrome, cough increased, and irritation of nose. Dose-response effects were noted for taste perversion, cold syndrome, and cough increased. The incidence and character of adverse events in patients 12 to 17 years of age was similar to that of the general study population. There were too few patients 65 years of age and older to analyze adverse events in this population. There were no clinically relevant differences in the proportions of patients with adverse events were similar to the proportion of patients without adverse events for male and female genders and for patients of Caucasian, Black, and other races. There were no deaths or serious adverse events in this study. There were 11 patients (1.9%) who withdrew from the study due to adverse events during the study treatment period. There were no adverse events that resulted in more than one withdrawal for any of the treatment groups. Safety data from vital signs, physical examinations, nasal examinations, and laboratory studies do not identify a safety signal.

In summary, this study supports the efficacy and safety of olopatadine nasal spray 0.6%, the concentration that is proposed for marketing, and of olopatadine 0.4%. Evidence of efficacy is provided by the primary efficacy endpoints, and most secondary efficacy endpoints. The study provides evidence of end-of-dosing interval efficacy and evidence of sustained efficacy throughout the two-week study treatment period. (b) (4) Evidence from the WPAI and the percentage of patients missing time from daily, leisure, and volunteer activities will not support labeling claims. Adverse events are similar to those associated with non-corticosteroid intranasal sprays approved for the SAR indication. Other safety endpoints also do not identify a safety signal.

10.1.1.2 Objective

The objectives of this study were to demonstrate the superiority of olopatadine HCl nasal spray 0.4% and olopatadine nasal spray 0.6% nasal sprays compared with olopatadine HCl nasal spray vehicle placebo for the treatment of patients with SAR [Module 5, Volume 47, page 60].

10.1.1.3 General study design

This study is a randomized, vehicle-controlled, parallel group, three-arm, multicenter, phase 3 clinical study of patients with seasonal allergic rhinitis (SAR). The applicant planned to screen 1225 patients to insure that there were approximately 720 patients who completed the study. There were 845 patients enrolled and 565 patients randomized. Up to 35 study centers were to participate in the study. There were 33 study centers that actually participated [Module 5, Volume 47, pages 3, 56, 61; Module 5, Volume 50, page 1211].

10.1.1.4 Inclusion criteria

Inclusion criteria for enrollment included [Module 5, Volume 47, pages 62-66]:

1. At least a two-year history of non-recalcitrant SAR during the fall allergy season
2. Allergy to a prevalent fall allergen that is present at the time of enrollment, defined by positive case history and positive skin prick test and/or intradermal test for a fall allergen within the one year prior to Visit 1
3. A sum of the AM and PM reflective scores of the TNSS for three of the four days prior to randomization must be least 36 out of the possible 72
4. The patient or guardian must be willing and able to give written informed consent.
5. Patients must be age 12 years or older.
6. Patients must be willing and able to attend required study visits.
7. Patients must be able to follow instructions.
8. Women of childbearing potential may participate only if they are not lactating, if they have a negative pregnancy test prior to study entry, and if they agree to use adequate birth control methods to prevent pregnancy.
9. Nasal examination must confirm the absence of significant anatomic abnormalities, infection, bleeding, and mucosal ulcerations.
10. Patients must observe the following drug washout times prior to enrollment (Table 26). Other drugs were only permitted if they are not expected to interfere with the ability of patients to participate in the study.

Table 26 Drug washout times [Module 5, Volume 47, page 63]

Drug or treatment	Washout prior to Visit 1, days
Initiation or change in dose of allergen immunotherapy	30
Systemic corticosteroids	30
Inhaled or ocular corticosteroids	30
Nasal corticosteroids	14
Nasal or inhaled ipratropium bromide, nedocromil, or cromolyn	14
Leukotriene pathway modifiers, systemic or topical anticholinergics	14
Oral or systemic antibiotics	14
Loratadine, desloratadine, levocabastine	14
Drugs that may prolong QT interval	14

Drug or treatment	Washout prior to Visit 1, days
Chlorpheniramine, clemastine, brompheniramine, hydroxyzine, azatadine, azelastine nasal spray	7
Ocular antiallergy medications	7
Topical nasal decongestants	3
Oral decongestants, diphenhydramine, cetirizine, fexofenadine, promethazine, cyproheptadine, triprolidine, acrivastine	3
NSAIDS, prn use	3
Aspirin, except low dose use of cardiac prophylaxis	3
Nasal saline and/or ocular saline	1

10.1.1.5 Exclusion criteria

Patients with the following exclusion criteria could not be enrolled [Module 5, Volume 47, pages 66-68]:

1. Rhinitis medicamentosa, obstructive nasal polyposis, or other aberration of nasal anatomy that could interfere with participation in the study
2. History of concurrent sinusitis
3. Asthma, more severe than mild intermittent asthma, and use of quick relief medications an average of more than three times per week in the four weeks prior to Visit 1
4. Nasal congestion capable of interfering with successful nasal drug
5. Use of prohibited medications or inadequate washout of prohibited medications
6. Chronic or intermittent use of inhaled, oral, intramuscular, intravenous, or potent or super-potent topical corticosteroids
7. Chronic use of long acting antihistamines and other concomitant medications (e.g., tricyclic antidepressants) that would affect assessment of the effectiveness of study drugs
8. Any systemic disorder that could interfere with the evaluation of study medications
9. Laboratory values for potassium, magnesium, and calcium that were below the normal range for the analyzing laboratory
10. Any ocular disorder other than allergic conjunctivitis which could interfere with evaluation of the study medication
11. Hypersensitivity to study drug or to any component of the test articles
12. History of drug or alcohol abuse in the past 10 years
13. History of severe or uncontrolled cardiovascular, hepatic, renal, and/or other disease/illness that could be expected to interfere with the study
14. Clinically significant abnormal 12-lead ECG findings at Visit 1 as determined by the investigator
15. Upper or lower respiratory tract infection within 14 days of Visit 1
16. History, or evidence, of nasolacrimal drainage system malfunction
17. Planned travel outside of the study area for more than 48 hours of the study period
18. Study site staff or relatives of study site staff or other individuals who would have access to the clinical study protocol
19. Any patient that received study treatment in any previous Alcon olopatadine nasal clinical trial
20. Participation in any other investigational study within 30 days before entry into this study or concomitantly with this study
21. The need for chronic or intermittent use of any nasal spray during the study period

10.1.1.6 Protocol Amendments

There were three protocol amendments. The first protocol amendment was dated August 20, 2002. It decreased the washout periods for several antihistamines and added a 14-day washout period for drugs that may prolong the QT interval. There were no patients enrolled in the study at the time of the amendment [Module 5, Volume 47, pages 82-83; Module 5, Volume 50, pages 1283-1286]. The second protocol amendment was dated September 24, 2002. It changed the inclusion criteria to allow patients with increased potassium, magnesium, and calcium levels to enroll at the discretion of the investigator. The amendment also moved the time period for Visit 4 by one day to accommodate patients' schedules. At the time of this amendment, approximately 425 patients had been enrolled and 175 had been randomized [Module 5, Volume 47, pages 82-83; Module 5, Volume 50, pages 1289-1292]. The third protocol amendment was dated January 3, 2003. It added multiple additional secondary efficacy variables. At the time of the amendment, all patients had completed the study but the database had not been locked [Module 5, Volume 47, pages 82-83; Module 5, Volume 50, pages 1295-1301].

Reviewer comment:
The protocol amendments should not impact the outcome of the study.

10.1.1.7 Study procedures

This was a randomized, placebo-controlled, parallel group, three-arm, multicenter phase 3 clinical study of patients with SAR. Approximately 1225 patients were to be screened so that approximately 720 patients would complete that study at up to 35 centers. Patients were to have a positive case history and positive skin test to a prevalent fall seasonal aeroallergen. There was a run-in period of three to 21 days during which patients will received single blind vehicle placebo nasal spray. Patients were to have a minimum qualifying score for entry into the study. The sum of all AM and PM reflective TNSS for three of the four consecutive calendar days prior to randomization was to be at least 36 out of a maximum possible score of 72 [Module 5, Volume 47, pages 3, 56, 61, 62; Module 5, Volume 50, page 1211].

Enrolled patients were randomized to either 0.4% or 0.6% olopatadine nasal spray or matching vehicle placebo for the 2-week treatment course. Patients evaluated the severity of symptoms of SAR twice daily during the study period. Symptoms assessed for severity are listed in Table 27. Patients were to assess the severity of their symptoms on the four-point, 0-3 scale, displayed in Table 28. Symptom assessments were both reflective of severity since their last symptom assessment and instantaneous. Patients recorded their assessments on diary cards. Symptoms were assessed twice daily prior to taking study medication—each morning upon awakening and each evening at bedtime. Patients also recorded study drug use on diary cards. Patients were required to attend four study visits (Screening, Randomization, Telephone Assessment, and Exit Visit) during the course of the study [Module 5, Volume 47, pages 61, 72]. A Total Nasal Symptom Score (TNSS) was calculated based on the sum of scores for runny nose, itchy nose, stuffy nose and sneezing. Itchy eyes and watery eyes were not part of the TNSS. A reflective TNSS was calculated from patients' reflective diary recordings and an instantaneous TNSS was calculated from patients' instantaneous diary recordings [Module 5, Volume 47, pages 76, 77].

Table 27 Symptoms of allergic rhinitis assessed by patients, C-02-37 [Module 5, Volume 47, pages 76, 77]

Runny nose
Itchy nose
Stuffy nose
Sneezing
Itchy eyes
Watery eyes

Table 28 Scale for assessment of allergic rhinitis symptoms, C-02-37 [Module 5, Volume 47, pages 76, 77]

Score	Definition
0 = Absent	No sign/symptom is evident
1 = Mild	Sign/symptom clearly present, but minimal awareness; easily tolerated
2 = Moderate	Definite awareness of sign/symptom that is bothersome but tolerable
3 = Severe	Sign/symptom that is hard to tolerate; causes interference with activities or daily living and/or sleeping

(b) (4)

The WPAI-AS is a patient self-administered instrument for evaluating the impact of allergic rhinitis on activities of daily life and work in seven domains: work time missed, work impairment, overall work impairment, activity impairment, classroom time missed, classroom impairment, and overall classroom impairment. Studies have established the discriminative and evaluative validity, reproducibility, and responsiveness of WPAI-AS measures of work impairment, overall work impairment, activity impairment, classroom impairment, and overall classroom impairment secondary to allergy symptoms. Validity was not established for work time missed and classroom time missed.[9] [Module 5, Volume 52, page 2002] Scores are reported as 0% to 100% impairment due to allergy symptoms within the previous seven days. WPAI-AS results are reported as percentage change in the scores for the seven individual domains. Overall work impairment and overall classroom impairment scores are calculated as a function of percentage of time actually spent working or in a class multiplied by the percentage of impairment in that setting. Activity impairment relates to the effect of allergy symptoms on other

regular daily activities (e.g., childcare, shopping). The mean percentage change from baseline at each treatment period visit is calculated for each of the seven domains. A reduction in score from baseline reflects an improvement in work/school productivity and activity impairment.[10] The WPAI-AS was completed at Visits 2, 3, and 4.

The life impact/health economics questionnaire was completed at Visits 2, 3, and 4. The applicant gathered information from the work time and class time missed data from the WPAI-AS and converted these data to monetary terms to assess indirect costs. The applicant also gathered information on health resource utilization (medical therapy and medical visits) from CRF data and converted these data to monetary terms and reported them as direct treatment costs [Module 5, Volume 47, pages 74, 76; Module 5, Volume 50, pages 1237, 1238; Module 5, Volume 51, pages 1650-1651; Module 5, Volume 55, pages 3138-3139].

Reviewer comments:

(b) (4)

The WPAI-AS is an incompletely validated instrument. There has been no MID established for the WPAI-AS. This instrument will not support a labeling claim.

The applicant's health resource utilization analysis is not a validated patient reported outcomes instrument and will not support a labeling claim. The health resource utilization analysis for indirect costs is derived from the WPAI-AS, which is incompletely validated. Interestingly, the applicant included costs associated with study visits, such as physical exam, nasal exam, laboratory studies in the calculation of health resource utilization [Module 5, Volume 55, pages 3152-3153]. Health resource utilization costs associated with the conduct of the study should be similar among the treatment groups. Including costs related to procedures required for conduct of the study is not appropriate and will obscure this analysis.

Adverse events were elicited by study staff and volunteered by patients at each study visit. Adverse events were not recorded by patients on diary cards [Module 5, Volume 47, pages 74, 75, 195]. Laboratory studies and physical exams were to be performed at baseline and at Visit 4. Vital signs and nasal examinations were to be performed at screening, baseline, Visit 2, and Visit 4 [Module 5, Volume 47, pages 74, 76, 77].

Reviewer comment:
Unfortunately, the protocol did not require adverse events to be recorded on patient diary cards. Eliciting adverse event reports at weekly intervals may result in underreporting of adverse events that are mild in severity, as patients may be less likely to recall them than if they wrote them down at the time that they occurred.

An outline of the study procedures is displayed in Table 29.

Table 29 Study outline, C-02-37 [Module 5, Volume 47, page 74]

Activity	Visit 1 Screening	Visit 2 Baseline	Visit 3 Phone	Visit 4 Exit
	Clinic	Clinic	Telephone call	Clinic
	Day –21 to 0	Day 0	Day 6-8	Day 14-16 or discontinuation
Informed consent	X			
Inclusion/exclusion criteria	X	X		
Medical and medication history	X			
Skin test	X			
Laboratory studies	X			X
Nasal exam	X	X		X
Physical exam	X			X
Adverse events	X	X	X	X
Dispense study medications	X	X		
Vital signs	X	X[a]		Xa
Dispense diary card	X	X		
Symptom severity assessment	X		X[a, b]----------X[b]	
RQLQ		X		X
WPAI-AS		X	X	X
Health economics questionnaire		X	X	X
Review compliance		X		X
Collect and weigh study medication		X		X

[a]Prior to administration of study drug
[b]Twice daily during treatment period

10.1.1.8 Study medication

All patients received nasal spray vehicle placebo twice daily during the 3- to 21-day, single blind, run-in period of the study. At Visit 2, patients were randomized to one of the following three study treatments in a 1:1:1 ratio for the double blind treatment period of the study [Module 5, Volume 47, pages 61, 70-72]:

- Olopatadine 0.4% nasal spray twice daily (1.77 mg olopatadine HCl twice daily or 1.6 mg olopatadine free base twice daily)
- Olopatadine 0.6% nasal spray twice daily (2.66 mg olopatadine HCl twice daily or 2.4 mg olopatadine free base twice daily)
- Nasal spray vehicle placebo twice daily

Patients were instructed to use 2 sprays of study medication into each nostril twice each day, in the morning and the evening for up to 37 days (up to a 21-day run in period and up to a 17-day treatment period). Patients were to take the study medication in the morning after they completed the morning symptom diary card evaluation and in the evening after they completed the evening symptom diary card evaluation [Module 5, Volume 47, pages 61, 70-72].

Study treatment was packaged in white, 30 mL HDPE plastic bottles with a white metered dose manual spray pump, white nasal adapter, and a blue dust cover. Each bottle contained a minimum fill of 30 mL of study treatment, providing 240 sprays. The nominal volume delivered was 0.1 mL/spray. Active and vehicle placebo treatments were in physically identical bottles to preserve blinding [Module 5, Volume 47, pages 71, 72]. Lot numbers of study treatment are displayed in Table 30.

The to-be-marketed formulation of drug product (olopatadine 0.6% nasal spray) and delivery device were used in this study [Module 2, Volume 2, Section 2.3.P, pages 8-9, 14-16].

Table 30 Study treatment lots used in C-02-37 [Module 5, Volume 47, pages 71, 72]

Study treatment	Lot number	Formulation identification
Olopatadine 0.6% nasal spray	02-600082-1	103718
Olopatadine 0.4% nasal spray	02-600081-1	103717
Olopatadine vehicle	02-600079-1	103784

10.1.1.9 Assessment of compliance

At each visit or contact, patients were asked questions to ascertain their level of compliance with study treatment. In addition, patients were required to enter the time of dosing on the diary card with each dose. Patient bottles of study treatment were weighed at each visit. Bottle weight data from the randomization and exit visits were analyzed to assess compliance over the study period. The difference in bottle weights from screening to the randomization visit was used as a criterion for randomization. Patients whose bottle weights fell outside an expected range for duration of treatment during the 3- to 21-day run-in period were not randomized and discontinued from the study [Module 5, Volume 47, pages 72-74].

10.1.1.10 Pollen counts

Pollen counts were performed daily by study staff or by a counting station in the community. Pollen counts were started one week before the first patient was screened until approximately one week after the last patient completed the study. The amount of daily rainfall was also recorded [Module 5, Volume 47, page 70].

10.1.1.11 Efficacy endpoints

Efficacy endpoints for this study are described below.

10.1.1.11.1 Primary efficacy endpoint

The primary efficacy endpoint was the percent change from baseline in the reflective TNSS. The reflective TNSS is defined as the average of the AM and PM reflective severity scores for the patients' assessments of runny nose, stuffy nose, itchy nose, and sneezing, averaged across all days [Module 5, Volume 47, pages 77, 79]. The applicant also provided an additional analysis of the absolute change from baseline in the reflective TNSS, defined as the average of the AM and PM reflective severity scores for the patients' assessments of runny nose, stuffy nose, itchy nose, and sneezing, averaged across all days [Module 5, Volume 47, pages 77, 109].

10.1.1.11.2 Secondary efficacy endpoints

There were multiple secondary efficacy endpoints in this study [Module 5, Volume 47, pages 77, 79, 81, 160-164]. They were:

- The percent change from baseline in the instantaneous TNSS, defined as the average of the AM and PM instantaneous severity scores for the patients' assessments of runny nose, stuffy nose, itchy nose, and sneezing, averaged across all days

- Changes from baseline in the AM and PM individual severity scores for patient diary symptoms (both reflective and instantaneous) of runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes, averaged across all days
- Percent change from baseline in the reflective TNSS at Week 1 and 2
- Percent change from baseline in the instantaneous TNSS at Week 1 and 2
- Percent change from baseline in the AM and PM reflective TNSS at each day
- Percent change from baseline in the AM and PM instantaneous TNSS at each day
- (b) (4)
- Change from baseline in WPAI-AS scores
- Difference between treatment groups in percentage of patients missing daily, leisure, and volunteer activities at all post-baseline visits
- Difference between treatment groups in health resource utilization at Visits 3 and 4
- Difference between treatment groups at time points to 180 minutes to evaluate onset of action

10.1.1.12 Safety variables

Adverse events, both volunteered and elicited, were collected at study visits. Adverse events were not recorded by patients on diary cards [Module 5, Volume 47, pages 74, 75, 195]. ECGs were performed at the screening visit. Hematology, blood chemistry, and urinalyses were obtained at the screening and the final visit. Physical examinations were performed at the screening and the final visit. Vital signs and a nasal examination were performed at the screening visit, the randomization visit, and at the final visit. Any clinically significant change from baseline in hematology, blood chemistry, urinalysis, vital signs, physical examination, and nasal examination were reported as an AE. Descriptive analyses of laboratory studies, vital signs, physical and nasal examinations were provided. Shift table analyses were performed for laboratory studies and vital signs [Module 5, Volume 51, pages 1631-1637, 1638-1639].

10.1.1.13 Statistics

Statistical considerations in this study follow below.

10.1.1.13.1 Datasets analyzed

All patients who received study drug and had at least one on-therapy visit were included in the intent-to-treat (ITT) analysis. Patients who missed a visit had their data from the previous visit carried forward to replace the missed data. Missing daily diary scores were replaced by the data from the previous day. The ITT analysis was the primary statistical analysis [Module 5, Volume 47, page 79; Module 5, Volume 51, page 1595].

All patients who receive randomized drug and meet inclusion and exclusion criteria were evaluated in the per protocol (PP) analysis. All patients who received study drug were evaluated in the safety analysis [Module 5, Volume 47, page 79].

10.1.1.13.2 Statistical power

The applicant calculated that 240 evaluable patients per treatment group, for a total of 720 patients, would have a 90% power to detect a 12.5% difference in the TNSS change from baseline between the olopatadine and vehicle placebo treatment groups. The applicant assumes a standard deviation of 42.16% and a 0.05 level of significance with two-sided tests [Module 5, Volume 47, page 82].

10.1.1.13.3 Statistical analyses

The applicant used a Dunnett's two-tailed t-test to compare changes from baseline between treatment groups for the primary and secondary efficacy endpoints [Module 5, Volume 47, page 81]. No adjustments for covariates were carried out. The applicant conducted a statistical inferential analysis for each of the primary and secondary efficacy endpoints. The applicant used Hommel's multiplicity correction for secondary efficacy variables and presented both corrected and uncorrected p values [Module 5, Volume 47, page 81-82].

10.1.1.14 Results

Results of the study are reviewed below.

10.1.1.14.1 Patient disposition

The protocol called for 720 evaluable patients with 240 in each treatment arm. A total of 845 patients were screened and 565 were enrolled and randomized to treatment. There were 565 patients in the ITT group. Table 31 summarizes patient disposition [Module 5, Volume 47, pages 85, 87-90].

Table 31 Patient disposition, C-02-37 [Module 5, Volume 47, pages 85, 87-90]

	Vehicle placebo n (%)	**Olopatadine NS, 0.4% n (%)**	**Olopatadine NS, 0.6% n (%)**	**Total n (%)**
Patients screened	--	--	--	845
Patients failing screening	--	--	--	280
Patients randomized	192 (100)	189 (100)	184 (100)	565 (100)
Patients discontinued	8 (4.2)	8 (4.0)	8 (4.3)	24 (4.3)
Adverse event	2 (1.0)	6 (3.2)	3 (1.6)	11 (1.9)
Lost to follow-up	1 (0.5)	2 (1.1)	0 (0)	3 (0.5)
Patient decision	1 (0.5)	0 (0)	1 (0.5)	2 (0.4)
Treatment failure	3 (1.6)	0 (0)	1 (0.5)	4 (0.7)
Protocol violation	1 (0.5)	0 (0)	2 (1.1)	3 (0.5)
Other	0 (0)	0 (0)	1 (0.5)	1 (0.2)
Patients in ITT analysis	192	189	184	565
Patients excluded from ITT analysis	0	0	0	0
Patients in PP analysis	175	178	169	522
Patients excluded from PP analysis	17	11	15	43
Patients in safety analysis	192	189	184	565
Patients excluded from safety analysis	0	0	0	0

There were 24 patients that discontinued from the study (Table 31). Adverse events were the most common reason for discontinuation from the study, however, the incidence of

discontinuation was low. The incidence of discontinuations due to adverse events was similar among the treatment groups. The proportion of patients discontinuing for other reasons was also similar among the treatment groups [Module 5, Volume 47, pages 85, 87-9].

Protocol deviations occurred in 9.4% of vehicle placebo patients, 5.8% of olopatadine 0.4% patients, and 9.2% of olopatadine 0.6% patients. The most common protocol deviation was use of excluded concomitant medication [Module 5, Volume 47, page 91; NDA 21-861, N-000 BZ, 5/2/05, Biostatistics report C-02-37, page 6-9]. The types of protocol deviations occurred were similarly distributed among treatment groups. These data are summarized in Table 32.

Table 32 Protocol deviations, C-02-37 [Module 5, Volume 47, page 91; NDA 21-861, N-000 BZ, 5/2/05, Biostatistics report C-02-37, page 6-9]

	Vehicle placebo N = 192		**Olopatadine NS, 0.4%** N = 189		**Olopatadine NS, 0.6%** N = 184		**Total** N = 565	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
All protocol deviations	18	(9.4)	11	(5.8)	17	(9.2)	46	(8.1)
Dosing noncompliance	0	(0)	0	(0)	1	(0.5)	1	(0.2)
Excluded medication	12	(6.2)	9	(4.8)	11	(6.0)	32	(5.7)
Exclusion criteria	3	(1.6)	1	(0.5)	1	(0.5)	5	(0.9)
Inclusion criteria	3	(1.6)	1	(0.5)	3	(1.6)	7	(1.2)
Visit noncompliance	0	(0)	0	(0)	1	(0.5)	1	(0.2)

Reviewer note: The applicant's data incorrectly identified 31 protocol deviations due to excluded medications. This table and Table 33 reflect 32 protocol deviations due to excluded medications, the correct Table.

10.1.1.14.2 Excluded concomitant medications

There were 32 protocol deviations (5.7%) for use of excluded medications among all randomized patients. This information is in Table 32. The frequency of protocol deviations for use of excluded medications was similar for olopatadine 0.6% (6.0%, 11/184), olopatadine 0.4% (4.8%, 9/189), and vehicle placebo (6.2%, 12/192) [NDA 21-861, N-000 BZ, 5/2/05, Biostatistics report C-02-37, page 6-9]. Types of excluded medications used by patients in the study are provided in Table 33.

Table 33 Excluded concomitant medications, C-02-37 [NDA 21-861, N-000 BZ, 5/2/05, Biostatistics report C-02-37, pages 6-9]

Type of excluded medication	**Vehicle placebo** N = 192		**Olopatadine NS, 0.4%** N = 189		**Olopatadine NS, 0.6%** N = 184		**Total** N = 565	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Allergy and cold medications	3	(1.6)	3	(1.6)	3	(1.6)	9	(1.6)
Antibiotics	2	(1.0)	4	(2.1)	3	(1.6)	9	(1.6)
Analgesics, NSAIDS	5	(2.6)	2	(1.1)	4	(2.2)	11	(1.9)
Other medications	2	(1.0)	0	(0)	1	(0.5)	3	(0.5)

Reviewer note: One protocol deviation was for a patient who took four excluded medications.

Reviewer comment:
Few patients used excluded medications in this study, and the types of medications used were similarly distributed among treatment groups.

10.1.1.14.3 Demographic and background characteristics

There were more females than males in the study. The population studied was largely of Caucasian race. Patients of Black and Hispanic races were represented at proportions fairly comparable to that of the general population. The mean age of patients in the study was 35.2 years. The large majority of patients ranged from 13-64 years of age. Patients greater than 64 years of age represented 1.9% of the total study population [Module 5, Volume 47, pages 95-96]. These data are displayed in Table 34.

Table 34 Demographics, C-02-37 [Module 5, Volume 47, pages 95-96]

Characteristic	Vehicle placebo N = 192		Olopatadine NS, 0.4% N = 189		Olopatadine NS, 0.6% N = 184		Total N = 565	
Gender	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Male	80	(41.7)	73	(38.6)	63	(34.2)	216	(38.2)
Female	112	(58.3)	116	(61.4)	121	(65.8)	349	(61.8)
Race	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Caucasian	142	(74.0)	147	(77.8)	138	(75.0)	427	(75.6)
Black	23	(12.0)	26	(13.8)	16	(8.7)	65	(11.5)
Asian	2	(1.0)	2	(1.1)	2	(1.1)	6	(1.1)
Hispanic	23	(12.0)	13	(6.9)	24	(13.0)	60	(10.6)
Other	2	(1.0)	1	(0.5)	4	(2.2)	7	(1.2)
Age, years								
Mean age	35.5		34.6		35.6		35.2	
SD	13.9		12.7		12.6		13.1	
Range	12-80		13-67		12-71		12-80	
Age subgroups, years	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
0-12	3	(1.6)	0	(0)	2	(1.1)	5	(0.9)
13-64	184	(95.8)	186	(98.4)	179	(97.3)	549	(97.2)
>64	5	(2.6)	3	(1.6)	3	(1.6)	11	(1.9)

10.1.1.14.4 Compliance

The applicant assessed compliance based on bottle weights during the double blind treatment phase of the study. The applicant calculated a range of acceptable bottle weight ranges by days of therapy, assuming eight sprays per day, 0.101 g/spray, and 5 priming sprays per bottle. Compliance based on bottle weight data is provided in Table 35. The frequency of acceptable compliance ranged from approximately 75-80% overall. The frequency of acceptable compliance was similar among the individual treatment groups [Module 5, Volume 47, pages 73, 102-103].

Table 35 Compliance, bottle weight data, C-02-37 [Module 5, Volume 47, page 103]

Treatment	Total N	Below range n	(%)	Acceptable n	(%)	Above range n	(%)
All patients	560	111	(19.8)	435	(77.7)	14	(2.5)
Olopatadine 0.6%	183	33	(18.0)	145	(79.2)	5	(2.7)
Olopatadine 0.4%	186	40	(21.5)	142	(76.3)	4	(2.2)
Vehicle placebo	191	38	(19.9)	148	(77.5)	5	(2.6)

Five patients had missing bottle weights.

<u>Reviewer comment:</u>
The observed frequency of acceptable compliance with study treatment is less than ideal, however the frequencies of acceptable compliance were similar among the treatment groups.

This degree of noncompliance may make it more difficult for the applicant to establish efficacy. There is an adequate degree of compliance to address efficacy and to provide safety information, however.

10.1.1.14.5 Pollen counts

Pollen counts were performed daily by study staff or by a counting station in the community. Pollen counts were started one week before the first patient was screened until approximately one week after the last patient completed the study. The amount of daily rainfall was also recorded [Module 5, Volume 47, page 70]. The vast majority of patients were dosed with study medication during times when fall seasonal aeroallergens were at a moderate to high level in the environment [Module 5, Volume 47, page 167].

Reviewer comment:
The pollen counts were at levels high enough to allow for an adequate assessment of efficacy.

10.1.1.14.6 Efficacy outcomes

Efficacy outcomes for this study are reviewed below.

10.1.1.14.6.1 Primary efficacy endpoint

The primary efficacy endpoint was the percent change from baseline in the reflective TNSS. The reflective TNSS is defined as the average of the AM and PM reflective severity scores for the patients' assessments of runny nose, stuffy nose, itchy nose, and sneezing, averaged across all days [Module 5, Volume 47, pages 77, 79].

Results for the primary efficacy endpoint are summarized in Table 36. Baseline reflective TNSS values were similar among the treatment groups. There were three patients excluded because of missing data at study visits [Module 5, Volume 47, page 106; Module 5, Volume 48, page 582]. The difference from vehicle placebo in the percent change from baseline was -12.2% for olopatadine 0.6% and -8.8% for olopatadine 0.4%. These values were statistically significant for olopatadine 0.6% ($p < 0.0001$) and for olopatadine 0.4% ($p = 0.0037$) [Module 5, Volume 47, page 106].

Table 36 Primary efficacy endpoint, percent change in reflective TNSS over treatment period, ITT group, C-02-37 [Module 5, Volume 47, page 106]

	Vehicle placebo **n = 191**	**Olopatadine NS, 0.4%** **n = 188**	**Olopatadine NS, 0.6%** **n = 183**
Baseline (SD)	8.8 (1.8)	8.9 (1.7)	8.7 (1.8)
Treatment Period (SD)	6.3 (2.5)	5.7 (2.6)	5.3 (2.6)
Percent change from baseline (SD)	-27.0 (27.8)	-35.8 (28.1)	-39.2 (26.9)
Difference from vehicle placebo, percent change from baseline	--	-8.8	-12.2
p value	--	0.0037	<0.0001

The applicant also provided an additional primary analysis based on the mean change from baseline in the reflective TNSS. These data are summarized in Table 37. The difference from vehicle placebo in the change from baseline was -1.0 for olopatadine 0.6% and -0.8% for

olopatadine 0.4%. These values were statistically significant for olopatadine 0.6% (p = 0.0002) and for olopatadine 0.4% (p = 0.0031) [Module 5, Volume 47, page 108].

Table 37 Additional analysis, mean change in reflective TNSS over treatment period, ITT group, C-02-37 [Module 5, Volume 47, page 109]

	Vehicle placebo	**Olopatadine NS, 0.4%**	**Olopatadine NS, 0.6%**
	n = 191	**n = 188**	**n = 183**
Baseline (SD)	8.8 (1.8)	8.9 (1.7)	8.7 (1.8)
Treatment Period (SD)	6.3 (2.5)	5.7 (2.6)	5.3 (2.6)
Change from baseline (SD)	-2.4 (2.5)	-3.2 (2.5)	-3.4 (2.5)
Difference from vehicle placebo, change from baseline	--	-0.8	-1.0
Effect size*	--	6.7%	8.3%
p value	--	0.0031	0.0002

* Effect size = $\frac{\text{Difference from vehicle placebo, change from baseline} \times 100}{\text{Maximum change from baseline} = 12}$

Reviewer comment:
These data provide convincing evidence of efficacy for olopatadine 0.6%, the applicant's proposed dose. Evidence of efficacy is also provided for olopatadine 0.4%, as well. Olopatadine 0.6% was superior to olopatadine 0.4%. This study was powered to detect a 12.5% difference in the percent change from baseline in reflective TNSS between the olopatadine and vehicle placebo treatment groups with 240 evaluable patients per treatment group. The applicant has achieved that degree of efficacy with approximately 180 patients per treatment group. The additional analysis provides evidence that the degree of efficacy is clinically relevant. The effect size for the olopatadine 0.6% was 8.3%, in the range expected for antihistamine drug products.

10.1.1.14.6.1.1 Subgroup analyses of primary efficacy endpoint

Patients 12 years of age and older were enrolled in the study. The difference from vehicle placebo in percent change from baseline in the reflective TNSS over the study treatment period for patients greater than 64 years of age appeared to be less than that for all patients, but there were few patients in the study who were greater than 64 years of age (11/565, 1.9%) [Module 5, Volume 47, pages 177-181].

The difference from vehicle placebo in percent change from baseline in the reflective TNSS over the study treatment period for patients 12 to 17 years of age was less than that for all patients. Patients 12 to 17 years of age represented 9.9% (56/565) of the study population [Module 5, Volume 47, page 179]. These data are presented in Table 38. There was an insufficient number of patients greater than 64 years of age to assess efficacy in this population.

Table 38 Comparison of percent change in reflective TNSS over treatment period, patients 12-17 years of age and all patients, ITT group, C-02-37 [Module 5, Volume 47, pages 106, 179; Table 34, Table 36]

	Vehicle placebo	**Olopatadine NS, 0.4%**	**Olopatadine NS, 0.6%**
Patients 12-17 years of age	**n = 18 (9.4%)**	**n = 18 (9.6%)**	**n = 20 (10.9%)**
Percent change from baseline (SD)	-25.0 (32.3)	-22.3 (26.7)	-20.8 (26.6)
Difference from vehicle placebo, percent change from baseline	--	2.7	4.2

	Vehicle placebo	Olopatadine NS, 0.4%	Olopatadine NS, 0.6%
All patients	**n = 191**	**n = 188**	**n = 183**
Percent change from baseline (SD)	-27.0 (27.8)	-35.8 (28.1)	-39.2 (26.9)
Difference from vehicle placebo, percent change from baseline	--	-8.8	-12.2

The difference from vehicle placebo in percent change from baseline in the reflective TNSS over the study treatment period for olopatadine 0.6% and olopatadine 0.4% in women was somewhat greater than that for men, however, olopatadine 0.6% and olopatadine 0.4% were superior to vehicle placebo for both genders [Module 5, Volume 47, pages 177-183].

Olopatadine 0.6% and olopatadine 0.4% were superior to vehicle placebo for patients of Caucasian, Black, and Hispanic races for difference from vehicle placebo in percent change from baseline in the reflective TNSS over the study treatment period. There were too few patients of Asian, and other races to assess efficacy in these subgroups. The difference from vehicle placebo in percent change from baseline in the reflective TNSS over the study treatment period for olopatadine 0.6% and olopatadine 0.4% was greater for patients of Hispanic race than for patients of Caucasian and Black races [Module 5, Volume 47, pages 185-187].

Reviewer comment:
Evidence of efficacy in patients 12-17 years of age was not demonstrated in this study, but patients 12-17 years represented approximately only 10% of the population. It is unclear why there should be a difference in the degree of efficacy in this population compared with the general population. The pathophysiology of SAR and the mechanism of action of the drug would be expected to be the same in patients 12-17 years of age as the general study population. Patients in this age group should be able to assess the severity of their symptoms. Data indicates that compliance for this population was comparable to that of the entire study population [NDA 21-861, N-000 BZ, 7/14/05, page 1 and attachments].

10.1.1.14.6.2 Secondary efficacy endpoints

There were multiple secondary efficacy endpoints in this study [Module 5, Volume 47, pages 77, 79, 160-164]. The following secondary efficacy endpoints are reviewed in depth below:

- The percent change from baseline in the instantaneous TNSS, defined as the average of the AM and PM instantaneous severity scores for the patients' assessments of runny nose, stuffy nose, itchy nose, and sneezing, averaged across all days
- Percent change from baseline in the AM and PM reflective individual severity scores for patient diary symptoms of runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes, averaged across all days
- (b) (4)
- Change from baseline in WPAI-AS scores

The following secondary efficacy endpoints are briefly reviewed below:

- Percent change from baseline in the AM and PM instantaneous individual severity scores for patient diary symptoms of runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes, averaged across all days
- Percent change from baseline in the reflective TNSS at Week 1 and Week 2
- Percent change from baseline in the instantaneous TNSS at Week 1 and Week 2
- Percent change from baseline in the AM and PM reflective TNSS at each day
- Percent change from baseline in the AM and PM instantaneous TNSS at each day
- Difference between treatment groups in percentage of patients missing time from daily, leisure, and volunteer activities at all post-baseline visits
- Difference between treatment groups in health resource utilization at Visits 3 and 4
- Difference between treatment groups at time points to 180 minutes to evaluate onset of action

10.1.1.14.6.2.1 Percent change from baseline in the instantaneous TNSS

Results for the percent change from baseline in the instantaneous TNSS are summarized in Table 39. Baseline instantaneous TNSS values were similar among the treatment groups. The difference from vehicle placebo in the percent change from baseline was -9.7% for olopatadine 0.6% and -8.0% for olopatadine 0.4% [Module 5, Volume 47, page 112].

Table 39 Secondary efficacy endpoint, percent change in instantaneous TNSS over treatment period, ITT group, C-02-37 [Module 5, Volume 47, pages 112, 171]

	Vehicle placebo **n = 191**	**Olopatadine NS, 0.4%** **n = 188**	**Olopatadine NS, 0.6%** **n = 183**
Baseline (SD)	8.2 (2.0)	8.5 (2.0)	8.1 (2.3)
Treatment Period (SD)	6.2 (2.7)	5.8 (2.6)	5.3 (2.6)
Percent change from baseline	-23.6 (32.0)	-31.6 (27.6)	-33.3 (27.9)
Difference from vehicle placebo, percent change from baseline	--	-8.0	-9.7
Derived from above data:			
Change from baseline	-2.0	-2.7	-2.8
Difference from vehicle placebo, change from baseline	--	-0.7	-0.8
Effect size*	--	5.8%	6.7%

* Effect size = $\frac{\text{Difference from vehicle placebo, change from baseline} \times 100}{\text{Maximum change from baseline} = 12}$

Reviewer comment:
Numerically, both olopatadine 0.6% and olopatadine 0.4% were superior to vehicle placebo. Olopatadine 0.6% was superior to olopatadine 0.4%. The effect sizes are comparable, but smaller that those noted for the primary efficacy endpoint. This is to be expected, as it requires a larger sample size to establish significance for an instantaneous TNSS than for a reflective TNSS. These data support the end of dosing interval efficacy for olopatadine 0.6% and olopatadine 0.4%.

10.1.1.14.6.2.2 Percent change from baseline for reflective individual severity scores

The percent change from baseline in the reflective individual severity scores for patient diary symptoms of runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes, averaged across all days are summarized in Table 40 [Module 5, Volume 47, pages 116, 120, 124, 128,

132, 136]. Baseline individual symptom scores for each treatment group were comparable. For the applicant's proposed concentration, olopatadine 0.6%, the difference from vehicle placebo in percent change from baseline in reflective individual severity scores ranged from -22.7% for sneezing to -2.5% for stuffy nose. The size of the values for percent change from baseline for runny nose, itchy nose, sneezing, itchy eyes, and watery eyes in the olopatadine 0.6% group were similar to the size of the values for the percent change from baseline for the reflective TNSS (the primary efficacy endpoint) and the percent change from baseline in the instantaneous TNSS. There was a dose response effect for runny nose, itchy nose, sneezing, itchy eyes, and watery eyes. There was only a small change from baseline in the stuffy nose score and there was no dose response effect noted for this symptom.

Table 40 Secondary efficacy endpoints, percent change in reflective individual severity scores over treatment period, ITT group, C-02-37 [Module 5, Volume 47, pages 116, 120, 124, 128, 132, 136]

	Vehicle placebo **n = 191**		**Olopatadine NS, 0.4%** **n = 188**		**Olopatadine NS, 0.6%** **n = 183**	
Runny nose						
Baseline (SD)	2.2	(0.6)	2.2	(0.6)	2.2	(0.6)
Treatment Period (SD)	1.6	(0.7)	1.5	(0.8)	1.4	(0.8)
Percent change from baseline	-24.9	(36.3)	-33.0	(36.4)	-38.5	(32.0)
Difference from vehicle placebo, percent change from baseline	--		-8.1		-13.6	
Stuffy nose						
Baseline (SD)	2.5	(0.5)	2.5	(0.5)	2.4	(0.6)
Treatment Period (SD)	1.9	(0.7)	1.8	(0.8)	1.7	(0.8)
Percent change from baseline	-22.0	(30.5)	-25.7	(30.1)	-24.5	(77.6)
Difference from vehicle placebo, percent change from baseline	--		-3.7		-2.5	
Itchy nose						
Baseline (SD)	2.2	(0.6)	2.2	(0.6)	2.2	(0.6)
Treatment Period (SD)	1.6	(0.8)	1.4	(0.8)	1.3	(0.8)
Percent change from baseline	-27.8	(34.0)	-38.1	(33.3)	-39.5	(32.5)
Difference from vehicle placebo, percent change from baseline	--		-10.3		-11.7	
Sneezing						
Baseline (SD)	2.0	(0.6)	2.0	(0.7)	2.0	(0.7)
Treatment Period (SD)	1.3	(0.7)	1.0	(0.7)	1.0	(0.7)
Percent change from baseline	-29.0	(51.7)	-49.5	(37.6)	-51.7	(32.4)
Difference from vehicle placebo, percent change from baseline	--		-20.5		-22.7	
Itchy eyes*						
Baseline (SD)	2.0	(0.7)	2.0	(0.7)	2.0	(0.8)
Treatment Period (SD)	1.4	(0.8)	1.3	(0.8)	1.2	(0.8)
Percent change from baseline	-30.2	(40.9)	-35.2	(43.1)	-41.4	(41.6)
Difference from vehicle placebo, percent change from baseline	--		-5.0		-11.2	
Watery eyes*						
Baseline (SD)	1.9	(0.7)	1.8	(0.8)	1.7	(0.8)
Treatment Period (SD)	1.2	(0.8)	1.0	(0.8)	0.9	(0.8)
Percent change from baseline	-37.1	(39.7)	-44.3	(40.2)	-46.7	(43.1)
Difference from vehicle placebo, percent change from baseline	--		-7.2		-9.6	

* Symptom not a component of TNSS

Reviewer comment:
These data provide additional supportive evidence for the efficacy of olopatadine 0.6% for the symptoms of SAR: primarily, runny nose, itchy nose, sneezing, itchy eyes, and watery eyes. There appear to be less effect for stuffy nose.

(b) (4)

Reviewer comment:
As noted previously, to support labeling claims, the Division requires that the MID for the active treatment be demonstrated for change from baseline compared to vehicle placebo.

(b) (4)

(b) (4)

(b) (4)

[redacted]

(b) (4)

[redacted]

(b) (4)

(b) (4)

10.1.1.14.6.2.4 Change from baseline in WPAI-AS scores

As noted previously, the WPAI-AS is a patient self-administered instrument for evaluating the impact of allergic rhinitis on activities of daily life and work [Module 5, Volume 52, page 2002]. Scores are reported as 0% to 100% impairment due to allergy symptoms within the previous seven days. WPAI-AS results are reported as percentage change in the scores for seven individual domains: work time missed, work impairment, overall work impairment, activity impairment, classroom time missed, classroom impairment, and overall classroom impairment. The mean percentage change from baseline at each treatment period visit is calculated for each of the seven domains. A reduction in score from baseline reflects an improvement in work/school productivity and activity impairment [9] [Module 5, Volume 52, page 2002]. The WPAI-AS was completed at Visits 2, 3, and 4. [Module 5, Volume 47, pages 74, 76].

Percent change from baseline in WPAI-AS scores are presented in Table 49. Baseline WPAI-AS scores were fairly similar. Numerically, changes from baseline in WPAI-AS for olopatadine 0.6% was superior to vehicle placebo for all domains and visits except for missed class time at Visit 3. Olopatadine 0.6% was statistically superior to vehicle placebo at Visit 3, Visit 4, and for all post-baseline visits for work impairment, overall work impairment, and activity impairment. Numerically, change from baseline in WPAI-AS for olopatadine 0.4% was superior to vehicle placebo for all domains and visits except for missed work time at Visit 4 and for all post-baseline visits and for missed class time at Visit 3 [Module 5, Volume 55, pages 3142-3147].

Table 49 Percent change from baseline in WPAI-AS domain scores, C-02-37 [Module 5, Volume 55, pages 3142-3147]

Treatment	Baseline score	Change from baseline at Visit 3, %	Change from baseline at Visit 4, %	Change from baseline for all post-baseline visits, %
Work impairment				
Vehicle placebo	39.6	-2.9	-4.4	-3.9
Olopatadine NS 0.4%	38.7	-8.3	-10.7	-9.8
Olopatadine NS 0.6%	44.8	**-16.7**	**-15.8**	**-16.3**
Missed work time				
Vehicle placebo	3.4	-1.0	-0.3	-0.7
Olopatadine NS 0.4%	3.2	-1.2	-0.3	-0.7
Olopatadine NS 0.6%	4.1	-3.0	-1.6	-2.2
Overall work impairment				
Vehicle placebo	41.0	-3.6	-4.9	-4.4
Olopatadine NS 0.4%	39.7	-8.6	-10.4	-9.8
Olopatadine NS 0.6%	46.3	**-17.6**	**-16.0**	**-16.7**
Classroom impairment				
Vehicle placebo	46.2	-7.3	-8.3	-8.0
Olopatadine NS 0.4%	48.4	-17.6	-16.1	-17.2
Olopatadine NS 0.6%	44.9	-12.7	-17.0	-15.6
Missed class time				
Vehicle placebo	9.4	-4.7	1.1	-2.1
Olopatadine NS 0.4%	8.4	-4.6	-3.2	-4.6
Olopatadine NS 0.6%	6.8	-1.8	-3.2	-2.5
Overall classroom impairment				
Vehicle placebo	50.4	-9.4	-8.7	-9.5
Olopatadine NS 0.4%	49.6	-16.8	-16.2	-16.7
Olopatadine NS 0.6%	46.5	-11.2	-16.7	-14.7
Activity impairment				
Vehicle placebo	47.7	-11.8	-13.3	-12.3
Olopatadine NS 0.4%	44.6	-16.1	-15.1	-15.3
Olopatadine NS 0.6%	49.7	**-20.3**	**-21.0**	**-20.4**

Values in bold typeface for $p < 0.05$, comparison vs. vehicle placebo

<u>Reviewer comment:</u>
As noted previously, there is no MID or clinically meaningful change defined for the WPAI-AS and validity was not established for work time missed and classroom time missed.[9] It should also be noted that overall work impairment and overall classroom impairment were derived from work or classroom impairment and work time or class time missed, variables that were not established to be valid.

Although the applicant's analysis showed that statistically significant changes from baseline occurred for olopatadine 0.6%, there was inconsistent evidence of a dose-response effect when the change from baseline values at each visit for olopatadine 0.6% and olopatadine 0.4% was

compared. It should be noted that it is not entirely appropriate to analyze these data inferentially, because the study was not designed or powered to detect a difference in this endpoint.

The WPAI-AS provides indirect supporting evidence for symptom scores and the (b) (4) *results. The instrument will not support a labeling claim, however.*

10.1.1.14.6.2.5 Additional secondary efficacy endpoints

Values for the difference from vehicle placebo in percent change from baseline in the AM and PM instantaneous individual severity scores for patient diary symptoms of runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes, averaged across all days were similar in magnitude to those noted for the reflective individual severity scores. There was a clear dose response effect for all instantaneous individual severity scores, except for sneezing, for which there was a similar but large decrease for both 0.6% olopatadine and 0.4% olopatadine [Module 5, Volume 47, pages 116-138].

The difference from vehicle placebo in percent change in reflective TNSS scores for Week 1 and for Week 2 compared to vehicle placebo, were similar to the primary efficacy endpoint (the percent change in reflective TNSS scores for the entire treatment period compared to vehicle placebo). The percent change in instantaneous TNSS scores for Week 1 and for Week 2 were also similar to the percent change in instantaneous TNSS scores for the entire treatment period. Both olopatadine 0.6% and olopatadine 0.4% were numerically superior to vehicle placebo for both the reflective and instantaneous TNSS scores for each of these time periods, but olopatadine 0.6% was numerically superior to olopatadine 0.4%. These data are summarized in Table 50.

Table 50 Difference from vehicle placebo in reflective and instantaneous TNSS scores for Week 1, Week 2, and entire treatment period, C-03-2-37 [Volume 47, pages 106, 112, 140-145, Table 36, Table 39]

Treatment	Week 1	Week 2	Entire treatment period
Reflective TNSS			
Vehicle placebo	0	0	0
Olopatadine NS 0.4%	-9.4	-8.1	-8.8
Olopatadine NS 0.6%	-11.6	-12.5	-12.2
Instantaneous TNSS			
Vehicle placebo	0	0	0
Olopatadine NS 0.4%	-8.7	-7.5	-8.0
Olopatadine NS 0.6%	-9.8	-9.3	-9.7

Percent change from baseline in the AM and PM reflective and instantaneous TNSS values at each day showed a separation from vehicle placebo at Day 1 for both olopatadine 0.6% and olopatadine 0.4%. Superiority over vehicle placebo for both olopatadine 0.6% and olopatadine 0.4% was maintained for each of the 14 study days for the AM and PM reflective TNSS values [Module 5, Volume 47, pages 148-152].

Reviewer comment:
Percent change from baseline in the reflective and instantaneous TNSS scores provide evidence of efficacy throughout the treatment period; there was no waning of efficacy noted.

The difference between treatment groups in percentage of patients missing time from daily, leisure, and volunteer activities at all post-baseline visits is summarized in Table 51. There was a dose-related decrease in difference from baseline in missed time from routine daily activities and missed time from leisure activities. Difference from baseline in missed time from volunteer activities was similar for olopatadine 0.4% and vehicle placebo, but was decreased for olopatadine 0.6%.

Reviewer comment:
Differences between treatment groups in the percentage of patients missing time from daily, leisure, and volunteer activities provide support for the efficacy of olopatadine 0.6% in the treatment of symptoms of SAR. In addition, this endpoint provides additional indirect support for conclusions from (b) (4)*. This endpoint will not support a labeling claim, however, because it is not a validated patient reported outcomes instrument.*

Table 51 Difference between treatment groups in percentage of patients missing time from daily, leisure, and volunteer activities, C-02-37 [Module 5, Volume 55, pages 3151-3152]

Treatment	N	Baseline		All post baseline visits		Difference from baseline	
		n	(%)	n	(%)	n	(%)
Missed time from routine daily activities							
Vehicle placebo	192	62	(32.3)	88	(45.8)	26	(13.5)
Olopatadine NS 0.4%	189	60	(31.7)	67	(35.4)	7	(3.7)
Olopatadine NS 0.6%	184	70	(38.0)	71	(38.6)	1	(0.6)
Missed time from leisure activities							
Vehicle placebo	192	67	(34.9)	91	(47.4)	24	(12.5)
Olopatadine NS 0.4%	189	58	(30.7)	65	(34.4)	7	(3.7)
Olopatadine NS 0.6%	184	71	(38.6)	66	(35.9)	-5	(-2.7)
Missed time from volunteer activities							
Vehicle placebo	192	26	(13.5)	32	(16.7)	6	(3.2)
Olopatadine NS 0.4%	189	21	(11.1)	27	(14.3)	6	(3.2)
Olopatadine NS 0.6%	184	22	(12.0)	13	(7.1)	-9	(-4.9)

The applicant gathered information on health resource utilization (medical therapy and medical visits) from CRF data and converted these data to monetary terms and reported them as direct treatment costs. These data were presented as difference between treatment groups in health resource utilization at Visits 3 and 4. There was little difference in health resources utilized by patients in this study. No patients had examinations performed at an unscheduled visit. There were only four patients who used concomitant medical therapy post-baseline for rhinitis and eight patients experienced at least one AE post-baseline that was considered for costing. Differences between active treatments and vehicle placebo were less than (b) (4) for direct costs, (b) (4) for total costs [Module 5, Volume 55, pages 3152, 3155-3156].

Reviewer comment:
These data provide little support for the efficacy of olopatadine and do not contribute to regulatory decision-making regarding the approvability of olopatadine. Health resource utilization is not a factor upon which approval decisions are based.

The applicant compared the change from baseline in the overall TNSS at 15 minute intervals from 15 minutes post-dose to 180 minutes post dose for each of the treatment groups to evaluate onset of action. Olopatadine 0.4% was statistically superior to vehicle placebo ($p<0.05$) at each time point from 75 minutes post-dose to 180 minutes post dose, except for the 120 minute time point. Olopatadine 0.6% was statistically superior to vehicle placebo ($p<0.05$) at only the 90 minute time point [Module 5, Volume 47, pages 153-154].

Reviewer comment:
These data do not support an onset of action claim. Durability of effect was not noted for olopatadine 0.6%, the concentration proposed for marketing. In addition, no assessment of efficacy was performed from the 180 mg time point to the end of the dosing interval.

10.1.1.14.7 Safety outcomes

Safety outcomes in the study are reviewed below.

10.1.1.14.7.1 Total drug exposure

Exposure to study treatment is summarized in Table 52. Of all patients treated with 0.6% olopatadine, 61.4% were treated for seven to 16 days, 35.9% were treated for more than 16 days, and 97.3% were treated for seven or more days. The mean duration of drug exposure to olopatadine 0.6% was 15.7 days.

Of all patients treated with 0.4% olopatadine, 60.8% were treated for seven to 16 days, 38.6% were treated for more than 16 days, and 99.5% were treated for seven or more days. The mean duration of drug exposure to olopatadine 0.4% was 16.0 days.

Table 52 Exposure to study treatment, C-02-37 [Module 5, Volume 47, page 193; Module 5, Volume 48, page 724]

Treatment	N	1 to 6 days		7-16 days		>16 days		Mean, days	Median, days	Range, days
		n	(%)	n	(%)	n	(%)			
Olopatadine NS 0.6%	184	5	(2.7)	113	(61.4)	66	(35.9)	15.7	16	1 – 21
Olopatadine NS 0.4%	189	1	(0.5)	115	(60.8)	73	(38.6)	16.0	16	2 – 26
Vehicle placebo	192	2	(1.0)	119	(62.0)	71	(37.0)	16.0	16	4 – 22

Reviewer comment:
Exposure to study drug was adequate to allow for assessment of safety.

10.1.1.14.7.2 Adverse events

Adverse events, both volunteered and elicited, were collected at study visits. Adverse events were not recorded by patients on diary cards [Module 5, Volume 47, pages 74, 75, 195]. Adverse events occurring in three or more patients and more frequently in olopatadine 0.6% than vehicle placebo during the treatment period are summarized in Table 53. There was a dose-response effect noted for patients with adverse events. There were 39.7% (73/184) of patients treated with olopatadine 0.6% with adverse events, compared with 30.7% (58/189) of patients treated with olopatadine 0.4%, and 26.6% (51/192) of patients treated with vehicle placebo. The most frequent adverse events for olopatadine 0.6% included taste perversion, hyperemia of eye, epistaxis, pharyngitis, back pain, cold syndrome, cough increased, and irritation of nose. Dose-response effects were noted for taste perversion, cold syndrome, and cough increased [Module 5, Volume 49, pages 785-790, 811-812].

Table 53 Adverse events occurring in three or more patients and more frequently in olopatadine 0.6% than vehicle placebo during study treatment period, C-02-37 [Module 5, Volume 49, pages 785-790, 811-812]

Adverse event	Olopatadine NS 0.6% N = 184		Olopatadine NS 0.4% N = 189		Vehicle placebo N = 192	
Patients with adverse events	73	(39.7)	58	(30.7)	51	(26.6)
All adverse events	114	(62.0)	70	(37.0)	70	(36.5)
Taste perversion	17	(9.2)	11	(5.8)	0	(0)
Hyperemia, eye	8	(4.3)	3	(1.6)	4	(2.1)
Epistaxis	7	(3.8)	4	(2.1)	4	(2.1)
Pharyngitis	7	(3.8)	2	(1.1)	5	(2.6)
Pain, back	4	(2.2)	0	(0)	0	(0)
Cold syndrome	3	(1.6)	1	(0.5)	0	(0)
Cough increased	3	(1.6)	1	(0.5)	0	(0)
Irritation, nose	3	(1.6)	0	(0)	2	(1.0)

Somnolence was reported by two patients treated with olopatadine 0.6% (1.1%, 2/184) and one patient treated with olopatadine 0.4% (0.5%, 1/189), compared to none in the vehicle placebo-treated patients. Dry mouth and throat irritation were each reported by one patient treated with olopatadine 0.6% (0.5%, 1/184) and one patient treated with olopatadine 0.4% (0.5%, 1/189) but none in vehicle placebo. For each of the study treatments, the majority of adverse events occurring during the treatment period were mild to moderate in severity and resolved without treatment [Module 5, Volume 49, pages 813-829].

Nasal adverse events occurring during this study are summarized in Table 54. This table includes nasal adverse events reported during the 3- to 21-day vehicle placebo run-in period, in addition to those noted during the double blind study treatment period. Epistaxis, rhinitis, irritation of the nose, sneezing, dry nose, and sinusitis were the most frequent nasal adverse events [Module 5, Volume 49, page 731].

Table 54 Nasal adverse events occurring in C-02-37 [Module 5, Volume 49, page 731]

Adverse event	Olopatadine NS 0.6% N = 184		Olopatadine NS 0.4% N = 189		Vehicle placebo N = 192		Vehicle placebo run-in N = 280	
Epistaxis	7	(3.8)	4	(2.1)	4	(2.1)	3	(1.1)
Rhinitis	2	(1.1)	2	(1.1)	3	(1.6)	0	(0)

Adverse event	Olopatadine NS 0.6% N = 184		Olopatadine NS 0.4% N = 189		Vehicle placebo N = 192		Vehicle placebo run-in N = 280	
Irritation, nose	3	(1.6)	0	(0)	2	(1.0)	0	(0)
Sneezing	2	(1.1)	0	(0)	2	(1.0)	0	(0)
Dry nose	2	(1.1)	1	(0.5)	0	(0)	0	(0)
Sinusitis	1	(0.5)	1	(0.5)	1	(0.5)	4	(1.4)
Pruritus, nasal	1	(0.5)	0	(0)	0	(0)	0	(0)
Nasal ulcer	0	(0)	0	(0)	1	(0.5)	1	(0.4)

The incidence and character of adverse events in patients 12 to 17 years of age were similar to that of the general study population. There were too few patients 65 years of age and older (11/565, 1.9%) to analyze adverse events in this population. There were no clinically relevant differences in the proportions of patients with adverse events were similar to the proportion of patients without adverse events for male and female genders and for patients of Caucasian, Black, and other races [Module 5, Volume 47, pages 96, 214; Module 5, Volume 49, pages 812-829].

Reviewer comment:
The adverse event profile was similar to that expected from non-corticosteroid intranasal sprays approved for the SAR indication. Taste perversion is associated with another intranasally administered antihistamine, azelastine (Astelin® Nasal Spray). A low frequency of adverse events due to somnolence and anticholinergic symptoms were reported with olopatadine, however, adverse events were only elicited at study visits and were not recorded on patient diaries; therefore milder adverse events may have been underreported. A review of the adverse event line listings did not identify adverse events that were coded with alternative terms for somnolence. There was no increase in the frequency of adverse events reported in subgroups.

10.1.1.14.7.3 Deaths and serious adverse events

There were no deaths or serious adverse events in this study [Module 5, Volume 47, page 216].

10.1.1.14.7.4 Withdrawals due to adverse events

There were 11 patients (1.9%) who withdrew from the study due to adverse events during the study treatment period. These data are summarized in Table 55. Of these 11 patients, three (0.5%) were treated with olopatadine 0.6%, six (1.1%) were treated with olopatadine 0.4%, and two (0.4%) were treated with vehicle placebo. There were no adverse events that resulted in more than one withdrawal for any of the treatment groups [Module 5, Volume 47, page 217-219].

Table 55 Withdrawals due to adverse events, C-02-37 [Module 5, Volume 47, page 217-219]

Adverse event	Olopatadine NS 0.6% N = 184		Olopatadine NS 0.4% N = 189		Vehicle placebo N = 192	
Patients withdrawing because of adverse events	3	(1.6)	6	(4.2)	2	(1.0)
All adverse events resulting in withdrawal	3	(1.6)	8		4	
Headache	1	(0.5)	1	(0.5)	1	(0.5)
Sinusitis	1	(0.5)	1	(0.5)	0	(0)
Pneumonia	1	(0.5)	0	(0)	0	(0)

Adverse event	Olopatadine NS 0.6% N = 184	Olopatadine NS 0.4% N = 189	Vehicle placebo N = 192
Dizziness	0 (0)	1 (0.5)	0 (0)
Dyspepsia	0 (0)	1 (0.5)	0 (0)
Pharyngitis	0 (0)	1 (0.5)	0 (0)
Bronchitis	0 (0)	1 (0.5)	1 (0.5)
Infection	0 (0)	1 (0.5)	0 (0)
Dermatitis Lichen	0 (0)	1 (0.5)	0 (0)
Nausea	0 (0)	0 (0)	1 (0.5)
Vomiting	0 (0)	0 (0)	1 (0.5)

Reviewer comment:
There were relatively few withdrawals in this fairly large study. These data do not identify a safety signal.

10.1.1.14.7.5 Vital signs

Vital signs were measured at screening (Visit 1), randomization (Visit 2), and at exit (Visit 4). There were no clinically significant changes from baseline in mean values of vital signs for any of the treatment groups, for the overall study population [Module 5, Volume 47, pages 246, 248-250]. There were small, but clinically insignificant decreases in pulse (-3.1 bpm), systolic blood pressure, (-3.4 mmHg) and diastolic blood pressure (-2.7 mmHg) in patients 12-17 years of age who were treated with olopatadine 0.6%. Similar decreases in pulse, systolic blood pressure, and diastolic blood pressure were not noted in the patients 12-17 years of age who were treated with vehicle placebo [Module 5, Volume 47, pages 248-250]. There were two patients who had clinically significant changes in vital signs that were reported as adverse events. One patient treated with vehicle placebo (#3919-1014) reported that he had an increase in pulse rate. Pulse rate at randomization and exit visits were normal, however. One patient treated with 0.6% olopatadine (#3619-3406) was noted as having a blood pressure of 154/85 at randomization [Module 5, Volume 47, pages 247, 279, 302; Module 5, Volume 50, pages 1103, 1119]. Analysis of shift tables and scatter plots for the overall study population identified no safety concerns [Module 5, Volume 47, pages 251-255,262, 285, 295-250; Module 5, Volume 49, pages 1131-1139].

10.1.1.14.7.6 Physical examination

Physical examinations were performed at the screening visit (Visit 1) and at exit (Visit 4). Clinically relevant changes in physical examinations were reported as adverse events. Nasal and ocular findings were not required to be reported as adverse events unless the investigator assessed the finding as related to study drug or due to a cause other than SAR. Adverse events have been reviewed earlier in this document in section 10.1.1.14.7.2. Overall, there were no clinically relevant changes in physical examination findings from baseline observed among treatment groups [Module 5, Volume 47, pages 325-329]

10.1.1.14.7.7 Nasal examination

Nasal examinations were performed at the screening visit (Visit 1), randomization (Visit 2) and at exit (Visit 4). Clinically relevant changes in nasal examinations were reported as adverse events. Adverse events have been reviewed earlier in this document in section 10.1.1.14.7.2. Overall there were no clinically relevant changes in nasal examination findings from baseline observed among treatment groups [Module 5, Volume 47, pages 242-243].

10.1.1.14.7.8 Laboratory studies

Laboratory studies were performed at the screening visit (Visit 1) and at exit (Visit 4). No clinically relevant changes in mean hematology values were noted among patients in the study. Shift table analysis revealed no clinically relevant changes in hematology values between treatment groups over the course of the study. Shifts in hematology values were similar in each of the treatment groups. One patient treated with olopatadine 0.4% (#1705) had an increase in eosinophils from 10.9% at screening to 17.3% at exit, which was reported as an adverse event. The event was reported as continuing, but did not require treatment, and the patient did not withdraw from the study. No other individuals had clinically relevant abnormalities in hematology values. [Module 5, Volume 47, pages 225, 241; Module 5, Volume 50, pages 1079-1081].

Mean CPK levels decreased 7.3 IU/L in the olopatadine 0.6% group, increased 0.3 IU/L in the olopatadine 0.4% group, and increased 20.4 IU.L in the vehicle placebo group. Shift table analysis of CPK levels indicated that the distribution of patients with shifts from normal to high and shifts from high to normal were similar in all of the treatment groups. The greatest number of patients with modest elevations in CPK was in the vehicle placebo treatment group. One patient treated with vehicle placebo had an increase in CPK level from 107 IU/L at baseline to 2200 IU/L at exit. The abnormality was reported as an adverse event. A note on the adverse event form indicated that the patient had exercised the day prior to the laboratory test. The event resolved without treatment and the patient did not discontinue from the study. The applicant concluded that the CPK elevations in this study are not clinically relevant and do not represent a safety concern [Module Volume 47, pages 231-236, 241].

No clinically relevant changes in other blood chemistry or urinalysis values were noted among patients in the study. Shift table analysis revealed no clinically relevant changes in other blood chemistry or urinalysis values over the course of the study. Shifts in other blood chemistry and urinalysis values were similar in each of the treatment groups. [Module 5, Volume 47, pages 229-231; Module 5, Volume 50, pages 1084-1090]. One patient treated with olopatadine 0.6% (#1129) had an abnormal urinalysis with an increase in leukocyte esterase and urine WBC due to a urinary tract infection. The abnormality was reported as an adverse event. The patient did not withdraw from the study. One patient treated with olopatadine 0.4% (#1126) experienced hyperlipemia, with an increase in triglycerides from 235 mg/dL at baseline to 869 mg/dL at exit. The abnormality was reported as an adverse event. A retest showed a triglyceride value of 480 mg/dL. The applicant concluded that other blood chemistry and urinalysis values in this study do not identify a safety concern [Module 5, Volume 47, pages 240, 241, 335].

Reviewer comment:
Safety data from vital signs, physical examinations, nasal examinations, and laboratory studies do not identify a safety signal.

10.1.2 C-02-10: A placebo controlled, efficacy and safety study of olopatadine nasal spray for the treatment of seasonal allergic rhinitis.

Study initiated: December 9, 2002
Study completed: March 3, 2003
Study report dated: December 10, 2004
[Module 5, Volume 56, page 1; Module 5, Volume 64, page 2910].

10.1.2.1 Summary and reviewer's conclusion of study results

This study is a randomized, vehicle-controlled, parallel group, three-arm, multicenter, phase 3 clinical study of patients with seasonal allergic rhinitis (SAR). The study had a two-week double blind treatment period. The objectives of this study were to demonstrate the superiority of olopatadine HCl nasal spray 0.4% and olopatadine nasal spray 0.6% nasal sprays compared with nasal spray vehicle placebo for the treatment of patients with SAR.

The primary efficacy endpoint was the percent change from baseline in the reflective TNSS. The difference from vehicle placebo in the percent change from baseline was -11.4% for olopatadine 0.6% and -8.9% for olopatadine 0.4%. These values were statistically significant for olopatadine 0.6% ($p < 0.0001$) and for olopatadine 0.4% ($p = 0.0002$). An additional primary analysis based on the mean change from baseline in the reflective TNSS also showed statistical superiority of olopatadine 0.6% and olopatadine 0.4%. The effect size for the olopatadine 0.6% was 9.2%, in the range expected for antihistamine drug products. Both olopatadine 0.6% and olopatadine 0.4% were superior to vehicle placebo for percent change from baseline in the instantaneous TNSS, which provides evidence of end-of-dosing interval efficacy. Data for individual symptom scores provides supportive evidence for the efficacy of olopatadine 0.6% for treatment of the SAR symptoms of runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes. Percent change from baseline in the reflective and instantaneous TNSS scores provide evidence of efficacy throughout the two-week treatment period for olopatadine 0.6% and olopatadine 0.4%. The percent change from baseline in the reflective TNSS over the study treatment period for patients 12 to 17 years of age (7.4% of the study population) was less than that for the general study population and the results of this study suggest that olopatadine 0.6% and olopatadine 0.4% were not effective in this age group. The significance of this finding is unclear since the disease characteristics are the same in this age group and these patients are old enough to administer a nasal spray and record symptoms. There were too few patients 65 years of age and older (5.3% of the study population) to provide a subgroup analysis of efficacy in this population.

The applicant did not demonstrate a minimally important difference (MID) in the RQLQ Overall score for olopatadine 0.6% or olopatadine 0.4%. Although the RQLQ (b) (4) data provide additional indirect support for the efficacy of the product.

The change from baseline in the Allergy-Specific Work Productivity and Activity Impairment Questionnaire (WPAI-AS) for olopatadine 0.6% and 0.4% were numerically superior to vehicle placebo for all domains and visits, however there was inconsistent evidence of a dose-response effect. These endpoints will not support a labeling claim because the WPAI-AS is incompletely validated and there has been no MID established.

Exposure to study drug was adequate to allow for assessment of safety. There was a dose-response effect noted for patients with adverse events. There were 43.0% (96/223) of patients treated with olopatadine 0.6% who had adverse events, compared with 35.4% (81/229) of patients treated with olopatadine 0.4%, and 32.4% (73/225) of patients treated with vehicle placebo. The most frequent adverse events for olopatadine 0.6% included taste perversion, headache, rhinitis, epistaxis, pharyngitis, flu syndrome, urinary tract infection, dizziness, CPK increased, fever, cough increased, and dyspepsia. Dose-response effects were noted for taste perversion, rhinitis, and urinary tract infection. The incidence and character of adverse events in patients 12 to 17 years of age was similar to that of the general study population. There were too few patients 65 years of age and older to analyze adverse events in this population (5.3% of the study population). There were no clinically differences in the proportions of patients with adverse events were similar to the proportion of patients without adverse events for male and female genders and for patients of Caucasian, Black, and other races. There were no deaths in this study. There was one serious adverse event in this study, a 59-year old Caucasian woman who experienced an episode of syncope on the sixth day of treatment with olopatadine 0.6%. She was hospitalized for two days for possible seizures, transient ischemic attack, or hypoglycemia and withdrew from the study. There were eight patients (1.2%) who withdrew from the study due to adverse events during the study treatment period. There were two patients treated with olopatadine 0.6% who withdrew from the study because of a flu syndrome. There were no other adverse events that resulted in more than one withdrawal for any of the treatment groups.

There was a mean change from baseline in CPK values of 42.8 IU/mL for the olopatadine 0.6% group, -13.8 IU/mL for the olopatadine 0.4% group, and 7.5 IU/mL for the vehicle placebo group. There was no dose-response relationship for mean change from baseline in CPK values, the shift table analysis of increases in CPK levels. A wide degree of variability in CPK results was present among all treatment groups. The increases in CPK levels in patients treated with olopatadine 0.6% do not appear to be drug related. Safety data from vital signs, physical examinations, nasal examinations, and laboratory studies do not identify a safety signal.

In summary, this study supports the efficacy and safety of olopatadine nasal spray 0.6%, the concentration that is proposed for marketing, and of olopatadine 0.4%. Evidence of efficacy is provided by the primary efficacy endpoints, and most secondary efficacy endpoints. The study provides evidence of end-of-dosing interval efficacy and evidence of sustained efficacy throughout the two-week study treatment period. (b) (4) Adverse events are similar to those associated with non-corticosteroid intranasal sprays approved for the SAR indication. Other safety endpoints also do not identify a safety signal.

10.1.2.2 Objective

The objectives of this study were to demonstrate the superiority of olopatadine HCl nasal spray 0.4% and olopatadine nasal spray 0.6% nasal sprays relative to nasal spray vehicle placebo and to evaluate the safety and systemic exposure of olopatadine nasal spray 0.4% and olopatadine nasal spray 0.6% as assessed by plasma concentrations of olopatadine and its metabolites [Module 5, Volume 56, page 61].

10.1.2.3 General study design

This study is a randomized, vehicle-controlled, parallel group, three-arm, multicenter, phase 3 clinical study of patients with seasonal allergic rhinitis (SAR). The applicant planned to screen 1182 patients to insure that there were approximately 720 patients who completed the study. There were 910 patients enrolled and 677 patients randomized. Up to 12 study centers were to participate in the study. There were 10 study centers that actually participated [Module 5, Volume 56, pages 3, 4, 62; Module 5, Volume 59, page 1228]. The design for this study was essentially the same as that for C-02-37, as described in Section 10.1.1 of this review. The design will not be reiterated. Points of difference for this study are described below.

10.1.2.4 Inclusion criteria

Inclusion criteria for enrollment were the same as for C-02-37, as described in Section 10.1.1.4 of this review [Module 5, Volume 56, pages 63-65].

10.1.2.5 Exclusion criteria

Exclusion criteria for enrollment were the same as for C-02-37, as described in Section 10.1.1.5 of this review, except for additional criteria for patients in the PK subset. Patients in the PK subset were not enrolled if they tested positive at Visit 1 for HIV and/or hepatitis B, hepatitis C, or active hepatitis A antigen [Module 5, Volume 56, pages 65-68].

10.1.2.6 Protocol Amendments

There was one protocol amendment, dated November 25, 2002. The protocol amendment added additional secondary efficacy variables, laboratory studies at end of treatment, corrected typographical errors, and clarified the language of the protocol. There were no patients enrolled prior to implementing the protocol amendment [Module 5, Volume 47, pages 84-85; Module 5, Volume 59, page 1297].

Reviewer comment:
The protocol amendment should not impact the outcome of the study.

10.1.2.7 Study procedures

This was a randomized, placebo-controlled, parallel group, three-arm, multicenter phase 3 clinical study of patients with SAR. Approximately 1182 patients were to be screened so that

approximately 720 patients would complete that study at up to 12 centers. Patients were to have a positive case history and positive skin test to a current prevalent aeroallergen. In this study, the current prevalent allergen was mountain cedar pollen. Study procedures were essentially the same as in C-02-37, as described in Section 10.1.1.7 of this review [Module 5, Volume 56, pages 73-78]. The few differences in study procedures are described below.

Adverse events were elicited by study staff and volunteered by patients at each study visit, and patients were provided a Patient Problem Log for them to record any medical problem or any use of concomitant medications during the run-in and treatment periods of the study. Information from the Patient Problem Logs was recorded on Adverse Event Forms or the Change in Concomitant Medication page of the Case Report Form [Module 5, Volume 56, page 76].

Reviewer comment:
Unlike C-02-37, this protocol required adverse events to be recorded by patients in diary logs. This procedure would be likely to capture a greater number of adverse events and adverse events of milder severity than were captured in C-02-37.

There were to be 42 evaluable patients ages 18 and older enrolled in the PK component of the study in a subset of the patient population for investigator 3619, Paul Ratner, M.D. These patients returned to the study center for six visits: at screening, Day 0, Day 7, Day 15, 24, and 48 hours after the last dose of study treatment. Blood samples for PK analysis were drawn pre-dose and at 5, 15, 30, 45, 60, 90 minutes, 2, 3, 4, 6, 8, and 12 hours post-dose on Day 0 and Day 15. PK samples were also collected 12 hours post dose and prior to the morning dose on Day 7. PK samples were collected at 24 and 48 hours post-dose. PK samples were used to determine single and multiple dose PK parameters for olopatadine and its identified human plasma metabolites, N-desmethylolopatadine (M1), N-didesmethylolopatadine (M2), and olopatadine N-oxide (M3). Plasma samples of patients assigned to vehicle placebo were not analyzed. The Associate Director of Bioanalytic Development was apprised of which patients were assigned to vehicle placebo, but no one outside of Bioanalytical Development was aware of the blinded assignments [Module 5, Volume 56, page 56; Module 5, Volume 59, page 1228, 1242].

Reviewer comment:
The results of the PK portion of this study are briefly summarized in Section 5 of this review.

10.1.2.8 Study medication

The method of administration of study medication in this study was the same as in C-02-37, as described in Section 10.1.1.8 of this review [Module 5, Volume 56, pages 69-72].

Lot numbers of study treatment are displayed in Table 56. The to-be-marketed formulation of drug product (olopatadine 0.6% nasal spray) and delivery device were used in this study [Module 2, Volume 2, Section 2.3.P, pages 8-9, 14-16].

Table 56 Study treatment lots used in C-02-10 [Module 5, Volume 56, page 71]

Study treatment	Lot number	Formulation identification
Olopatadine 0.6% nasal spray	02-600094-1	103718
Olopatadine 0.4% nasal spray	02-600093-1	103717
Olopatadine vehicle	02-600092-1	103784

10.1.2.9 Assessment of compliance

Compliance was assessed in the same manner as C-02-37, as described in Section 10.1.1.9 of this review [Module 5, Volume 56, pages 72-73].

10.1.2.10 Pollen counts

Pollen counts were performed in the same manner as C-02-37, as described in Section 10.1.1.10 of this review [Module 5, Volume 56, page 69].

10.1.2.11 Efficacy endpoints

Efficacy endpoints for this study are addressed below.

10.1.2.11.1 Primary efficacy endpoint

The primary efficacy endpoint was the percent change from baseline in the reflective TNSS over the treatment period of the study. The primary efficacy endpoint analysis was the same as in C-02-37, as described in Section 10.1.1.11.1 of this review [Module 5, Volume 56, pages 78, 111].

10.1.2.11.2 Secondary efficacy endpoints

The secondary efficacy endpoints in this study were the same as in C-02-37, as described in Section 10.1.1.11.2 of this review [Module 5, Volume 56, pages 81-83, 160-164].

10.1.2.12 Pharmacokinetic variables

The primary PK analysis comprised descriptions of the data with means and 95% confidence intervals for plasma concentration of olopatadine and its metabolites at each sampling time and C_{max}, T_{max}, $t_{½}$, and AUC after single and multiple dose administration [Module 5, Volume 56, pages 83, 169-170].

10.1.2.13 Safety variables

Adverse events, both volunteered and elicited, were collected at study visits. Adverse events were recorded by patients on Patient Problem Logs [Module 5, Volume 56, pages 76-78, 194]. The remainder of the safety variables were assessed as in C-02-37, as described in Section 10.1.1.12 of this review [Module 5, Volume 56, pages 74, 76-78; Module 5, Volume 59, pages 1259-1260; Module 5, Volume 60, pages 1537-1549].

10.1.2.14 Statistics

Statistical considerations in this study follow below.

10.1.2.14.1 Datasets analyzed

Populations for the intent-to-treat (ITT), per protocol (PP), and safety analyses were defined as in C-02-37, as described in Section 10.1.1.13.1 of this review [Module 5, Volume 56, pages 80, 86; Module 5, Volume 60, page 1540].

All patients who received randomized study treatment, had at least one plasma sample, and for whom adequate PK data were collected were evaluable for the ITT PK analysis. All patients who received randomized study treatment, satisfied protocol criteria, had at least one plasma sample, and for whom adequate PK data were collected were evaluable for the PP PK analysis [Module 5, Volume 56, page 81].

10.1.2.14.2 Statistical power

The applicant calculated that 240 evaluable patients per treatment group, for a total of 720 patients, would have a 90% power to detect an 8.33% difference in the TNSS change from baseline between the olopatadine and vehicle placebo treatment groups. The applicant assumes a standard deviation of 28.11% and a 0.05 level of significance with two-sided tests [Module 5, Volume 56, page 84].

Reviewer comment:
Study C-02-37 was powered to detect a 12.5% difference in the TNSS change from baseline between olopatadine and vehicle placebo treatment groups.

10.1.2.14.3 Statistical analyses

Statistical analyses were carried out as in C-02-37, as described in Section 10.1.1.13.3 of this review [Module 5, Volume 56, page 83-84].

10.1.2.15 Results

Results of the study are reviewed below.

10.1.2.15.1 Patient disposition

The protocol called for 720 evaluable patients with 240 in each treatment arm. A total of 910 patients were screened and 677 were enrolled and randomized to treatment. There were 675 patients in the ITT group. Table 57 summarizes patient disposition [Module 5, Volume 56, pages 84, 87, 85, 87-90].

Table 57 Patient disposition, C-02-10 [Module 5, Volume 56, pages 87, 89-92]

	Vehicle placebo n (%)	Olopatadine NS, 0.4% n (%)	Olopatadine NS, 0.6% n (%)	Total n (%)
Patients screened	--	--	--	910
Patients failing screening	--	--	--	233
Patients randomized	225 (100)	229 (100)	223 (100)	677 (100)
Patients discontinued	9 (4.0)	5 (2.2)	10 (4.5)	24 (3.5)
Adverse event	1 (0.4)	1 (0.4)	6 (2.7)	8 (1.2)
Lost to follow-up	1 (0.4)	0 (0)	2 (0.9)	3 (0.4)
Patient decision	2 (0.9)	2 (0.9)	1 (0.4)	5 (0.7)
Treatment failure	3 (1.3)	1 (0.4)	1 (0.4)	5 (0.7)
Protocol violation	1 (0.4)	0 (0)	0 (0)	1 (0.2)
Other	1 (0.4)	1 (0.4)	0 (0)	2 (0.3)
Patients in ITT analysis	224	229	222	675
Patients excluded from ITT analysis	1	0	1	2
Patients in PP analysis	217	221	220	658
Patients excluded from PP analysis	7	8	2	17
Patients in safety analysis	225	229	223	677
Patients excluded from safety analysis	0	0	0	0

There were 24 patients that discontinued from the study (Table 57). Adverse events were the most common reason for discontinuation from the study. The incidence of discontinuation was low, however. Discontinuations because of adverse events were more common in patients treated with olopatadine 0.6% (2.7%, 6/223) than with olopatadine 0.4% (0.4%, 1/229) or vehicle placebo (0.4%, 1/225). The proportion of patients discontinuing for other reasons was similar among the treatment groups [Module 5, Volume 56, pages 87, 92].

Protocol deviations were uncommon and occurred in 3.6% of vehicle placebo patients, 2.6% of olopatadine 0.4% patients, and 1.3% of olopatadine 0.6% patients. The most common protocol deviation was use of excluded concomitant medication. Protocol deviations were similarly distributed among treatment groups [Module 5, Volume 56, page 93]. These data are summarized in Table 58.

Table 58 Protocol deviations, C-02-10 [Module 5, Volume 56, page 93]

	Vehicle placebo N = 225 n (%)	Olopatadine NS, 0.4% N = 229 n (%)	Olopatadine NS, 0.6% N = 223 n (%)	Total N = 677 n (%)
All protocol deviations	8 (3.6)	6 (2.6)	3 (1.3)	17 (2.5)
Left medication in office, Visit 3	1 (0.4)	0 (0)	0 (0)	1 (0.1)
Received dose prior to blood draw	2 (0.9)	1 (0.4)	1 (0.4)	4 (0.6)
Used excluded medication	5 (2.2)	5 (2.2)	2 (0.9)	12 (1.8)

10.1.2.15.2 Excluded concomitant medications

There were 12 protocol deviations (1.8%, 12/677) for use of excluded medications among all randomized patients. This information is in Table 58 and Table 59. The frequency of protocol deviations for use of excluded medications was less for olopatadine 0.6% (0.9%, 2/223) than for

olopatadine 0.4% (2.2%, 5/229), and vehicle placebo (2.2%, 5/225) [Module 5, Volume 56, page 93].

Table 59 Excluded concomitant medications, C-02-10 [Module 5, Volume 56, page 93; NDA 21-861, N-000 BZ, 5/2/05, Biostatistics report C-02-10, page 11]

Type of excluded medication	Vehicle placebo N = 225		Olopatadine NS, 0.4% N = 229		Olopatadine NS, 0.6% N = 223		Total N = 677	
	n	(%)	n	(%)	n	(%)	n	(%)
Allergy, asthma, and cold medications	1	(0.9)	4	(1.7)	5	(2.2)	10	(1.5)
Antibiotics	1	(0.9)	0	(0)	0	(0)	1	(0.1)
Analgesics, NSAIDS	0	(0)	1	(0.4)	1	(0.4)	2	(0.3)

Note: Total does not equal number of protocol deviations for excluded concomitant medications because one protocol deviation was for a patient who took two excluded medications

Reviewer comment:
There was less frequent use of excluded concomitant medications in the olopatadine 0.6% treatment group. Frequency of use of allergy, asthma, and cold products was dose related and highest in the olopatadine 0.6% group. This may reflect efficacy of the product, although there are too few patients to firmly draw this conclusion.

10.1.2.15.3 Demographic and background characteristics

There were more females than males in the study. The population studied was largely of Caucasian race. Patients of Hispanic race were represented at higher proportions than in the general population. Patients of Black race were represented at lower proportions than in the general population. The mean age in the study was 38.9 years. The majority of patients ranged from 13-64 years of age. Patients greater than 64 years of age represented 5.3% of the total study population [Module 5, Volume 56, page 98]. These data are displayed in Table 60.

Table 60 Demographics, C-02-10 [Module 5, Volume 56, page 98]

Characteristic	Vehicle placebo N = 225		Olopatadine NS, 0.4% N = 229		Olopatadine NS, 0.6% N = 223		Total N = 675	
Gender	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Male	86	(38.4)	62	(27.1)	79	(35.6)	227	(33.6)
Female	138	(61.6)	167	(72.9)	143	(64.4)	448	(66.4)
Race	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Caucasian	149	(66.5)	147	(64.2)	140	(63.1)	436	(64.6)
Black	6	(2.7)	8	(3.5)	16	(7.2)	30	(4.4)
Asian	1	(0.4)	1	(0.4)	7	(3.2)	9	(1.3)
Hispanic	67	(29.9)	72	(31.4)	58	(26.1)	197	(29.2)
Other	1	(0.4)	1	(0.4)	1	(0.5)	3	(0.4)
Age, years								
Mean age	40.3		39.1		37.2		38.9	
SD	14.9		14.3		14.9		14.7	
Range	12-80		12-81		12-75		12-81	
Age subgroups, years	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
0-12	3	(1.3)	3	(1.3)	4	(1.8)	10	(1.5)
13-64	206	(92.0)	216	(94.3)	207	(93.2)	629	(93.2)
>64	15	(6.7)	10	(4.4)	11	(5.0)	36	(5.3)

10.1.2.15.4 Compliance

The applicant assessed compliance based on bottle weights during the double blind treatment phase of the study. The applicant calculated a range of acceptable bottle weight ranges by days of therapy, assuming eight sprays per day, 0.101 g/spray, and 5 priming sprays per bottle. Compliance based on bottle weight data is provided in Table 61. The frequency of acceptable compliance ranged from approximately 80-85% overall. The frequency of acceptable compliance was fairly similar among the individual treatment groups, with acceptable compliance in 79.0% of the olopatadine 0.6% group, 83.8% in the olopatadine 0.4% group, and 85.2% in the vehicle placebo group [Module 5, Volume 56, pages 72-73, 103-105].

Table 61 Compliance, bottle weight data, C-02-10 [Module 5, Volume 56, page 105]

Treatment	Total	Below range		Acceptable		Above range	
	N	n	(%)	n	(%)	n	(%)
All patients	670	112	(16.7)	554	(82.7)	4	(0.6)
Olopatadine 0.6%	219	44	(20.1)	173	(79.0)	2	(0.9)
Olopatadine 0.4%	228	35	(15.4)	191	(83.8)	2	(0.9)
Vehicle placebo	223	33	(14.8)	190	(85.2)	0	(0)

Five patients had missing bottle weights.

<u>Reviewer comment:</u>
There is a suggestion of a dose-related decrease in compliance in the olopatadine 0.6% and olopatadine 0.4% groups, perhaps due to the taste of the product. There is an adequate degree of compliance to assess efficacy and provide safety information.

10.1.2.15.5 Pollen counts

Pollen counts were performed daily by study staff or by a counting station in the community. Pollen counts were started one week before the first patient was screened until approximately one week after the last patient completed the study. The amount of daily rainfall was also recorded [Module 5, Volume 56, page 69]. The vast majority of patients were dosed with study medication during times when fall seasonal aeroallergens were at a high to very high level in the environment [Module 5, Volume 56, page 166].

<u>Reviewer comment:</u>
The pollen counts were at levels high enough to allow for an adequate assessment of efficacy.

10.1.2.15.6 Efficacy outcomes

Efficacy outcomes for this study are reviewed below.

10.1.2.15.6.1 Primary efficacy endpoint

The primary efficacy endpoint was the percent change from baseline in the reflective TNSS. The reflective TNSS is defined as the average of the AM and PM reflective severity scores for the patients' assessments of runny nose, stuffy nose, itchy nose, and sneezing, averaged across all days [Module 5, Volume 56, pages 78, 81].

Results for the primary efficacy endpoint are summarized in Table 62. Baseline reflective TNSS values were similar among the treatment groups. There were four patients excluded because of missing data at study visits [Module 5, Volume 56, page 107; Module 5, Volume 57, page 547].

The difference from vehicle placebo in the percent change from baseline was -11.4% for olopatadine 0.6% and -8.9% for olopatadine 0.4%. These values were statistically significant for olopatadine 0.6% (p <0.0001) and for olopatadine 0.4% at (p = 0.0002) [Module 5, Volume 56, page 108].

Table 62 Primary efficacy endpoint, percent change in reflective TNSS over treatment period, ITT group, C-02-10 [Module 5, Volume 56, page 108]

	Vehicle placebo n = 223	**Olopatadine NS, 0.4%** n = 228	**Olopatadine NS, 0.6%** n = 220
Baseline (SD)	9.1 (1.8)	9.3 (1.8)	9.2 (1.8)
Treatment Period (SD)	7.3 (2.3)	6.7 (2.4)	6.4 (2.7)
Percent change from baseline (SD)	-18.7 (22.3)	-27.6 (22.4)	-30.1 (27.6)
Difference from vehicle placebo, percent change from baseline	--	-8.9	-11.4
p value	--	0.0002	<0.0001

The applicant also provided an additional primary analysis based on the mean change from baseline in the reflective TNSS. These data are summarized in Table 63. The difference from vehicle placebo in the change from baseline was -1.1 for olopatadine 0.6% and -0.9 for olopatadine 0.4%. These values were statistically significant for olopatadine 0.6% (p = 0.0002) and for olopatadine 0.4% (p < 0.0001) [Module 5, Volume 56, page 111].

Table 63 Additional analysis, mean change in reflective TNSS over treatment period, ITT group, C-02-10 [Module 5, Volume 56, page 111]

	Vehicle placebo n = 223	**Olopatadine NS, 0.4%** n = 228	**Olopatadine NS, 0.6%** n = 220
Baseline (SD)	9.1 (1.8)	9.3 (1.8)	9.2 (1.8)
Treatment Period (SD)	7.3 (2.3)	6.7 (2.4)	6.4 (2.7)
Change from baseline (SD)	-1.7 (2.0)	-2.6 (2.1)	-2.8 (2.5)
Difference from vehicle placebo, change from baseline	--	-0.9	-1.1
Effect size*	--	7.5%	9.2%
p value	--	0.0002	<0.0001

* Effect size = $\frac{\text{Difference from vehicle placebo, change from baseline} \times 100}{\text{Maximum change from baseline} = 12}$

Reviewer comment:
These data provide convincing evidence of efficacy for olopatadine 0.6%, the applicant's proposed dose and also for olopatadine 0.4%. Olopatadine 0.6% was superior to olopatadine 0.4%. This study was powered to detect an 8.3% difference in the percent change from baseline in reflective TNSS between the olopatadine and vehicle placebo treatment groups with 240 evaluable patients per treatment group. The applicant has achieved that degree of efficacy with approximately 220 patients per treatment group. The additional analysis provides evidence that the degree of efficacy is clinically relevant. The effect size for the olopatadine 0.6% was 9.2%, in the range expected for antihistamine drug products.

10.1.2.15.6.1.1 Subgroup analyses of primary efficacy endpoint

Patients 12 years of age and older were enrolled in the study. The difference from vehicle placebo in percent change from baseline in the reflective TNSS over the study treatment period in patients greater than 64 years of age who were treated with olopatadine 0.6% (-33.6%) and

olopatadine 0.4% (-17.8%) appeared to be greater than that for the entire study population treated with olopatadine 0.6% (-11.4%) and olopatadine 0.4% (-8.9%). However, there were few patients in the study who were greater than 64 years of age (36/675, 5.3%) [Module 5, Volume 56, page 181; Table 60, Table 62].

The difference from vehicle placebo in percent change from baseline in the change from baseline in reflective TNSS over the study treatment period for patients 12 to 17 years of age was less than that for all patients. Patients 12 to 17 years of age represented 7.4% (50/675) of the study population [Module 5, Volume 56, page 182]. These data are presented in Table 64.

Table 64 Comparison of percent change in reflective TNSS over treatment period, patients 12-17 years of age and all patients, ITT group, C-02-10 [Module 5, Volume 56, pages 98, 182; Table 60, Table 62]

	Vehicle placebo	**Olopatadine NS, 0.4%**	**Olopatadine NS, 0.6%**
Patients 12-17 years of age	**n = 18 (8.1%)**	**n = 14 (6.1%)**	**n = 18 (8.2%)**
Percent change from baseline (SD)	-19.9 (20.4)	-16.1 (26.4)	-8.7 (28.8)
Difference from vehicle placebo, percent change from baseline	--	3.8	11.2
All patients	**n = 223**	**n = 228**	**n = 220**
Percent change from baseline (SD)	-18.7 (22.3)	-27.6 (22.4)	-30.1 (27.6)
Difference from vehicle placebo, percent change from baseline	--	-8.9	-11.4

The difference from vehicle placebo in percent change from baseline in the reflective TNSS over the study treatment period for olopatadine 0.6% and olopatadine 0.4% in women was somewhat greater than that for men, however, olopatadine 0.6% and olopatadine 0.4% were superior to vehicle placebo for both genders [Module 5, Volume 56, page 186].

Olopatadine 0.6% and olopatadine 0.4% were superior to vehicle placebo for patients of Caucasian and Hispanic races for difference from vehicle placebo in percent change from baseline in the reflective TNSS over the study treatment period. There were too few patients of Asian and Black races to assess efficacy in these subgroups. The difference from vehicle placebo in percent change from baseline in the reflective TNSS over the study treatment period for olopatadine 0.6% and olopatadine 0.4% was greater for patients of Caucasian race than for patients of Hispanic race [Module 5, Volume 56, pages 188-189].

Reviewer comment:
Evidence of efficacy in patients 12-17 years of age was not demonstrated in this study, but patients 12-17 years of age represented only 7.4% of the population. Improvement in symptom scores appeared to be inversely related to the concentration of olopatadine and was greatest in patients treated with vehicle placebo. It is unclear why there should be a difference in the degree of efficacy in this population compared with the general population. The pathophysiology of SAR and the mechanism of action of the drug would be expected to be the same in patients 12-17 years of age as the general study population. Patients in this age group should be able to assess the severity of their symptoms. Data indicates that compliance for this population was comparable to that of the entire study population [NDA 21-861, N-000 BZ, 7/14/05, page 1 and attachments].

10.1.2.15.6.2 Secondary efficacy endpoints

There were multiple secondary efficacy endpoints in this study [Module 5, Volume 56, pages 81-83, 160-164]. The following secondary efficacy endpoints are reviewed in depth below:

- The percent change from baseline in the instantaneous TNSS, defined as the average of the AM and PM instantaneous severity scores for the patients' assessments of runny nose, stuffy nose, itchy nose, and sneezing, averaged across all days
- Percent change from baseline in the AM and PM reflective individual severity scores for patient diary symptoms of runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes, averaged across all days
- (b) (4)
- Change from baseline in WPAI-AS scores

The following secondary efficacy endpoints are briefly reviewed below:

- Percent change from baseline in the AM and PM instantaneous individual severity scores for patient diary symptoms of runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes, averaged across all days
- Percent change from baseline in the reflective TNSS at Week 1 and Week 2
- Percent change from baseline in the instantaneous TNSS at Week 1 and Week 2
- Percent change from baseline in the AM and PM reflective and instantaneous TNSS at each day
- Difference between treatment groups in percentage of patients missing time from daily, leisure, and volunteer activities at all post-baseline visits
- Difference between treatment groups in health resource utilization at Visits 3 and 4

10.1.2.15.6.2.1 Percent change from baseline in the instantaneous TNSS

Results for the percent change from baseline in the instantaneous TNSS are summarized in Table 65. Baseline instantaneous TNSS values were similar among the treatment groups. The difference from vehicle placebo in the percent change from baseline was -10.4% for olopatadine 0.6% and -8.5% for olopatadine 0.4% [Module 5, Volume 56, page 114].

Table 65 Secondary efficacy endpoint, percent change in instantaneous TNSS over treatment period, ITT group, C-02-10 [Module 5, Volume 56, pages 114, 175]

	Vehicle placebo n = 223	Olopatadine NS, 0.4% n = 228	Olopatadine NS, 0.6% n = 220
Baseline (SD)	8.4 (2.2)	8.6 (2.1)	8.5 (2.2)
Treatment Period (SD)	7.0 (2.4)	6.5 (2.5)	6.3 (2.8)
Percent change from baseline	-15.8 (26.4)	-24.3 (23.3)	-26.2 (29.6)
Difference from vehicle placebo, percent change from baseline	--	-8.5	-10.4
Derived from above data:			
Change from baseline	-1.4	-2.1	-2.2
Difference from vehicle placebo, change from baseline	--	-0.7	-0.8
Effect size*	--	5.8%	6.7%

* Effect size = $\frac{\text{Difference from vehicle placebo, change from baseline} \times 100}{\text{Maximum change from baseline} = 12}$

Reviewer comment:
Numerically, both olopatadine 0.6% and olopatadine 0.4% were superior to vehicle placebo. Olopatadine 0.6% was superior to olopatadine 0.4%. The effect sizes are comparable, but smaller that those noted for the primary efficacy endpoint. These data support the end of dosing interval efficacy for olopatadine 0.6% and olopatadine 0.4%.

10.1.2.15.6.2.2 Percent change from baseline for reflective individual severity scores

The difference from vehicle placebo in percent change from baseline in the reflective individual severity scores for patient diary symptoms of runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes, averaged across all days are summarized in Table 66 [Module 5, Volume 56, pages 118, 122, 126, 130, 134, 138]. Baseline individual symptom scores for each treatment group were comparable. For the applicant's proposed concentration, olopatadine 0.6%, the difference from vehicle placebo for percent change from baseline in reflective individual severity scores ranged from -18.4% for itchy eyes to -8.5% for stuffy nose. The size of the values for percent change from baseline for runny nose, itchy nose, sneezing, itchy eyes, and watery eyes in the olopatadine 0.6% group were similar to the size of the values for the percent change from baseline for the reflective TNSS (the primary efficacy endpoint) and the percent change from baseline in the instantaneous TNSS. There was a dose response effect for each of the individual symptoms.

Table 66 Secondary efficacy endpoints, percent change in reflective individual severity scores over treatment period, ITT group, C-02-10 [Module 5, Volume 56, pages 118, 122, 126, 130, 134, 140]

	Vehicle placebo n = 223	Olopatadine NS, 0.4% n = 228	Olopatadine NS, 0.6% n = 223
Runny nose			
Baseline (SD)	2.4 (0.5)	2.4 (0.6)	2.4 (0.5)
Treatment Period (SD)	1.9 (0.6)	1.8 (0.7)	1.6 (0.8)
Percent change from baseline	-18.4 (24.1)	-22.3 (32.4)	-30.0 (31.5)
Difference from vehicle placebo, percent change from baseline	--	-3.9	-11.6

	Vehicle placebo n = 223		Olopatadine NS, 0.4% n = 228		Olopatadine NS, 0.6% n = 223	
Stuffy nose						
Baseline (SD)	2.5	(0.5)	2.5	(0.5)	2.5	(0.5)
Treatment Period (SD)	2.1	(0.7)	2.0	(0.6)	1.9	(0.7)
Percent change from baseline	-13.2	(26.0)	-21.3	(24.0)	-21.7	(31.7)
Difference from vehicle placebo, percent change from baseline	--		-8.1		-8.5	
Itchy nose						
Baseline (SD)	2.2	(0.7)	2.3	(0.6)	2.2	(0.6)
Treatment Period (SD)	1.7	(0.8)	1.6	(0.7)	1.5	(0.8)
Percent change from baseline	-19.4	(38.0)	-30.8	(27.5)	-32.4	(32.5)
Difference from vehicle placebo, percent change from baseline	--		-11.4		-13.0	
Sneezing						
Baseline (SD)	2.0	(0.7)	2.1	(0.7)	2.1	(0.6)
Treatment Period (SD)	1.6	(0.7)	1.4	(0.7)	1.3	(0.8)
Percent change from baseline	-18.8	(43.4)	-33.4	(37.9)	-35.7	(38.9)
Difference from vehicle placebo, percent change from baseline	--		-14.6		-16.9	
Itchy eyes*						
Baseline (SD)	2.0	(0.8)	2.0	(0.8)	2.1	(0.7)
Treatment Period (SD)	1.6	(0.9)	1.5	(0.8)	1.4	(0.8)
Percent change from baseline	-12.3	(45.7)	-25.3	(41.9)	-30.7	(53.8)
Difference from vehicle placebo, percent change from baseline	--		-13.0		-18.4	
Watery eyes*						
Baseline (SD)	1.9	(0.7)	1.9	(0.8)	1.9	(0.8)
Treatment Period (SD)	1.5	(0.8)	1.3	(0.8)	1.3	(0.9)
Percent change from baseline	-18.0	(43.8)	-29.9	(40.3)	-31.9	(46.7)
Difference from vehicle placebo, percent change from baseline	--		-11.9		-13.9	

* Symptom not a component of TNSS

<u>Reviewer comment:</u>
These data provide additional supportive evidence for the efficacy of olopatadine 0.6% for the following individual symptoms of SAR: runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes.

(b) (4)

(b) (4)

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Reviewer comment:

(b) (4)

10.1.2.15.6.2.4 Change from baseline in WPAI-AS scores

As noted previously, the WPAI-AS is a patient self-administered instrument for evaluating the impact of allergic rhinitis on activities of daily life and work. It is described in greater detail in Section 10.1.1.7 and Section 10.1.1.14.6.2.4 of this review.

Percent change from baseline in WPAI-AS scores are presented in Table 75. Baseline WPAI-AS scores were generally comparable. Numerically, changes from baseline in WPAI-AS for olopatadine 0.6% and olopatadine 0.4% were superior to vehicle placebo for all domains and visits, but there was inconsistent evidence of a dose response effect. Olopatadine 0.6% was statistically superior to vehicle placebo only for all post-baseline visits for activity impairment. Olopatadine 0.4% was statistically superior to vehicle placebo for change from baseline at Visit 3 and change from baseline for all post-baseline visits for work impairment, overall work impairment. Olopatadine 0.4% was statistically superior to vehicle placebo for change from baseline at Visit 3, change from baseline at Visit 4, and change from baseline for all post-baseline visits for activity impairment [Module 5, Volume 64, pages 32890-2897].

Table 75 Percent change from baseline in WPAI-AS domain scores, C-02-10 [Module 5, Volume 64, pages 2890-2897]

Treatment	Baseline score	Change from baseline at Visit 3, %	Change from baseline at Visit 4, %	Change from baseline for all post-baseline visits, %
Work impairment				
Vehicle placebo	44.8	-7.7	-8.9	-8.4
Olopatadine NS 0.4%	47.4	**-17.2**	-14.4	**-15.8**
Olopatadine NS 0.6%	48.8	-13.8	-13.8	-13.7
Missed work time				
Vehicle placebo	6.2	-2.5	-2.3	-2.4
Olopatadine NS 0.4%	5.6	-3.1	-2.2	-2.7
Olopatadine NS 0.6%	4.4	-3.2	-1.9	-2.4
Overall work impairment				
Vehicle placebo	46.9	-8.5	-9.5	-8.7
Olopatadine NS 0.4%	49.5	**-18.1**	-15.2	**-16.5**
Olopatadine NS 0.6%	50.4	-15.0	-14.6	-14.5
Classroom impairment				
Vehicle placebo	42.6	-15.3	-2.6	-9.5
Olopatadine NS 0.4%	47.2	-14.8	-13.1	-13.7
Olopatadine NS 0.6%	37.3	-8.5	-2.3	-5.0
Missed class time				
Vehicle placebo	2.5	-2.1	2.9	0.6
Olopatadine NS 0.4%	4.9	-2.2	-3.1	-2.5
Olopatadine NS 0.6%	3.6	-2.2	-2.3	-1.6
Overall classroom impairment				
Vehicle placebo	43.6	-15.9	-2.7	-9.1
Olopatadine NS 0.4%	49.3	-15.6	-14.4	-14.7
Olopatadine NS 0.6%	39.0	-9.1	-3.4	-5.5
Activity impairment				
Vehicle placebo	49.5	-12.3	-11.9	-12.1
Olopatadine NS 0.4%	53.0	**-19.1**	**-18.5**	**-18.9**
Olopatadine NS 0.6%	52.4	-18.3	-16.8	**-17.6**

Values in bold typeface for $p < 0.05$, comparison vs. vehicle placebo

<u>Reviewer comment:</u>
As noted previously, there is no MID or clinically meaningful change defined for the WPAI-AS and validity was not established for work time missed and classroom time missed.[9]

Although the applicant's analysis showed that statistically significant changes from baseline occurred for olopatadine 0.6%, there was inconsistent evidence of a dose-response effect when the change from baseline values at each visit for olopatadine 0.6% and olopatadine 0.4% was compared. It should be noted that it is not appropriate to analyze these data inferentially, because the study was not designed or powered to detect a difference in this endpoint.

The WPAI-AS provides little supporting evidence for symptom score and RQLQ results in this study. (b) (4)

10.1.2.15.6.2.5 Additional secondary efficacy endpoints

Values for the difference from vehicle placebo in percent change from baseline in the AM and PM instantaneous individual severity scores for patient diary symptoms of runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes, averaged across all days were generally similar in magnitude to those noted for the reflective individual severity scores. The difference from vehicle placebo in percent change from baseline for olopatadine 0.4% for the instantaneous score for watery eyes was less than the reflective score.

There was a clear dose response effect for all instantaneous individual severity scores, except for stuffy nose and sneezing. For stuffy nose, there was a similar, but small effect, for both olopatadine 0.6% and olopatadine 0.4%. For sneezing, there was a similar but large decrease for both olopatadine 0.6% and olopatadine 0.4% [Module 5, Volume 56, pages 118-147].

The percent change in reflective TNSS scores for Week 1 and for Week 2 compared to vehicle placebo were similar to the primary efficacy endpoint (the percent change in reflective TNSS scores for the entire treatment period compared to vehicle placebo). The percent change in instantaneous TNSS scores for Week 1 and for Week 2 were also similar to the values for the percent change in instantaneous TNSS scores for the entire treatment period. Both olopatadine 0.6% and olopatadine 0.4% were numerically superior to vehicle placebo for both the reflective and instantaneous TNSS scores for each of these time periods, but olopatadine 0.6% was numerically superior to olopatadine 0.4%. These data are summarized in Table 76.

Table 76 Difference from vehicle placebo in percent change from baseline in reflective and instantaneous TNSS scores for Week 1, Week 2, and entire treatment period, C-02-10 [Module 5, Volume 56, pages 108, 114; Module 5, Volume 57, pages 376-379; Table 63, Table 65]

Treatment	Week 1	Week 2	Entire treatment period
Reflective TNSS			
Vehicle placebo	0	0	0
Olopatadine NS 0.4%	-8.1	-9.7	-8.9
Olopatadine NS 0.6%	-11.4	-11.5	-11.4
Instantaneous TNSS			
Vehicle placebo	0	0	0
Olopatadine NS 0.4%	-7.1	-9.9	-8.5
Olopatadine NS 0.6%	-9.8	-10.8	-10.4

Percent change from baseline in the AM and PM reflective and instantaneous TNSS values at each day showed a separation from vehicle placebo at Day 2 for both olopatadine 0.6% and olopatadine 0.4%. Superiority over vehicle placebo for both olopatadine 0.6% and olopatadine 0.4% was maintained for each of the 14 study days for the AM and PM reflective TNSS values. Olopatadine 0.6% was superior to olopatadine 0.4% in percent change for both the AM and PM reflective TNSS values for most days [Module 5, Volume 56, pages 150, 153].

Reviewer comment:
Percent change from baseline in the reflective and instantaneous TNSS scores provide evidence of efficacy throughout the treatment period.

The difference between treatment groups in percentage of patients missing time from daily, leisure, and volunteer activities at all post-baseline visits is summarized in Table 77. There was no consistent relationship between treatment groups in difference from baseline in percentage of patients missing time from daily, leisure, and volunteer activities [Module 5, Volume 64, pages 2899-2900].

Reviewer comment:
These data do not provide support for the efficacy of olopatadine 0.6% or olopatadine 0.4% in the treatment of symptoms of SAR.

Table 77 Difference between treatment groups in percentage of patients missing time from daily, leisure, and volunteer activities, C-02-10 [Module 5, Volume 64, pages 2899-2900]

Treatment	N	Baseline		All post baseline visits		Difference from baseline	
		n	(%)	n	(%)	n	(%)
Missed time from routine daily activities							
Vehicle placebo	224	91	(40.6)	105	(46.9)	14	(6.2)
Olopatadine NS 0.4%	229	101	(44.1)	99	(43.2)	-2	(-0.9)
Olopatadine NS 0.6%	222	84	(37.8)	88	(39.6)	4	(1.8)
Missed time from leisure activities							
Vehicle placebo	224	107	(47.8)	91	(40.6)	-16	(-7.1)
Olopatadine NS 0.4%	229	104	(45.4)	89	(38.9)	-15	(-6.6)
Olopatadine NS 0.6%	222	93	(41.9)	100	(45.0)	7	(3.2)
Missed time from volunteer activities							
Vehicle placebo	224	28	(12.5)	30	(13.4)	2	(0.9)
Olopatadine NS 0.4%	229	30	(13.1)	28	(12.2)	-2	(-0.9)
Olopatadine NS 0.6%	222	19	(8.6)	36	(16.2)	17	(7.7)

The applicant gathered information on health resource utilization (medical therapy and medical visits) from CRF data and converted these data to monetary terms and reported them as direct treatment costs. These data were presented as difference between treatment groups in health resource utilization at Visits 3 and 4 and for all post-baseline visits. No patients had examinations performed at an unscheduled visit. There were only six patients who used concomitant medical therapy post-baseline for rhinitis and 13 patients experienced at least one AE post-baseline that was considered for costing and these patients were similarly distributed among treatment groups. Differences between active treatments and vehicle placebo were (b) (4) for direct costs. The average indirect costs for all post-baseline visits for olopatadine 0.6%, olopatadine 0.4%, and vehicle placebo were (b) (4), respectively. The average total costs for all post-baseline visits for olopatadine 0.6%, olopatadine 0.4%, and vehicle placebo were (b) (4), respectively [Module 5, Volume 64, pages 2901, 2903-2906].

Reviewer comment:
These data provide little support for the efficacy of olopatadine and do not contribute to regulatory decision-making regarding the approvability of olopatadine. Health resource information is not a factor upon which approval decisions are based.

10.1.2.15.7 Safety outcomes

Safety outcomes in the study are reviewed below.

10.1.2.15.7.1 Total drug exposure

Exposure to study treatment is summarized in Table 78. Of all patients treated with 0.6% olopatadine, 92.4% were treated for seven to 16 days, 5.4% were treated for more than 16 days, and 97.8% were treated for seven or more days. The mean duration of drug exposure to olopatadine 0.6% was 14.9 days.

Of all patients treated with 0.4% olopatadine, 89.5% were treated for seven to 16 days, 9.6% were treated for more than 16 days, and 99.1% were treated for seven or more days. The mean duration of drug exposure to olopatadine 0.4% was 15.2 days.

Table 78 Exposure to study treatment, C-02-10 [Module 5, Volume 56, page 197; Module 5, Volume 57, page 629]

Treatment	N	1 to 6 days		7-16 days		>16 days		Mean, days	Median, days	Range, days
		n	(%)	n	(%)	n	(%)			
Olopatadine NS 0.6%	223	5	(2.2)	206	(92.4)	12	(5.4)	14.9	15	1 – 18
Olopatadine NS 0.4%	229	2	(0.9)	205	(89.5)	22	(9.6)	15.2	15	2 – 19
Vehicle placebo	225	2	(0.9)	206	(91.6)	17	(7.6)	15.1	15	1 – 22

Reviewer comment:
Exposure to study drug was adequate to allow for assessment of safety.

10.1.2.15.7.2 Adverse events

Adverse events, both volunteered and elicited, were collected at study visits. Adverse events were recorded by patients on Patient Problem Logs [Module 5, Volume 56, pages 76-78, 194]. Adverse events occurring in three or more patients and more frequently in olopatadine 0.6% than vehicle placebo during the treatment period of the study are summarized in Table 79. There was a dose-response effect noted for patients with adverse events. There were 43.0% (96/223) of patients treated with olopatadine 0.6% who had adverse events, compared with 35.4% (81/229) of patients treated with olopatadine 0.4%, and 32.4% (73/225) of patients treated with vehicle placebo. There was also a dose-response effect noted for all adverse events. The frequency of adverse events in patients treated with olopatadine 0.6% was 74.9% (167/223), compared with 65.9% (151/229) in patients treated with olopatadine 0.4%, and 50.2% (113/225) in patients treated with vehicle placebo. The most frequent adverse events for olopatadine 0.6% included taste perversion, headache, rhinitis, epistaxis, pharyngitis, flu syndrome. urinary tract infection, dizziness, CPK increased, fever, cough increased, and dyspepsia. Dose-response effects were noted for taste perversion, rhinitis, and urinary tract infection [Module 5, Volume 56, page 218; Module 5, Volume 57 pages 637-652].

Table 79 Adverse events occurring in three or more patients and more frequently in olopatadine 0.6% than vehicle placebo during study treatment period, C-02-10 [Module 5, Volume 56, page 218; Module 5, Volume 57 pages 637-652]

Adverse event	Olopatadine NS 0.6% N = 223		Olopatadine NS 0.4% N = 229		Vehicle placebo N = 225	
Patients with adverse events	96	(43.0)	81	(35.4)	73	(32.4)
All adverse events	167	(74.9)	151	(65.9)	113	(50.2)
Taste perversion	36	(16.1)	20	(8.7)	2	(0.9)
Headache	19	(8.5)	15	(6.6)	17	(7.6)
Rhinitis	8	(3.6)	3	(1.3)	1	(0.4)
Epistaxis	7	(3.1)	12	(5.2)	4	(1.8)
Pharyngitis	5	(2.2)	7	(3.1)	4	(1.8)
Flu syndrome	5	(2.2)	0	(0)	1	(0.4)
Urinary tract infection	4	(1.8)	3	(1.3)	2	(0.9)
Dizziness	4	(1.8)	2	(0.9)	1	(0.4)
CPK increased	4	(1.8)	1	(0.4)	1	(0.4)
Fever	3	(1.3)	5	(2.2)	2	(0.9)
Cough increased	3	(1.3)	3	(1.3)	2	(0.9)
Dyspepsia	3	(1.3)	3	(1.3)	1	(0.4)

Somnolence was reported by two patients treated with olopatadine 0.6% (0.9%, 4/223) two patients treated with olopatadine 0.4% (0.9%, 2/229), compared to one patient treated with vehicle placebo (0.4%, 1/225). Dry mouth was reported by two patients treated with olopatadine 0.6% (0.9%, 2/223), one patient treated with olopatadine 0.4% (0.4%, 1/229), and one patient treated with vehicle placebo (0.4%, 1/225) [Module 5, Volume 57 pages 637-652]. For each of the study treatments, the majority of adverse events occurring during the treatment period were mild to moderate in severity and resolved without treatment [Module 5, Volume 58, pages 709-728, 738-762].

Nasal adverse events occurring in this study are summarized in Table 80. This table includes nasal adverse events reported during the 3- to 21-day vehicle placebo run-in period, in addition to those noted during the double blind study treatment period. Epistaxis, rhinitis, and irritation of the nose were the most frequently noted nasal adverse events during the study. A dose-response effect was noted for rhinitis [Module 5, Volume 57, page 637].

Table 80 Nasal adverse events occurring in C-02-10 [Module 5, Volume 57, page 637]

Adverse event	Olopatadine NS 0.6% N = 223		Olopatadine NS 0.4% N = 229		Vehicle placebo N = 225		Vehicle placebo run-in N = 233	
Epistaxis	7	(3.1)	12	(5.2)	4	(1.8)	5	(2.1)
Rhinitis	8	(3.6)	3	(1.3)	1	(0.4)	0	(0)
Discomfort, nasal	4	(1.8)	7	(3.1)	4	(1.8)	0	(0)
Irritation, nose	1	(0.4)	1	(0.4)	1	(0.4)	0	(0)
Dry nose	1	(0.4)	0	(0)	0	(0)	0	(0)
Sneezing	1	(0.4)	0	(0)	0	(0)	0	(0)
Sinusitis	0	(0)	2	(0.9)	2	(0.9)	2	(0.9)

The incidence and character of adverse events in patients 12 to 17 years of age were similar to that of the general study population. There were too few patients 65 years of age and older (36/675, 5.3%) to analyze adverse events in this population. There were no clinically relevant differences in the proportions of patients with adverse events were similar to the proportion of patients without adverse events for male and female genders and for patients of Caucasian,

Black, and other races [Module 5, Volume 56, page 209-218; Module 5, Volume 58, pages 736-737].

Reviewer comment:
It is not unexpected that taste perversion, headache, rhinitis, epistaxis, and pharyngitis would be reported by patients taking an intranasal antihistamine. The incidence of epistaxis for non-corticosteroid intranasal spray medications approved for the SAR indication ranges from 2.0% for Astelin Nasal Spray to 6.0% for Atrovent Nasal Spray 0.06% and 9.0% for Atrovent Nasal Spray 0.03%.

A low frequency of adverse events due to somnolence and anticholinergic symptoms were reported with olopatadine. A review of the adverse event line listings did not identify adverse events that were coded with alternative terms for somnolence. Patients were instructed by the Patient Problem Log to record medical problems and medications that were taken during the study. A sprained ankle treated with Tylenol was given as an example of such a problem [NDA 21-861, N-000 BZ, 7/14/05, page 3 and attachments]. It is possible that the example given by the form may have led people to not record less severe adverse events.

There was no increase in the frequency of adverse events reported in subgroups.

10.1.2.15.7.3 Deaths and serious adverse events

There were no deaths in this study. There was one serious adverse event in this study. Patient #3207-1512 was a 59-year old Caucasian woman who experienced a six minute episode of syncope on the (b) (6) day of treatment with olopatadine 0.6%. She was hospitalized for two days and withdrew from the study. She was treated in the hospital with saline and potassium chloride intravenously. The investigator and medical monitor concluded that the episode of syncope was not related to study drug [Module 5, Volume 58, pages 745, 877; Module 5, Volume 120, page 157; NDA 21-861, N-000 BZ, 7/14/04, page 2 and attachments]. The case report form and hospital admission history and physical indicates that the patient was admitted with possible seizures, transient ischemic attack, hypoglycemia or vasovagal attack.

10.1.2.15.7.4 Withdrawals due to adverse events

There were eight patients (1.2%) who withdrew from the study due to adverse events during the study treatment period. These data are summarized in Table 81. Of these eight patients, six (2.7%) were treated with olopatadine 0.6%, one (0.4%) was treated with olopatadine 0.4%, and one (0.4%) were treated with vehicle placebo. There were two patients treated with olopatadine 0.6% who withdrew from the study because of a flu syndrome. There were no other adverse events that resulted in more than one withdrawal for any of the treatment groups [Module 5, Volume 56, pages 222-225].

Table 81 Withdrawals due to adverse events, C-02-10 [Module 5, Volume 47, pages 222-225]

Adverse event	Olopatadine NS 0.6% N = 223		Olopatadine NS 0.4% N = 229		Vehicle placebo N = 225	
Patients withdrawing because of adverse events	6	(2.7)	1	(0.4)	1	(0.4)
All adverse events resulting in withdrawal	7	(3.1)	2	(0.9)	1	(0.4)
Flu syndrome	2	(0.9)	0	(0)	0	(0)
Epistaxis	1	(0.4)	0	(0)	0	(0)
Dizziness	1	(0.4)	0	(0)	0	(0)
Headache	1	(0.4)	0	(0)	0	(0)
Migraine	1	(0.4)	0	(0)	0	(0)
Cellulitis	0	(0)	1	(0.4)	0	(0)
Sinusitis	0	(0)	1	(0.4)	1	(0.4)

Reviewer comment:
There were more withdrawals in the study in patients treated with olopatadine 0.6% than with olopatadine 0.4% or vehicle placebo. However, there were relatively few withdrawals in this fairly large study and flu syndrome was the only adverse for which there were more than one withdrawal in any treatment group. One patient, #3207-1441, treated with olopatadine 0.6% withdrew because of epistaxis. This patient had a nosebleed that was moderate in severity and lasted two minutes on day 13 of treatment. It resolved without treatment. The event did not meet the criteria for a serious adverse event. The patient requested to withdraw from the study [Module 5, Volume 58, page 738; Module 5, Volume 120, pages 80-83]. As noted previously, epistaxis is associated with non-corticosteroid intranasal sprays approved for the SAR indication.

These data do not identify a safety signal.

10.1.2.15.7.5 Vital signs

Vital signs were measured at screening (Visit 1), randomization (Visit 2), and at exit (Visit 4). There were no clinically significant changes from baseline in mean values for vital signs for any of the treatment groups, for the overall study population, for patients 12 to 17 years of age, or for patients greater than 65 years of age [Module 5, Volume 56, pages 255-257]. There was a small, but clinically insignificant decrease in pulse (-3.2 bpm) in patients 12-17 years of age who were treated with olopatadine 0.6%. A similar decrease in pulse was not noted in patients 12 to 17 years of age who were treated with vehicle placebo [Module 5, Volume 56, pages 255-257]. There were three patients who had clinically significant changes in vital signs that were reported as adverse events. One patient treated with olopatadine 0.6% (#3641-1607) had a blood pressure of 160/98 at randomization, but had a blood pressure of 116/84 at the exit visit. One patient treated with 0.6% olopatadine (#3652-1874) was noted as having a blood pressure of 158/87 at randomization and 168/87 at the exit visit. One patient treated with olopatadine 0.4% (#3641-1626) had a blood pressure of 143/96 at randomization and 149/104 at the exit visit [Module 5, Volume 56, pages 254-257; Module 5, Volume 59, pages 1119, 1146, 1148-1151]. Analysis of shift tables and scatter plots for the overall study population identified no safety concerns [Module 5, Volume 56, pages 271, 294, 316; Module 5, Volume 59, pages 1157-1166].

10.1.2.15.7.6 Physical examination

Physical examinations were performed at the screening visit (Visit 1) and at exit (Visit 4). Clinically relevant changes in physical examinations were reported as adverse events. Nasal and ocular findings were not required to be reported as adverse events unless the investigator assessed the finding as related to study drug or due to a cause other than SAR. Adverse events have been reviewed earlier in this document in Section 10.1.2.15.7.2. Overall, there were no clinically relevant changes in physical examination findings from baseline observed among treatment groups [Module 5, Volume 56, pages 332-336].

10.1.2.15.7.7 Nasal examination

Nasal examinations were performed at the screening visit (Visit 1), randomization (Visit 2) and at exit (Visit 4). Clinically relevant changes in nasal examinations were reported as adverse events. Adverse events have been reviewed earlier in this document in Section 10.1.2.15.7.2. Overall, there were no clinically relevant changes in nasal examination findings from baseline observed among treatment groups [Module 5, Volume 56, pages 249-252].

10.1.2.15.7.8 Laboratory studies

Laboratory studies were performed at the screening visit (Visit 1) and at exit (Visit 4). No clinically relevant changes in mean hematology values were noted among patients in the study. Shift table analysis revealed no clinically relevant changes in hematology values between treatment groups over the course of the study. Shifts in hematology values were similar in each of the treatment groups. One patient treated with olopatadine 0.4% (#3652-1836) had a platelet count that was high at baseline (435,000/mm3) and remained high at the exit visit (613,000/mm3). The platelet count at the exit visit was reported as an adverse event. The patient did not comply with a request for retest. The event was reported as continuing, without treatment. No other individuals had clinically relevant abnormalities in hematology values [Module 5, Volume 56, pages 228-231; Module 5, Volume 58, page 885; Module 5, Volume 59, pages 1092-1094].

The mean change from baseline in CPK values was 42.8 IU/mL for the olopatadine 0.6% group, -13.8 IU/mL for the olopatadine 0.4% group, and 7.5 IU/mL for the vehicle placebo group [Module 5, Volume 59, pages 1084-1089]. There was a high degree of variability in CPK values for all treatment groups. These data are summarized in Table 82.

Table 82 Mean change from baseline in CPK values, C-02-10 [Module 5, Volume 59, pages 1084-1089]

Treatment group	Mean change from baseline, IU/mL (SD)	Minimum change from baseline, IU/mL	Maximum change from baseline, IU/mL
Olopatadine 0.6%	42.8 (285.5)	-293.0	2820.0
Olopatadine 0.4%	-13.8 (199.1)	-2857.0	205.0
Vehicle placebo	7.5 (191.1)	-778.0	1988.0

Shift table analysis for CPK values is summarized in Table 83. Shift table analysis showed that the percentage of patients with increases in CPK values was 6.8% (15/221) for olopatadine 0.6%, 1.8% (4/227) for olopatadine 0.4%, and 3.6% (8/222) for vehicle placebo. The percentage of patients with decreases in CPK values was 2.3% (5/221) for olopatadine 0.6%, 2.3% (5/212) for olopatadine 0.4%, and 5.9% (13/222) for vehicle placebo. There was a higher percentage of

patients with increases in CPK values than decreases in CPK values (6.8% increase, 2.3% decrease) for olopatadine 0.6%. There was a higher percentage of patients with decreases in CPK values than increases in CPK values for olopatadine 0.4% (2.3% decrease, 1.8% increase) and vehicle placebo (5.9% decrease, 3.6% increase).

Table 83 Shift table for CPK values, C-02-10 [Module 5, Volume 59, pages 1095-1100]

Treatment	Baseline	Final Visit	
		Normal	High
Olopatadine 0.6%	Normal	192	15
	High	5	9
Olopatadine 0.4%	Normal	212	4
	High	5	6
Vehicle placebo	Normal	190	8
	High	13	11

Normal values ranged from 0-235 for men and 0-190 for women. It was therefore impossible to have a "low" CPK value.

Patients in the study with clinically relevant CPK changes are summarized in Table 84. There were 12 patients with clinically relevant changes in CPK values. Of these 12 patients, six were in the olopatadine 0.6% group, one was in the olopatadine 0.4% group, and five were in the vehicle placebo group. The AAC/AHA/NHLBI clinical advisory committed on the use and safety of statin drugs defined modest CPK elevations as 3 to 10 times the upper limit of normal and marked CPK elevations as greater than 10 times the upper limit of normal.[11] The reference range for CPK for the laboratory used in this study was 0-235 for men and 0-190 for women [Module 5, Volume 59, page 1105; Module 5, Volume 60, page 1613]. Using these criteria, there were two patients in the olopatadine 0.6% group who had marked CPK elevations. There were no patients in the olopatadine 0.4% or vehicle placebo group who had marked CPK elevations. There were four patients in the olopatadine 0.6% group, no patients in the olopatadine 0.4% group, and three patients in the vehicle placebo group who had modest CPK elevations. Of the patients with clinically relevant increases in CPK, four of the olopatadine 0.6% patients, the olopatadine 0.4% patient, and two of the vehicle placebo patients had concomitant physical activity or medication known to be associated with increased CPK levels. Only six of the 12 clinically relevant CPK values were reported as adverse events.

Table 84 Patients with clinically relevant changes in CPK values [Module 5, Volume 56, page 239; Module 5, Volume 58, pages 939, 941, 949, 956, 960]

Patient number	Age	Race	Gender	Comments	CPK value	AE reported
Olopatadine 0.6%						
3207-1490	16	Caucasian	M	Runner	3000	No
3207-1572	27	Caucasian	M	Increased activity at work	481	Yes
3643-1240	24	Hispanic	F		319	Yes
3652-1846	66	Caucasian	F	Medication for hyperlipidemia	641	Yes
3653-2286	33	Caucasian	M	Worked out before test	490	No
3652-1904	56	Caucasian	M		367	Yes

Patient number	Age	Race	Gender	Comments	CPK value	AE reported
Olopatadine 0.4%						
3653-2228	45	Black	M	Preceding trauma	3294	Yes
Vehicle placebo						
3207-1495	29	Caucasian	M	Started working out	646	No
3207-1568	68	Caucasian	M		1096	No
3642-1073	29	Caucasian	F		281	No
3653-2221	53	Hispanic	F		448	Yes
3653-2332	35	Hispanic	M	Worked out prior to test	2126	No

In addition, there were also four other patients treated with olopatadine 0.6% who had modest elevations in CPK levels that ranged from 774 IU/mL to 2857 IU/mL, patients #3619-2062, #3619-2094, #3642-1066, and #3653-2267 [Module 5, Volume 56, pages 243-245; Module 5, Volume 58, pages 939, 941, 949, 956, 960]. The cause of the CPK elevations in three of these patients was attributed to exercise. Assessment of causality for the fourth patient was not provided. These patients are summarized in Table 85.

Table 85 Patients with increases in CPK values, recorded as not being clinically relevant [Module 5, Volume 56, pages 243-245; Module 5, Volume 58, pages 939, 941, 949, 956, 960]

Patient number	Age	Race	Gender	Comments	CPK value	Degree of increase*	AE reported
Olopatadine 0.6%							
3619-2062	32	Hispanic	M	Started exercise program	1001	Modest	No
3619-2094	35	Hispanic	M		2857	Marked	No
3642-1066	24	Black	M	Vigorous exercise	774	Modest	No
3653-2267	22	Caucasian	F	Vigorous exercise	806	Modest	No

* Degree of increase: Marked—10 times the upper limit of normal
Modest—3 to 10 time the upper limit of normal

The applicant notes that serum CPK levels can be variable and are influenced by gender, age, and body mass and may vary as the result of variability due to factors such as exercise and concomitant medications. The applicant concludes that the elevated CPK levels noted in this study are a result of variability due to these reasons and are not a safety concern for olopatadine 0.6% [Module 5, Volume 56, page 242].

Reviewer comments:
The increases in CPK levels in patients treated with olopatadine 0.6% do not appear to be drug related. There was no dose-response relationship for mean change from baseline in CPK values, the shift table analysis of increases in CPK levels. A wide degree of variability in CPK results was present among all treatment groups. Although there were more patients with elevated CPK levels in the olopatadine 0.6% group than in the olopatadine 0.4% or vehicle placebo groups, there was no dose-response relationship noted. Dr. Gary Bond, Pharmacology/Toxicology reviewer for this NDA, indicates that there was no signal for skeletal muscle myositis, myopathy, or rhabdomyolysis in non-clinical studies in this NDA.

No clinically relevant changes in other blood chemistry or urinalysis values were noted among patients in the study. Shift table analysis revealed no clinically relevant changes in other blood chemistry or urinalysis values over the course of the study. Shifts in other blood chemistry and

urinalysis values were similar in each of the treatment groups. [Module 5, Volume 56, pages 231-236; Module 5, Volume 59, pages 1084-1091]. One patient treated with olopatadine 0.4% (#3652-1908) had a cholesterol level of 383 mg/dL and a triglyceride level of 1927 mg/dL at the exit visit. Serum cholesterol and triglycerides were elevated at the screening visit and at a follow-up visit. The abnormalities were reported as adverse events. One patient treated with vehicle placebo (#3643-1223) a GGTP of 287 U/L and SGTP levels of 86 U/L at exit. Her GGTP (192 U/L) and SGPT (53 U/L) elevated at baseline. A re-test, 52 days after exit showed that the GGTP level had lowered to 105 U/L and the SGPT had returned to normal. Adverse events were reported for the elevated GGTP and SGTP levels [Module 5, Volume 58, pages 885-886]. The applicant concluded that other blood chemistry and urinalysis values in this study do not identify a safety concern [Module 5, Volume 56, pages 231, 235, 248].

Reviewer comment:
Safety data from vital signs, physical examinations, nasal examinations, and laboratory studies do not identify a safety signal.

10.1.3 C-01-92: Long term safety study of olopatadine nasal spray

Study initiated: May 17, 2003
Study completed: August 3, 2004
Study report dated: December 10, 2004
[Module 5, Volume 65, page 1; Module 5, Volume 76, page 3985].

10.1.3.1 Summary and reviewer's conclusion of study results

This study was a randomized, vehicle-controlled, parallel group, two arm, multicenter, phase 3, clinical study of patients with perennial allergic rhinitis (PAR). Initially, the objective of this study was to demonstrate the long-term safety of olopatadine 0.6% nasal spray. (b) (4) The revised objectives of the study were to demonstrate the long-term safety (b) (4) of olopatadine 0.6% nasal spray when given as two sprays per nostril twice daily for up to one year in patients with PAR.

(b) (4) Effect sizes for population subgroups were similar to the overall effect size. These data provide some evidence that patients actually used study medication and provide support for conclusions drawn from the safety endpoints in the study, (b) (4) (b) (4) The mean number of days of rescue medication use and the maximum number of days of rescue medication use were lower for the olopatadine 0.6% group than for the vehicle placebo group. The applicant performed a number of exploratory efficacy analyses, including the mean response for the patient-assessed relief questionnaire at each of the 12 monthly study visits and compared the percentages of patients with various degrees of relief. The results of each of the exploratory analyses numerically favored olopatadine 0.6% over vehicle placebo.

Exposure to study drug was adequate to allow for assessment of safety. Adverse events were frequent, but occurred in a similar proportion of patients in the treatment groups in this one-year study. Of all patients treated with olopatadine 0.6%, 80.0% (367/459) had adverse events. Of all patients treated with vehicle placebo, 82.1% (382/465) had adverse events. The frequency of adverse events was high but was similar in both treatment groups, with a frequency of 273.0% (1253/459) for olopatadine 0.6% and 264.9% (1232/465) in the vehicle placebo group.

Of those adverse events occurring more frequently in olopatadine 0.6% than vehicle placebo, the most frequent included epistaxis, cold syndrome, taste perversion, arthralgia, cough increased, and otitis media, among others. Both olopatadine 0.6% and the vehicle placebo are irritating to the nose. Epistaxis (19.2% olopatadine 0.6%, 12.0% vehicle placebo), rhinitis (12.2% olopatadine 0.6%, 15.3% vehicle placebo), and sinusitis (12.4% olopatadine 0.6%, 13.3% vehicle placebo) were frequent in this study in both treatment groups. Nasal ulcer was reported frequently in the olopatadine 0.6% group (4.1%, 19/459) and the vehicle placebo group (4.5%, 21/465). Nasal septum perforation was noted in one patient treated with olopatadine 0.6% (0.2%, 1/459) and in two patients treated with vehicle placebo (0.4%, 2/465). In comparison, nasal septum perforations were not reported in the development programs for Astelin Nasal Spray and Atrovent Nasal Sprays 0.03% and 0.06%, non-corticosteroid nasal spray products with SAR indications. Non-clinical data in this application suggests that the formulation for the applicant's proposed product is toxic to nasal mucosa and that the toxicity may be related to the povidone excipient.

There were no clinically relevant differences in the frequency or character of adverse events in patients 12 to 17 years of age and patients 65 years of age and older, compared with the general study population. There were no clinically relevant differences in the proportions of patients with adverse events were similar to the proportion of patients without adverse events for male and female genders and for patients of Caucasian, Black, and other races.

There was one death in the study, a 41-year old woman who was treated with olopatadine 0.6% who had obesity and underwent elective gastric bypass surgery. She developed a perforated gastric ulcer, bacterial peritonitis, and died from sepsis. Serious adverse events occurred in treatment groups at similar frequencies in the olopatadine 0.6% group (2.2%, 10/459) and vehicle placebo group (2.4%, 11/465). Appendicitis and surgical/medical procedure were the only serious adverse events that occurred in more than one patient. Deaths and serious adverse events did not suggest a safety signal.

The frequency of patients withdrawing from the study because of adverse events was similar for the olopatadine 0.6% group (5.0%, 23/459) and vehicle placebo group (5.4%, 25/465). Taste perversion, nasal discomfort, headache, nasal ulcer, and epistaxis were the most frequent adverse events resulting in withdrawal of patients treated with olopatadine 0.6%. Headache, dizziness, nasal ulcer, infection, migraine, and nasal septum disorder (nasal septum perforation) were the most frequent adverse events resulting in withdrawal of patients treated with vehicle placebo. There were two patients in the vehicle placebo group that withdrew from the study because of nasal septum perforation. Nasal discomfort, nasal ulcer, epistaxis, and nasal septum perforation are likely to be related to the nasal toxicity of the product, as previously noted.

Vital signs, physical examinations, and ECGs revealed no safety signal. Nasal examinations identified a safety signal for nasal septum perforation and nasal ulcerations occurring in both treatment groups. There was one patient treated with olopatadine 0.6% and two patients treated with vehicle placebo who developed nasal septum perforations. Nasal ulcerations were common and occurred at similar frequencies in the olopatadine 0.6% group (3.8%, 17/451) and in the vehicle placebo group (4.0%, 18/451).

(b) (4)

In addition, the study does not provide support for the long-term safety of olopatadine nasal spray 0.6% or the vehicle placebo. The formulation for the proposed product appears to be toxic to the nasal mucosa, and is associated with epistaxis, nasal ulcer, and nasal septum perforation. Non-clinical data suggest that this signal may be related to the povidone excipient. Based on AERS data, it appears that nasal septum perforation is extremely rare among non-steroid nasal sprays with allergic rhinitis indications. Even among corticosteroid nasal sprays with allergic rhinitis indications, nasal septum perforation appears to be uncommon. The findings in this study represent a major safety signal.

10.1.3.2 Objective

Initially, the objective of this study was to demonstrate the long-term safety of olopatadine 0.6% nasal spray when given as two sprays per nostril twice daily (BID) for up to one year in patients with PAR [Module 5, Volume 71, page 3984].

(b) (4)

10.1.3.3 General study design

This study was a randomized, vehicle-controlled, parallel group, two arm, multicenter, phase 3, clinical study of patients with PAR. The applicant planned to screen 900 patients to insure that there were approximately 800 patients randomized and 300 evaluable patients on active drug at six months and 100 evaluable patients on active drug at 12 months. There were 924 patients enrolled and randomized. Approximately 40 study centers were to participate in the study. There were 43 study centers that actually participated [Module 5, Volume 65, pages 3, 4, 82, 84; Module 5, Volume 71, page 2189].

10.1.3.4 Inclusion criteria

Inclusion criteria for enrollment included [Module 5, Volume 65, pages 69-71]:

1. A two-year history of non-recalcitrant PAR
2. Allergy to a perennial allergen, defined by positive case history and positive skin prick test and/or intradermal test within the one year prior to Visit 1
3. The patient or guardian must be willing and able to give written informed consent.
4. Patients must be age 12 years or older.
5. Patients must be willing and able to attend required study visits.
6. Patients must be able to follow instructions.
7. Women of childbearing potential must be postmenopausal (at least 2 years) or surgically sterile, not pregnant or lactating, and agree to use adequate birth control, as described in the protocol

8. Absence of significant anatomic abnormalities, infection, bleeding, and mucosal ulcerations by nasal examination at Visit 1
9. Patients must observe the following drug washout times prior to enrollment (Table 86). Other drugs were only permitted if they are not expected to interfere with the ability of patients to participate in the study.

Table 86 Drug washout times, C-01-92 [Module 5, Volume 65, page 70]

Drug or treatment	Washout prior to Visit 1, days
Nasal corticosteroids	14
Nasal ipratropium bromide, nedocromil, sodium cromolyn	14
Loratadine, desloratadine, levocabastine	14
Drugs that may prolong QT interval	14
Chlorpheniramine, clemastine, brompheniramine, hydroxyzine, azatadine, azelastine nasal spray, cetirizine, fexofenadine	7
Any nasal herb product or any herbal product used to relieve allergy symptoms	7
Topical nasal decongestants	7
Oral decongestants, diphenhydramine, cetirizine, fexofenadine, promethazine, cyproheptadine, triprolidine, acrivastine	3
Sleep aids, including one of the antihistamines noted above	As for the applicable antihistamine in sleep aid product

10.1.3.5 Exclusion criteria

Patients with the following exclusion criteria could not be enrolled [Module 5, Volume 65, pages 71-72]:

1. Concurrent disease that might complicate or interfere with investigation or evaluation of the study medications, such as rhinitis medicamentosa, obstructive nasal polyposis, history of current chronic sinusitis, or other aberration of nasal anatomy that could interfere with successful nasal drug administration/absorption
2. Any systemic disorder that could interfere with the evaluation of the study medication
3. Any clinically relevant laboratory values outside the normal range
4. Hypersensitivity to study drug or to any component of the test articles
5. History of drug or alcohol abuse that would interfere with the patient's participation in the study
6. History of severe, unstable, or uncontrolled cardiovascular, hepatic, renal, or other condition that could interfere with the study
7. Study site employee or any person with access to the study protocol
8. Cohabitating with a patient who has been randomized into the study
9. Received test article in any previous Alcon olopatadine nasal spray clinical trial
10. Participant in any other study within 30 days before entry into the study
11. Clinically relevant abnormal 12-lead ECG findings at Visit 1
12. Clinically relevant abnormal vital signs

10.1.3.6 Protocol amendments

There were three protocol amendments. The first protocol amendment was dated May 20, 2003. It allowed, at the discretion of the investigator, limited and intermittent use of excluded oral and topical medications, with the exclusion of intranasal preparations and antiarrhythmic agents. It also corrected some typographic errors. There were no patients enrolled in the study at the time

of the amendment [Module 5, Volume 65, page 83; Module 5, Volume 71, pages 2245-2253]. The second protocol amendment was dated January 30, 2004. It removed the requirement for an interim database lock after the last participant completed six months. It also ensured that study patients were exposed to medication for at least six and 12 months at Visits 8 and 14, transferred the Study Manager responsibilities, and updated the requirement for pollen counts during the winter months. At the time of this amendment, all patients had been enrolled [Module 5, Volume 65, page 83; Module 5, Volume 71, pages 2254-2264]. The third protocol amendment was dated June 22, 2004. It incorporated a primary efficacy analysis because an efficacy measurement was already being collected. The analysis of ECG components was also expanded. At the time of the amendment, all patients had been enrolled in the study [Module 5, Volume 65, page 83; Module 5, Volume 71, pages 2269-2275].

Reviewer comment:
The protocol amendments should not impact the outcome of the study. It is acceptable for the applicant to add a (b) (4)

10.1.3.7 Study procedures

This study was a randomized, vehicle-controlled, parallel group, double blind, two-arm, multicenter, long-term safety study of patients with PAR [Protocol, page 1]. There were to be up to 40 US and Canadian study centers. After meeting inclusion and exclusion criteria, patients received olopatadine nasal spray 0.6% or olopatadine nasal spray vehicle for use twice daily. Patients returned to the study centers for monthly visits. There were 14 study visits during the one-year study period. Patients recorded the time of each dose of study treatment and usage of rescue medication in their daily diaries. (b) (4)

Reviewer comment:
This instrument is a rather blunt and crude measure of (b) (4)*. It is acceptable for this study, in which evaluation of* (b) (4) *is secondary in importance to the assessment of safety. This instrument may serve the purpose of verifying that patients used study drug during this long-term safety study. A similar* (b) (4) *instrument was used in the long-term safety study in the ebastine NDA and no assessment of efficacy was performed in the long-term safety study in the*

tecastemizole NDA. (b) (4)

Patients had nasal examinations at each study visit. Vital signs were completed at screening, Visit 3, Visit 5, Visit 8, Visit 11, and the Exit Visit. Physical examinations and ECGs were completed at screening, Visit 8, and the Exit visit. Adverse events were volunteered by patients at study visits and also were recorded in a home patient log. Study staff also elicited adverse events at office visits [Module 5, Volume 65, pages 3, 62, 66-67, 77-78].

An outline of the study procedures is displayed in Table 87.

Standard 12-lead ECGs were performed at Visits 1, 8, Exit, and unscheduled visits. At Visit 8 and Exit, three sequential ECGs, at 5 minute intervals, were performed 45 to 90 minutes after the dose of study medication. ECGs were recorded and transmitted digitally to (b) (4) Cardiologists from (b) (4) reviewed all ECGs. Manual measurements were performed for RR, PR, QRS, and QT interval durations. Mean HR, QTcB, and QTcF were derived from interval duration measurements. Cardiologists and (b) (4) personnel were blinded to study treatment [Module 5, Volume 65, pages 64, 67-68].

10.1.3.8 Study medication

Olopatadine nasal spray 0.6% and nasal spray vehicle placebo were randomly assigned to all qualifying patients at Visit 2. Study treatments were:

- Olopatadine 0.6% nasal spray twice daily (2.66 mg olopatadine HCl twice daily or 2.4 mg olopatadine free base twice daily)
- Nasal spray vehicle placebo twice daily

Patients were instructed to use 2 sprays of study medication into each nostril twice each day, in the morning and the evening for up to one year. Patients were to maintain a 12-hour interval between the morning and evening doses [Module 5, Volume 65 page 74].

Study treatment was packaged in white, 30 mL HDPE plastic bottles with a white metered dose manual spray pump, white nasal adapter, and a blue dust cover. Each bottle contained a minimum fill of 30 mL of study treatment, providing 240 sprays. The nominal volume delivered was 0.1 mL/spray. Active and vehicle placebo treatments were in physically identical bottles to preserve blinding [Module 5, Volume 65, pages 73-74]. Lot numbers of study treatment are displayed in Table 88.

The to-be-marketed formulation of drug product (olopatadine 0.6% nasal spray) and delivery device were used in this study [Module 2, Volume 2, Section 2.3.P, pages 8-9, 14-16; Module 5, Volume 65, page 74].

Table 87 Study outline, C-01-92 [Module 5, Volume 47, page 74]

Activity	V 1	V2 Day 1	V3 Day 30	V4 Day 60	V5 Day 90	V6 Day 120	V7 Day 150	V8 Day 180	V9 Day 210	V10 Day 240	V11 Day 270	V12 Day 300	V13 Day 330	V14 Final or Early Termination Day 365
Informed consent	X													
Inclusion/Exclusion criteria	X	X												
Pregnancy test	X		X	X	X	X	X	X	X	X	X	X	X	X
Screening medical and medication history	X													
Allergy test	X													
Laboratory studies	X													
Nasal examination	X		X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X							X						X
Vital signs	X		X		X			X			X			X
Review medical history and concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X							X						X
Collect adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study medication		X	X	X	X	X	X	X	X	X	X	X	X	
Dispense dosing diary		X	X	X	X	X	X	X	X	X	X	X	X	
Review compliance		X	X	X	X	X	X	X	X	X	X	X	X	X
Collect study medication			X	X	X	X	X	X	X	X	X	X	X	X
Collect dosing diary			X	X	X	X	X	X	X	X	X	X	X	X
Efficacy assessment			X	X	X	X	X	X	X	X	X	X	X	X
Exit form completed														X

Table 88 Study treatment lots used in C-01-92 [Module 5, Volume 65, page 74]

Study treatment	Lot number	Formulation identification
Olopatadine 0.6% nasal spray	02-600096-1 03-600119-1	103718 103718
Olopatadine vehicle	02-600092-1 03-600122-1	103784 103784

10.1.3.9 Rescue medication

If, in the opinion of the investigator, the patient was not obtaining adequate relief from symptoms of SAR, the patient was allowed to use pseudoephedrine HCl tablets 30 mg, provided by the study site. Use of rescue medication was logged on patient diaries. Pseudoephedrine HCl was used within the established labeling. Patients were encouraged to stop the use of the rescue medication as soon as possible [Module 5, Volume 65, page 66].

10.1.3.10 Assessment of compliance

Patent were required to enter the time of the morning and evening doses of study treatment in the patient diary each day during the study. Site personnel were instructed to review the completion of the dosing times in the diary with the patient at each study visit. [Module 5, Volume 65, pages 65, 75]. Dosing compliance was defined as the percent of time an individual dosed with the study medication. The number of times that an individual dosed within a given month was added and divided by two times the number of days the patient was on the study in that month, and then multiplied by 100 to get a percentage [Module 5, Volume 65, page 132; Module 5, Volume 72, page 2555].

10.1.3.11 Pollen counts

Pollen counts were performed by study staff or by a counting station in the community. Pollen counts were started one week before the first patient was screened until approximately one week after the last patient completed the study. Pollen counts were not performed during the winter months at sites that do not normally measure pollen during the winter. The amount of daily rainfall was also recorded [Module 5, Volume 65, page 65].

(b) (4)

(b) (4)

10.1.3.13 Safety variables

The primary safety variables analyzed were adverse events and nasal examination. Adverse events were volunteered by patients at study visits and were recorded in a home patient log. Study staff also elicited adverse events at office visits. Patients had nasal examinations at each study visit. [Module 5, Volume 65, pages 3, 62, 66-67, 76-78]

Additional safety variables included vital signs, physical examination, and 12-lead ECG intervals. Vital signs were completed at screening, Visit 3, Visit 5, Visit 8, Visit 11, and the Exit Visit. Physical examinations and ECGs were completed at screening, Visit 8, and the Exit visit [Module 5, Volume 65, pages 64, 67-68, 76].

Any clinically significant change from baseline in nasal examination, vital signs, physical examination, and ECG were reported as an adverse event. Descriptive analyses of changes in nasal examinations, vital signs, physical examinations, and ECGs were provided. Shift table analyses were performed for vital signs [Module 5, Volume 65, page 81; Module 5, Volume 72, pages 2525-2537].

10.1.3.14 Statistics

Statistical considerations in this study follow below.

10.1.3.14.1 Datasets analyzed

All patients who received study drug and had at least one on-therapy visit were included in the intent-to-treat (ITT) analysis. All patients who receive randomized drug and met inclusion and exclusion criteria were evaluated in the per protocol (PP) analysis. All patients who received study drug were evaluated in the safety analysis [Module 5, Volume 65, page 81].

10.1.3.14.2 Statistical power

This study was initially designed primarily to assess the long-term safety of olopatadine 0.6% nasal spray. Assessment of efficacy was added as an objective of the study with Protocol Amendment Number 3 [Module 5, Volume 65, page 60; Module 5, Volume 71, page 2268]. There was no formal statistical power calculation. The applicant's goal was to have 300 patients on olopatadine nasal spray 0.6% complete six months of enrollment and 100 patients on olopatadine nasal spray 0.6% complete 12 months of enrollment. Based on attrition, it was assumed that approximately 900 patients would need to be initially screened to obtain approximately 800 patients randomized into the study [Module 5, Volume 65, page 82].

10.1.3.14.3 Statistical analyses

The applicant used a two-sample t-test to compare the difference between treatment groups for the primary efficacy endpoint, the mean response to the patient-related relief assessment question over the duration of the study. The applicant used a two-sample t-test to compare the difference between treatment groups in the secondary efficacy endpoint, the average number of days that rescue medication was used [Module 5, Volume 65, page 82].

Reviewer comment:
This study was not powered to detect a difference between treatment groups for this endpoint and it is not appropriate to analyze the data inferentially.

Descriptive analyses of adverse events, changes in nasal examinations, vital signs, physical examinations, and ECGs were provided. Shift table analyses were performed for vital signs [Module 5, Volume 65, page 81-82; Module 5, Volume 72, pages 2525-2537].

10.1.3.15 Results

Results of the study are reviewed below.

10.1.3.15.1 Patient disposition

A total of 924 patients were enrolled and randomized to treatment. There were 924 patients in the ITT group. Table 89 summarizes patient disposition [Module 5, Volume 65, pages 84, 92].

Table 89 Patient disposition, C-01-92 [Module 5, Volume 65, pages 84, 92]

	Vehicle placebo n (%)	Olopatadine NS, 0.6% n (%)	Total n (%)
Patients randomized	465 (100)	459 (100)	924 (100)
Patients discontinued	152 (32.7)	124 (27.0)	276 (29.9)
Adverse event	25 (5.4)	23 (5.0)	48 (5.2)
Lost to follow-up	33 (7.1)	29 (6.3)	62 (6.7)
Patient decision	24 (5.2)	19 (4.1)	43 (4.6)
Treatment failure	40 (8.6)	35 (7.6)	75 (8.1)
Protocol violation	10 (2.1)	10 (2.2)	20 (2.2)
Other	20 (4.3)	8 (1.7)	28 (3.0)
Patients in ITT analysis	465	459	924
Patients excluded from ITT analysis	0	0	0
Patients in PP analysis	448	441	889
Patients excluded from PP analysis	17	18	35
Patients in safety analysis	465	459	924
Patients excluded from safety analysis	0	0	0

There were 276 patients that discontinued from the study (Table 89). Treatment failure was the most common reason for discontinuation from the study. The frequencies of discontinuations due to treatment failure and because of adverse events were similar in the two treatment groups. The frequency of discontinuations due to patient decision unrelated to an adverse event was higher in the vehicle placebo group (4.3%, 20/465) than in the olopatadine 0.6% group (1.7%, 8/459). The frequency of discontinuations due to other reasons was similar among the treatment groups [Module 5, Volume 65, pages 84, 92].

Protocol deviations occurred in 3.7% of vehicle placebo patients and 3.9% of olopatadine 0.6% patients. The most common protocol deviation was exclusion criteria [Module 5, Volume 65, page 92]. The types of protocol deviations occurred were similarly distributed among treatment groups. These data are summarized in Table 90.

Table 90 Protocol deviations, C-01-92 [Module 5, Volume 65, page 92]

	Vehicle placebo		**Olopatadine NS, 0.6%**		**Total**	
	N = 465		**N = 459**		**N = 924**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
All protocol deviations	17	(3.7)	18	(3.9)	35	(3.8)
Exclusion criteria	13	(2.8)	15	(3.3)	28	(3.1)
Inclusion criteria	4	(0.9)	3	(0.6)	7	(0.8)

10.1.3.15.2 Demographic and background characteristics

There were more females than males in the study. The population studied was largely of Caucasian race. Patients of Black and Hispanic races were represented at acceptable proportions compared with that of the general population. The mean age of patients in the study was 36.1 years. The large majority of patients ranged from 13-64 years of age. Patients greater than 64 years of age represented 1.9% of the total study population [Module 5, Volume 65, pages 99-100]. These data are displayed in Table 91.

Table 91 Demographics, C-01-92 [Module 5, Volume 65, pages 99-100]

Characteristic	**Vehicle placebo**		**Olopatadine NS, 0.6%**		**Total**	
	N = 465		**N = 459**		**N = 924**	
Gender	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Male	165	(35.5)	156	(34.0)	321	(34.7)
Female	300	(64.5)	303	(66.0)	603	(65.3)
Race	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Caucasian	368	(79.1)	360	(78.4)	728	(78.8)
Black	33	(7.1)	29	(6.3)	62	(6.7)
Asian	19	(4.1)	16	(3.5)	35	(3.8)
Hispanic	42	(9.0)	49	(10.7)	91	(9.8)
Other	3	(0.6)	5	(1.1)	8	(0.9)
Age, years						
Mean age	35.2		36.9		36.1	
SD	13.9		13.9		13.9	
Range	12-79		12-78		12-79	
Age subgroups, years	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
0-12	7	(1.5)	7	(1.5)	14	(1.5)
13-64	447	(96.1)	445	(96.9)	892	(96.5)
>64	11	(2.4)	7	(1.5)	18	(1.9)

10.1.3.15.3 Compliance

Dosing compliance was defined as the percent of dosing times that an individual took study medication. The number of doses that an individual took within a given month was added and divided by two times the number of days the patient was on the study in that month, and then

multiplied by 100 to get a percentage [Module 5, Volume 65, page 132; Module 5, Volume 72, page 2555].

Compliance data are provided in Table 92. Patients in both treatment groups took more than 95% of doses of the dosing regimen specified by the protocol. Compliance in the two treatment groups was similar [Module 5, Volume 65, page 132].

Table 92 Compliance, C-01-92 [Module 5, Volume 65, page 132]

Study treatment	Percent dosing compliance, mean (SD)
Olopatadine 0.6%	97.6 (6.7)
Vehicle placebo	97.3 (6.7)

Reviewer comment:
There is an adequate degree of compliance to address efficacy and to provide safety information.

10.1.3.15.4 Pollen counts

Pollen counts were performed by study staff or by a counting station in the community. Pollen counts were started one week before the first patient was screened and continued until approximately one week after the last patient completed the study. Pollen counts were not performed during the winter months at sites that do not normally measure pollen during the winter. The amount of daily rainfall was also recorded [Module 5, Volume 65, page 65]. The period of time that patients in the study received study treatment covered 16 months. This 16-month period, which started in May 2003, included one tree pollen season, two grass pollen seasons, and two weed pollen seasons [Module 5, Volume 65, pages 1, 123-131].

Reviewer comment:
The pollen counts provide no useful information in this study of patients with PAR.

(b) (4)

(b) (4)

Reviewer comment:
(b) (4) *was not the original objective of this study. This objective was not added until after the Pre-NDA meeting. This* (b) (4) *was originally added by the applicant at the recommendations of the Division to provide additional support for the validity of safety assessments [Medical Officer Review, Charles E. Lee, M.D., IND 60,116, N-024, MR, 7/9/02]. This study was not powered to detect a difference between treatment groups for this endpoint and it is not appropriate to analyze these data inferentially.*

This instrument is a rather blunt and crude measure (b) (4)*, but is acceptable to support the validity of safety conclusions from this study.* (b) (4) *[Medical Officer Review, Charles E. Lee, M.D., IND 60,116, N-032, PN, 2/4/03].*

The effect size for the primary efficacy endpoint (6.7%) is similar in magnitude to the effect sizes of efficacy endpoints in the SAR pivotal efficacy and safety studies, C-02-37 (8.3%) and C-02-10 (9.2%). These data provide some evidence that patients used study medication and provide support for conclusions drawn from the safety endpoints in the study.

10.1.3.15.5.1.1 Subgroup analyses of primary efficacy endpoint

Patients 12 years of age and older were enrolled in the study. Olopatadine 0.6% was numerically superior to vehicle placebo for the following subgroups. Effect sizes were similar to the overall effect size:

- Patients 12 years of age
- Patients 12-17 years of age
- Patients 13-64 years of age
- Patients greater than 64 years of age
- Female and male genders
- Patients of Caucasian, Black, and Hispanic races

There were few patients of Asian (3.8%, 35/924) and Other (0.9%, 8/924) races in this study. Olopatadine 0.6% was numerically inferior to vehicle placebo for these subgroups [Module 5, Volume 65, pages 100, 135-143].

Reviewer comment:
These data provide evidence to provide support for safety data from subgroups in the study.

(b) (4)

[redacted]

Reviewer comment:
These data also provide evidence to provide support the safety data in this study.

(b) (4)

[redacted]

The applicant concluded that olopatadine 0.6% was statistically superior to vehicle placebo for all of the categorical analyses [Module 5, Volume 65, pages 108-120].

Reviewer comment:
None of the (b) (4) *were established prior to the start of the study. In addition, the study was not powered to detect a difference between treatment groups for these endpoints. It is not appropriate to analyze these data inferentially.*

The results of the exploratory analyses favored olopatadine 0.6% over vehicle placebo numerically and provide support for the safety data in the study.

10.1.3.15.6 Safety outcomes

Safety outcomes in the study are reviewed below.

10.1.3.15.6.1 Total drug exposure

Exposure to study treatment is summarized in Table 95. Duration of exposure was calculated as the number of days from the first administration of study medication to the last date of study drug administration as recorded on the case report form or to the date of the last study visit. The applicant's goal was to have 300 patients on olopatadine nasal spray 0.6% complete six months of enrollment and 100 patients on olopatadine nasal spray 0.6% complete 12 months of enrollment [Module 5, Volume 65, page 82]. There were 388 patients treated with 0.6% olopatadine for at least six months and 303 patients who were treated for at least one year. There were 370 patients treated with vehicle placebo for at least six months and 281 patients treated with vehicle placebo for at least one year. The mean duration of exposure was 310.2 days for olopatadine 0.6% and 292.8 days for vehicle placebo [Module 5, Volume 65, pages 149-150].

Table 95 Exposure to study treatment, C-01-92 [Module 5, Volume 65, pages 149-150]

Treatment	N	≥1 day n (%)	>30 days n (%)	>60 days n (%)	>120 days n (%)	>180 days n (%)	>240 days n (%)	>300 days n (%)	>365 days n (%)	Mean days
Total	924	924 (100)	870 (94.1)	837 (90.6)	797 (86.2)	758 (82.0)	716 (77.5)	685 (74.1)	584 (63.2)	301.4
Olopatadine 0.6%	459	459 (100)	441 (96.1)	427 (93.0)	408 (88.9)	388 (84.5)	367 (80.0)	352 (76.7)	303 (66.0)	310.2
Vehicle placebo	465	465 (100)	429 (92.3)	410 (88.2)	389 (83.7)	370 (79.6)	349 (75.1)	333 (71.6)	281 (60.4)	292.8

Reviewer comment:
Exposure to study drug was adequate to allow for assessment of safety. The applicant achieved their goal for duration of exposure at six months and one year.

10.1.3.15.6.2 Adverse events

Adverse events were volunteered by patients at study visits and were recorded in a home patient log. Study staff also elicited adverse events at office visits [Module 5, Volume 65, pages 3, 62, 66-67, 76-78].

Adverse events occurring at a frequency greater than 2.0% and more frequently in olopatadine 0.6% than vehicle placebo are summarized in Table 96.

Adverse events were frequent, but occurred in a similar proportion of patients in the treatment groups in this one-year study. Of all patients treated with olopatadine 0.6%, 80.0% (367/459) had adverse events. Of all patients treated with vehicle placebo, 82.1% (382/465) had adverse events. The frequency of adverse events was high but was similar in both treatment groups, with a frequency of 273.0% (1253/459) for olopatadine 0.6% and 264.9% (1232/465) in the vehicle placebo group [Module 5, Volume 67, pages 779-793, 917]. Most adverse events occurring in this study were mild to moderate in severity and resolved without treatment [Module 5, Volume 67, pages 843-912].

Of those adverse events occurring more frequently in olopatadine 0.6% than vehicle placebo, the most frequent included epistaxis, cold syndrome, taste perversion, arthralgia, cough increased, otitis media, among others [Module 5, Volume 67, pages 779-793, 917].

Table 96 Adverse events occurring at a frequency greater than 2% and more frequently in olopatadine 0.6% than vehicle placebo, C-01-92 [Module 5, Volume 67, pages 779-793, 917]

Adverse event	Olopatadine NS 0.6% N = 459		Vehicle placebo N = 465	
Patients with adverse events	367	(80.0)	382	(82.1)
All adverse events	1253	(273.0)	1232	(264.9)
Epistaxis	88	(19.2)	56	(12.0)
Cold syndrome	76	(16.6)	75	(16.1)
Taste perversion	44	(9.6)	4	(0.9)
Arthralgia	23	(5.0)	12	(2.6)
Cough increased	22	(4.8)	15	(3.2)
Otitis media	15	(3.3)	14	(3.0)
Dyspepsia	14	(3.1)	9	(1.9)
Toothache	13	(2.8)	7	(1.5)
Diarrhea	13	(2.8)	6	(1.3)
Dermatitis	12	(2.6)	9	(1.9)
Injury, accidental	11	(2.4)	7	(1.5)
Pain, extremity	11	(2.4)	7	(1.5)
Pain, ear	10	(2.2)	8	(1.7)
Depression	9	(2.0)	3	(0.6)
Dry nose	9	(2.0)	2	(0.4)

There were no clinically relevant differences in the frequency or character of adverse events in patients 12 to 17 years of age and patients 65 years of age and older, compared with the general study population. The proportions of patients with and without adverse events were similar for patients of male and female genders and for patients of Caucasian, Black, and other races [Module 5, Volume 65, page 177-184; Module 5, Volume 67, pages 794-833, 917].

Reviewer comment:
Epistaxis has been noted with other intranasal spray products with the SAR and/or PAR indications. Epistaxis and other nasal adverse events are discussed in a subsequent section of this review. Taste perversion has been noted in the clinical development programs for Astelin Nasal Spray and Atrovent Nasal Spray 0.03% and 0.06% [Product Labels, Astelin Nasal Spray, Atrovent Nasal Spray 0.03%, Atrovent Nasal Spray 0.06%].

10.1.3.15.6.2.1 Adverse events associated with antihistamine and anticholinergic drugs

Adverse events occurring during the study that have been noted with antihistamines and anticholinergic drugs are summarized in Table 97. In general, these adverse events occurred more frequently in the olopatadine 0.6% group than the vehicle placebo group, but were at low frequencies [Module 5, Volume 67, pages 779-793].

Table 97 Adverse events associated with antihistamine and anticholinergic drugs occurring at a frequency greater than 2% and more frequently in olopatadine 0.6% than vehicle placebo, C-01-92 [Module 5, Volume 67, pages 779-793]

Adverse event	Olopatadine NS 0.6% N = 459		Vehicle placebo N = 465	
Dyspepsia	14	(3.1)	9	(1.9)
Nausea	6	(1.3)	4	(0.9)
Fatigue	5	(1.1)	1	(0.2)
Somnolence	3	(0.7)	1	(0.2)
Constipation	3	(0.7)	0	(0)
Dry mouth	2	(0.4)	2	(0.4)
Weight increase	1	(0.2)	0	(0)
Urinary retention	0	(0)	1	(0.2)

Reviewer comments:
As in the two pivotal SAR efficacy and safety studies in this application, C-02-37 and C-12-10, somnolence was uncommonly reported. Somnolence and fatigue occurred more commonly in the olopatadine 0.6% group than the vehicle placebo group, but it is difficult to draw conclusions because of the small number of reports of these adverse events. Patients were instructed by the home patient log to record medical problems and medications that were taken during the study. A sprained ankle treated with Tylenol was given as an example of such a problem [NDA 21-861, N-000 BZ, 7/14/05, page 3 and attachments]. It is possible that the example given by the form may have led people to not record less severe adverse events.

10.1.3.15.6.2.2 Nasal adverse events

Nasal adverse events occurring during this study are summarized in Table 98. Epistaxis was frequent in both the olopatadine 0.6% group (19.2%, 88/459) and the vehicle placebo group (12.0%, 56/465). Rhinitis, pharyngitis, nasal ulcer, and sneezing were the other most frequent nasal adverse events [Module 5, Volume 67, page 779].

The applicant notes that adverse events were reported for any changes in the nasal examination and that all changes were defined as being clinically relevant, as specified in the protocol. The applicant points out that this conservative method of collecting adverse events may have resulted in the reporting of adverse events that are not meaningful in clinical practice or worrisome to the patient [Module 5, Volume 65, page 215]. The applicant notes that most adverse events for epistaxis reported in patients receiving olopatadine 0.6% were mild and resolved without treatment. The incidence of epistaxis in the olopatadine 0.6% group (19.2%) and the vehicle placebo group (12.0%) was higher than that noted in studies of Astelin Nasal Spray (2%) and Astelin vehicle placebo (1.4%) [Product Label, Astelin Nasal Spray]. According to the applicant, possible explanations for the higher incidence of epistaxis included a longer duration of treatment (12 months compared with two weeks) and repeated opportunities on nasal examination to observe nasal bleeding that otherwise may have been unnoticed by the patient.

The applicant concludes that the higher incidence of epistaxis in the olopatadine 0.6% nasal spray group is not a safety concern because of the mild nature of the adverse events and the similar incidence of discontinuation from epistaxis in the two treatment groups [Module 5, Volume 65, pages 216-217].

Table 98 Nasal adverse events occurring in C-01-92 [Module 5, Volume 67, pages 779, 1042, 1073, 1083]

Adverse event	Olopatadine NS 0.6% N = 459		Vehicle placebo N = 465	
Epistaxis	88	(19.2)	56	(12.0)
Rhinitis	56	(12.2)	71	(15.3)
Sinusitis	57	(12.4)	62	(13.3)
Pharyngitis	34	(7.4)	39	(8.4)
Nasal ulcer	19	(4.1)	21	(4.5)
Sneezing	10	(2.2)	14	(3.0)
Irritation, throat	8	(1.7)	9	(1.9)
Nasal discomfort	7	(1.5)	9	(1.9)
Dry nose	9	(2.0)	2	(0.4)
Nasal septum disorder	5	(1.1)	6	(1.3)
Nasal septum perforation	1	(0.2)	2	(0.4)
Neoplasm*	4	(0.9)	3	(0.6)
Irritation, nose	2	(0.4)	2	(0.4)
Nasal pruritus	1	(0.2)	2	(0.4)
Pain, throat	1	(0.2)	0	(0)
Nasal paresthesia	1	(0.2)	0	(0)

*Nasal polyposis was coded as neoplasm [Module 5, Volume 67, pages 1000-1087]

<u>*Reviewer comment:*</u>
Both olopatadine 0.6% and the vehicle placebo appear to be quite irritating to the nose. Epistaxis, rhinitis, and sinusitis were frequent in this study in both treatment groups.

*The incidence of epistaxis in the two-week SAR studies in this application was lower than that noted in this one-year study. In C-02-37, the incidence of epistaxis was 3.8% for olopatadine 0.6%, 2.1% for olopatadine 0.4%, and 2.1% for vehicle placebo [*Table 54*, Module 5, Volume 49, page 731]. In C-02-10, the incidence of epistaxis was 3.1% for olopatadine 0.6%, 5.2% for olopatadine 0.4%, and 1.8% for vehicle placebo [*Table 80*, Module 5, Volume 57, page 637]. It is likely that the longer duration of treatment and repeated opportunities on nasal examination to observe minor nasal bleeding contributed, in part, to the higher incidence of epistaxis in this study. Although there may have been an increased sensitivity in detecting epistaxis in this long-term safety study, the incidence of epistaxis in the two olopatadine SAR studies was greater than that noted in labeling for Astelin Nasal Spray.*

The high incidence of nasal ulcer and the presence of nasal septum perforation are more concerning safety signals than the incidence of epistaxis. Not only was nasal ulcer reported frequently in the olopatadine 0.6% group (4.1%, 19/459) and the vehicle placebo group (4.5%, 21/465), but nasal septum perforation was noted in one patient treated with olopatadine 0.6% (0.2%, 1/459) and in two patients treated with vehicle placebo (0.4%, 2/465). These findings represent a strong safety signal.

Nasal septum perforation is associated with use of intranasal corticosteroids, as well as abuse of intranasal cocaine. In a12-month, open label, long term safety study of triamcinolone acetate

aqueous nasal spray in 172 patients with perennial allergic rhinitis, there was one patient with nasal septum perforation [Module 5, Volume 73, pages 304-3053]. [12] *The labels for Flonase and Nasonex Nasal Sprays advise the prescriber that nasal septum perforations were noted in postmarketing adverse event reports. Labels for these drugs do not note nasal septum perforations occurring in the clinical development program. There is also no mention of nasal septum perforations in the labels for Astelin Nasal Spray and Atrovent Nasal Sprays 0.03% and 0.06%, non-corticosteroid nasal spray products with SAR indications.*

Searches of AERS using the DataMart application were performed on May 18 and 25, 2005 to identify postmarketing cases of nasal septum perforation associated with intranasal spray medications with SAR and PAR indications. The search term was "nasal septum perforation." These searches identified 11 cases of nasal septum perforation associated with Flonase and eight cases associated with Nasonex. There were no cases associated with the use of Atrovent Nasal Spray 0.03% and 0.06% and NasalCrom Nasal Spray. There was one case associated with the use of Astelin Nasal Spray. This patient was also using Flonase. Astelin was not the primary suspect drug.

It should also be noted that the pharmacology-toxicology team has safety concerns about the chronic intranasal use of the to-be-marketed product, which contains 1.8% povidone. There was olfactory epithelium degeneration and turbinate epithelium vacuolation observed in the applicant's six-month rat study with intranasal povidone. These effects were observed to be dose responsive in incidence and severity [Communication to Applicant dated 5/25/05; Pharmacology-Toxicology Review, Gary Bond, Ph.D., NDA 21-861, N-000, 12/24/04].

In support of their product formulation, the applicant notes that povidone is used in various Afrin Nasal Spray products at concentrations up to approximately 2.7% w/v. As noted above, the concentration of povidone in the to-be marketed product and the vehicle placebo is 1.8% [Module 2, Section 2.3.P, page 7]. However, it should be noted that Afrin is not intended for chronic use, and that the language specified by the OTC monograph for decongestant drug products warns the consumer not to use the product for more than three days [21 CFR 341.80(c)(2)(iii)]. The fact that Afrin Nasal Spray contains povidone at a concentration of 2.7% w/v does not provide support for the proposed product, which will be used for periods much longer than three days. Interestingly, there was one report in the AERS database of nasal septum perforation associated with the use of Afrin Nasal Spray. The report for this case, which was not confounded with use of other intranasal medications, indicates that the patient used Afrin daily for eight years, which provides additional concern regarding chronic intranasal exposure to the povidone excipient.

The applicant provided additional information about the three patients with nasal septum perforations, patients #3812-5905, #3795-8503, and #3652-9021, all in study C-01-92.

The applicant stated that patient #3812-5905 in study C-01-92 had a nasal septum perforation at baseline and had been enrolled in violation of the protocol. This patient was treated with olopatadine 0.6% "Nasal septal perforation" was added to the patient's baseline history in the Case Report Form (CRF) and the Exit Form in the CRF accurately reflected that the patient

exited the study with a protocol violation [NDA 21-861, N-000 BM, 7/18/05, Nasal Perforation Safety Information, page not numbered].

This patient was enrolled at the study center of (b) (4) *The screening medical history, physical examination, and nasal examination, performed on* (b) (6) *had been completed and did not note a history of presence of nasal septum perforation. At Visit 3, on* (b) (6)*, the nasal examination "revealed nasal septal perforation was present at Visit #1 but inadvertently not recorded." Bleeding was initially marked as being absent but the CRF was changed to reflect that bleeding was present. There is no Data Clarification Form for this CRF change. At Visit 4, the nasal examination noted the presence of a "Small perforation nasal septum. This was missed on initial PE. May have been secondary to trauma in past but not drug." Significant nasal abnormalities was originally marked as being absent, but the CRF was changed to reflect that significant nasal abnormalities were present. There is no Data Clarification Form for this CRF change. Data Clarification Forms were generated on June 21, 2004 and September 20, 2004, approximately* (b) (6) *after the original data was entered on the CRF. The Data Clarification Forms for June 21, 2004 change the response of inclusion/exclusion criteria met from "Yes" to "No" and add a comment to the that the nasal exam at Visit 3 revealed the nasal septum perforation was present at Visit 1, but missed. Data Clarification Forms for September 20, 2004 add nasal septal perforation to the medical history page, to add that the nasal septal perforation was due to trauma prior to baseline, and was present at baseline [NDA 21-861, N-000 BM, 7/18/05, Nasal Perforation Safety Information, CRF 3812-5905, pages 1-39].*

The changes in the CRFs are irregular and it is somewhat concerning that the Data Clarification Forms were not completed until one year after the data was entered into the CRF. In addition, there are no Data Clarification Forms for some of the other changes to the CRF. It is concerning that the abnormality was not picked up by the screening history or nasal examination, was associated with bleeding when noted at Visit 4, as one would expect a new nasal septum perforation to present. DSI will be performing a for cause audit of this site because of these irregularities.

In a teleconference with the Division on May 26, 2005, the applicant suggested that pre-existing nasal disease was a factor in one of the nasal septal perforations [NDA 21-861, Teleconference Minutes, 5/26/05]. Additional information was submitted by the applicant [NDA 21-861, N-000 BM, 7/18/05, Nasal Perforation Safety Information, page not numbered]. The applicant stated that patient #3795-8503 in study C-01-92 had several pertinent nasal baseline history conditions that were not reported to the investigator until the patient was informed that a nasal septum perforation was present. This patient was treated with vehicle placebo. The applicant notes that the patient had a history of a "thin septal wall", daily epistaxis, a history of nasal cauterization, and nasal saline irrigation three to four times a week. The applicant notes that had the investigator been aware of the nasal history at screening, it is unlikely that the patient would have been enrolled in the study.

This patient was enrolled at the study center of (b) (4)*. The case report form for patient #3796-8503 indicates that this patient had a history of a "thin*

septal wall" and "epistaxis QD" [Module 5, Volume 142, page 1981]. The entries for these conditions on the screening medical history are in clearly different handwriting than entries higher up on the page. No correction marks or initials are present on the page. The date of the screening history was June 4, 2003. Adverse Event Forms for "significant nasal abnormality" were changed to "anterior bilateral ulcerations (nasal septum)" and "ulcerations of mucosa" were changed to "septal hole" on (b) (6) *[Module 5, Volume 142, pages 1992, 1994]. These changes are in the same handwriting as the entries on the screening medical history for thin septal wall and epistaxis. The CRF indicates that there were no anatomic abnormalities at the screening visit on physical or nasal examinations, however.*

Concurrent nasal disease that might complicate or interfere with investigation or evaluation of the study medication was an exclusion criterion for this study. Strictly speaking, based on the medical history, the patient should have been excluded from the study. The development of nasal ulceration and nasal septal perforation in this patient is an important safety finding regardless of whether there was a pre-existing "thin septal wall." DSI will be also performing a for cause audit of this site because of irregularities in the CRF.

The applicant stated that patient #3652-9021 in study C-01-92 was observed to have a nasal septum perforation at Visit 9, on February 9, 2004. This patient was treated with vehicle placebo. The patient was withdrawn from the study on February 11, 2004. The applicant notes that the patient was subsequently diagnosed with fibromyalgia syndrome and systemic lupus erythematosus as a result of the work-up initiated when the nasal septum perforation was discovered. The investigator notes that autoimmune disease are a common cause for nasal septum perforations and that the autoimmune condition was the most likely cause of the perforation.

This patient was enrolled at the study center of (b) (4) *The case report form for patient #3652-9021 indicates that the patient was noted to have a nasal septum perforation with bleeding margins at Visit 9 and that after consulting with the applicant, the patient was withdrawn from the study.*

Nasal septum perforations may occur in systemic lupus erythematosus, as the applicant notes.[7,8] *However, given that the non-clinical data suggest that the formulation is toxic to the nasal mucosa and that there were two other cases of nasal septum perforations in the drug development program, one must also consider the possibility that this event is attributable to study treatment.*

Even if one accepts the nasal septum perforation in patient #3812-5905 as being pre-existing, and in #3652-9021 because of previously undiagnosed autoimmune disease, the third case remains a problem. It is difficult to accept the diagnosis of "thin nasal septum" as a predisposing factor for this event, even without the irregularities in the CRF. The development of nasal ulceration and nasal septal perforation in this patient is an important safety finding regardless of whether there was a pre-existing "thin septal wall."

In summary, the formulation for the proposed product appears to be toxic to the nasal mucosa, and is associated with epistaxis, nasal ulcer, and with chronic use is associated with a significant risk of nasal septum perforation. Non-clinical data suggest that the signal may be related to the povidone excipient. The three cases noted in this one-year study of 924 patients are particularly remarkable, given that the AERS database contains only 11 cases of nasal septum perforation for Flonase Nasal Spray and eight cases for Nasonex Nasal Spray. Both Flonase and Nasonex are products known to be associated with nasal septum perforation and both products have had extensive postmarketing exposures. Even accounting for underreporting, these data suggest that the frequency of this adverse event is much higher for the applicant's proposed product than for Flonase and Nasonex.

Based on AERS data, it appears that nasal septum perforation is extremely rare among non-steroid nasal sprays with allergic rhinitis indications. Even among corticosteroid nasal sprays with allergic rhinitis indications, nasal septum perforation appears to be uncommon. The findings in this study represent a major safety signal.

10.1.3.15.6.3 Deaths and serious adverse events

There were 15 patients who experienced 22 serious adverse events during the study. One of the serious adverse events resulted in a death. Patient #3206-7818 was a 41-year old woman with carpal tunnel syndrome, sinus headaches, gastric reflux, SAR, obesity, and menstrual cramps who was treated with olopatadine 0.6%. She underwent elective gastric bypass surgery on Study Day (b) (6) to treat obesity. She developed abdominal pain, perforated gastric ulcer, bacterial peritonitis, and sepsis on Study Day (b) (6). Sepsis resulted in death of the patient on Study Day (b) (6) This adverse event was considered not to be related to study treatment [Module 5, Volume 65, page 198; Module 5, Volume 69, page 1417; Module 5, Volume 143, pages 28, 84].

There were 15 patients who experienced 21 other serious adverse events during the study. Serious adverse events occurred in treatment groups at similar frequencies in the olopatadine 0.6% group (2.2%, 10/459) and vehicle placebo group (2.4%, 11/465). Appendicitis and surgical/medical procedure were the only serious adverse events that occurred in more than one patient. Appendicitis occurred in one patient in the olopatadine 0.6% group (0.2%, 1/459) and one patient in the vehicle placebo group (0.2%, 1/465). There were two patients in the olopatadine 0.6% group that had medical/surgical procedures (0.4%, 2/459); one patient had a hysterectomy and reconstruction of the bladder, and another had gastric bypass surgery. There was one patient in the vehicle placebo group that had a medical/surgical procedure (0.2%, 1/465). This patient had installation of a cardiac pacemaker [Module 5, Volume 65, page 200].

Reviewer comment:
Deaths and serious adverse events do not suggest a safety signal.

10.1.3.15.6.4 Withdrawals due to adverse events

There were 48 patients (5.2%, 48/924) who withdrew from the study due to adverse events. Withdrawals due to adverse events occurring in more than one patient in the study are summarized in Table 99. The frequency of patients withdrawing from the study because of adverse events was similar for the olopatadine 0.6% group (5.0%, 23/459) and vehicle placebo

group (5.4%, 25/465). The frequency of adverse events resulting in withdrawal was similar in the olopatadine 0.6% group (6.3%, 29/549) and the vehicle placebo group (6.0%, 28/465) [Module 5, Volume 65, pages 203-204].

Taste perversion, nasal discomfort, headache, nasal ulcer, and epistaxis were the most frequent adverse events resulting in withdrawal of patients treated with olopatadine 0.6%. Headache, dizziness, nasal ulcer, infection, migraine, and nasal septum disorder (nasal septum perforation) were the most frequent adverse events resulting in withdrawal of patients treated with vehicle placebo [Module 5, Volume 65, pages 203-204]. There was one patient treated with olopatadine 0.6% (#3792-9510) and one patient treated with vehicle placebo (#2945-7214) that withdrew from the study because of allergic reactions. Patient #3792-9510 was a 21-year old woman who developed angioedema, urticaria, and rash on Study Day 24, longer than one hour but less than 24 hours after a dose of study treatment. Symptoms were moderate in severity and resolved over two days with treatment with prednisone and fexofenadine. The event was attributed to study drug, a URI, hair dye, or ibuprofen [Module 5, Volume 65, page 208; Module 5, Volume 142, page 1968]. Patient #2945-7214 was a 35-year old woman who developed facial and ocular swelling, itching, and flushing on Study Day 14, within 24 hours of a dose of vehicle placebo. Symptoms were moderate in severity and resolved over one day with treatment with fexofenadine. The event was attributed to study treatment or Neutrogena Astringent Facial Cream [Module 5, Volume 65, page 209; Module 5, Volume 138, page 535].

Table 99 Withdrawals due to adverse events occurring in more than one patient in the study, C-01-92 [Module 5, Volume 65, pages 203-204]

Adverse event	Olopatadine NS 0.6% N = 459		Vehicle placebo N = 465	
Patients withdrawing because of adverse events	23	(5.0)	25	(5.4)
All adverse events resulting in withdrawal	29	(6.3)	28	(6.0)
Taste perversion	4	(0.9)	0	(0)
Nasal discomfort	3	(0.7)	1	(0.2)
Headache	2	(0.4)	4	(0.9)
Nasal ulcer	2	(0.4)	2	(0.4)
Epistaxis	2	(0.4)	1	(0.2)
Allergic reaction	1	(0.2)	1	(0.2)
Asthma	1	(0.2)	1	(0.2)
Sinusitis	1	(0.2)	1	(0.2)
Dizziness	0	(0)	3	(0.6)
Infection	0	(0)	2	(0.4)
Migraine	0	(0)	2	(0.4)
Nasal septum disorder*	0	(0)	2	(0.4)

*These patients had nasal septum perforations, which were coded as nasal septum disorder

<u>Reviewer comment:</u>
There were relatively few withdrawals in this fairly large study. Taste perversion was significant enough to cause four patients in the olopatadine 0.6% group to withdraw from the study. Nasal discomfort, nasal ulcer, epistaxis, and nasal septum perforation are likely to be related to the nasal toxicity of the product, as previously discussed in Section 10.1.3.15.6.2.2 of this review. These data provide additional support for the significance of nasal adverse events occurring in this study.

10.1.3.15.6.5 Vital signs

Vital signs were completed at screening, Visit 3, Visit 5, Visit 8, Visit 11, and the Exit Visit [Module 5, Volume 65, pages 64, 67-68, 76]. There were no clinically significant changes from baseline to Exit visit or to any visit for mean values of vital signs for any of the treatment groups for the overall study population [Module 5, Volume 65, pages 222-233]. There were small increases in pulse (3.3 bpm), decreases in systolic blood pressure, (-4.4 mmHg), and decreases in diastolic blood pressure (-8.3 mmHg) in patients greater than 64 years of age who were treated with olopatadine 0.6%. There were small increases in pulse (9.5 bpm), and decreases in systolic blood pressure, (-4.2 mmHg) in patients greater than 64 years of age who were treated with vehicle placebo 0.6%. There were few patients greater than 64 years of age in the study population (1.9%, 18/924), however [Module 5, Volume 65, pages 99-100, 226]. There were 20 adverse events in 18 patients who had clinically significant changes in vital signs that were reported as adverse events. These adverse events included seven patients treated with olopatadine 0.6% and eight patients treated with vehicle placebo who had hypertension. There was one patient treated with olopatadine 0.6% and three patients treated with vehicle placebo that had tachycardia and one patient treated with vehicle placebo that had bradycardia [Module 5, Volume 65, page 233]. Analysis of shift tables and scatter plots for the overall study population identified no safety concerns [Module 5, Volume 65, pages 222-233].

Reviewer comment:
Vital signs reveal no safety signal.

10.1.3.15.6.6 Physical examination

Physical examinations were performed at screening, Visit 8, and the Exit visit [Module 5, Volume 65, pages 64, 67-68, 76]. Clinically relevant changes in physical examinations were reported as adverse events. Nasal and ocular findings were not required to be reported as adverse events unless the investigator assessed the finding as related to study drug or due to a cause other than SAR. Adverse events have been reviewed earlier in this document in section 10.1.3.15.6.2. Nasal examination findings are discussed in a following section of this review. Overall there were no clinically relevant changes in physical examination findings from baseline observed among treatment groups [Module 5, Volume 65, pages 336-337].

Reviewer comment:
Physical examinations reveal no safety signal.

10.1.3.15.6.7 Nasal examination

Patients had nasal examinations at each study visit. [Module 5, Volume 65, pages 3, 62, 66-67, 76-78]. Changes in nasal examinations were reported as adverse events and each change was defined as being clinically relevant, according to the protocol. Nasal adverse events have been reviewed earlier in this document in section 10.1.3.15.6.2.2. Changes in nasal examination findings from baseline to any visit are summarized in Table 100. Development of nasal bleeding on nasal examination was more frequent in patients treated with olopatadine 0.6% (14.6%, 66/541) than in patients treated with vehicle placebo (10.4%, 47/451). Nasal ulcerations were common and occurred at similar frequencies in the olopatadine 0.6% group (3.8%, 17/451) and in the vehicle placebo group (4.0%, 18/451). Development of anatomic abnormalities and

infection occurred at similar frequencies in the olopatadine 0.6% and vehicle placebo treatment groups [Module 5, Volume 65, page 218].

The applicant notes that there were two patients treated with vehicle placebo who developed nasal septum perforations, patients #3652-9021 and #3795-8503. Both of these patients discontinued from the study. The applicant concluded that there were no safety concerns identified in patients receiving olopatadine 0.6% based on a review of nasal examination parameters [Module 5, Volume 65, page 216-217].

Table 100 Changes in nasal examinations, C-01-92 [Module 5, Volume 65, page 218]

Nasal examination finding	Olopatadine NS 0.6% N = 451		Vehicle placebo N = 451	
Anatomic abnormalities	7	(1.6)	7	(1.6)
Bleeding	66	(14.6)	47	(10.4)
Infection	31	(6.9)	28	(6.2)
Ulcerations	17	(3.8)	18	(4.0)

Reviewer comment:
Contrary to the applicant's conclusions, this reviewer concludes that the nasal examinations identify a safety concern. Nasal ulcerations were common and nasal septum perforations were noted in this study. In addition to the two patients with nasal septum perforations in the vehicle placebo group (patients #3652-9021 and #3795-8503), there was also one patient with a nasal septum perforation in the olopatadine 0.6% group (patient #3812-5905). Apparently this patient was not represented in the applicant's review of nasal examination findings because the event was considered not to be related to study treatment [Module 5, Volume 67, page 1042]. It is difficult to understand how the development of a nasal septum perforation could be considered not to be related to study treatment, given that patients were prohibited from using any other nasal spray products. This reviewer will consider the nasal septum perforation in patient #3812-5905 to be related to study treatment.

In addition, as noted previously in this review in Section 10.1.3.15.6.2.2, nasal septum perforation is extremely rare among non-steroid nasal sprays with allergic rhinitis indications. Even among corticosteroid nasal sprays with allergic rhinitis indications, nasal septum perforation appears to be uncommon. The pharmacology-toxicology team notes that there was olfactory epithelium degeneration and turbinate epithelium vacuolation observed in the applicant's six-month intranasal study of povidone in rats [Communication to Applicant dated 5/25/05; Pharmacology-Toxicology Review, Gary Bond, Ph.D., NDA 21-861, N-000, 12/24/04.

The formulation for the proposed product appears to be toxic to the nasal mucosa, and is associated with epistaxis, nasal ulcer, and with chronic use is associated with a significant risk of nasal septum perforation. These findings represent a major safety signal.

10.1.3.15.6.8 ECGs

ECGs were completed at screening, Visit 8, and the Exit visit [Module 5, Volume 65, pages 64, 67-68, 76]. Any clinically significant changes from baseline in ECGs were reported as an adverse event. Descriptive analyses of changes in ECGs were provided. Although the protocol

called for shift table analysis of ECG results, this analysis was not performed [Module 5, Volume 65, pages 81, 306; Module 5, Volume 72, pages 2525-2537].

Mean change from baseline to Visit 8 and mean change from baseline to Exit visit in PR, QRS, RR, QT, QTcB, and QTcF intervals were similar for olopatadine 0.6% and vehicle placebo and were not clinically relevant [Module 5, Volume 65, pages 310-311]. The percentage of patients with a QTcB interval greater than normal (>450 msec for males, >470 msec for females) was similar for the olopatadine 0.6% group (0.5%, 2/434) and the vehicle placebo group (0.5%, 2/432). There were no patients in either treatment group with a QTcF interval greater than normal [Module 5, Volume 65, pages 326-327].

The percentage of patients with changes in QTcB interval from baseline to any visit of ≥30 to ≤60 msec was similar for the olopatadine 0.6% (6.5%, 28/434) and the vehicle placebo group (8.8%, 38/432). There was one patient with a change in QTcB interval from baseline to any visit of >60 msec in the olopatadine 0.6% group (0.2%, 1/434) and the vehicle placebo group (0.2%, 1/432) [Module 5, Volume 65, page 328].

The percentage of patients with changes in QTcF interval from baseline to any visit of ≥30 to ≤60 msec was similar for the olopatadine 0.6% (3.7%, 16/434) and the vehicle placebo group (4.6%, 20/432). There were no patients in either group with a change in QTcB interval from baseline to any visit of >60 msec [Module 5, Volume 65, page 328].

ECGs were interpreted by cardiologists at the ECG reading center and abnormalities were assessed for clinical relevance. The percentages of patients determined to have clinically relevant changes in ECGs were similar for both treatment groups [Module 5, Volume 65, page 330-332]. Adverse events associated with abnormal ECGs were noted in three patients in the olopatadine 0.6% group (0.6%, 3/459) and six patients in the vehicle placebo group (1.3%, 6/465). Review of these adverse events did not identify a safety concern [Module 5, Volume 65, pages 333-335].

Reviewer comment:
Although the applicant did not perform shift table analyses of ECGs in this study, the application includes two PK/PD studies specifically designed to assess the cardiovascular safety of olopatadine, C-02-54 and C-00-23. The safety data from ECGs in this study do not identify a safety signal.

10.1.4 C-01-83: Dose response of olopatadine nasal spray vs. placebo in treating seasonal allergic rhinitis in an environmental exposure chamber (EEC)

Study initiated: May 30, 2002
Study completed: July 7, 2002
Study report dated: December 15, 2004
[Module 5, Volume 37, page 1; Module 5, Volume 41, page 1588]

10.1.4.1 Summary and reviewer's conclusion of study results

This was a single center, randomized, vehicle-controlled, double blind, parallel group, single dose, clinical study utilizing an environmental exposure chamber (EEC). The objective of this study was to determine if a dose response relationship exists for olopatadine nasal spray administered as 0.2%, 0.4%, 0.6% concentrations compared with vehicle placebo. Patients had at least a 2-year history of non-recalcitrant seasonal allergic rhinitis due to ragweed pollen.

The primary efficacy variable was the change from baseline in the instantaneous Total Nasal Symptom Score (TNSS). Secondary efficacy variables included changes from baseline in individual allergic rhinitis symptom scores and change from baseline in peak nasal inspiratory flow (PNIF) using the In-Check® PNIF device. The applicant performed an exploratory analysis on the Patient Global Rating Scale, a seven-point scale used to assess allergic rhinitis symptoms at the end of the dosing interval compared to that before dosing. The difference from baseline in TNSS for each of the treatment groups was measured at each time point to determine onset of action.

Olopatadine 0.6% was statistically superior to vehicle placebo and numerically superior to olopatadine 0.4% and olopatadine 0.2% for change from baseline in the TNSS at a majority of time points post-dose. Although a dose response was noted, the differences between the treatment groups were small. Olopatadine 0.6%, 0.4%, and 0.2% were numerically superior to vehicle placebo for most time points for change from baseline in runny nose, itchy nose, and sneezing scores. There was little difference between the active treatments and vehicle placebo in change from baseline in stuffy nose scores. There were no meaningful differences in change from baseline in PNIF for each of the treatment groups. There were more patients in the “Very Much Better” and “Moderately Better” categories for each of the active treatments than for vehicle placebo for the analysis of the Patient Global Rating Scale. For olopatadine 0.6%, onset of action was noted at 90 minutes post-dose and the therapeutic effect was maintained until the final assessment, at 720 minutes post-dose.

Safety variables included adverse events, vital signs, and nasal examinations. There were a small number of adverse events in this single dose study. The most common adverse event noted was headache. Epistaxis was noted in one patient treated with olopatadine 0.6%, one patient treated with olopatadine 0.4%, and two patients treated with vehicle placebo. There were no deaths, serious adverse events, or withdrawals due to adverse events in this study. Vital signs did not

identify a safety signal. There were two patients with clinically relevant changes in nasal examination; both patients were noted to have epistaxis. One of these patients was treated with olopatadine 0.2% and the other was treated with vehicle placebo.

In summary, olopatadine 0.6%, 0.4%, and 0.2% were numerically superior to vehicle placebo for most time points for change from baseline in TNSS. Although a dose response was noted, the differences between the treatment groups were small. For olopatadine 0.6%, onset of action was noted at 90 minutes post-dose and the therapeutic effect was maintained until the final assessment, at 720 minutes post-dose. There were a small number of adverse events in this single dose study. The most common adverse event noted was headache. Epistaxis was noted in one patient treated with olopatadine 0.6%, one patient treated with olopatadine 0.4%, and two patients treated with vehicle placebo in this single dose study. One patient in the olopatadine 0.2% group and one patient was in the vehicle placebo group were noted to have epistaxis on nasal examination. These safety findings suggest that the formulation may be irritating to the nose.

10.1.4.2 Objective

The objective of this study was to determine if a dose response relationship exists for olopatadine nasal spray administered as 0.2%, 0.4%, 0.6% concentrations compared with vehicle placebo [Module 5, Volume 37, page 30].

10.1.4.3 General study design

This study was a single center, randomized, vehicle-controlled, double blind, parallel group, single dose, clinical study utilizing an environmental exposure chamber (EEC) [Module 5, Volume 37, page 31]. The study center was at (b) (4) The principal investigator was Piyush Patel, M.D. [Module 5, Volume 37, page 1].

10.1.4.4 Patient population

Approximately 320 patients were to be enrolled and randomized to one of the four treatment groups. Patients were to be male or female, age 16 years of age or older [Module 5, Volume 37, page 34].

10.1.4.5 Notable inclusion and exclusion criteria

Patients were to have at least a 2-year history of non-recalcitrant seasonal allergic rhinitis during the fall pollen season. Patients were to have allergy to short ragweed pollen, as defined by a positive history and skin test [Module 5, Volume 37, page 34].

Patients were not to be enrolled if they had concurrent disease that might complicate or interfere with investigation of study medication, if they had taken prohibited medications, or if they had an insufficient washout of medications that would be expected to interfere with investigation of

the study medication. Patients with mild intermittent asthma could be enrolled, but patients with mild, moderate, or severe persistent asthma were excluded [Module 5, Volume 37, pages 35-37].

10.1.4.6 Protocol amendments

There were two protocol amendments. Amendment 1 revised the minimum age for enrollment from 12 to 16 years. No patients had been enrolled at the time of this protocol amendment. Notable changes to the protocol in Amendment 2, dated July 8, 2002, included deletion of an onset of action assessment, and added normal ranges for vital signs. At the time of this amendment, no patients had reached the first priming visit in the study [Module 5, Volume 37, pages 48-49; Module 5, Volume 38, pages 425, 429]

10.1.4.7 Study treatments

Patients randomized to active study treatment received single doses of olopatadine nasal spray, 0.100 mL, 0.2%, 0.4%, or 0.6%, two sprays each nostril, which delivered either 0.8 mg, 1.6 mg, or 2.4 mg of olopatadine free base, respectively. Patients randomized to placebo received single doses of olopatadine nasal spray vehicle, 0.100 mL, two sprays each nostril. Study treatments were packaged in a white, 30 mL HDPE plastic bottle with a white metered dose manual spray pump, white nasal adapter, and a blue dust cover [Module 5, Volume 37, pages 37-38]. The to-be-marketed formulation of olopatadine 0.6% nasal spray and the to-be-marketed delivery device were used in this study [Module 2, Volume 2, Section 2.3.P, pages 8-9, 14-16].

Table 101 Study treatment lots used in C-01-83 [Module 5, Volume 37, page 39]

Study treatment	Lot number	Formulation identification
Olopatadine 0.6% nasal spray	02-600082-1	103718
Olopatadine 0.4% nasal spray	02-600081-1	103717
Olopatadine 0.4% nasal spray	02-600080-1	103716
Olopatadine vehicle	02-600079-1	103784

10.1.4.8 Study visits

Patients had informed consent, a medical history, vital signs, nasal examination, and skin testing at the screening visit. Patients meeting screening criteria returned for two to four priming visits. The time between priming visits was not less than 24 hours and not more than 3 weeks. Patients were exposed to short ragweed pollen for three hours at the priming visits. During the exposure, patients recorded the severity of their SAR symptoms on a diary card at 30-minute intervals. Symptom scores are described below in “Assessment of Symptoms.” A Total Nasal Symptom Score (TNSS) was calculated from the sum of individual symptom scores. Patients were to have a TNSS of 6 out of 12, including a score of at least 2 for runny nose on two consecutive measurements at two priming visits to qualify for the treatment visit [Module 5, Volume 37, pages 31-33].

Patients meeting these criteria returned for the treatment visit, no longer than 3 weeks after the second qualifying priming visit. Patients were exposed to short ragweed pollen and recorded the severity of their symptoms. Patients were to have a TNSS of 6 out of 12 to be randomized into the study. Randomized patients received test medication and continued to record the severity of

their SAR symptoms on diary cards every 30 minutes for 4 hours after dosing and then every hour for the subsequent 8 hours. Patients also measured their peak nasal inspiratory flow rates (PNIF) with the In-Check PNIF device during the treatment visit [Module 5, Volume 37, pages 31-33]. Vital signs, nasal examination were performed and adverse events were recorded [Module 5, Volume 37, pages 43, 44].

10.1.4.9 Pollen procedures

Pollen particles were dispersed in the EEC by an aerosol generator designed to aerosolize dry non-defatted pollen consistently and reliably. The aerosolized pollen particles were dispersed and circulated by a set of fans placed throughout the chamber. The EEC was designed to produce consistent airborne pollen particle counts between 3000 to 4000 pollen grains/m^3. Pollen levels were documented every 30 minutes using seven rotational impact samplers. Study subjects were moved to new positions in the EEC approximately every 60 minutes to maximize equal pollen exposures [Module 5, Volume 37, pages 32-33].

10.1.4.10 Assessment of symptoms

Patients assessed the severity of their allergic rhinitis symptoms in a diary record during the priming and treatment visits. These allergic symptoms are displayed in Table 102. Symptoms were rated in severity using the scale displayed in Table 103. The patient assessment of symptoms was instantaneous, representing the severity of symptoms at the immediate time of assessment [Module 5, Volume 37, page 31].

Table 102 Symptoms of allergic rhinitis assessed by patients, C-01-83 [Module 5, Volume 37, page 31]

Runny nose (anterior rhinorrhea/posterior drainage
Itchy nose
Stuffy nose
Sneezing

Table 103 Scale for assessment of allergic rhinitis symptoms, C-01-83 [Module 5, Volume 37, page 31]

Score	Definition
0	None
1	Mild
2	Moderate
3	Severe

Patients also assessed their allergic rhinitis symptoms at the end of the dosing interval relative to before dosing using a 7-point, 0 to 6, Patient Global Rating Scale [Module 5, Volume 37, page 48].

10.1.4.11 Efficacy variables

The primary efficacy variable was the change from baseline in the instantaneous TNSS. The TNSS was defined as the sum of the severity scores for the patients' assessments of runny nose, stuffy nose, itchy nose, and sneezing [Module 5, Volume 37, page 45]. Secondary efficacy variables included changes from baseline in individual allergic rhinitis symptom scores and change from baseline in PNIF using the In-Check® PNIF device [Module 5, Volume 37, page

47]. The applicant performed an exploratory analysis using the Patient Global Rating Scale, a seven-point scale used to assess allergic rhinitis symptoms at the end of the dosing interval compared to that before dosing [Module 5, Volume 37, pages 47-48].

Initially, the applicant planned to measure baseline between the different concentrations of olopatadine nasal spray and vehicle placebo at each time point to determine onset of action. The applicant defined onset of action as the first time point after initiation of treatment when the drug demonstrates a change from baseline greater than that of the vehicle placebo treatment in the TNSS score [Module 5, Volume 38, page 381]. The plan to measure onset of action was deleted from the protocol in Amendment 2, but was carried out despite the protocol amendment, however [Module 5, Volume 37, pages 48, 154].

10.1.4.12 Safety variables

Safety variables included adverse events, vital signs, and nasal examinations [Module 5, Volume 37, page 44].

10.1.4.13 Statistics

All patients who received drug and had at least one on-therapy visit were evaluable for the intent-to-treat analysis. All patients who received drug and met inclusion and exclusion criteria were evaluable for the per-protocol analysis. All patients who received drug were evaluable for the safety analysis [Module 5, Volume 37, page 47].

The applicant used two sample t-tests to compare changes from baseline between 0.2%, 0.4%, 0.6%, and vehicle placebo for the TNSS, individual symptom scores, and PNIFs. The applicant used Cochran-Mantel-Haenzel rank scores using two-tailed level alpha = 0.05 tests for the analysis of patient global ratings [Module 5, Volume 38, pages 517, 518, 520, 522].

Descriptive analyses of adverse events, vital signs, and changes in nasal examinations were provided. Shift table and scatter plot analyses and were performed for vital signs [Module 5, Volume 38, pages 529-534].

The applicant estimated that with 80 evaluable patients per group, and a total of 320 patients, the study would detect a 1.5 unit difference in treatment groups in change from baseline in the TNSS. The maximum possible TNSS was 12 units. The applicant assumed a standard deviation of 2.909 units, and specified a 5% level of statistical significance with two-sided tests [Module 5, Volume 38, page 513].

10.1.4.14 Results

10.1.4.14.1 Patient disposition and demographics

There were 367 patients screened for the study. Of these, 320 were randomized to study treatment and received study drug, with 80 patients in each of the four treatment groups. All 320

patients were considered evaluable for the intent-to-treat, per protocol, and safety analyses. There were no patients who were discontinued from the study. There were no protocol deviations and no patients were excluded from the analyses [Module 5, Volume 37, pages 50-51].

The average age of patients in the study was 36.2 years and the age of patients ranged from 17 to 65 years. Of the 320 patients in the study, 155 (48.4%) were male and 165 (51.6%) were female. There were 188 (58.8%) patients of Caucasian race, 50 (15.6%) of Black race, 59 (18.4%) of Asian race, and 23 (7.2%) of Hispanic race in the study [Module 5, Volume 37, page 53].

10.1.4.14.2 Efficacy outcomes

Baseline TNSS, individual symptom scores, and PNIF were similar in the treatment groups [Module 5, Volume 37, page 55]. Results of the primary and secondary efficacy analyses are reviewed below.

10.1.4.14.2.1 Primary efficacy analysis

The primary efficacy variable was the change from baseline in the instantaneous Total Nasal Symptom Score (TNSS) [Module 5, Volume 37, page 45].

Results of the primary efficacy variable at each of the time points in the study are displayed in Figure 3. Olopatadine 0.6% was statistically superior to vehicle placebo and numerically superior to olopatadine 0.4% and olopatadine 0.2% at a majority of time points post-dose. The applicant concluded that a dose response exists and that olopatadine 0.6% was the most effective of the three doses [Module 5, Volume 37, page 57].

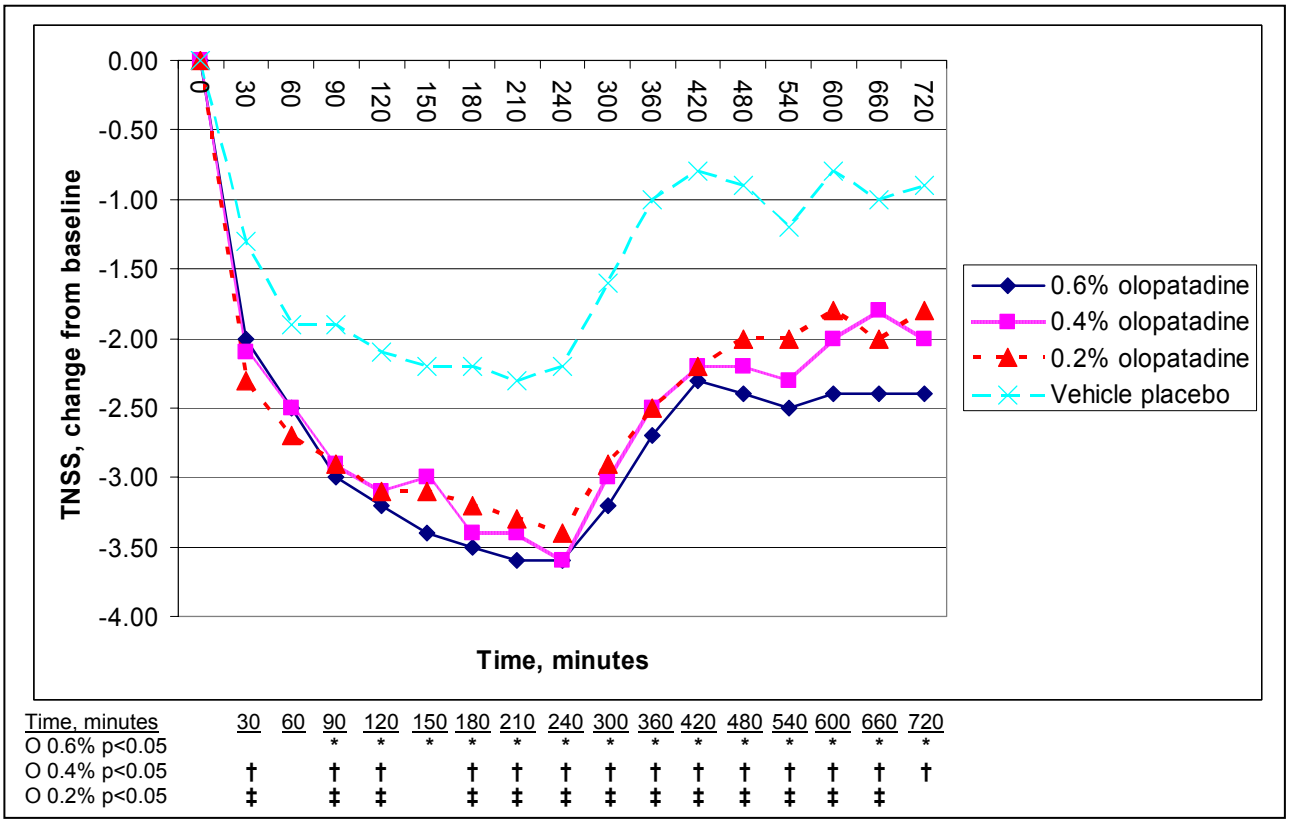

Figure 3 Change in baseline in TNSS, C-01-83 [plotted from data, Module 5, Volume 37, page 153]

Mean changes from baseline in TNSS scores were similar among patient of male and female genders and among patients of Caucasian, Black, Hispanic, and Asian races. All but one of the patients in the study were 12-64 years of age and no subgroup analysis of efficacy by age was performed [Module 5, Volume 37, pages 54, 81-83].

Reviewer comment:
The applicant's dose response analysis was less than rigorous. Although olopatadine 0.6% achieved a statistically significant difference from vehicle placebo for a greater number of assessments than did olopatadine 0.4% and 0.2%, there was only a small difference in effect between the different doses, as displayed in Figure 3. This reviewer carried out additional analyses of the primary efficacy variable. These data are summarized in Table 104. There was only a small difference between the different doses and vehicle placebo in the mean change from baseline in TNSS scores for each of the assessments. Although a dose response was noted in the effect size, the differences between the treatment groups were small. The maximum difference from vehicle placebo in change from baseline in TNSS was similar for each of the treatment groups and occurred at 360 minutes post-dose.

Although these data provide some evidence of a dose response, the difference in effect between the treatment groups is small and it is likely that the doses are at the high end of the dose response curve for this drug product.

Table 104 Difference from vehicle placebo in change from baseline in TNSS scores, [derived from data, Module 5, Volume 37, page 153]

	Olopatadine 0.6%	Olopatadine 0.4%	Olopatadine 0.2%
Mean difference from vehicle placebo in change from baseline in TNSS	-1.30	-1.11	-1.06
Effect size*	10.8%	9.2%	8.8%
Maximum difference from vehicle placebo in change from baseline in TNSS	-1.7	-1.5	-1.5
Time of maximum difference from vehicle placebo in change from baseline in TNSS	360 minutes	360 minutes	360 minutes

* Effect size = $\frac{\text{Difference from vehicle placebo, change from baseline} \times 100}{\text{Maximum change from baseline} = 12}$

10.1.4.14.2.2 Secondary efficacy analysis

Secondary efficacy variables included changes from baseline in individual allergic rhinitis symptom scores and change from baseline in PNIF using the In-Check® PNIF device [Module 5, Volume 37, page 47].

Olopatadine 0.6%, 0.4%, and 0.2% were numerically superior to vehicle placebo for most time points for change from baseline in runny nose, itchy nose, and sneezing scores. There was little difference between the active treatments in the degree of effect. There was little difference between the active treatments and vehicle placebo in change from baseline in stuffy nose scores [Module 5, Volume 37, pages 60-68].

There were no meaningful differences in change from baseline in PNIF for each of the treatment groups [Module 5, Volume 37, pages 69-71]. There were more patients in the "Very Much Better" and "Moderately Better" categories for each of the active treatments than for vehicle placebo for the analysis of the Patient Global Rating Scale [Module 5, Volume 37, page 72].

Reviewer comment:
This study was not powered to detect a difference in the secondary efficacy endpoints and this reviewer examined the results inferentially. Overall response to the drug in this study appears to be driven mainly by its effect on runny nose, itchy nose, and sneezing. There was little evidence of efficacy for nasal congestion in this study, as reflected by stuffy nose scores and PNIF. The Patient Global Relief Scale is an unvalidated exploratory instrument and will not provide support for efficacy.

10.1.4.14.2.3 Onset of action

As noted previously, the plan to measure onset of action was deleted from the protocol in Amendment 2. This analysis was carried out despite the protocol amendment [Module 5, Volume 37, pages 48, 154]. Based on the data for the primary efficacy analysis (Figure 3), the applicant concluded that onset of action was noted at 90 minutes post-dose and that the therapeutic effect was maintained until the final assessment, at 720 minutes post-dose [Module 5, Volume 37, pages 154-155].

Reviewer comment:
It is less than ideal that the analysis was carried out even though it had been deleted from the protocol. However, the definition of "onset of action" and its analysis were specified in the original protocol, prior to the start of the study. Given this information, it is reasonable to draw conclusions on onset of action from these data.

A statistically significant difference from vehicle placebo in TNSS was noted at 90 minutes post-dose for olopatadine 0.6% and the statistically significant difference was maintained at each of the remaining time points in the study. The applicant's data support an onset of action at 90 minutes post-dose for olopatadine 0.6%. This data must be replicated however, preferably in a natural environment exposure study, for a labeling or advertising claim. The data also provide additional support for the proposed twice daily dosing interval. The difference from vehicle placebo in TNSS for olopatadine 0.6% at 90 minutes was similar to the difference from vehicle placebo in TNSS over the treatment period noted in the two pivotal SAR efficacy and safety studies, approximately 1 point. This finding suggests that the effect noted at onset of action is clinically relevant.

10.1.4.14.3 Safety outcomes

Safety outcomes in the study are reviewed below.

10.1.4.14.3.1 Total drug exposure

A total of 320 patients were exposed to a single dose of study treatment. There were 80 patients exposed in the olopatadine 0.6%, 0.4%, 0.2%, and vehicle placebo treatment groups [Module 5, Volume 37, page 87].

10.1.4.14.3.2 Adverse events

Adverse events occurring in this study are summarized in Table 105.

There were a small number of adverse events in this single dose study. There was in inverse dose response effect for adverse events and for patients with adverse events, suggesting that some of the adverse events may have been related to symptoms from the exposure to pollen in the EEU. The most common adverse event noted was headache. Epistaxis was noted in one patient treated with olopatadine 0.6%, one patient treated with olopatadine 0.4%, and two patients treated with vehicle placebo. There were no relevant differences in adverse events among patients of different age, gender, and race [Module 5, Volume 37, page 98].

There were no deaths, serious adverse events, or withdrawals due to adverse events in this study [Module 5, Volume 37, pages 99-100].

Table 105 Adverse events, C-01-83 [Module 5, Volume 37, pages 290-291, 298-299]

Adverse event	Olopatadine 0.6% N = 80		Olopatadine 0.4% N = 80		Olopatadine 0.2% N = 80		Vehicle placebo N = 80	
	n	(%)	n	(%)	n	(%)	n	(%)
All adverse events	1	(1.2)	4	(5.0)	6	(7.5)	12	(15.0)
Patients with adverse events	1	(1.2)	3	(3.8)	6	(7.5)	10	(12.5)
Epistaxis	1	(1.2)	0	(0)	1	(1.2)	2	(2.5)

Adverse event	Olopatadine 0.6% N = 80		Olopatadine 0.4% N = 80		Olopatadine 0.2% N = 80		Vehicle placebo N = 80	
	n	(%)	n	(%)	n	(%)	n	(%)
Headache	0	(0)	2	(2.5)	2	(2.5)	4	(5.0)
Nausea	0	(0)	1	(1.2)	0	(0)	1	(1.2)
Vomiting	0	(0)	1	(1.2)	0	(0)	1	(1.2)
Nasal discomfort	0	(0)	0	(0)	2	(2.5)	0	(0)
Paresthesia	0	(0)	0	(0)	1	(1.2)	0	(0)
Pharyngitis	0	(0)	0	(0)	0	(0)	2	(2.5)
Rhinitis	0	(0)	0	(0)	0	(0)	1	(1.2)
Dyspnea	0	(0)	0	(0)	0	(0)	1	(1.2)

Reviewer comment:
Epistaxis was noted in patients treated with active and vehicle placebo in this single dose study, suggesting that the formulation is irritating to the nasal mucosa.

10.1.4.14.3.3 Vital signs

There were small, 3-5 bpm decreases in mean pulse rate for the olopatadine 0.6%, 0.4%, and 0.2% treatment groups. These decreases in pulse rate were noted in analyses using shift tables and scatter plots. There were no adverse events reported based on changes in pulse [Module 5, Volume 37, pages 105-107].

Small, 2-3 mm decreases in mean systolic blood pressure were noted for the olopatadine 0.4% and 0.2% treatment groups. Analyses of systolic blood pressure using shift tables and scatter plots identified no clinically relevant changes. There were no adverse events reported based on changes in systolic blood pressure [Module 5, Volume 37, pages 105, 107-108].

There were no meaningful changes in mean diastolic blood pressure for treatment groups in the study. Analyses of diastolic blood pressure using shift tables and scatter plots identified no clinically relevant changes. There were no adverse events reported based on changes in diastolic blood pressure [Module 5, Volume 37, pages 105, 109].

Reviewer comment:
There were no clinically meaningful changes in vital signs in the study. Vital signs did not identify a safety signal.

10.1.4.14.3.4 Nasal examination

Nasal examinations were performed at screening, priming, and treatment visits. An adverse event was reported for any clinically relevant increase in signs on nasal examination, defined as a change from baseline at any visit. There were two patients with clinically relevant changes in nasal examination. Both patients were noted to have epistaxis. One patient was in the olopatadine 0.2% group and the other was in the vehicle placebo group. Neither patient required treatment [Module 5, Volume 37, pages 103-104].

Reviewer comment:
As noted above, the occurrence of epistaxis in this single dose study suggests that the formulation is irritating to the nasal mucosa.

10.1.5 C-03-52: Olopatadine nasal spray 0.6% vs. placebo vehicle vs. Nasonex in treating seasonal allergic rhinitis in an environmental exposure chamber (EEC)

Study initiated: April 15, 2004
Study completed: June 12, 2004
Study report dated: November 16, 2004
[Module 5, Volume 42, page 1; Module 5, Volume 46, page 1863]

10.1.5.1 Summary and reviewer's conclusion of study results

This was a single center, randomized, vehicle-controlled, parallel group, double blind, single dose, clinical study utilizing an environmental exposure chamber (EEC). The objective of this study was to demonstrate the superiority of olopatadine HCl nasal spray 0.6% compared to vehicle placebo, when given as a single dose for the treatment of SAR over a 12-hour period. Secondary objectives were assessment of individual symptom severity scores over the treatment period and global assessment of SAR symptoms at four and 12 hours post-dose. The objectives of the exploratory analysis were to compare the effect of mometasone furoate monohydrate nasal spray 50 mcg (Nasonex® Nasal Spray, MFNS) to olopatadine nasal spray 0.6% and vehicle placebo, when given as a single dose for the treatment of SAR over a 12-hour period. Patients had at least a 2-year history of non-recalcitrant seasonal allergic rhinitis due to ragweed pollen.

The primary efficacy variable was the change from baseline in the instantaneous Total Nasal Symptom Score (TNSS). Secondary efficacy variables included changes from baseline in individual allergic rhinitis symptom scores and the Patient Global Rating Scale, a seven-point scale used to assess allergic rhinitis symptoms. The difference from baseline in TNSS for each of the treatment groups was measured at each time point to determine onset of action.

Olopatadine 0.6% was statistically superior to vehicle placebo at 30 minutes post-dose and at all of the subsequent time points. MFNS was statistically superior to vehicle placebo at 150 minutes post-dose and at all of the subsequent time points. For olopatadine 0.6%, onset of action was noted at 30 minutes post-dose and the therapeutic effect was maintained until the final assessment, at 720 minutes post-dose. For MFNS, onset of action was noted at 150 minutes post-dose and the therapeutic effect was maintained until the final assessment, at 720 minutes post-dose.

Olopatadine 0.6% was numerically superior to vehicle placebo for most time points for change from baseline in runny nose, itchy nose, stuffy nose, and sneezing scores. There was little difference in the degree of effect of olopatadine 0.6% on each of the individual symptoms. MFNS was numerically superior to vehicle placebo for most time points for change from baseline in runny nose, itchy nose, stuffy nose, and sneezing scores. The degree of effect of MFNS was similar for runny nose, stuffy nose, and sneezing, but less for itchy nose. There were more patients in the “Very Much Better” and “Moderately Better” categories for each of the active treatments than for vehicle placebo for both olopatadine 0.6% and MFNS in the analysis

of the Patient Global Rating Scale at four and twelve hours post-dose. The Patient Global Relief Scale is an unvalidated exploratory instrument and will not provide support for efficacy.

Safety variables included adverse events, vital signs, and nasal examinations. There were a small number of adverse events in this single dose study. The most common adverse event noted was headache. Taste perversion was reported by two patients in the olopatadine 0.6% group (1.4%). Epistaxis was noted in one patient treated with vehicle placebo (0.7%). There were no deaths, serious adverse events, or withdrawals due to adverse events in this study. Vital signs did not identify a safety signal. There was one patient treated with vehicle placebo that was noted on nasal examination to have epistaxis.

In summary, olopatadine 0.6% and MFNS were numerically superior to vehicle placebo for most time points for change from baseline in TNSS. For olopatadine 0.6%, onset of action was noted at 30 minutes post-dose and the therapeutic effect was maintained until the final assessment, at 720 minutes post-dose. For MFNS, onset of action was noted at 150 minutes post-dose and the therapeutic effect was maintained until the final assessment, at 720 minutes post-dose. There were a small number of adverse events in this single dose study. The most common adverse event noted was headache. Taste perversion was noted by two patients treated with olopatadine 0.6%. Epistaxis was noted in one patient treated with vehicle placebo in this single dose study.

10.1.5.2 Objective

The objective of this study was to demonstrate the superiority of olopatadine HCl nasal spray 0.6% compared to vehicle placebo, when given as a single dose for the treatment of SAR over a 12-hour period. Secondary objectives were assessment of individual symptom severity scores over the treatment period and global assessment of SAR symptoms at four and 12 hours post-dose. The objectives of the exploratory analysis were to compare the effect of mometasone furoate monohydrate nasal spray 50 mcg (Nasonex® Nasal Spray) to olopatadine nasal spray 0.6% and vehicle placebo, when given as a single dose for the treatment of SAR over a 12-hour period [Module 5, Volume 42, page 42].

10.1.5.3 General study design

This study was a single center, randomized, vehicle-controlled, double blind, parallel group, single dose, clinical study utilizing an environmental exposure chamber (EEC) [Module 5, Volume 42, page 43]. The study center was at (b) (4) . The principal investigator was Deepen Patel, M.D. [Module 5, Volume 42, page 1].

The design for this study was similar to that in study C-01-83, as described in Section 10.1.4 of this review. The design will not be reiterated. Points of difference for this study are described below.

10.1.5.4 Patient population

Approximately 420 patients were to be enrolled and randomized to one of the three treatment groups. Patients were to be male or female, age 18 years of age or older [Module 5, Volume 42, pages 4, 52].

10.1.5.5 Notable inclusion and exclusion criteria

Inclusion criteria and exclusion criteria were essentially the same as in study C-01-83, as described in Section 10.1.4.5 of this review [Module 5, Volume 42, pages 51-53]. Exclusion criteria that were different from study C-01-83 included [Module 5, Volume 42, pages 54-55]:

- Nasal congestion that would interfere with successful nasal drug administration or absorption
- Nasal septal ulcers, nasal surgery, or nasal trauma within 90 days of enrollment
- Presence of active or quiescent tuberculous infection of the respiratory tract, untreated local or systemic viral or parasitic infections, or ocular herpes simplex
- Diagnosis of chickenpox or measles
- Receiving immunosuppressive therapy

10.1.5.6 Protocol amendments

There were no protocol amendments [Module 5, Volume 42, page 64]

10.1.5.7 Study treatments

Patients randomized to active study treatment received single doses of olopatadine nasal spray, 0.6%, 0.100 mL per spray, two sprays each nostril, which delivered 2.4 mg of olopatadine free base. Patients randomized to active control treatment received single doses of mometasone furoate monohydrate nasal spray (Nasonex® Nasal Spray, MFNS) 50 mcg, 0.100 mL per spray, two sprays each nostril. Patients randomized to vehicle placebo control treatment received single doses of olopatadine nasal spray vehicle, 0.100 mL per spray, two sprays each nostril. Active study treatment and vehicle placebo control study treatment were packaged in a white, 30 mL HDPE plastic bottle with a white metered dose manual spray pump, and a white nasal adapter. Active control study treatment was packaged in a white, 20 mL HDPE plastic bottle with a white metered dose manual spray pump, and a white nasal adapter [Module 5, Volume 42, pages 57-58]. The to-be-marketed formulation of olopatadine 0.6% nasal spray and the to-be-marketed delivery device were used in this study [Module 2, Volume 2, Section 2.3.P, pages 8-9, 14-16]. The MFNS used in the study was a marketed product [Module 5, Volume 42, page 58].

Dosing regimens and outer packaging of study treatments were identical. The identity of study treatments was masked by a foil overwrap that disguised the shape and appearance of the bottle, pump, and nasal adapter [Module 5, Volume 42, pages 51, 59].

Reviewer comment:
Although the shape and appearance of the study treatments were masked, the size of the bottles and the taste and smell of the treatments were not. It is possible that study staff may have been

able to distinguish between MFNS and the other treatments because of the bottle size. In addition, MFNS is a suspension and the other study treatments are solutions. Patients may have been able to distinguish between the study treatment because of the bottle sizes, smell, and appearance of the study treatments, particularly patients who may have been treated in the past with MFNS or another corticosteroid nasal spray in a suspension formulation. These deficiencies in blinding are not likely to have had a major impact on the study results, in this reviewer's opinion.

Table 106 Study treatment lots used in C-03-52 [Module 5, Volume 42, page 57]

Study treatment	Lot number	Formulation identification
Olopatadine nasal spray 0.6%	03-600126-1	10378
MFNS 50 mcg	04-500591-1	106270
Olopatadine nasal spray vehicle	03-600122-1	103784

10.1.5.8 Study visits

The conduct of study visits was the same as for study C-01-83 (Section 10.1.4.8 of this review), with the exception that peak nasal inspiratory flow rates (PNIF) were not assessed by patients [Module 5, Volume 42, pages 47-50, 60-61].

10.1.5.9 Pollen procedures

The procedures for pollen dispersion and exposure were the same as for study C-01-83, previously reviewed in Section 10.1.4.9 of this review, with the exception that this study report does not indicate that study subjects were moved to new positions in the EEC in order to maximize equal pollen exposures [Module 5, Volume 42, pages 44-45].

10.1.5.10 Assessment of symptoms

Patients assessed individual symptom scores and Patient Global Rating Scores in the same fashion as in study C-01-83 (Section 10.1.4.10) [Module 5, Volume 42, pages 43, 60].

10.1.5.11 Efficacy variables

The primary efficacy variable was the same as for study C-01-83 (Section 10.1.4.11) [Module 5, Volume 42, pages 43-44, 60, 62]. Differences in the primary efficacy variable between treatments at each time point were used to evaluate onset and duration of action [Module 5, Volume 42, page 64]. The comparison of MFNS to olopatadine nasal spray 0.6% and vehicle placebo vehicle was a planned exploratory analysis of the primary efficacy variable [Module 5, Volume 42, page 60].

Secondary efficacy variables included changes from baseline in individual allergic rhinitis symptom scores and the Patient Global Rating Scale [Module 5, Volume 42, page 60], described in study C-01-83 (Section 10.1.4.11).

10.1.5.12 Safety variables

Safety variables were the same as for study C-01-83 (Section 10.1.4.12) [Module 5, Volume 42, page 60].

10.1.5.13 Statistics

All patients who received drug were evaluable for the intent-to-treat analysis [Module 5, Volume 42, page 65]. Definitions for those patients evaluable for the per-protocol and safety analyses were the same as for study C-01-83 (Section 10.1.4.13) [Module 5, Volume 42, page 65].

Statistical analyses were carried out on the primary and secondary efficacy variables as described for study C-01-83 (Section 10.1.4.13) [Module 5, Volume 42, page 65]. The exploratory analysis comparing MFNS to olopatadine nasal spray 0.6% and vehicle placebo used the same statistical tests as the other efficacy variable in this study [Module 5, Volume 42, page 65].

Analyses of safety variables were carried out in the same fashion as study C-01-83 (Section 10.1.4.13) [Module 5, Volume 43, pages 668-674].

The applicant estimated that with 140 evaluable patients per group, and a total of 420 patients, the study would detect a 1.2 unit difference in treatment groups in change from baseline in the TNSS. The maximum possible TNSS was 12 units. The applicant assumed a standard deviation of 2.90 units, and specified a 5% level of statistical significance with two-sided tests [Module 5, Volume 42, page 64].

Reviewer comment:
This study was powered to detect a smaller difference between treatment groups than study C-01-83, which was powered to detect a 1.5 unit difference.

10.1.5.14 Results

10.1.5.14.1 Patient disposition and demographics

There were 905 patients enrolled in the study. There were 21 patients who withdrew after receiving screening numbers but before signing informed consent. There were 609 patients who entered the study for at least one priming session. There were 425 patients randomized to treatment and received study drug. Reasons for screening failure included: failed allergy skin test (214 patients), failure to meet TNSS score requirements at the priming visit (148 patients), failure to meet inclusion and/or exclusion criteria (41 patients), voluntary withdrawal or loss to follow-up (30 patients), and fulfillment of the targeted study enrollment (26 patients) [Module 5, Volume 42, page 66].

There were no patients who were discontinued from the study. There were four protocol deviations. Three patients had participated in a previous Alcon study and one failed to meet

minimum TNSS score criteria prior to dosing at the treatment visit. These four patients were excluded from the per protocol analysis [Module 5, Volume 42, page 68].

The average age of patients in the study was 35.7 years and the age of patients ranged from 18 to 84 years. Of the 425 patients in the study, 199 (46.8%) were male and 226 (53.2%) were female. There were 238 (56.0%) patients of Caucasian race, 111 (26.1%) of Black race, 50 (11.7%) of Asian race, 19 (4.5%) of Hispanic race, and 7 (1.6%) of "other" race in the study [Module 5, Volume 42, page 71].

10.1.5.14.2 Efficacy outcomes

Baseline TNSS and individual symptom scores were similar in the treatment groups [Module 5, Volume 42, page 73]. Results of the primary and secondary efficacy analyses are reviewed below.

10.1.5.14.2.1 Primary efficacy analysis

The primary efficacy variable was the change from baseline in the instantaneous Total Nasal Symptom Score (TNSS) [Module 5, Volume 42, page 62].

Results of the primary efficacy variable at each of the time points in the study are displayed in . Olopatadine 0.6% was statistically superior to vehicle placebo at 30 minutes post-dose and at all of the subsequent time points. MFNS was statistically superior to vehicle placebo at 150 minutes post-dose and at all of the subsequent time points [Module 5, Volume 42, pages 76, 78].

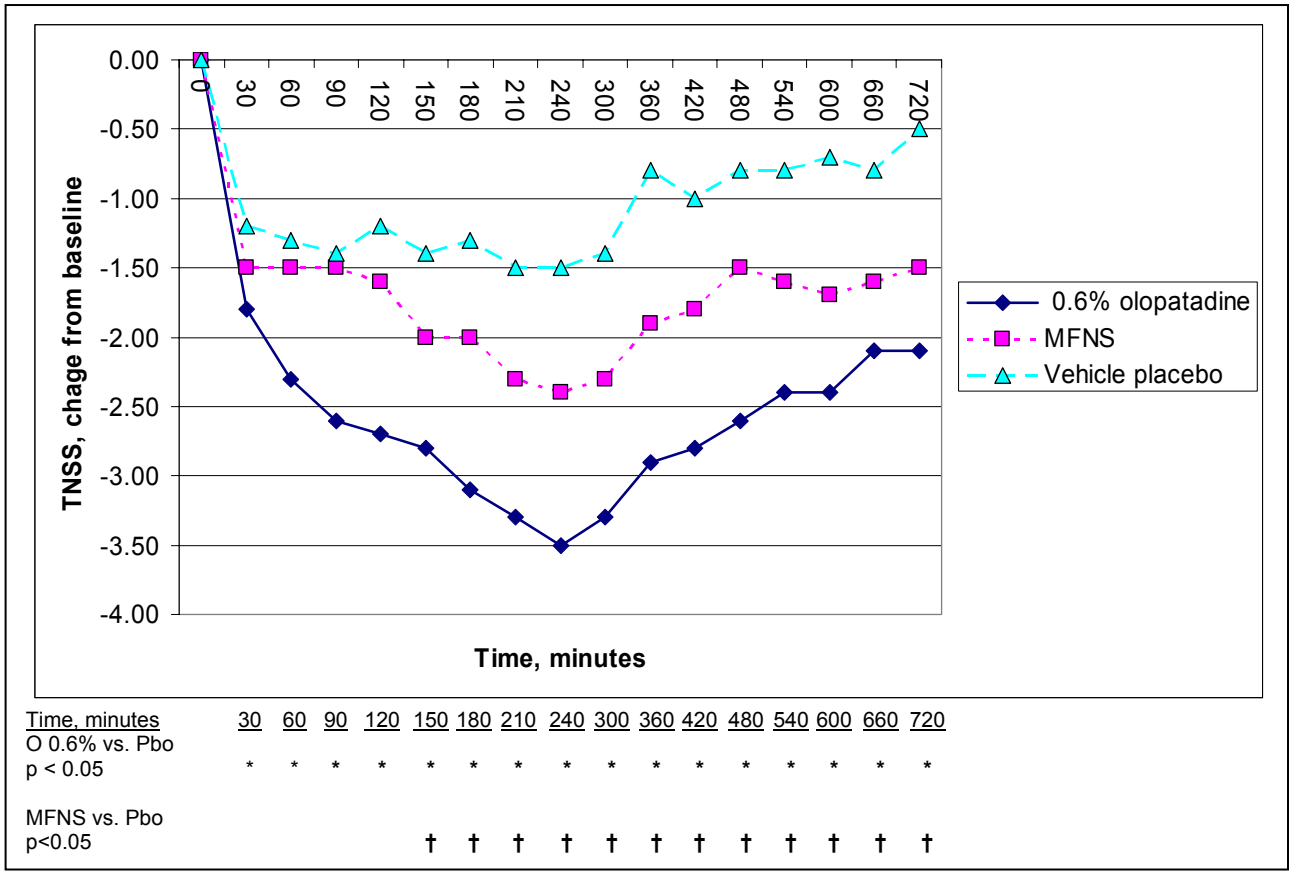

Figure 4 Change in baseline in TNSS, C-03-52 [plotted from data, Module 5, Volume 42, pages 209-211, 219-221]

Mean changes from baseline in TNSS scores were similar among patient of male and female genders and among patients of Caucasian, Black, Hispanic, and Asian races. Four of the patients in the study were 65-74 years of age. The remainder of the patients in the study were 18-64 years of age and no subgroup analysis of efficacy by age was performed [Module 5, Volume 42, pages 129-130, 349-354, 355-370].

The applicant concluded that for olopatadine 0.6%, onset of action was noted at 30 minutes post-dose and that the therapeutic effect was maintained until the final assessment, at 720 minutes post-dose. For MFNS, onset of action was noted at 150 minutes post-dose and that the therapeutic effect was maintained until the final assessment, at 720 minutes post-dose [Module 5, Volume 42, pages 76, 78].

Reviewer comment:
Both olopatadine 0.6% and MFNS achieved statistical superiority over vehicle placebo in change from baseline in TNSS at most time points in the study.

A statistically significant difference from vehicle placebo in TNSS was noted at 30 minutes post-dose for olopatadine 0.6% and the statistically significant difference was maintained at each of

the remaining time points in the study. The applicant's data support an onset of action at 30 minutes post-dose for olopatadine 0.6%. This data must be replicated however, preferably in a natural exposure study, for a labeling or advertising claim. The data also provide additional support for the proposed twice daily dosing interval. The difference from vehicle placebo in TNSS for olopatadine 0.6% at 30 minutes was smaller than the difference from vehicle placebo in TNSS over the treatment period noted in the two pivotal SAR efficacy and safety studies. This finding suggests that the effect noted at 30 minutes is not clinically relevant. The difference from vehicle placebo in TNSS for olopatadine 0.6% at 90 minute, however, was similar to the difference from vehicle placebo in TNSS over the treatment period noted in the two pivotal SAR efficacy and safety studies, approximately 1 point. This finding suggests that the effect noted at 90 minutes is clinically relevant..

A statistically significant difference from vehicle placebo in TNSS was noted at 150 minutes post-dose for MFNS and the statistically significant difference was maintained at each of the remaining time points in the study.

This reviewer carried out additional analyses of the primary efficacy variable. These data are summarized in Table 107. The effect size for olopatadine 0.6% was similar to that noted in the other EEC study, C-01-83.

The mean and maximum differences from vehicle placebo in change from baseline in TNSS scores for the assessment period were greater for olopatadine 0.6% than for MFNS. The time of maximum difference from vehicle placebo in change from baseline in TNSS occurred at 360 minutes post-dose for both active study treatments.

(b) (4)

The Nasonex Nasal Spray product label states that improvement in nasal symptoms of allergic rhinitis has been shown to occur within 11 hours after the first dose based on one single-dose, parallel-group study of patients in an outdoor "park" setting and one EEC study. The label states that the maximum benefit from Nasonex is usually achieved within 1 to 2 weeks. It is interesting that a statistically significant difference from vehicle placebo in change from baseline in TNSS scores was noted at 150 minutes post-dose.

Table 107 Difference from vehicle placebo in change from baseline in TNSS scores, [derived from data, Module 5, Volume 42, pages 209-211, 219-221]

	Olopatadine 0.6%	MFNS
Mean difference from vehicle placebo in change from baseline in TNSS	-13.07	-0.69
Effect size*	13.1	5.8
Time of maximum difference from vehicle placebo in change from baseline in TNSS	360	360
Maximum difference from vehicle placebo in change from baseline in TNSS	-2.10	-1.10

* Effect size = $\frac{\text{Difference from vehicle placebo, change from baseline} \times 100}{\text{Maximum change from baseline} = 12}$

10.1.5.14.2.2 Secondary efficacy analysis

Secondary efficacy variables included changes from baseline in individual allergic rhinitis symptom scores and the Patient Global Rating Scale [Module 5, Volume 42, page 60].

Olopatadine 0.6% was numerically superior to vehicle placebo for most time points for change from baseline in runny nose, itchy nose, stuffy nose, and sneezing scores. There was little difference in the degree of effect of olopatadine 0.6% on each of the individual symptoms [Module 5, Volume 42, pages 79-82].

MFNS was numerically superior to vehicle placebo for most time points for change from baseline in runny nose, itchy nose, stuffy nose, and sneezing scores. The degree of effect of MFNS was similar for runny nose, stuffy nose, and sneezing, but less for itchy nose [Module 5, Volume 42, pages 95-98].

There were more patients in the "Very Much Better" and "Moderately Better" categories for each of the active treatments than for vehicle placebo for both olopatadine 0.6% and MFNS in the analysis of the Patient Global Rating Scale at four and twelve hours post-dose [Module 5, Volume 42, pages 83-85, 99-101].

Reviewer comment:
This study was not powered to detect a difference in the secondary efficacy endpoints and this reviewer examined the results inferentially.

In this study, olopatadine 0.6% had a similar degree of effect on each of the individual nasal symptoms, unlike in C-01-83, where the effect was mainly on runny nose, itchy nose, and sneezing. The overall response to MFNS was driven mainly by its effect on runny nose, itchy nose, stuffy nose, and sneezing.

The Patient Global Relief Scale is an unvalidated exploratory instrument and will not provide support for efficacy.

10.1.5.14.3 Safety outcomes

Safety outcomes in the study are reviewed below.

10.1.5.14.3.1 Total drug exposure

A total of 425 patients were exposed to a single dose of study treatment. There were 142 patients exposed in the olopatadine 0.6% and MFNS groups and 141 patients exposed in the vehicle placebo treatment group [Module 5, Volume 42, page 135].

10.1.5.14.3.2 10.1.4.14.3.2 Adverse events

Adverse events occurring in this study are summarized in Table 108.

There were a small number of adverse events in this single dose study. There was in inverse dose response effect for adverse events and for patients with adverse events, suggesting that some of the adverse events may have been related to symptoms from the exposure to pollen in the EEU. The most common adverse event noted was headache. Taste perversion was reported by two patients in the olopatadine 0.6% group (1.4%). Epistaxis was noted in one patient treated with vehicle placebo (0.7%). There were no relevant differences in demographic characteristics (age, gender, and race) between patients with and without adverse events [Module 5, Volume 42, page 146; Module 5, Volume 43, pages 408-410].

There were no deaths, serious adverse events, or withdrawals due to adverse events in this study [Module 5, Volume 42, page 147].

Table 108 Adverse events, C-03-52 [Module 5, Volume 43, pages 408-410, 425-426]

Adverse event	Olopatadine 0.6% N = 142		MFNS N = 142		Vehicle placebo N = 141	
	n	(%)	n	(%)	n	(%)
All adverse events	5	(3.5)	5	(3.5)	18	(12.8)
Patients with adverse events	4	(2.8)	4	(2.8)	15	(10.6)
Taste perversion	2	(1.4)	0	(0)	0	(0)
Dizziness	1	(0.7)	1	(0.7)	0	(0)
Palpitations	1	(0.7)	0	(0)	0	(0)
Tachycardia	1	(0.7)	0	(0)	0	(0)
Headache	0	(0)	2	(1.4)	2	(1.4)
Rhinitis	0	(0)	0	(0)	2	(1.4)
Epistaxis	0	(0)	0	(0)	1	(0.7)
Irritation, throat	0	(0)	0	(0)	1	(0.7)
Pharyngitis	0	(0)	0	(0)	1	(0.7)
Hypertension	0	(0)	0	(0)	1	(0.7)
Hyperemia, eye	0	(0)	1	(0.7)	0	(0)
Tearing	0	(0)	1	(0.7)	0	(0)
Cough increased	0	(0)	0	(0)	2	(1.4)
Dyspepsia	0	(0)	0	(0)	1	(0.7)
Gastroenteritis	0	(0)	0	(0)	1	(0.7)
Nausea	0	(0)	0	(0)	1	(0.7)
Erythema	0	(0)	0	(0)	1	(0.7)
Pruritus	0	(0)	0	(0)	1	(0.7)
Conjunctivitis	0	(0)	0	(0)	1	(0.7)
Pain, ear	0	(0)	0	(0)	1	(0.7)
Pruritus, eye	0	(0)	0	(0)	1	(0.7)

Reviewer comment:
Taste perversion was noted only in patients treated with olopatadine 0.6%, and has been noted in other studies in this application. This study identifies no other safety signal.

10.1.5.14.3.3 Vital signs

There were small, 4-5 bpm decreases in mean pulse rate for all treatment groups. All treatment groups had decreases in pulse rate from baseline using shift table and scatter plot analyses. One patient in the olopatadine 0.6% group, #3954-2053, had an adverse event reported for palpitation and tachycardia. The event was reported as mild and resolved within two hours without treatment. There were no adverse events reported based on decreases in pulse [Module 5, Volume 42, pages 152, 154-158, 164-165; Module 5, Volume 43, page 427].

Small, 2-3 mm decreases in mean systolic blood pressure were noted for the olopatadine 0.6% and MFNS treatment groups. Small decreases in pulse rate from baseline were also noted in analyses using shift tables and scatter plots for olopatadine 0.6% and MFNS. Analyses of systolic blood pressure using scatter plots identified no clinically relevant changes. There was one patient in the vehicle placebo group, (#3954-2205) who had an adverse event for hypertension. The event was mild in severity and did not require treatment [Module 5, Volume 42, pages 152, 158-159; Module 5, Volume 43, page 427].

Small, 2-4 mm decreases in mean diastolic blood pressure were noted in all treatment groups. Small decreases in pulse rate from baseline were also were noted in analyses using shift tables for MFNS and vehicle placebo. Analyses of diastolic blood pressure using scatter plots identified small decreases in all treatment groups. There was one patient in the vehicle placebo group with hypertension, as noted above [Module 5, Volume 42, pages 152, 159-161; Module 5, Volume 43, page 427].

Reviewer comment:
There were no clinically meaningful changes in vital signs in the study. Vital signs did not identify a safety signal.

10.1.5.14.3.4 Nasal examination

Nasal examinations were performed at screening, priming, and treatment visits. An adverse event was reported for any clinically relevant increase in signs on nasal examination, defined as a change from baseline at any visit. There was one patient with clinically relevant changes in nasal examination. The patient was in the vehicle placebo group and was noted to have epistaxis [Module 5, Volume 42, pages 150-151].

Reviewer comment:
Although there was only one patient noted to have epistaxis on nasal examination, epistaxis was noted in two patients in another single dose study, C-01-83, and was noted in both SAR efficacy and safety studies. Epistaxis, nasal ulcerations, and nasal septal perforations were noted in the long-term safety study.

10.1.6 C-97-59: A crossover comparison of a single topical dose of olopatadine, emedastine, azelastine, and a randomly allocated placebo on a nasal provocation test with grass pollen in adult allergic volunteers (a pilot study)

Study initiated: November 3, 1997
Study completed: December 12, 1997
Study report dated: January 22, 2002
[Module 5, Volume 77, page 1]

10.1.6.1 Summary and reviewer's conclusion of study results

This was a single center, randomized, active and vehicle-controlled, four period, four way crossover, double blind, single dose, pilot nasal challenge study. The objective of this study was to compare the efficacy of olopatadine 0.1% and emedastine 0.05% to each other and to azelastine 0.1% and olopatadine vehicle placebo in inhibiting clinical symptoms of allergic rhinitis and nasal airflow obstruction induced by nasal allergen challenge with grass pollen. Patients were adult volunteers with a two year history of allergic rhinitis. There were 12 patients who were randomized into the study. In each study period, patients received a single dose of study treatment, one spray each nostril, three hours prior to nasal allergen challenge with grass pollen. The primary efficacy variables included patient-assessed nasal congestion scores (0 to 3 scale, none to severe), sneeze counts, tissue weights for rhinorrhea, and passive anterior rhinomanometry. Assessments were performed at 0, 5, 10, 30, and 60 minutes post-challenge. The nasal allergen challenge was performed three hours post-dose. There was no primary comparison identified in the protocol. There was no correction for multiplicity. Safety endpoints included adverse events [Module 5, Volume 77, pages 1-4, 35, 38].

The applicant concluded that [Module 5, Volume 77, pages 33-36]:

- Olopatadine 0.1% showed a statistical trend toward superiority over emedastine 0.05% in inhibiting sneezing at 30 minutes post-challenge
- Olopatadine 0.1% showed a statistical trend toward superiority over azelastine 0.1% in inhibiting nasal congestion at 30 minutes post-challenge
- Olopatadine 0.1% was superior to vehicle at five minutes post-challenge in inhibiting rhinorrhea, sneezing, and nasal congestion and at 10 minutes post-challenge in inhibiting rhinorrhea and nasal congestion
- There were no significant differences between emedastine 0.05% and azelastine 0.1% in any variable post-challenge

There were four adverse events in the study. One patient had an episode of asthma while receiving olopatadine 0.1%, one patient had fever and herpes zoster while receiving emedastine 0.05%, and one patient had rhinitis while receiving vehicle placebo. There were no serious adverse events or deaths in the study. There were no patients who withdrew from the study because of adverse events [Module 5, Volume 77, pages 43-47].

Reviewer comment:
The olopatadine product used in this pilot study was not the to-be-marketed product. Study treatment was administered to patients immediately prior to allergen challenge, a study design that will not allow assessment of the drug's effect on treatment of symptoms of SAR—the proposed indication for this application. Allergen challenges were performed with single doses of allergen extracts, which is quite different than the manner and amount of exposure that SAR patients receive during the natural pollen season. These findings have unknown clinical relevance to use of the drug, as recommended in the proposed labeling, but may provide for the applicant some general proof-of-concept for olopatadine as a nasal spray product.

This study had multiple primary efficacy variables, and was largely observational in design. There was no correction for multiplicity. It is not appropriate to draw conclusions based on an inferential analysis of the data. Results suggest that olopatadine 0.1% did have a treatment effect compared with vehicle placebo. It is difficult to draw any conclusions from the differences in effect between the active study treatments. The results of this small nasal challenge study do not provide support for the efficacy and safety of the proposed, to-be-marketed olopatadine 0.6% product.

10.1.7 C-00-10: A placebo-controlled, environmental study of olopatadine HCl nasal spray in the treatment of allergic rhinoconjunctivitis

Study initiated: May 17, 2000
Study completed: August 15, 2000
Study report dated: August 25, 2004
[Module 5, Volume 78, page 1; Module 5, Volume 82, page 1714]

10.1.7.1 Summary and reviewer's conclusion of study results

This was a multiple center, randomized, placebo-controlled, double blind, parallel group, safety and efficacy study. The objective of this study was to demonstrate the safety and efficacy of olopatadine HCl nasal spray 0.2% and 0.1% compared with vehicle placebo when given once or twice daily in the treatment of SAR for a two-week period during the grass pollen season. Patients were adults and children 12 years of age and older with a two year history of allergic rhinitis. There were 192 patients who were randomized into the study. Study treatments included the following:

- Olopatadine HCl nasal spray 0.2%, two sprays each nostril, once daily in the morning
- Olopatadine HCl nasal spray 0.2%, two sprays each nostril, twice daily
- Olopatadine HCl nasal spray 0.1%, two sprays each nostril, once daily in the morning
- Olopatadine HCl nasal spray 0.1%, two sprays each nostril, twice daily
- Olopatadine HCl nasal spray vehicle, two sprays each nostril, once daily in the morning
- Olopatadine HCl nasal spray vehicle, two sprays each nostril, twice daily

After a seven day run-in period, patients were randomized to study treatment. While on study treatment, patients assessed the severity of their SAR symptoms twice daily. Severity was assessed on a four point (0 to 3, none to severe) scale. Symptoms assessed included runny nose, itchy nose, stuffy nose, sneezing, itchy eyes, watery eyes, eye redness, postnasal drainage, headache, and itchy palate. A Major Rhinitis Symptom Complex (MRSC) was calculated based on the sum of scores for runny nose, itchy nose, stuffy nose, and sneezing. A Major Conjunctivitis Symptom Complex (MCSC) was calculated based on the sum of scores for itchy eyes, watery eyes, and eye redness. The primary efficacy variable was the percent reduction from baseline in the AM instantaneous and PM reflective MRSC. Secondary efficacy endpoints included absolute reductions from baseline in the MRSC, reduction from baseline in the AM and PM MCSC, reductions from baseline in the AM and PM individual symptom scores, and reduction from baseline in symptom scores at 20 minutes post-dose after the first administration of study treatment. Safety endpoints included adverse events, vital signs, physical examinations, laboratory studies, and ECGs [Module 5, Volume 78, pages 1-4, 42-44, 50, 55].

The applicant concluded that none of the comparisons of olopatadine versus vehicle placebo were statistically significant for percent reduction in AM instantaneous or PM reflective MRSC scores. Olopatadine 0.2% and 0.1% once daily and olopatadine 0.2% and 0.1% twice daily were numerically but not statistically superior to their respective vehicle placebos for AM and PM

MRSC scores. There were no statistically significant differences for most of the secondary efficacy endpoints [Module 5, Volume 78, pages 80, 83-92].

Taste perversion was the most common adverse event noted in the olopatadine treatment groups. The frequency of taste perversion ranged from 15.2% (5/33) in the olopatadine 0.1% twice daily group to 9.4% in the olopatadine 0.1% once daily group, compared with 0% (0/33) in the vehicle placebo group. Epistaxis was noted in 6.5% (2/31) of the olopatadine 0.2% once daily group, 6.3% (2/32) in the olopatadine 0.1% once daily group, 3.0% (1/33) in the olopatadine 0.1% twice daily group, and 3.0% (1/33) in the vehicle placebo group [Module 5, Volume 78, pages 286-289]. There were no serious adverse events or deaths in the study. Three patients discontinued the study due to adverse events. One patient in the vehicle placebo group (#2865-218) discontinued because of headache. One patient in the vehicle placebo group (#2865-217) discontinued because of dermatitis, paresthesia, asthenia, headache, and malaise. One patient treated with olopatadine, (#2865-218) 0.2% once daily discontinued because of taste perversion, somnolence, dizziness, and nausea [Module 5, Volume 78, pages 115-116]. No clinically relevant changes in vital signs, physical examination, laboratory studies, or ECGs were noted [Module 5, Volume 78, pages 120-127, 129-186].

Reviewer comment:
The olopatadine product used in the study was not the to-be-marketed product. Based on these data, the applicant concluded that there was not evidence of a dose response effect for the two olopatadine concentrations but that there was evidence that twice daily dosing was more effective than once daily dosing. The applicant concluded that higher concentrations of olopatadine should be studied.

10.1.8 C-00-33: Placebo-controlled, environmental study of (b) (4) Nasal spray versus Astelin Nasal Spray in the treatment of seasonal allergic rhinitis

Study initiated: August 31, 2000
Study completed: November 9, 2000
Study report dated: June 29, 2004
[Module 5, Volume 83, page 1; Module 5, Volume 86, page 1413]

10.1.8.1 Summary and reviewer's conclusion of study results

This was a multiple center, randomized, active and placebo-controlled, double blind, parallel group, safety and efficacy study. The objective of this study was to demonstrate the safety and efficacy of olopatadine HCl nasal spray 0.1% and azelastine HCl 0.1% compared with vehicle placebo when given once or twice daily in the treatment of SAR for a two-week period in patients with SAR. Patients were adults and children 12 years of age and older with a two year history of allergic rhinitis to a prevalent fall allergen. There were 166 patients who were randomized into the study. Study treatments included the following:

- Olopatadine HCl nasal spray 0.1%, two sprays each nostril, twice daily
- Azelastine HCl nasal spray 0.1%, two sprays each nostril, twice daily
- Olopatadine HCl nasal spray vehicle, two sprays each nostril, twice daily

After a four day vehicle placebo run-in period, patients were randomized to study treatment. While on study treatment, patients assessed the severity of their SAR symptoms twice daily. Severity was assessed on a four point (0 to 3, none to severe) scale. Symptoms assessed included runny nose, itchy nose, stuffy nose, sneezing, itchy eyes, watery eyes, eye redness, postnasal drainage, headache, and itchy palate. A Major Rhinitis Symptom Complex (MRSC) was calculated based on the sum of scores for runny nose, itchy nose, stuffy nose, and sneezing. A Major Conjunctivitis Symptom Complex (MCSC) was calculated based on the sum of scores for itchy eyes, watery eyes, and eye redness. The primary efficacy variable was the percent reduction from baseline in the AM instantaneous and PM reflective MRSC scores. Secondary efficacy endpoints included absolute reductions from baseline in the MRSC, reduction from baseline in the AM and PM MCSC scores, reductions from baseline in the MCSC scores, reductions from baseline in the AM and PM individual symptom scores, and reduction from baseline in symptom scores at 30 and 60 minutes post-dose after the first administration of study treatment. Safety endpoints included adverse events, vital signs, physical examinations, laboratory studies, and ECGs [Module 5, Volume 83, pages 1-4, 38, 39, 40, 48-49, 51].

The applicant concluded that there were no statistically significant differences in percent reduction in AM or PM MRSC scores for any of the comparisons of patients receiving olopatadine 0.1%, azelastine 0.1%, or vehicle placebo. There were no statistically significant differences for most of the secondary efficacy endpoints [Module 5, Volume 83, pages 4-6, 71-72].

Notable adverse events included taste perversion, headache, nasal discomfort, and epistaxis. These adverse events are summarized in Table 109.

Table 109 Notable adverse events, C-00-33 [Module 5, Volume 83, pages 274-275, 285]

Adverse event	Olopatadine 0.1% N = 44		Azelastine 0.1% N = 45		Vehicle placebo N = 44	
	n	(%)	n	(%)	n	(%)
All adverse events	29	(65.9)	47	(104.4)	19	(43.2)
Patients with adverse events	17	(38.6)	25	(55.6)	16	(36.4)
Taste perversion	4	(9.1)	16	(35.6)	0	(0)
Headache	5	(11.4)	2	(4.4)	3	(6.8)
Nasal discomfort	1	(2.3)	5	(11.1)	1	(2.3)
Epistaxis	3	(6.8)	2	(4.4)	0	(0)

There were no serious adverse events or deaths in the study. One patient discontinued the study due to adverse events. Patient #2589-204, in the azelastine 0.1% treatment group, discontinued the study because of headache and sinusitis [Module 5, Volume 83, pages 108-110, 274-275]. No clinically relevant changes in vital signs, physical examination, laboratory studies, or ECGs were noted [Module 5, Volume 83, pages 111-191].

Reviewer comment:
The olopatadine product used in the study was not the to-be-marketed product. Although the applicant did not demonstrate a statistically significant difference between olopatadine 0.1% and vehicle placebo and azelastine 0.1% and vehicle placebo for the primary efficacy endpoint, both olopatadine 0.1% and azelastine 0.1% were numerically superior to vehicle placebo. The comparison between olopatadine 0.1% and azelastine 0.1% numerically favored azelastine 0.1% [Module 5, Volume 83, page 75]. Taste perversion, headache, nasal discomfort, and epistaxis have been noted in other studies in this application.

10.1.9 C-00-70: Olopatadine nasal challenge study

Study initiated: February 6, 2001
Study completed: May 9, 2001
Study report dated: December 15, 2004
[Module 5, Volume 87, page 1; Module 5, Volume 89, page 1017]

10.1.9.1 Summary and reviewer's conclusion of study results

This was a single center, randomized, active and vehicle-controlled, single blind, three phase, two way crossover, single dose, nasal challenge study. Each of the three study phases included two crossover periods. The objective of this study was to identify the optimal concentration of olopatadine required to suppress the allergic response elicited by nasal allergen challenge. Patients were adult volunteers, 18-65 years of age, with a history of SAR to short ragweed or Timothy grass pollen. Patients were to be asymptomatic during the period of study enrollment. There were 20 patients who were randomized into the study. Study treatments included olopatadine nasal spray 0.1%, olopatadine nasal spray 0.2%, azelastine HCl nasal spray 0.1%, and vehicle placebo. In the first phase of the study, patients were randomized to treatment with a single dose of either olopatadine HCl nasal spray 0.1% or vehicle placebo, two sprays in each nostril. In the second phase of the study, patients were randomized to treatment with a single dose of either olopatadine HCl nasal spray 0.2% or vehicle placebo, two sprays in each nostril. In the first phase of the study, patients were randomized to treatment with a single dose of either olopatadine HCl nasal spray 0.1% or azelastine nasal spray 0.1%, two sprays in each nostril. Patients were crossed over to the alternative treatment in the second period of each phase. After receiving study medication, patients were exposed to a nasal allergen challenge with 70 microliters of a nasal spray containing ragweed pollen extract or Timothy pollen extract. The extracts for the challenge were in three concentrations: 1X (5 Protein Nitrogen Units, PNU), 10X (50 PNU), or 100X (500 PNU) for ragweed and 1X (12.5 Bioequivalent Activity Units, BAU), 10X (125 BAU), and 3X (1250 BAU) for Timothy. There was a washout period of two weeks between each study period and each study phase [Module 5, Volume 87, pages 1-6, 39-40, 51-52].

The primary efficacy variables included allergen-induced sneezes, allergen-induced changes in the levels of mast cell tryptase, albumin, and lysozyme in nasal lavage fluids. Secondary efficacy variables included allergen-induced changes in the levels of immunoreactive LTC_4 and histamine in nasal lavage fluids, and patient-assessed SAR symptom severity. The severity of SAR symptoms was measured using visual analog scales. Allergen challenge was performed 25, 50, and 75 minutes after study drug administration for 1X, 10X, and 100X concentrations of allergen, respectively. Nasal symptoms were assessed five minutes after each allergen administration. Sneeze counts were measured for ten minutes after each allergen administration. Nasal lavage was performed 10 minutes after each allergen administration. There was no primary comparison noted. Safety endpoints included adverse events [Module 5, Volume 87, pages 1-6, 39-40, 52, 62].

The applicant concluded the following [Module 5, Volume 87, pages 92-93, 99-100, 111-112, 165-166]:

- Olopatadine 0.1% and 0.2% were superior to vehicle placebo for sneezing after all three allergen doses
- Olopatadine 0.1% was non-inferior to azelastine 0.1% for sneezing after all three allergen doses
- There were no statistically significant differences between olopatadine 0.1% or 0.2% and vehicle placebo for mast cell tryptase level after any of the allergen doses
- Olopatadine 0.1% was non-inferior to azelastine 0.1% for mast cell tryptase level all three allergen doses
- There were no statistically significant differences between olopatadine 0.1% and vehicle placebo for albumin level after any of the allergen doses
- Olopatadine 0.2% was superior to vehicle placebo for albumin level after 10X and 100 X allergen doses
- Olopatadine 0.1% was non-inferior to azelastine 0.1% for albumin level all three allergen doses
- There were no statistically significant differences between olopatadine 0.1% and vehicle placebo for lysozyme level after any of the allergen doses
- Olopatadine 0.2% was superior to vehicle placebo for lysozyme level after the 100X allergen dose
- Olopatadine 0.1% was non-inferior to azelastine 0.1% for lysozyme level after all three allergen doses
- Olopatadine 0.1% was non-inferior to azelastine 0.1% for immunoreactive LTC_4 level after all three allergen doses

There were 19 adverse events in the study. Headache was the most common adverse event and occurred in three patients treated with vehicle placebo (3/20, 7.5%), one patient treated with olopatadine 0.2% (5.3%, 1/19), and one patient treated with azelastine 0.1% (5.6%, 1/18). There were no serious adverse events or deaths in the study. There was one patient treated with vehicle placebo (#3019-101) who withdrew from the study because of rhinitis and headache [Module 5, Volume 87, pages 202-203, 326-327].

Reviewer comment:
The olopatadine product used in the study was not the to-be-marketed product. This study was primarily an observational study. The study was not formally powered to identify a difference between treatments the primary efficacy variables. There was no correction for multiplicity and no primary comparison was specified. It is not appropriate to make non-inferiority conclusions; the study was not designed as a non-inferiority study and no delta was specified.

Although the effects of olopatadine in decreasing the amount of albumin and lysozyme in nasal lavage fluids after allergen challenge are interesting, these findings have unknown clinical relevance to use of the drug, as recommended in the proposed labeling.

Study treatment was administered to asymptomatic SAR patients immediately prior to allergen challenge. (b) (4)

(b) (4) *It is intended for the treatment of the symptoms of allergic rhinitis. The allergen challenges were performed with single doses of allergen extracts; quite different than the manner and amount of exposure that SAR patients receive during the natural pollen season. The clinical relevance of this information is uncertain and it is unclear how this information would guide or instruct the practitioner to use this medication more knowledgeably.*

(b) (4) *The safety data do not identify a safety signal.*

10.1.10 C-01-05: Safety and efficacy study of olopatadine nasal spray 0.1% versus olopatadine nasal spray vehicle in the prevention and treatment of symptoms of seasonal allergic rhinitis with azelastine HCl nasal spray 0.1% (Astelin®) as a reference standard

Study initiated: April 5, 2001
Study completed: August 22, 2001
Study report dated: October 14, 2004
[Module 5, Volume 90, page 1; Module 5, Volume 95, page 1884]

10.1.10.1 Summary and reviewer's conclusion of study results

This was a multiple center, randomized, active and placebo-controlled, parallel group, single blind, efficacy and safety study. The objective of this study was to demonstrate the superiority of olopatadine HCl nasal spray 0.1% relative to olopatadine HCl nasal spray vehicle placebo for the prevention and treatment of SAR and conjunctivitis symptoms for an eight-week period during the spring allergy season. Azelastine nasal spray 0.1% was included as a positive control. An additional objective was to evaluate the efficacy and safety olopatadine 0.1% with once daily dosing versus twice daily dosing. Patients were adults and children 12 years of age and older with a two year history of allergic rhinitis to a prevalent fall allergen.

There were 397 patients who were randomized into the study. Study treatments included the following:

- Olopatadine HCl nasal spray 0.1%, two sprays each nostril, once daily
- Olopatadine HCl nasal spray 0.1%, two sprays each nostril, twice daily
- Olopatadine HCl nasal spray vehicle placebo, two sprays each nostril, once daily
- Olopatadine HCl nasal spray vehicle placebo, two sprays each nostril, twice daily
- Azelastine HCl nasal spray 0.1%, two sprays each nostril, twice daily

Patients who met enrollment criteria were randomized to study treatment. While on study treatment, patients assessed the frequency of their SAR symptoms over the preceding three days at each of the ten study visits. Symptom frequency was assessed on a six point (0 to 5, none to continuously) scale. Symptoms assessed included runny nose, itchy nose, stuffy nose, sneezing, itchy eyes, watery eyes, eye redness, headache, postnasal drainage, itchy palate, and itchy ears. A Major Rhinitis Symptom Complex (MRSC) was calculated based on the sum of frequency scores for runny nose, itchy nose, stuffy nose, and sneezing. A Major Conjunctivitis Symptom Complex (MCSC) was calculated based on the sum of frequency scores for itchy eyes, watery eyes, and eye redness. The primary efficacy variable was the MRSC score. ANOVA was used to compare treatment differences in the slopes for MRSC as a function of grass pollen counts. Secondary efficacy endpoints included MCSC and individual symptoms. ANOVA was used to compare treatment differences in the slopes for MCSC and individual symptoms as a function of grass pollen counts. Safety endpoints included adverse events, vital signs, physical examinations, nasal examinations, and ECGs [Module 5, Volume 90, pages 1-6, 46-49, 53-55, 63-64, 69-70].

The applicant made the following conclusions [Module 5, Volume 90, page 92]:

- The slope of the line predicting the frequency of MRSC due to grass pollen for olopatadine 0.1% twice daily was significantly less than the slope for vehicle placebo twice daily and azelastine 0.1% twice daily in the homogeneity of slopes analysis
- The slope of the line predicting itchy nose due to grass pollen for olopatadine 0.1% twice daily was significantly less than the slope for azelastine 0.1% twice daily and the slope for vehicle placebo twice daily in the homogeneity of slopes analysis
- Olopatadine 0.1% once daily was superior to vehicle once daily for the overall mean itchy palate frequency scores
- The slope of the line predicting itchy ears due to grass pollen for olopatadine 0.1% twice daily was significantly less than the slope for vehicle placebo twice daily in the homogeneity of slopes analysis
- Less than 4% of the patients in any treatment group indicated that they had used rescue medication on any week of the study

The most common adverse events reported for olopatadine 0.1% once daily and olopatadine 0.1% twice daily were epistaxis and headache. Epistaxis was reported in 7.1% (7/99) of the olopatadine 0.1% once daily group and in 9.3% (9/97) of patients in the olopatadine 0.1% twice daily group. Epistaxis was noted in 9.8% (10/102) of patients treated with azelastine 0.1%, 12.2% (6/49) of patients treated with vehicle placebo once daily, and in 8.0% (4/50) of patients treated with vehicle placebo twice daily. Headache was reported in 5.1% (5/99) of patients treated with olopatadine 0.1% once daily and 10.3% (10/97) of patients treated with olopatadine 0.1% twice daily. Headache was noted in 10.8% (11/102) of patients treated with azelastine 0.1%, 6.1% (3/49) of patients treated with vehicle placebo once daily, and in 8.0% (4/50) of patients treated with vehicle placebo twice daily [Module 5, Volume 90, pages 138-140; Module 5, Volume 91, 407-415]

There were no serious adverse events or deaths in the study. There were 24 (6.0%, 24/397) patients who discontinued the study due to adverse events. The incidence of discontinuation due to adverse events was similar among treatment groups. No clinically relevant changes in vital signs, physical examination, laboratory studies, or ECGs were noted [Module 5, Volume 90, pages 172-179, 227-251].

Reviewer comment:
The olopatadine product used in the study was not the to-be-marketed product. The efficacy variables and analysis in this study is unorthodox. The clinical significance of a decrease in the frequency of SAR symptoms, as measured in this study, is not clear. The clinical relevance of a change in the slopes of symptom scores as a function of grass pollen count is also not clear. The applicant does not provide an estimate of a clinically significant change in this endpoint. These data do not provide support for the efficacy of the proposed product. Epistaxis and headache have been noted in other studies in this application. No new safety signal is identified in this study.

10.1.11 C-03-48: Comparison of olopatadine nasal spray 0.6%, placebo, and fluticasone propionate 0.05% in treating seasonal allergic rhinitis in an allergen exposure unit

Study initiated: November 11, 2003
Study completed: November 21, 2003
Study report dated: June 29, 2004
[Module 5, Volume 96, page 1; Module 5, Volume 98, page 942]

10.1.11.1 Summary and reviewer's conclusion of study results

This was a single center, randomized, vehicle- and active-controlled, parallel group, double blind, single dose, clinical study utilizing an allergen exposure unit (AEU). The objective of this study was to determine the superiority of olopatadine HCl nasal spray 0.6% compared to vehicle placebo when given as a single dose for the treatment of SAR over a 12-hour period and to document the onset of action of olopatadine nasal spray 0.6%. Patients were adult and children, 12 years of age and older, with at least a 2-year history of non-recalcitrant seasonal allergic rhinitis due to short ragweed pollen [Module 5, Volume 96, pages 1-6, 29-30, 35]. There were 90 patients who were randomized into the study. Study treatments included olopatadine nasal spray 0.6%, fluticasone propionate nasal spray 0.05% (Flonase®, FPNS), and vehicle placebo. The to-be-marketed formulation of olopatadine 0.6% nasal spray and the to-be-marketed delivery device were used in this study [Module 2, Volume 2, Section 2.3.P, pages 8-9, 14-16; Module 5, Volume 96, pages 41-42]. The FPNS used in the study was a marketed product [Module 5, Volume 96, page 42].

Patients had informed consent, a medical history, vital signs, nasal examination, and skin testing at the screening visit. Patients meeting screening criteria returned for up to two priming visits. The time between priming visits was not less than 24 hours and not more than 3 weeks. Patients were exposed to short ragweed pollen for three hours at the priming visits. During the exposure, patients recorded the severity of their SAR symptoms on a diary card at 30-minute intervals. Patients assessed the severity of their SAR symptoms using a four-point (0 to 3, none to severe) scale. Symptoms assessed included runny nose, stuffy nose, itchy nose, and sneezing. A Total Nasal Symptom Score (TNSS) was calculated from the sum of individual symptom scores. Patients were to have a TNSS of 6 out of 12, including a score of at least 2 for runny nose on two consecutive measurements one of the two priming visits to qualify for the treatment visit [Module 5, Volume 96, pages 30-33, 35, 45, 48, 52].

Patients meeting these criteria returned for the treatment visit, no longer than 3 weeks after the second qualifying priming visit. Patients were exposed to short ragweed pollen and then recorded the severity of their symptoms. Patients were to have a TNSS of 6 out of 12 to be randomized into the study. Randomized patients received test medication and continued to record the severity of their SAR symptoms on diary cards every 30 minutes for four hours after dosing and then every hour for the subsequent eight hours [Module 5, Volume 96, pages 31-32]. Vital signs, nasal examination were performed and adverse events were recorded [Module 5, Volume 96,

pages 31-32]. Pollen particles were dispersed in the AEU and the air distribution system employs high-aspiration ratio diffusers to endure that the allergen concentrations are maintained uniform throughout the room. The AEU was designed to produce consistent airborne pollen particle counts between 3500 pollen grains/m^3. Pollen levels were documented every 30 minutes using seven Rotorod impact samplers [Module 5, Volume 96, pages 34-35].

The primary efficacy variable was the change from baseline in TNSS. Secondary efficacy variables included changes from baseline in individual symptom scores and the Patient Global Rating Scale, a seven-point scale (0 to 6, very much better to very much worse) used to assess SAR symptoms at the end of the dosing period relative to before dosing [Module 5, Volume 96, pages 47-48]. Safety endpoints included adverse events, vital signs, and nasal examinations [Module 5, Volume 96, page 44].

The applicant concluded the following [Module 5, Volume 96, pages 59-67, 72]:

- Olopatadine nasal spray 0.6% was numerically, but not statistically, superior to vehicle placebo at each of the time points, from 30 minutes to 720 minutes post-dose
- Olopatadine nasal spray 0.6% was numerically, but not statistically, superior to FPNS at nine of the 16 time points post-dose
- Olopatadine nasal spray 0.6% was numerically superior to vehicle placebo at the majority of time points for change from baseline in individual symptoms
- A larger percentage of patients treated with olopatadine 0.6% reported on the Patient Global Rating Scale that their symptoms were very much better, moderately better, or a little better when compared to FPNS and to vehicle placebo

There were eight adverse events in the study. Epistaxis was the most frequent adverse event in the study and occurred in 2 patients receiving olopatadine 0.6% (6.7%, 2/30), one patient receiving vehicle placebo (3.3%, 1/30), and no patients receiving FPNS (0%, 0/30). There were no deaths or serious adverse events in the study. One patient receiving vehicle placebo, #3077-8077, withdrew from the study because of nausea and vomiting. Small decreases in mean change from baseline in systolic and diastolic blood pressures were noted in the olopatadine 0.6% group, but the magnitude of the decreases were small; 3 to 4 mm Hg. No clinically relevant changes in vital signs were noted in the study. On nasal examination, two patients treated with olopatadine 0.6% were noted to have bleeding (6.7%, 2/30). One patient treated with vehicle placebo was noted to have bleeding (3.3%, 3/30). No patients treated with FPNS were noted to have bleeding on nasal examination [Module 5, Volume 96, pages 90, 102-112, 200].

Reviewer comment:
This study does not support the efficacy of olopatadine 0.6%. The applicant did not demonstrate a statistically significant difference from vehicle placebo for olopatadine 0.6%. As with C-03-52, the mechanisms of action of an antihistamine, such as olopatadine, and an intranasal corticosteroid are quite different. (b) (4)

As in this study, epistaxis was noted in patients treated with olopatadine 0.6% and vehicle placebo in other single dose studies in this application—C-03-52 and C-01-83. The product appears to be irritating to the nasal mucosa.

10.1.12 C-00-23: A double masked, randomized, placebo controlled, multiple dose, two-way crossover, safety and pharmacokinetic study of oral solution doses of olopatadine versus placebo in healthy volunteers

Study initiated: June 23, 2000
Study completed: September 5, 2000
Study report dated: February 25, 2001
[Module 5, Volume 25, pages 1-2]

10.1.12.1 Summary and reviewer's conclusion of study results

This was a double blind, randomized, multiple dose, single center, two period, two-way crossover, pharmacokinetics and cardiac safety study. The primary objective was to assess the effect on the QTc interval of 5 mg of olopatadine oral solution twice daily for 2 ½ days compared to placebo oral solution in healthy, male and female volunteers from 18 to 75 years of age. Secondary objectives were to assess the pharmacokinetics of olopatadine and the relationship, if any, between QTc interval and plasma olopatadine concentrations. The study was conducted at (b) (4) There was a washout period of 5 days between study periods. The study enrolled 117 subjects. There were 102 subjects in the pharmacokinetics and pharmacodynamics analysis and 117 subjects in the safety analysis [Module 5, Volume 25, pages 3-4, 21-22].

Serial 12-lead ECGs were obtained at baseline, and at 15 and 30 minutes, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after the first dose and after the last does in each of the two study periods. Holter monitoring was performed at steady state for both study periods. Plasma samples for determination of olopatadine serum levels were obtained prior to each morning and evening dose, one and 12 hours after the first dose, and at the same times that ECGs were performed. Safety endpoints included adverse events, vital signs, physical examinations, clinical laboratory studies and ECGs [Module 5, Volume 25, pages 4-5].

The study enrolled 117 subjects. There were 102 subjects in the pharmacokinetics and pharmacodynamics analysis and 117 subjects in the safety analysis [Module 5, Volume 25, pages 4, 38]. The majority of the subjects this study were of Caucasian race (65.7%, 67/102). Patients of Hispanic race represented 22.5% (23/102) of the evaluable population, followed by patients of Other race (6.9%, 7/102), patients of Black race (2.9%, 3/102), and patients of Asian race (2.0%, 2/102). The majority of subjects were females (52.0%, 53/102). The mean age for subjects in this study was 40 years (range 18-75 years) [Module 5, Volume 25, page 42].

PK results are presented in Table 110. AUC and C_{max} values were slightly higher for women than for men. AUC and C_{max} values were slightly higher for in patients 46-75 years of age than for patients 18-45 years of age.

Table 110 Pharmacokinetic parameters, C-00-23 [Module 5, Volume 25, pages 48, 51]

Parameter	Ages 18-45 years N = 64	Ages 46-75 years N = 38	Men N = 49	Women N = 53
AUC_{0-12}, ng.h./mL	228.8	265.3	239.7	253.3
C_{max}, ng/mL	71.1	79.3	71.4	79.0
T_{max}, Hours	1.0	0.5	0.5	1.0

Single dose and steady-state QTc interval change from baseline is presented in Table 111. Median and mean QTcB and QTcF values for olopatadine were less than that for placebo [Module 5, Volume 25, page 53].

Table 111 Single dose and steady-state QTc interval change from baseline, C-00-23 [Module 5, Volume 25, page 53]

Parameter, single dose	Olopatadine	Placebo
QTcB change, msec		
Mean (SD)	-1.5 (9.24)	0.1 (9.29)
Median	-1.3	-0.6
Minimum, maximum	-46.4, 19.5	-27.3, 32.6
N	102	102
QTcF change, msec		
Mean (SD)	-1.3 (8.71)	-0.2 (9.24)
Median	-1.8	-1.1
Minimum, maximum	-32.2, 22.1	-32.5, 26.8
N	102	102
Parameter, steady-state	**Olopatadine**	**Placebo**
QTcB change, msec		
Mean (SD)	-3.8 (9.94)	-1.1 (9.37)
Median	-3.1	-0.7
Minimum, maximum	-42.3, 19.5	-31.2, 29.9
N	102	102
QTcF change, msec		
Mean (SD)	-5.3 (9.13)	-3.4 (8.85)
Median	-4.5	-3.5
Minimum, maximum	-32.1, 19.3	-36.7, 25.0
N	102	102

Maximum positive single dose and steady-state QTc interval change from baseline (Emax) values are presented in

Table 112. Emax values for olopatadine were less than or the same as those for placebo [Module 5, Volume 25, page 54].

Table 112 Maximum positive single dose and steady-state QTc interval change from baseline (Emax), C-00-23 [Module 5, Volume 25, page 54]

Parameter, single dose	Olopatadine	Placebo
QTcB Emax, msec		
Mean (SD)	23.5 (13.24)	25.8 (15.92)
Median	22.5	24.0
Minimum, maximum	-7, 62	-4, 78
N	102	102
QTcF Emax, msec		
Mean (SD)	18.4 (12.02)	19.7 (12.41)
Median	18.0	18.0
Minimum, maximum	-13, 50	-13, 53
N	102	102
Parameter, steady-state	**Olopatadine**	**Placebo**
QTcB Emax, msec		
Mean (SD)	20.1 (12.85)	24.6 (13.12)
Median	19.5	24.0
Minimum, maximum	-10, 55	-9, 62
N	102	102
QTcF Emax, msec		
Mean (SD)	12.6 (11.37)	16.3 (11.3)
Median	12.5	15.5
Minimum, maximum	-16, 37	-14, 43
N	102	102

The incidence of single dose and steady-state Emax values are displayed in Table 113. The incidences of patients with QTcB Emax values <30 msec or ≥30 to ≤60 msec in the olopatadine group were comparable to those in the placebo group. The incidence of patient with QTcB values >60 seconds was lower in the olopatadine group than in the placebo group. The incidences of patients with QTcF Emax values <30 msec or ≥30 to ≤60 msec was higher in the olopatadine group than in the placebo group. The incidence of patients with QTcB values >60 seconds was comparable in both treatment groups.

Table 113 Incidence of single dose and steady-state Emax values, C-00-23 [Module 5, Volume 25, page 55]

Parameter, single dose	Olopatadine N= 102		Placebo N= 102	
	n	(%)	n	(%)
QTcB Emax				
<30 msec	74	(72.5)	71	(69.6)
≥30 to ≤60 msec	27	(26.5)	26	(25.5)
>60 msec	1	(1.0)	5	(4.9)
Parameter, steady-state	**Olopatadine N= 102**		**Placebo N= 102**	
	n	**(%)**	**n**	**(%)**
QTcF Emax				
<30 msec	78	(76.5)	68	(66.7)
≥30 to ≤60 msec	24	(23.5)	33	(32.4)
>60 msec	0	(0)	1	(1.0)

The applicant concluded that olopatadine 5 mg twice daily did not prolong the QTc interval relative to placebo [Module 5, Volume 25, page 74].

Adverse events at a frequency of greater than 2.0% are displayed in Table 114. There were adverse events experienced by 31 subjects in this study. There were more adverse events in the olopatadine group (28.1%, 32/114) than in the placebo group (12.3%, 13/106). There were more subjects with adverse events in the olopatadine group (18.4%, 21/114) than in the placebo group (9.4%, 10/106). Somnolence, dizziness, and headache occurred more frequently in the olopatadine treatment group than in the placebo group. There were no serious adverse events or deaths in the study. There were seven subjects that discontinued the study because of adverse events, with five discontinuations in the olopatadine group and two discontinuations in the placebo group. There were two patients with short non-sustained episodes of ventricular tachycardia lasting a few seconds in the olopatadine group. One of the patients had a ventricular triplet prior to receiving treatment with olopatadine, suggesting a pre-existing condition. One patient in the placebo group experienced a short, non-sustained episode of ventricular tachycardia. These episodes were detected during Holter monitoring [Module 5, Volume 25, pages 65, 68, 69, 72].

Table 114 Adverse events occurring at a frequency of greater than 2.0%, C-00-23 [Module 5, Volume 25, page 65]

Adverse event	Olopatadine N= 114		Placebo N= 106	
	n	(%)	n	(%)
All adverse events	32	(28.1)	13	(12.3)
Subjects with adverse events	21	(18.4)	10	(9.4)
Somnolence	5	(4.4)	2	(1.9)
Dizziness	3	(2.6)	1	(0.9)
Headache	3	(2.6)	2	(1.9)

Laboratory studies, vital signs, and ECGs showed no clinically relevant differences between treatment groups [Module 5, Volume 25, pages 70-73].

Reviewer comments:
These data suggest that there is no QTc prolongation with olopatadine 5 mg twice daily by mouth, approximately twice the dose administered by the labeled dose for the proposed nasal spray product. Adverse event data suggest that this dose of olopatadine is associated with somnolence and dizziness. It is likely that the short non-sustained episodes of ventricular tachycardia would not have been detected if Holter monitoring were not performed. These events do not represent a safety signal. Other safety endpoints also do not suggest a safety signal.

This study was not reviewed by the Clinical Pharmacology and Biopharmaceutics reviewer, Dr. Sandra Suarez, because higher exposures were achieved in Study 02-54.

10.1.13 C-02-54: A double masked, multiple dose, two-period, two-way crossover study of the cardiovascular safety and pharmacokinetics of olopatadine 20 mg oral solution versus placebo administered twice daily (BID) for fourteen days in healthy subjects

Study initiated: May 22, 2003
Study completed: July 22, 2003
Study report dated: January 14, 2004
[Module 5, Volume 20, page 1; Module 5, Volume 24, page 1764]

10.1.13.1 Summary and reviewer's conclusion of study results

This was a double blind, randomized, multiple dose, single center, two period, two-way crossover, cardiac safety and pharmacokinetics study. The primary objective was to assess the cardiovascular effects of 20 mg of olopatadine oral solution twice daily for 14 days compared to placebo oral solution in healthy, male and female volunteers from 18 to 75 years of age. Secondary objectives were to assess the steady state plasma pharmacokinetics of olopatadine and its major metabolites and to evaluate the relationship, if any, between QTc interval and plasma olopatadine concentration. The study was conducted at (b) (4) There was a washout period of 6 days between study periods. The study enrolled 34 subjects. There were 32 subjects in the pharmacokinetics and pharmacodynamics analysis and 34 subjects in the safety analysis. The 20 mg dose was chosen to achieve levels eight to 10-fold greater than levels achieved with the proposed dose of the nasal spray in patients with SAR [Module 5, Volume 20, pages 1, 3, 45-46, 61, 68-69].

Serial 12-lead ECGs were obtained at baseline, and at 15, 30, and 45 minutes, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, and 12 hours after dosing on Day of 12 each study period. Plasma samples for determination of olopatadine serum levels were obtained prior to the morning dose on Days 2, 4, 6, 8, and 10 of each study period and at 15 and 30 minutes, 1, 1.5, 2, 4, 8, and 12 hours after dosing on Day of 12 each study period. Safety endpoints included adverse events, vital signs, physical examinations, clinical laboratory studies and ECGs [Module 5, Volume 20, pages 50-51, 54-56, 64].

The study enrolled 34 subjects. There were 32 subjects in the pharmacokinetics and pharmacodynamics analysis and 34 subjects in the safety analysis [Module 5, Volume 20, pages 3, 68]. The majority of the subjects this study were of Hispanic race (50.0%, 16/32). Patients of Caucasian race represented 46.9% (15/62) of the evaluable population. There was one patient of Black race (3.1%, 1/32). There was an equal number of male (50.0%, 16/32) and female (50.0%, 16/32) subjects. The mean age for subjects in this study was 41.2 years (range 22-65 years) [Module 5, Volume 20, page 70].

PK results are presented in Table 115. Plasma concentrations of N-desmethyl olopatadine (metabolite M1) and olopatadine N-oxide (metabolite M3) were substantially lower than those for olopatadine. Levels of N-didesmethyl olopatadine (metabolite M2) were below the limit of

quantitation. Plasma concentrations for metabolite M3 were approximately three-fold higher than those for metabolite M1 [Module 5, Volume 20, pages 77-79].

Table 115 Pharmacokinetic parameters for olopatadine, C-02-54 [Module 5, Volume 20, pages 77-79]

N = 32	C_{max}, ng/mL (SD)	T_{max}, h (SD)	AUC_{0-12}, ng.h/mL (SD)	$AUC0_{-24}$, ng.h/mL (SD)	AUC_{0-inf}, ng.h/mL (SD)	$t_{½}$, h (SD)
Olopatadine	302* (53)	0.84* (0.40)	987* (146)	1082 (176)	1155 (200)	11.2 (3.7)
M1	2.39 (0.64)	1.66 (0.55)	13.5 (4.3)	15.8 (5.2)	17.6 (6.1)	9.1 (3.4)
M2	BLQ**	BLQ	BLQ	BLQ	BLQ	BLQ
M3	8.22 (1.83)	1.17 (0.29)	29.7 (8.2)	32.4 (17.6)	34.1 (9.2)	7.9 (2.4)

*Day 12 values; other values are fore Day 14
**Below the limit of quantitation

QTc interval change from baseline is presented in Table 116. In addition to analyzing QTcF, QTcB, and uncorrected QTc values, the applicant also analyzed QTc data with a correction formula that renders a slope of zero when plotted versus RR by subject (QTcI). Median and mean QTcF, QTc, and QTcI values for olopatadine were less than that for placebo. QTcB values were similar to those for the other analyses [Module 5, Volume 20, pages 86, 91-93].

Table 116 QTc interval change from baseline, C-02-54 [Module 5, Volume 20, pages 91-93]

Parameter	Olopatadine	Placebo
QTcF change, msec		
Mean (SD)	-2.6 (8.6)	-3.9 (8.8)
Median	-1.9	-4.3
Minimum, maximum	-22.0, 16.8	-19.7, 11.4
N	32	32
QTc change, msec		
Mean (SD)	-13.6 (14.8)	-11.6 (12.2)
Median	-10.8	-12.8
Minimum, maximum	-47.9, 10.1	-38.7, 14.3
N	32	32
QTcI change, msec		
Mean (SD)	-3.0	-5.4 (8.2)
Median	-1.8	-5.6
Minimum, maximum	-26.0, 16.1	-21.7, 8.7
N	32	32

Maximum positive QTc interval change from baseline (Emax) values are presented in Table 118. QTcF and QTcI Emax values for olopatadine were comparable with those for placebo. QTcB Emax values were similar to those for the other analyses [Module 5, Volume 20, pages 93-94].

Table 117 Maximum positive QTc interval change from baseline (Emax), C-00-23 [Module 5, Volume 25, pages 93-94]

Parameter	Olopatadine	Placebo
QTcF Emax, msec		
Mean (SD)	22.5 (14.5)	20.4 (14.3)
Median	16.9	17.8
Minimum, maximum	5.3, 63.1	3.1, 752.1
N	32	32
QTcI Emax, msec		
Mean (SD)	18.6 (14.1)	16.1 (12.41)
Median	15.2	15.5
Minimum, maximum	-11.9, 57.7	-6.6, 39.4
N	32	32

The incidence of change from baseline in Emax values are displayed in Table 118. The incidences of patients with changes in QTcF Emax and QTc I Emax values <30 msec, ≥30 to ≤60 msec, and >60 msec were comparable in the olopatadine and placebo groups. Results for incidence of change from baseline in QTcB Emax were similar QTcF Emax and QTcI Emax [Module 5, Volume 20, pages 95-96].

Table 118 Incidence of change from baseline in Emax values, C-02-54 [Module 5, Volume 20, pages 95-96]

Parameter, steady-state	Olopatadine N= 32		Placebo N= 102	
	n	(%)	n	(%)
QTcF Emax				
<30 msec	23	(72)	24	(75)
≥30 to ≤60 msec	8	(25)	8	(25)
>60 msec	0	(0)	0	(0)
Parameter, single dose	**Olopatadine N= 32**		**Placebo N= 32**	
	n	**(%)**	**n**	**(%)**
QTcI Emax				
<30 msec	26	(81)	29	(91)
≥30 to ≤60 msec	6	(19)	3	(9)
>60 msec	0	(0)	0	(0)

Morphologic assessment of ECG data did not reveal a safety signal [Module 5, Volume 20, page 105]. The applicant concluded that olopatadine 20 mg twice daily did not prolong the QTc interval relative to placebo [Module 5, Volume 20, page 196].

Adverse events occurring in two or more patients in any treatment group are displayed in Table 119. There were more adverse events in the olopatadine group (90.6% 29/32) than in the placebo group (68.8%, 22/34). There were more subjects with adverse events in the olopatadine group (56.2%, 18/32) than in the placebo group (43.8%, 14/34). Somnolence, fatigue, and pain were notable adverse events that occurred more frequently in the olopatadine treatment group than in the placebo group. There were no serious adverse events, deaths, or withdrawals due to adverse events in the study [Module 5, Volume 20, pages 118, 223-225].

Table 119 Adverse events occurring in two or more patients in any treatment group, C-02-54 [Module 5, Volume 20, pages 223-225, 237]

Adverse event	Olopatadine N= 32		Placebo N= 34	
	n	(%)	n	(%)
All adverse events	29	(90.6)	22	(68.8)
Subjects with adverse events	18	(56.2)	14	(43.8)
Constipation	4	(12.5)	5	(14.7)
Fatigue	4	(12.5)	1	(2.9)
Somnolence	4	(12.5)	0	(0)
Pain	3	(9.4)	0	(0)
Headache	2	(6.3)	2	(6.3)
Nausea	2	(6.3)	2	(5.9)
Back pain	1	(3.1)	2	(5.9)
Insomnia	0	(0)	2	(5.9)

Laboratory studies, vital signs, and physical examinations showed no clinically relevant differences between treatment groups [Module 5, Volume 20, pages 120-127, 127-136].

Reviewer comments:
These data suggest that there is no QTc prolongation with olopatadine 20 mg twice daily by mouth for 14 days. Somnolence and fatigue appear to be associated with this dose of olopatadine, approximately eight times the dose delivered by the proposed nasal spray product. Safety endpoints do not suggest a safety signal.

More details may be found in Dr. Sandra Suarez's Clinical Pharmacology and Biopharmaceutics Review [S. Suarez, Ph.D., Clinical Pharmacology and Biopharmaceutics Review NDA 21-861, N-000, 12/24/04].

10.1.14 C-02-46: An open label, single dose pharmacokinetic study of olopatadine 0.6% nasal spray in healthy subjects and subjects with renal impairment

Study initiated: April 14, 2003
Study completed: July 27, 2003
Study report dated: January 13, 2004
[Module 5, Volume 16, page 1; Module 5, Volume 19, page 1311]

10.1.14.1 Summary and reviewer's conclusion of study results

This was an open label, single dose, pharmacokinetics study. The primary objective was to characterize the plasma pharmacokinetic and urinary excretion of olopatadine following a single dose of olopatadine 0.6% nasal spray in subjects with varying degrees of renal impairment compared to subjects with normal renal function. The study was conducted at (b) (4) The study enrolled 25 subjects. There were 24 subjects in the pharmacokinetics and pharmacodynamics analysis and 25 subjects in the safety analysis. Patients received a single dose of two sprays in each nostril of olopatadine nasal spray 0.6% [Module 5, Volume 16, pages 1, 3, 53, 60, 70, 76].

Subjects had blood samples drawn for analysis of olopatadine and olopatadine metabolites pre-dose and 5, 15, 30, 45, 60, 90 minutes and 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours post-dose. Urine was collected at intervals of 0-2, 2-4, 4-8, 18-12, and 12-24 hours post-dose [Module 5, Volume 16, pages 61-64]. Pharmacokinetic variables included C_{max}, AUC, T_{max}, and $t_{½}$ for olopatadine and key metabolites in plasma, urinary recovery, and renal clearance. Safety endpoints included adverse events, vital signs, physical examinations, nasal examination, clinical laboratory studies, and ECGs [Module 5, Volume 16, page 72].

The study enrolled 25 subjects. There were 24 subjects in the pharmacokinetics and pharmacodynamics analysis and 25 subjects in the safety analysis [Module 5, Volume 16, pages 76-77]. The majority of the subjects this study were of Caucasian race (68.0%, 17/25). Patients of Black race represented 28.0% (7/25) of the evaluable population. There was one patient of Asian race (4.0%, 1/25). There majority of subjects were male (60.0%, 15/25). Females represented 40.0% (10/25) of the population. Of the 25 patients in the study, 56.0% (14/25) were less than 65 years of age and 44.0% (11/25) were 65 years of age or greater. Of the 25 patients in this study, 24.0% (6/25) had normal renal function, 28.0% (7/25) had mild renal impairment, 24.0% (6/25) had moderate renal impairment, and 24.0% (6/25) had severe renal impairment [Module 5, Volume 16, page 70].

Peak plasma concentrations of olopatadine in healthy subjects averaged 18.1 ng/mL. No significant differences were seen in C_{max} values among the four study groups. Mean $AUC_{0\text{-}inf}$ values were similar in healthy subjects and patients with mild or moderate renal impairment. The mean $AUC_{0\text{-}inf}$ value in subjects with severe renal impairment was 2.5-fold higher than that of

healthy subjects. Mean $t_{½}$ values were significantly prolonged in severely impaired subjects (15.5 hours) compared to healthy subjects (11.5 hours) [Module 5, Volume 16, pages 6-7].

Mean plasma concentrations of the N-desmethyl metabolite of olopatadine (metabolite M1) in subjects with normal renal function were not greatly different than those in subjects with mild or moderate renal impairment. Mean plasma concentrations of M1 were markedly higher in patients with severe renal impairment. C_{max}. AUC values for M1 in patients with increasing renal impairment were 2.6-fold and 5.4-fold higher than those in healthy subjects. The mean $t_{½}$ for M1 was 4.0 to 4.2 hours in healthy subjects and subjects with mild impairment, and was increased up to 14.9 hours in severely impaired subjects [Module 5, Volume 16, pages 8-9].

The N-didesmethyl metabolite of olopatadine (metabolite M2) was quantifiable only in one patient with severe renal impairment at one time point [Module 5, Volume 16, page 10].

Maximal plasma concentrations of the olopatadine N-oxide metabolite (metabolite M3) were seen within 45 minutes to 4 hours post-dose in healthy subjects and subjects with mild or moderate renal impairment. Peak concentrations were observed from 4 to 12 hours in patients with severe renal impairment. With increasing renal impairment, C_{max} values were up to 3.6-fold higher in patients with severe renal impairment than in healthy patients. AUC values in severely impaired patients were approximately 6- to 13-fold higher than in healthy patients. M3 $t_{½}$ values averaged 2.5 hours in healthy subjects and 15.7 hours in patients with severe renal impairment [Module 5, Volume 16, pages 10-11].

Predicted steady-state levels of olopatadine in patients with severe renal impairment were predicted to be up to 2-fold higher than those in healthy subjects. For M1 and M3, the predicted levels in patients with severe renal impairment were up to 5.7- and 7-fold higher than in healthy subjects, respectively. The higher systemic exposure to olopatadine and its metabolites in patients with severe renal impairment were still 8-fold lower than those observed in subjects administered a 20 mg twice daily oral dose. The applicant considers the higher systemic exposures to olopatadine and its metabolites to be not clinically meaningful [Module 5, Volume 16, page 12].

There was one adverse event in this study. One subject with moderate renal impairment who was treated with olopatadine 0.6% reported urinary frequency that was mild in intensity and resolved without treatment [Module 5, Volume 16, page 122; Module 5, Volume 17, pages 359-360; Module 5, Volume 100, page 4]. . There were no deaths or serious adverse events in the study and no subjects withdrew from the study [Module 5, Volume 16, pages 12, 125].

Laboratory studies, vital signs, physical examinations, nasal examinations, and ECGs showed no clinically relevant differences between treatment groups [Module 5, Volume 16, pages 127-185; Module 5, Volume 17, pages 397-408].

Reviewer comment:
Mean olopatadine C_{max} values in subjects with mild, moderate, and severe renal impairment were comparable to those in healthy subjects. AUC values were comparable in healthy subjects

and subjects with mild and moderate renal impairment. AUC values were approximately 2.5-fold higher in subjects with severe renal impairment than in healthy subjects. Predicted peak concentrations of olopatadine at steady state for patients with renal impairment are from 8-fold lower than those observed in healthy subjects administered 20 mg olopatadine orally twice daily. Systemic exposure to metabolites M1, M2, and M3 were low and not clinically meaningful. No safety signal was identified in this study. This reviewer concurs with the applicant that no adjustment of dose is warranted in SAR patients with renal impairment.

More details may be found in Dr. Sandra Suarez's Clinical Pharmacology and Biopharmaceutics Review [S. Suarez, Ph.D., Clinical Pharmacology and Biopharmaceutics Review NDA 21-861, N-000, 12/24/04].

10.2 Line-by-Line Labeling Review

Labeling review is not necessary at this time because the product is not recommended for approval.

11 REFERENCES

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Reviewed by:

_____
Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

_____
Lydia Gilbert-McClain, M.D.
Medical Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original NDA
IND 60,116
HFD-570/Division File
HFD-570/Gilbert-McClain/Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-870/Suarez/Clinical Pharmacology and Biopharmaceutics Reviewer
HFD-715/Guo/Biometrics Reviewer
HFD-570/Bertha/CMC Reviewer
HFD-570/Bond/Pharmacology Reviewer
HFD-570/Zeccola/CSO
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/s/

Charles Lee
8/24/2005 04:07:52 PM
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Lydia McClain
8/24/2005 04:26:35 PM
MEDICAL OFFICER
I concur

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	IND 60,116	**TRADE NAME:**	Patanase
APPLICANT/SPONSOR:	Alcon Research, Ltd.	**USAN NAME:**	Olopatadine HCl
MEDICAL OFFICER:	Charles E. Lee, M.D.		
TEAM LEADER:	Lydia Gilbert-McClain, M.D.	**CATEGORY:**	Antihistamine
DATE:	8/18/05	**ROUTE:**	Intranasal spray

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
3/11/05	3/14/05	IND 60,116, N-063, IM, PN	Phase 3 protocol, ages 6-11 years, protocol outline, ages 2-5 years

RELATED APPLICATIONS

Document Date	Application Type	Comments
3//11/05	IND 60,116, N-063, IM, PN	Phase 3 protocol, ages 6-11 years
12/24/04	NDA 21-861, N-000	NDA, olopatadine nasal spray
12/20/04	IND 60,116 N-060, PA	PPSR
9/13/04	IND 60,116 N-058, PN	PK and safety protocol, pediatrics
4/12/04	IND 60,116, N-050, PN	PK and safety protocol, pediatrics
7/2/03	IND 60,116, N-039, MR	Pre-NDA meeting package
9/5/01	IND 60,116, N-019, MR	EOP2 meeting package

REVIEW SUMMARY: The sponsor is developing olopatadine HCl 0.6% for use as an intranasal spray for treatment of the symptoms of seasonal allergic rhinitis (SAR) (b) (4) The sponsor has completed studies in patients 12 years of age and older, and recently submitted an NDA seeking approval for SAR (b) (4) indications in adults and children 12 years of age and older. The NDA is currently under review. The sponsor is interested in developing the product for use in children. This submission, which was reviewed on April 19, 2005, included a summary of the sponsor's pediatric development plan, a synopsis for C-03-51, a final protocol and statistical analysis plan for an efficacy and safety study in SAR patients six to 11 years of age (b) (4) , and a protocol outline for a PK and safety study in SAR patients from two to 5 years of age (b) (4) However, the Division was aware that one of the excipients (povidone) in the formulation had caused nasal pathology in longer-term preclinical studies and that there was no NOAEL for this toxicity. (b) (4) is now ongoing [NDA 21-861, N-000 SU, 7/7/05, 1. Clinical Safety, pages 4-5, 16]. (b) (4) Since the original review of this submission, study C-03-51 has been completed, and safety data was submitted to NDA 21-861 in the 120-day safety update. During the NDA review, nasal ulceration was noted in 3.7% (10/271) of patients in study C-03-51 [NDA 21-861, N-000, SU, 7/7/05, 1. Clinical Safety, pages 9-10]. In comparison, nasal ulcerations were noted in only 0.1% (2/1755) of patients 12 years of age and older in the 2-week pivotal efficacy and safety studies (C-02-37 and C-02-10) in adults and children 12 years of age and older. In addition, nasal perforation was reported in 3/924 patients in the one-year long-term safety in adults, C-01-92 [NDA 21-861, N-000, 12/24/04, Module 5, Volume 65, pages 203-204]. Patients less than 12 years of age appear to be more sensitive to nasal ulceration than older patients and it is unclear if the nasal ulcerations reported in patients less than 12 years of age healed without sequelae. (b) (4) In addition, patients under 12 years of age are unable to give informed consent and are not capable of understanding the nature of this medical risk in order to make an informed choice about study participation. Study (b) (4) will be put on clinical hold. Comments are provided for the sponsor.

OUTSTANDING ISSUES: Clinical hold, toxicity to nasal mucosa

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES:	**SAFE TO PROCEED**	**CLINICAL HOLD—X**
OTHER ACTION:	**COMMENTS FOR THE SPONSOR—X**	

1. COMMENTS FOR THE SPONSOR

The following comments should be communicated to the sponsor:

Human subjects ages 5 to 11 years of age in study (b) (4) *will be exposed to an unreasonable and significant risk of illness and injury. In your study C-03-51, conducted in subjects 5 to 11 years of age, the reported incidence of nasal ulceration was 3.7% , as compared to the reported incidence of nasal ulceration of approximately 0.1% in subjects 12 years of age and older. This information suggests that the formulation is poorly tolerated by subjects 11 years of age and younger, compared to older subjects. Furthermore, your already completed adult and adolescent human studies and pre-clinical studies suggest that the inactive ingredient povidone is irritating to the nasal mucosa.*

Information needed to resolve clinical hold deficiency:

1. *Reformulate your drug product in order to reduce the risk of nasal pathology in humans.*

2. *Provide support for the safety of the product in subjects 12 years of age and older before conducting studies in subjects less than 12 years of age.*

Reviewed by:

_____
Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

_____
Lydia Gilbert-McClain, M.D.
Medical Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original IND
HFD-570/Division File
HFD-570/Gilbert-McClain/Medical Team Leader
HFD-570/Chowdhury/Division Director
HFD-570/Lee/Medical Reviewer
HFD-570/Bond/Pharmacology/Toxicology Reviewer
HFD-570/Sun/ Pharmacology/Toxicology Team Leader
HFD-570/Zeccola/CSO

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/s/

Charles Lee
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MEDICAL OFFICER

Lydia McClain
8/18/2005 05:18:36 PM
MEDICAL OFFICER
I concur

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 21-861	**TRADE NAME:**	Patanase® Nasal Spray
APPLICANT/SPONSOR:	Alcon, Inc.	**USAN NAME:**	Olopatadine HCl
MEDICAL OFFICER:	Charles E. Lee, M.D.		
TEAM LEADER:	Lydia Gilbert-McClain, M.D.	**CATEGORY:**	H_1-antihistamine
DATE:	2/8/05	**ROUTE:**	Intranasal, solution

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
12/24/04	12/27/04	NDA 21-861, N-000	Paper CTC submission, 224 clinical volumes

RELATED APPLICATIONS

Document Date	Application Type	Comments
1/26/96	NDA 20-688, N-000	NDA, Patanol Ophthalmic Solution, 0.1%
12/24/04	NDA 21-545, N-000	NDA, Patanol ES Ophthalmic Solution, 0.2%
3/31/00	IND 60,116, N-000	Opening IND
9/5/01	IND 60,116, N-019	End-of-phase 2 meeting package
7/2/03	IND 60,116, N-039 MR	Pre-NDA meeting package

REVIEW SUMMARY:

This NDA is an application for a nasal spray solution formulation of olopatadine HCl. The drug is a selective H_1-histamine receptor antagonist and a structural analog of doxepin. The applicant is Alcon, Inc. The applicant seeks to develop this drug for use as an intranasal spray for treatment of symptoms of seasonal allergic rhinitis (SAR) (b) (4). The product is a nonsterile, multiple dose, nasal spray solution containing 600 mcg/spray (0.6%) of olopatadine base or 665 mcg/spray (0.665%) of olopatadine HCl. The proposed indication is the (b) (4) treatment of the symptoms of SAR (b) (4) in adults and children 12 years of age and older. The proposed dose is two sprays per nostril twice daily. The application is a paper Common Technical Document (CTD) submission. The applicant's drug development program included pivotal clinical efficacy and safety studies, supportive clinical efficacy and safety studies, and pharmacokinetic (PK) and pharmacodynamic (PD) studies. There were five clinical efficacy and safety studies considered by the applicant to be pivotal in their drug development program. There were six supportive clinical efficacy and safety studies in the applicant's drug development program. There were seven PK and PD studies in the applicant's drug development program. The study reports are appropriately indexed and organized to allow review. The applicant has provided an Integrated Summary of Efficacy, Integrated Summary of Safety, copies of proposed labeling, and appropriate case report forms and case report tabulations. The applicant did not provide postmarketing safety data for olopatadine tablets, which are approved in Japan. The applicant should provide a review and summary of these data. The applicant did not provide a review of the medical literature for safety information relevant to use of olopatadine. The applicant should provide a review of the medical literature and submit copies of the articles cited in their literature review. A brief review of the proposed labeling reveals that patient reported outcomes, health economics, onset of action, and comparative efficacy claims may not be supported. (b) (4) The submission is adequate to allow clinical review. The submission is fileable.

OUTSTANDING ISSUES: Postmarketing data for oral olopatadine and review of the medical literature will be requested.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	X	**FILEABLE**	____	**NOT FILEABLE**
	____	**APPROVAL**	____	**APPROVABLE**
				NOT APPROVABLE
OTHER ACTION:	**X—COMMENTS FOR SPONSOR**			

1. GENERAL INFORMATION AND BACKGROUND

Olopatadine HCl ophthalmic solution, 0.1%, Patanol®, was approved for the treatment of the signs and symptoms of allergic conjunctivitis on December 18, 1996. The applicant seeks to develop this drug for use as an intranasal spray for treatment of symptoms of seasonal allergic rhinitis (SAR) (b) (4) The applicant is Alcon, Inc.

The product is a selective H_1-histamine receptor antagonist and a structural analog of doxepin [Module 2, Volume 2, Section 2.3P, page 1]. The applicant also claims that the product inhibits the release of histamine and other pro-inflammatory mediators from human mast cells [Module 2, Volume 2, Section 2.5., page 4].

The product is a nonsterile, multiple dose, nasal spray solution containing 600 mcg/spray (0.6%) of olopatadine base or 665 mcg/spray (0.665%) of olopatadine HCl. It contains the following excipients: benzalkonium chloride, edentate disodium, (b) (4) sodium chloride, dibasic sodium phosphate, sodium hydroxide, hydrochloric acid, and purified water. The product is packaged in a plastic bottle (b) (4) with a metered dose spray pump and fitted with a plastic actuator and overcap [Module 2, Volume 2, Section 2.3.P, pages 2-3].

The proposed indication is the (b) (4) treatment of the symptoms of SAR (b) (4) in adults and children 12 years of age and older [Module 1, Volume 1, Section 3.B, page 8]. The proposed dose is two sprays per nostril twice daily, (b) (4) [Module 1, Volume 1, Sections 3.B and 3.C]

The application is a paper Common Technical Document (CTD) submission.

2. CLINICAL DEVELOPMENT PROGRAM

The applicant's drug development program included pivotal clinical efficacy and safety studies, supportive clinical efficacy and safety studies, and pharmacokinetic (PK) and pharmacodynamic (PD) studies. These studies are briefly described below.

There were five clinical efficacy and safety studies considered by the applicant to be pivotal in their drug development program [Module 2, Volume 4, Section 2.5, pages 10-11, 44]:

1. C-02-37, a randomized, double blind, active and placebo controlled, parallel group, pivotal phase 3, natural exposure, efficacy and safety study of olopatadine 0.4% and 0.6% nasal spray administered twice daily in patients with SAR [Module 2, Volume 20, C-02-37 Synopsis, page]
2. C-02-10, a randomized, double blind, active and placebo controlled, parallel group, pivotal phase 3, natural exposure, efficacy and safety study of olopatadine 0.4% and 0.6% nasal spray administered twice daily in patients with SAR [Module 2, Volume 20, C-02-10 Synopsis, page 1]

3. C-01-92, a randomized, double blind, active and placebo controlled, parallel group, pivotal phase 3, natural exposure, long-term (b) (4) safety study of olopatadine 0.6% nasal spray administered twice daily in patients with PAR [Module 2, Volume 20, C-01-92 Synopsis, page 1]
4. C-01-83, a randomized, double blind, placebo controlled, parallel group, pivotal phase 2, single dose, dose response and onset of action EEU study of olopatadine 0.2%, 0.4%, and 0.6% nasal spray in patients with SAR [Module 2, Volume 20, C-01-83 Synopsis, page 1]
5. C-03-52, a randomized, double blind, active and placebo controlled, parallel group, pivotal phase 2, single dose, onset of action EEU study of olopatadine 0.6% nasal spray and mometasone furoate 50 mcg nasal spray in patients with SAR [Module 2, Volume 20, C-03-52 Synopsis, page 1]

Reviewer comment:
The pivotal clinical studies will be reviewed in depth in the NDA clinical review.

There were six supportive clinical efficacy and safety studies in the applicant's drug development program [Module 2, Volume 4, Section 2.5, pages 8-9]:

1. C-97-59, a randomized, triple masked, placebo and active controlled, 4 period, crossover, single dose, phase 2, nasal allergen challenge study comparing the efficacy of olopatadine 0.1% nasal spray, emedastine 0.05% nasal spray, azelastine 0.1% nasal spray, and placebo in patients with SAR [Module 2, Volume 20, C-97-59 Synopsis, page 1]
2. C-00-10, a randomized, double blind, active and placebo controlled, parallel group, phase 2, dose response, efficacy and safety study of olopatadine 0.1% and 0.2% nasal spray administered once daily and twice daily in patients with SAR [Module 2, Volume 20, C-00-10 Synopsis, page 1]
3. C-00-33, a randomized, double blind, active and placebo controlled, parallel group, phase 2, efficacy and safety study of olopatadine 0.1% nasal spray and azelastine 0.1% nasal spray administered twice daily in patients with SAR [Module 2, Volume 20, C-00-33 Synopsis, page 1]
4. C-00-70, a randomized, single blind, active and placebo controlled, crossover, single dose, phase 2, nasal allergen challenge study of olopatadine 0.1% and 0.2% nasal spray and azelastine 0.1% nasal spray in patients with SAR [Module 2, Volume 20, C-00-70 Synopsis, page 1]
5. C-01-05, a randomized, single blind, active and placebo controlled, parallel group, phase 2, efficacy and safety study of olopatadine 0.1% nasal spray administered once and twice daily and azelastine 0.1% nasal spray administered twice daily in patients with SAR [Module 2, Volume 20, C-01-05 Synopsis, pages 1-3]
6. C-03-48, a randomized, double blind, active and placebo controlled, parallel group, single dose, phase 3, onset of action environmental exposure unit (EEU) study of olopatadine 0.6% nasal spray and fluticasone propionate 0.05% nasal spray in patients with SAR [Module 2, Volume 20, C-03-48 Synopsis, pages 1-3]

Reviewer comment:

The supporting clinical efficacy and safety studies will receive abbreviated reviews in the NDA clinical review.

There were seven PK and PD studies in the applicant's drug development program [Module 2, Volume 4, Section 2.5, pages 7-8, 42]:

1. C-00-58, a multiple dose, phase 1 PK study of olopatadine nasal spray 0.1% and 0.2% in healthy subjects
2. C-02-21, a double blind, placebo controlled, parallel group, single dose, phase 1, single dose, PK study of olopatadine nasal spray 0.6% and placebo nasal spray
3. C-03-11, a randomized, three-way crossover, single dose, phase 1, absolute bioavailability study of topical nasal versus intravenous infusion of olopatadine solution in healthy subjects
4. C-02-46, a open label, parallel group, single dose, phase 1 PK study of olopatadine nasal spray 0.6% in healthy subjects and patients with renal impairment
5. C-03-10, an open label, single dose, phase 1 study of the excretion of oral olopatadine in healthy subjects
6. C-02-54, a randomized, double blind, placebo controlled, crossover, multiple dose, phase 1, PK/PD study of cardiovascular safety of olopatadine solution, 20 mg orally or placebo in healthy subjects
7. C-00-23, a randomized, double blind, placebo controlled, crossover, multiple dose, phase 1, PK/PD study of cardiovascular safety of olopatadine solution, 5 mg orally or placebo in healthy subjects

Reviewer comment:
The cardiac safety studies, C-02-54 and C-00-23, and the PK study in patients with renal impairment, C-02-46, will receive a focused review. The safety data for the other four PK and PD studies will be reviewed as part of the NDA clinical review's review of the Integrated Safety Summary.

3. FOREIGN MARKETING AND REGULATORY HISTORY

An ophthalmic formulation of 0.1% olopatadine solution is approved in more than 70 countries, including the United States, Canada, and the European Union. It is marketed for the treatment of the signs and symptoms of ocular signs and symptoms of seasonal allergic conjunctivitis. The ophthalmic product is marketed in the United States and Canada with the trade name Patanol®. The trade name in the European Union is Opatanol®. An oral dosage form, as 2.5 mg and 5 mg tablets, is approved as Allelock® in Japan, for the treatment of allergic conditions, including allergic rhinitis, urticaria, and itching resulting from skin diseases [Module 2, Volume 4, Section 2.5, Clinical Overview, page 5].

The applicant's opening IND was submitted on March 31, 2000 [IND 60,116, N-000, 3/31/00]. An End-of-phase 2 meeting was held on October 11, 2001. At that time, the applicant was pursuing (b) (4) SAR (b) (4) indications, and had completed two phase 2 nasal allergen challenge studies, and two phase 2 natural exposure SAR studies with 0.1% and 0.2% olopatadine, and had submitted protocols for phase 3 studies with 0.1%

olopatadine. The Division advised the applicant that they must establish the cardiac safety of the product, that one SAR study (b) (4) could support approval of (b) (4) indications, and that long-term safety data would also be required. The Division also recommended that the applicant firmly establish the correct dose prior to conducting phase 3 studies [Meeting Minutes and Medical Officer Review, IND 60,116, N-019, 9/5/01]. The applicant chose to reformulate their product and to conduct additional dose ranging studies with 0.2%, 0.4%, and 0.6% olopatadine nasal spray. Following the completion of additional dose ranging studies, the applicant conducted their pivotal phase 3 efficacy and safety studies (C-02-37 and C-02-10) and their long-term safety study (C-01-92). A pre-NDA meeting was held on September 30, 2003. Points of discussion included data necessary to support onset of action and patient-reported outcome claims, and patient exposure necessary to support the safety of the product [Meeting Minutes and Medical Officer Review, IND 60,116, N-039 MR, 7/2/03].

4. ITEMS REQUIRED FOR FILING AND REVIEWER COMMENTS (21 CFR 314.50)

The following items were included in this submission:

- Form FDA 356h [Module 1, Volume 1, Section 1, Application Form, pages 1-2]
- Debarment certification [Module 1, Volume 1, Section 3.A.3., Debarment Certification, page 1]
- Financial disclosure statement [Module 1, Volume 1, Section 3.A.6., Financial Disclosure]
- Statements of Good Clinical Practice [Module 5, Volume 1, page 5; Module 5, Volume 5, page 2; Module 5, Volume 8, page 1; Module 5, Volume 11, page 1; Module 5, Volume 16, page 1; Module 5, Volume 20, page 1; Module 5, Volume 25, page 2; Module 5, Volume 37, page 1; Module 5, Volume 42, page 2; Module 5, Volume 47, page 1; Module 5, Volume 56, page 1; Module 5, Volume 65, page 1 ; Module 5, Volume 77, page 1; Module 5, Volume 78, page 1; Module 5, Volume 83, page 2; Module 5, Volume 87, page 1; Module 5, Volume 90, page 2; Module 5, Volume 96, page 1]
- Integrated Summary of Efficacy [Module 2, Volume 4, Section 2.5, pages 44-84; Module 2, Volume 6, Section 2.7.3, pages 1-181] included the following:
  - Comparison of results of pivotal studies, primary efficacy endpoints [Module 2, Volume 4, Section 2.5, pages 66-67]
  - Comparison of results of pivotal studies, secondary efficacy endpoints [Module 2, Volume 4, Section 2.5, pages 67-69]
  - Comparison of efficacy by dose [Module 2, Volume 4, Section 2.5, pages 69-70]
  - Onset of action [Module 2, Volume 4, Section 2.5, pages 70-74]
  - RQLQ [Module 2, Volume 4, Section 2.5, pages 74-76]
  - Efficacy in subpopulations [Module 2, Volume 6, Section 2.7.3, pages 154-155]
- Integrated Summary of Safety (ISS) [Module 2, Volume 4, Section 2.5, pages 85-112; Module 2, Volumes 6-9] included the following:

  - Summary of adverse event data from clinical, PK, and PD studies in the application [Module 2, Volume 6, Section 2.7.4.2, pages 91-118; Module 2, Volume 7, Section 2.7.4.2, pages1-118]
  - Summary of laboratory data from clinical, PK, and PD studies in the application [Module 2, Volume 7, Section 2.7.4.3, pages 1-49]
  - Summary of vital signs data from clinical, PK, and PD studies in the application [Module 2, Volume 7, Section 2.7.4.4, pages 16-75]
  - Summary of ECG data from clinical, PK, and PD studies in the application [Module 2, Volume 7, Section 2.7.4.4, pages 76-113]
  - Summary of nasal examination and physical examination data from clinical, PK, and PD studies in the application [Module 2, Volume 7, Section 2.7.4.4, pages 2-15; Module 2, Volume 7, Section 2.7.4.4, pages 114-130]
  - Deaths, serious adverse events, withdrawals due to adverse events, and other significant adverse events in clinical, PK, and PD studies in the application [Module 2, Volume 7, Section 2.7.4.2, pages 75-87];
  - Adverse events in subgroups in clinical, PK, and PD studies in this application [Module 2, Volume 8, Section 2.7.4.5, pages 1-39]
  - Drug-drug and drug-disease interactions [Module 2, Volume 8, Section 2.7.4.5, pages 40-123]
  - Drug abuse and overdose information [Module 2, Volume 8, Section 2.7.4.5, page 124]
  - Postmarketing and spontaneous adverse event reports for olopatadine ophthalmic solution 0.1% [Module 2, Volume 8, Section 2.7.4., pages 1-9]
- Proposed labeling and annotated labeling [Module 1, Volume 1, Sections 3.B and 3.C]
- Case report forms for patients with serious adverse events or discontinuing studies and case report tabulations [Module 5, Volumes 98-221]
- List of referenced DMFs [Module 1, Volume 1, Section 3.A.7]
- Environmental assessment [Module 1, Volume 1, Sections 3.A.9, page 1]
  - The applicant has requested a categorical exclusion from this requirement
- Request for waiver of pediatric studies [Module 1, Volume 1, Section 3.A.8, page 1]
  - The applicant has requested a waiver of pediatric studies for children less than 2 years of age. The applicant states that it is unlikely that the product would be used in a substantial number of patients less than 2 years of age that non-pharmacologic treatment, such as allergen avoidance, may be used. The applicant also notes that it is not practical to treat children less than 2 years of age with nasal spray formulations. The applicant has also submitted a proposed pediatric study request (PPSR) [IND 60,116, N-060 PA, 12/20/04]. The Division is currently discussing whether to issue a Written Request (WR) for pediatric studies. In the past, the Division has issued WRs for pediatric studies in children 6 months of age and older for oral antihistamines (fexofenadine, desloratadine, loratadine, cetirizine) and in children 2 years of age and older for nasal spray preparations intended to treat allergic rhinitis (azelastine, beclomethasone, cromolyn, fluticasone, mometasone).

Reviewer comment:
The applicant did not provide postmarketing safety data for olopatadine tablets, which are approved in Japan. The applicant should provide a review and summary of these data.

The applicant did not provide a review of the medical literature for safety information relevant to use of olopatadine. The applicant should provide a review of the medical literature and submit copies of the articles cited in the literature review.

5. CLINICAL STUDIES

There were five clinical efficacy and safety studies considered by the applicant to be pivotal in their drug development program [Module 2, Volume 4, Section 2.5, pages 10-11, 44]. There were six supportive clinical efficacy and safety studies in the applicant's drug development program [Module 2, Volume 4, Section 2.5, pages 8-9]. There were seven pharmacokinetic (PK) and pharmacodynamic (PD) studies in the applicant's drug development program [Module 2, Volume 4, Section 2.5, pages 7-8, 42].

The clinical review of this application will focus on the five pivotal clinical efficacy and safety studies, which will be reviewed in depth. The supporting clinical efficacy and safety studies will receive abbreviated review. The cardiac safety studies, C-02-54 and C-02-23, will receive a focused review in the NDA clinical review. The safety data for the other five PK and PD studies will be reviewed as part of the review of the Integrated Safety Summary.

The study reports are appropriately indexed to allow review. The pivotal efficacy and safety studies are summarized in Table 1. More detailed descriptions of the pivotal efficacy and studies follow below. Brief descriptions of supporting clinical efficacy and safety studies and clinical pharmacology studies are found in Section 2 of this review, "Clinical Development Program."

5.1. Pivotal efficacy and safety studies

5.1.1. Study C-02-37

Study C-02-37 was a randomized, double blind, placebo controlled, parallel group, pivotal phase 3, natural exposure, efficacy and safety study of olopatadine 0.4% and 0.6% nasal spray administered twice daily in patients with SAR [Module 2, Volume 20, C-02-37 Synopsis, page 1]. There were 565 male and female patients with fall seasonal allergic rhinitis, 12 years of age and older who were randomized. There was a three to 21 day placebo run-in period. The primary efficacy endpoint was percent change from baseline in reflective Total Nasal Symptom Score over the two week double blind treatment period. Secondary efficacy endpoints included percent change from baseline in instantaneous Total Symptom Score over the two week double blind treatment period, percent change from baseline in reflective and instantaneous individual symptom scores, (b) (4)
and Work Productivity and Activity Improvement (WPAI-AS) among others. Safety endpoints included adverse events, vital signs, physical examinations, nasal

examinations, and clinical laboratory studies. Eleven of the 565 patients who were exposed to study treatment withdrew from the study because of adverse events. There were no deaths or serious adverse events in the study [Module 2, Volume 20, C-02-37 Synopsis, pages 1-6]

5.1.2. Study C-02-10

Study C-02-10 was a randomized, double blind, placebo controlled, parallel group, pivotal phase 3, natural exposure, efficacy and safety study of olopatadine 0.4% and 0.6% nasal spray administered twice daily in patients with SAR. There were 677 male and female patients with seasonal allergic rhinitis to mountain cedar pollen, 12 years of age and older who were randomized. There was a three to 21 day placebo run-in period. The primary efficacy endpoint was percent change from baseline in reflective Total Nasal Symptom Score over the two week double blind treatment period. Secondary efficacy endpoints included percent change from baseline in instantaneous Total Symptom Score over the two week double blind treatment period, percent change from baseline in reflective and instantaneous individual symptom scores, (b) (4) and health economics (WPAI-AS) assessments. A subset of patients had blood samples taken for PK analysis. Safety endpoints included adverse events, vital signs, physical examinations, nasal examinations, and clinical laboratory studies. Eight of the 677 patients who were exposed to study treatment withdrew from the study because of adverse events. There were no deaths in this study. There was one serious adverse event (syncope) in the study [Module 2, Volume 20, C-02-10 Synopsis, pages 1-7; Module 5, Volume 56, page 220].

5.1.3. Study C-01-92

Study C-01-92 was a randomized, double blind, placebo controlled, parallel group, pivotal phase 3, natural exposure, long-term (b) (4) safety study of olopatadine 0.6% nasal spray administered twice daily in patients with PAR. There were 924 male and female patients with PAR, 12 years of age and older who were randomized. There was a three to 21 day placebo run-in period. The treatment period was one year. (b) (4) Safety endpoints included adverse events, vital signs, physical examinations, nasal examinations, and ECGs. Forty-eight of the 924 patients who were exposed to study treatment withdrew from the study because of adverse events. Of the 48 patients who withdrew from the study, 23 were treated with olopatadine 0.6% and 25 were treated with placebo. There was one death in the study, a patient treated with olopatadine 0.6% who died of sepsis after a gastric bypass operation. There were 15 serious adverse events in the study, with seven treated with olopatadine 0.6% and eight treated with placebo [Module 2, Volume 20, C-01-92 Synopsis, pages 1-5; Module 2, Volume 65, pages 198-202].

<u>Reviewer comment:</u>
(b) (4) *This*

(b) (4)

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5.1.4. Study C-01-83

C-01-83, a randomized, double blind, placebo controlled, parallel group, pivotal phase 2, single dose, dose response and onset of action EEU study of olopatadine 0.2%, 0.4%, and 0.6% nasal spray in patients with SAR. There were 320 male and female patients with seasonal allergic rhinitis to short ragweed pollen, 16 years of age and older who were randomized. Patients that met minimum total nasal symptom scores on each of two priming visits were enrolled in the study. Patients were exposed to pollen in the EEU and diary cards were completed and peak nasal inspiratory flow rates were measured at various intervals during the study period. The primary efficacy endpoint was percent change from baseline in reflective Total Nasal Symptom Score over the challenge period. Secondary efficacy endpoints included percent change from baseline in individual symptom scores over the challenge period, change from baseline in nasal inspiratory flow rate, and patient global rating over the challenge period. Safety endpoints included adverse events, vital signs, and nasal examinations. There were no patients who withdrew from the study because of adverse events. There were no deaths or serious adverse events in the study [Module 2, Volume 20, C-01-83 Synopsis, pages 1-4; Module 2, Volume 37, pages 90].

5.1.5. Study C-03-52

C-03-52, a randomized, double blind, active and placebo controlled, parallel group, pivotal phase 2, single dose, onset of action EEU study of olopatadine 0.6% nasal spray and mometasone furoate 50 mcg nasal spray in patients with SAR. There were 425 male and female patients with seasonal allergic rhinitis to short ragweed pollen, 18 years of age and older who were randomized. Patients that met minimum total nasal symptom scores at two priming visits and predose were enrolled and entered the treatment phase of the study. Patients were exposed to pollen in the EEU and diary cards were completed and peak nasal inspiratory flow rates were measured at various intervals during the study period. The primary efficacy endpoint was percent change from baseline in reflective Total Nasal Symptom Score over the challenge period. Secondary efficacy endpoints included percent change from baseline in individual symptom scores over the challenge period and patient global rating over the challenge period. Safety endpoints included adverse events, vital signs, and nasal examinations. There were no patients who withdrew from the study because of adverse events. There were no deaths or serious adverse events in the study [Module 2, Volume 20, C-03-52 Synopsis, pages 1-5].

6. BRIEF REVIEW OF PROPOSED LABELING

Proposed package labeling has been included in this submission [Module 1, Volume 1, Sections 3.B and 3.C]. A brief review of proposed labeling was performed. Labeling comments are noted below.

1. The proposed label includes a statement that olopatadine is (b) (4) This claim must be supported by data in the NDA submission.

Table 1. Summary of studies NDA 21-861 [Module 5,Volume 20, Section 2.7.6, pages 1-9; Module 5,Volume 20, Section 2.7.6, Study Synopses].

Study Number	Study Type	Treatment Groups	Treatment duration	Design	Number of subjects	Diagnosis, age of subjects	Materials submitted in this application
Pivotal Clinical Studies							
C-02-37	Pivotal efficacy and safety study	Olopatadine NS 0.4%, 2 sp ea nostril BID Olopatadine NS 0.6%, 2 sp ea nostril BID Placebo, 2 sp ea nostril BID	2 weeks	Multicenter, randomized, double blind, active and placebo controlled, parallel group	565	Patients with SAR, men and women, =12 years	Protocol Study report Tabulations Case report forms
C-02-10	Pivotal efficacy and safety study	Olopatadine NS 0.4%, 2 sp ea nostril BID Olopatadine NS 0.6%, 2 sp ea nostril BID Placebo, 2 sp ea nostril BID	2 weeks	Multicenter, randomized, double blind, active and placebo controlled, parallel group	677	Patients with SAR, men and women, =12 years	Protocol Study report Tabulations Case report forms
C-01-92	Long-term safety study	Olopatadine NS 0.6%, 2 sp ea nostril BID Placebo, 2 sp ea nostril BID	1 year	Multiple center, randomized, double blind, placebo controlled, parallel group	924	Patients with PAR, men and women, =12 years	Protocol Study report Tabulations Case report forms
C-01-83	Pivotal dose response EEU study	Olopatadine NS 0.2%, 2 sp ea nostril Olopatadine NS 0.4%, 2 sp ea nostril Olopatadine NS 0.6%, 2 sp ea nostril Placebo, 2 sp ea nostril	1 day	Single center, randomized, double blind, placebo controlled, parallel group	320	Patients with SAR, men and women, =16 years	Protocol Study report Tabulations Case report forms
C-03-52	Pivotal onset of action EEU study	Olopatadine NS 0.6%, 2 sp ea nostril Mometasone furoate 50 mcg, 2 sp ea nostril Placebo, 2 sp ea nostril	1 day	Single center, randomized, double blind, active and placebo controlled, parallel group	425	Patients with SAR, men and women, =18 years	Protocol Study report Tabulations Case report forms
Supportive Clinical Studies							
C-97-59	Pilot phase 2 EEU study	Olopatadine NS 0.1%, 1 sp ea nostril Azelastine NS 0.1%, 1 sp ea nostril Emedastine NS 0.05%, 1 sp ea nostril Placebo, 1 sp ea nostril	1 day	Single center, randomized, double blind, active and placebo controlled, four-way crossover	12	Patients with SAR, men and women, =16 years	Protocol Study report Tabulations Case report forms
C-00-10	Phase 2 dose response efficacy and safety study	Olopatadine NS 0.1%, 2 sp ea nostril QD Olopatadine NS 0.1%, 2 sp ea nostril BID Olopatadine NS 0.2%, 2 sp ea nostril QD Olopatadine NS 0.2%, 2 sp ea nostril BID Placebo, 2 sp ea nostril QD Placebo, 2 sp ea nostril BID	2 weeks	Multicenter, randomized, double blind, active and placebo controlled, parallel group	192	Patients with SAR, men and women, =12 years	Protocol Study report Tabulations Case report forms

C-00-33	Phase 2-3 efficacy and safety study	Olopatadine NS 0.1%, 2 sp ea nostril BID Azelastine NS 0.1%, 2 sp ea nostril BID Placebo, 2 sp ea nostril BID	2 weeks	Multicenter, randomized, double blind, active and placebo controlled, parallel group	166	Patients with SAR, men and women, =12 years	Protocol Study report Tabulations Case report forms
C-00-70	Phase 2 EEU study	Olopatadine NS 0.1%, 2 sp ea nostril Olopatadine NS 0.2%, 2 sp ea nostril Azelastine NS 0.1%, 2 sp ea nostril Placebo, 2 sp ea nostril	1 day	Single center, randomized, single blind, active and placebo controlled, three-phase, two-way crossover	20	Patients with SAR, men and women, =16 years	Protocol Study report Tabulations Case report forms
C-01-05	Phase 2-3 efficacy and safety study	Olopatadine NS 0.1%, 2 sp ea nostril QD Olopatadine NS 0.1%, 2 sp ea nostril BID Azelastine NS 0.1%, 2 sp ea nostril BID Placebo, 2 sp ea nostril QD Placebo, 2 sp ea nostril BID	8 weeks	Multicenter, randomized, double blind, active and placebo controlled, parallel group	397	Patients with SAR, men and women, =12 years	Protocol Study report Tabulations Case report forms
C-03-48	Phase 3 pilot onset of action EEU study	Olopatadine NS 0.6%, 2 sp ea nostril Fluticasone propionate 0.05%, 2 sp ea nostril Placebo, 2 sp ea nostril	1 day	Single center, randomized, double blind, active and placebo controlled, parallel group	90	Patients with SAR, men and women, =12 years	Protocol Study report Tabulations Case report forms
Clinical Pharmacology Studies							
C-00-58	Phase 1 PK study	Olopatadine NS 0.1%, 2 sp ea nostril QD Olopatadine NS 0.1%, 2 sp ea nostril BID Olopatadine NS 0.2%, 2 sp ea nostril QD	2.5 days	Single center, randomized, open label, multiple dose, parallel group	36	Healthy men and women, 18-75 years	Protocol Study report Tabulations Case report forms
C-02-21	Phase 1 PK study	Olopatadine NS 0.6%, 2 sp ea nostril Placebo NS, 2 sp ea nostril	1 day	Single center, randomized, double blind, single dose, parallel group	36	Healthy men and women, =18 years	Protocol Study report Tabulations Case report forms
C-03-11	Phase 1 BA study	Olopatadine NS 0.4%, 2 sp ea nostril Olopatadine NS 0.6%, 2 sp ea nostril Olopatadine iv solution 0.01%, 1.5 mg	1 day	Single center, randomized, open label, single dose, three way crossover	12	Healthy men and women, 18-45 years	Protocol Study report Tabulations Case report forms
C-02-46	Phase 1 PK study	Olopatadine NS 0.6%, 2 sp ea nostril	1 day	Single center, randomized, open label, single dose	25	Adult men and women with renal impairment, =18 years	Protocol Study report Tabulations Case report forms
C-03-10	Phase 1 mass balance excretion study	Olopatadine oral solution 0.67%, 5 mg/200 µCi ^{14}C olopatadine	1 day	Single center, open label, single dose	8	Healthy men and women, 19-45 years	Protocol Study report Tabulations Case report forms

C-02-54	Phase 1 cardiac safety and PK study	Olopatadine oral solution, 0.2%, 20 mg BID Placebo solution BID	2 weeks	Single center, randomized, double blind, placebo controlled, multiple dose, 2-way crossover	34	Healthy men and women, 18-75 years	Protocol Study report Tabulations Case report forms
C-00-23	Phase 1 cardiac safety and PK study	Olopatadine oral solution, 5 mg BID Placebo solution BID	2.5 days	Single center, randomized, double blind, placebo controlled, multiple dose, 2-way crossover	117	Healthy men and women, 18-75 years	Protocol Study report Tabulations Case report forms

2. The CLINICAL PHARMACOLOGY section includes references to (b) (4) These claims are troublesome because the clinical relevance of these effects is not known and the information does not guide the prescriber to use the drug more knowledgeably.

3. The Clinical Trials subsection includes a (b) (4) claim. However, a brief look at the data does not show a minimally important difference in effect between the active treatment group and the placebo group. If this is found to be the case with the formal review of the data, the claim will not be supported.

4. The Clinical Trials subsection includes a (b) (4) Data supporting this claim will be reviewed in depth, including information regarding the validation of the instrument. It is not likely that this claim will be supported

5. The Clinical Trials subsection includes an (b) (4) and a (b) (4) . A brief examination of the data reveals that neither of the claims is replicated. These claims will not be supported by the data in this submission.

6. The applicant's proposed indication includes (b) SAR (b) (4) (b) (4)

7. The INDICATIONS AND USAGE section of the label makes reference to (b) (4) These symptoms were not part of the total nasal symptom score, and therefore not part of the primary efficacy endpoints for the pivotal studies. The data for these claims will be reviewed in depth. It is possible that the submission may not support these claims.

Detailed label review will be performed later in the course of review of this NDA.

7. DSI REVIEW/AUDIT

DSI will be notified that the following sites have been identified for inspection:

Sandra Gawchik (3203)
Asthma & Allergy Research Associates
President's House
One Medical Center
Upland, PA 19013
Phone: (610) 876-2103
Fax: (210) 876-6565

Subinvestigators:
(b) (4)

(b) (4)

This center was one of the centers that randomized the greatest number of patients in pivotal Study C-02-37 [Module 5, Volume 51, page 1514]

Paul Ratner, MD (3619)
Sylvana Research
7711 Louis Pasteur Dr., Suite 406
San Antonio, TX 78229
Phone: (210) 614-6673
Fax: (210) 614-5340

Subinvestigators:
(b) (4)

This center was one of the centers that randomized the greatest number of patients in pivotal Study C-02-10 [Module 5, Volume 60, page 1444].

A request for DSI consultation will be submitted. The consultation request will include selected values from the submission for comparison with the original data source.

8. SUMMARY

This NDA is an application for a nasal spray solution formulation of olopatadine HCl. The drug is a selective H_1-histamine receptor antagonist and a structural analog of doxepin. The applicant is Alcon, Inc. The applicant seeks to develop this drug for use as an intranasal spray for treatment of symptoms of SAR (b) (4). The product is a nonsterile, multiple dose, nasal spray solution containing 600 mcg/spray (0.6%) of olopatadine base or 665 mcg/spray (0.665%) of olopatadine HCl). The proposed indication is the (b) (4) treatment of the symptoms of SAR (b) (4) in adults and children 12 years of age and older. The proposed dose is two sprays per nostril twice daily. The application is a paper CTD submission.

The applicant's drug development program included pivotal clinical efficacy and safety studies, supportive clinical efficacy and safety studies, and PK and PD studies. There were five clinical efficacy and safety studies considered by the applicant to be pivotal in their drug development program. There were six supportive clinical efficacy and safety studies in the applicant's drug development program. There were seven PK and PD studies in the applicant's drug development program. The study reports are appropriately indexed and organized to allow review. The applicant has provided an Integrated Summary of Efficacy, Integrated Summary of Safety, copies of proposed labeling, and

appropriate case report forms and case report tabulations.

The applicant did not provide postmarketing safety data for olopatadine tablets, which are approved in Japan. The applicant should provide a review and summary of these data. The applicant did not provide a review of the medical literature for safety information relevant to use of olopatadine. The applicant should provide a review of the medical literature and submit copies of the articles cited in their literature review. The applicant will be advised that the proposed (b) (4) is not supported.

A brief review of the proposed labeling reveals that (b) (4) claims may not be supported. The (b) (4) The submission is adequate to allow clinical review. The submission is fileable.

9. TIME LINE FOR REVIEW

Write-up will be concomitant with the review process. The schedule for review is displayed in Table 2. Clinical review will focus initially on the pivotal clinical studies and will the review will be performed for each study before moving to the next. Review of pivotal studies will be completed by May 20, 2005. Review of supportive clinical studies will be complete by June 3, 2005. Review of clinical pharmacology studies C-00-23, C-02-54, and C-02-46 will be completed by June 10, 2005. The review of the ISS will take place next and will be completed by June 24, 2005. Review of the ISE will be completed by July 8, 2005. Label review will be complete by July 22, 2005. Draft review will be complete by August 5, 2005, and the review will be complete by August 26, 2005, two months before the action date.

Table 2. Proposed schedule for review of NDA 21-861.

Milestone	Target Date for Completion
Pivotal efficacy and safety study C-02-37	3/25/05
Pivotal efficacy and safety study C-02-10	4/8/05
Pivotal long-term safety study C-01-92	4/22/05
Pivotal dose response study C-01-83	5/6/05
Pivotal onset of action study C-03-52	5/20/05
Supportive clinical studies	6/3/05
Clinical pharmacology studies C-00-23, C-02-54, and C-02-46	6/10/05
ISS	6/24/05
ISE	7/8/05
Label Review	7/22/05
Draft Review Complete	8/5/05
Division Due Date, 8 months	8/26/05
Action Date, 10 months	10/27/05

10. COMMENTS FOR THE SPONSOR

The following comments should be communicated to the applicant.

(b) (4)

2. *Provide a review and summary of postmarketing safety data for olopatadine tablets, which are approved in Japan.*

3. *Provide a review of the medical literature for safety information relevant to use of olopatadine. Submit copies of the articles cited in the literature review.*

Reviewed by:

_____
Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

_____
Lydia Gilbert-McClain, M.D.
Medical Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original NDA
HFD-570/Division File
HFD-570/McClain/Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-870/Suarez/Clinical Pharmacology and Biopharmaceutics Reviewer
HFD-715/Guo/Biometrics Reviewer
HFD-570/Bertha/CMC Reviewer
HFD-570/J. Shah/Pharmacology Reviewer
HFD-570/A. Zeccola/CSO

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/s/

Charles Lee
3/11/05 06:00:44 PM
MEDICAL OFFICER

Lydia McClain
3/14/05 08:26:54 AM
MEDICAL OFFICER