

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-862

**ADMINISTRATIVE
DOCUMENTS/CORRESPONDENCE**

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use**

NDA NUMBER

21-862

NAME OF APPLICANT / NDA HOLDER

Alcon, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

NEVANAC™ (nepafenac ophthalmic suspension) 0.1%

ACTIVE INGREDIENT(S)

Nepafenac

STRENGTH(S)

0.1%

DOSAGE FORM

Ophthalmic Suspension

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

5,475,034

b. Issue Date of Patent

12/12/1995

c. Expiration Date of Patent

6/6/2014

d. Name of Patent Owner

Alcon Manufacturing, Ltd.

Address (of Patent Owner)

6201 South Freeway

City/State

Fort Worth, Texas

ZIP Code

76134

FAX Number (if available)

817-551-4610

Telephone Number

817-551-3066

E-Mail Address (if available)

patrick.ryan@alconlabs.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

 Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

 Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) 1 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)
 _____ treatment of inflammation associated with _____ surgery

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) 2 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) — treatment of inflammation associated with — surgery
---	---

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
---	---

4.2 Patent Claim Number (as listed in the patent) 3	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
--	---

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) — treatment of inflammation associated with — surgery
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4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
---	---

4.2 Patent Claim Number (as listed in the patent) 4	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
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4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) — treatment of inflammation associated with — surgery
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4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
---	---

4.2 Patent Claim Number (as listed in the patent) 5	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
--	---

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) — treatment of inflammation associated with — surgery
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4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
---	---

4.2 Patent Claim Number (as listed in the patent) 6	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
--	---

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) — treatment of inflammation associated with — surgery
---	---

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?

Yes No

4.2 Patent Claim Number (as listed in the patent)

7

Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?

Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

— treatment of inflammation associated with — surgery

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Patrick M. Ryan

10/28/04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Patrick M. Ryan

Address

6201 South Freeway

City/State

Fort Worth, Texas

ZIP Code

76134

Telephone Number

817-551-3066

FAX Number (if available)

817-551-3066

E-Mail Address (if available)

patrick.ryan@alconlabs.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Appears This Way
On Original

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-862 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: February 28, 2005 Action Date: August 2005

HFD-520 Trade and generic names/dosage form: NEVANAC (nepafenac ophthalmic suspension) 0.1%

Applicant: Alcon, Inc. Therapeutic Class: 4041430 Nonsteroidal anti-inflammatory

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: treatment of pain and inflammation associated with cataract surgery.

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

Yes: Please proceed to Section A.

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

NOTE: More than one may apply

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

Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: No pediatric studies are planned.

~~Other: Other development in the pediatric population is being planned in this indication.~~

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. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Adult studies ready for approval

Formulation needed

Other: _____

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

Section C: Deferred Studies

Age/weight range being deferred:

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. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:


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

This page was completed by:

{See appended electronic signature page}

Raphael R. Rodriguez _____
RPM

Martin Nevitt, M.D., MPH _____
Clinical Reviewer

Wiley A. Chambers, M.D. 
Deputy Director, HFD-520

cc: NDA 21-862
HFD-960/ Grace Carmouze

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

EXCLUSIVITY SUMMARY FOR NDA # 21-862 SUPPL # _____

TradeName NEVANAC

GenericName nepafenac ophthalmic suspension 0.1%

Applicant Name Alcon, Inc. HFD-520

Approval Date If Known August 25, 2005

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 /XX/ 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 /XX / 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 / XX / NO / /

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

5 years -

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

YES / / NO / XX /

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 / XX /

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 / XX /

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

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 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 /_ _/ 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.")

product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_ __/

Investigation #2 YES /___/ NO /_ __/

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 /_ __/

Investigation #2 YES /___/ NO /_ __/

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"):

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 # ____ YES /_ _/ ! NO /___/ Explain: _____
!
!
Investigation #2 !
IND # ____ YES /_ _/ ! 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 /___/

If yes, explain: _____

If yes, explain: _____

Signature _____ Date _____
Raphael R. Rodriguez
RPM

Signature _____ Date _____
Martin Nevitt, M.D., MPH
Clinical Reviewer

Signature _____ Date _____
Wiley A. Chambers, M.D.
Deputy Director HFD-520

Form OGD-011347 Revised 05/10/2004

cc:

Archival NDA 21-862
HFD-520 /Division File
HFD-520 /RPM / RodriguezR
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

3.A.10. STATEMENTS OF CLAIMED EXCLUSIVITY AND ASSOCIATED CERTIFICATIONS

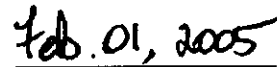
The applicant hereby requests a five-year period of exclusivity.

Pursuant to 21CFR§314.50(j) and 21CFR§314.104(b)(4), I hereby certify that:

- To the best of my knowledge each of the clinical investigations included in the application meets the definition of "new clinical investigation".
- The new clinical investigations are essential to the approval of the application.
- Alcon Laboratories, Inc., Alcon Universal, Ltd. or Alcon, Inc. were named as the sponsor on the form FDA 1571 for an investigational new drug application (IND # 49,924) under which the clinical investigations that are essential to the approval of this application were conducted. The change in name from Alcon Laboratories, Inc. to Alcon Universal, Ltd. and subsequently to Alcon, Inc. was submitted to the IND.



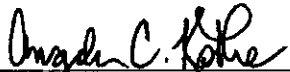
Angela C. Kothe, OD, PhD
Associate Director, Regulatory Affairs
(817) 551-4933



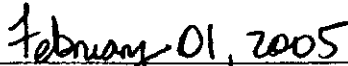
Date

3.A.3. DEBARMENT CERTIFICATION

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



Angela C. Kothe, OD, PhD
Associate Director, Regulatory Affairs
(817) 551-4933



Date

Deputy Office Director Memo

Applicant: Alcon Research Limited
NDA #: NDA 21-862
Drug: nepafenac ophthalmic suspension, 0.1%
Trade Name: Nevanac™
Indications: the treatment of pain and inflammation associated with cataract surgery
Date of submission: February 28, 2005
PDUFA goal date: August 28, 2005

Recommended Regulatory Action:

Approval for NDA 21-862

The review team has reviewed the issues in their respective disciplines in detail with regards to the safety and efficacy of Nevanac, NDA 21-862. For a detailed discussion of NDA 21-862, the reader is referred to the individual discipline specific reviews.

The Chemistry for Nevanac™ is discussed in Dr. Rodriguez's review and he has recommended approval for NDA's 21-862 with regards to Chemistry. Nevanac (nepafenac ophthalmic suspension) is a sterile aqueous 0.1% suspension of a nonsteroidal anti-inflammatory prodrug for topical ophthalmic use. Dr. Pawar's Product Quality Microbiology Review also recommends approval for NDA 21-862.

The Pharmacology/Toxicology studies for nepafenac are discussed in Dr. Chen's review. He concludes that there were no drug-related safety issues relevant to clinical use of Nevanac and from a pharm/tox standpoint the application can be approved. Nepafenac penetrates the cornea and is hydrolyzed to amfenac, a nonsteroidal anti-inflammatory drug. Nevanac is labeled as Pregnancy Category C.

The Clinical Pharmacology of nepafenac is described in Dr. Ghosh's Clinical Pharmacology and Biopharmaceutics Review. The plasma concentrations of nepafenac and amfenac were low, but quantifiable with TID human bilateral ophthalmic topical human administration in healthy subjects. The mean steady-state Cmax in

plasma following ocular administration for nepafenac was a 0.310 +/- 0.104 ng/mL and for amfenac was 0.422 +/- 0.121 ng/mL.

The results of the clinical trials have been discussed in Dr. Nevitt's Medical Officer's review and Dr. Qi's Statistical review. The NDA provides adequate and well controlled studies of Nevanac at the proposed clinical dose along with supportive dose response trials. These studies demonstrate the efficacy of Nevanac for the indication of the treatment of pain and inflammation associated with cataract surgery. For the FDA analyses evaluating efficacy, the reader is referred to Dr. Nevitt's and Dr. Qi's reviews. The safety database derived from the clinical trials in the NDA provide sufficient data to characterize the safety of Nevanac. The risk benefit ratio for Nevanac for the indication of the treatment of pain and inflammation associated with cataract surgery is acceptable.

DMETS and DDMAC have consulted on the proprietary name and do not object to the use of the proprietary name Nevanac. The Division of Scientific Investigation inspection of selected clinical study sites were completed and they conclude that the data submitted in support of the NDA appear to be acceptable.

Summary Recommendation:

Approval for the indication of the treatment of pain and inflammation associated with cataract surgery.

**Appears This Way
On Original**

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

/s/

Edward Cox
8/19/2005 04:25:13 PM
MEDICAL OFFICER



August 12, 2005

Wiley A. Chambers, M.D.
Division of Anti-Infective and
Ophthalmology Products
FDA / CDER, HFD-520
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

**RE: NDA 21-862
NEPAFENAC OPHTHALMIC SUSPENSION, 0.1%
LABELING AMENDMENT**

Dear Dr. Chambers:

In response to the Division's e-mail of August 11, 2005, enclosed please find revised color mockups of the container and carton labeling for NEVANACTM (nepafenac ophthalmic suspension) 0.1%. In addition, please find the revised package insert for NEVANAC (correction of a typographical error in the DESCRIPTION section of the insert).

If you have any questions concerning this amendment, please contact me via telephone at 817-551-4933 or via facsimile at 817-551-4630.

Sincerely

A handwritten signature in black ink, appearing to read "Angela C. Kothe".

Angela C. Kothe, OD, PhD
Associate Director, Regulatory Affairs

Encl.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT ALCON, Inc.	DATE OF SUBMISSION 8/12/05
TELEPHONE NO. (Include Area Code) 817-551-4933	FACSIMILE (FAX) Number (Include Area Code) 817-551-4630
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): ALCON, Inc. P.O. Box 62 Bosch 69 CH-6331 Hunenberg Switzerland	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Alcon Research, Ltd. Mail Code R7-18 6201 South Freeway Fort Worth, TX 76134-2099

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 21-862

ESTABLISHED NAME (e.g., Proper name, USP/USAN name) nepafenac ophthalmic suspension, 0.1%	PROPRIETARY NAME (trade name) IF ANY NEVANAC™
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)	CODE NAME (if any)
DOSAGE FORM: ophthalmic suspension	STRENGTHS: 0.1%
ROUTE OF ADMINISTRATION: topical ocular	
(PROPOSED) INDICATION(S) FOR USE: treatment of pain and inflammation associated with cataract surgery	

APPLICATION DESCRIPTION

APPLICATION TYPE (check one) NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b)(1) 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION (check one) ORIGINAL APPLICATION AMENDMENT TO APENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION
revised product labeling (container, carton and package insert)

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

DMF# — DMF# — DMF# — DMF# — DMF# — DMF# — DMF# —

This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21 CFR 314.50 (c))
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
 - B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306 (k)(1))
- 17. Field copy certification (21 CFR 314.50 (l)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify)

CERTIFICATION

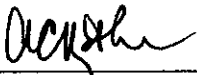
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Angela C. Kothe, OD, PhD / Associate Director, Regulatory Affairs	DATE: 8/12/05
ADDRESS (Street, City, State, and ZIP Code) Alcon Research Ltd., Mail Code R7-16, 6201 South Freeway, Fort Worth, TX 76134		Telephone Number (817) 551-4933

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CDER, HFD-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER (HFD-94) 12229 Wilkins Avenue Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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4 Page(s) Withheld

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

 / § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

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

**ODS POSTMARKETING SAFETY
REVIEW**

Janice Soreth, M.D., Director
Division of Anti-Infective and Ophthalmology Products
HFD-520

FROM: Ronald Wassel, Pharm.D.
Division of Drug Risk
Evaluation, HFD-430

ODS PID # D050442
8/11/05

DATE RECEIVED: 7/19/2005

REQUESTOR/phone #: Raphael Rodriguez
Project Manager, DAIOP
301-827-2519

DRUG: Nevanac™ (nepafenac 0.1% ophthalmic suspension)

THERAPEUTIC CLASSIFICATION:
Ophthalmic non-steroidal anti-inflammatory

NDA/IND: # 21-862

SPONSOR: Alcon

EVENT: Safety review of drug class

Executive Summary: Nepafenac is a new molecular entity submitted for priority review. A request was received for a review of adverse events reported post-marketing for other drugs in the same class to determine if there is a significant risk with this group of drugs not noted in the pre-approval data. A search of the Adverse Event Reporting System showed the most frequently reported events with this class of drugs included Corneal disorder, Visual acuity reduced, Eye pain, Conjunctivitis, Face edema, Drug ineffective, Hypersensitivity, Application site reaction, Mydriasis, and Eye hemorrhage. The reported events were determined to be typical and labeled reactions seen with this group of drugs and/or manifestations of the settings in which these drugs are used. Currently, the data do not indicate any significant risks with this class of drugs.

Reason for Request/Review: Nepafenac is a new molecular entity submitted for priority review. No significant safety issues for the drug were noted in the Medical Officer's review. A request was received for a review of adverse events reported post-marketing for other drugs in the same class to determine if there is a significant risk with this group of drugs not noted in the pre-approval data.

Search Date: 8/8/2005

Search Type(s): AERS SRS Literature Other _____

Search Criteria: The following ophthalmic non-steroidal anti-inflammatory products were searched for all reports: Acular (ketorolac tromethamine), Voltaren (diclofenac), Ocufer (flurbiprofen), Xibrom (bromfenac), and Profenal (suprofen).

Search Results: A total of 852 cases were retrieved for the 5 products, distributed as follows: Acular---222, Voltaren---117, Ocufer---471, Xibrom---1, Profenal---41. Standard reports for All Preferred Terms in Cases were generated, which showed the most frequently reported events included Corneal disorder, Visual acuity reduced, Eye pain, Conjunctivitis, Face edema, Drug ineffective, Hypersensitivity, Application site reaction, Mydriasis, and Eye hemorrhage.

Findings / Conclusions: The Standard Reports were reviewed in conjunction with the Medical Officer to look for any significant serious risks. The reported events were determined to be typical and labeled reactions seen with this group of drugs and/or manifestations of the settings in which these drugs are used. Currently, the data do not indicate any significant risks with this class of drugs. We will continue to monitor reports for these drugs and those for nepafenac post-marketing to determine any changes.

Reviewer's Signature / Date: Ronald Wassel, Pharm.D.
8/11/05

Team Leader's Signature / Date: Melissa Truffa, R.Ph.
8/11/05

cc: NDA # 21-862
HFD-520 Division File / Chambers / Boyd / Nevitt / Rodriguez
HFD-430 Avigan / Truffa / Beam / Chron / Drug



August 05, 2005

Wiley A. Chambers, M.D.
Division of Anti-Infective and
Ophthalmology Products
FDA / CDER, HFD-520
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

**RE: NDA 21-862
NEPAFENAC OPHTHALMIC SUSPENSION, 0.1%
LABELING AMENDMENT**

Dear Dr. Chambers:

In response to the Division's e-mail of August 4, 2005, enclosed please find a revised proposed package insert for NEVANAC™ (nepafenac ophthalmic suspension) 0.1%. A 'track changes' and clean copy are provided.

If you have any questions concerning this amendment, please contact me via telephone at 817-551-4933 or via facsimile at 817-551-4630.

Sincerely

A handwritten signature in black ink, appearing to read "A. Kothe".

Angela C. Kothe, OD, PhD
Associate Director, Regulatory Affairs

Encl.



July 27, 2005

Wiley A. Chambers, M.D.
Deputy Director, DAAODP
FDA / CDER, HFD-550
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

RE: NDA 21-862
NEPAFENAC OPHTHALMIC SUSPENSION, 0.1%
CMC AMENDMENT: Responses to CMC Reviewer's Questions

Dear Dr. Chambers:

Enclosed please find responses to the chemistry reviewer's questions reviewed via facsimile on July 5, 2005 for the above referenced NDA.

A copy of this response has been sent to the Dallas District Office.

If you have any questions concerning this amendment, please contact me via telephone at 817-551-4933 or via facsimile at 817-551-4630.

Sincerely

A handwritten signature in black ink, appearing to read "A. Kothe".

Angela C. Kothe, OD, PhD
Associate Director, Regulatory Affairs

Encl.

cc. Dallas District Office



June 24, 2005

Wiley A. Chambers, M.D.
Deputy Director, DAAODP
FDA / CDER, HFD-520
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

RE: NDA 21-862
NEPAFENAC OPHTHALMIC SUSPENSION, 0.1%
NDA AMENDMENT: Four Month Safety Update

Dear Dr. Chambers:

Enclosed please find the four-month safety update for NEVANACT™ (nepafenac ophthalmic suspension) 0.1%.

Also included in this submission are color mockups of the draft container and carton labeling for NEVANAC.

If you have any questions or comments concerning this amendment, please contact me via telephone at 817-551-4933 or via facsimile at 817-551-4630.

Sincerely

A handwritten signature in black ink, appearing to read "Angela C. Kothe".

Angela C. Kothe, OD, PhD
Associate Director, Regulatory Affairs

Encl.



June 20, 2005

Wiley A. Chambers, M.D.
Deputy Director, DAAODP
FDA / CDER, HFD-550
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

RE: NDA 21-862
NEPAFENAC OPHTHALMIC SUSPENSION, 0.1%
CMC AMENDMENT: Responses to CMC Reviewer's Questions

Dear Dr. Chambers:

Enclosed please find responses to the chemistry reviewer's questions reviewed via facsimile on May 31, 2005 for the above referenced NDA.

A copy of this response has been sent to the Dallas District Office.

If you have any questions concerning this amendment, please contact me via telephone at 817-551-4933 or via facsimile at 817-551-4630.

Sincerely

A handwritten signature in black ink, appearing to read "ACKo", is written over a faint, illegible typed name.























Angela C. Kothe, OD, PhD
Associate Director, Regulatory Affairs

Encl.

cc. Dallas District Office

Rodriguez, Raphael R

From: Angela.Kothe@AlconLabs.com
nt: Wednesday, June 15, 2005 5:19 PM
o: RODRIGUEZR@cder.fda.gov
Cc: GhoshT@cder.fda.gov
Subject: RE: Emailing: N21862_nepafenac

-  10 - STUDY
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-  11 -
Events.doc (69 KB)
-  12-2 Adverse
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-  12-3 Deaths Other
Laboratory Evalu...
-  12-4 Clinical
Physical Find...
-  12-5 Vital Signs
Conclusions.doc (2..
-  12-6 Safety
-  12 - SAFETY
/ALUATION.doc (35
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-  14-3-3 Narratives
of Deaths Ot...
-  14-3-4 Abnormal
Laboratory Val...
-  14-3 Safety
Data.doc (45 KB)
-  14 - TABLES
URES AND GRAPHIC

Raphael

Attached please find the Word files from Sections 10, 11, 12 and 14 of the Clinical Study report for C-04-08. These are the same sections for which we previously sent files for C-93, C-97-30, C-02-53 and C-03-32.

Please advise if you need any further information.

Thanks
ANGELA

-----Original Message-----

From: Rodriguez, Raphael R [mailto:RODRIGUEZR@cder.fda.gov]
Sent: Friday, June 10, 2005 1:55 PM
To: Kothe,Angela,FORT WORTH,Regulatory Affairs
Cc: Ghosh, Tapash
Subject: FW: Emailing: N21862_nepafenac

Angela - see request from the PK reviewer. Thanks in advance. Raphael

-----Original Message-----

From: Ghosh, Tapash
Sent: Friday, June 10, 2005 2:50 PM
To: Rodriguez, Raphael R
Subject: RE: Emailing: N21862_nepafenac

Please request the sponsor if they can send us full Study report of C-04-08 preferably in MS Word format. Thanks

---Original Message-----

From: Rodriguez, Raphael R
Sent: Friday, June 10, 2005 2:46 PM
To: Ghosh, Tapash

Subject: Emailing: N21862_nepafenac

Your files are attached and ready to send with this message.

This e-mail (including any attachments) is confidential and may be legally privileged. If you are not an intended recipient or an authorized representative of an intended recipient, you are prohibited from using, copying or distributing the information in this e-mail or its attachments. If you have received this e-mail in error, please notify the sender immediately by return e-mail and delete all copies of this message and any attachments. Thank you.

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June 02, 2005

Wiley A. Chambers, M.D.
Deputy Director, DAAODP
FDA / CDER, HFD-550
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

6/8/05
NAI
(DAG LOG)
MAN.

N-000(BM)

ORIG AMENDMENT

RECEIVED

JUN 03 2005

MEGA / CDER

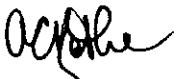
RE: NDA 21-862
NEPAFENAC OPHTHALMIC SUSPENSION, 0.1%
CLINICAL AMENDMENT

Dear Dr. Chambers:

Enclosed please find the tabulation requested May 26th by the Medical Reviewer for the above-referenced NDA.

If you have any questions concerning this amendment, please contact me via telephone at 817-551-4933 or via facsimile at 817-551-4630.

Sincerely



Angela C. Kothe, OD, PhD
Associate Director, Regulatory Affairs

Encl.

ORIGINAL

Rodriguez, Raphael R

From: Angela.Kothe@AlconLabs.com
Sent: Wednesday, June 01, 2005 6:04 PM
To: RODRIGUEZR@cder.fda.gov
Subject: RE: NDA 21-862

Raphael

In response to Dr. Nevitt's request, attached please find a Word document with a revision of Table 2.7.4.2.1.6-1 splitting out patients in C-02-53 according to their assigned dosing regimen.

Please advise if this adequately responds to Dr. Nevitt's request, and we will submit formally to the document control room.

Thanks
ANGELA

-----Original Message-----

From: Rodriguez, Raphael R [mailto:RODRIGUEZR@cder.fda.gov]
Sent: Thursday, May 26, 2005 7:51 AM
To: Kothe,Angela,FORT WORTH,Regulatory Affairs
Subject: FW: NDA 21-862

Angela - see information request from the clinical reviewer. Thanks. R-

-----Original Message-----

From: Nevitt, Martin
Sent: Wednesday, May 25, 2005 11:10 AM
To: Rodriguez, Raphael R
Cc: Boyd, William M
Subject: NDA 21-862

Raphael,

I need the following information from the sponsor for NDA 21-862:

In Table 2.7.4.2.1.6 - 1 (Adverse Reactions for Inclusion in Package Insert of the NDA submission), Study C-02-53 has an N=161. Of the 161 subjects, 58 were dosed TID, 53 BID and 50 QD. Given the proposed indication for use will be a dosing of TID, please reformat this table reflecting an N=58 for the TID dosed subjects for Study C-02-53.

Thank you.

This e-mail (including any attachments) is confidential and may be legally privileged. If you are not an intended recipient or an authorized representative of an intended recipient, you are prohibited from using, copying or distributing the information in this e-mail or its attachments. If you have received this

8/8/2005

e-mail in error, please notify the sender immediately by return e-mail and delete all copies of this message and any attachments.

Thank you.

Appears This Way
On Original

Rodriguez, Raphael R

From: Angela.Kothe@AlconLabs.com
Sent: Thursday, May 26, 2005 10:02 AM
To: RODRIGUEZR@cder.fda.gov
Subject: RE: NDA 21-862

Raphael

We'll get working on Dr. Nevitt's request and hope to have it to you by Wednesday June 1st.

I was going to give you a call today since it had been about a month since we had received any requests for information. Specifically, to date, we have not received any questions from the CMC reviewer.

Thanks and have a good Memorial Day weekend.

ANGELA

-----Original Message-----

From: Rodriguez, Raphael R [mailto:RODRIGUEZR@cder.fda.gov]
Sent: Thursday, May 26, 2005 7:51 AM
To: Kothe,Angela,FORT WORTH,Regulatory Affairs
Subject: FW: NDA 21-862

Angela - see information request from the clinical reviewer. Thanks. R-

-----Original Message-----

From: Nevitt, Martin
Sent: Wednesday, May 25, 2005 11:10 AM
To: Rodriguez, Raphael R
Cc: Boyd, William M
Subject: NDA 21-862

Raphael,

I need the following information from the sponsor for NDA 21-862:

In Table 2.7.4.2.1.6 - 1 (Adverse Reactions for Inclusion in Package Insert of the NDA submission), Study C-02-53 has an N=161. Of the 161 subjects, 58 were dosed TID, 53 BID and 50 QD. Given the proposed indication for use will be a dosing of TID, please reformat this table reflecting an N=58 for the TID dosed subjects for Study C-02-53.

Thank you.

This e-mail (including any attachments) is confidential and may be legally privileged. If you are not an intended recipient or an authorized representative of an intended recipient, you are prohibited from using, copying or distributing the information in this e-mail or its attachments. If you have received this e-mail in error, please notify the sender immediately by return e-mail and delete all copies of this message and any attachments.

8/8/2005

5 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

Rodriguez, Raphael R

From: Angela.Kothe@AlconLabs.com
Sent: Monday, May 09, 2005 4:51 PM
To: NevittM@cder.fda.gov
Cc: RODRIGUEZR@cder.fda.gov
Subject: NDA 21-862 (Nepafenac Ophthalmic Suspension, 0.1%)



Nepafenac Tables
of Patients b...

Dr. Nevitt

Attached please find a Word file that includes the requested information regarding the enrollment by investigator for the Nepafenac clinical studies C-02-53, C-03-32, C-95-93 and C-97-30. Also included is the requested information regarding discontinued patients (with reason for discontinuation and patient number) by investigator for the above-mentioned clinical studies.

<<Nepafenac Tables of Patients by Inv and DC'ed Patients by Inv (pci1774 s03).doc>>
An official copy of this information will be sent to the Document Control Room and a desk copy to your attention.

Thanks
ANGELA

Angela C. Kothe, OD, PhD
Associate Director, Regulatory Affairs
Alcon Research, Ltd.
tel 817-551-4933
fax 817-551-4630
pager 817-327-0161

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Rodriguez, Raphael R

From: Angela.Kothe@AlconLabs.com
Sent: Wednesday, April 27, 2005 3:58 PM
To: RODRIGUEZR@cder.fda.gov
Subject: RE: Results of filing meeting NDA 21-862

Thank you for the good news.

Could you please advise as to how August 31st, 2005 was chosen as the PDUFA date based on receipt of February 28th? While we are perfectly happy with August 31st, we're just curious as to how the date was derived.

Also, will you be sending us another letter that indicates that we received priority review (as you may recall, the letter we received mid-April said standard review but had the August PDUFA date)?

Thanks
ANGELA

-----Original Message-----

From: Rodriguez, Raphael R [mailto:RODRIGUEZR@cder.fda.gov]
Sent: Wednesday, April 27, 2005 2:48 PM
To: Kothe,Angela,FORT WORTH,Regulatory Affairs
Subject: RE: Results of filing meeting NDA 21-862

THANKS. I have received 4 diskettes. Will load on our shared drive. You will be receiving your filing letter - no issues identified.

-----Original Message-----

From: Angela.Kothe@AlconLabs.com [mailto:Angela.Kothe@AlconLabs.com]
Sent: Tuesday, April 26, 2005 6:04 PM
To: RODRIGUEZR@cder.fda.gov
Subject: RE: Results of filing meeting NDA 21-862

Raphael

In response to the e-mail below and our teleconference of April 20th, today we are sending you (via DHL overnight courier) CD-Roms with the SAS transport files, and version 9 SAS datasets and programs. This packet is being sent directly to your attention and marked as "DESK COPY".

Thanks
ANGELA

-----Original Message-----

From: Rodriguez, Raphael R [mailto:RODRIGUEZR@cder.fda.gov]
Sent: Friday, April 15, 2005 9:24 AM
To: Kothe,Angela,FORT WORTH,Regulatory Affairs

Subject: FW: Results of filing meeting NDA 21-862

Angela - let me know when is the best time to call your Stat reviewer. Thanks.
Raphael

-----Original Message-----

From: Qi, Karen
Sent: Thursday, April 14, 2005 4:14 PM
To: Rodriguez, Raphael R; Lin, Stan
Cc: Chambers, Wiley A; Nevitt, Martin
Subject: RE: Results of filing meeting NDA 21-862

I think it will be very helpful.

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From: Rodriguez, Raphael R
Sent: Thursday, April 14, 2005 4:14 PM
To: Lin, Stan; Qi, Karen
Cc: Chambers, Wiley A; Nevitt, Martin
Subject: RE: Results of filing meeting NDA 21-862

let me know if we need to setup a quick t-con regarding this dataset.

-----Original Message-----

From: Lin, Stan
Sent: Thursday, April 14, 2005 4:09 PM
To: Qi, Karen; Rodriguez, Raphael R
Cc: Chambers, Wiley A; Nevitt, Martin
Subject: RE: Results of filing meeting NDA 21-862

Also, need clarification why there are two pp dataset for C-02-53, and two of each itt and pp datasets for C-03-32. -Stan

-----Original Message-----

From: Qi, Karen
Sent: Thursday, April 14, 2005 3:55 PM
To: Rodriguez, Raphael R
Cc: Chambers, Wiley A; Lin, Stan; Nevitt, Martin
Subject: RE: Results of filing meeting NDA 21-862

Raphael,

I checked the datasets sent by the sponsor. So far, I have the following questions:

1. C-95-93

The sponsor did not provide the datasets used for the efficacy analysis (intent-to-treat or per protocol population). I would like to have the

datasets that include all efficacy parameters (i.e., scores for aqueous cells, flare and inflammation, on Day 1 (baseline), Days 4, 8 and 15, cure rate, treatment failure).

2. C-97-30

a) The sponsor did not provide the datasets used for the efficacy analysis (intent-to-treat or per protocol population). I would like to have the datasets that include all efficacy parameters (i.e., scores for aqueous cells, flare and inflammation, on Day 1 (baseline), Days 4, 8 and 15, cure rate, treatment failure).

b) The file FORMAT.XPF is empty.

3. C-02-53

a) In both EFFICA01.XPT (EFFICACY_ITT) and EFFICA03.XPT (EFFICACY_PPCF), each of the efficacy parameters has 3 variables listed in the following table. The label for the variable does not provide clear definition. I cannot tell which variable was used in the final efficacy analysis.

Efficacy parameter	Variables in SAS dataset	Label for the variable in SAS dataset
Treatment failure	FAILUR01	failure
	FAILUR02	failure_cf
	FAILUR03	failure_old
Inflammation	INFLAM01	inflammation
	INFLAM02	inflammation_cf
	INFLAM03	inflammation_old
Response	RESPON01	responder
	RESPON02	responder_cf
	RESPON03	responder_old
Aqueous cells	AQUEOU01	aqueous_cell
	AQUEOU03	aqueous_cell_cf
	AQUEOU05	aqueous_cell_old
Aqueous flare	AQUEOU02	aqueous_flare
	AQUEOU04	aqueous_falre_cf
	AQUEOU06	aqueous_cell_old

b) There are 2 datasets for analysis using per protocol population: EFFICA02.XPT (EFFICACY_PP) and EFFICA03.XPT (EFFICACY_PPCF). I am not certain which one was used in the final analysis.

4. C-03-32

There are 2 dataset for intent-to-treat and per protocol populations, respectively. Could I assume that EFFICA01.XLP (EFFICACY_FINAL_ITT) and EFFICA02.XLP (EFFICACY_FINAL_PP) are used in the final analysis?

Thanks,
Karen

-----Original Message-----

From: Rodriguez, Raphael R
Sent: Thursday, April 14, 2005 11:05 AM
To: Qi, Karen .
Subject: RE: Results of filing meeting NDA 21-862

K - your SAS data in CD/ROM has arrived.

This e-mail (including any attachments) is confidential and may be legally privileged. If you are not an intended recipient or an authorized representative of an intended recipient, you are prohibited from using, copying or distributing the information in this e-mail or its attachments. If you have received this e-mail in error, please notify the sender immediately by return e-mail and delete all copies of this message and any attachments.

Thank you.

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Thank you.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NO FILING ISSUES IDENTIFIED

NDA 21-862

Alcon, Inc.
Alcon Research, Ltd.
Attention: Angela C. Kothe, O.D., Ph.D.
Mail Code R7-18
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Dr. Kothe:

Please refer to your February 25, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nevanac (nepafenac ophthalmic suspension) 0.1%.

We have completed our filing review of your application. At this time, we have not identified any potential review issues. Our filing review is only a preliminary review and deficiencies may be identified during substantive review of your application.

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 Management Staff
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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

/s/

Carmen DeBellas
4/26/05 02:08:45 PM

Rodriguez, Raphael R

From: Angela.Kothe@AlconLabs.com
Sent: Tuesday, April 26, 2005 6:04 PM
To: RODRIGUEZR@cder.fda.gov
Subject: RE: Results of filing meeting NDA 21-862

Raphael

In response to the e-mail below and our teleconference of April 20th, today we are sending you (via DHL overnight courier) CD-Roms with the SAS transport files, and version 9 SAS datasets and programs. This packet is being sent directly to your attention and marked as "DESK COPY".

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From: Rodriguez, Raphael R [mailto:RODRIGUEZR@cder.fda.gov]
Sent: Friday, April 15, 2005 9:24 AM
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Subject: FW: Results of filing meeting NDA 21-862

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Cc: Chambers, Wiley A; Lin, Stan; Nevitt, Martin
Subject: RE: Results of filing meeting NDA 21-862

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	FAILUR02	failure_cf
	FAILUR03	failure_old
Inflammation	INFLAM01	inflammation
	INFLAM02	inflammation_cf

INFLAM03	inflammation_old
Response	RESPON01 responder
RESPON02	responder_cf
RESPON03	responder_old
Aqueous cells	AQUEOU01 aqueous_cell
AQUEOU03	aqueous_cell_cf
AQUEOU05	aqueous_cell_old
Aqueous flare	AQUEOU02 aqueous_flare
AQUEOU04	aqueous_falre_cf
AQUEOU06	aqueous_cell_old

b) There are 2 datasets for analysis using per protocol population: EFFICA02.XPT (EFFICACY_PP) and EFFICA03.XPT (EFFICACY_PPCF). I am not certain which one was used in the final analysis.

4. C-03-32

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Thanks,
Karen

-----Original Message-----

From: Rodriguez, Raphael R
Sent: Thursday, April 14, 2005 11:05 AM
To: Qi, Karen
Subject: RE: Results of filing meeting NDA 21-862

K - your SAS data in CD-ROM has arrived.

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Thank you.

Rodriguez, Raphael R

From: Angela.Kothe@AlconLabs.com
Sent: Tuesday, April 12, 2005 1:55 PM
To: RODRIGUEZR@cder.fda.gov
Subject: RE: Results of filing meeting NDA 21-862

Raphael

SAS transport files for C-95-93, C-97-30, C-02-53 and C-03-32 are being sent to you as a desk copy via overnight courier today.

Thanks
ANGELA

Angela C. Kothe, OD, PhD
Associate Director, Regulatory Affairs
Alcon Research, Ltd.
tel. 817-551-4933
fax 817-551-4630

[Kothe,Angela,FORT WORTH,Regulatory Affairs] -----Original Message-----

From: Rodriguez, Raphael R [mailto:RODRIGUEZR@cder.fda.gov]
Sent: Tuesday, April 05, 2005 8:05 AM
To: Kothe,Angela,FORT WORTH,Regulatory Affairs
Subject: FW: Results of filing meeting NDA 21-862

Angela - see attached information request from stat reviewer. Thanks. Raphael

-----Original Message-----

From: Chambers, Wiley A
Sent: Monday, April 04, 2005 4:02 PM
To: Lin, Stan; Rodriguez, Raphael R; Nevitt, Martin; Boyd, William M; Ng, Linda L; Rodriguez, Libaniel; Bashaw, Edward D; Ghosh, Tapash; Yang, Josie; Chen, Zhou; Qi, Karen

Cc: Pawar, Vinayak; Tesch, Dianne; Ball, Leslie; Hussong, David; Holquist, Carol A; Berkman, Suzanne; Beam, Sammie
Subject: RE: Results of filing meeting NDA 21-862

I do not see SAS datasets included, these should be requested.

Wiley

Rodriguez, Raphael R

From: Angela.Kothe@AlconLabs.com
sent: Wednesday, April 06, 2005 5:03 PM
to: RODRIGUEZR@cder.fda.gov
Subject: NDA 21-862 (NEVANAC)

Raphael

Today we are shipping you (via overnight courier) the Word files for Module 1 (the financial disclosure section), Module 2.5 and 2.7 (clinical overview and summary), as well as sections 10, 11, 12 and 14 of the 4 Clinical Study Reports (C-95-93, C-97-30, C-02-53 and C-03-32) for the NEVANAC NDA. Per your request, this information is being sent to your attention as "Desk Copies".

We should be sending you the SAS transport files for the above-mentioned studies on Friday.

We heard from the Division of Scientific Investigations today regarding NDA 21-862. They have requested clinical materials to support their conduct of audits at 2 sites (1 site for C-03-32 and 1 site for C-02-53).

Thanks
ANGELA

Angela C. Kothe, OD, PhD
Associate Director, Regulatory Affairs
Alcon Research, Ltd.
tel 817-551-4933
fax 817-551-4630
pager 817-327-0161

This e-mail (including any attachments) is confidential and may be legally privileged. If you are not an intended recipient or an authorized representative of an intended recipient, you are prohibited from using, copying or distributing the information in this e-mail or its attachments. If you have received this e-mail in error, please notify the sender immediately by return e-mail and delete all copies of this message and any attachments. Thank you.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-862

Alcon, Inc.
c/o Alcon Research, Ltd.
Attention: Angela C. Kothe, O.D., Ph.D.
Associate Director, Regulatory Affairs
6201 South Freeway
Mail Code R7-16
Fort Worth, Texas 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: Nevanac (nepafenac ophthalmic suspension) 0.1%

Review Priority Classification: Standard (S)

Date of Application: February 25, 2005

Date of Receipt: February 28, 2005

Our Reference Number: NDA 21-862

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 April 29, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 31, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

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:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug products, HFD-550
Attention: Division Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

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: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 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 Management
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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

/s/

Raphael Rodriguez
4/4/05 03:26:22 PM

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: March 9, 2005	DESIRED COMPLETION DATE: May 31, 2005	ODS CONSULT #: 04-0100-1
DATE OF DOCUMENT: February 25, 2005	PUDFA DATE: August 31, 2005	

TO: Janice Soreth, MD
Director, Division of Anti-Infective and Ophthalmology Drug Products
HFD-520

THROUGH: Raphael Rodriguez
Project Manager
HFD-520

PRODUCT NAME: Nevanac (Nepafenac Ophthalmic Suspension) 0.1%	NDA SPONSOR: Alcon, Inc
NDA #: 21-862	

SAFETY EVALUATOR: Felicia Duffy, RN

COMMENDATIONS:

DMETS has no objections to the use of the proprietary name, Nevanac. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name and its associated labels and labeling must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names.

- DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.
- DDMAC finds the proprietary name Nevanac acceptable from a promotional perspective.

/S/

/S/

Denise Toyer, PharmD
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 11, 2005

NDA #: 21-862

NAME OF DRUG: Nevanac
(Nepafenac Ophthalmic Suspension)
0.1%

NDA HOLDER: Alcon, Inc.

***** NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Infective and Ophthalmology Drug Products (HFD-520), for re-review of the proprietary name, Nevanac. The proposed name was found acceptable by DMETS in ODS consult #04-0100 dated June 2, 2004. Draft labels, labeling, and package insert were provided for review and comment.

PRODUCT INFORMATION

Nevanac is a sterile, topical, nonsteroidal anti-inflammatory product for ophthalmic use. Nevanac is indicated for the treatment of postoperative pain and inflammation associated with cataract surgery. The usual dose of Nevanac is one drop applied to the affected eye(s) three times daily. Dosing should begin 24 hours prior to cataract surgery, and continue on the day of surgery, and through the first two weeks of the postoperative period. Nevanac has been administered safely in conjunction with other ophthalmic medications such as antibiotics, beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics. Nevanac will be supplied in LDPE plastic bottles containing 3 mL of suspension in a 4 mL bottle.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Nevanac to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Nevanac. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Nevanac acceptable from a promotional perspective.
2. The Expert Panel identified two proprietary names that were thought to have the potential for confusion with Nevanac. These products are listed in table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Nevanac	Nepafenac Topical Ophthalmic Suspension 0.1%	1 drop in affected eye(s) three times daily	
Kinevac	Sincalide Injection: 5 mcg/vial	Gallbladder contraction: 0.02 mcg/kg injected IV over 30 to 60 seconds. Pancreatic secretion stimulation: 30 mins after initiating secretin, give a separate IV infusion of Kinevac at a total dose of 0.02 mcg/kg over 30 mins. Barium meal transit time acceleration: 0.04 mcg/kg IV over a 30-60 second interval.	LA/SA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike) *** Name pending approval. Not FOI releasable.			

¹ MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.


B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

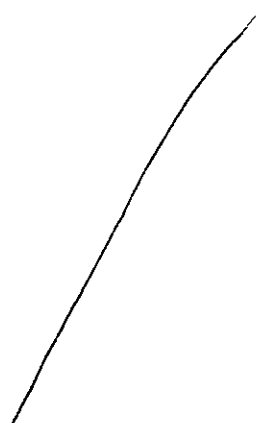
As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Nevanac were discussed by the Expert Panel (EPD).

C. PRESCRIPTION STUDY ANALYSIS

Three separate prescription studies (written inpatient, written outpatient, and verbal) were conducted during the initial review of Nevanac (ODS consult #04-0100). Therefore, prescription studies were not repeated for this review.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Nevanac, the primary concerns related to look-alike and sound-alike confusion with  and Kinevac. Upon further review of the names gathered from EPD, the name Kinevac was not reviewed further due to a lack of convincing look-alike and sound-alike similarities with Nevanac in addition to numerous differentiating product characteristics such as the product strength, indication for use, frequency of administration, route of administration, and dosage form.



III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the labeling of Nevanac, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENT

Draft copies of the labels and labeling were provided in black and white, and may not represent the true color of the labels and labeling. It is not possible to fully assess the safety of the proposed labels and labeling because the information provided does not reflect the presentation that will actually be used in the marketplace (i.e., color, placement of name, design, etc.). Please forward copies of the revised labels and labeling when they are available.

B. CONTAINER LABEL (1.5 mL professional sample and 3 mL bottle)

1. Ensure the established name is at least $\frac{1}{2}$ the size of the proprietary name per 21 CFR 201.10(g)(2).
2. To avoid confusion, please ensure the net quantity statement appears away from the product strength and is less prominent than the product strength.



C. CARTON LABELING (1.5 mL professional sample and 3 mL bottle)

1. See comments B1-B3.
2. Please ensure the sponsor's name is less prominent than the proprietary name, established name, and strength on the primary display panel.

D. INSERT LABELING

PRECAUTIONS Section: The statement, "It is recommended that Nevanac be used with caution in patients with known bleeding tendencies or who are receiving medications which may prolong bleeding time," is ambiguous. Please define "known bleeding tendencies". It may also be helpful to include examples of the drug products that may prolong bleeding time.

IV. RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name Nevanac. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
- B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
- C. DDMAC finds the proprietary name Nevanac acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

/s/

Felicia Duffy, RN
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

/s/

Alina Mahmud, RPh, MS
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Felicia Duffy
6/24/05 10:58:32 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
6/24/05 11:44:29 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
6/24/05 12:36:46 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/24/05 12:48:10 PM
DRUG SAFETY OFFICE REVIEWER

3.A.9. ENVIRONMENTAL ASSESSMENT OR REQUEST FOR CATEGORICAL EXCLUSION

Pursuant to 21 CFR 25.31(b), Alcon Inc. hereby claims a categorical exclusion from the requirement of preparing an Environmental Assessment for the NDA for Nepafenac Ophthalmic Suspension.

Alcon Inc. meets the requirements of 21 CFR 25.31(b) because, even though the Application increases the use of the active moiety, the estimated concentration of the substance at the point of entry into the aquatic environment will be below one (1) part per billion (see Exhibit 4.A.5-1). In addition, to the Applicant's knowledge, no extraordinary circumstances exist [21 CFR 25.15(d)].



1/7/05

Richard W. Ray

Date

Senior Director

Corporate Safety and Environmental Affairs

**Estimation of the Concentration of Nepafenac Ophthalmic Suspension
at Point of Entry Into the Aquatic Environment**

$$\text{EIC - Aquatic (ppb)} = A \times B \times C \times D$$

A = kg/year sales (active moiety)

[Annual (kg / year) estimate for Nepafenac to be used in the production of Nepafenac Ophthalmic Suspension is — This is an estimated average over five years based on projected sales.]

B = — per day entering publicly owned treatment works (POTWs)
— liters/days]

C = year / 365 days

D = 10^9 $\mu\text{g/kg}$ (conversion factor)

$$\begin{aligned} \text{EIC} &= \text{— / year} \times \text{— per day} \times 1 / 365 \text{ days} \times 10^9 \mu\text{g/kg} \\ &= \text{— } \mu\text{g/kg (ppb)} \end{aligned}$$

3.A.8. WAIVER REQUESTS

3.A.8.1 CARCINOGENICITY WAIVER

A request for a carcinogenicity waiver was submitted to IND 49,924 on July 28, 2006 [SN:061] and was granted on October 19, 2004.

3.A.8.2 PEDIATRIC WAIVER

In accordance with 21 CFR 314.55(c)(2)(i) Alcon is requesting a full waiver from the requirements for pediatric use information. As summarized below, Alcon believes that Nepafenac Ophthalmic Suspension, 0.1% does not represent a meaningful therapeutic benefit over existing treatments (i.e., corticosteroids) for pediatric patients and is not likely to be used in a substantial number of patients.

In the last 15 years, cataract extraction with intraocular lens implantation has become more common in younger children. Today, approximately 85% of ophthalmologists perform cataract surgery in children under 2 years of age, compared with approximately 12% of ophthalmologists in 1993 (1). Better surgical techniques, improvements in intraocular lens design, and advances in perioperative drug regimens have reduced postoperative complications. However, despite these improvements, a high incidence of inflammation is still a major obstacle to visual rehabilitation in children (2). As a consequence, cataract surgeons use postoperative corticosteroids in their pediatric patients (1). Wilson *et al.* recently surveyed the practice styles and preferences of the 2001 memberships of the American Society of Cataract and Refractive Surgery (ASCRS) and the American Association for Pediatric Ophthalmology and Strabismus (AAPOS) (1). They found that 90% of ASCRS and 97% of AAPOS members used topical steroids postoperatively, while only 8.4% of AAPOS members used NSAIDs postoperatively in their pediatric cataract surgery patients.


Compared with adults, children have a heightened postoperative inflammatory response (3) that may make them especially sensitive to surgical technique and intraocular lens materials. Infants have a rapid postoperative inflammatory response with the potential for secondary membrane formation and a high incidence of posterior capsular opacification (4). The severity of the inflammatory response decreases with age until, as they approach the teenage

years, the inflammatory response in children becomes more like that of adults (4). It is anticipated that the safety and efficacy of Nepafenac Ophthalmic Suspension, 0.1% in the adolescent population would be well predicted by that of the adult population. Adolescents with cataract are more likely to have traumatic cataract 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.

Since withholding steroids in a pediatric population would be unethical, no studies have been conducted to study the safety and efficacy of Nepafenac Ophthalmic Suspension, 0.1% in this patient population. Alcon does not plan to pursue a pediatric indication for Nepafenac Ophthalmic Suspension, 0.1% and requests a full waiver from the requirements for pediatric use information.

References:

1. Wilson ME, Bartholomew LR, Trivedi RH. Pediatric cataract surgery and intraocular lens implantation: practice styles and preferences of the 2001 ASCRS and AAPOS memberships. *J Cataract Refract Surg.* 2003;29:1811-20.
2. Raina UK, Mehta DK, Monga S, Arora R. Functional outcomes of acrylic intraocular lenses In pediatric cataract surgery. *J Cataract Refract Surg.* 2004;30:1082-1091.
3. Buckley EG. Pediatric cataracts and lens anomalies. In: Nelson LB, ed, *Harley's Pediatric Ophthalmology*, 4th ed. Philadelphia, PA, WB Saunders Co, 1998;272.
4. Müllner-Eidenböck A, Amon M, Moser E, Kruger A, Abela C, Schlemmer Y, et al. Morphological and functional results of AcrySof intraocular lens implantation in children. *J Cataract Refract Surg.* 2003;29:285-93.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		PRESCRIPTION DRUG USER FEE COVER SHEET		Form Approved: OMB No. 0910-0297 Expiration Date: December 31, 2006.
See Instructions on Reverse Side Before Completing This Form				
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdofa/default.htm				
1. APPLICANT'S NAME AND ADDRESS Alcon, Inc. P.O. Box 62 Bosch 69 CH-6331 Hünenberg Switzerland		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER NDA 21-862		
2. TELEPHONE NUMBER (Include Area Code) (817) 551-4933		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA).		
3. PRODUCT NAME NEVANACT™ (nepafenac ophthalmic suspension) 0.1%		6. USER FEE I.D. NUMBER 4867		
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.				
<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.) <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)				
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO (See Item 8, reverse side if answered YES)				
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:				
Department of Health and Human Services Food and Drug Administration CDER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448		Food and Drug Administration CDER, HFD-94 and 12420 Parklawn Drive, Room 3046 Rockville, MD 20852		An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 		TITLE Associate Director, Regulatory Affairs		DATE 12/21/2004

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning Dr _____, who
Name of clinical investigator
participated as a clinical investigator in the submitted study Nepafenac (Cataract Surgery) _____
Name of clinical study, is submitted in accordance with 21 CFR

54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

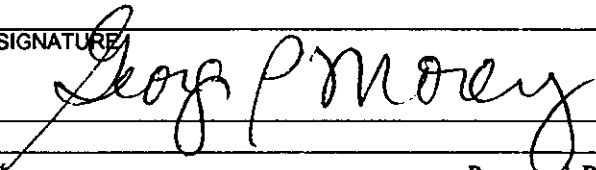
any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

any proprietary interest in the product tested in the covered study held by the clinical investigator;

any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME George P. Morey	TITLE Vice President, Controller
FIRM / ORGANIZATION Alcon Research, Ltd.	
SIGNATURE 	DATE 22 October 2004

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

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Name of clinical study
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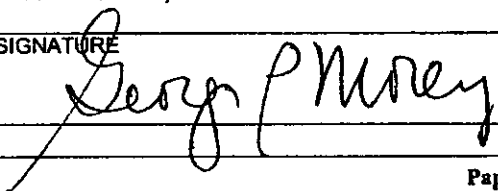
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Please mark the applicable checkboxes.

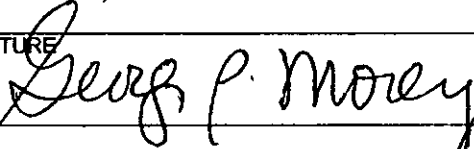
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Rockville, MD 20857

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TO BE COMPLETED BY APPLICANT

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Name of clinical investigator
participated as a clinical investigator in the submitted study _____
Name of clinical study
(Nepafenac (Cataract Surgery)), is submitted in accordance with 21 CFR

54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

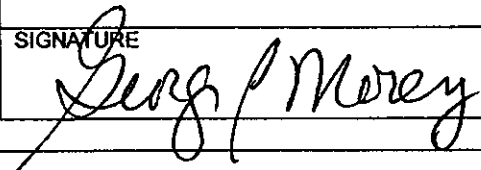
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Rockville, MD 20857

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TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

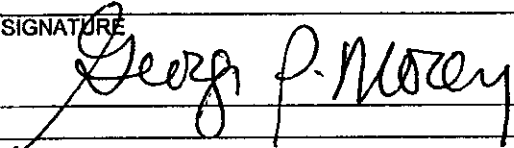
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	<input type="checkbox"/> All investigators on the attached list participating	
	<input type="checkbox"/> in Nepafenac (Cataract Surgery) study C-04-08	
	<input type="checkbox"/>	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME George P. Morey		TITLE Vice President, Controller	
FIRM / ORGANIZATION Alcon Research Ltd.			
SIGNATURE 		DATE 21 October 2004	

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 5600 Fishers Lane, Room 14C-03
 Rockville, MD 20857

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The following information concerning Dr. _____, Name of clinical investigator who participated as a clinical investigator in the submitted study Nepafenac (Cataract Surgery), Name of clinical study is submitted in accordance with 21 CFR 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

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Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

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FIRM / ORGANIZATION Alcon Research, Ltd.	
SIGNATURE <i>George P. Morey</i>	DATE <i>21 October 2004</i>

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The following information concerning Dr. _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR _____.

Name of clinical investigator
Name of clinical study

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Please mark the applicable checkboxes.

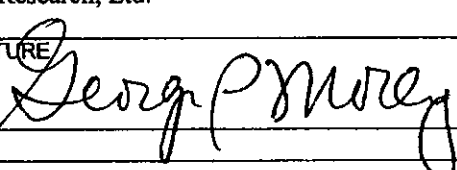
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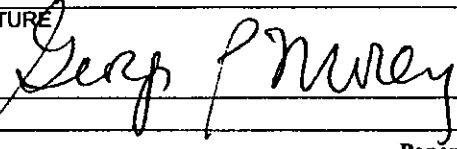
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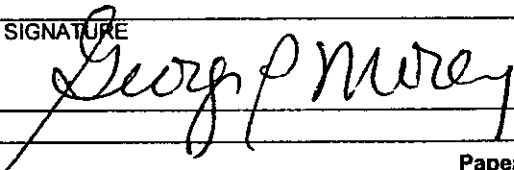
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Clinical Investigators	All investigators on the attached list participating	—
	in Nepafenac (Cataract Surgery)	—
	except for Dr.	—

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

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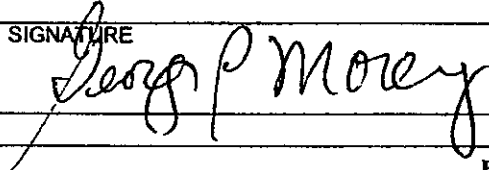
any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

any proprietary interest in the product tested in the covered study held by the clinical investigator;

any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME George P. Morey	TITLE Vice President, Controller
FIRM / ORGANIZATION Alcon Research, Ltd.	
SIGNATURE 	DATE 21 October 2004

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning Dr. _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR _____.

Name of clinical investigator
Name of clinical study

54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

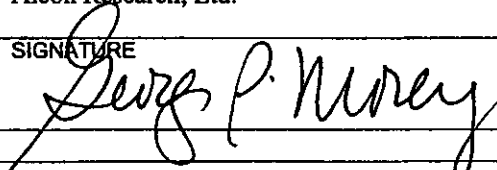
any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

any proprietary interest in the product tested in the covered study held by the clinical investigator;

any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME George P. Morey	TITLE Vice President, Controller
FIRM / ORGANIZATION Alcon Research, Ltd.	
SIGNATURE 	DATE 21 October 2004

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An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

**CERTIFICATION: FINANCIAL INTERESTS AND
 ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

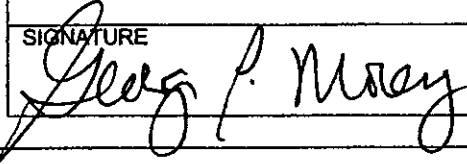
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	All investigators on the attached list participating	subinvestigators,	<input type="checkbox"/>
	in Nepafenac (Cataract Surgery) study		<input type="checkbox"/>
	except for Dr.		<input type="checkbox"/>

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME George P. Morey		TITLE Vice President, Controller	
FIRM / ORGANIZATION Alcon Research Ltd.			
SIGNATURE 		DATE 21 October 2004	

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
 Food and Drug Administration
 5600 Fishers Lane, Room 14C-03
 Rockville, MD 20857

3.A.6. FINANCIAL DISCLOSURE

3.A.6.1. CERTIFICATION AND DISCLOSURE STATEMENTS

Pursuant to 21 CFR§314.50(k), §312.53(c)(4), and §54.4, the following is certification and disclosure information for the covered clinical studies submitted in this application.

The covered clinical studies include: C-02-53, C-03-32 and C-04-08.

The applicant has determined that there were no financial interests or arrangements to disclose from investigators that participated in one study — . However, there are financial interests or arrangements to disclose from ten investigators that participated in two of the clinical trials (/ . The investigators, by covered study, are presented in Table 3.A.6.1-1.

Table 3.A.6.1-1

Investigators with Financial Interests or Arrangements by Clinical Study

Covered Clinical Study	Investigators with Financial Interests or Arrangements to Disclose
	/

Completed Certification Forms (FDA form-3454) and Disclosure Forms (FDA form-3455) signed by the applicant’s Financial Officer are provided in Module 1, Section 3.A.6.3. The claims in the signed form FDA-3454 and form FDA-3455 have been verified by documentation obtained from the investigators who participated in the clinical studies listed above. The list of investigators for each of these covered clinical studies is provided in Module 1, Section 3.A.6.2.

**Description of Financial Interests and Arrangements by Investigator for
Reporting Period: January 9, 2003 to June 12, 2004**

(sub-investigators:

Description		
Honorarium & Reimbursement -		5,191.35
Consulting -		68,000.00
Honorarium -		32,500.00
Expense Reimbursement -		33,413.11
Educational Grant		12,000.00
Study Coordinator		30,000.00
		252,382.00
- Misc. Grants		1,218.55
- Other		
	Total	\$434,705.01
(sub-investigator for		
Description		
	- Consulting	67,500.00
	Travel and	3,295.52
Expense Reimbursement		
Honorarium		6,650.00
	Total	\$77,445.52
Description		
Grant - Consulting		153,036.00
Honorarium		2,500.00
Expense Reimbursement		72,977.79
	Total	\$228,513.79
Description		
Grant - Consulting		25,000.00
	Honorarium	3,000.00
	Total	\$28,000.00

Description of Financial Interests and Arrangements by Investigator for
Reporting Period: November 24, 2003 to August 6, 2004

Description	
Consulting	96,666.65
Travel and Expense Reimbursement	37,318.38
Honorarium	6,000.00
Total	\$139,985.03
Description	
Consulting	100,750.00
Honorarium	10,500.00
Expense Reimbursement	27,030.90
Grant -	13,192.41
Total	\$151,473.31
Description	
Consulting	64,588.00
Honorarium	6,000.00
Expense Reimbursement	25,425.60
Total	\$96,013.60
Description	
Consulting	56,000.00
Expense Reimbursement	2,116.14
Total	\$58,116.14
Description	
Honorarium	32,950.00
Expense Reimbursement	4,586.32
Total	\$37,536.32

Study-Related Factors For C-02-53 and C-03-32 That Minimized Bias Regardless of Financial Interests and Arrangements:

- The studies were double-masked such that neither the investigators nor patients were aware of the treatment assignment.
- Assignment of treatment code was randomized.
- Since study medications in C-02-53 were required to be dosed once-daily, twice-daily or three-times-daily, a double-dummy design was employed. This provided for patients to be randomized 3:1 (active:placebo) dosed once-daily, 3:1 (active:placebo) dosed twice-daily, and 3:1 (active:placebo) dosed three-times-daily.
- Since the active medication (Nepafenac Ophthalmic Suspension, 0.1%) is a yellowish colored suspension formulation, study medications were supplied in identical appearing opaque white DROP-TAINER® bottles.
- Additionally, because of the difference in the appearance of the active and placebo formulations, study sites were instructed that neither the investigator nor any other study staff involved in the assessment of efficacy or safety parameters dose the patients or be assigned the task of dispensing study medication to patients. A dedicated individual(s) at each site dosed patients and dispensed study medication.
- The safety variables, which included visual acuity, fundus parameters, slit-lamp biomicroscopy, and adverse events, were assessed by a masked observer.
- The treatment code was not broken at any time during any of the studies by either the investigator or the Sponsor.
- Frequent on-site monitoring was performed during the conduct of the studies to ensure compliance with protocol guidelines.

3.A.6.2. TABULATION OF CLINICAL INVESTIGATORS IN COVERED STUDIES

Tabulations of clinical investigators for the three covered clinical studies of Nepafenac Ophthalmic Suspension, 0.1% can be found in Tables 3.A.6.2-1 through 3.A.6.2-3.

Table 3.A.6.2-1
Tabulation of Investigators in Covered Study C-02-53

C-02-53			
	Inv. #	Principal Investigator and Address	Sub-investigator(s)
1	1678	Dwight Cavanagh, M.D. UTSW Medical Center 5323 Harry Hines Blvd. Dallas, TX 75390-9057	
2	3725	Ezra Maguen, M.D. Ophthalmic Clinical Trials Center 444 S. San Vicente Blvd., # 703 Los Angeles, CA 90048	
3	1434	W. Andrew Maxwell, M.D. California Eye Institute 1360 E. Herndon Ave., # 401 Fresno, CA 93720	
4	3747	Harvey Reiser, M.D. Eye Care Specialist of Northeast PA 703 Rutter Ave. Fresno, CA 93720	None
5	1806	Kenneth Sall, M.D. Sall Eye Surgery Center 9604 Artesia Blvd., #203 Bell Flower, CA 90706	None
6	271	Robert Stewart, M.D. Houston Eye Associates 2855 Gramercy Dr. Houston, TX 77025	
7	2631	William Colby Stewart, M.D. Middle Tennessee Eye Associates 345 N. Washington Ave. Cookeville, TN 38501	None

Table 3.A.6.2-1 (continued)
Tabulation of Investigators in Covered Study C-02-53

C-02-53			
	Inv. #	Principal Investigator and Address	Sub-investigator(s)
8	1007	Tom Walters, M.D. Texas Eye Care, P.A. 1700 South Mopac Expressway Austin, TX 78746	—
9	350	Arthur J. Weinstein, M.D. Eye Associates of New Mexico 809 Martin Luther King Blvd. Albuquerque, NM 87102	—
10	1405	Stefan Trocme, M.D. University of Texas Medical Branch, University Medical Center 700 University Blvd. Galveston, TX 77550	None

Appears This Way
On Original

**Table 3.A.6.2-2
Tabulation of Investigators in Covered Study C-03-32**

C-03-32			
	Inv. #	Principal Investigator and Address	Sub-investigator(s)
1	2666	Louis M. Alpern, M.D. The Cataract, Glaucoma & Refractive Surgery Center 2201 N. Stanton St. El Paso, TX 79902	—
2	3471	Robert J. Arleo, M.D. Arleo Eye Institute 10 Brentwood Dr., Suite A Ithaca, NY 14850	—
3	847	Stephen F. Brint, M.D. Brint Cataract Institute 3900 Veterans Memorial Blvd., # 203 Metairie, LA 70002	—
4	3904	Mike Caplan, M.D. Berkeley Eye Center 3100 Wesleyan, Suite 400 Houston, TX 77027	—
5	3900	Lisa Marie Cibik, M.D. Associates in Ophthalmology 500 N. Lewis Run Road, Suite 218 Pittsburgh, PA 15122	—
6	2902	Robert J. Cionni, M.D. Cincinnati Eye Institute 10494 Montgomery Road Cincinnati, OH 45242	—
7	2678	Peter S. Dawson, M.D. Surgical Eye Associates 1631 N. Loop W., Suite 500 Houston, TX 77008	—
8	3899	Arthur M. Fishman, M.D. Eye Surgery Associates 603 N. Flamingo Road, # 250 Pembroke Pines, FL 33028	—

**Table 3.A.6.2-2
Tabulation of Investigators in Covered Study C-03-32**

C-03-32			
	Inv. #	Principal Investigator and Address	Sub-investigator(s)
9	3903	Gary Foster, M.D. The Eye Center of Northern Colorado 1725 Prospect Rd. Fort Collins, CO 80525	—
10	3889	Henry M. Haley, Jr., M.D. Eye Surgery Center of Louisiana 5646 Read Blvd., # 220 New Orleans, LA 70127	—
11	3472	Edward J. Holland, M.D. Cincinnati Eye Institute 10494 Montgomery Rd. Cincinnati, OH 45242	—
12	3481	Jeffrey D. Horn, M.D. Vanderbilt University Medical Center Dept. of Ophthalmology & Visual Sciences 8000 Medical Center East Nashville, TN 37232-8808	—
13	3901	Ronald A. Landry, M.D. Eye Care Associates 4324 Veterans Memorial Blvd., #102 Metairie, LA 70006	/
14	1204	Stephen S. Lane, M.D. Associated Eye Physicians & Surgeons, Ltd. 232 N. Main Street Stillwater, MN 55082	—
15	970	Robert P. Lehmann, M.D. Lehmann Eye Center 5300 North Street Nacogdoches, TX 75965	/
16	3828	Satish S. Modi, M.D. 23 Davis Avenue Poughkeepsie, NY 12603	—

Table 3.A.6.2-2 (continued)
Tabulation of Investigators in Covered Study C-03-32

C-03-32			
	Inv. #	Principal Investigator and Address	Sub-investigator(s)
17	3025	Matthew D. Paul, M.D. Danbury Eye Physicians and Surgeons 69 Sand Pit Rd., # 101 Danbury, CT 06810	
18	1908	E. Ronald Salvitti, M.D. Southwestern Pennsylvania Eye Center 750 East Beau St. Washington, PA 15301	
19	1238	Stephen V. Scoper, M.D. Virginia Eye Consultants 400 Gresham Dr., # 403 Norfolk, VA 23507	
20	3807	Steven Silverstein, M.D. Silverstein Eye Centers 4240 Blue Ridge Blvd., # 1000 Kansas City, MO 64133	
21	2435	Jeffrey C. Whitsett, M.D. Whitsett Vision Group 1237 Campbell Rd. Houston, TX 77055	

Appears This Way
On Original

Table 3.A.6.2-3
Tabulation of Investigators in Covered Study C-04-08

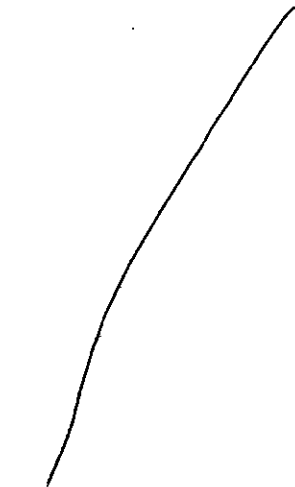

C-04-08			
	Inv. #	Principal Investigator and Address	Sub-investigator(s)
1	2090	Thomas Marbury, M.D. Orlando Clinical Research Center 5055 South Orange Ave. Orlando, FL 32809	

Appears This Way
On Original

3.A.6.3. COMPLETED CERTIFICATION AND DISCLOSURE FORMS

Completed certification (form FDA-3454) and disclosure (form FDA-3455) forms for the three covered clinical studies of Nepafenac Ophthalmic Suspension, 0.1% are included in this submission as per Table 3.A.6.3-1.

**Table 3.A.6.3-1:
Financial Certification and Disclosure Forms Included in this Submission**

Clinical Protocol	Form	Investigator(s)
C-02-53	Form FDA-3454 (certification)	All investigators with the exception of: 
	Form FDA-3455 (disclosure)	
C-03-32	Form FDA-3454 (certification)	All investigators with the exception of: 
	Form FDA-3455 (disclosure)	
C-04-08	Form FDA-3454 (certification)	

Memo To IND 49,924 File

Dated: Oct 4, 2004

From: Asoke Mukherjee, Ph.D., Pharmacologist

To: Josie Yang, Ph.D., Team Leader

Re: Waiver request for carcinogenicity studies

IND 49, 924 serial number 061 was submitted on July 28, 2004 by Alcon Research Ltd for a request of carcinogenicity waiver of Nepafenac (AL-6515) 0.1% ophthalmic suspension for the treatment of the inflamed eye. The treatment will be given three times a day for about two weeks into

The sponsor discussed following issues in support of the waiver.

1. Carcinogenic potential of NSAIDs.

Amfenac amide is a prodrug that crosses the cornea and hydrolyzes to form the active molecule amfenac. The oral formulation of amfenac sodium (AL-1275) is used outside the USA as Fenazox in Japan. The sponsor stated that the chronic treatment of mice with amfenac sodium up to 30 mg/kg for 2 years did not show any carcinogenic potential. However, the data were not reviewed for the IND. Amfenac is structurally related to ketoprofen that is approved in the USA for the treatment of rheumatoid and osteoarthritis. Ketoprofen did not show any carcinogenic potential in rats and mice. Several NSAIDs i.e., ketorolac, flurbiprofen and diclofenac approved for the treatment of ocular inflammation did not show carcinogenic potential in rats and mice. Based on the structural similarity of amfenac with ketoprofen and lack of tumorigenic findings of above mentioned NSAIDs in rodents, amfenac does not have carcinogenic potential in the systemic organs at ophthalmic doses. The sponsor also indicated that amfenac does not have a potential for the formation of reactive metabolites and does not pose a structure alert for carcinogenicity.

2. Evidence of pre-neoplastic lesions in repeat dose studies:

The sponsor indicated that a six-month rat toxicity study of amfenac amide did not show any preneoplastic lesion up to 10 mg/kg/oral. However, the summary of six-month toxicity studies in rats and dogs showed mesenteric lymph node adenitis at 16 and 2 mg/kg/oral doses of amfenac, respectively. In addition IND 49,924 Pharmacology/Toxicology review dated Feb 26, 1996 suggests GI toxicity at 8 and 2 mg/kg/oral doses in rats and dogs, respectively. Six-month and 3-month ocular toxicity studies in rabbits and monkeys did not show any pre-neoplastic lesions. Amfenac amide showed negative results for the Ames assay, mouse lymphoma assay for forward mutation, and mouse micronucleus test *in vivo*. However, amfenac amide showed a positive response in chromosomal aberration assay in CHO cell line in the presence and absence of S-9 rat liver homogenates when cells were incubated for 44 hours at 313, 625 and 1250 µg/ml. Precipitation of the drug substance was noted in the incubation mixture. The sponsor indicated that ketorolac tromethamine also showed chromosomal aberration in CHO cells in the absence of tumorigenicity.

3. Pharmacokinetics:

The estimated ophthalmic dose is about 2.4 µg/kg/day from 0.1% ophthalmic suspensions and estimated human plasma C_{max} of amfenac is about 0.39 ng/ml. The mean plasma concentration of amfenac after 100 mg daily dose is about 5600 ng/ml in humans. The ratio of the plasma levels after oral and ophthalmic doses in human is about 14,358. The sponsor did not indicate whether 100 mg is the maximum recommended daily oral human dose. Determination of carcinogenic potential of

amfenac amide is not necessary due to a low plasma level of amfenac after ophthalmic doses and a short duration of human exposure (two weeks).

Evaluation:

On the basis of the short duration of treatment, low plasma exposure of amfenac following ophthalmic doses, the request for a carcinogenicity waiver for amfenac amide 0.1% ophthalmic suspension is granted.

C.C.

IND 49,924 Div File
HFD-550/Pharmacologist/ A. Mukherjee
HFD-550/Team Leader/ J. Yang
HFD-550/PM/R. Rodriguez
HFD-550/Chemist/Khorshidi, Shawn
HFD-550/MO/Lloyd, R

Revised on Oct 12, 2004
IND49924cacwaiveroct42004.doc

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

/s/

Asoke Mukherjee
10/12/04 03:02:16 PM
PHARMACOLOGIST

Josie Yang
10/12/04 03:26:48 PM
PHARMACOLOGIST

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-862	Efficacy Supplement Type SE-	Supplement Number
Drug: Nevanac (nepafenac ophthalmic suspension)0.1%		Applicant: Alcon, Inc. Alcon Research, Ltd.
RPM: Raphael R. Rodriguez		HFD- 520 Phone # (301) 827-2090
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review, if completed for this application. If not completed, or you otherwise have questions about whether an application is a 505(b)(1) or 505(b)(2) NDA, see Appendix A.)</p> <p>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 that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Reference Listed Drug (NDA #, Drug name):
Application Classifications:		
<ul style="list-style-type: none"> • Review priority • Chem class (NDAs only) • Other (e.g., orphan, OTC) 		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority 1P
❖ User Fee Goal Dates		8/31/2005
❖ Special programs (indicate all that apply)		<input type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee 		<input checked="" type="checkbox"/> Paid UF ID number 4867
<ul style="list-style-type: none"> • User Fee waiver 		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify) _
<ul style="list-style-type: none"> • User Fee exception 		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)

<p>Application Integrity Policy (AIP)</p> <ul style="list-style-type: none"> • Applicant is on the AIP • This application is on the AIP • Exception for review (Center Director's memo) • OC clearance for approval 	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<p>❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.</p>	<p><input checked="" type="checkbox"/> Verified</p>
<p>❖ Patent</p> <ul style="list-style-type: none"> • Information: Verify that form FDA-3542a was submitted. • Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug in the Orange Book and identify the type of certification submitted for each patent. • [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be granted effective approval (but may be tentatively approved if it is otherwise ready for approval) until the date that the patent to which the certification pertains expires. 	<p><input checked="" type="checkbox"/> Verified</p> <p>21 CFR 314.50(i)(1)(i)(A)</p> <p><input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV</p> <p>21 CFR 314.50(i)(1)</p> <p><input type="checkbox"/> (ii) <input type="checkbox"/> (iii)</p>
<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 (certification of notification and documentation of receipt of notice). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity))</i> • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>(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)).</p> <p><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i></p> <p>(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)?</p> <p><i>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 next box below (Exclusivity).</i></p> <p><i>If "No," continue with question (3).</i></p> <p>(3) Has the patent owner, its representative, or the exclusive patent licensee</p>	<p><input type="checkbox"/> N/A (no paragraph IV certification)</p> <p><input type="checkbox"/> Verified</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>

filed a lawsuit for patent infringement against the applicant?

(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)). The patent owner (or its representative) may, but is not required, to provide such notification (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 next box below (Exclusivity).

If "No," continue with question (5).

- (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?

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)). (The patent owner (or its representative) may, but is not required, to provide such notification (see 21 CFR 314.107(f)(2))). Note that the applicant has until the later of the following dates to provide the Division with this written notice: (a) the date marking the end of the 45-day period described in question (1), above, or (b) the date that the Division completes its review of the application (see 21 CFR 314.107(f)(2)).

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 next box below (Exclusivity).

If "Yes," a stay of approval may be in effect; answer the following questions.

- (6) (a) Was the patent subject to the paragraph IV certification submitted to FDA on or after August 18, 2003?

Yes No

(Note: This can be determined by checking with [the Orange Book staff?].)

If "No," skip to question 7. If "Yes," continue with part (b).

Yes No

(b) Was the patent also submitted to FDA before the date that this 505(b)(2) application was submitted as substantially complete?

If "No," there is no stay of approval based on the paragraph IV certification for this patent. If "Yes," continue with question (7).

Yes No

(7) (a) Have 30 months (or an alternate length of time ordered by the court, if any) passed from the date the patent owner received the applicant's notice of certification for the patent?

(Note: In general, approval of a 505(b)(2) application cannot be made effective (although the application can be tentatively approved) for 30 months from the date that the patent owner receives the applicant's notice of certification if a patent infringement suit is timely initiated as described in question (5) above. However, the court may order that the 30-month period be shortened or lengthened under certain circumstances. If the court has ordered that the 30-month period be altered in a particular case, the applicant is required to submit a copy of the court order to the Division within 10 working days (see 21 CFR 314.107(e)).

If "No," go to question (8). If "Yes," continue with part (b) of this question.

Yes No

(b) Before the expiration of the 30-month (or other) period described in part (a), above, did the district court hearing the patent infringement action decide whether the patent subject to the certification is invalid, unenforceable, or not infringed? (For purposes of this question, a district court decision would include a statement regarding the patent's invalidity, unenforceability, or noninfringement that is part of a settlement order or consent decree entered by the court, or a substantive determination by the court that there is no cause of action for patent invalidity or noninfringement.)

(Note: To answer this question, you should check whether the Division has received a copy of a court order or judgment. The applicant is required to submit a copy of any such document to the Division within 10 working days (see 21 CFR 314.107(e)).

If "No," there is no stay of approval based on the paragraph IV certification for this patent. Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," continue with part (c) of this question.

Yes No

(c) Did the district court decide that the patent was invalid, unenforceable, or not infringed?

If "Yes," there is no stay of approval based on the paragraph IV certification for this patent. Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," (i.e., the district court decided that the patent was valid, enforceable, and infringed), continue with part (d) of this question.

Yes No or N/A

(d) If the district court's decision was appealed, has the appellate court issued a decision finding the patent invalid, unenforceable, or not

infringed (including a statement to this effect that is part of a settlement order or consent decree entered by the appellate court, or a substantive determination by the court that there is no cause of action for patent invalidity or noninfringement)?

(Note: As mentioned above, the applicant is required to submit a copy of all court orders or judgments to the Division within 10 working days (see 21 CFR 314.107(e)); therefore, you can check to see whether a copy of an appellate court's order or judgment has been submitted.)

If "Yes," there is no stay of approval based on the paragraph IV certification for this patent. Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, go to the next box below (Exclusivity).

If "N/A" (i.e., the district court decision was not appealed) or "No" (i.e., the appellate court has not yet issued a decision, or has decided that the patent was infringed), the application cannot be effectively approved until the date the patent expires. (If, before the date the patent expires, the appellate court decides that the patent is invalid, unenforceable, or not infringed, the application may be effectively approved as of the date of the appellate decision, if it otherwise qualifies for effective approval.) Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

Yes No

- (8) (a) Has the district court hearing the patent infringement action decided whether the patent subject to the certification is invalid, unenforceable, or not infringed? (For purposes of this question, a district court decision would include a statement regarding the patent's invalidity, unenforceability, or noninfringement that is part of a settlement order or consent decree entered by the court, or a substantive determination by the court that there is no cause of action for patent invalidity or noninfringement.)

(Note: To answer this question, you should check whether the Division has received a copy of a court order or judgment. The applicant is required to submit a copy of any such document to the Division within 10 working days (see 21 CFR 314.107(e)).

If "No," a stay of approval is currently in effect until the expiration of the time period described in (7)(a), above. The stay may be terminated or altered if the district court issues a decision regarding the patent's validity, enforceability, or infringement before the expiration of the time period described in (7)(a). If such a decision is issued before this time period expires, answer question (b) below.

If "Yes," continue with part (b) of this question.

Yes No

- (b) Did the district court decide that the patent was invalid, unenforceable, or not infringed?

If "Yes," there is no stay of approval based on the paragraph IV certification for this patent. Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," (i.e., the district court decided that the patent was valid, enforceable, and infringed), continue with part (c) of this question.

(c) If the district court's decision was appealed, has the appellate court issued a decision finding the patent invalid, unenforceable, or not infringed (including a statement to this effect that is part of a settlement order or consent decree entered by the appellate court, or a substantive determination by the court that there is no cause of action for patent invalidity or noninfringement)?

(Note: As mentioned above, the applicant is required to submit a copy of all court orders or judgments to the Division within 10 working days (see 21 CFR 314.107(e)); therefore, you can check to see whether a copy of an appellate court's order or judgment has been submitted.)

If "Yes," there is no stay of approval based on the paragraph IV certification for this patent.

If "N/A" (i.e., the district court decision was not appealed) or "No" (i.e., the appellate court has not yet issued a decision, or has decided that the patent was infringed), the application cannot be effectively approved until the date the patent expires. (If, before the date the patent expires, the appellate court decides that the patent is invalid, unenforceable, or not infringed, the application may be effectively approved as of the date of the appellate decision, if it otherwise qualifies for effective approval.) Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, go to the next box below (Exclusivity).

Yes No or N/A

❖ Exclusivity (approvals only)		
<ul style="list-style-type: none"> 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.) 		N/A
<ul style="list-style-type: none"> Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification! 		<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		
General Information		
❖ Actions		
<ul style="list-style-type: none"> Proposed action AP 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 		<input checked="" type="checkbox"/> Materials requested in TA letter <input type="checkbox"/> Reviewed for Subpart H
<ul style="list-style-type: none"> Status of advertising (approvals only) 		
❖ Public communications		
<ul style="list-style-type: none"> Press Office notified of action (approval only) 		<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Not applicable
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 		<input checked="" type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))		
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission) 		

of labeling)	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling • Original applicant-proposed labeling • Labeling reviews (including DDMAC, DMETS, DSRCs) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>) • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	<p>8/5/2005; 8/12/05</p> <p>2/25/2005</p> <p>ODS – 8/11/05</p> <p>DDMAC – 5/25/05</p> <p>DMETS – 6/24/05, 8/11/04</p>
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> • Division proposed (only if generated after latest applicant submission) • Applicant proposed • Reviews 	<p>8/11/2005</p> <p>2/25/2005</p> <p>8/11/2005</p>
❖ Post-marketing commitments	
<ul style="list-style-type: none"> • Agency request for post-marketing commitments • Documentation of discussions and/or agreements relating to post-marketing commitments 	<p>N/A</p> <p>N/A</p>
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • EOP2 meeting (indicate date) • Pre-NDA meeting (indicate date) • Pre-Approval Safety Conference (indicate date; approvals only) • Other 	<p>8/11/2003</p> <p>none</p> <p>6/21/2005 ODS reviews 8/11/05</p>
❖ Advisory Committee Meeting	
<ul style="list-style-type: none"> • Date of Meeting • 48-hour alert 	<p>N/A</p> <p>N/A</p>
❖ 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) (<i>indicate date for each review</i>)	XXXXXXXXXX
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	8/12/2005; 8/15/2005
❖ Microbiology (efficacy) review(s) (<i>indicate date for each review</i>)	N/A
❖ Safety Update review(s) (<i>indicate date or location if incorporated in another review</i>)	8/15/2005
❖ Risk Management Plan review(s) (<i>indicate date/location if incorporated in another rev</i>)	N/A
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	ages 2-7 years
❖ Demographic Worksheet (<i>NME approvals only</i>)	N/A
❖ Statistical review(s) (<i>indicate date for each review</i>)	8/5/2005
❖ Biopharmaceutical review(s) (<i>indicate date for each review</i>)	7/25/2005
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date for each review</i>)	N/A
❖ Clinical Inspection Review Summary (DSI)	
<ul style="list-style-type: none"> • Clinical studies 	8/3/2005

• Bioequivalence studies	
CMC Information	
❖ CMC review(s) (<i>indicate date for each review</i>)	8/12/2005
❖ Environmental Assessment	
• Categorical Exclusion (<i>indicate review date</i>)	8/12/2005
• Review & FONSI (<i>indicate date of review</i>)	N/A
• Review & Environmental Impact Statement (<i>indicate date of each review</i>)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (<i>indicate date for each review</i>)	6/20/2005
❖ Facilities inspection (provide EER report)	Date completed: <input checked="" type="checkbox"/> Acceptable 4/26/2005 <input type="checkbox"/> Withhold recommendation
❖ Methods validation	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	7/25/2005
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	N/A
❖ CAC/ECAC report	10/12/2004

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NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # **21-862** Supplement # SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: **Nevanac**
Generic Name: **nepafenac ophthalmic suspension**
Strengths: **0.1%**

Applicant: **Alcon, Inc. / Alcon Research, Ltd.**

Date of Application: **February 25, 2005**
Date of Receipt: **February 28, 2005**
Date clock started after UN:
Date of Filing Meeting: **April 4, 2005**
Filing Date: **April 29, 2005**
Action Goal Date: **August 26, 2005** User Fee Goal Date: **August 31, 2005**

Indication(s) requested: — **treatment of pain and inflammation associated w/ cataract surgery**

Type of Original NDA: (b)(1) X (b)(2) _____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____

NOTE: 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). If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. If the application is a (b)(2) application, complete Appendix B. **Completion of Appendix B is mandatory for all 505(b)(2) applications, even if the other parts of this Regulatory Filing Review are not completed.**

Therapeutic Classification: S _____ P X
Resubmission after withdrawal? _____ Resubmission after refuse to file? _____
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) _____

Form 3397 (User Fee Cover Sheet) submitted: User Fee ID# **4867** YES

User Fee Status: Paid X Exempt (orphan, government) _____
Waived (e.g., small business, public health) _____

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for use that that has not been approved under section 505(b). Examples of a new indication for use include a new indication, a new dosing regime, a new patient population, and an Rx to OTC switch. The best way to determine if the applicant is claiming a new indication for use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for use, please contact the user fee staff.

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? N/A

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A

Is the application affected by the Application Integrity Policy (AIP)? N/A
 If yes, explain.

If yes, has OC/DMPQ been notified of the submission? N/A

- Does the submission contain an accurate comprehensive index? YES
- Was form 356h included with an authorized signature? YES
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES If
 no, explain:
- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all certifications must be in paper and require a signature.
 Which parts of the application were submitted in electronic format?

Additional comments:

- If in Common Technical Document format, does it follow the guidance? N/A YES NO
- Is it an electronic CTD? N/A YES NO
If an electronic CTD, all certifications must be in paper and require a signature.
 Which parts of the application were submitted in electronic format?

Additional comments:

- Patent information submitted on form FDA 3542a? YES
- Exclusivity requested? YES, 5 years
 Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? **YES**
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."

- Financial Disclosure forms included with authorized signature? **YES**
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? **YES**

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? **YES**
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
- List referenced IND numbers: **49,924**
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **YES 3/8/2005**
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? **YES 3/8/2005**
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES
- If no, did applicant submit a complete environmental assessment? YES NO
 - If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES

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ATTACHMENT

MEMO OF FILING MEETING

DATE:

BACKGROUND:

(Provide a brief background of the drug, e.g., it was already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES:

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	NevittM
Statistical:	LinS
Pharmacology:	ChenZ
Chemistry:	RodriguezL
Biopharmaceutical:	GhoshT
Microbiology	PawarV
DSI:	TeschD
Regulatory Project Management:	RodriguezR
Consults:	DMETS, DDMAC

Per reviewers, are all parts in English or English translation? **YES**

CLINICAL FILE REFUSE TO FILE _____

- Clinical site inspection needed: **YES**
- Advisory Committee Meeting needed? **NO**

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A YES NO

CLINICAL MICROBIOLOGY N/A _____ FILE _____ REFUSE TO FILE _____

STATISTICS FILE REFUSE TO FILE _____

BIOPHARMACEUTICS FILE REFUSE TO FILE _____

- Biopharm. inspection needed: **NO**

PHARMACOLOGY NA _____ FILE REFUSE TO FILE _____

- GLP inspection needed:
-

N/A

CHEMISTRY

FILE

REFUSE TO FILE _____

- Establishment(s) ready for inspection?
- Microbiology
-

YES

YES

ELECTRONIC SUBMISSION:

Any comments: **CD-ROM has been provided. It contains clinical studies, SAS data sets, and package insert labels.**

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74.

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

Raphael R. Rodriguez
Regulatory Project Manager, HFD-550

Appendix A to NDA Regulatory Filing Review

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

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval, publicly available FDA reviews, or labeling of another drug sponsor's drug product to meet any of the approval requirements (unless application includes written right of reference to data in another sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to supply data that are normally required 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 published general information (e.g., about disease etiology, support for particular endpoints, methods of analysis) or to general knowledge causes the application to be a 505(b)(2) application)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought.

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), because a sponsor often owns or has a right of reference for one of the drugs in the combination but not the other.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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

/s/

Raphael Rodriguez
4/4/05 03:36:01 PM

9 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

August 11, 2003

End-of-Phase 2 meeting minutes

IND 49,924 AL-6515 Nepafenac Ophthalmic Suspension 0.1%

FDA Attendees:

Wiley Chambers
Jonca Bull
Jennifer Harris
William Boyd
Matt Feinsod
Josie Yang
Linda Ng
Asoke Mukherjee
Su Tso
Laura Lu
Lori Gorski
Mike Puglisi
Carmen Debellas
Raphael Rodriguez

Alcon Attendees:

Scott Krueger
Stella Robertson
Terry Wiernas
Andrew Maxwell
Kerry Markwardt
Dana Sager
Patricia Meuse

Introduction

This document serves to inform the Division as to Alcon's development plans for Nepafenac Ophthalmic Suspension 0.1%, a topical ophthalmic nonsteroidal anti-inflammatory preparation. The active substance nepafenac is a prodrug, variously referred to as nepafenac, AL-6515, or amfenac amide. Guidance is sought concerning the acceptability of available data, and whether the Division concurs with the next steps to be taken in preparation for NDA filing. It is Alcon's assertion that Nepafenac Ophthalmic Suspension, 0.1% has utility in the treatment of inflammation associated with cataract extraction. Presented below are specific questions and issues that we would like addressed by the Division during the course of this meeting.

Chemistry, Manufacturing and Controls

Does the Division agree that the drug product tests and specifications are acceptable (see Table 2.3.P.5.1-1 and 2.3.P.5.2-1)?

Response:

The drug product specification should include

- *The test should include a*
- *If the test should be included.*
- *An acceptance criterion of "record data" is not acceptable. A range or limit, as appropriate, should be proposed.*

Acceptance criteria values are review issues. The acceptance criteria should be supported by toxicity and stability data, and production capability. Analytical procedures should be supported by validation data.

Other chemistry comments:

- *Reporting of impurities should follow the format in the ICH Q3A(R) and Q3B(R) guidances.*
- *In the drug substance specification, the acceptance criterion for "no other single imp." should be expressed as any individual unspecified impurity < 0.1%.*
- *Stability of the drug substance after _____ should be demonstrated.*
- *The _____ drug product manufacturing process should be addressed.*
- *Please address how the _____ affect the drug substance solubility and stability in the drug product*
- *The issue of potential extractables/leachables in the drug product should be addressed.*

Non-Clinical Safety

1. Alcon intends to request a waiver of the requirement for conducting carcinogenicity studies with nepafenac given the short treatment duration, lack of structural alerts in the molecule, favorable results from genotoxicity and repeated dose toxicity studies and pending supportive exposure data on toxicokinetics in accordance with guidance set forth in the ICH Topic S1A Guideline on the *Need for Carcinogenicity Studies of Pharmaceuticals* regarding ocular drugs. Does the Division support this development approach ?

Response: *The Division recommends that a waiver request be submitted and the request will be reviewed and acted upon consistent with the ICH guidance document.*

2. A segment III perinatal and postnatal study was conducted in rats with nepafenac (Alcon Technical Report No. 158:30:0801, see Table 2.4.3.1-4). The study demonstrated that nepafenac produced dystocia and associated maternal mortality in F0 females at levels =3 mg/kg/day, and developmental toxicity in F1 offspring at levels =10 mg/kg/day. The no-observed- effect-level (NOEL) for developmental toxicity in F1 offspring was determined to be 3 mg/kg/day. A NOEL for maternal effects in F0 females was not established in this study.

Alcon proposes that available data regarding general reproductive effects of nepafenac and amfenac, the major metabolite and active compound, are sufficient to establish that Nepafenac Ophthalmic Suspension, 0.1% will be safe for topical ocular administration in the absence of determining the NOEL for maternal effects in F0 female rats in a Segment III repeat study based on the following considerations:

–The findings observed in the Alcon sponsored Segment III study in rats are very similar to those elicited by other nonsteroidal anti-inflammatory drugs (NSAIDs), which have been shown

to cause prolonged gestation, delayed parturition, reduced offspring weights, and reduced survival in rats.

–Nepafenac Ophthalmic Suspension, 0.1% administered in a single 40 μ l drop three-times-daily to one eye by the topical ocular route results in a nepafenac dose of approximately 0.12 mg per day and a theoretical patient exposure of 2.4 μ g/kg/day (based on 50 kg body weight) during a 16 day treatment period.

–The NOEL of amfenac for F0 rat dams as determined in a Segment III Perinatal and Postnatal Study is 1 mg/ kg/day (Table 2.4.3.1-3). The maternal NOEL for reproductive effects in both rats and rabbits of nepafenac in Segment II studies sponsored by Alcon Research was determined to be 3 mg/kg/day (Table 2.4.3.1-4). Thus, the NOEL for general reproductive effects for the drug substance, as well as the active and major metabolite in animal studies is approximately 400 to 1000 times higher than the topical ocular daily dose.

On the basis of the high margin of safety afforded by the low patient dose versus dose administered to animals in safety studies, and the abbreviated duration of the clinical regimen, does the Division agree with this proposal ?

Response: *Full review of the studies will need to be completed, but the proposal on the face of it appears acceptable. Since the class effects are well known, the Division does not feel that the Segment III studies need to be repeated.*

3. Alcon plans to complete the characterization of Nepafenac Ophthalmic Suspension's safety profile by conducting a three-month topical ocular safety study in monkeys (see Section 2.4.3.2.1, Table 2.4.3.1-6) and a guinea pig maximization assay (see Section 2.4.3.2.2, Table 2.4.3.1-7) to assess sensitization. Does the Division agree with the design of these studies ?

Response: *Acceptable.*

4. Assuming that the outcome of the planned preclinical safety studies (Tables 2.4.3.1-6, 2.4.3.1-7, and Table 2.4.2-1) continue to support the safety of Nepafenac Ophthalmic Suspension, Alcon is of the opinion that the systemic and topical ocular preclinical data package summarized in section 2.4.3 and Tables 2.4.3.1-4 and 2.4.3.1-5 should be sufficient to support the New Drug Application for Nepafenac Ophthalmic Suspension, 0.1%. Does the Division agree ?

Response: *Full review of the studies will need to be completed, but the proposal on the face of it appears acceptable.*

Clinical

1. The results of the Phase 2 / 3 safety and efficacy study (C-02-53) indicate that the three-times-daily dosing regimen, rather than the once- or twice-daily dosing regimen, is optimal in reducing the incidence of treatment failures compared to placebo. Therefore, Alcon believes it is appropriate to utilize a three-times-daily dosing regimen in the proposed Phase 3 safety and efficacy study (C-03-32). Does the Division support this dosing regimen as appropriate for further study ?

Response: *Based on the information submitted, we agree that TID use of the 0.1% formulation appears to demonstrate efficacy earlier than the QD or BID regimen based on the percentage of patients cured. However, there does not appear to be any difference between the doses at the end of the 2 week trial. Additionally, it is concerning that the dose ranging studies for this drug have not established a superior concentration.*

2. Alcon proposes to develop Nepafenac Ophthalmic Suspension, 0.1% based on the safety and efficacy results of two dose-response studies (C-95-93 and C-97-30) conducted in cataract surgery patients in which the 0.1% concentration showed the greatest reduction in aqueous flare at the end of treatment. Furthermore, preclinical studies demonstrated plateau efficacy beginning at 0.1%. Nepafenac 0.1% is the lowest concentration that is pharmaceutically viable. Does the Division agree with this choice of concentration?

Response: *Reduction in aqueous flare scores alone is not an informative endpoint to use for evaluation of this product. These studies fail to establish the most effective concentration of this drug for ocular inflammation. There does not appear to be a clinical difference between the 0.03%, 0.10% and 0.3% concentrations. The explanation provided at the meeting regarding stability limiting the lower concentration and efficacy limiting the upper concentration should be submitted.*

3. Assuming the results of the clinical studies are successful, does the Division support the following proposed Indication, and Dose and Administration statements:

Indication: Nepafenac Ophthalmic Suspension, 0.1% is indicated for the treatment of the inflammation associated with

Dosage and Administration: Instill one drop in the affected eye three-times-daily beginning the day prior to surgery, continuing on the day of surgery and throughout the first two weeks of the post-operative period.

Response: *The content of the labeling will be determined after review of the NDA. However, the*

4. Does the Division agree that the prior clinical studies conducted in patients with post-surgical inflammation (C-95-93, C-97-30) and studies conducted in patients with macular edema (C-00-35, C-00-60, C-00-61) support the safety of Nepafenac Ophthalmic Suspension, 0.1% dosed three-times-daily for a total of 16 days ?

Response: *Based on the package submitted, approximately 229 patients have been exposed to Nepafenac at a concentration of 0.1% or higher and frequency of t.i.d. or more for at least 2 weeks duration. Based on ICH guidance documents, at the time of NDA filing we expect to see*

approximately 500 patients or more with the above exposures. Below 300 patients would clearly be insufficient.

5. Are the number of studies, proposed study designs, and number of patients proposed in the Clinical Development Plan adequate for supporting the fileability of Nepafenac Ophthalmic Suspension, 0.1% for the _____ treatment of inflammation associated with _____

Response: *The fileability of an application cannot be determined until after an initial review of the NDA. However, there are several concerns that the division has about the development plan for this product. See responses to questions 1, 2, 3, 4, and 6. There are issues concerning efficacy endpoints, the safety database, dose ranging studies, and proposed indications that need to be addressed.*

6. Does the Division agree with the selection and definition of treatment failures (defined as: cells greater than or equal to Grade 3 a, or flare equal to Grade 3 b, or moderately severe to severe ocular pain c) as the primary efficacy variable for the planned Phase 3 safety/efficacy study?

Response: *No. The Division does not agree. Acceptable efficacy endpoints for post-cataract inflammation are:*

Statistically superior percentage of cured patients (i.e. cell + flare = 0) in the test group compared to the vehicle group. The test group should also have a percentage of cured patients greater than 50%.

or

Statistically superior mean cell score and at least 1 unit greater in the vehicle group compared to the test group.

7. Alcon requests a waiver for conducting pediatric studies based on the target patient population for the proposed indication. Does the Division agree?

Response: *The pediatric rule is not currently in effect, therefore, a waiver request is not required.*

Other

Does the Division have any other advice concerning our development of Nepafenac Ophthalmic Suspension, 0.1% that the Division believes is important in ensuring the fileability of our proposed NDA?

Stat comments:

Please provide a method in assessing treatment by center interaction for the primary endpoint.

If a random effect model is used to analyze longitudinal non-normal data, Glimmix or Nlmixed (not Genmod) procedure should be used to include random intercept or slope of subjects. A

nonstructural covariance matrix is more favorable than an exchangeable one in terms of providing robust results.

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

/s/

Wiley Chambers

8/19/03 12:44:04 PM

December 21, 2004

ORIGINAL

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DEC 22 2004

CDER

MOOD

RE: NDA 21-862

Nepafenac Ophthalmic Suspension, 0.1%

CHEMISTRY, MANUFACTURING AND CONTROLS PRE-SUBMISSION
NEW DRUG APPLICATION (NDA #21-862; USER FEE ID #4867)

Dear Dr. Chambers:

As an authorized U.S. representative of Alcon, Inc., I hereby submit a New Drug Application (NDA) for Nepafenac Ophthalmic Suspension, 0.1%. Pursuant to 314.50(d)(1)(iv) and discussions with the Division, this is a pre-submission of the chemistry, manufacturing and controls section (Module 2.3 - Quality Overall Summary; and Module 3 - Quality). Within 90 to 120 days of this submission, the remainder of the application will be submitted.

This NDA is being submitted pursuant to 21 CFR§314.54 and Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act. The drug product will be marketed as a prescription product and is indicated for the treatment of pain and inflammation associated with cataract surgery. The proprietary name NEVANAC™ has been reviewed and tentatively approved by DMETS for this drug product.

The user fee (ID #4867) has been paid for this application. A copy of the user fee cover sheet is attached.

Alcon Laboratories, Inc was the owner of IND 49,924 under which the original IND was submitted in February 1996. Ownership was transferred from Alcon Laboratories, Inc to Alcon Universal, Ltd. in May 2001, and from Alcon Universal, Ltd. to Alcon, Inc. in November 2002. Notification of these changes has been submitted to the IND.

DAAODP, HFD-550, CDER
Food and Drug Administration
February 25, 2005
Page 2

A list of the facilities listed in this application is also included as an attachment to the form FDA356h. All the facilities listed are ready for inspection.

A true copy of the Chemistry, Manufacturing and Controls information (Quality -- Modules 2.3 and 3) was provided to the District Office in Dallas, TX at the time of the pre-submission of the Quality information.

The application consists of a paper archival copy and the appropriate number of review copies, and was prepared in the common technical document format. An electronic copy of the labeling will be provided in accordance with Guidance for Industry -- Providing Regulatory Submissions in Electronic Format -- Content of Labeling (February 2004) and Guidance for Industry -- Providing Regulatory Submissions in Electronic Format -- NDAs (January 1999).

If you have any questions or comments concerning this submission, please contact me by telephone at 817-551-4933 or via facsimile at 817-551-4630.

Sincerely



Angela C. Kothe, OD, PhD
Associate Director, Regulatory Affairs

Attach.

cc. Dallas District Office