CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-861s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 19, 2007
To:	Badrul Chowdhury, M.D., Director Division of Pulmonary and Allergy Drug Products
Through:	Jodi Duckhorn, M.A., Team Leader Patient Labeling and Education Team Division of Risk Management (DRISK)
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist Patient Labeling and Education Team Division of Risk Management (DRISK)
Subject:	Review of Patient Labeling (Patient Package Insert and Patient Instructions for Use
Drug Name(s):	Patanase (oloptadine hydrochloride) Nasal Spray
Application Type/Number:	NDA 21-861
Applicant/sponsor:	Alcon
OSE RCM #:	2007-2398

1 INTRODUCTION

The sponsor submitted New Drug Application (NDA) #21-861 on December 24, 2004 for Patanase (oloptadine hydrochloride) Nasal Spray. The Agency took a Not-Approvable Action on October 27, 2005. The sponsor resubmitted their application under the referenced NDA on September 26, 2007. The labeling contained in the resubmission includes Prescribing Information (PI), which contains patient labeling in the form of a Patient Package Insert (PPI) and Patient Instructions for Use. DRISK received a request from the Review Division to review the patient labeling. This review is written in response to that request.

2 MATERIAL REVIEWED

- Patanase Nasal Spray Prescribing Information (PI) submitted by the sponsor on September 26, 2007 and revised by the Review Division on March 13, 2008.
- Patanase Nasal Spray Patient Package Insert submitted by the sponsor on September 26, 2007 and revised by the Review Division on March 13, 2008.
- Patient Instructions for Use submitted by the sponsor on September 26, 2007 and revised by the Review Division on March 13, 2008.

3 DISCUSSION

The purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

In our review of the PPI, we have:

- simplified wording where possible,
- made it consistent with the Professional Information
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the PPI. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised PPI. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the PPI.

4 CONCLUSIONS AND RECOMMENDATIONS

1. Consult with DDMAC to evaluate the onset of action claim in the PPI.
2. We have re-titled the PPI section (b) (4) to "What should I avoid while using Patanase Nasal Spray?"

3. We added a section to the PPI called “General information about Patanase Nasal Spray.”
4. The Review Division provided the PPI and Patient Instructions for Use to DRISK as separate documents; however, they are both included in the PI, with the Patient Instructions for Use appearing first. We recommend that the PPI be located first with the Patient Instructions for Use following at the end of the PPI in section 17 of the PI, as well as in the Final Printed Labeling to be included with the packaged product. The important safety information should be the first thing the patient reads.
5. The figures that are in the sponsor’s original submission are missing from both the pdf version of the PI sent to the sponsor on March 13, 2008 and provided to DRISK, as well as the word version of the Patient Instructions for Use provided to DRISK for review. The figures should be added back to the Patient Instructions for Use to illustrate the parts of the nasal spray and how to use it correctly. We have noted in the Patient Instructions for Use where additional figures would be useful.
6. We have added the statement, “Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.” This verbatim statement is required for all Medication Guides effective January 2008 (see 21 CFR 208.20 (b)(7)(iii); also see Interim Final Rule, Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products in Federal Register Vol. 73, No. 2, p.402-404, 1/3/2008). Although not required for voluntary PPIs, we recommend adding this language to all FDA-approved patient labeling for consistency.

Please let us know if you have any questions.

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/s/

Sharon Mills
3/19/2008 06:00:12 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
3/19/2008 09:39:16 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

MEMORANDUM

Pre-Decisional Agency Information

Date: November 19, 2007

To: Miranda Raggio, RN, BSN, MA – Regulatory Project Manager
Division of Pulmonary and Allergy Products

From: Michelle Safarik, PA-C – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: DDMAC labeling comments for Patanase (olopatadine hydrochloride) Nasal Spray
NDA 21-861

DDMAC has reviewed the proposed product labeling (PI), proposed Patient Package Insert (PPI), proposed Patient's Instructions for Use, and proposed carton and container labeling for Patanase (olopatadine hydrochloride) Nasal Spray (Patanase) submitted for consult on November 13, 2007.

Reference is made to a Not Approvable Letter for Patanase dated October 27, 2005, and a resubmission from the sponsor dated September 26, 2007.

We offer the following comments.

HIGHLIGHTS

General

1. "**Initial U.S. Approval: NA**." (emphasis original)

   DDMAC is unclear as to why Patanase's initial U.S. approval is "NA." We recommend using a year placeholder.

Indications and Usage

1. "PATANASE® Nasal Spray is a (b) (4) selective H1 antihistamine indicated for the (b) (4) treatment of the symptoms of seasonal allergic rhinitis (b) (4)

(b) (4) in patients 12 years of age and older." (emphasis added)

(b) (4) minimizes the risks of Patanase therapy; therefore, we strongly recommend deletion.

Also, we recommend deletion of the four components of the rTNSS and the two components of the rTOSS for consistency with other drug products indicated for seasonal allergic rhinitis (SAR).

Furthermore, we recommend adding the word "Seasonal" to the Full Prescribing Information section listings on the bottom half of the page under the "Indications and Usage" header (i.e., as written, "Treatment of Allergic Rhinitis" broadens the indication for Patanase).

Drug Interactions

1. DDMAC is unclear as to where this information came from. We recommend specifying all interactions and not just including the word "etc." as this minimizes the risks of Patanase therapy.

Use in Specific Populations

1. Is it appropriate to simply list a reference to section 8 of the full prescribing information? According to the draft "Guidance for Industry Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements" (page 13), "Ordinarily, the absence of information about the safety and effectiveness of a drug in a specific population (e.g., pregnant women, children) should not be included under this heading."

PI

Indications and Usage

1. (Please see comment under Highlights – Indications and Usage).

Adverse Reactions

1. "Nasal adverse drug reactions occurring at an incidence of 1% to 4% in the long-term clinical trials and at a rate greater than in vehicle nasal spray-treated patients included nasal ulceration and rhinitis. . . . Additional nasal and systemic adverse drug reactions occurring at an incidence of greater than 0.5% in the long-term clinical trials and a rate greater than in vehicle nasal spray-treated patients include the following. . . ."

Would it be possible to provide further context for the nasal adverse drug reactions (1-4%) and nasal and systemic adverse drug reactions (>0.5%)?

2. (b) (4)

   This claim is promotional in tone and minimizes the risks of Patanase therapy; therefore, we recommend deletion.

Description

1. (b) (4)

2. "PATANASE® Nasal Spray contains 0.6% w/v olopatadine (base) in a (b) (4) nonsterile aqueous solution."

   (b) (4) is promotional in tone. While DDMAC acknowledges (b) (4) has been used in Nasonex promotional materials, such language is not included in the Nasonex PI. Therefore, we recommend deletion.

Clinical Pharmacology

<u>Mechanism of Action</u>

1. (b) (4)

   These phrases are promotional in tone and may be unsubstantiated superiority claims for Patanase. Therefore, we recommend deletion.

<u>Pharmacokinetics – Absorption</u>

1. "Olopatadine was (b) (4) absorbed. . . ."

   (b) (4) is promotional in tone. Since context is provided later in this section (between 30 minutes and 1 hour for healthy subjects, between 15 minutes and 2 hours for SAR patients), we recommend deletion.

Nonclinical Toxicology

Pharmacology

(b) (4)

Clinical Studies

Adult and Adolescent Patients 12 Year of Age and Older

1. (b) (4)
2. (b) (4)

Quality of Life Data

1. We recommend consulting SEALD for their evaluation of whether these data constitute substantial evidence to include in labeling.

Onset- and Duration-of-Action Trials

1. (b) (4)

   Were the reductions in TNSS truly clinically meaningful? Or only statistically significant?

   Also, (b) (4) and (b) (4) are promotional in tone (b) (4)).
   Therefore, we recommend deletion of these misleading phrases.

2. (b) (4)

How Supplied/Storage and Handling

1. "Each trade size bottle contains 30.5 g of clear, colorless liquid and will provide (b) (4) 240 metered sprays."

   While the bottle may indeed provide (b) (4) 240 sprays, we recommend deleting (b) (4) for consistency with the remainder of this section of the proposed PI (i.e., "The correct amount of medication cannot be assured before the initial priming and after 240 sprays have been used, even though the bottle is not completely empty. The nasal device should be discarded after 240 sprays (enough for 30 daily doses) have been used").

Patient Counseling Information

Local Nasal Effects

1. We recommend including (b) (4) headache in this section for consistency with the Adverse Reactions section of the proposed PI.

Use When Needed

1. (b) (4)

   " (b) (4) is promotional in tone. We recommend deletion since context (within the first 30 minutes) is provided later in the sentence.

2. (b) (4)

(b) (4)

PPI

General

1. We recommend referring to DSRCS for comments on formatting, ease of readability, and consistency.

2. We recommend providing the pronunciation for "PATANASE®" and revising "INTRANASAL USE" (emphasis original), "nasal," "ocular," and "rhinitis" into consumer-friendly language.

What is PATANASE Nasal Spray?

1. ". . .and your eyes to become (b) (4) itchy, and watery. . .as well as red, itchy, watery eyes." (emphasis added)

   For consistency with the Clinical Studies section of the proposed PI, we recommend deleting (b) (4) as rTOSS included only itchy eyes and watery eyes.

2. (b) (4)

   .

3. (b) (4)

What are the possible side effects of PATANASE Nasal Spray?

1. For consistency with the most common adverse events presented in the Adverse Reactions section of the proposed PI, we recommend adding "bad or bitter taste" and "headache."

What are the other risks of using PATANASE Nasal Spray?

1. (b) (4)

   This section minimizes the risks of treatment with Patanase; therefore, we strongly recommend deleting.

What should I know about allergic rhinitis?

1. "Allergic rhinitis can be caused by allergies (b) (4) If you have allergic rhinitis. . . ."

   For consistency with the Indications and Usage and Clinical Studies sections of the proposed PI, we recommend placing the word "seasonal" before "allergic rhinitis." We also recommend deleting the (b) (4)

(b) (4) as these are (b) (4) and not seasonal, allergic rhinitis triggers.

2. "You may also have (b) (4) itchy, watery eyes and (b) (4) or (b) (4) "

   For consistency with the Clinical Studies section of the proposed PI, we recommend deleting (b) (4) as rTOSS included only itchy eyes and watery eyes, and recommend deleting (b) (4) and (b) (4) as the rTNSS only included congestion, rhinorrhea, nasal pruritis, and sneezing.

Patient's Instructions for Use

1. We recommend referring to DSRCS for comments on formatting, ease of readability, and consistency.

2. We recommend revising "doctor" to "heath care professional" to reflect the variety of health care professionals who may diagnose and treat patients with SAR (e.g., nurse practitioners, physician assistants).

3. For consistency with the proposed and established name, we recommend moving "Nasal Spray" to before "665 mcg" (i.e., "Patanase (olopatadine HCl) Nasal Spray 665 mcg").

4. (b) (4)

   Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials.

   As the proposed PPI contains the above efficacy claims for Patanase but fails to present <u>any</u> risk information for the drug, we strongly recommend their deletion. Even if appropriate balancing risk information were provided, the above claims lack context for (b) (4) and (b) (4) as well as overstate the drug's efficacy by stating how (b) (4) relief is. Therefore, we strongly recommend their deletion.

Carton and Container Labeling

1. For consistency with the proposed and established name, we recommend moving "Nasal Spray" to before "665 mcg" (i.e., "Patanase (olopatadine HCl) Nasal Spray 665 mcg").

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/s/

Michelle Safarik
11/19/2007 02:43:37 PM
DDMAC REVIEWER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 22, 2005

TO: Anthony Zeccola, Regulatory Project Manager
Vicki Goodman, M.D., Clinical Reviewer
Division of Oncology Drug Products, HFD-150

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Ele Ibarra-Pratt, R.N., MPH
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 21-861

APPLICANT: Alcon, Inc.

DRUG: Patanase Nasal Spray® (olopatadine)

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Seasonal allergic rhinitis (SAR)

CONSULTATION REQUEST DATE: March 25, 2005

DIVISION GOAL DATE: October 27, 2005

PDUFA GOAL DATE: October 27, 2005

I. BACKGROUND:

The sponsor, Alcon, Inc., submitted NDA 21-861 for olopatadine in support of a new indication for SAR. Olopatadine ophthalmic formulation of 0.1% (Patanol®) is currently approved and marketed in the U.S. for signs and symptoms of seasonal allergic conjunctivitis. Olopatadine is a selective H1-histamine receptor antagonist and a structural analog of doxepin. The sponsor has reformulated their product for nasal spray use in adults and children 12 years or older with seasonal allergic rhinitis (SAR). Two pivotal studies were submitted in support of this application, protocols C-02-037 (565 enrolled) and C-02-10 (677 enrolled). A total of 3 clinical investigator sites (Gawchik, Ratner, and Amar) were selected due to high enrollments.

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State	Protocol	Insp. Date	EIR Recd.	Classn.
Sandra Gawchik, D.O. (#3203)	Upland, PA	C-02-37	6/6/05-6/13/05	6/28/05	VAI
Paul Ratner, M.D. (#3619)	San Antonio, TX	C-02-37 C-02-10	6/9/05-6/16/05	7/19/05	NAI
Niram Amar, M.D. (#3642)	Waco, TX	C-02-10	7/11-7/15/05	7/19/05	NAI
Kenneth Kim, M.D. (#3795)	Long Beach, CA	C-01-92	8/9-8/16/05	pending	NAI
John Zora, M.D. (#3812)	Lawrence, GA	C-01-92	8/2005	pending	NAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

Routine Inspections:

Two pivotal studies were submitted in support of this application, protocols C-02-037 and C-02-10. Protocol C-02-37 was a randomized double-blind, placebo-controlled, parallel group, pivotal phase 3, natural exposure, efficacy and safety study of 0.4% and 0.6% nasal spray bid in patients with SAR. A total of 565 subjects were enrolled (adults and children 12 years or older). The primary efficacy endpoint was the percent change from baseline in reflective Total Nasal Symptom Score over two weeks double blind treatment period. Safety evaluations include adverse event reporting, vital signs, physical examinations, nasal examinations and clinical laboratory assessments.

Protocol C-02-10 was a randomized, double blind, placebo controlled, parallel group, natural exposure, efficacy and safety study of olopatadine 0.4% and 0.6% nasal spray bid in patients with SAR. A total of 677 adults and children 12 years or older were enrolled with SAR to mountain cedar pollen. The primary efficacy endpoint was the percent change from baseline in reflective Total Nasal Symptom Score over two weeks double blind treatment period. Safety evaluations include adverse event reporting, vital signs, physical examinations, nasal examinations and ECGs.

A total of 3 U.S. clinical investigator sites (Gawchik, Ratner, and Amar) were selected for auditing the pivotal trials due to high enrollments.

For-Cause/Directed Inspections:

After the issuance of the routine assignments for this application, the review division requested that two sites (Drs. Zora and Kim) be audited for their participation in a long-term study (protocol C-01-92) to verify safety data. This study was a randomized, double-blind, placebo controlled, parallel group, pivotal phase 3, natural exposure, long-term efficacy and safety study of olopatadine in patients with PAR. The treatment period was 1 year with a 3-21 day run-in period. This study is not intended to support a PAR indication but used to support the safety data for olopatadine. The objective of the study was to demonstrate the safety of olopatidine 0.6% Nasal Spray given BID for up to one year in patients with PAR

who have a positive skin test to a PAR allergen. Subjects were excluded if their concurrent disease might complicate or interfere with the investigation or evaluation of the study medication 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 at visit 1; history of current chronic sinusitis (within the past year); congestion that would interfere with nasal drug administration/absorption (in either nostril). The primary safety variables under analysis were adverse events and nasal examination (significant anatomic abnormalities, evidence of infection, bleeding, and ulcerations of the mucosa). Study visits included safety evaluations such as, physical examination, ECG, and vital signs.

In this study, at least 3 occurrences of nasal perforations were reported in protocol C-01-92. Of the 3, one was randomized to olopatadine 0.6% (#5905) and two were randomized to placebo treatment (#8503 and #9021). Two sites were specifically selected for inspection because there is concern about the reliability of the safety data that was reported on the case report forms for subjects 8503 and 5905, who were enrolled at site 3795 (Dr. Kim) and site 3812 (Dr. Zora), respectively. The sponsor claims that each of the subjects had either a pre-existing nasal perforation or physical conditions predisposing the subjects to the perforations. However, the case report forms that would appear to support the sponsor's claim were altered in such a manner (e.g., different handwriting used for the same visit, insertion of new information without dating or initialing, multiple sponsor requested changes or additions were made to the adverse event form, baseline medical history...) that would raise suspicion about the accuracy of the changed or inserted data recorded on these forms. Therefore, the review division requested that these adverse events and patient's medical history be thoroughly audited to ensure that data recorded on these forms accurately reflect the source data and patient's actual medical history.

Review of Routine Inspections:

1. Sandra Gawchik, D.O. (#3203)
   Asthma & Allergy Research Associate
   President's House
   One Medical Center
   Upland, PA 19013

   a. Dr. Gawchik was audited for her conduct in protocol C-02-37. A total of 28 subjects were enrolled in protocol C-01-37 at this site. The CRFs, data listings provided in the assignment, and source documents were reviewed in depth for all 28 subjects enrolled. Source documents were compared to data sent with the assignment and found no significant discrepancies. No serious adverse events were reported during the study at this site. Form FDA 483, Inspectional Observations, was issued at the end of inspection for protocol violations.

   b. There were no known limitations of the inspection.

   c. The following deviation was noted during the inspection:

      The clinical investigator did not conduct the studies according to the approved protocol [21 CFR 312.60]. According to the protocol, at visit 1 (screening) and visit 2 (randomization), if any of the blood pressure measurement averages are outside the established ranges for systolic (95-160 mmHg) and diastolic (55-90 mmHg), the patient will be discontinued from the study. However, the investigator enrolled subjects 1806 and 1815 with an average blood pressure reading of 92/63 at visit 1 and 90/61 at visit 2, respectively.

   d. The investigator was issued an untitled letter addressing the issue above. The inspection was classified VAI. The data at this site appear acceptable.

2. Paul Ratner, M.D. (#3619)
   Sylvana Research
   7711 Louis Pasteur Drive, Suite 406
   San Antonio, TX 78229

   a. The inspection audited two protocols, C-02-37 and C-02-10. A total of 157 subjects were enrolled in protocol C-02-10 and 34 enrolled in protocol C-02-037 from this site. The records and source documents were reviewed for those subjects on the data listings; the only discrepancy found was that subject 2069 in study C-02-10 should be listed as 70 y/o and not 67 y/o. Source documents were compared to data sent with the assignment and found no other discrepancies. No serious adverse events were reported during the study. In general, the site adhered to the investigational plan and applicable regulatory requirements. No Form FDA 483 was issued.

   b. There were no known limitations of the inspection.

   c. In general, the site adhered to the investigational plan and applicable regulatory requirements. The inspection is classified NAI. Data at this site appear acceptable.

3. Niram Amar, M.D. (#3642)
   Allergy and Asthma Center
   405 Londonderry Drive, Suite 100
   Waco, TX 76712

   a. The inspection audited protocol C-02-10. A total of 124 subjects were enrolled in protocol C-01-10 at this site. The records and source documents were reviewed in depth for 20 subjects of the 124 enrolled. Source documents were compared to data sent with the assignment and found no significant discrepancies. No serious adverse events were reported during the study. The inspection confirmed the protocol violation in the NDA that subject 1095 was inappropriately randomized with TNSS < 36. No 483 was issued.

   b. After the routine assignment was issued for this inspection, DSI received an anonymous complaint from a previous employee against Dr. Amar in protocol (b) (4) [redacted] No Form FDA 483 was issued.

   c. There were no known limitations of the inspection.

   d. In general, the site adhered to the investigational plan and applicable regulatory requirements. The inspection is classified NAI. Data at this site appear acceptable.

Review of For-Cause/Directed Inspections:

The purpose of the directed inspections was to review study C-01-92 and related on-site documentation and verification by site personnel regarding the concern about the reliability of the safety data that was reported for subjects 8503 and 5905, who were enrolled at site 3795 (Dr. Kim) and site 3812 (Dr. Zora), respectively. The sponsor reported that each of the subjects had either a pre-existing nasal perforation or physical conditions predisposing the subjects to the perforations. However, the case report forms that would appear to support the sponsor's claim were altered in such a manner (e.g., different handwriting used

for the same visit, insertion of new information without dating or initialing, multiple sponsor requested changes or additions were made to the adverse event form, baseline medical history...) that would raise suspicion about the accuracy of the changed or inserted data recorded on these forms.

Note: These reviews are based on the discussions with the field investigator since the inspectional reports have not yet been received by DSI.

1. John A. Zora, M.D.
   Rx Research
   1990 Riverside Parkway
   Lawrenceville, GA 30043

The inspection was initiated on August 29, 2005. No 483 was issued. As per discussion with the field investigator who conducted the inspection, there were no significant findings and the sponsor reports were verified as accurate by the source documents and site personnel verification.

2. Kenneth T. Kim, M.D.
   2600 Redondo Avenue
   Fourth Floor, Suite 401
   Long Beach, CA 90806

The inspection was conducted from 8/9/05-8/16/05. No 483 was issued. As per discussion with the field investigator who conducted the inspection, there were no significant findings and the sponsor reports were verified as accurate by the source documents and site personnel verification. Of note, subject 8503 participates in a number of clinical trials; the perforation of the thin septal wall was reportedly from participation in repeated studies that included the use of nasal sprays. The subject failed to report this condition, however, it was reportedly documented in a prior study.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

In general, the sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The inspection of documents support that audited subjects exist, met eligibility criteria, received assigned study medication, adhered to protocol and signed informed consent, with a few exceptions. The inspection documented regulatory violations at Dr. Gawchik's site for protocol violations.

There were no significant discrepancies noted with the data listings and source documents at each site.

The For-Cause/Directed inspections verified that the sponsor reported safety data appeared to be accurate for subjects 8503 and 5905.

The data submitted in support of this NDA appear to be acceptable.

Follow-up action: None needed.

[Note: The review of the For-Cause/Directed Inspections was based on the discussions with the field investigators since the inspectional reports have not yet been received by DSI. Should the final review of EIRs and exhibits contain information that would significantly effect the classification or have an impact on the approval process, I will inform the Review Division in an amendment.]

{See appended electronic signature page}

Ele Ibarra-Pratt, R.N., MPH
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Elinita Ibarra-Pratt
9/23/2005 02:03:43 PM
CSO

Leslie Ball
9/23/2005 02:54:03 PM
MEDICAL OFFICER

NDA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

NDA # 21-861 Supplement # Efficacy Supplement Type SE-

Trade Name: Patanase Nasal Spray
Established Name: olopatadine hydrochloride
Strengths: 0.6%

Applicant: Alcon, Inc.
Agent for Applicant:

Date of Application: 12/24/04
Date of Receipt: 12/27/04
Date clock started after UN:
Date of Filing Meeting: 2/10/05
Filing Date: 2/25/05
Action Goal Date (optional): User Fee Goal Date: 10/27/05

Indication(s) requested: Management and treatment of the symptoms of seasonal and perennial allergic rhinitis

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☒ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the*

product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

? Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☒ NO ☐
If yes, explain: New clinical investigations required for approval of this indication.

? Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☐

? If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

? Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
If yes, explain:

? If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

? Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

? Was form 356h included with an authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. agent must sign.

? Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
If no, explain:

? If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:

? If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☐ YES ☒ NO ☐

? Is it an electronic CTD (eCTD)? N/A ☐ YES ☒ NO ☐
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments: eCTD, but complete paper copies also provided

? Patent information submitted on form FDA 3542a? YES ☒ NO ☐

? Exclusivity requested? YES, 3 Years NO ☐
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

? Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it 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 this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

? Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

? Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

? PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

? Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

? List referenced IND numbers: I60116

? End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☐
If yes, distribute minutes before filing meeting.

? Pre-NDA Meeting(s)? Date(s) _____ NO ☐
If yes, distribute minutes before filing meeting.

Project Management

? Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
If no, request in 74-day letter.

? All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
YES ☐ NO ☐

? Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐

? Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐

? MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☐ YES ☐ NO ☐

? If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

? OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

? Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

? If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

Chemistry

? Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐

? Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐

? If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: 2/10/05

BACKGROUND: Patanase (olopatadine hydrochloride) Nasal Spray 0.6% for the management and treatment of seasonal and perennial allergic rhinitis.

(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: In addition to the reviewers listed below, others present a this meeting included Dr.s Chowdhury, Lostritto, Fadiran, McGovern, Wang and Sullivan

ASSIGNED REVIEWERS (including those not present at filing meeting) : All assigned reviewers present

Discipline	**Reviewer**
Medical:	Lee
Secondary Medical:	Gilbert-McClain
Statistical:	Guo
Pharmacology:	J.Shah, reassigned to Bond
Statistical Pharmacology:	
Chemistry:	Bertha
Environmental Assessment (if needed):	
Biopharmaceutical:	Suarez
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Regulatory Project Management:	Zeccola
Other Consults:	

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☒ NO ☐
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ☒

PHARMACOLOGY N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☒

CHEMISTRY FILE ☐ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Microbiology YES ☒ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Anthony M. Zeccola, M.A.
Regulatory Project Manager, HFD-570

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

   *If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   *If "**No**," skip to question 5. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

   ***NOTE:** If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ☐

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☐

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☐ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES ☐ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A ☐ YES ☐ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A ☐ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

    - Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

      YES ☐ NO ☐

    - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

      YES ☐ NO ☐

    - EITHER

      The number of the applicant's IND under which the studies essential to approval were conducted.

      IND# _____ NO ☐

      OR

      A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

      YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

    YES ☐ NO ☐

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

/s/

Anthony Zeccola
8/31/2005 03:07:16 PM
CSO