CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-545

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY FOR NDA # 21-545 SUPPL #_____

Trade Name _____ Generic Name olopatadine

hydrochloride ophthalmic solution 0.2%

Applicant Name Alcon Research, Ltd. Division # HFD-550

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /X/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES / / NO /_X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /__/ NO /_X_/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-688 _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations"

to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain:

---

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

1) Study #C-02-67 3)C-00-36 5)C-01-100 7) C-01-77

2) Study #C-02-45 4) C-01-18 6) C-01-10 8) C-00-23

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 - 8 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 - 8 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

C-02-45 C-00-36 C-01-100 C-01-77

C-02-67 C-01-18 C-01-10 C-00-23

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question

3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 60,911 YES /_X_/ ! NO /___/ Explain: _____

Investigation #2 - 8

IND # 60,911 YES /_X_/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

(See appended electronic signature page)

Signature: Wiley A. Chambers, M.D. Date: December 22, 2004
Title: Deputy Division Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products

Form OGD-011347 Revised 05/10/2004

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/s/

Wiley Chambers
12/22/04 05:08:31 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-545 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** N/A: RS

Stamp Date: August 15, 2002 **Action Date:** December 22, 2004

HFD -550 **Trade and generic names/dosage form:** olopatadine hydrochloride ophthalmic solution, 0.2%

Applicant: Alcon Research Ltd. **Therapeutic Class:** olopatadine hydrochloride ophthalmic solution, 0.2%

Indication(s) previously approved: None.

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

Number of indications for this application(s): 1

Indication #1: ocular itching associated with allergic conjunctivitis

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** ____ **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.** 3	**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 below the age of 3 years.**
- ☐ **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:

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:

Min _____ kg_____ mo._____ yr._3___ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments: We note that the pediatric study requirement for this application has been fulfilled.

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: Alison Rodgers

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 21-545
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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/s/

Wiley Chambers
12/22/04 05:14:55 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V

FACSIMILE TRANSMITTAL SHEET

DATE: December 14, 2004

To: Angela Kothe	**From:** Alison Rodgers
Company: Alcon Research, Ltd.	Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550
Fax number: 817-551-4630	**Fax number:** 301-827-2531
Phone number: 817-551-4933	**Phone number:** 301-827-2019

Subject: NDA 21-545
Proposed label

Total no. of pages including cover: 5

Comments:
Hi Angela:
Attached is a proposed label. I will send it electronically as well once I have your email address.
Alison

Document to be mailed: ☐ YES ☑ NO

Attachment

A

4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative-_____

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-545

Alcon, Inc.
c/o Alcon Research, Ltd.
Attention: Angela C. Kothe, OD, PhD
Associate Director, Regulatory Affairs
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Dr. Kothe:

We acknowledge receipt on November 8, 2004 of your November 5, 2004 resubmission to your new drug application for — (olopatadine hydrochloride ophthalmic solution), 0.2%.

We consider this a complete, class 1 response to our June 4, 2004 action letter. Therefore, the user fee goal date is January 8, 2005.

If you have any question, call Alison Rodgers, Regulatory Project Manager, at (301) 827-2019.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, RPH
Chief Project Manager
Division of Anti-Inflammatory, Analgesics,
and Ophthalmics
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Carmen DeBellas
11/19/04 11:18:29 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V

FACSIMILE TRANSMITTAL SHEET

DATE: November 19, 2004

To: Angela Kothe	**From:** Alison Rodgers
Company: Alcon Research, Ltd.	Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550
Fax number: 817-551-4630	**Fax number:** 301-827-2531
Phone number: 817-551-4933	**Phone number:** 301-827-2019

Subject: Request Safety Update

Total no. of pages including cover: 1

Comments:

Re: NDA 21-545 (Patanol)

Hi Angela:

Under 21 CFR 314.50(d)(5)(vi)(*b*), you are required to update your NDA by submitting all new safety information you now have regarding your new drug.

Please contact me if you have any questions. Thank you.
Alison Rodgers

Document to be mailed: • YES ☑ NO

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/s/

Alison Rodgers
11/19/04 11:34:37 AM
CSO

Alison Rodgers
11/19/04 11:36:47 AM
CSO

Rodgers, Alison

From: Hussong, David
Sent: Tuesday, November 16, 2004 4:29 PM
To: Rodgers, Alison
Cc: Ng, Linda L; McVey, James
Subject: 21-545

Alison,

I have looked at this resubmission and compared it with Dr Stinavage's review of the original submission. The significant CMC/microbiology changes appear to be the trade-size containers are consolidated from [redacted] bottles to a 4 mL oval bottle.

What appears unreported is whether the closures and dropper tips are the same as described in the original submission, and whether the oval polypropylene bottles are [redacted] The new container system should [redacted] test. The method of [redacted] should be described and validated (or referenced).

I don't believe there is anything here to review by microbiology.

Dave

David Hussong, Ph.D.
Associate Director for New Drug Microbiology
Office of Pharmaceutical Science/CDER
US Food and Drug Administration
(301) 827-7490
FAX (301) 827-3084

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-545

Alcon, Inc.
c/o Alcon Research, Ltd.
Attention: Angela C. Kothe, O.D., Ph.D.
Associate Director, Regulatory Affairs
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Dr. Kothe:

Please refer to the meeting between representatives of your firm and FDA on July 23, 2004. The purpose of the meeting was to discuss the deficiencies listed in the approvable letter issued June 4, 2004.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Raphael R. Rodriguez, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

CDER
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	July 23, 2004
SCHEDULED START TIME:	1:00 – 2:00 pm
START TIME:	1:05 pm
END TIME:	2:05 pm
LOCATION:	9201 Corporate Boulevard
APPLICATION (DRUG):	NDA 21-545
Drug:	**Olopatadine HCl Ophthalmic Solution 0.2%**
Indication:	**Treatment of ocular itching associated with allergic conjunctivitis**
SPONSOR:	Alcon, Inc c/o Alcon Research, Ltd.
TYPE OF MEETING:	Guidance Meeting (Type C meeting)
MEETING CHAIR:	Wiley A. Chambers, M.D.
MEETING RECORDER:	Raphael R. Rodriguez

FDA Attendees: Wiley Chambers, Jonca Bull, William Boyd, Jennifer Harris, Lucious Lim, Rhea Lloyd, Martin Nevitt, Linda Ng, Terri Rumble, Carmen Debellas, Lori Gorski, Raphael Rodriguez

Alcon Attendees: Scott Kruger, Stella Robertson, Angela Kothe, Michael Pfleger, Ken Sullivan

The sponsor did not provide specific questions for Agency response prior to the meeting.

Alcon presented a proposal to substitute a modified packaging system for Olopatadine 0.2% to address Agency concerns that the originally proposed
lead to consumer complaints. The modified package would be Alcon's 4mL LDPE white oval DROP-TAINER (previously approved). Alcon believes the existing data support the approval of this packaging configuration for Olopatadine 0.2% and plans to file an NDA Amendment for this change. Based on the information provided in the meeting package, Chemistry agreed with the proposal to submit an amendment for review.

Alcon presented a summary of their clinical conclusions. The Division disagrees with the Alcon's clinical conclusions for the following reasons:

1. The Division does not consider subject recall over a 3 previous day period to be a reliable measure.
2. There are no assessments adequately addressing the duration of the effect to support once a day dosing.
3. The Division believes that the "analysis of slopes" provides a method to assess a clinically significant effect.
4. The duration of action studies demonstrate that the effect wears off before 16 hours.

The Division concludes that the data may support the use of olopatadine HCl ophthalmic solution but that the data does not support a duration of use suggesting once a day therapy.

Options include conducting another study directed at establishing the efficacy at the end of the dosing period or The agency is also willing to review other alternatives.

APPEARS THIS WAY
ON ORIGINAL

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/s/

Wiley Chambers
7/30/04 01:20:24 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-545

Alcon, Inc.
c/o Alcon Research, Ltd.
Attention: Angela C. Kothe, O.D., Ph.D.
Associate Director, Regulatory Affairs
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Dr. Kothe:

Please refer to your new drug application (NDA) dated August 14, 2002, received August 15, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [redacted] (olopatadine hydrochloride ophthalmic solution) 0.2%.

We also refer to your June 18, 2003, correspondence; received June 21, 2004, requesting a meeting to discuss what further steps must be taken before your application can be approved.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled Formal Meetings with Sponsors and Applicants for PDUFA Products (February 2000). The meeting is scheduled for:

Date: July 23, 2004
Time: 1:00 PM
Location: 9201 Corporate Blvd.
Rockville, MD, 20850
Room S300

CDER participants will be provided in another correspondence.

If you decide to have a face to face meeting, please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at halonenn@cder.fda.gov. so I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room:
Nancy Halonen at 301-827-2199 or Ms. Lori Benner at 301-827-2040.

I f you decide on a teleconference, please provide call-in phone number and pass code arrangements for the Agency to call you.

Provide the background information for this meeting (three copies to the NDA and 25 desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by July 6, 2004, we may cancel or reschedule the meeting.

If you have any questions, call Nancy Halonen, Regulatory Project Manager, at (301) 827-2199.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Nancy Halonen
6/22/04 07:36:07 AM
Nancy Halonen signing for Carmen DeBellas

B

31 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	1836
CONNECTION TEL	918175514630
CONNECTION ID	ALCON LABS
ST. TIME	04/28 13:29
USAGE T	00'24
PGS. SENT	2
RESULT	OK

FACSIMILE TRANSMISSION RECORD

From: Yong de Lu, Ph.D.

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550

Phone 301-827-2040
Fax 301-827-2531

Date: 4/28/04

TO:

Name Angela Kothe
Company Alcon
City Fort Worth State TX
Phone # 817-551-4933

FAX # 817-551-4630

Number of Pages (INCLUDING COVER PAGE) 2

Please telephone (301) 827-2040 IMMEDIATELY if re-transmission is necessary.

Additional message:

April 28, 2004

NDA 21-545

PATANOL® (Olopatadine Ophthalmic Solution) 0.2%

CMC COMMENTS

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the 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 are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, provide the appropriate information as an amendment to the submission.

1.

2. Please submit the mock-up of the labels for the sample size of the drug product.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-545

Alcon, Inc.
c/o Alcon Research, Ltd.
Attention: Angela C. Kothe, O.D., Ph.D.
Associate Director, Regulatory Affairs
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Dr. Kothe:

We acknowledge receipt on December 12, 2003, of your December 11, 2003, resubmission to your new drug application for olopatadine hydrochloride ophthalmic solution 0.2%.

We consider this a complete, class 2 response to our May 28, 2003, action letter. Therefore, the user fee goal date is June 12, 2004.

If you have any question, call Nancy Halonen, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Nancy Halonen
12/18/03 08:31:07 AM
Nancy Halonen signing for Carmen DeBellas

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-545

Alcon Research, Ltd.
Attention: Angela C. Kothe, O.D., Ph.D.
Assistant Director, Regulatory Affairs
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Dr. Kothe:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: —— . (olopatadine Hcl ophthalmic solution) 0.2%

Review Priority Classification: Standard

Date of Application: August 14, 2002

Date of Receipt: August 16, 2002

Our Reference Number: NDA 21-545

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 14, 2002, in accordance with 21 CFR 314.101(a). If the application is filed, the goal date will be June 15, 2003.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Attention: Document Room N115
9201 Corporate Blvd
Rockville, MD 20850

If you have any questions, call Raphael R. Rodriguez, Regulatory Project Manager, at (301) 827-2090

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief Project Manager
Division of Anti-Inflammatory, Analgesic
And Ophthalmic Drugs, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Carmen DeBellas
10/11/02 02:02:22 PM

PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST

NDA Number: 21-545 **Applicant: ALCON, INC.** **Stamp Date: August 15, 2002**
Drug Name: Olopatadine Hydrochloride Ophthalmic Solution, 0.2%

IS THE PHARM/TOX SECTION OF THE APPLICATION FILABLE? Yes [X] No [ ]

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

	Parameters	Yes	No	Comment
1	On its face, is the Pharmacology/Toxicology section of the NDA organized in a manner to allow substantive review to begin?	√		
2	Is the Pharmacology/Toxicology section of the NDA indexed and paginated in a manner to allow substantive review begin?	√		
3	On its face, is the Pharmacology/Toxicology section of the NDA legible so that substantive review can begin?	√		
4	Are ALL required* and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, ocular toxicity studies*, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)?	√		The preclinical section includes studies previously submitted under NDA 20-688 (PATANOL®). The new formulation differs from that in PATANOL® by increased concentration of the active ingredient from 0.1 to 0.2% and the addition of two excipients. Two local tolerance studies and a 3-month topical ocular safety and systemic toxicity study with the new formulation were submitted.
5	If the formulation to be marketed is different from that used in the toxicology studies, has the sponsor made a appropriate effort to either repeat the studies with the to be marketed product or to explain why such repetition should not be required?	√		See comments in #4.
6	Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	√		
7	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions?	√		
8	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?	√		Both topical ocular (intended) and oral route of administration were used in the preclinical studies.
9	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	√		
10	Has the sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?		√	The Sponsor did not submit a statement but the protocol reflects that animals were treated humanely.
11	From a pharmacology perspective, is this NDA fileable?	√		

Note:

Reviewing Pharmacologist:

Maria I. Rivera, Ph.D. Date:

Acting Team Leader:

Josie Yang, Ph.D. Date

cc:
NDA 21-545/Original NDA
HFD-550/Division File
HFD-550/Pharm-Tox/M. Rivera
HFD-550/Pharm-ToxTL/J. Yang
HFD-550/MO/M. Feinsod
HFD-550/PM/R. Rodriguez

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/s/

Maria I. Rivera
8/29/02 04:16:58 PM
PHARMACOLOGIST

Josie Yang
8/29/02 04:37:16 PM
PHARMACOLOGIST

IND 60,991 Olopatadine HCl Ophthalmic Solution 0.2%
EOP2 Meeting May 14, 2001

FDA Attendees:
Wiley Chambers
Jonca Bull
Lucious Lim
Jennifer Harris
Zhou Chen
William Boyd
Linda Ng
Allan Fenselau
Yong-de Lu
Mike Puglisi
Lori Gorski
Chiwan Chen
Stan Lin
Choi Suktae
Raphael Rodriguez

Alcon Attendees:
Scott Krueger
Stella Robertson
Darell Turner
Terri Pasquine
Michael Bergamini
Kurtis Klein
Angela Kothe

Chemistry:

1. Preliminary stability studies have shown that the degradation profile for Olopatadine QD could be different from the current marketed Olopatadine ophthalmic solution 0.1%. Alcon intend to set specifications based on primary stability batches and all degradation products above ICH limits will be biologically qualified. Does the Division concur with this approach?

   Response: Setting of acceptance criteria for impurities should be based on manufacturing capability using actual stability data. Impurities above 1.0% or 50 mcg TDI, whichever is lower, should be biologically qualified if not already done so for the approved product. (YL)

2. Alcon plans to assess particulate matter in unit dose sample size by

   Response: No. Using is not a reliable approach to assess the particulate matter of the drug product. (YL)

   Alcon asked if it is acceptable to provide long term stability data in the NDA submission. **Response:** long term stability data will be acceptable, but agency prefers to see long term stability data in the NDA submission. (LN)

Toxicology:

1. Alcon plans to address the non-clinical ocular safety of Olopatadine Ophthalmic Solution 0.2% by referencing the NDA for PATANOL® 0.1% (NDA #20-688) for which 3 topical ocular studies were conducted in 2 species (a one month and a six month study in rabbit utilizing concentrations up to 0.2% and 1%, respectively; and a one six month study conducted in monkey utilizing a maximum concentration of 0.5%). In addition, Alcon is conducting two topical ocular studies in rabbit (one acute dosing study and one three month study) in which the olopatadine QD formulation is being dosed at concentrations up to 0.4%. Does the Division concur with this approach ?

   Response: Concur. (ZC)

2. Does the Agency have any comment concerning our development plan for addressing non-clinical safety ?

   Response: The development plan looks fine. No comments at this time. (ZC)

Pharmacokinetics / ADME:

1. Alcon plans to address the non-clinical pharmacokinetics/ADME of Olopatadine Ophthalmic Solution 0.2% by referencing the NDA for PATANOL® 0.1% (NDA #20-688), and by conducting an ocular pharmacokinetic distribution study in rabbits with Olopatadine QD. Does the Division concur with this approach ?

   Response: Concur. (ZC)

2. Does the Agency have any comment concerning our data package for non-clinical PK / ADME ?

   Response: The data seem adequate to support an NDA filing. No comments at this time. (ZC)

Clinical:

1. Are the number of studies, proposed study designs and number of patients proposed in the clinical development plan adequate for supporting the approvability of Olopatadine HCl Ophthalmic Solution 0.2% for the treatment of allergic conjunctivitis ?

   Response: The agency strongly recommends 2 controlled trials with reproducible results with a minimum of 300 patients exposed to the drug product at the time of NDA filling. One allergen challenge study and one environmental study are acceptable to study the efficacy for the allergic conjunctivitis. The agency requires that the proposed drug show clinical superiority to placebo for

2. Assuming the results of the clinical studies (as outlined in the clinical development plan contained herein) are successful, does the Agency support the following proposed Dosage and Administration statement:

Indications and Usage:

Dosage and Administration: The recommended dose is one drop in each eye once daily.

Response: A decision on the content of the label will be made after review of the NDA; however, the proposed clinical studies are .

3. Does the Division agree that positive results in a 16hour duration-of-action CAC study support once-daily dosing ?

Response: Agree. (JDH)

4. Does the Division agree that one CAC study and one 12 week environmental study are sufficient to establish the efficacy of Olopatadine QD for once-daily dosing ?

Response: Agree. (JDH)

5. The proposed clinical plan will result in 200 patients exposed to Olopatadine HCl Ophthalmic Solution 0.2%, 120 patients for up to 12 weeks. Does the Division agree that this number, together with the safety experience of PATANOL 0.1% dosed twice-daily is sufficient for supporting the safety of Olopatadine QD ?

Response: The agency strongly recommends that at least 300 patients be exposed to the study drug at or above the proposed concentration for at least 6 weeks at the time of NDA filing. (JDH)

6. Alcon believes that accumulated experience with PATANOL (Olopatadine HCl Ophthalmic Solution) 0.1% dosed twice-daily is sufficient to confirm the safety of Olopatadine QD (0.2%) dosed once-daily in patients as young as three years of age, and does not warrant that Alcon conduct a safety study in an additional pediatric population. Is the Division in agreement with this approach ?

Response: Disagree. The agency recommends a separate pediatric safety study in pediatric patients with Olopatadine QD. (JDH)

7. Alcon believes that the pharmacokinetic studies conducted using 2 drops of Olopatadine Ophthalmic Solution 0.15% administered twice-daily to both eyes

are sufficient to establish that once-daily dosing of one drop Olopatadine QD (0.2%) to both eyes will result in negligible plasma levels of Olopatadine. Is the Division in agreement with this conclusion ?

Response: Yes. However, the label for 0.2% Olopatadine ophthalmic solution would state that information regarding systemic bioavailability upon topical ocular administration from this formulation is not available. The label —

8. Does the Division agree that the clinical studies are adequate for demonstrating safety and efficacy in adults and children 3 years of age and older

Response: Disagree. See comments for questions 1, 5 and 6. (JDH)

Other:

9. Does the Division have any other advice concerning our development of Olopatadine HCl Ophthalmic Solution 0.2% for the treatment of the signs and symptoms of allergic conjunctivitis that the Division believes is important in ensuring the fileability / approvability of our proposed NDA ?

Response: The drug product will not be able to make — without additional studies. (WAC)

Environmental study - Itching questionnaire should be for the study day, not before. Clinical significance will need to be defined and agreed to by agency. (WAC)

Administrative:

Financial Disclosure:

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective, or that makes a significant contribution to demonstration of safety. Please refer to "Financial Disclosure by Clinical Investigators" Final Rule February 2, 1998.

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/s/

Jonca Bull
5/17/01 08:32:50 AM

Wiley Chambers
nulldate

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-545	Efficacy Supplement Type SE-	Supplement Number	
Drug: olopatadine HCl ophthalmic solution, 0.2%		Applicant: Alcon Research, Ltd.	
RPM: Alison Rodgers		HFD-550	Phone # 301-827-2019

Application Type: **(X)** 505(b)(1) ( ) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	**(X)** Standard ( ) Priority
• Chem class (NDAs only)	New formulation
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	January 8, 2005
❖ Special programs (indicate all that apply)	**(X)** None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	**X)** Paid UF ID number
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes **(X)** No

• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).*	( ) Yes ( ) No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE 5-28-03, AE 6-4-04
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	12-20-04
• Original applicant-proposed labeling	8-14-02
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC: 3-25-04 DMETS: 1-17-02, 10-23-02, 3-10-03, 6-3-04
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	12-17-04
• Reviews	See Chemist and Medical Officer reviews
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	In package
❖ Memoranda and Telecons	None
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	5-14-01
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	In package
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	12-21-04
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	5-2-03, 5-2-03, 5-21-03, 6-3-04, 12-13-04
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	9-19-02, See clinical reviews 12-13-04
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	6-4-04
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	See clinical review
❖ Biopharmaceutical review(s) *(indicate date for each review)*	3-3-03
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	5-1-03, 6-2-0, 12-21-04
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	Waived, see CMC Review 5-1-03
• Review & FONSI *(indicate date of review)*	Not required.
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	9-19-02
❖ Facilities inspection (provide EER report)	Date completed: November 4, 2003 **(X)** Acceptable ( ) Withhold recommendation
❖ Methods validation	**(X)** Completed Waived, see CMC review, 5-1-03 ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	8-29-02, 2-24-03, 8-31-04
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

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/s/

Alison Rodgers
12/22/04 05:17:18 PM