CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-861s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-861 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: 12/27/04 **Action Date:** 10/27/05

HFD 570 **Trade and generic names/dosage form:** Patanase (olopatadine) Nasal Spray 3S

Applicant: Alcon, Inc **Therapeutic Class:**

Indication(s) previously approved: _____

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: Management and Treatment of Symptoms Seasonal Allergic Rhinitis

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

X **No: Please check all that apply:** X **Partial Waiver** X **Deferred** X **Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min	**kg**	**mo.**	**yr.** 0	**Tanner Stage**
Max	**kg**	**mo.**	**yr.** <2	**Tanner Stage**

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- X **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

- ❑ **Other:**_____

Section C: Deferred Studies

Age/weight range being deferred:

Min ____ **kg**____ **mo.**____ **yr.** 2 **Tanner Stage**____
Max____ **kg**____ **mo.**____ **yr.** <12 **Tanner Stage**____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- **X** **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____ **kg**____ **mo.**____ **yr.** 12 **Tanner Stage**____
Max____ **kg**____ **mo.**____ **yr.** <18 **Tanner Stage**____

Comments:

Indication #2: **Management and Treatment of Symptoms Perennial Allergic Rhinitis**

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**

X **No: Please check all that apply: X Partial Waiver X Deferred X Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min ____	**kg**____	**mo.**____	**yr.** 0	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.** <2	**Tanner Stage**____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- **X** **Disease/condition does not exist in children less than 6 months of age**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- **X** **Other: Inappropriate formulation for <2 years of age**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____ **kg**____ **mo.**____ **yr.** 2 **Tanner Stage**____
Max____ **kg**____ **mo.**____ **yr.** <12 **Tanner Stage**____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- **X** **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____ **kg**____ **mo.** 12 **yr.**____ **Tanner Stage**____
Max____ **kg**____ **mo.** <18 **yr.**____ **Tanner Stage**____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Anthony M. Zeccola, M.A.
Senior Regulatory Management Officer

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/s/

Anthony Zeccola

10/27/2005 12:15:08 PM

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21861 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: Resubmission 9-27-07 **PDUFA Goal Date:** 3-27-08

HFD 570 **Trade and generic names/dosage form:** Patanase (olopatadine)Nasal Spray

Applicant: Alcon, Inc. **Therapeutic Class:** Respiratory

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- x **Yes. Please proceed to the next question.**
- ❑ **No. PREA does not apply. Skip to signature block.**

**** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.***

Indication(s) *previously approved* (please complete this section for supplements only): N/A

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): ONE

Indication #1: Management and Treatment of Symptoms of Seasonal Allergic Rhinitis

Is this an orphan indication?

- ❑ **Yes. PREA does not apply. Skip to signature block.**
- x **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**
- X **No: Please check all that apply:** xx **Partial Waiver** xx **Deferred** xx **Completed**

PPSR submitted 3-20-07; WR issues to Alcon 7-23-07. Patients currently being enrolled. Data to be submitted by 7-1-09. (ages 2-12) Waiver requested for patients under 2 yrs of age.

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr.___0__ Tanner Stage_____
Max_____ kg_____ mo._____ yr.___2__ Tanner Stage_____
Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

X Other: It is unlikely that Patansase Nasal Spray would be used in children <2; non-pharmacologic treatment options would be used; impractical to treat children <2 with nasal sprays.

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr.___2__ Tanner Stage_____
Max_____ kg_____ mo._____ yr.___12__ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**

X There are safety concerns

- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): ____7-1-09_____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr.__12__ Tanner Stage_____
Max_____ kg_____ mo._____ yr.__18__ Tanner Stage_____

Comments: Clinical studies enrolled subjects down to 12 years of age.

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered

into DFS.

This page was completed by:

{See appended electronic signature page}
_____*Miranda Raggio*_____
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- ❑ **Yes. PREA does not apply. Skip to signature block.**
- ❑ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**
- ❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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/s/

Miranda Raggio

3/4/2008 01:14:33 PM

NDA 21-861

We are currently reviewing your NDA submission dated September 26, 2007, received September 27, 2007, for Patanase Nasal Spray and have the following labeling comments.

If you have any questions, contact Miranda Raggio, Regulatory Project Manager, 301-796-2109.

NDA 21-861

Drafted by Miranda Raggio/3-27-08

Initialed by Sandy Barnes/3-27-08
Sally Seymour/3-27-08

Finalized by Miranda Raggio/3-27-08

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/s/

Miranda Raggio
3/27/2008 12:11:56 PM
CSO

NDA 21-861

We are currently reviewing your NDA submission dated September 26, 2007, received September 27, 2007, for Patanase Nasal Spray and have the following labeling comments (the revised PI follows the comments). Submit a response by COB today, if possible, or early tomorrow morning at the latest.

General

- The indication was revised to relief of the symptoms of SAR. This is consistent with recently approved antihistamines (e.g. Xyzal). We make a distinction between the relief of symptoms with antihistamines and the treatment of SAR for corticosteroids because corticosteroids are thought to affect the underlying inflammation. We note some older antihistamines (e.g. Astelin Nasal Spray) may have the treatment of SAR indication; however, we plan to address this when the label is converted to the PLR format. Please also revise accordingly in the PPI.

- Revise the second sentence of the last paragraph of PPI as follows. (b) (4)

- When using the term H1 receptor, please make the 1 a subscript.

- "Twice-daily" was changed to "twice daily" for consistency throughout the label.

- There still appear to be formatting problems in some paragraphs with early returns and extra spaces. Please revise accordingly.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PATANASE® Nasal Spray safely and effectively. See full prescribing information for PATANASE Nasal Spray.
PATANASE (olopatadine hydrochloride) Nasal Spray
Initial U.S. Approval: 1996
----------INDICATIONS AND USAGE----------
PATANASE Nasal Spray is an H_1 receptor antagonist indicated for the (b) (4) relief of the symptoms of seasonal allergic rhinitis in patients 12 years of age and older. (1)
----------DOSAGE AND ADMINISTRATION----------
For intranasal use only.
The recommended dose of PATANASE Nasal Spray in patients 12 years and older is two sprays per nostril twice daily (2).
Priming Information: Prime PATANASE Nasal Spray before initial use and when PATANASE Nasal Spray has not been used for more than 7 days. (2.2)
----------DOSAGE FORMS AND STRENGTHS----------
Nasal spray 0.6%: 665 mcg of olopatadine hydrochloride in each 100- microliter spray. (3) Supplied as a 30.5 g bottle containing 240 sprays.
----------CONTRAINDICATIONS----------
None.
----------WARNINGS AND PRECAUTIONS----------
• Epistaxis, nasal ulceration, and nasal septal perforation. Monitor patients periodically for signs of

9 pp withheld immed after this page as (b)(4) draft labeling

If you have any questions, please contact Miranda Raggio, Regulatory Project Manager, at 301-796-2109.

NDA 21-861

Drafted by Miranda Raggio/3-26-08
Initialed by Sally Seymour/3-26-08
Badrul Chowdhury/3-26-08
Finalized by Miranda Raggio/3-26-08

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/s/

Miranda Raggio
3/26/2008 02:49:18 PM
CSO

NDA 21-861

We are currently reviewing your NDA submission dated September 26, 2007, received September 27, 2007, for Patanase Nasal Spray. We have the following comments pertaining to the SPL DLDE table:

1. Revise the single entry of "hydrochloric acid and/or sodium hydroxide to adjust pH" to two separate entries of "hydrochloric acid" and "sodium hydroxide."

2. Revise the entry for "dibasic sodium phosphate" to (b) (4)

3. Revise the entry for "purified water" to (b) (4)

4. Revise the strength of the active to be given in terms of the micrograms of drug substance per volume of formulation, not weight of formulation.

We request that you provide a statement agreeing to these revisions with your revised labeling.

If you have any questions, please contact Miranda Raggio, Regulatory Project Manager, at 301-796-2109.

NDA 21-861

Drafted by Miranda Raggio/3-18-08
Initialed by Sandy Barnes/ 3-25-08
Craig Bertha/per phone call from Sandy Barnes/March 25, 2008
Finalized by Miranda Raggio/March 25, 2008

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/s/

Miranda Raggio
3/25/2008 01:56:12 PM
CSO

Miranda Raggio
3/25/2008 01:56:39 PM
CSO

NDA 21-861

We are currently reviewing your NDA submission dated September 26, 2007, received September 27, 2007, for Patanase Nasal Spray and have the following labeling comments. These comments reflect changes discussed in the March 20, 2008, teleconference. Further edits may follow.

Highlights

1. Initial US Approval should only include the year per 21 CFR 201.57(a)(3).
2. Revision date should be updated.
3. There should be a white space between major headings.

FPI

1. Add a separate subheading under section 2 titled 'Administration Information' and move the priming information there.
2. In Section 5.1, sentence removed from end of first paragraph as discussed in the March 20, 2008, labeling teleconference for consistency with Warning language.
3. In Section 6, numbers revised in first sentence to reflect exposure to Patanase.
4. In Section 12.1, we included the term 'selective' as this has been used in other labels (e.g. Xyzal).
5. Include the manufactured by and for information at the end of Section 17.
6. There are general formatting issues throughout the label. Please revise accordingly to eliminate spaces in the middle of sentences or early returns.

PPI and PIU

1. As discussed in the teleconference, the PPI and PIU have extensive revisions primarily to provide information in more patient friendly terms. There appear to be more issues with the formatting of the PIU as compared to the PPI. Revise accordingly. Include the figures requested in the document.
2. Your PPI indicates that the PIU will follow, but you currently have in opposite order. Please address this discrepancy.

Carton

1. Revise the "t" in the trade name as discussed in the teleconference.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PATANASE® Nasal Spray safely and effectively. See full prescribing information for PATANASE Nasal Spray.
PATANASE (olopatadine hydrochloride) Nasal Spray
Initial U.S. Approval: (b) (4) **1996**
----------**INDICATIONS AND USAGE**----------
PATANASE Nasal Spray is an H_1 receptor antagonist indicated for the (b) (4) of the symptoms of seasonal allergic rhinitis in patients 12 years of age and older. (1)
----------**DOSAGE AND ADMINISTRATION**----------
For intranasal use only.
The recommended dose of PATANASE Nasal Spray in patients 12 years and older is two sprays per nostril twice-daily (2).
Priming Information: Prime PATANASE Nasal Spray before initial use and when PATANASE Nasal Spray has not been used for more than 7 days. (2.2)
----------**DOSAGE FORMS AND STRENGTHS**----------

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NDA 21-861

Drafted by Miranda Raggio/3-124-08

Initialed by Sandy Barnes/3-24-08
Sally Seymour/3-24-08
Badrul Chowdhury/3-24-08
Finalized by Miranda Raggio/3-24--08

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/s/

Miranda Raggio
3/24/2008 04:17:32 PM
CSO

Miranda Raggio
3/24/2008 04:17:49 PM
CSO

We are currently reviewing your NDA submission dated September 26, 2007, received September 27, 2007, for Patanase Nasal Spray and have the following labeling comments. These comments are the initial labeling recommendations. Additional labeling recommendations may follow.

General

- Refer to your product consistently as Patanase Nasal Spray throughout the label; however, the established name and Trade Name are still under review.
- Language that was promotional in nature was removed. (b) (4)
- The trademark should not appear in the Highlights portion of the label. It is preferable that the trademark symbol also does not appear in the FPI. However, you may choose to use the trademark symbol once - at the beginning of the FPI. Remove the trademark from the rest of the label.
- Provide information represented by x, y, z throughout the label.
- The Adverse Reaction section (6) is still under review within the Agency. The data set that forms the basis of adverse reaction analyses and the table may change. In the interim, expand the table to report down to 0.5% frequency.

Highlights

- The initial US approval date refers to the date that FDA initially approved the new molecular entity, olopatadine. Insert the date to reflect the initial approval date for olopatadine.
- Priming information was added as this is important handling information.
- The warning regarding sedation and activities requiring mental alertness was included to reflect the clinical trial data and post-marketing data with oral olopatadine.
- Drug Interactions was deleted as there are no drug interaction studies with your product.
- Special Populations was deleted as there is limited information in the special populations and there is no recommendation for dose adjustment.

FPI

- Update the Table of Contents to reflect changes to the FPI.
- In Section 1, the (b) (4) were removed from the indication as (b) (4) typically are not included in the indication for SAR. This is consistent with other products recently approved for SAR.
- In Section 2, priming information was moved to be consistent with other product labels.
- In Section 5, the warning regarding sedation and activities requiring mental alertness was included to reflect the clinical trial data and post-marketing data with oral olopatadine.
- In Section 6.2, include post-marketing data for the oral formulation of olopatadine.

- In Section 7, metabolism information was moved to Section 12.3
- In Section 8.1, the reproductive toxicology findings for labeling a pregnancy category C were added.
- Section 10 needs to be substantially modified. Remove statement such as (b) (4) [redacted]
- In Section 12.1, promotional language and information implying (b) (4) [redacted] (also promotional) were removed.
- In Section 12.2, please provide the requested information.
- In Section 13.1, the findings regarding the impairment of fertility in rats were added.
- In Section 13.2, pharmacology information with a reference was removed. Instead, detailed animal reproductive toxicology findings were added.
- The references were removed (Section 15) as they are not necessary for the safe and effective use of Patanase.
- Section 17 was expanded to include the additional Warnings

Patient Information

- Provide pronunciation for Patanase.
- Ensure that you use consumer friendly language throughout the Patient Information leaflet.

Patients Instructions for Use

- Please submit the PIU in a format appropriate for editing, with the figures if possible. (b) (4) [redacted]
- Consider a figure showing the parts of Patanase Nasal Spray.

Carton and Container Labeling

- Decrease the prominence of the company name on the container label so that it does not compete with the prominence of the drug name.
- Decrease the prominence of the main graphics (i.e. nasal spray with mist) and relocate it away from the principal display panel so that it does not compete with the prominence of the drug name. See 21 CFR 201.15(a)(6) and 21 CFR 201.10(g)(2). *(carton label)*

- Remove the spray graphic above the letter "t" in the trademark "Patanase" as it obscures and crowds the proprietary name. In addition, by increasing the prominence of the proprietary name, the presence of the graphic decreases the relative prominence of the established name. See 21 CFR 201.15(a)(6) and 21 CFR 201.10(g)(2).
- Change the font color of the information written against the blue background of the top third of the carton label or change the blue background so that the information can be easily read.
- Include the route of administration (i.e. For Intranasal Use Only) per 21 CFR 201.100(b)(3).
- Increase the size of the established name so that it is at least ½ size of the proprietary name in its font length and width per 21 CFR 201.10(g)(2).
- Replace the abbreviation for hydrochloride in the established name, i.e., "HCl" with "hydrochloride."
- Move the dosage form descriptor "nasal spray" next to the established name "olopatadine hydrochloride" outside of the parentheses surrounding the established name "olopatadine hydrochloride," e.g. PATANASE® (olopatadine hydrochloride) Nasal Spray. Revise the font and color of the dosage form descriptor such that it is the same as that used for the established name.
- The strength "665 mcg" should be close to or below the established name and dosage form descriptor.

The strike-out versions of the Patanase PI and PPI are below.

20 pp withheld immed after this page as (b)(4) draft labeling

NDA 21-861

Drafted by Miranda Raggio/3-13-08
Initialed by Sally Seymour/3-13-08
Badrul Chowdhury/3-13-08
Finalized by Miranda Raggio/2-27-08

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/s/

Miranda Raggio
3/13/2008 01:58:56 PM
CSO

NDA 21-861

We are currently reviewing your NDA submission dated September 26, 2007, received September 27, 2007, for Patanase nasal spray and have the following request for information:

Provide the following tables, modeled after tables in your integrated summary of safety (for example, Table 5-1 and 5-2 of Section 2.7.4.-5):

a. Summary tables of subjects discontinuing study C-02-10 because of adverse events by event term and treatment group, regardless of attribution of drug causality. The table should also include the total number of subjects and % of treatment group. Present the data coded in COSTART and MedDRA with COSTART-coded terms in one table and MedDRA terms in another.

b. Summary tables as in (a) for C-02-37.

c. Summary tables as in (a) for C-04-70. Omit the events in the azelastine treatment group.

d. Summary tables as in (a) combining treatment groups for trials C-02-10, C-02-37, and C-04-70.

We request that you provide the following information by February 29, 2008. Fax the document to my attention to 301-796-2798. The document will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio, Regulatory Project Manager, at 301-796-2109.

NDA 21-861

Drafted by Miranda Raggio/2-25-08
Initialed by Sandy Barnes/ 2-25-08
Jim Kaiser/2-25-08
Charles Lee/2-25-08
Finalized by Miranda Raggio/2-25-08

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/s/

Miranda Raggio
2/25/2008 05:35:06 PM
CSO

Miranda Raggio
2/25/2008 05:35:28 PM
CSO

NDA 21-861

Dear Ms. Jones:

We are reviewing your NDA for Patanase Nasal Spray and we have the following requests for information. We ask that you provide the response to these questions by the close of business on March 5, 2008.

1. Provide the following tables, modeled after tables in your integrated summary of safety (for example Tables 5-1 and 5-2 of Section 2.7.4.-5.):

    a. Summary tables of subjects (and % of treatment group) experiencing adverse events by event type, regardless of attribution of drug causality, occurring in trial C-02-10, by treatment group, presented separately as coded in COSTART and MedDRA. The COSTART-coded terms (olopatadine and control) should be in one table and MedDRA terms in another.

    b. Summary tables as in (a), for C-02-37.

    c. Summary tables as in (a), for C-04-70. Omit the events in the azelastine treatment group.

    d. Summary tables as in (a), combining treatment groups of trials C-02-10, C-02-37, and C-04-70.

    e. Summary tables as in (a), for C-01-92.

    f. Summary tables as in (a), for C-05-69.

2. Provide the case report form for subject 4955/7101, who experienced the adverse event "anaphylaxis" on April 1, 2007.

If you have any questions, please contact Miranda Raggio at 301-796-2109.

NDA 21-861

Drafted by: LJ/2-21-08

Initialed by: Barnes
Kaiser
Lee

Filename: N21861IR.doc

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/s/

Ladan Jafari
2/21/2008 04:14:52 PM
CSO

NDA 21-861

We are currently reviewing your NDA submission dated September 26, 2007, received September 27, 2007, for Patanase nasal spray. We request that you provide the following information by January 10, 2008.

Clarify the method of classifying adverse events from Sections A and B of the nasal examination in clinical trial C-05-69,. Your response should address the following issues:

a. Provide the adverse event terms to which Sections A and B findings were coded (for example, "blood in the nose" in Section A and "epistaxis" as an adverse event term), and the proportion of the subjects for each term, separated by treatment group, that derived from Section A or B, respectively.

b. Section 12.5.1 of the protocol states that "a Grade I or II epithelial erosion translated to an adverse event with a code of nasal ulceration." Table 14.3.1.3.1-1 shows that 39 subjects in the olopatadine treatment arm and 26 subjects in the vehicle treatment arm experienced the adverse event "ulcer nasal." However, Table 12.5.1.-5 shows that in the olopatadine treatment arm 41 subjects in the olopatadine treatment arm had an epithelial erosion (37 "Grade I" and 4 "Grade II") and 27 subjects in the placebo treatment arm had an epithelial erosion (27 "Grade I" and 1 "Grade II"). Provide an explanation for this discrepancy.

If you have any questions, please contact Miranda Raggio, Regulatory Project Manager, at 301-796-2109.

NDA 21-861

Drafted by Miranda Raggio/1-3-08
Initialed by Sandy Barnes/ 1-3-08
Charles Lee/1-3-08
Finalized by Miranda Raggio/1-3-08

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/s/

Miranda Raggio
1/3/2008 04:23:41 PM
CSO

Miranda Raggio
1/3/2008 04:24:18 PM
CSO

NDA 21-861

We are currently reviewing your NDA submission dated September 26, 2007, received September 27, 2007, for Patanese nasal spray. We request that you provide the following information by January 2, 2008.

Provide a tabulation of daily trial medication usage by treatment group and subject for one week prior to and one week after each visit at which a nasal examination abnormality was reported so that we can determine whether trial medication usage was decreased at or around the time of the finding of a "grade 1" or "grade 2" nasal physical exam abnormality.

A sample table is below:

Treatment group	Subject ID	date	finding	# of doses taken (am +pm = 2; am or pm only = 1)
active	xxxxxxxx	January 12, 2007		2
		January 13, 2007		2
		January 14, 2007		2
		January 15, 2007		2
		January 16, 2007		2
		January 17, 2007		2
		January 18, 2007	Grade 2	2
		January 19, 2007		2
		January 20, 2007		2
		January 21, 2007		2
		January 22, 2007		2
		January 23, 2007		2
		January 24, 2007		2
		January 25, 2007		2

In the table present subjects in order by investigator and subject ID. Group all subjects of one treatment group together. You may start with either treatment group.

If you have any questions, please contact Miranda Raggio, Regulatory Project Manager, at 301-796-2109.

NDA 21-861

Drafted by Miranda Raggio/December 13, 2007
Initialed by Sandy Barnes/December 13, 2007
Lydia Gilbert-McClain/December 13, 2007
Jim Kaiser/December 13, 2007

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/s/

Miranda Raggio
12/13/2007 12:13:30 PM
CSO

Miranda Raggio
12/13/2007 12:13:49 PM
CSO

NDA 21-861
November 14, 2007

Your NDA 21-861 for Patanase® Nasal Spray, submission dated September 26, 2007, is currently under review. We have the following requests for information:

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 table of contents for case report forms sorted by subject for trial C-05-69.

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

7. Provide electronic data and analysis programs for all the newly submitted controlled clinical studies, including documents that explain the data set, variable meaning, methods used for deriving variables, and SAS programs that generate the statistical analyses.

8. Submit the individual plasma concentrations of olopatadine in a tabulated format (time post-administration, concentration, treatment, etc.) and as a SAS transport file for study C-05-69 (randomized, double-blind, vehicle-controlled, parallel-group, long term safety study with efficacy component).

Submit a response by December 14, 2007, via facsimile correspondence to 301-796-9728. Submit the response in the form of an amendment in triplicate to the IND, as well.

If you have any questions please contact Miranda Raggio, Regulatory Project Manager, at 301-796-2109.

NDA 21-861
November 14, 2007

Drafted by M. Raggio/November 14, 2007
Initialed by Sandy Barnes, Sandra Suarez, Qui Wei, Ted Guo, Qian Li, Jim Kaiser, Charlie Lee/November 14, 2007
Finalized by M. Raggio/November 14, 2007

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/s/

Miranda Raggio
11/14/2007 03:37:03 PM
CSO

Miranda Raggio
11/14/2007 03:37:30 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Division of Drug Marketing, Advertising, and Communications (DDMAC)

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Miranda Raggio, Regulatory Project Manager, OND/ODEII/DPAP 301-796-2109

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 13, 2007		21-861	Resubmission (BZ)	September 26, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Patanase (olopatadine hydrochloride) Nasal Spray		3	February 11, 2008

NAME OF FIRM: Alcon

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☒ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: NDA 21-861 was originally submitted December 24, 2004. We issued a Not-Approvable action on October 27, 2005. Please perform a DDMAC review of this resubmission. The PDUFA goal date is March 27, 2008. If you have any questions, please contact me at 301-796-2109.
SPL is not available in the EDR at this time. We are working on this issue. I will send a PDF of the labeling via email.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Miranda Raggio, RN, BSN, MA	☒ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Miranda Raggio

11/13/2007 12:05:48 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION
TO: *(Division/Office)* James McVey, Ph.D., Director, New Drug Microbiology Staff Team Leader (OPS)	FROM: Miranda Raggio, RPM, Division of Pulmonary and Allergy Products, ODEII, OND 301-796-2109

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
16-OCT-2007	I60,116	21-861	Resubmission	26-SEP-2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Patanase® (olopatadine hydrochloride nasal spray)	3	S	15-JAN-2008

NAME OF FIRM: Alcon Inc.

REASON FOR REQUEST

I. GENERAL

9 NEW PROTOCOL 9 PROGRESS REPORT 9 NEW CORRESPONDENCE 9 DRUG ADVERTISING 9 ADVERSE REACTION REPORT 9 MANUFACTURING CHANGE/ADDITION 9 MEETING PLANNED BY	9 PRE-NDA MEETING 9 END OF PHASE II MEETING 9 RESUBMISSION 9 SAFETY/EFFICACY 9 PAPER NDA 9 CONTROL SUPPLEMENT	9 RESPONSE TO DEFICIENCY LETTER 9 FINAL PRINTED LABELING 9 LABELING REVISION 9 ORIGINAL NEW CORRESPONDENCE 9 FORMULATIVE REVIEW : OTHER *(Specify below)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
9 TYPE A OR B NDA REVIEW 9 END OF PHASE II MEETING 9 CONTROLLED STUDIES 9 PROTOCOL REVIEW 9 OTHER	9 CHEMISTRY 9 PHARMACOLOGY 9 BIOPHARMACEUTICS 9 OTHER

III. BIOPHARMACEUTICS

9 DISSOLUTION 9 BIOAVAILABLITY STUDIES 9 PHASE IV STUDIES	9 DEFICIENCY LETTER RESPONSE 9 PROTOCOL-BIOPHARMACEUTICS 9 *IN-VIVO* WAIVER REQUEST

IV. DRUG EXPERIENCE

9 PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL 9 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES 9 CASE REPORTS OF SPECIFIC REACTIONS *(List below)* 9 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	9 REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY 9 SUMMARY OF ADVERSE EXPERIENCE 9 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

9 CLINICAL	9 PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please evaluate the microbial limits methods (b) (4) and (b) (4) (3.2.P.5.2, vol. 10, module 3, Tabs 36 and 37), the microbial limits specification acceptance criteria for the drug product (Table 3.2.P.5.1-1 in 3.2.P.5.1, vol. 10, module 3, pp. 1-2), and preservative effectiveness testing and other microbiological information (3.2.P.2.5 including tabs 1-8, vols. 9-10, module 3).

cc: Orig. NDA # 21-861
OND/DPAP/Div. File

ONDQA/DIV 1/AAl-Hakim/CBertha OPS/Microbiology/JMcVey OND/DPAP/SBarnes/MRaggio	
SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)* 9 MAIL XX 9 HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Miranda Raggio

10/17/2007 01:54:23 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO: *(Division/Office)* J. Sun, Ph.D., Pharmacology Team Leader (DPAP)			FROM: Craig M. Bertha (ONDQA/Div 1)	
DATE 16-OCT-2007	IND NO. I60,116	NDA NO. 21-861	TYPE OF DOCUMENT Original	DATE OF DOCUMENT 26-SEP-2007
NAME OF DRUG Patanase (olopatadine HCl nasal spray)		PRIORITY CONSIDERATION 3	CLASSIFICATION OF DRUG S	DESIRED COMPLETION DATE 16-JAN-2008
NAME OF FIRM: Alcon, Inc.				

REASON FOR REQUEST

I. GENERAL

□ NEW PROTOCOL □ PROGRESS REPORT □ NEW CORRESPONDENCE □ DRUG ADVERTISING □ ADVERSE REACTION REPORT □ MANUFACTURING CHANGE/ADDITION □ MEETING PLANNED BY	□ PRE-NDA MEETING □ END OF PHASE II MEETING □ RESUBMISSION □ SAFETY/EFFICACY □ PAPER NDA □ CONTROL SUPPLEMENT	□ RESPONSE TO DEFICIENCY LETTER □ FINAL PRINTED LABELING □ LABELING REVISION □ ORIGINAL NEW CORRESPONDENCE □ FORMULATIVE REVIEW ☒ OTHER *(Specify below)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER	☐ CHEMISTRY ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER

III. BIOPHARMACEUTICS

☐ DISSOLUTION ☐ BIOAVAILABLITY STUDIES ☐ PHASE IV STUDIES	☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL-BIOPHARMACEUTICS ☐ *IN-VIVO* WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)* ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: See attached.

cc: Orig. NDA # 21-861
OND/DPAP/Div. File
ONDQA/DIV 1/AAl-Hakim/CBertha
OND/DPAP/JSun
OND/DPAP/SBarnes/MRaggio

SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)* ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Please evaluate the applicant's response to comment 37 of the 27-OCT-2005, NA letter that resulted from the 15-JUN-2005, consult review (G. Bond, Ph.D.).

Tighten the acceptance criteria for the (b) (4) *and* (b) (4) *degradants in the drug product to less than (<)* (b) (4) *relative to the olopatadine, or conduct a carcinogenicity assay with the isolated impurities. This is based on the positive genotoxicity results of* (b) (4) *and* (b) (4) *(Mouse Lymphoma Assays and Syrian Hamster Embryo Assays).*

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/s/

Ali Al-Hakim

10/16/2007 04:05:32 PM

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 76234-2009

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

Dear Ms. Jones:

We acknowledge receipt on September 27, 2007 of your September 26, 2007, resubmission to your new drug application for Patanase Nasal Spray (olopatadine hydrochloride).

We consider this a complete, class 2 response to our October 27, 2005, action letter. Therefore, the user fee goal date is March 27, 2008.

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. We note that you have not fulfilled the requirement. We are deferring submission of your pediatric studies until July 1, 2009. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of section 2 of the Pediatric Research Equity Act (PREA) within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

If you have any question, call Miranda Raggio, Regulatory Project Manager, at (301) 796-2109.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Chief, Project Management Staff
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Miranda Raggio
10/15/2007 02:57:16 PM
Signing for Sandy Barnes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 30, 2006

TIME: 10:00 AM

LOCATION: White Oak Conference Room 1415

APPLICATION: NDA 21-861 Patanase Nasal Spray

FDA Representatives:

Badrul Chowdhury, M.D., Ph.D., Division Director
Emmanuel Fadiran, Ph.D., Clinical Pharmacology Team Leader
Lydia Gilbert-McClain, M.D., Medical Team Leader
Shinja Kim, Ph.D., Clinical Pharmacology Reviewer
Charles Lee, M.D., Medical Officer
Joseph Sun, Ph.D., Pharmacology/Toxicology Team Leader
Anthony M. Zeccola, M.A., Senior Regulatory Management Officer

Alcon Laboratories Representatives:

Michael Pfleger, JD, Vice President, Regulatory Affairs
Seane Jones, MS, Associate Director, Regulatory Affairs
Michael Wall, Ph.D., Senior Director, Pharmaceutical Product Development
Leslie Lemke, Ph.D., Senior Toxicologist
Scott Krueger, Ph.D., Vice President, Pharmaceutical Product Development
Joe Hiddemen, Ph.D., Vice President, Pre-Clinical Sciences
Masood Chowhan, Ph.D., Senior Director, Otic/Nasal Research Support
David Wells, BS, Senior Product Safety Specialist
(b) (4)

Background

Alcon Laboratories submitted a Type C meeting request dated May 6, 2006, to discuss their path forward in response to the FDA Not Approvable letter dated October 27, 2005, which contained a list of questions to be discussed at this meeting. Upon review of the briefing fax package, the division responded to Alcon's questions via fax on June 28, 2006. The content of that fax is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. Alcon's questions are in ***bold italics***; FDA's response is in *italics*; meeting discussion is in normal font following the FDA responses to Alcon's questions.

Clinical Questions

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 reduction in PVP, 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?***

   Although we do not agree that clinical equivalency of products can be based on results from different environmental chamber studies, we generally agree with your approach of bridging and agree that an additional SAR study may not be necessary to support efficacy of your product in SAR. To support the bridging strategy, we will expect that the completed study report for C-05-64 demonstrates similar efficacy to studies C-01-83 and C-03-52. In addition, we would expect demonstration of efficacy in a similar disease, e.g., perennial allergic rhinitis (see response to Clinical Question 5).

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?***

   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 for the final label, as long as 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?

We disagree with your statement that the one-year clinical trial demonstrated safety of Patanase. In fact, safety of Patanase was not established, for which the product was not approved for marketing in the United States. You correctly note that the major safety concerns with the product were unacceptable high frequencies of nasal irritation and damage to the nasal mucosa at the proposed labeled dose.

Provided the assumptions you are making hold (e.g., the reformulated product stays as a solution, systemic exposure is not expected to change, etc.,) it will be acceptable to rely on the original NDA for cardiovascular safety and other systemic safety. Therefore, it is not necessary to included ECGs and laboratory studies as safety endpoints in your new clinical trial.

We disagree that the new clinical trial C-05-69 should be designed to establish nasal safety only. This new clinical trial will provide the long-term safety data needed to support approval and labeling of your product and should be a standard long term safety study focusing on both nasal and non-nasal adverse events, physical examinations, vital signs, etc.

4. ***The FDA raised concerns over the incidence of local nasal effects (epistaxis, ulceration, and septal perforation) in implicated PVP as the contributing component of the formulation. The FDA required Alcon to lessen or remove PVP. 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 clinically demonstrate that the reformulation of Patanase to a lower level of PVP (b) (4)) has had its intended effect, Alcon proposes a three-month clinical nasal safety study of 900 patients (Patanase vs. vehicle vs. Astelin) to closely examine the local nasal effects of the reduced PVP formulation.***

    - ***Based on the analysis demonstrating that the key adverse events are not related to duration of exposure, does the Agency agree that three months of exposure to Patanase (b) (4) PVP) is sufficient to demonstrate that the reformulation has had its intended effect?***
    - ***Does the Agency agree that exposure of an additional 300 patients is sufficient to assess the nasal safety of the reduced PVP formulation?***

We agree that the rates of epistaxis and nasal ulceration were independent of the duration of exposure to test article. However, the data are insufficient to conclude that the rate of nasal septal perforation is independent of the duration of exposure. Furthermore, as you point out in your safety discussion, the safety data do not suggest that there is any relationship suggestive of a progression from epistaxis and/or nasal ulceration to nasal septum perforation. Hence, these events cannot be used as a surrogate signal for the future development of nasal septum perforation.

Therefore, we do not agree that an exposure of an additional 300 patients to the new formulation in a three month study is sufficient. Longer term safety data from a reasonably large sample size will be necessary to support safety of your product. Twelve months of safety data will be necessary to support the safety of your reformulated product. Alternatively, you may provide six months of safety data for a larger number of patients exposed to the reformulated product.

Alcon asked if 300 patients in a 6 month study would be acceptable. Dr. Lee agreed that 300 patients per treatment arm would be acceptable. Dr. Chowdhury added that extending a subset of patients beyond 6 months is recommended. It would be acceptable to submit the data for the 12 month subset at a later time; perhaps as part of the safety update for the response. The safety decision would be based on the 6 month data, the subset would be used as supporting data.

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 (b) (4) PVP (see safety discussion in Tab 2). Does the Agency agree that the proposed nasal exam and classification are acceptable?***

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. Note that 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 study staff is to prime the bottles and the bottles are of different shapes and sizes and the tips are of different appearances.

- *History of ulcers or medical treatment for epistaxis should 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 random 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. You may choose to conduct this study in patients with perennial allergic rhinitis (PAR). Demonstration of efficacy in such a study could form the basis of a PAR indication if you wish to pursue that.*

- *Any change in physical examination or vital signs should be reported as an adverse event. Provide an analysis of adverse events due to changes in physical examination and vital signs as well as an analysis of clinically relevant changes in physical examination and vital signs.*

- *Some epistaxis and other local nasal adverse events are to be expected with use of a nasal spray for the treatment of allergic rhinitis. Incidences of these events 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 if the results of this study show an incidence of epistaxis and other local nasal adverse events that are substantially lower than in other studies of olopatadine or in other products.*

- *Currently you do not have preclinical support for clinical studies longer than three months in duration. You must have preclinical data to support the proposed study duration.*

Regarding reporting of adverse events, Alcon wanted to confirm that the AEs seen in nasal exam after nasal irrigation would be acceptable. Dr. Lee confirmed that this would be acceptable.

Alcon indicated that they had intended to engage in patient education as a means of lowering overall AE rates, in an attempt to decrease the likelihood of nasal adverse events resulting from mechanical irritation due to improper administration of the medication. The Division acknowledged Alcon's intent, but noted that the use of very specialized and detailed education would make it very difficult to compare the results from this study with previously completed study C-01-92 or other nasal sprays. This study should not be specifically designed to assess the nasal safety of the product—it should be designed to assess the overall safety of the product. Dr. Chowdhury pointed out that in order for this study to be considered acceptable, the frequencies of epistaxis should be in the same range as study C-01-92 and other similar programs. If the overall frequency of epistaxis were to drop to zero, when history across the board shows an expected and consistent range of frequencies, the validity of the study results would be called into question.

Dr. Chowdhury advised Alcon that a study with two placebo arms (one arm with PVP and one arm without PVP) would be a better trial than a trial with an Astelin arm or a single placebo arm. If a study with olopatadine 0.6% and two placebo arms was performed, the results of all three arms would be taken into consideration. The Division pointed out that the second placebo arm would not be a requirement; it is a suggestion to make it a stronger study. The point of the two placebo arms would be to try to determine if, in fact, the PVP excipient is responsible for higher frequencies of nasal adverse events. If a two placebo, three arm study design is chosen, patients could be randomized to active drug at a higher ratio if necessary to allay IRB concerns. Alcon inquired as to whether it would be appropriate to split out the placebo groups for safety and pool for efficacy. Dr. Chowdhury said that we understand the rationale, but this would not be appropriate.

Regarding PK sampling, the Division pointed out that PK analyses will help to show compliance. These samples can be collected from as few as 25% of the patients at a few points in the program. The analysis should include sampling time-points and plasma concentrations of olopatadine measured, and samples from patients who received placebo and the safety of the drug should be analyzed.

6. ***Alcon proposes to rely on all other clinical data (e.g., renal impairment, dose response, etc.), other that local nasal safety data, previously submitted in NDA 21-861 for our final label. Doe the Agency agree?***

   This will be a review issue. In principle, we agree that you may rely on other clinical data as you propose.

   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?***

   We disagree with your contention that there are a limited number of sites that are qualified to participate in a long term safety study in allergic rhinitis patients.

   To support a broader applicability of your safety findings and for unrestricted use of the product, if approved, we suggest that sites previously used in the NDA should not participate in this study.

   Alcon stated their intention that two thirds of the study sites will be new with one third sites that previously participated. Dr. Lee said that the Division's concern is limiting clinical sites to only selected specially qualified or specialized sites, since it is anticipated that this product will be widely prescribed. Alcon acknowledged the Division's concerns. Dr. Lee stated that no more than one third of the sites participating should have previously participated in studies in the NDA. Dr. Chowdhury added that our concern is not just with the number and mix of sites, but also the number of patients from new and previously used sites.

8. ***Alcon anticipates the enrollment of some of the same patients previously used in NDA 21-861. Is this acceptable to the Agency?***

This is not acceptable. Enrollment of the same patients will compromise blinding and the validity of the study results.

Toxicology Questions

1. ***The Agency previously notified Alcon that a 6-month treatment duration would be required for the final reformulated product requalification study. Does the Agency agree that the following study design will be sufficient to support the approval of this product?***

   In order to validate the proposed 6-month intranasal study in rats, an additional positive control group (e.g., (b) (4) PVP) should be added. The study will be adequate to support the approval of the new formulation from a preclinical standpoint if the vehicle and the drug-treated groups are the NOAEL.

   During the meeting, Alcon provided a revised 3-month study protocol of different concentrations of PVP and wanted to know if they could add a 20 animals/sex/arm to extend the 3 month study to 6 months in order to satisfy this requirement. The study will include positive control. Dr. Sun stated that given what they are described, it appears acceptable. Alcon should formally submit the proposed 6-month extension intranasal study protocol for review. Furthermore the study must identify a NOAEL with adequate safety margin to support the new formulation. Dr. Sun said that this is crucial since the 6-month NOAEL might not be the same as the 3-month NOAEL.

   Given there were 3-month studies of the (b) (4) formulation submitted previously, Alcon may conduct the 6-month intranasal study in rats concurrently with the human clinical studies under the following conditions. (1) Provide the Agency with their rationale for this approach. (2) Submit a timeline, which should describe the timing of the animal studies, with respect to the timing of the human studies. (3) Submit their plan for addressing safety concerns in the event that the animal studies show adverse findings. Dr. Chowdhury noted that this is a risky approach, similar to the approach taken during the original program. Had the original program been conducted serially (i.e., completion of the animal studies prior to initiation of the clinical trials), rather than concurrently the original clinical trial would have been placed on hold. Dr. Chowdhury added that if Alcon chooses to conduct concurrent animal and human studies, their plan to address adverse findings in the animal studies would be critical. The human 6-month study may need to be put on clinical hold if the 6-month intranasal study in rats does not provide support for treatment duration longer than 3 months. Alcon replied that they will submit the 6-month intranasal study prior to initiation of 3rd month treatment in humans.

2. ***If the impurity profile of the reformulation product in the final package configuration are below ICH qualification thresholds when appropriately aged to predict end-of-shelf-life conditions, does the Agency agree that no further toxicological testing of aged product will be required?***

If the impurities/degradants are not structural alert/genotoxic/carcinogenic, no qualification is required if their acceptance criteria are below ICH qualification thresholds. Otherwise, they should be qualified (genotox and/or carcinogenicity testing) or their acceptance criteria be 0.1%. At this time we can not conclude that the local injection site sarcoma observed in the (b) (4) and (b) (4) transgenic carcinogenicity study represented a rodent specific and not clinically relevant until the study reports are reviewed.

3. ***Does the Agency agree that the conduct of a 6-month intranasal toxicity study with Patanase Nasal Spray, 0.6% (with (b) (4)), in addition to data previously filed in NDA 21-861, is sufficient bridge to support the approval of the product provided that Alcon can demonstrate preclinically that (b) (4) PVP is safe for nasal administration?***

   If you can identify NOAELs from the recommended 6-month intranasal study in rats to demonstrate the safety of (b) (4) PVP for nasal administration, then we agree that the 6-month intranasal toxicity study in addition to data previously filed in NDA 21-861 will be a sufficient bridge to support the approval of the product.

4. ***Are there any additional studies that should be conducted to support the approval of Patanase containing (b) (4) PVP?***

   No additional preclinical studies are required from a preclinical standpoint. However, studies may be needed to qualify the impurities/degradants.

5. ***Would the agency like to receive the (b) (4) and (b) (4) carcinogenicity study reports (or any other outstanding toxicology reports) in advance of the official NDA amendment?***

   You can submit the (b) (4) and (b) (4) carcinogenicity study reports or any other outstanding toxicology reports in the amendment and/or resubmission.

Additional Toxicology comment: Leachable profile of the new formulation and their qualification if necessary should be provided in the resubmission.

Additional Overall Meeting Comment:

At the close of the meeting, Dr. Chowdhury suggested that Alcon could look into the "Special Protocol Assessment" process to have their final protocol reviewed, if they think that this protocol would fit the scope of the Guidance document on this topic. Alcon stated that they had already thought of doing so and agreed that this would be an acceptable approach.

Drafted by: Zeccola/7.5.06
Revised by: Lee/7.6.06, Fadiran/7.10.06, Sun/7.12.06, Gilbert-McClain/7.13.06
Reviewed and Approved by: Chowdhury/7.14.06
Finalized: Zeccola/7.15.06

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
7/17/2006 10:55:38 AM

Memorandum of Telephone Facsimile Correspondence

Date: June 28, 2006

To: Seane Jones

From: Anthony M. Zeccola

Subject: FDA Response to NDA Meeting Questions dated May 31, 2006
Alcon Labs, NDA 21-861, Patanase Nasal Spray.

Number of Pages: 9 (Including this page and electronic signature page)

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 796-1318 and return it to us at 10903 New Hampshire Ave, Building 22, Room 3371, DPAP, Silver Spring, MD 20903.

Thank you.

{See appended electronic signature page}

_____

Anthony M. Zeccola, M.A.
Senior Regulatory Management Officer
Division of Pulmonary and Allergy Products

Attached are the FDA responses to the questions (in **bold**) in your meeting package regarding Patanase Nasal Spray. You have the option of canceling our meeting scheduled for June 30, 2006, if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan or additional questions, for which you would like FDA feedback, should be submitted as a new meeting request. Please let me know as soon as possible if you would like to cancel the meeting or change it to a teleconference.

Clinical Questions

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 reduction in PVP, 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?**

   Although we do not agree that clinical equivalency of products can be based on results from different environmental chamber studies, we generally agree with your approach of bridging and agree that an additional SAR study may not be necessary to support efficacy of your product in SAR. To support the bridging strategy, we will expect that the completed study report for C-05-64 demonstrates similar efficacy to studies C-01-83 and C-03-52. In addition, we would expect demonstration of efficacy in a similar disease, e.g., perennial allergic rhinitis (see response to Clinical Question 5).

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?**

   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 for the final label, as long as 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?**

   We disagree with your statement that the one-year clinical trial demonstrated safety of Patanase. In fact, safety of Patanase was not established, for which the product was not approved for marketing in the United States. You correctly note that the major safety concerns with the product were unacceptable high frequencies of nasal irritation and damage to the nasal mucosa at the proposed labeled dose.

   Provided the assumptions you are making hold (e.g., the reformulated product stays as a solution, systemic exposure is not expected to change, etc.,) it will be acceptable to rely on the original NDA for cardiovascular safety and other systemic safety. Therefore, it is not necessary to included ECGs and laboratory studies as safety endpoints in your new clinical trial.

   We disagree that the new clinical trial C-05-69 should be designed to establish nasal safety only. This new clinical trial will provide the long-term safety data needed to support approval and labeling of your product and should be a standard long term safety study focusing on both nasal and non-nasal adverse events, physical examinations, vital signs, etc.

4. **The FDA raised concerns over the incidence of local nasal effects (epistaxis, ulceration, and septal perforation) in implicated PVP as the contributing component of the formulation. The FDA required Alcon to lessen or remove PVP. 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 clinically demonstrate that the reformulation of Patanase to a lower level of PVP (b) (4) has had its intended effect, Alcon proposes a three-month clinical nasal safety study of 900 patients (Patanase vs. vehicle vs. Astelin) to closely examine the local nasal effects of the reduced PVP formulation.**

   - **Based on the analysis demonstrating that the key adverse events are not related to duration of exposure, does the Agency agree that three months**

of exposure to Patanase (b) (4) PVP) is sufficient to demonstrate that the reformulation has had its intended effect?

- **Does the Agency agree that exposure of an additional 300 patients is sufficient to assess the nasal safety of the reduced PVP formulation?**

We agree that the rates of epistaxis and nasal ulceration were independent of the duration of exposure to test article. However, the data are insufficient to conclude that the rate of nasal septal perforation is independent of the duration of exposure. Furthermore, as you point out in your safety discussion, the safety data do not suggest that there is any relationship suggestive of a progression from epistaxis and/or nasal ulceration to nasal septum perforation. Hence, these events cannot be used as a surrogate signal for the future development of nasal septum perforation.

Therefore, we do not agree that an exposure of an additional 300 patients to the new formulation in a three month study is sufficient. Longer term safety data from a reasonably large sample size will be necessary to support safety of your product. Twelve months of safety data will be necessary to support the safety of your reformulated product. Alternatively, you may provide six months of safety data for a larger number of patients exposed to the reformulated product.

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 (b) (4) PVP (see safety discussion in Tab 2). Does the Agency agree that the proposed nasal exam and classification are acceptable?**

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. Note that 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 study staff are to prime the bottles and the bottles are of different shapes and sizes and the tips are of different appearances.

- History of ulcers or medical treatment for epistaxis should 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 random 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. You may choose to conduct this study in patients with perennial allergic rhinitis (PAR). (b) (4)

- Any change in physical examination or vital signs should be reported as an adverse event. Provide an analysis of adverse events due to changes in physical examination and vital signs as well as an analysis of clinically relevant changes in physical examination and vital signs.

- Some epistaxis and other local nasal adverse events are to be expected with use of a nasal spray for the treatment of allergic rhinitis. Incidences of these events 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 if the results of this study show an

incidence of epistaxis and other local nasal adverse events that are substantially lower than in other studies of olopatadine or in other products.

- Currently you do not have preclinical support for clinical studies longer than three months in duration. You must have preclinical data to support the proposed study duration.

6. **Alcon proposes to rely on all other clinical data (e.g., renal impairment, dose response, etc.), other that local nasal safety data, previously submitted in NDA 21-861 for our final label. Doe the Agency agree?**

   This will be a review issue. In principle, we agree that you may rely on other clinical data as you propose.

   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?**

   We disagree with your contention that there are a limited number of sites that are qualified to participate in a long term safety study in allergic rhinitis patients.

   To support a broader applicability of your safety findings and for unrestricted use of the product, if approved, we suggest that sites previously used in the NDA should not participate 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?**

   This is not acceptable. Enrollment of the same patients will compromise blinding and the validity of the study results.

Toxicology Questions

1. **The Agency previously notified Alcon that a 6-month treatment duration would be required for the final reformulated product requalification study. Does the Agency agree that the following study design will be sufficient to support the approval of this product?**

In order to validate the proposed 6-month intranasal study in rats, an additional positive control group (e.g., (b) (4) PVP) should be added. The study will be adequate to support the approval of the new formulation from a preclinical standpoint if the vehicle and the drug-treated groups are the NOAEL.

2. **If the impurity profile of the reformulation product in the final package configuration are below ICH qualification thresholds when appropriately aged to predict end-of-shelf-life conditions, does the Agency agree that no further toxicological testing of aged product will be required?**

   If the impurities/degradants are not structural alert/genotoxic/carcinogenic, no qualification is required if their acceptance criteria are below ICH qualification thresholds. Otherwise, they should be qualified (genotox and/or carcinogenicity testing) or their acceptance criteria be 0.1%. At this time we can not conclude that the local injection site sarcoma observed in the (b) (4) and (b) (4) transgenic carcinogenicity study represented a rodent specific and not clinically relevant until the study reports are reviewed.

3. **Does the Agency agree that the conduct of a 6-month intranasal toxicity study with Patanase Nasal Spray, 0.6% (with (b) (4)), in addition to data previously filed in NDA 21-861, is sufficient bridge to support the approval of the product provided that Alcon can demonstrate preclinically that (b) (4) PVP is safe for nasal administration?**

   If you can identify NOAELs from the recommended 6-month intranasal study in rats to demonstrate the safety of (b) (4) PVP for nasal administration, then we agree that the 6-month intranasal toxicity study in addition to data previously filed in NDA 21-861 will be a sufficient bridge to support the approval of the product.

4. **Are there any additional studies that should be conducted to support the approval of Patanase containing (b) (4) PVP?**

   No additional preclinical studies are required from a preclinical standpoint. However, studies may be needed to qualify the impurities/degradants.

5. **Would the agency like to receive the (b) (4) and (b) (4) carcinogenicity study reports (or any other outstanding toxicology reports) in advance of the official NDA amendment?**

   You can submit the (b) (4) and (b) (4) carcinogenicity study reports or any other outstanding toxicology reports in the amendment and/or resubmission.

Additional Toxicology comment: Leachable profile of the new formulation and their qualification if necessary should be provided in the resubmission.

Drafted by: Zeccola/June 26, 2006

Initialed by: Barnes/June 26, 2006, Kim/June 26, 2006, Fadiran/June 26, 2006, Gilbert-McClain/June 27, 2006, Lee/June 27, 2006, Sun/June 27, 2006

Revised by: Lee/June 28, 2006, Chowdhury/June 28, 2006

Finalized: Zeccola/June 23, 2006

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
6/28/2006 04:03:19 PM
CSO

MEMORANDUM OF TELECONFERENCE MINUTES

DATE: May 24, 2006

APPLICATION: Alcon Research Ltd.
NDA 21-861 Patanase Nasal Spray

FDA Representative:

Badrul Chowdhury, M.D., Ph.D., Division Director
Emmanuel Fadiran, Ph.D., Clinical Pharmacology Team Leader
Charles Lee, M.D., Medical Officer
Prasad Peri, Ph.D., Pharmaceutical Assessment Lead
Anthony Zeccola, M.A., Senior Regulatory Management Officer
Craig M. Bertha, Ph.D., CMC Reviewer

Alcon Representatives:

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Michael Pfleger, JD, Vice President, Regulatory Affairs
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Michael Wall, Ph.D., Sr. Director, Otic / Nasal Development
Masood Chowhan, Ph.D., Sr. Director, Pharmaceutical Sciences
Michael Brubaker, Ph.D., Director, Dry Eye Development
Seane Jones, MS, Associate Director, Regulatory Affairs
Randall Kolega, Ph.D., Sr. Scientist III – Analytical Chemistry

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Background

Alcon submitted a Type C meeting request dated April 21, 2006, to discuss CMC isses regarding the reformulated Patanase Nasal Spray . Upon review of the briefing documet package, the division responded to Alcon's questions via fax on May 17, 2006. The content of that fax is printed below. By responded by cancelling the scheduled meeting but requested clarification on one point and posed a question in response to the Division's April 25 fax. The discussion that took place during the telephone conversation is captured directly under the relevant original response including any changes in our original position. BI's questions are in ***bold italics***; FDA's response is in *italics*; meeting discussion is in normal font.

Question 4.1 - The solubility and freeze-thaw cycle data presented in this package demonstrate that the reformulated Patanase product is a stable solution with a proposed pH specification of 3.7 (b) (4) **Does the Agency agree?**

The data appear to support that olopatadine is soluble in the current intended formulation up to pH of 4.0 at room temperature. As no numerical turbidity data or other quantitative data (e.g., filtration and assay) were provided in conjunction with the freeze-thaw studies, it is not completely established that there are no olopatadine solubility issues under these conditions.

Is the Agency requesting that turbidity or other quantitative data (e.g., filtration and assay) be generated for the freeze-thaw cycled samples from our new primary stability batches? Dr. Bertha referred Alcon to the guidance on the CMC requirements for nasal sprays (item 4c) for details regarding the freeze-thaw data that would be required. Alcon agreed to comply with the guidance.

Question 4.2 - Based on the information provided above, does the Agency agree that the reformulated PATANASE is a qualitative match to the current NDA formulation?

Yes.

Question 4.3 - If the Agency agrees that the reformulated PATANASE is a qualitative match, will Alcon be allowed to invoke the *in vitro* bioequivalence approach to establish comparability to the original PATANASE NDA 21-861 formulation as per the "Guidance for Industry, Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, Draft Guidance, April 2003?

No, since the inactive ingredients in the two formulations are not quantitatively the same as required by the Draft Guidance. In addition, we remind you of the comment provided during our January 12, 2006 meeting, "… in order to use bridging, there must be an existing approved label to bridge to. Since no label exists, in theory, the reformulated product would bridge to the old product containing povidone that the Agency has already determined not to be safe**.**"

Alcon recognizes that it has the obligation to "demonstrate that the change (reduction in PVP) has had its intended effect (i.e., reduce the potential for nasal safety issues)" (as per FDA letter to Alcon 10/27/05).

In the minutes from our 1/12/06 meeting, it was stated that "Additional efficacy studies may be necessary depending on the CMC effects of the proposed changes." It is Alcon's belief that the proposed change in PATANASE (reduction of PVP from (b) (4) *does not have any CMC effects related to efficacy. This statement is supported by the results of a recently completed environmental chamber study, C-05-64, demonstrating that PVP does not affect the efficacy of PATANASE. These data were not available in time to support the CMC meeting but are being provided to the Agency in our Clinical/Toxicology briefing package in support of our meeting on June 30th.*

Alcon believes that the Draft Guidance provides sufficient latitude to permit bridging to the efficacy data from our initial pivotal studies. Since (a) the revised formulation is

merely a reduction of PVP from (b) (4) *(b) the results of C-05-64 demonstrate that the reduction in PVP has no affect on efficacy (onset or duration of action), and (c) the BE draft guidance allows for the use of in vitro testing to ensure that the to-be-marketed product is comparable to very similar clinical trial batches as a result of excipient optimization during NDA development, we propose that Alcon should be able to invoke in vitro bioequivalence in lieu of any further efficacy clinical trials.*

We understand this matter will need to be discussed at the June 30 meeting with the Division and seek your support for this position.

Dr. Fadiran reiterated that this is not possible and cited section 4.B of the BA/BE guidance (Q1/Q2 requirement) and noted that Q2 must not be more than 5% different as noted in 21 CFR 314.94(a)(9)(5). Alcon requested clarification as why 4.A of the BA/BE guidance did not apply. Dr. Fadiran noted that there is no approved reference product. Dr. Chowdhury added that while in principle this Alcon's proposal might be acceptable, they will still be required to bridge the efficacy and safety of the new formulation to the formulation used in the clinical trials. This will be a discussion item for the June 30, 2006 clinical/toxicology meeting. Dr. Chowdhury also noted the Division does not agree with Alcon's response (above) as worded, "…we propose that Alcon should be able to invoke in vitro bioequivalence in lieu of any further efficacy clinical trials…", since some level of efficacy bridging will be required.

Question 4.4 - Due to the minor quantitative changes to the current NDA formulation and the transparency of the pump configuration change, Alcon proposes that the one time CMC Product Characterization Studies do not need to be repeated with the reformulated PATANASE product except for priming/repriming, tail-off characterization and temperature cycling studies. Does the Agency agree?

Yes.

Question 4.5 - Due to the minor quantitative changes to the current NDA formulation, Alcon proposes that (b) (4) **real time** (b) (4) **) and** (b) **accelerated (** (b) (4) **) primary stability data for three batches (** (b) (4) **would be sufficient to bridge to the reformulated PATANASE product. Does the Agency agree that this is sufficient stability data to support approval for a shelf-life of** (b) (4)

No.

The expiration dating period will be based on the analysis of the long-term (real time) data provided for the newly formulated product in the modified container closure system. The targeted expiration date can be stated in the stability protocol, and the approved protocol can be used to extend the approved expiry to the target via the statistical analysis of the long term data reported in annual reports.

To provide support for extrapolation beyond the available data for the newly formulated product, it is recommended that your response provide a comparison, with graphical

presentations and analysis, of the available data for the new product with the analogous data already presented for the old version.

Question 4.6 - From a CMC standpoint, Alcon plans to provide all of the information described above in an NDA Amendment. Is there any additional information needed to support approval of this formulation?

Yes. Provide complete responses to comments 3-46 of the NA letter of 27-OCT-2005, with the appropriate revisions accounting for the new version of the drug product.
Include a tabular list identifying and providing reference to all of the changes that have been made to the application for the change to the new version of the drug product (e.g., new manufacturing procedure, revised methods and validation data).
Provide the updated sections with the changes flagged relative to what was originally provided. The tabular listing should provide reference to the location of the updated and flagged sections.

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/s/

Anthony Zeccola
6/9/2006 09:49:10 AM

Memorandum of Telephone Facsimile Correspondence

Date: May 17, 2006

To: Seane D. Jones, M.S.

Fax No.: 817-551-4630

From: Anthony M. Zeccola

Subject: FDA Response to Pre-NDA Questions dated March 22, 2005
Alcon Laboratories, Inc., NDA 21-861 – Patanase Nasal Spray

Number of Pages: 4 (Including this page and electronic signature page)

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

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Thank you.

{See appended electronic signature page}

Anthony M. Zeccola, M.A.
Senior Regulatory Management Officer
Division of Pulmonary Drug Products

Attached are the FDA responses to the questions (in **bold**) in your meeting package regarding Patanase Nasal Spray. You have the option of canceling our meeting scheduled for May 24, 2006, if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan or additional questions, for which you would like FDA feedback should be submitted as a new meeting request. Please let me know as soon as possible if you would like to cancel the meeting or change it to a teleconference.

Question 4.1 - The solubility and freeze-thaw cycle data presented in this package demonstrate that the reformulated Patanase product is a stable solution with a proposed pH specification of 3.7 (b) (4) Does the Agency agree?

The data appear to support that olopatadine is soluble in the current intended formulation up to pH of 4.0 at room temperature. As no numerical turbidity data or other quantitative data (e.g., filtration and assay) were provided in conjunction with the freeze-thaw studies, it is not completely established that there are no olopatadine solubility issues under these conditions.

Question 4.2 - Based on the information provided above, does the Agency agree that the reformulated PATANASE is a qualitative match to the current NDA formulation?

Yes.

Question 4.3 - If the Agency agrees that the reformulated PATANASE is a qualitative match, will Alcon be allowed to invoke the *in vitro* bioequivalence approach to establish comparability to the original PATANASE NDA 21-861 formulation as per the "Guidance for Industry, Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, Draft Guidance, April 2003?

No, since the inactive ingredients in the two formulations are not quantitatively the same as required by the Draft Guidance. In addition, we remind you of the comment provided during our January 12, 2006 meeting, "… in order to use bridging, there must be an existing approved label to bridge to. Since no label exists, in theory, the reformulated product would bridge to the old product containing povidone that the Agency has already determined not to be safe**.**"

Question 4.4 - Due to the minor quantitative changes to the current NDA formulation and the transparency of the pump configuration change, Alcon

proposes that the one time CMC Product Characterization Studies do not need to be repeated with the reformulated PATANASE product except for priming/repriming, tail-off characterization and temperature cycling studies. Does the Agency agree?

Yes.

Question 4.5 - Due to the minor quantitative changes to the current NDA formulation, Alcon proposes that (b) (4) real time (b) (4)) and (b) (4) accelerated (b) (4) primary stability data for three batches stored horizontally would be sufficient to bridge to the reformulated PATANASE product. Does the Agency agree that this is sufficient stability data to support approval for a shelf-life of (b) (4)

No.

The expiration dating period will be based on the analysis of the long-term (real time) data provided for the newly formulated product in the modified container closure system. The targeted expiration date can be stated in the stability protocol, and the approved protocol can be used to extend the approved expiry to the target via the statistical analysis of the long term data reported in annual reports.

To provide support for extrapolation beyond the available data for the newly formulated product, it is recommended that your response provide a comparison, with graphical presentations and analysis, of the available data for the new product with the analogous data already presented for the old version.

Question 4.6 - From a CMC standpoint, Alcon plans to provide all of the information described above in an NDA Amendment. Is there any additional information needed to support approval of this formulation?

Yes. Provide complete responses to comments 3-46 of the NA letter of 27-OCT-2005, with the appropriate revisions accounting for the new version of the drug product.
Include a tabular list identifying and providing reference to the all of the changes that have been made to the application for the change to the new version of the drug product (e.g., new manufacturing procedure, revised methods and validation data).
Provide the updated sections with the changes flagged relative to what was originally provided. The tabular listing should provide reference to the location of the updated and flagged sections.

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/s/

Anthony Zeccola
5/17/2006 02:23:08 PM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: January 12, 2006

TIME: 11:30 AM

LOCATION: White Oak Conference Room 1419

APPLICATION: NDA 21-861 Patanase Nasal Spray

FDA Representatives:

Craig Bertha, Ph.D., CMC Reviewer
Gary Bond, Ph.D., Pharmacologist/Toxicologist
Badrul Chowdhury, M.D., Ph.D., Division Director
Emmanuel Fadiran, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader
Lydia Gilbert-McClain, M.D., Medical Officer
Charles Lee, M.D., Medical Officer
Joseph Sun, Ph.D., Pharmacology/Toxicology Team Leader
Anthony M. Zeccola, Regulatory Management Officer

Alcon Laboratories Representatives:

Michael Pfleger, JD, Vice President, Regulatory Affairs
Seane Jones, MS, Associate Director, Regulatory Affairs
Michael Wall, Ph.D., Senior Director, Pharmaceutical Product Development
Michael Brubaker, Ph.D., Director, Pharmaceutical Product Development
Lewis Silver, Ph.D., Senior Director, Product Safety
Leslie Lemke, Ph.D., Senior Toxicologist
Scott Krueger, Ph.D., Vice President, Pharmaceutical Product Development
Joe Hiddemen, Ph.D., Vice President, Pre-Clinical Sciences
David Wells, BS, Senior Product Safety Specialist
(b) (4)

Background

Alcon Laboratories submitted a Type A meeting request dated November 22, 2005, to discuss their path forward in response to the FDA Not Approvable letter dated October 27, 2005, which contained a list of questions to be discussed at this meeting. Upon review of the briefing fax package, the division responded to Alcon's questions via fax on January 10, 2006. The content of that fax is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. Alcon's questions are in ***bold italics***; FDA's response is in *italics*; meeting discussion is in normal font following the FDA responses to Alcon's questions.

1. **Does the Agency agree that the preclinical study outlined in Table 1, Tab 2 should be sufficient to evaluate the safety profile of the reformulated product?**

   The new formulation does not contain povidone and has a reduced pH of 3.7 compared to (b) (4) *for the previous formulation. Provide the rationale for the proposed nonclinical study without any proposed clinical study/studies with regard to the safety assessment of the new product. (see CMC and Clinical comments)*

2. **Regarding the study design outlined in Table 2, Tab 2 does the agency agree:**

   a. **That accelerated aged product, defined as product stored** (b) (4) **at 50°C for 8 weeks, would be sufficient for use in evaluating the intranasal irritation potential of the revised formulation?**

   b. **That the design should be sufficient to evaluate the safety profile of the accelerated aged PVP-free product formulation?**

   c. **That the results of the accelerated aged product study can be reported to the agency within 6-months of product approval (as per point 36 of the FDA letter of October 27, 2005)?**

   If the proposed nonclinical study is intended to qualify degradants/impurities and/or leachables/extractables of the new product,

   a. the intended aged marketed product to be used should contain the maximum levels of any degradants/impurities and/or leachables/extractables at the end of its shelf life.

   b. a full protocol toxicology study would be required to assess local and systemic toxicity.

   c. the results of the study must be submitted with the NDA resubmission.

Additional Comments:

CMC

The proposed reformulation removing the povidone solubility enhancer from the formulation has serious implications for the CMC aspects for the drug product. Povidone is known to substantially increase solubility (b) (4) *. The data on p. 9 of your pre-meeting package suggests that the drug product without povidone is formulated near the limit of the solubility of the drug substance. As a result of this major change in the formulation it*

is imperative that you provide all appropriate CMC data to characterize the performance and support the stability of the new drug product. No assumptions can be made regarding any relationship to the previously formulated drug product with povidone. As such, the CMC information and extent of the data necessary to support approval of the newly formulated product will rely fully on the reformulated drug product data to support approval and expiry. The earlier formulation containing povidone is too different to be useful in any supportive capacity for CMC review.

Clinical

As noted in our letter of October 27, 2005, data submitted in the NDA showed that Patanase Nasal Spray had unacceptable high frequencies of nasal septal perforation, nasal ulceration, and epistaxis. Additional clinical studies will be necessary to support the safety of the reformulated product. Additional efficacy studies may be necessary depending on the CMC effects of the proposed changes.

Discussion

Alcon sent in an Agenda (Appendix 1) the two days before the meeting, which was different than then the agenda submitted with the meeting package. The revised agenda included a presentation of their NDA and additional data to alleviate the Agency's safety concerns because they do not believe that Patanase Nasal Spray is as unsafe as the clinical data depicts. The Agency pointed out that we are aware of the data, but agreed to give Alcon the opportunity to present their data. The presentation filled most of the allotted time and allowed minimal time for discussion. Slides used by Alcon at the meeting are attached as Appendix 2.

Alcon's presentation was divided into a clinical portion and a pre-clinical portion.

During the clinical portion of the presentation, Alcon, with the assistance of their two Consultants, stated that the adverse events recorded in the clinical trials were an overestimation of the true frequency because the coding requirement for the adverse events, such as epistaxis and nasal ulceration, had a binary choice of present or absent. Alcon's position is that this resulted in more adverse events being recorded as being present. Alcon also pointed out that these adverse events were often transient in nature and did not progress in all cases. With regard to the three cases of perforation, Alcon stated that two of the cases may have had other confounding factors, although for one, no confounding factors were present. Alcon presented findings from a comparative study of Olopatadine Nasal Spray and Astelin Nasal Spray to show that adverse events for the two drugs were similar. The Agency pointed out that the study was not part of the NDA and was also not submitted in the briefing package. Without the Agency's review of the study, it is not possible for the Agency to comment. Nevertheless, the Agency pointed out that the comparative study results do not negate the findings of the NDA study findings and Agency determination that Olopatadine Nasal Spray is not safe for human use.

In the preclinical portion of Alcon's presentation, Alcon stated that they also have concluded that povidone is irritating to the nasal mucosa either by itself or through generation of some degradants when the formulation comes in contact with the valve assembly when the product is stored in horizontal position and aged. Based on the pre-clinical finding Alcon has decided to remove povidone from the formulation.

The Agency pointed out that Alcon contends that the drug product is clinically safe, however, Alcon has concluded the drug product is not safe based on the preclinical data and will reformulate to remove povidone. The Agency refered Alcon to the guidance for Industry regarding the Formal Dispute Resolution Process should they choose to dispute the scientific conclusion reached by the Division.

Following Alcon's presentation, the Agency made a brief presentation to outline to Alcon participants the basis for the Agency's conclusions. The slides used in the presentation are included as Appendix 3. The Agency stated that the basis of determining that Patanase Nasal Spray was not safe was the combination of findings in the clinical studies, including unusually high frequencies of nasal ulceration, epistaxis, and nasal septal perforation, along with the preclinical findings that demonstrated that povidone, which is present in the formulation, is toxic to the animal nasal mucosa. The Agency pointed out that there no marketed nasal spray product in the United Stated approved for chronic use that has povidone as an excipient. The Agency stated that the frequency of nasal adverse events seen in the Patanase Nasal Spray clinical development program is remarkably high compared to other nasal spray formulation that are marketed in the United States. For example, nasal septal perforation is a very rare adverse event that has been reported in only a few products, such as nasal corticosteroids, and those have been only reported in the post-marketing setting. The three reports of nasal septal perforation in the clinical trials for Patanase Nasal Spray is a huge safety signal. In response to Alcon's explanation regarding the captured of the adverse events that they contend could have resulted in over-reporting, the Agency pointed out that even when one looks at the Patanase Nasal spray program itself, there were more nasal adverse events in higher dose compared to lower dose, long-term studies compared to short-term studies, and pediatric patients compared to adult patients. This lead the Agency to conclude that the nasal toxicity were real and could not be argued as artifacts of the recording method used in the Patanase Nasal Spray clinical trials. On direct questioning by the Agency to Alcon's Consultants, the Consultants did not seem to disagree with these statements.

After the lengthy discussion documented above, the meeting proceeded to the questions that Alcon provided in the meeting package.

Alcon wanted to know if two 3-month preclinical studies would satisfactorily confirm that the reformulation has its intended effect. Dr. Chowdhury responded that this approach would not be acceptable and that the required studies would be based on the extent of the reformulation. Dr. Chowdhury also commented that Alcon's presumption that the BA/BE guidance would apply is not true since the two products would not be Q1 the same or Q2 essentially the same because one product will not have povidone. Furthermore, in order to use bridging, there must be an existing approved label to bridge

to. Since no label exists, in theory, the reformulated product would bridge to the old product containing povidone that the Agency has already determined not to be safe. Furthermore, the safety data for the label will be the data that has shown that the product has an unacceptably high frequency of nasal ulceration, epistaxis, and nasal septal perforation.

Alcon requested comment on the type of pre-clinical and clinical studies that will be required. Dr. Chowdhury responded that it will all come down to the extent of the reformulation. Since povidone was added to the original formulation to enhance solubility, removing it from the formulation could present stability issues (such as the product degrading from a solution to a suspension over time), which would necessitate different types of clinical studies. Dr. Chowdhury advised Alcon to work out the details of their reformulation and request a meeting with the CMC group prior to proposing alternative pre-clinical and clinical development plans. Dr. Bertha pointed that the new product with povidone removed will be a different product and is likely to be substantially different from the current product. Dr. Bertha indicated that Alcon had a reason to include the povidone excipient in the original formulation, thus there will be consequences with regard to its removal. The Alcon representative indicated that the formulators may just have been overly cautious. Nevertheless, the Agency indicated that without any detailed data supporting the new formulation, it is not possible to have a meaningful chemistry discussion regarding the extent of data that will be required in the complete response to support such a major formulation change.

Appendix 1 – Alcon Amended Agenda
Received January 11, 2006

Patanase Nasal Spray FDA Meeting Agenda
January 12, 2006 11:30am – 1pm (EST)

- Alcon – Opening greeting and introductions
- Alcon – Primary Basis and objective of meeting
- Alcon – Pre-Clinical Safety Presentation
    - FDA Comments / Questions
- Alcon – Nasal Adverse Events Safety Presentation
    - FDA Comments / Questions
- Alcon – Review of Proposal From Meeting Briefing Package
- FDA – Presentation / Responses to Meeting Briefing Package and Proposal
    - Alcon Comments / Questions / Discussion
- Alcon - Meeting wrap up

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/s/

Anthony Zeccola

2/2/2006 03:50:03 PM

Memorandum of Telephone Facsimile Correspondence

Date: January 10, 2006

To: Seane Jones

From: Anthony M. Zeccola

Subject: FDA Response to NDA Meeting Questions dated November 22, 2005
Alcon Labs, NDA 21-861, Patanase Nasal Spray.

Number of Pages: 4 (Including this page and electronic signature page)

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Thank you.

{See appended electronic signature page}

_____

Anthony M. Zeccola, M.A.
Senior Regulatory Management Officer
Division of Pulmonary Drug Products

Attached are the FDA responses to the questions (in **bold**) in your meeting package regarding Patanase Nasal Spray. You have the option of canceling our meeting scheduled for January 12, 2006, if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan or additional questions, for which you would like FDA feedback should be submitted as a new meeting request. Please let me know as soon as possible if you would like to cancel the meeting or change it to a teleconference.

1. **Does the Agency agree that the preclinical study outlined in Table 1, Tab 2 should be sufficient to evaluate the safety profile of the reformulated product?**

   The new formulation does not contain Povidone and has a reduced pH of 3.7 compared to (b) (4) for the previous formulation. Provide rationale for the proposed nonclinical study without any proposed clinical study/studies with regard to the safety assessment of the new product. (see CMC and Clinical comments)

2. **Regarding the study design outlined in Table 2, Tab 2 does the agency agree:**

   a. **That accelerated aged product, defined as product stored (b) (4) at 50°C for 8 weeks, would be sufficient for use in evaluating the intranasal irritation potential of the revised formulation?**

   b. **That the design should be sufficient to evaluate the safety profile of the accelerated aged PVP-free product formulation?**

   c. **That the results of the accelerated aged product study can be reported to the agency within 6-months of product approval (as per point 36 of the FDA letter of October 27, 2005)?**

   If the proposed nonclinical study is intended to qualify degradants/impurities and/or leachables/extractables of the new product,

   a. the intended aged marketed product to be used should contain the maximum levels of any degradants/impurities and/or leachables/extractables at the end of its shelf life.

   b. a full protocol toxicology study would be required to assess local and systemic toxicity.

   c. the results of the study must be submitted with the NDA resubmission.

Additional Comments:

CMC

The proposed reformulation removing the povidone solubility enhancer from the formulation has serious implications for the CMC aspects for the drug product. Povidone is known to substantially increase solubility (b) (4) . The data on p. 9 of your pre-meeting package suggests that the drug product without povidone is formulated near the limit of the solubility of the drug substance. As a result of this major change in the formulation it is imperative that you provide all appropriate CMC data to characterize the performance and support the stability of the new drug product. No assumptions can be made regarding any relationship to the previously formulated drug product with povidone. As such, the CMC information and extent of the data necessary to support approval of the newly formulated product will rely fully on the reformulated drug product data to support approval and expiry. The earlier formulation containing povidone is too different to be useful in any supportive capacity for CMC review.

Clinical

As noted in our letter of October 27, 2005, data submitted in the NDA showed that Patanase Nasal Spray had unacceptable high frequencies of nasal septal perforation, nasal ulceration, and epistaxis. Additional clinical studies will be necessary to support the safety of the reformulated product. Additional efficacy studies may be necessary depending on the CMC effects of the proposed changes.

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/s/

Anthony Zeccola
1/10/2006 02:09:02 PM
CSO

Memorandum of Telephone Facsimile Correspondence

Date: May 25, 2005

To: Seane D. Jones, M.S.

From: Anthony M. Zeccola
Regulatory Management Officer

Subject: Comments for NDA 21-861
Patanol® (Olopatadine Hydrochloride) Nasal Spray

Number of Pages: 3 (Including this page and electronic signature page)

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Thank you.

{See appended electronic signature page}

Anthony M. Zeccola
Regulatory Management Officer
Division of Pulmonary Drug Products

As discussed in previous correspondence, this facsimile is to confirm our teleconference scheduled for Thursday, May 26, 2005 at 3:30 PM EDT. The FDA will be represented by the following personnel:

Badrul A. Chowdhury, M.D., Ph.D.
Gary Bond, Ph.D.
Charles Lee, M.D.
Lydia Gilbert-McClain, M.D.
Joseph Sun, Ph.D.
Anthony Zeccola

In preparation for the teleconference, we have the following comments

We have safety concerns about the chronic intranasal use of Patanase® containing (b) (4) Povidone (PVP) based on the local effects of olfactory epithelium degeneration and turbinate epithelium vacuolation observed in the 6 month intranasal study of PVP in rats. These effects were observed to be dose-responsive as to incidence and severity. Your rationalization as to the lack of toxicological relevance of these effects based on comparison to a NOAEL for the NVP monomer of PVP is not considered acceptable as they are different compounds. In addition, your determination that the observed effects are minimal in severity and that they are reversible, which is undocumented, are also not acceptable. Please provide alternative rationalization as to why these PVP-related observations should not be considered toxicologically relevant.

Provide documentation that the levels of genotoxic impurities (b) (4) and (b) (4) structurally related genotoxic structural alert (b) (4) are present at comparable or higher levels in the compound administered in rat or mouse carcinogenicity studies with Olopatadine. If this is not that case, based on the lack of negative SHE cell assay results with (b) (4) and (b) (4), it will be necessary to limit these impurities and (b) (4) to < (b) (4) in the drug product or conduct a carcinogenicity assay with the isolated impurities.

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Anthony Zeccola
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CSO

Your NDA 21-861, N-000, dated December 24, 2004, is under review and we have the following requests:

1. Table 11.3.-2, ITT – Bottle Weight Data, provides information on treatment compliance for the entire study population for study C-02-37 [Module 5, Volume 47, page 103] and for study C-02-10 [Module 5, Volume 56, page 105]. Provide similar tables that include information on treatment compliance in patients 12-17 years of age for both study C-02-37 and study C-02-10.

2. In study C-02-10, patient 1512 at study site (b)(4) 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. The case report form indicates that possible explanations for this serious adverse event included seizures, transient ischemic attack, and hypoglycemia. No hospital discharge diagnoses are provided, however. [Module 5, Volume 58, pages 745, 877; Module 5, Volume 120, page 157]. Provide the hospital discharge diagnoses for this patient.

3. Patient Problem Logs were used in study C-02-10 [Module 5, Volume 56, pages 76-78, 194] and patient medical problems logs were used in study C-01-92 [Module 5, Volume 65, page 62; Module 5, Volume 71, page 2201]. Provide a copy of the Patient Problem Log used in study C-02-10 and the patient medical problem log used in study C-01-92.

4. An oral dosage form of olopatadine, 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]. Provide a copy of the product label, in Japanese and translated into English, for Allelock® Tablets, 2.5 mg and 5 mg.

   Provide a summary and analysis of postmarketing adverse event reports for Allelock® Tablets, 2.5 mg and 5 mg. Include postmarketing adverse events reported since the approval of the product in Japan.

If there are any questions, please contact Anthony Zeccola, Regulatory Management Officer, at 301-827-1058.

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/s/

Anthony Zeccola
5/13/05 02:51:47 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-861

DISCIPLINE REVIEW LETTER

Alcon Research LTD
Attention: Seane D. Jones, M.S.,R.A.C.
Assistant Director, Regulatory Affairs
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Ms. Jones:

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

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

1. 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 (e.g., (b) (4)

2. (b) (4)

3.

(b) (4)

4. 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)

5. (b) (4)

6. (b) (4)

7.

8.

9.

16 Page(s) has been Withheld in Full following this page as B4 (CCI/TS)

43. 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.

44. 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.

45. 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.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Anthony Zeccola, Regulatory Management Officer, at 301-827-1058.

Sincerely,

Richard Lostritto, Ph.D.
Chemistry Team Leader for the
Division of Pulmonary and Allergy Drug Products, HFD-570
DNDC DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Richard Lostritto

4/25/05 03:13:21 PM

Your submission, NDA 21-861, N-000, dated December 24, 2004, is under review and we have the following request(s):

For C-02-37

1. Table 10.2-1, Summary of Significant Protocol Deviations by Treatment, provides the following information [Module 5, Volume 47, page 91]:
   - Protocol deviations, total: 45
   - Protocol deviations, vehicle: 17
   - Protocol deviations, olopatadine 0.4%: 11
   - Protocol deviations, olopatadine 0.6%: 17

   Table 16.2.2.-1, By-Patient List of Significant Protocol Deviations for C-02-37, provides the following information [Module 5, Volume 53, pages 2127-2128]:
   - Protocol deviations, total: 47
   - Protocol deviations, vehicle: 18
   - Protocol deviations, olopatadine 0.4%: 11
   - Protocol deviations, olopatadine 0.6%: 18

   Reconcile the difference in the numbers of protocol deviations.

2. Table 10.2-1, Summary of Significant Protocol Deviations by Treatment, provides the following information [Module 5, Volume 47, page 91]:
   - Protocol deviations for excluded concomitant medication, total: 31
   - Protocol deviations for excluded concomitant medication, vehicle: 11
   - Protocol deviations, for excluded concomitant medication, olopatadine 0.4%: 9
   - Protocol deviations, for excluded concomitant medication, olopatadine 0.6%: 11

   Table 16.2.2.-1, By-Patient List of Significant Protocol Deviations for C-02-37, provides the following information [Module 5, Volume 53, pages 2127-2128]:
   - Protocol deviations for excluded concomitant medication, total: 32
   - Protocol deviations for excluded concomitant medication, vehicle: 12
   - Protocol deviations, for excluded concomitant medication, olopatadine 0.4%: 9
   - Protocol deviations, for excluded concomitant medication, olopatadine 0.6%: 11

   Reconcile the difference in the numbers of protocol deviations for excluded medication.

3. Provide a listing of the excluded concomitant medications taken by each of the patients with protocol deviations for excluded concomitant medications in Table 16.2.2.-1, By-Patient List of Significant Protocol Deviations for C-02-37 [Module 5, Volume 53, pages 2127-2128].

For C-02-10

4. Table 10.2-1, Summary of Protocol Deviations during the Conduct of C-02-10, provides the following information [Module 5, Volume 56, page 93]:
   - Protocol deviations, total: 17
   - Protocol deviations, vehicle: 8
   - Protocol deviations, olopatadine 0.4%: 6
   - Protocol deviations, olopatadine 0.6%: 3

   Table 16.2.2.-1, Protocol Deviations/Violations Occurring during the Conduct of C-02-10, provides the following information [Module 5, Volume 61, page 2076]:
   - Protocol deviations, total: 24
   - Protocol deviations, vehicle: 11
   - Protocol deviations, olopatadine 0.4%: 9
   - Protocol deviations, olopatadine 0.6%: 4

   Reconcile the difference in the numbers of protocol deviations.

5. Provide a listing of the excluded concomitant medications taken by each of the patients with protocol deviations for excluded concomitant medications in Table 16.2.2.-1, Protocol Deviations/Violations Occurring during the Conduct of C-02-10 [Module 5, Volume 61, page 2076].

If there are any questions, please contact Anthony Zeccola, Project Manager, at 301-827-1058.

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/s/

Sandra Barnes
4/5/05 03:46:43 PM
CSO

Your submission, NDA 21-861, N-000, dated December 24, 2004, is under review and we have the following request(s):

1. Describe the manner in which the average was calculated from the individual reflective severity scores for clinical study report C-02-37 described in section 9.7.1.2 (Module 5, Volume 47, page 79) and section 11.4.1 (Module 5, Volume 47, page 104).

2. Clarify what is represented by the column entitled "Diary Period" in table 11.4.1.1-1 "ITT- Percent Change in Reflective TNSS Scores by Treatment" [Module 5, Volume 47, page 106] in the clinical study report C-02-37. Does this column represent the average of the AM and PM reflective severity scores for the sum of the patients' diary assessments of runny nose, stuffy nose, itchy nose, and sneezing (averaged across all days) or another value?

3. Clarify what is represented by the column entitled "Exit" in table 16.2.6-1 "Individual Primary Efficacy response Data (Reflective TNSS)" [Module 5, Volume 53, pages 2148-2160] in the clinical study report C-02-37. Does this column represent the reflective TNSS at the exit visit, or the average of the AM and PM reflective severity scores for the sum of the patients' diary assessments of runny nose, stuffy nose, itchy nose, and sneezing (averaged across 14 days), or another value?

If there are any questions, please contact Anthony Zeccola, Project Manager, at 301-827-1058.

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/s/

Sandra Barnes

3/31/05 04:21:36 PM

CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Division of Scientific Investigations
HFD-46

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Anthony M. Zeccola
Division of Pulmonary and Allergy Drug Products
HFD-570

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
3/29/05		21-861	N	12/27/04

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Patanase (olopatadine HCL) Nasal Spray	S	3	9/15/05

NAME OF FIRM:

REASON FOR REQUES T

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☒ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: See attachment

SIGNATURE OF REQUESTOR
{See appended electronic signature page}

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PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Anthony Zeccola
3/30/05 09:11:00 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420
PKLN Rm. 6-34

FROM:
Anthony M. Zeccola
Regulatory Management Officer, HFD-570

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
3/23/05		**21-861**	**N**	**10/24/05**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Patanase (olopatadine hyrdrochloride) Nasal Spray	**S**	**3**	**9/15/05**

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Trade name review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

EDR Location of Package Insert: \\Cdsesub1\n21861\N_000\2004-12-24\CD_ROM_08

Tradename Consult previously submitted under IND 60,116, 2/27/03

PDUFA DATE: **10/27/05**

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
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SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Anthony Zeccola

3/23/05 01:05:48 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-861

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

Attention: Seane Jones
Associate Director, Regulatory Affairs

Dear Ms. Jones,

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

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 25, 2005 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue:

(b) (4)

We are providing the above comment to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We do not expect a response to this letter, and we may not review any such response during the current review cycle.

We also request that you submit the following information:

1. Provide a review and summary of postmarketing safety data for olopatadine tablets, from countries where the drug is currently marketed.
2. 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.

3. For studies C-02-54 and C-00-23 (cardiovascular safety and pharmacokinetic studies) submit the following information in a tabulated form and as SAS transport files: ID, Study, Day, Visit, Time (actual time), Treatment, RR, HR, QT, QTB, QTF, ΔQTB, ΔQTF (change from baseline), parent drug concentration, major metabolite concentration, time of PK samples, and other relevant parameters useful to evaluate QT prolongation.

4. For the dose response studies (C-00-10, C-00-70, and C-01-83) submit the following information in a tabulated form and as SAS Transport files: ID, Treatment, Dose, Time, Visit primary end point for efficacy and most relevant AEs, and other relevant information useful to evaluate Dose-Response.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Anthony M. Zeccola, Senior Regulatory Project Management Officer, at (301) 827-1058.

Sincerely,

{See appended electronic signature page}

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

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/s/

Badrul Chowdhury
3/9/05 04:50:44 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION

TO: *(Division/Office)* Tim McGovern, Ph.D., Pharmacology Team Leader (HFD-570)	FROM: Craig M. Bertha (HFD-570)

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
02-FEB-2005	I60,116	21-861	Original	21-DEC-2004

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Patanase (olopatadine HCl nasal spray)	3	S	02-JUN-2005

NAME OF FIRM: Alcon, Inc.

REASON FOR REQUEST

I. GENERAL

9 NEW PROTOCOL 9 PROGRESS REPORT 9 NEW CORRESPONDENCE 9 DRUG ADVERTISING 9 ADVERSE REACTION REPORT 9 MANUFACTURING CHANGE/ADDITION 9 MEETING PLANNED BY	9 PRE-NDA MEETING 9 END OF PHASE II MEETING 9 RESUBMISSION 9 SAFETY/EFFICACY 9 PAPER NDA 9 CONTROL SUPPLEMENT	9 RESPONSE TO DEFICIENCY LETTER 9 FINAL PRINTED LABELING 9 LABELING REVISION 9 ORIGINAL NEW CORRESPONDENCE 9 FORMULATIVE REVIEW : OTHER *(Specify below)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
9 TYPE A OR B NDA REVIEW 9 END OF PHASE II MEETING 9 CONTROLLED STUDIES 9 PROTOCOL REVIEW	9 CHEMISTRY 9 PHARMACOLOGY 9 BIOPHARMACEUTICS 9 OTHER

III. BIOPHARMACEUTICS

9 DISSOLUTION 9 BIOAVAILABLITY STUDIES 9 PHASE IV STUDIES	9 DEFICIENCY LETTER RESPONSE 9 PROTOCOL-BIOPHARMACEUTICS 9 *IN-VIVO* WAIVER REQUEST

IV. DRUG EXPERIENCE

9 PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL 9 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES 9 CASE REPORTS OF SPECIFIC REACTIONS *(List below)* 9 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	9 REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY 9 SUMMARY OF ADVERSE EXPERIENCE 9 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

9 CLINICAL	9 PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: See attached.

cc: Orig. NDA # 21-861
HFD-570/Div. File
HFD-570/RLostritto/CBertha
HFD-570/TMcGovern/JShah
HFD-570/SBarnes/AZeccolla

SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)* 9 MAIL 9 HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Please evaluate the toxicological assessments provided for the various packaging components in module 3 (3.2.P.2.4 Container Closure System). The documents are included in the following tabs below from that section. Note that the virole gasket currently used is the type 404B but will change to the 404C in the near future and will be in the commercial device:

Table 3.2.P.2.4-3

Physicochemical / Toxicological Testing of Packaging Components for Olopatadine Nasal 0.6%

(b) (4)

[redacted]

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/s/

Richard Lostritto

2/7/05 11:35:21 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION

TO: *(Division/Office)* Tim McGovern, Ph.D., Pharmacology Team Leader (HFD-570)	FROM: Craig M. Bertha (HFD-570)

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
02-FEB-2005	I60,116	21-861	Original	21-DEC-2004

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Patanase (olopatadine HCl nasal spray)	3	S	02-JUN-2005

NAME OF FIRM: Alcon, Inc.

REASON FOR REQUEST

I. GENERAL

9 NEW PROTOCOL 9 PROGRESS REPORT 9 NEW CORRESPONDENCE 9 DRUG ADVERTISING 9 ADVERSE REACTION REPORT 9 MANUFACTURING CHANGE/ADDITION 9 MEETING PLANNED BY	9 PRE-NDA MEETING 9 END OF PHASE II MEETING 9 RESUBMISSION 9 SAFETY/EFFICACY 9 PAPER NDA 9 CONTROL SUPPLEMENT	9 RESPONSE TO DEFICIENCY LETTER 9 FINAL PRINTED LABELING 9 LABELING REVISION 9 ORIGINAL NEW CORRESPONDENCE 9 FORMULATIVE REVIEW : OTHER *(Specify below)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
9 TYPE A OR B NDA REVIEW 9 END OF PHASE II MEETING 9 CONTROLLED STUDIES 9 PROTOCOL REVIEW	9 CHEMISTRY 9 PHARMACOLOGY 9 BIOPHARMACEUTICS 9 OTHER

III. BIOPHARMACEUTICS

9 DISSOLUTION 9 BIOAVAILABLITY STUDIES 9 PHASE IV STUDIES	9 DEFICIENCY LETTER RESPONSE 9 PROTOCOL-BIOPHARMACEUTICS 9 *IN-VIVO* WAIVER REQUEST

IV. DRUG EXPERIENCE

9 PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL 9 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES 9 CASE REPORTS OF SPECIFIC REACTIONS *(List below)* 9 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	9 REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY 9 SUMMARY OF ADVERSE EXPERIENCE 9 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

9 CLINICAL	9 PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: See attached.

cc: Orig. NDA # 21-861
HFD-570/Div. File
HFD-570/RLostritto/CBertha
HFD-570/TMcGovern/JShah
HFD-570/SBarnes/AZeccolla

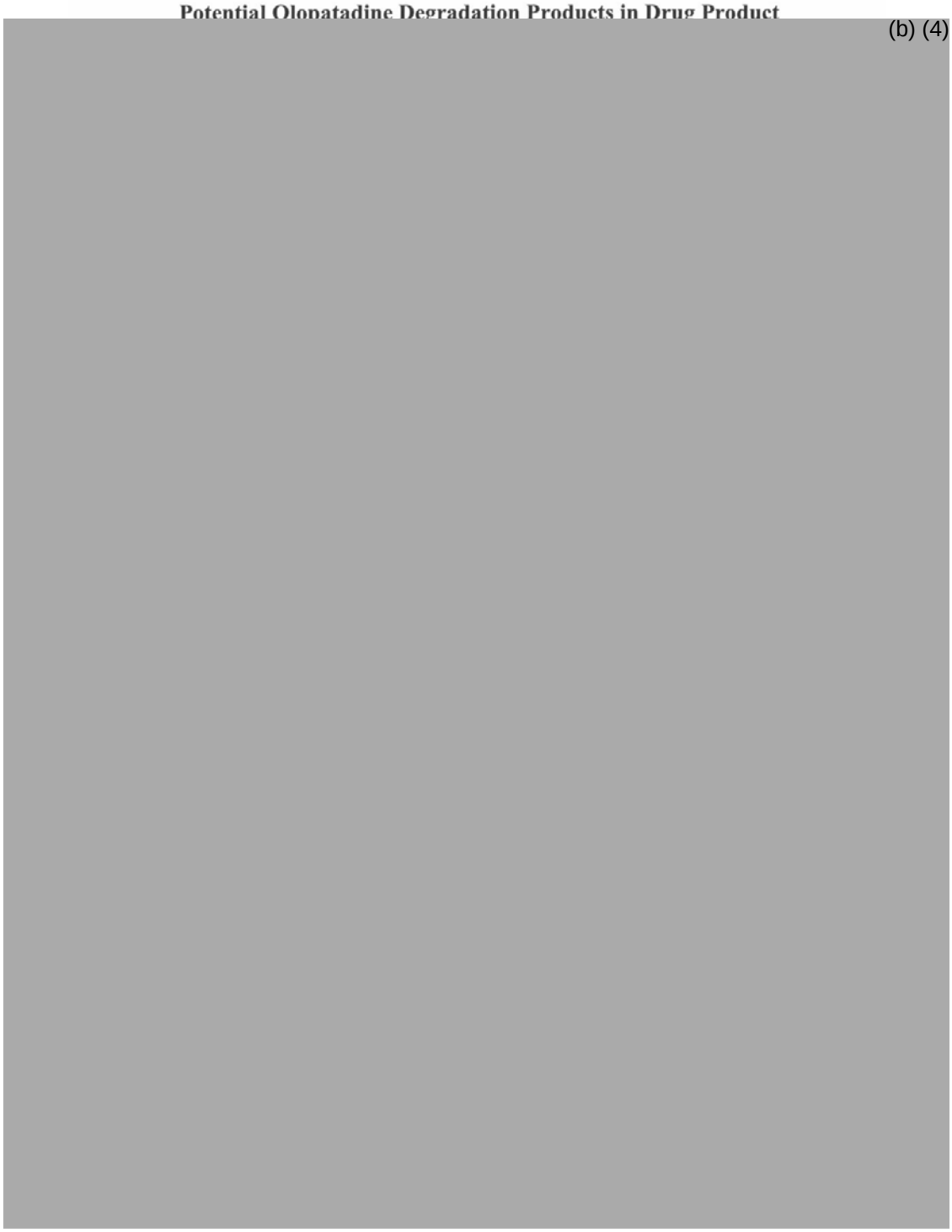
SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)* 9 MAIL 9 HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Please evaluate acceptability of the allowance of (b) (4) (relative to olopatadine) of degradant (b) (4) (relative to olopatadine) of (b) (4) in the drug product formulation. The structures of (b) (4) both have the (b) (4) moieties. With a proposed daily dose of 4.80 mg of olopatadine this would **allow a daily exposure of** (b) (4) **and** (b) (4)**, respectively**.

Table 3.2.P.5.5-1

Potential Olopatadine Degradation Products in Drug Product

(b) (4)



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/s/

Richard Lostritto

2/7/05 11:41:54 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO: *(Division/Office)* D. Hussong, Ph.D., Microbiology Team Leader			FROM: Craig M. Bertha, Ph.D. (HFD-570)	
DATE 2/03/05	IND NO. I60,116	NDA NO. 21-861	TYPE OF DOCUMENT Original (presubmission CMC)	DATE OF DOCUMENT 12/21/04
NAME OF DRUG Patanase® (olopatadine hydrochloride nasal spray)		PRIORITY CONSIDERATION 3	CLASSIFICATION OF DRUG S	DESIRED COMPLETION DATE 6/3/05
NAME OF FIRM: Alcon Inc.				

REASON FOR REQUEST

I. GENERAL

9 NEW PROTOCOL 9 PROGRESS REPORT 9 NEW CORRESPONDENCE 9 DRUG ADVERTISING 9 ADVERSE REACTION REPORT 9 MANUFACTURING CHANGE/ADDITION 9 MEETING PLANNED BY	9 PRE-NDA MEETING 9 END OF PHASE II MEETING 9 RESUBMISSION 9 SAFETY/EFFICACY 9 PAPER NDA 9 CONTROL SUPPLEMENT	9 RESPONSE TO DEFICIENCY LETTER 9 FINAL PRINTED LABELING 9 LABELING REVISION 9 ORIGINAL NEW CORRESPONDENCE 9 FORMULATIVE REVIEW : OTHER *(Specify below)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
9 TYPE A OR B NDA REVIEW 9 END OF PHASE II MEETING 9 CONTROLLED STUDIES 9 PROTOCOL REVIEW 9 OTHER	9 CHEMISTRY 9 PHARMACOLOGY 9 BIOPHARMACEUTICS 9 OTHER

III. BIOPHARMACEUTICS

9 DISSOLUTION 9 BIOAVAILABLITY STUDIES 9 PHASE IV STUDIES	9 DEFICIENCY LETTER RESPONSE 9 PROTOCOL-BIOPHARMACEUTICS 9 *IN-VIVO* WAIVER REQUEST

IV. DRUG EXPERIENCE

9 PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL 9 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES 9 CASE REPORTS OF SPECIFIC REACTIONS *(List below)* 9 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	9 REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY 9 SUMMARY OF ADVERSE EXPERIENCE 9 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

9 CLINICAL	9 PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please evaluate the microbial limits method (SB.M97.2MTP.S0007.R04 in 3.2.P.5.2, vol. 10, module 3, Tab 38), the microbial limits specification acceptance criteria for the drug product (Table 3.2.P.5.1-1 in 3.2.P.5.1, vol. 9, module 3, pp. 1-2), the validation data for the microbial limits and preservative effectiveness testing (3.2.P.2.5 including tabs 1-7, vol. 8, module 3).

cc: Orig. NDA # 21-861
HFD-570/Div. File
HFD-570/RLostritto/CBertha
HFD-570/DHussong
HFD-570/SBarnes/AZecolla

SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)* 9 MAIL 9 HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Richard Lostritto

2/7/05 12:12:15 PM