CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-861s000

CHEMISTRY REVIEW(S)

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

DATE: 24-MAR-2008

TO: N 21-861 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division I, Branch II

THROUGH: Ali Al-Hakim, Ph.D.
Branch Chief
ONDQA, Division I, Branch II

SUBJECT: Revised package insert, patient instructions for use, and product container and carton labels for Patanase® (olopatadine hydrochloride) Nasal Spray, NDA 21-861, 19-MAR-2008, amendment received on 20-MAR-2008

EVALUATION:

Carton and Container Labels

With regard to section V.A.2 of the *Guidance for Industry, Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation*, the information contained on the cartons (both trade and sample) is consistent with the Agency recommendations. Furthermore, the labels for the trade and sample containers comply with the regulation 21 CFR 210.10(i). However, the DMETS may have additional comments on the graphical presentation, font sizes, readability, etc.

Package Insert

No significant changes were made to the DOSAGE FORMS AND STRENGTHS and the HOW SUPPLIED/STORAGE AND HANDLING sections. In the DESCRIPTION section, the applicant has include the target pH and has not included the possible pH range allowed by the specification, as had been recommended by the Agency (e.g., 3.50 – 3.95). The inclusion of the target should still suffice in providing information on the comparative acidity of this drug product formulation compared to the formulations of other similar products on the market that may include such pH information in their label.

Patient Instructions for Use

The CLEANING, STORING, and section entitled BEFORE USING are adequate from a CMC perspective and are supported by the cleaning studies provided in the original application, the current updated stability data, and the priming/repriming studies that were updated in the resubmission, respectively. The ingredients listed are the same as those listed in the DESCRIPTION section of the package insert, which are consistent with the current formulation.

ACTION ITEM: NAI

_____
Craig M. Bertha, Ph.D.
CMC Reviewer, ONDQA

cc:
DPAP/MRaggio
ONDQA/DIV 1/CBertha
ONDQA/DIV 1/PPeri
ONDQA/DIV 1/AAl-Hakim_____

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/s/

Craig Bertha
3/24/2008 07:06:23 AM
CHEMIST

Ali Al-Hakim
3/25/2008 11:48:15 AM
CHEMIST

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

DATE: 18-MAR-2008

TO: N 21-861 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division I, Branch II

THROUGH: Ali Al-Hakim, Ph.D.
Branch Chief
ONDQA, Division I, Branch II

SUBJECT: Review of Drug Listing Data Elements (DLDE) Table for Patanase (olopatadine hydrochloride) Nasal Spray, NDA 21-861

EVALUATION: The DLDE tables for trade and physician sample presentations of the product were reviewed in the SPL. Currently, the following inactive ingredients do not have UNIIs assigned: benzalkonium chloride and hydrochloric acid. The applicant will be asked to revise the single entry of "hydrochloric acid and/or sodium hydroxide to adjust pH" (b) (4) The strength should be given in terms of amount of active per volume of formulation. Other minor edits to the presentation of the inactive ingredients are also needed.

ACTION ITEM: The PM is requested to send the following comments on the DLDE table to the applicant:

1. *Revise the single entry of "hydrochloric acid and/or sodium hydroxide to adjust pH" to* (b) (4)
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.*

_____
Craig M. Bertha, Ph.D.
CMC Reviewer, ONDQA

cc:
DPAP/MRaggio
ONDQA/DIV 1/CBertha
ONDQA/DIV 1/PPeri
ONDQA/DIV 1/AAl-Hakim_____

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/s/

Craig Bertha
3/18/2008 12:21:30 PM
CHEMIST

Ali Al-Hakim
3/18/2008 02:24:08 PM
CHEMIST

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

DATE: 04-MAR-2008

TO: N 21-861 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division I, Branch II

THROUGH: Ali Al-Hakim, Ph.D.
Branch Chief
ONDQA, Division I, Branch II

SUBJECT: Nasal Spray pump configuration for Phase III clinical trial C-05-64 drug product

BACKGROUND:

During the course of the review it was confirmed by contact with Alcon[1] that clinical trial C-05-64 utilized drug product that had the older (b) (4) pump, yet the new povidone free formulation (109941).

EVALUATION: A re-examination of chemistry review #2 dated 14-NOV-2007, revealed that the applicant had provided, as per our earlier request, comparative stability data for the original versus the new povidone-free product. The original product had a formulation containing (b) (4) povidone which was matched with a (b) (4) pump (from now on the (b) (4) pump). The new product, or to-be-marketed configuration, uses a slightly modified (b) (4) pump (from now on (b) (4)) in combination with a povidone-free formulation. The previous (b) (4) pump used in the original product is the same one confirmed to have been used in the C-05-64 clinical trial drug product, however, the formulation in this case was also povidone-free, as it will be in the to-be-marketed product. Thus the clinical trial drug product for C-05-64 is a hybrid between the original product and the to-be-marketed version, where the pump is as in the original but the formulation is as in the new to-be-marketed version.

The (b) (4) version of the (b) (4) pump differs only slightly from the to-be-marketed (b) (4). Specifically, the to-be-marketed (b) (4) pump no longer contains the (b) (4) and the (b) (4) is slightly enlarged to account for (b) (4) As a result, there is no longer any contact of the

[1]A telephone conference was held on 04-MAR-2008, between Miranda Raggio, PM and Craig Bertha, Chemist of the Agency and Seane Jones, Regulatory Affairs and (b) (4) Packaging Engineer from Alcon. At this telecon, Alcon confirmed that clinical trial drug product had a configuration that used the new povidone free formulation 109941 but which used the previous (b) (4) nasal spray pump. This pump was the same as that which had been used with the drug product that had previously been formulated with (b) povidone and which was used in the previous phase III trials and for the former primary stability studies evaluated in chemistry review #1 dated 20-APR-2005.

formulation with the (b) (4) These changes yield a product demonstrating improved stability both in terms of degradants and leachables.

In comparing (b) (4) with (b) (4), no changes have been made to the components of the pump that would be expected to alter the delivery performance. In fact, the stability data provided for the product with the (b) (4) povidone formulation in the original application, which used the (b) (4) pumps, was later found to be sufficiently comparable to the data from the povidone-free product, which used the to-be-marketed (b) (4) pumps, in terms of the typical *in vitro* pump performance test-related parameters of Spray Content Uniformity (SCU), pump delivery, and droplet size distribution (see pp. 44-46, 47-49 of chemistry review #2 dated 14-NOV-2007). Comparability did not extend to the parameters of assay, degradants, and leachables, whereby the new povidone-free formulation with (b) (4) pumps (to-be-marketed configuration), was seen to have superior stability. These stability improvements were directly related to the changes made in going from the older (b) (4) to the newer (b) (4) pump and relate to the improved pump/formulation compatibility.

Thus, even though there have been no *in vitro* performance data presented in the CMC section of the application for the drug product configuration used in the clinical trial C-05-64, i.e., with the new povidone-free formulation and old (b) (4) pump, it is reasonable to expect that had such data been collected, it would also be comparable to that observed for both the (b) (4) povidone/(b) (4) combination and the final to-be-marketed configuration. In other words, if changing both the pump and formulation in going from the original to the to-be-marketed version was not seen to significantly alter the *in vitro* delivery performance, then it is reasonable to expect that the change in the formulation alone, when comparing the C-05-64 trial drug to the original drug, would also yield products with comparable *in vitro* delivery performance.

_____
Craig M. Bertha, Ph.D.
CMC Reviewer, ONDQA

cc:
DPAP/MRaggio
DPAP/CLee
DPAP/JKaiser
ONDQA/DIV 1/CBertha
ONDQA/DIV 1/PPeri
ONDQA/DIV 1/AAl-Hakim_____

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/s/

Craig Bertha
3/4/2008 04:50:45 PM
CHEMIST

Ali Al-Hakim
3/4/2008 05:33:25 PM
CHEMIST

PATANASE (OLOPATADINE HYDROCHLORIDE) NASAL SPRAY
NDA 21-861

Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls

Applicant: Alcon, Inc.
6201 South Freeway, Mail Code R7-18
Fort Worth, TX 76134-2099

Indication: PATANASE is indicated for the (b) (4) treatment of seasonal allergic rhinitis ((b) (4)

Presentation: One strength. Olopatadine hydrochloride 665 mcg per actuation (equivalent to 600 mcg of olopatadine free base). There are (b) (4) presentations, a 30.5 g fill (trade) (b) (4) . The container closure system (CCS) for the trade and the sample size product is the same, (b) (4) The CCS consists of an HPDE bottle fitted with a (b) (4) nasal spray metering pump with dip-tube. The pump is fitted with a nasal actuator designed to produce a fine mist of the metered formulation. The CCS also includes a protective overcap.

EER Status: Withhold. Firm not ready for inspection during week proposed by the Office of Compliance.

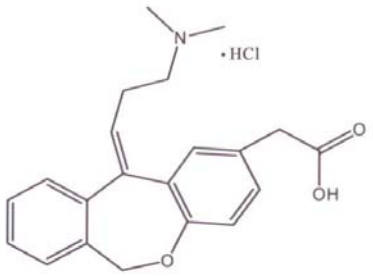
Consults: EA – categorical exclusion provided
Biometrics – No consult forwarded but expiry period of 18 months for trade size (b) (4) for sample size found acceptable.
Methods Validation – Deemed not necessary to be forwarded to Agency laboratory.

Original Submission: 24-DEC-2004
Re-submissions: 26-SEP-2007 (response to AE letter with stamp date 27-SEP-2007)

Post-Approval Agreements: None beyond the typical stability commitment.

Drug Substance: The drug substance olopatadine hydrochloride has the chemical name 11-[(*Z*)-3-(Dimethylamino)propylidene]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-acetic acid, hydrochloride and the structure, molecular formula, and molecular weight shown below (reproduced from application):

- Structural Formula:



- Molecular Formula:

  $C_{21}H_{23}NO_3$•HCl

- Relative Molecular Mass:

  373.88

Conclusion: Drug substance is acceptable.

Drug Product: Patanase® (olopatadine hydrochloride) Nasal Spray 665 mcg (per actuation) is a solution-based product that has two presentations, a 30.5 g fill (trade) and (b) (4) fill (sample).[1] The container closure system (CCS) for the trade and the sample size product is the same. The CCS consists of an HPDE bottle fitted with a (b) (4) nasal spray metering pump with dip-tube. The pump is fitted with a nasal actuator designed to produce a fine mist of 100 mg of the metered formulation. The CCS also includes a protective overcap. The drug substance is an antihistamine related to doxepin, but with an additional acetic acid moiety at the C-2 position. The density of the formulation is (b) (4) The formulation is acidic with a target pH of 3.7 (below the pK_a of the protonated dimethylamine moiety of olopatadine). The relatively low pH is used to improve the solubility of the olopatadine hydrochloride drug substance such that the concentration of 0.6% could be achieved in the formulation. The formulation contains a preservative, benzalkonium chloride, and a preservative aid, edetate disodium, (b) (4) The planned commercial batch size for the drug product solution formulation is (b) (4)

With respect to the original application, the drug product described in the resubmission was reformulated (formulation ID 109941) to remove the povidone (1-vinyl-2-pyrrolidinone polymer) excipient (old formulation ID (b) (4). This change was made in combination with a drop in the target pH from (b) (4) to 3.7.

Povidone was removed from the formulation because of undesirable clinical and pre-clinical findings. Povidone had been used as a (b) (4) for the drug substance.

Contact of the previous formulation with the (b) (4) portion of the previous nasal spray pump was found to lead to the formation of degradants, some of which were suspected of being carcinogenic based on preliminary data (b) (4) In order to reduce the degradation of the drug substance from contact with the (b) (4), the applicant worked with the

[1] As the pump delivers 100 mg per actuation, there is a (b) (4) overfill of formulation for both the trade and sample size of the drug product.

pump manufacturer to design a modified version of the nasal spray pump. The combination of the new pump and the modified formulation has resulted in a drug product that is observed to have an increase in stability with respect to drug substance degradation and leachables levels. In addition, changes were made (b) (4)

The applicant performed a clinical study for seasonal allergic rhinitis (SAR study C-05-64) and perennial allergic rhinitis (PAR study C-05-69) using the new version of the product (new formulation 109941, modified container closure system).

Conclusion: Drug product is satisfactory.

Additional Items: The applicant has adequately responded to all deficiencies noted in the 25-OCT-2005 non-approved (NA) letter.

Adequate stability data were provided to support an 18 month (b) (4) expiration dating periods for the trade and sample sizes, respectively. All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

Overall Conclusion: From a CMC perspective, the application is recommended for approval pending an acceptable recommendation from the Office of Compliance regarding GMPs. Currently, the recommendation is WITHHOLD as the firm was not ready to be inspected at the time proposed by the Office of Compliance.

Ali Al-Hakim, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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/s/

Ali Al-Hakim

2/27/2008 01:36:42 PM

CHEMIST

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

DATE: 26-FEB-2008

TO: N 21-861 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division I, Branch II

SUBJECT: Establish Evaluation Request Status

See the attached summary reproduced from the Establishment Evaluation System regarding the overall recommendation of WITHHOLD from the Office of Compliance for the N21-861 application.

cc:
DPAP/MRaggio
DPAP/CLee
DPAP/JKaiser
ONDQA/DIV 1/CBertha
ONDQA/DIV 1/PPeri
ONDQA/DIV 1/AAl-Hakim
ONDQA/DIV 1/SGoldie

□(s0P□&k4S□&17.27c66F 26-FEB-2008 FDA CDER EES
Page 1 of 1

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21861/000
Org Code : 570
Priority : 3S

Sponsor: ALCON
6201 SOUTH FREEWAY
FORT WORTH, TX 761342099

Stamp Date : 27-DEC-2004
PDUFA Date : 27-MAR-2008
Action Goal :
District Goal: 28-SEP-2007

Brand Name : PATANASE NASAL SPRAY
(OLOPATADINE HCL)
Estab. Name:
Generic Name: OLOPATADINE HCL 0.6%
Dosage Form: (SPRAY)
Strength : 665 MCG/SPRAY OLO.HCL

FDA Contacts:			
	A. ZECCOLA	Project Manager	301-796-1318
	C. BERTHA	Review Chemist	301-796-2410
	R. LOSTRITTO	Team Leader	301-796-2430

Overall Recommendation: WITHHOLD on 07-JAN-2008by S. ADAMS (HFD-325) 301-796-3193
ACCEPTABLE on 05-JUL-2005by DAMBROGIOJ

Establishment : (b) (4) FEI :
ALCON CUSI S A
CAMIL FABRA 58
EL MASNOU, , SP

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile : LIQ OAI Status: NONE
Last Milestone: INSPECTION SCHEDULED

Milestone Date: 12-FEB-08

Establishment : CFN : (b) (4) FEI : (b) (4)

(b) (4)

DMF No: (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : (b) (4) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 29-NOV-07

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

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/s/

Craig Bertha
2/26/2008 08:58:28 AM
CHEMIST

CHEMISTRY REVIEW

NDA 21-861

Patanase® (olopatadine hydrochloride) Nasal Spray 665 mcg

Alcon, Inc.

Craig M. Bertha, Ph.D.
Division I of the
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-861

2. REVIEW #:2

3. REVIEW DATE: 13-NOV-2007

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Pre-submission of modules 2.3 and 3 (QOS and CMC)	21-DEC-2004
Original application	24-DEC-2004
Stability update for batches with "new" (b) (4)	03-FEB-2005
Amendment (response to CMC DR of 25-APR-2005)	11-JUL-2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (resubmission for reformulated product with revised pump)	26-SEP-2007 (stamped 01-OCT-2007)

7. NAME & ADDRESS OF APPLICANT:

Name:	Alcon, Inc.
Address:	6201 South Freeway, Mail Code R7-18 Fort Worth, TX 76134-2099
Representative:	(b) (4)
Telephone:	(b) (4)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Patanase® (proposed)
b) Non-Proprietary Name (USAN): olopatadine hydrochloride nasal spray
c) Code Name/# (ONDQA only): AL-4943A (Alcon code); CAS 140462-76-6 (HCl salt), 113806-05-6 (base)
d) Chem. Type/Submission Priority (ONDQC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: anti-allergic

11. DOSAGE FORM: nasal spray (solution)

12. STRENGTH/POTENCY: 665 mcg olopatadine HCl/spray (equiv. to 600 mcg base/spray), 240 actuations per container (Note: proposed daily dose of two sprays per nostril twice a day or (b) (4)); 100 mg pump delivery

13. ROUTE OF ADMINISTRATION: nasal inhalation

14. Rx/OTC DISPENSED: __X__Rx ___OTC

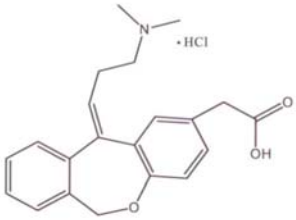
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Olopatadine Hydrochloride ((b) (4)-4679)

- Structural Formula:



- Molecular Formula:
$C_{21}H_{23}NO_3 \bullet HCl$

- Relative Molecular Mass:
373.88

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	2		(b) (4)	3	Adequate	31-JAN-2007	Reviewed for ophthalmic drug of N21-545
	3			3	Adequate	14-MAR-2007	
	3			1	Adequate	19-JUL-2005	
	3			3	Adequate[4]	17-AUG-2006	(b) (4)
	3			1	Adequate	25-OCT-2007	Pump changed from (b) (4)
	3			1	Adequate	25-OCT-2007	

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

[3] Include reference to location in most recent CMC review

[4] With the change to the CP pump configuration, DMF (b) (4) is no longer applicable.

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	60,116	Alcon Inc.	Supporting IND for N21-861 for Patanase® Nasal Spray
NDA	21-545	Alcon Inc.	NDA for Pataday® (olopatadine ophthalmic solution) 0.2% (approved)
NDA	20-688	Alcon Inc.	NDA for Patanol® (olopatadine ophthalmic solution) 0.1% (approved)

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	Not needed.			
EES	PAI	09-FEB-2005		EES Status from OC ACCEPTABLE on 05-JUL-2005
	Update request for resubmission	16-OCT-2007	***Pending***	Cover letter of 26-SEP-2007, amendment states that facilities are "ready for inspection."
Pharm/Tox	-Biological reactivity testing of CCS components	02-FEB-2005	Final, Review of 02-JUN-2005	The CCS components tested negative according to ISO 10993, consistent with compliance to USP <87> and <88> Biological Reactivity Tests
	(b) (4) impurities at (b) (4) %, respectively	02-FEB-2005	Final, Review of 15-JUN-2005	Positive genotoxicity results for (b) (4) impurities. (b) (4) should be controlled to levels of < (b) (4) % relative to active.
	Review of applicant response to NA letter comment 37	16-OCT-2007	***Pending***	Drug product acceptance criteria for degradants (b) (4) depend on the outcome of this consult. Refer to the response and associated evaluation for comment 37 on p. 55.
Biopharm	N/A			
LNC	Not needed.			
Methods Validation	N/A			See evaluation in R6 below on p. 21.
DMETS/DDMAC	Patanase® trademark review	27-FEB-2003	Acceptable	Both forwarded by PM
	Updated labels and labeling	15-NOV-2005	***Pending***	To be forwarded by PM
EA		N/A		Categorical Exclusion based on estimated concentration into aquatic environment of < 1 ppb. See response to comment 46 on p. 63
Microbiology	-Microbial limits/PET and validation	16-OCT-2007	***Pending***	

The Chemistry Review for NDA 21-861

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approve.

However, there are three out-standing consults (Establishment Evaluation Request, Microbiology, Pharmacology/Toxicology) that may further impact the CMC portion of the application and require revisions to be made by the applicant.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Patanase® (olopatadine hydrochloride) Nasal Spray 665 mcg (per actuation) is a solution-based product that has two presentations, a 30.5 g fill (trade) and (b) (4) fill (sample).[1] The container closure system (CCS) for the trade and the sample size product is the same. The CCS consists of an HPDE bottle fitted with a (b) (4) nasal spray metering pump with dip-tube. The pump is fitted with a nasal actuator designed to produce a fine mist of 100 mg of the metered formulation. The CCS also includes a protective overcap. The drug substance is an antihistamine related to doxepin, but with an additional acetic acid moiety at the C-2 position. The density of the formulation is (b) (4). The formulation is acidic with a target pH of 3.7 (below the pK_a of the protonated dimethylamine moiety of olopatadine). The relatively low pH is used to improve the solubility of the olopatadine hydrochloride drug substance such that the necessary concentration of 0.6% could be achieved in the formulation. The formulation contains a preservative, benzalkonium chloride, and a preservative aid, edetate disodium, (b) (4) The planned commercial batch size for the drug product solution formulation is (b) (4)

With respect to the original application, the drug product described in the resubmission was reformulated (formulation ID (b) (4)) to remove the povidone

[1] As the pump delivers 100 mg per actuation, there is a (b) (4) overfill of formulation for both the trade and sample size of the drug product.

(1-vinyl-2-pyrrolidinone polymer) excipient (old formulation ID (b) (4)). This change was made in combination with a drop in the target pH from (b) (4) to 3.7. Povidone was removed from the formulation because of undesirable clinical and pre-clinical findings. Povidone had been used as a solubility enhancer for the drug substance.

Contact of the previous formulation with the (b) (4) portion of the previous nasal spray pump was found to lead to the formation of degradants, some of which were suspected of being carcinogenic based on preliminary data (b) (4); see structures in attachment 3). In order to reduce the degradation of the drug substance from contact with the (b) (4), the applicant worked with the pump manufacturer to design a modified version of the nasal spray pump. The combination of the new pump and the modified formulation has resulted in a drug product that is observed to have an increase in stability with respect to drug substance degradation and leachables levels. In addition, changes were made to the actuator and overcap to increase robustness of the product with regard to shipping and to ease the replacement of the actuator after cleaning by the patient.

The applicant performed a clinical study for seasonal allergic rhinitis (SAR study C-05-64) and perennial allergic rhinitis (PAR study C-05-69) using the new version of the product (new formulation 109941, modified container closure system).

B. Description of How the Drug Product is Intended to be Used

The drug product has a target delivery of 665 mcg olopatadine HCl/spray (equiv. to 600 mcg base/spray) and it is claimed that there are 240 actuations per container for the trade presentation. The proposed daily dose is two sprays per nostril twice a day or (b) (4) The trade size of the product is granted an **18 month expiry**. The sample size (40 actuations) of the product is granted a **12 month expiry**.

C. Basis for Approvability or Not-Approval Recommendation

N/A

III. Administrative

A. Reviewer's Signature (electronic)
B. Endorsement Block (electronic)
C. CC Block

Orig. NDA 21-861
OND/DPAP/Division File
ONDQA/Div 1/CBertha/11/13/07
ONDQA/Div 1/AAl-Hakin
OND/DPAP/MRaggio
OND/DPAP/SBarnes
R/D Init. by: AAl-Hakim_____
Filename and Location: c:\data\mydocuments\reviews etc\NDA\21861\07-09-26_rev.doc

63 pp withheld as (b)(4) CCI/TS.

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/s/

Craig Bertha
11/13/2007 05:49:51 AM
CHEMIST

Ali Al-Hakim
11/14/2007 10:52:12 AM
CHEMIST

CHEMISTRY REVIEW

NDA 21-861

Patanase® (olopatadine hydrochloride) Nasal Spray 665 mcg

Alcon, Inc.

Craig M. Bertha, Ph.D.
Division I of the
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-861

2. REVIEW #:2 addendum

3. REVIEW DATE: 03-MAR-2007

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Pre-submission of modules 2.3 and 3 (QOS and CMC)	21-DEC-2004
Original application	24-DEC-2004
Stability update for batches with "new" virole pump gasket	03-FEB-2005
Amendment (response to CMC DR of 25-APR-2005)	11-JUL-2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (resubmission for reformulated product with revised pump)	26-SEP-2007 (stamped 27-SEP-2007)

7. NAME & ADDRESS OF APPLICANT:

Name:	Alcon, Inc.
Address:	6201 South Freeway, Mail Code R7-18 Fort Worth, TX 76134-2099
Representative:	Seane Jones, MS, RAC, Assoc. Director, Regulatory Affairs
Telephone:	817-568-6296

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Patanase® (proposed)
b) Non-Proprietary Name (USAN): olopatadine hydrochloride nasal spray
c) Code Name/# (ONDQA only): AL-4943A (Alcon code); CAS 140462-76-6 (HCl salt), 113806-05-6 (base)
d) Chem. Type/Submission Priority (ONDQC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: anti-allergic

11. DOSAGE FORM: nasal spray (solution)

12. STRENGTH/POTENCY: 665 mcg olopatadine HCl/spray (equiv. to 600 mcg base/spray), 240 actuations per container (Note: proposed daily dose of two sprays per nostril twice a day or [redacted] (b) (4); 100 mg pump delivery

13. ROUTE OF ADMINISTRATION: nasal inhalation

14. Rx/OTC DISPENSED: __X__Rx ___OTC

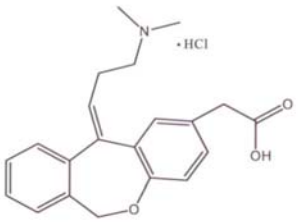
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Olopatadine Hydrochloride (KW-4679)

- Structural Formula:



- Molecular Formula:
$C_{21}H_{23}NO_3 \bullet HCl$

- Relative Molecular Mass:
373.88

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	2		(b) (4)	3	Adequate	31-JAN-2007	Reviewed for ophthalmic drug of N21-545
	3			3	Adequate	14-MAR-2007	
	3			1	Adequate	19-JUL-2005	
	3			3	Adequate[4]	17-AUG-2006	(b) (4)
	3			1	Adequate	25-OCT-2007	Pump changed from (b) (4)
	3			1	Adequate	25-OCT-2007	

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

[3] Include reference to location in most recent CMC review

[4] With the change to the CP pump configuration, DMF (b) (4) is no longer applicable.

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	60,116	Alcon Inc.	Supporting IND for N21-861 for Patanase® Nasal Spray
NDA	21-545	Alcon Inc.	NDA for Pataday® (olopatadine ophthalmic solution) 0.2% (approved)
NDA	20-688	Alcon Inc.	NDA for Patanol® (olopatadine ophthalmic solution) 0.1% (approved)

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	Not needed.			
EES	PAI	09-FEB-2005		EES Status from OC ACCEPTABLE on 05-JUL-2005
	Update request for resubmission	16-OCT-2007	**WITHHOLD**	Cover letter of 26-SEP-2007, amendment states that facilities are "ready for inspection." However, Alcon did not accept inspection dates of Jan. 21-25, 2008, proposed by Agency.
Pharm/Tox	-Biological reactivity testing of CCS components	02-FEB-2005	Final, Review of 02-JUN-2005	The CCS components tested negative according to ISO 10993, consistent with compliance to USP <87> and <88> Biological Reactivity Tests
	(b) (4) impurities at (b) (4) respectively	02-FEB-2005	Final, Review of 15-JUN-2005	Positive genotoxicity results for (b) (4) impurities. (b) (4) should be controlled to levels of (b) (4) relative to active.
	Review of applicant response to NA letter comment 37	16-OCT-2007	Final, Review of 16-OCT-2008	The acceptance criteria for degradants (b) (4) and (b) (4) are acceptable. For more detail refer to p. 55 of chemistry review #2.
Biopharm	N/A			
LNC	Not needed.			
Methods Validation	N/A			See evaluation in R6 on p.21 of chemistry review #2.
DMETS/DDMAC	Patanase® trademark review	27-FEB-2003	Acceptable	
	Updated labels and labeling	15-NOV-2005	Final, Review of 06-NOV-2007	
EA		N/A		Categorical Exclusion based on estimated concentration into aquatic environment of < 1 ppb. See response to comment 46 on p. 63 of chemistry review #2.
Microbiology	-Microbial limits/PET and validation	16-OCT-2007	Final, Review of 28-JAN-2008	Recommended for approval on the basis of microbiological product quality.

The Chemistry Review for NDA 21-861

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable, due to the issuance from the Office of Compliance of a WITHHOLD recommendation for the application. See the attached notes for more detail.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Patanase® (olopatadine hydrochloride) Nasal Spray 665 mcg (per actuation) is a solution-based product that has two presentations, a 30.5 g fill (trade) and (b) (4) fill (sample).[1] The container closure system (CCS) for the trade and the sample size product is the same. The CCS consists of an HPDE bottle fitted with a (b) (4) nasal spray metering pump with dip-tube. The pump is fitted with a nasal actuator designed to produce a fine mist of 100 mg of the metered formulation. The CCS also includes a protective overcap. The drug substance is an antihistamine related to doxepin, but with an additional acetic acid moiety at the C-2 position. The density of the formulation is (b) (4) The formulation is acidic with a target pH of 3.7 (below the pK_a of the protonated dimethylamine moiety of olopatadine). The relatively low pH is used to improve the solubility of the olopatadine hydrochloride drug substance such that the concentration of 0.6% could be achieved in the formulation. The formulation contains a preservative, benzalkonium chloride, and a preservative aid, edetate disodium, (b) (4). The planned commercial batch size for the drug product solution formulation is (b) (4)

With respect to the original application, the drug product described in the resubmission was reformulated (formulation ID 109941) to remove the povidone (1-vinyl-2-pyrrolidinone polymer) excipient (old formulation ID (b) (4)). This change was made in combination with a drop in the target pH from (b) (4) to 3.7.

[1] As the pump delivers 100 mg per actuation, there is a (b) overfill of formulation for both the trade and sample size of the drug product. The trade and sample sizes deliver 240 and 40 actuations, respectively.

Povidone was removed from the formulation because of undesirable clinical and pre-clinical findings. Povidone had been used as a (b) (4) for the drug substance.

Contact of the previous formulation with the (b) (4) portion of the previous nasal spray pump was found to lead to the formation of degradants, some of which were suspected of being genotoxic based on preliminary data (b) (4). In order to reduce the degradation of the drug substance from contact with the (b) (4), the applicant worked with the pump manufacturer to design a modified version of the nasal spray pump. The combination of the new pump and the modified formulation has resulted in a drug product that is observed to have increased stability with respect to drug substance degradation and leachables levels. In addition, changes were made (b) (4)

The applicant performed a clinical study for seasonal allergic rhinitis (SAR study C-05-64) and perennial allergic rhinitis (PAR study C-05-69) using the new version of the product (new formulation 109941, modified container closure system).

B. Description of How the Drug Product is Intended to be Used

The drug product has a target delivery of 665 mcg olopatadine HCl/spray (equiv. to 600 mcg base/spray) and delivers 240 actuations per container for the trade presentation. The proposed daily dose is two sprays per nostril twice a day or (b) which contains (b) (4). The trade size of the product is granted an **18 month expiry**. (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

N/A

III. Administrative

A. Reviewer's Signature (electronic)
B. Endorsement Block (electronic)
C. CC Block

Orig. NDA 21-861
OND/DPAP/Division File
ONDQA/Div 1/CBertha/03/03/08
ONDQA/Div 1/AAl-Hakin
OND/DPAP/MRaggio
OND/DPAP/SBarnes
ONDQA/Div 1/PPeri
R/D Init. by: AAl-Hakim_____
Filename and Location: c:\data\mydocuments\reviews etc\NDA\21861\07-09-26_rev_addendum.doc

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/s/

Craig Bertha
3/3/2008 11:27:01 AM
CHEMIST

Ali Al-Hakim
3/3/2008 12:51:39 PM
CHEMIST

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

DATE: 25-AUG-2005

TO: N 21-861 File

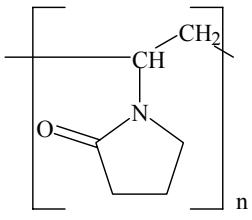
THROUGH: Richard T. Lostritto, Ph.D.
Chemistry Team Leader
Division of Pulmonary and Allergy Drug Products
(HFD-570)

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
Division of Pulmonary and Allergy Drug Products (HFD-570)

SUBJECT: Applicability of CMC-related comments from the 25-APR-2005, CMC DR letter for the upcoming action letter for N21-861 for Patanase® (olopatadine hydrochloride) Nasal Spray

SUMMARY:

The original submission dated 24-DEC-2004, was the subject of chemistry review #1 dated 20-APR-2005. A CMC DR letter dated 25-APR-2005, was forwarded to Alcon Research Ltd. and their response was included in the amendment dated 11-JUL-2005. An internal wrap-up meeting was held in the Division of Pulmonary and Allergy Drug Products (DPADP) on 10-AUG-2005. At this meeting it was revealed by the clinical and pharmacology/toxicology teams that there is an unacceptable level of nasal irritation and damage observed both in preclinical and clinical studies that will require the applicant to remove the povidone excipient from the formulation. Povidone (a homopolymer of 1-vinyl-2-pyrrolidinone) is:



(b) (4)

(b) (4)

Dr. C. Lee's (clinical reviewer) 24-AUG-2005, review concludes the following:

"*The safety data from your clinical program indicate that your drug product is toxic to the nasal mucosa. Clinical and preclinical data suggest that the toxicity is related to the inactive ingredient povidone in the formulation.*

3. These deficiencies may be addressed by the following:

> *b. Reformulate the drug product in order to reduce the risk of nasal pathology in humans."*

Many of the comments of the 25-APR-2005, DR letter are directly or indirectly related to the formulation of the DP. And considering the fact that the Division will be informing the applicant in the upcoming action letter to reformulate the product without povidone, it is not thought to be prudent use of resources to perform a review of the 11-JUL-2005, response of the applicant to the earlier 25-APR-2005, CMC DR letter. But it will be necessary to modify or qualify the previous CMC DR letter comments resulting from the chemistry review of the original application for inclusion in the upcoming action letter. The simplest way to accomplish this would be to preface the CMC-related comments from the DR letter with a statement indicating that some of them may be irrelevant depending on their response to the comment (3.b above) requesting the removal of povidone from the formulation. This will ensure that the applicant will take the responsibility to modify, as appropriate, the responses they have provided in the 11-JUL-2005, amendment to the CMC DR letter, as they apply to their response to the upcoming action letter. They should also be informed in the action letter that we have not reviewed the 11-JUL-2005, amendment.

ACTION ITEM for PM: It is requested that the CMC-related comments from the 25-APR-2005, discipline review letter be included in the upcoming action letter for the application with a prefacing statement indicating that some of them may be irrelevant depending on their response to the comment requesting the removal of povidone from the formulation (refer to comment 3.b from Dr. Lee's clinical review). They should also be informed in the action letter that we have not reviewed the 11-JUL-2005, amendment submitted in response to the CMC DR letter.

_____
Craig M. Bertha, Ph.D.
Chemistry Reviewer

cc:
Orig. NDA 21-861
HFD-570/Div. Files
HFD-570/CBertha 8/25/05
HFD-570/RLostritto
HFD-570/AZeccola

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/s/

Craig Bertha
8/29/2005 06:58:07 AM
CHEMIST

Richard Lostritto
9/1/2005 02:56:01 PM
CHEMIST

CHEMISTRY REVIEW

NDA 21-861

Patanase® (olopatadine hydrochloride nasal spray) 665 mcg

Alcon, Inc.

Craig M. Bertha, Ph.D.
Division of Pulmonary and Allergy Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-861

2. REVIEW #:1

3. REVIEW DATE: 20-APR-2005

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Pre-submission of modules 2.3 and 3 (QOS and CMC)	21-DEC-2004
Original application	24-DEC-2004
Stability update for batches with "new" (b) (4)	03-FEB-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Alcon, Inc.
Address:	6201 South Freeway Fort Worth, TX 76134-2099
Representative:	Seane Jones, MS, RAC, Assoc. Director, Regulatory Affairs
Telephone:	817-551-4052

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Patanase® (proposed)
b) Non-Proprietary Name (USAN): olopatadine hydrochloride nasal spray
c) Code Name/# (ONDC only): AL-4943A (Alcon code); CAS 140462-76-6 (HCl salt), 113806-05-6 (base)
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3

- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: anti-allergic

11. DOSAGE FORM: nasal spray (solution)

12. STRENGTH/POTENCY: 665 mcg olopatadine HCl/spray (equiv. to 600 mcg base/spray), 240 actuations per container (Note: proposed daily dose of two sprays per nostril twice a day or (b) (4) ; 100 mg pump delivery

13. ROUTE OF ADMINISTRATION: nasal inhalation

14. Rx/OTC DISPENSED: __X__Rx ___OTC

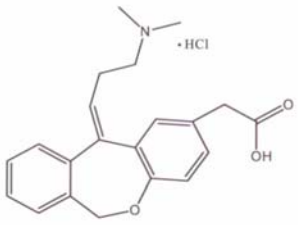
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Olopatadine Hydrochloride ((b) (4)-4679)

- Structural Formula:



- Molecular Formula:
$C_{21}H_{23}NO_3 \bullet HCl$

- Relative Molecular Mass:
373.88

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	2	(b) (4)		3	Adequate	25-FEB-2003	See 21-DEC-2004 review of N21-545
	3			3	Adequate	30-AUG-2001	(b) (4)
	3			1	Inadequate	04-FEB-2005	Deficiency letter forwarded.
	3			3	Adequate	31-JAN-2005	(b) (4)
	3			1	Inadequate	09-FEB-2005	Deficient due to supporting DMF (b) Deficiency letter forwarded.
	3			1	Inadequate	09-FEB-2005	Deficiency letter forwarded.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	60,116	Alcon Inc.	Supporting IND for N21-861 for Patanase® Nasal Spray
NDA	21-545	Alcon Inc.	NDA for Patanol® (olopatadine ophthalmic solution) 0.2% (approved)
NDA	20-688	Alcon Inc.	NDA for Patanol® (olopatadine ophthalmic

			solution) 0.1% (approved)

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				Once impurities acceptance criteria are finalized with the applicant following the (b) (4) a consult to biometrics may be necessary.
EES	PAI	09-FEB-2005	Pending	
Pharm/Tox	-Biological reactivity testing of CCS components (b) (4) impurities at (b) and (b) respectively	02-FEB-2005 02-FEB-2005	Pending Pending	
Biopharm				
LNC	Not needed.			
Methods Validation				Will be forwarded if necessary after methods and specifications are finalized.
DMETS	Patanase® trademark review	27-FEB-2003 (through I60-116) 23-MAR-2005	Pending Pending	From 17-FEB-2003 (SN 033) submission to I60-116
EA		N/A		Categorical Exclusion based on estimated concentration into aquatic environment of < 1 ppb. Will request calculation of estimate.
Microbiology	-Microbial limits/PET and validation	03-FEB-2005	Pending	

The Chemistry Review for NDA 21-861

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The applicant will be asked to agree to undertake a study to determine the cause of the increased rate of drug substance degradation when the drug product is stored in a (b) (4) The goal should be to improve the product to limit this undesirable degradation.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Patanase® (olopatadine hydrochloride) Nasal Spray 665 mcg (per actuation) is a solution-based product that has two presentations, a 30.5 g fill (trade) and (b) (4) fill (sample). The container closure system (CCS) for the trade and the sample size product is the same, (b) (4). The CCS consists of an HPDE bottle fitted with a (b) (4) nasal spray metering pump with dip-tube. The pump is fitted with a nasal actuator designed to produce a fine mist of the metered formulation. The CCS also includes a protective overcap. The drug substance is an antihistamine related to doxepin, but with an additional acetic acid moiety at the C-2 position. It is this additional moiety that allows the formation of two degradants that contain the (b) (4) structural alert for mutagenicity. The density of the formulation is (b) (4) The formulation is somewhat acidic with a target pH of (b) (4) The lower pH is used to improve the solubility of the olopatadine HCl drug substance such that the necessary concentration of 0.6% could be achieved in the formulation. (b) (4) The formulation contains two preservatives, benzalkonium chloride and edetate disodium, (b) (4) The planned commercial batch size for the drug product formulation is (b) (4)

There were numerous preclinical studies cited in the application, but only some of these used the formulation (b) (4) that is to-be-marketed, a two week rat intranasal study, and two three month rat intranasal studies for degradants and

leachables. The pivotal clinical trials used the to-be-marketed formulation, however, there were some minor changes made to the CCS for the version to be commercialized. (b) (4)

B. Description of How the Drug Product is Intended to be Used

The drug product has a target delivery of 665 mcg olopatadine HCl/spray (equiv. to 600 mcg base/spray) and it is claimed that there are 240 actuations per container for the trade presentation. The proposed daily dose is two sprays per nostril twice a day or (b) (4) The drug product has labeling that specifies (b) (4) The applicant proposes a (b) (4) expiration dating period for the trade product and (b) (4) for the physician sample product.

C. Basis for Approvability or Not-Approval Recommendation

After a complete review of the ~6500 pages (22 volumes plus amendment) of CMC information submitted to support the approval of the product, multiple deficiencies have been identified and these are included in the attached draft discipline review letter to be forwarded to the applicant. While some of these comments merely seek clarification of issues and findings, others address more serious CMC problems. These are stratified in the Draft Letter comments.

The formulation development appears limited and has taken, as a starting point, the formulation of the related Patanol ophthalmic products that the applicant has already had approved. However, a larger concentration of olopatadine HCl was needed for the current nasal product requiring the addition of povidone to the formulation and lowering of the pH from 7.0 of the Patanol formulations to (b) The use of a phosphate buffer at this pH is a poor choice and is a sign of the limited formulation development that has gone into the current product.

The applicant's procedure for the collection of the spray content uniformity (SCU) data, considered a direct measurement of product dosing performance, uses a (b) (4) strategy which leads to serious questions regarding the representative nature of the collected SCU data to the true product dosing performance.

Tail-off data are provided and point to a potential problem with samples from one of the tested batches. It is unclear that the current label claim of 240 available actuations is supported.

The design of the actuator is such that it is very difficult to replace it onto the pump, for example, after the actuator cleaning procedure is applied. The applicant is asked to make modifications to the design of the actuator that would make the replacement practical. (b) (4)

Stability studies have revealed that the olopatadine is more susceptible to degradation if the product (b) (4) The applicant merely plans to (b) (4) As patients are unlikely to consistently comply with this guidance, and some of the impurities of olopatadine that are identified have structural alert moieties (b) (4) the applicant will be informed that their routine post-approval stability studies will need to include samples stored horizontally. The Division's pharmacology/toxicology team is currently assessing the qualification data for the impurities with the structural alert moieties. The outcome of this may impact on the impurities acceptance criteria and/or the expiry period for the drug product, particularly since the applicant will need to include (b) (4) in their post-approval stability protocol.

In addition to these specific issues, many of the applicant's proposed drug product acceptance criteria for parameters are much broader than the ranges of data collected at release and on stability for these parameters. As such, there is the potential that higher variability of future drug product will go unchecked.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

C. CC Block

Orig. NDA 21-592
HFD-570/Division File
HFD-570/CBertha
HFD-570/RLostritto
HFD-570/AZecolla
HFD-570/SBarnes
R/D Init. by: RLostritto_____
Filename and Location: c:\data\mydocuments\reviews etc\NDA\21861\04-12-24_rev.doc

106 pp withheld immediately after this page as (b)(4) CCI/TS.

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/s/

Craig Bertha
4/20/05 06:11:20 AM
CHEMIST

Richard Lostritto
4/20/05 12:10:23 PM
CHEMIST

CHEMISTRY NDA FILEABILITY CHECKLIST

NDA: 21-861

Applicant: Alcon, Inc.

Letter Date: 24-DEC-2004

FILING REVIEW
DATE: 24-JUN-2004

TO: N21-861 File

THROUGH: Richard T. Lostritto, Ph.D.
Chemistry Team Leader
Division of Pulmonary Drug Products (HFD-570)

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
Division of Pulmonary Drug Products (HFD-570)

SUBJECT: Filing Review for N21-861 Patanase® (olopatadine hydrochloride nasal spray) 665 mcg

IS THE CMC SECTION OF APPLICATION FILEABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		

12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		Covered in 2.3.P.2 under Product Development
14	Is there a Methods Validation package?		X	Available upon request as stated in 3.2.R.6
15	Is a separate microbiological section included?	Not applicable		Product is not sterile. Microbiological information is in 3.2.P.2.5

Have all DMF References been identified? YES

DMF (b) from (b) (4) for the (b) (4) for the bottle
DMFs (b) (4) from
(b) (4) for the (b) (4)
DMF (b) (4) from (b) for the (b) (4)

7 pp withheld immed after this page as (b)(4) CCI/TS

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

/s/

Craig Bertha
2/9/05 07:33:43 AM
CHEMIST

Filing Review, see hardcopy in box

Richard Lostritto
2/9/05 04:28:22 PM
CHEMIST