CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-861s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-861

Alcon Research, Ltd.
6201 South Freeway
Fort Worth, TX 76134-2099

Attention: Seane Jones, M.S.
Associate Director, Regulatory Affairs

Dear Ms. Jones:

Please refer to your new drug application (NDA) dated December 24, 2004, received December 27, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Patanase Nasal Spray (olopatadine hydrochloride) 665 mcg.

We also refer to your amendments dated: February 3, April 6, 11 (2), 14, May 2, June 27, and July 11 (2), 14 (2), 18 and 22, 2005.

We also acknowledge receipt of your submission dated July 11, 2005. This submission was not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

1. 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. Therefore, the use of povidone in the proposed commercial formulation may be, in part or wholly, responsible for the nasal irritation and damage to the nasal mucosa. To support the approval of olopatadine as a nasal spray product for treatment of symptoms of allergic rhinitis, you will need to reformulate the drug product (e.g., remove or lessen the povidone concentration) to lessen the nasal toxicity and perform studies to confirm the reformulation has had its intended effects.

2. (b) (4)

(b) (4)

The deficiencies listed below were communicated to you in a Discipline Review letter dated April 25, 2005. A number of the deficiencies are related to the proposed commercial formulation that contains povidone. Depending on the extent of the reformulation that may be necessary to alleviate the safety concerns, much of the current CMC information including those in your July 11, 2005, submission will need to be revised or updated.

3. Tighten the acceptance criterion for the drug product formulation pH to reflect the release and stability data. There is no indication in the pharmaceutical development report (3.2.P.2.1.1) or in the drug product stability section (3.2.P.8.3) that the pH range could not be tightened (b) (4)

4. (b) (4)

5. (b) (4)

6. Clarify what are the acceptance criterion for pH range of the bulk formulation when tested as an in-process control during production. In-process control criteria in table 3.2.P.3.4-1 indicate the criterion is (b) (4) but the "target" in table 3.2.P.3.4-2 for the tested bulk formulation is (b) (4)

7. (b) (4)

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44. Revise the HOW SUPPLIED section of the Package Insert and the Patient's Instructions for Use to indicate that the correct amount of medication in each spray can not be assured after the labeled number of sprays have been dispensed, even if the unit is not completely empty.

45. Revise the Patient's Instructions for Use to include instructions for the patient to keep a count of the number of sprays that have been used since the nasal spray units do not have an incorporated counter mechanism.

46. Provide the calculations that were done to estimate that the increased use of the olopatadine would not lead to and expected introduction concentration into the environment of more than one (1) part per billion. Your reference to exhibit 4.A.5-1 in 3.A.9 could not be located in the application.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division of Pulmonary and Allergy Products regarding the extent and format of your safety update prior to responding to this letter.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the

application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Pulmonary and Allergy Drug Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Anthony M. Zeccola, Senior Regulatory Management Officer, at (301) 796-1318.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Badrul Chowdhury

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