

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
203491Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 203491

SUPPL #

HFD #

Trade Name: none

Generic Name: nepafenac ophthalmic suspension

Applicant Name: Alcon Research, Ltd.

Approval Date, If Known: October 16, 2012

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 questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES

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

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

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

Three years

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

YES

NO

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

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

NO

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

NDA# 21862

Nevanac

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**

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 NDAs 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 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 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

(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

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

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:

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	C-09-053	YES <input type="checkbox"/>	<u>NO</u>
Investigation #2	C-11-003	YES <input type="checkbox"/>	<u>NO</u>
Investigation #3	C-09-055	YES <input type="checkbox"/>	<u>NO</u>

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	C-09-053	YES <input type="checkbox"/>	<u>NO</u>
Investigation #2	C-11-003	YES <input type="checkbox"/>	<u>NO</u>
Investigation #3	C-09-055	YES <input type="checkbox"/>	<u>NO</u>

(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

!

!

! NO

Explain:

! 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

If yes, explain:

Name of person completing form: Diana Willard

Title: Chief, Project Management Staff

Date: October 4, 2012

Name of Division Director signing form: Renata Albrecht, M.D.

Title: Director, Division of Transplant and Ophthalmology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

DIANA M WILLARD
10/15/2012

RENATA ALBRECHT
10/16/2012

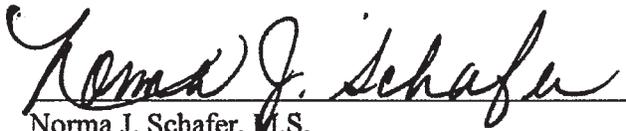
Excerpted from the April 25, 2012 Minutes of the PeRC Meeting

Nepafenac Full Waiver

- NDA 203-491, Nepafenac, oral suspension was studied for the treatment of pain and inflammation associated with cataract surgery.
- The application was submitted on December 16, 2011 and has a PDUFA Date of October 16, 2012.
- The application triggered PREA as a new dosing regimen.
-  (b) (4)
- The PeRC agreed with the Division to grant a full waiver in pediatrics patients because studies are not feasible.

1.3.3. Debarment Certification

Alcon Research, Ltd. and its affiliated companies (Alcon Pharmaceuticals, Ltd. and Alcon Laboratories, Inc.) hereby certify that it did not and will not use in any capacity the service of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



Norma J. Schafer, M.S.
Senior Manager, Regulatory Affairs
(817) 551-8568

12/15/2011
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 203491 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Request for proprietary name review submitted September 10, 2012; 2 previous names denied Established/Proper Name: nepafenac Dosage Form: ophthalmic suspension		Applicant: Alcon Research, Ltd. Agent for Applicant (if applicable):
RPM: Diana Willard		Division: Division of Transplant and Ophthalmology Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>10/16/12</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None

¹ Application Information Section is (only) a checklist. The Contents of Action Package Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 5</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input checked="" type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>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.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDA only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [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). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [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). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> 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?

Yes No

(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)?

Yes No

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 the rest of the patent questions.

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

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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)?

Yes No

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 section below (Summary Reviews).

If “No,” continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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).</p> <p><i>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 section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

Copy of this Action Package Checklist ⁴	X Included
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Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters

❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval: 10/16/12
---	---

Labeling

❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Included
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	Included

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. • Original applicant-proposed labeling • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	Included
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • <i>Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</i> 	<p>1. 3 names submitted 9/9/12 - applicant withdrew name (b) (4) on 10/15/12</p> <p>2. 8/17/12 - Proprietary Name (b) (4) Unacceptable Letter issued</p> <p>8/9/12 - Proprietary Name review for (b) (4)</p> <p>3. 6/14/12 - Proprietary Name (b) (4) Unacceptable Letter issued</p> <p>6/14/12 - Proprietary Name review for (b) (4)</p>
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM - 2/1/12 PLR Labeling Review <input checked="" type="checkbox"/> DMEPA 6/29/12 <input type="checkbox"/> DMPP/PLT (DRISK) <input type="checkbox"/> ODPD (DDMAC) <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	RPM Filing REview - 3/6/12
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC 4/25/12 If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	Included
❖ Internal memoranda, telecons, etc.	None
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 10/5/09
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	1/10/11
Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None Division Deputy Director Review: 10/16/12 Division Director Summary Review: 10/16/12
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/16/12
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	NOTE: Team Leader signed 10/9/12 and 9/14/12 Primary Clinical Reviews
• Clinical review(s) (<i>indicate date for each review</i>)	10/9/12; 9/14/12
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None

⁶ Filing reviews should be filed with the discipline reviews.

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Review of Financial Disclosure in the 9/14/12 Clinical Review on Page 9
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 8/8/12
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None NOTE: Team Leader signed 9/12/12 Primary Biostatistical Review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/12/12
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None NOTE: Team Leader signed 8/28/12 Primary Clinical Pharmacology Review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/28/12
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None NOTE: Team Leader signed 9/13/12 Primary Nonclinical Review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/13/12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None NOTE: 9/13/12 Product Quality Review signed by Branch Chief
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None 10/12/12 (2); 10/11/12; 9/19/12; 9/13/12
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)	<input type="checkbox"/> Not needed 5/28/12
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)	<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	NOTE: See pages 156 and 157 of 9/13/12 Product Quality Review
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	

❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: 4/23/12 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

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

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRRA.



NDA 203491

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Alcon Research, Ltd.
6201 South Freeway (R3-52)
Fort Worth, TX 76134-2099

Attention: Norma J. Schafer, M.S.
Senior Manager, Regulatory Affairs

Dear Ms. Schafer:

Please refer to your New Drug Application (NDA) dated December 15, 2011, received December 16, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Nepafenac Ophthalmic Suspension, 0.3 %.

We also refer to your correspondence, dated and received July 16, 2012, requesting review of your proposed proprietary name, (b) (4). We also refer to your amendment, dated and received July 25, 2012, to revise the product details. We have completed our review of (b) (4) and have concluded that this name is unacceptable for the following reason:

(b) (4)

We note that you have proposed an alternate proprietary name in your submission dated July 16, 2012. In order to initiate the review of the alternate proprietary name, (b) (4) submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Diana Willard at (301) 796-0833.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
08/17/2012



NDA 203491

INFORMATION REQUEST

Alcon Research, Ltd.
Attention: Norma J. Schafer
Sr. Manager, Regulatory Affairs
6201 South Freeway (R3-52)
Fort Worth, TX 76134-2099

Dear Ms. Schafer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nepafenac Ophthalmic Suspension, 0.3%.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1.

[Redacted] (b) (4)

2. You have proposed a shelf-life of (b) (4) for the storage of (b) (4) nepafenac drug substance on the basis of the 30 week long-term (25°C/60%RH) stability data. At this point, we recommend a shelf-life of (b) (4). Since (b) (4) nepafenac is considered as the (b) (4), indicate how you determine the date of the manufacture of drug product.

3.

[Redacted] (b) (4)

4.

[Redacted] (b) (4)

If you have any questions, call Althea Cuff, Regulatory Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURAWA
08/15/2012



NDA 203491

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Alcon Research, Ltd.
6201 South Freeway (R3-52)
Fort Worth, TX 76134-2099

Attention: Norma J. Schafer, M.S.
Senior Manager, Regulatory Affairs

Dear Ms. Schafer:

Please refer to your New Drug Application (NDA) dated December 15, 2011, received December 16, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Nepafenac Ophthalmic Suspension, 0.3 %.

We also refer to your correspondence, dated March 15, 2012, and received March 16, 2012 requesting review of your proposed proprietary name, (b) (4). We have completed our review of (b) (4) and have concluded that this name is unacceptable for the following reasons:

(b) (4)

(b) (4)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Victor Ng at (301) 796-0735.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
06/14/2012



NDA 203491

INFORMATION REQUEST

Alcon Research, Ltd.
Attention: Norma J. Schafer
Sr. Manager, Regulatory Affairs
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Ms. Schafer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nepafenac Ophthalmic Suspension, 0.3%.

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a prompt written response by June 7, 2012, in order to continue our evaluation of your NDA.

1. Three out of four batches (3.2.P.3.4) showed significant increase (+1.5%) or decrease (-1.0%, -1.3%) of average assay value (b) (4) of nepafenac drug substance, however, no significant change in the total impurities content was observed. Provide an explanation.
2. (b) (4) include a metals test either in the final drug product specification or as an in-process control test.
3. The executed batch record provided for bulk lot 192972F (used in PSB #3) indicates (b) (4) nepafenac was used (b) (4). Clarify how much (b) (4) nepafenac drug substance is present (b) (4). Drug product batches PSB #1 and PSB #2 that were (b) (4) at Alcon's Process Development facility and (b) (4) have lower assay values (96-98% label claim) in comparison to batch BSP #3 that was (b) (4). (b) (4) had an assay value of 103% of label claim. Explain the difference and provide the number of nepafenac (b) (4).

4. On the basis of lot release and stability data, we recommend the following changes to some of the proposed acceptance criteria in the drug product specification:

Test	Alcon proposed Acceptance Criteria	FDA Recommended Acceptance Criteria
Impurities:		
		(b) (4)
Osmolality		(b) (4)
Appearance Suspension: Color		
Uniformity		
Redispersibility		
Particle Size, Suspension (b) (4) (b) (4)		

5. You have provided 39 wks (9 months) of real time long-term stability data for one primary stability batch and 26 wks (6 months) of real time long-term data for two batches for a proposed expiration dating period of 78 wks (18 months). Per ICH Q1A, 12-months of long-term and 6-months of accelerated stability data are expected at the time of NDA submission. Expiration date granted will commensurate with the amount and quality of data provided. If a stability update with a summary of the range of results observed is provided by the due date of this information request, we are agreeable to reviewing the additional information. Any stability updates provided later may not be reviewed in this review cycle depending on the resources available at that time.
6. As (b) (4) are part of the drug product manufacturing process, changes beyond the ranges provided for in the submission should also be reported to the NDA in accordance with 21 CFR 314.70.

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURAWA
05/24/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: March 21, 2012

To: Norma J. Schafer, M.S.	From: Mr. Victor Ng Project Manager
Company: Alcon Research, Ltd	Division of Transplant and Ophthalmology Products
Email: norma.schafer@alconlabs.com	Email: victor.ng@fda.hhs.gov
Telephone number: 817-551-8568	Phone number: 301-796-1600

Subject: NDA 203491 – nepafenac ophthalmic suspension, 0.3%

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES NO

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Dear Ms. Schafer,

Please refer to your December 15, 2011, submission of NDA 203491. We have the following comments regarding your submission:

Product Quality Microbiology Comments:

1. Regarding the description of the manufacturing process, it is stated in the Multiple Module Information Amendment of 2/14/2012 that (b) (4)

[Redacted]

2. (b) (4)

[Redacted]

3. (b) (4)

[Redacted]

4. (b) (4)

[Redacted]

5. Regarding container/closure bacterial endotoxin control, please indicate how endotoxin contamination of the container/closure system is monitored and controlled. Indicate if procedures are initiated to reduce endotoxin burden on the container/closure or provide the rationale for not including such studies. Also include any supporting information as necessary, such as component endotoxin specifications, component endotoxin monitoring data and/or BER validation data.

6. (b) (4)

[Redacted]

7. Regarding endotoxin testing, it is stated that bacterial endotoxin testing is not to be performed at a dilution higher than the MVD, which is not stated. Please provide the MVD for bacterial endotoxin testing of the subject drug product and confirm the dilution of the drug product that will be used for routine endotoxin testing.

If you have any questions regarding this communication, please contact me at (301) 796-1600.

Sincerely,

Victor Ng
Regulatory Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

VICTOR F NG
03/23/2012



NDA 203491

FILING COMMUNICATION

Alcon Research, Ltd.
Attention: Norma J. Schafer
Sr. Manager, Regulatory Affairs
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Ms. Schafer:

Please refer to your New Drug Application (NDA) dated December 15, 2011, received December 16, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for nepafenac ophthalmic suspension, 0.3%.

We also refer to your submissions dated February 10, and February 13, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application was considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 16, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 4, 2012.

During our filing review of your application, we identified the following potential review issues:

1.



2.

(b) (4)

3. Regarding testing validation, it is stated that bacterial endotoxin testing is not to be performed at a dilution higher than the MVD, which is not provided. Please provide the MVD for bacterial endotoxin testing of the subject drug product and confirm the dilution of the drug product that will be used for routine endotoxin testing.
4. Please indicate how endotoxin contamination of the container/closure system is monitored and controlled. Indicate if procedures are initiated to reduce endotoxin burden on the container/closure or provide the rationale for not including such studies. Also include any supporting information as necessary, such as component endotoxin specifications, component endotoxin monitoring data and/or BER validation data.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

In addition, we request that you provide the *in vitro* drug release profile data from the bio-batches and stability batches supporting the selection of the acceptance criteria (i.e., specification-sampling time points and specification values). The acceptance criteria will be finalized upon review of the overall *in vitro* drug release data.

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

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research

Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you of our decision and if a pediatric drug development plan is required.

If you have any questions, call Victor Ng, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

RENATA ALBRECHT
02/24/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: February 6, 2012

To: Norma J. Schafer, M.S.	From: Mr. Victor Ng Project Manager
Company: Alcon Research, Ltd	Division of Transplant and Ophthalmology Products
Email: norma.schafer@alconlabs.com	Email: victor.ng@fda.hhs.gov
Telephone number: 817-551-8568	Phone number: 301-796-1600
Subject: NDA 203491 – nepafenac ophthalmic suspension, 0.3%	

Total no. of pages including cover: 5

Comments:

Document to be mailed: YES NO

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Dear Ms. Schafer,

Please refer to your December 15, 2011, submission of NDA 203491. We have the following comments regarding your submission:

By February 13, 2012, please provide us with a timeline to complete these requests so that we can plan for our review accordingly (please note separate timeline for labeling/labels).

Pharmacology and Toxicology Comments:

1. For the ease of review, please identify the Study Numbers and locations of additional toxicity studies described in the Question 3 (Toxicology) during the EOP2 meeting for IND 49924 on October 5, 2009.
2. Please comment on the comparative systemic exposure of 0.3% and 0.1% nepafenac ophthalmic suspensions in the animal ocular toxicity studies.
3. In the Pregnancy Section of proposed labeling, please identify the PK studies and show the calculation of how the multiples of animal dose versus human dose are derived.

Product Quality Microbiology Comments:

4. Please provide separate (b) (4) validation studies for all (b) (4)
5. Please include (b) (4) testing parameters and acceptance criteria for all (b) (4) testing.
6. (b) (4)

Biostatistical List of Requests:

7. Please provide a reviewer's guide for each trial explaining which datasets and which SAS code were used for the main analyses for primary and secondary endpoints.
8. Please provide the following datasets: note that each dataset should have a subject id, study id, study center id, treatment assignment (drug and frequency of dose):
 - a) An integrated demographic dataset with demographic and geographic information on all subjects from both trials. Dataset should include variables of study eye, age, sex, race, iris color, country and center. This dataset should include these variables as used in the main efficacy and subgroup analyses.
 - b) An integrated subject disposition dataset. This dataset should include variable indicator whether subject is in intent to treat analysis, indicator whether subject is in the per protocol analysis, indicator whether subject completed the study, indicator of whether subject discontinued from the study, date of surgery, date of last visit, date of first taking drug, discontinuation date, reason for discontinuation, and protocol violation and reason for protocol violation.
 - c) An integrated efficacy dataset. For each subject and visit, visit number, visit date, study day (counting surgery date as day 1), flare score (observed, imputed and

imputation flag), aqueous cell score (observed, imputed and imputation flag), pain score (observed, imputed and imputation flag).

Provide documentation for the datasets (a define.pdf document). For all variables directly copied from CRF, provide CRF page number and/or link to annotated CRF. For all derived variables, specify (in English) how the variables were derived from CRF data.

Biostatistical Comments:

9. You are encouraged to submit standardized datasets following the CDISC guidelines for SDTM and ADaM datasets.
10. Provide all raw datasets, as well as analysis datasets (including all efficacy and safety variables) used to generate the results presented in your study report. In addition, provide a data definition file (in pdf format or xml format) that includes information on how efficacy variables are derived.
11. Include the programs used for creating main efficacy analysis datasets from submitted raw datasets and the programs used for the efficacy and main safety analyses. In addition, provide a document that explains the use of each program.
12. Provide the analysis datasets (with definition file) and programs (with documentation) used to generate the specific analyses results in each report.
13. Provide the analysis datasets (with definition file) and programs (with documentation) used to generate the inferential analyses results in the ISS reports.
14. You may check the following FDA website to find the information about current document and guidance:

Link to Study Data Specifications

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf>

15. You submitted the efficacy data separately for each study and did not integrate the study (with same naming of variables) in an integrated summary of efficacy folder.
16. You did not distinguish between the tabulation datasets (containing all that is collected from the CRF) and analyses datasets (containing data used in main efficacy and safety analyses, with some CRF data and some derived variables).
17. The define.pdf documentation file does not specify how all the derived variables were derived.
18. You did not provide a reviewer's guide explaining which dataset and which code was used in the main primary and secondary analyses.
19. You did not follow CDISC standards for naming the variables.

Labeling/Labels Comments:

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

20. The section headings and subheadings in the Table of Contents must match the headings and subheadings in the Full Prescribing Information. In the Table of Contents, Subheading 6.1 should be revised to read, "Ocular Adverse Reactions" and subheading 6.2 should be revised to read, "Non-Ocular Adverse Reactions."
21. A Patient Package Insert (PPI) was not submitted for this application. The words, (b) (4) [REDACTED] should therefore be removed from the Patient Counseling Information statement in the Highlights. The Patient Counseling Information statement should now read, "**See 17 for PATIENT COUNSELING INFORMATION.**"
22. Please submit proposed carton and container mock-ups which include color, font size, graphics, etc, so that they can be preliminarily reviewed prior to the Filing deadline.
23. We note that a request for proprietary name review has not been submitted. Please comment on whether or not you plan to submit a request for proprietary name review. If you do plan to submit a request for proprietary name review, please submit a timeline for this request.

We request that you resubmit labeling/labels that addresses these issues by February 10, 2012. The resubmitted labeling/labels will be used for further labeling discussions.

If you have any questions regarding this communication, please contact me at (301) 796-1600.

Sincerely,

Victor Ng
Regulatory Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

VICTOR F NG
02/06/2012



NDA 203,491

NDA ACKNOWLEDGMENT

Alcon Research, Ltd.
Attention: Norma J. Schafer
Sr. Manager, Regulatory Affairs
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Ms. Schafer:

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

Name of Drug Product: Nepafenac Ophthalmic Suspension, 0.3%

Date of Application: December 15, 2011

Date of Receipt: December 16, 2011

Our Reference Number: NDA 203,491

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 February 14, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call Victor Ng, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Victor Ng
Regulatory Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

VICTOR F NG
12/28/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 49,924

Alcon, Inc.
Alcon Research, Ltd.
Attn: Norma J. Schafer, M.S.
Senior Manager, Regulatory Affairs
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Ms. Schafer:

Please refer to the End-of-Phase 2 video conference between representatives of your firm and FDA on October 5, 2009. The purpose of the meeting was to discuss the development plan for Nepafenac (AL-6515) Ophthalmic Suspension 0.3% dosed once daily for treatment of postoperative pain and inflammation associated with cataract surgery.

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) 796-0798.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective and
Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure



MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 5, 2009 (Video conference)
START TIME: 2:05 pm
END TIME: 2:20 pm
LOCATION: White Oak, Bldg #22, Room #1311

APPLICATION (DRUG): **IND 49,924**
DRUG: Nepafenac (AL-6515) Ophthalmic Suspension 0.3%
INDICATION: treatment of postoperative pain and inflammation associated with cataract surgery.

SPONSOR: Alcon, Inc.
Alcon Research, Ltd.

TYPE OF MEETING: End-of-Phase 2 meeting

MEETING CHAIR: Wiley A. Chambers, MD

MEETING RECORDER: Raphael R. Rodriguez

FDA Attendees: Wiley Chambers, William Boyd, Rhea Lloyd, Martin Nevitt, Linda Ng, Aryun Kim, Yan Wang, Dongliang Zhuang, Wendy Schmidt, Lin Qi, Sonal Wadhwa, Raphael Rodriguez

Alcon Attendees: Michael Pflieger, Angela Kothe, Jean-Michael Gries, Michael Brubaker, Kerry Markwardt, Kenny Sullivan, Dana Sager, Norma Schafer

MEETING OBJECTIVE: To discuss the development plan for Nepafenac (AL-6515) Ophthalmic Suspension 0.3% dosed once daily for treatment of postoperative pain and inflammation associated with cataract surgery.

SUMMARY OF DISCUSSION:

Responses to the applicant's meeting questions were provided via email September 28, 2009. This meeting served to clarify those responses. The Applicant's questions and the Agency's responses are as follows:

Chemistry

1. In accordance with the *International Committee on Harmonization (ICH) Guidance M4Q(R1)*, an excipient is considered novel if it is "...used for the first time in a drug product or by a new route of administration...". Even though one of the excipients of Nepafenac Ophthalmic Suspension, 0.3%, guar gum, has not been used in a US ophthalmic drug product approved via the NDA process, it has been used extensively in foods, pharmaceuticals and topical cosmetics (including eye care cosmetics). Guar gum, a well-known and characterized compendial material, is a naturally occurring material consisting primarily of guar galactomannan. The main components of guar galactomannan are polysaccharides composed of D-galactose and D-mannose.

Additionally, a derivative of guar gum, commonly known as HP guar (hydroxypropyl guar), has been used in Alcon's topical over-the-counter (OTC) SYSTANE® family of lubricant eye drops. These ophthalmic products, SYSTANE® Lubricant Eye Drops and SYSTANE® ULTRA have been on the US market for up to six years without any significant adverse reports (i.e., adverse events possibly associated with the use of these products are reported rarely, are typically non-serious and are expected to resolve without sequelae). (b) (4)

Alcon believes that guar gum should not be considered a "novel" excipient via an ophthalmic route of administration because of its extensive use in foods, pharmaceutical products and cosmetic products (including eye care cosmetics) as well as the use of a very similar derivative of guar gum in a topical OTC ophthalmic product.

Therefore, Alcon does not consider guar gum to be a novel excipient in Nepafenac Ophthalmic Suspension, 0.3% and does not plan to treat it as such. Does the Agency agree?

Agency Response:

No, Guar gum is considered to be a novel excipient as it has not been used in a NDA approved product administered by the topical ocular route.

For the upcoming NDA, please report degradation products according to the model described in ICH Q3B (R2):

- *Specified identified impurity*
- *Specified unidentified impurity*
- *Any individual unspecified impurity*
- *Total impurities/degradation products*

It is recommended that the acceptance criteria for any individual unspecified impurity for the drug product be set at NMT (b) (4)

Nonclinical**Safety Pharmacology**

2. Extensive nonclinical evaluations were conducted to support the safety of nepafenac for the new drug application for NEVANAC. Nepafenac up to 100 μ M concentration did not interact with 21 different receptors or binding sites including steroid receptors in binding assays. At doses that were 46 to 833 fold the current proposed theoretical maximum daily therapeutic dose (assuming once a day dosing of both eyes, 100% systemic absorption, and complete bioavailability) nepafenac showed no neuropharmacological signs, pro-convulsant effects, hemodynamic or ECG effects. No effects on pulmonary, renal or gastrointestinal functions were noted. Therefore, Nepafenac Ophthalmic Suspension, 0.3% is not expected to cause significant adverse effects in human beings when dosed once daily for 16 days.

Based on the existing nonclinical safety pharmacology data, Alcon does not intend to conduct any additional safety pharmacology investigations for the development of Nepafenac Ophthalmic Suspension, 0.3%. Is this acceptable to the Agency?

Agency response: Yes.

TOXICOLOGY

3. The nonclinical pharmacokinetics of nepafenac have been well studied and reported in the new drug application for NEVANAC. These previously reported studies are summarized in Section 3.2.2, Table 3.2.2-1. Additional nonclinical evaluation is warranted since Nepafenac Ophthalmic Suspension, 0.3% differs from the marketed product with respect to a higher concentration of nepafenac, (b) (4). Therefore, Alcon plans to conduct two additional nonclinical pharmacokinetic studies to support the new drug application for Nepafenac Ophthalmic Suspension, 0.3%. The first study will compare the ocular uptake of nepafenac and its pharmacologically active metabolite amfenac in rabbits following single topical ocular doses of Nepafenac Ophthalmic Suspension, 0.3% and NEVANAC. The second study will determine the toxicokinetics of nepafenac and amfenac in the proposed 1-month topical ocular toxicology study.

Does the Agency agree that these two additional studies, as well as previously submitted data, are sufficient nonclinical data to support a new drug application for Nepafenac Ophthalmic Suspension, 0.3%?

Agency response: Yes.

4. A comprehensive nonclinical GLP regulated toxicology package was submitted in support of the safety of NEVANAC Ophthalmic Suspension, 0.1% (See Section 3.2.3; Table 3.2.3.1-1). These studies were designed to evaluate the single and repeated dose toxicity of nepafenac following topical ocular administration (clinical route) as well as the systemic toxicity, genotoxicity, reproductive and developmental toxicity, sensitization, and phototoxicity potentials of this compound. Chronic topical ocular toxicity studies conducted in rabbits and primates with concentrations of 1.5 and 1% nepafenac, respectively, were free of adverse ocular effects. The safety demonstrated via the conduct of these studies was found sufficient

to support both clinical evaluation and eventual marketing approval of NEVANAC. Due to the proposed change from a three times daily to a once daily dosing schedule, the total dose of nepafenac administered per day is equivalent between the currently approved NEVANAC and the proposed Nepafenac Ophthalmic Suspension, 0.3% products. While one of the excipients in the proposed formulation, guar, has not previously been utilized in a US prescription ophthalmic product, it has a long history of safe use in food, cosmetics and consumer care ocular products. In keeping with the principals set forth in the Agency's *Guidance for Industry; Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, Alcon plans to reference guar safety data from the literature (Section 3.2.3; Appendix A).

Based on the existing nonclinical toxicology data for both nepafenac and guar (See Section 3.2.3.1), Alcon intends to limit the nonclinical toxicology development plan for Nepafenac Ophthalmic Suspension, 0.3% to a single 1-month topical ocular bridging study in pigmented rabbits.

Does the Agency agree that a demonstration of product safety in a single 1-month topical ocular pigmented rabbit study is sufficient to bridge the safety of the proposed Nepafenac Ophthalmic Solution, 0.3% formula containing guar to the existing toxicology data package for the purpose of supporting both clinical trials and a new drug application?

Agency response: *Yes, unless there are further issues seen in either the one month rabbit study or in the clinical studies.*

Clinical

5. Alcon is requesting a waiver for conducting clinical trials with Nepafenac Ophthalmic Suspension, 0.3% in patients under the age of 18 for the following reasons: 1) The incidence of congenital cataract in the pediatric population is reported to be less than 3 in 10,000 births (0.03%) (Abrahamsson et al., 1999; Bermejo et al., 1998; Foster et al., 1997) and the majority of these patients undergo cataract surgery by the age of 2; 2) There are ethical issues resulting from inclusion of this population in investigative, vehicle controlled clinical trials; 3) Postoperative ocular inflammation is more severe in the very young pediatric age group, necessitating the use of a steroid (Alexandrakis et al., 2002); 4) Assessing the primary endpoint via slit lamp is only possible under anesthesia in young patients; and 5) Adolescents are more likely to have traumatic cataract (incidence of 0.02%; Haargaard et al., 2004) which is frequently associated with other complications that would confound the assessment of safety and efficacy of the drug product being studied, and require treatment with postoperative steroids. Additionally, the severity of the inflammatory response decreases with age until, as children approach the teenage years the inflammatory response becomes more like that of adults (Müllner-Eidenböck et al., 2003). Consequently, it is anticipated that the safety and efficacy of Nepafenac Ophthalmic Suspension, 0.3% in the adolescent population would be well predicted by that of the adult population. This is supported by data indicating that the pharmacokinetics of NSAIDs (ketorolac and ketoprofen) are similar in children, adolescents and adults (Hamunen et al., 1999; Kokki et al., 2000).

Based upon the extremely low incidence of cataracts and the difficulty of establishing safety and efficacy in the pediatric population, Alcon is requesting a waiver for conducting clinical trials with Nepafenac Ophthalmic Suspension, 0.3% in patients under the age of 18.

Does the Agency agree with our proposal for a waiver to conduct studies in patients under 18 years of age?

Agency Response: *Agree that a waiver for conducting pediatric clinical trials should be submitted.*

6. Based on the existing clinical and nonclinical pharmacokinetic/pharmacodynamic data and the fact that nepafenac is already approved for the same indication in NEVANAC, Alcon considers that a single Phase 3 trial with Nepafenac Ophthalmic Suspension, 0.3% dosed once daily is sufficient to establish the safety and efficacy of the medicinal product and to support a new drug application.

The Phase 3 clinical development plan is also supported by the following:

- Once daily dosed nepafenac 0.1% was efficacious in treating ocular pain and inflammation associated with cataract surgery in study C-02-53;
- In an animal model, nepafenac demonstrated efficacy beyond 30 hours following a single topical ocular dose;
- Nonclinical pharmacokinetics support a decrease in the dosing frequency with the new formulation; and
- No safety issues were observed in prior clinical trials which included formulations containing nepafenac at a concentration of 0.3%.

Detailed information supporting the above is provided in Section 3.3.3.1.

Does the Agency agree that a single Phase 3 trial with Nepafenac Ophthalmic Suspension, 0.3% dosed once daily is sufficient to establish the safety and efficacy of the product?

Agency Response: *Agree.*

7. Aqueous cells and flare, which are the hallmarks of post-cataract surgery inflammation, serve as the basis for evaluating the primary efficacy of this class of product. As is the standard in ophthalmic practice, aqueous cells and flare will be evaluated using slit-lamp biomicroscopy. Patients will be assessed on Days 1, 3, 7 and 14. Alcon plans to demonstrate non-inferiority of nepafenac 0.3% dosed once daily relative to NEVANAC dosed three times daily for the percent of patients with a clinical cure (no ocular inflammation, i.e., absence of aqueous cells and flare) at Day 14 as the primary objective. Superiority tests between Nepafenac Ophthalmic Suspension, 0.3% and vehicle, and between NEVANAC and vehicle, for the primary endpoint will be included for study validation. Subjective assessment of ocular pain, rated by the investigator on a 6-point scale will be evaluated as the secondary efficacy variable. The scales for aqueous cells, flare and ocular pain were used previously for clinical trials in the development of NEVANAC and are presented in Section 3.3.3.3

Does the Agency agree that the proposed endpoints and design of the study are appropriate to establish safety and efficacy for the treatment of postoperative pain and inflammation associated with cataract surgery?

Agency Response: *Agree.*

- Alcon proposes to use the percent of patients with a clinical cure (i.e., absence of aqueous cells and flare) at Day 14 as the primary efficacy endpoint. The primary efficacy analysis will be a test of non-inferiority between Nepafenac Ophthalmic Suspension, 0.3% and NEVANAC utilizing a chi-square analysis and a non-inferiority margin of 10 percentage points. Last-observation-carried-forward (LOCF) will be used to impute missing data in the intent-to-treat analysis. Superiority tests between Nepafenac Ophthalmic Suspension, 0.3% and vehicle, and between NEVANAC and vehicle, for the primary endpoint will be included for study validation.

Does the Agency agree with the proposed analyses?

Agency Response: *The Agency agrees that the primary efficacy analysis is a test of non-inferiority between Nepafenac Ophthalmic Suspension 0.3% and NEVANAC utilizing a chi-square analysis. The Agency also agrees that a non-inferiority margin of 10% is acceptable when it is used to determine the sample size. It is recommended that the treatment difference between Nepafenac Ophthalmic Suspension 0.3% and NEVANAC and the 95% confidence interval of the difference be presented. This will allow the Agency to make a determination whether Nepafenac Ophthalmic Suspension 0.3% has acceptable efficacy compared to NEVANAC.*

- The clinical development program for NEVANAC included a comprehensive battery of examinations, both ocular and systemic, which demonstrated the safety and tolerability of NEVANAC administered three times daily to adult and elderly patients. Nepafenac Ophthalmic Suspension, 0.3% contains guar (b) (4). Although the addition of (b) (4) is not expected to adversely affect the safety profile of the new formulation relative to the currently marketed product, Alcon is proposing to conduct a Phase 1 trial to evaluate the safety, tolerability and steady-state pharmacokinetics of nepafenac and amfenac after topical ocular administration of Nepafenac Ophthalmic Suspension, 0.3% in healthy subjects.

Does the Agency agree that the proposed Phase 1 study is sufficient to evaluate systemic exposure of nepafenac and amfenac resulting from topical ocular administration of Nepafenac Ophthalmic Suspension, 0.3% in humans?

Agency Response: *Agree; however, the final protocol will be subject to review.*

10. Does the Agency have any other advice concerning our development of Nepafenac Ophthalmic Suspension, 0.3% that it believes is important in ensuring the fileability of our proposed NDA?

Agency Response:

The Agency believes that it is important to have a head to head comparison between nepafenac ophthalmic solution 0.3%, nepafenac ophthalmic solution 0.1% and vehicle. In the absence of a direct comparison, there is an increased safety concern for the higher concentration of a product without any additional demonstration of benefit. The proposed less frequent dosing regimen has not been demonstrated to provide an additional benefit.

The submission of an application without data from a head to head comparison between nepafenac ophthalmic solution 0.3%, nepafenac ophthalmic solution 0.1% and vehicle may result in a refusal-to-file the application.

From the listing of previous or ongoing clinical studies conducted with nepafenac in the meeting package, 117 patients have received nepafenac ophthalmic solution 0.3% dosed TID or QID. It is recommended that approximately 500 or more subjects using the test drug product complete treatment with a concentration of the test drug product at least as high as proposed for marketing with a frequency at least as frequent as proposed for marketing. Prior to an NDA submission, it is recommended that at least 300 patients would have completed at least 7 days of treatment.

Addendum:

The Division reiterated the importance of the head to head comparison between nepafenac ophthalmic solution 0.1% and nepafenac ophthalmic solution 0.3%. In the absence of a direct comparison, there is an increased safety concern for the higher concentration of a product without any additional demonstration of benefit.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-49924

GI-1

ALCON INC

AL-6515 OPHTHALMIC
SUSPENSION

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/s/

WILEY A CHAMBERS
12/31/2009