

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
203491Orig1s000

OTHER REVIEW(S)

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: August 8, 2012

TO: Rhea A. Lloyd, M.D., Medical Officer
Victor Ng, Project Manager
Division of Transplant and Ophthalmology Products

FROM: Kassa Ayalew, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader
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Susan Thompson, M.D.
Acting Branch Chief
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Division of Good Clinical Practice Compliance
Office of Scientific Investigators

SUBJECT: Evaluation of Clinical Inspections

NDA: 203491

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

DRUG: Nepafenac Ophthalmic Suspension, 0.3%

NME: No

THERAPEUTIC CLASSIFICATIONS: Standard

INDICATION: Treatment of pain and inflammation associated with cataract surgery

Consultation Request Date: February 15, 2012

PDUFA: October 16, 2012

Action Goal Date: October 16, 2012

I. BACKGROUND:

Alcon Research Ltd. submitted a New Drug Application (NDA) for Nepafenac Ophthalmic Suspension to market a new prescription formulation of nepafenac ophthalmic suspension for the indication of treatment of pain and inflammation associated with cataract surgery. In the new formula, the concentration of the active ingredient was increased to 0.3% and (b) (4) guar, was introduced (b) (4). According to the sponsor, this provides similar safety and efficacy to NEVANAC (NDA 21-862) with a once daily dosing regimen. The proposed indication for the new product is the same as that approved for NEVANAC[®] (i.e. the treatment of pain and inflammation associated with cataract surgery).

Nepafenac is a member of the pharmacologic class known as nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are used pre and post cataract surgery to minimize the magnitude and duration of the inflammatory response resulting from surgical trauma. Nepafenac (amfenac amide) is a prodrug which is converted to amfenac by intraocular hydrolases. This product was the first ophthalmic NSAID approved by the FDA for preoperative dosing, which takes advantage of the drug's mechanism of action (i.e., inhibition of cyclooxygenase) by having drug in the target tissue prior to the surgical insult. Amfenac inhibits cyclooxygenase activity. Nepafenac is formulated as a suspension applied by the topical ocular route, and it is indicated for the prevention and treatment of pain and inflammation associated with cataract surgery. Nepafenac ophthalmic suspension, 0.1% dosed three times daily (NEVANAC) is currently marketed for treatment of pain and inflammation associated with cataract surgery.

The sponsor submitted results from two studies (Study C-09-055 & Study C-11-003).

Study C-09-055, entitled "Clinical Evaluation of Nepafenac Ophthalmic Suspension 0.3% for Prevention and Treatment of Ocular Inflammation and Pain after Cataract Surgery" was a double-masked, parallel-group, multicenter, vehicle and active-controlled, randomized study. Patients were randomized 4:1 to Nepafenac 0.3% or Nepafenac Vehicle 0.3%, and 4:1 to NEVANAC or NEVANAC Vehicle by an interactive web response system (IWRS).

Study C-11-003 entitled "Clinical Evaluation of Nepafenac Ophthalmic Suspension, 0.3% Compared to Nepafenac Ophthalmic Suspension 0.1% and Vehicle for Prevention and Treatment of Ocular Inflammation and Pain Associated with Cataract Surgery" was a double-masked, parallel-group, multicenter, vehicle and active-controlled, randomized, 16 day study. This study was designed to determine whether Nepafenac 0.3% had a clinical benefit over Nepafenac 0.1% (NEVANAC) dosed once a day in a head-to-head comparison. Planned enrollment for this study was 1250 patients.

Two domestic clinical investigators were selected for inspection on the basis of enrollment of large numbers of study subjects per site, information in the OSI database concerning number of INDs, and lack of previous inspectional history.

II. RESULTS (by Site): There were two sites inspected:

Name of CI	Protocol # and # of Subjects:	Inspection Date	Classification
Raymond Fong, M.D. 109 Lafayette Street, 4th Floor New York, NY 10013 Phone #: 212-274-1900 Site #5758	Study C-09-055/ n=90 Study C-11-003/ n=70	March, 28, 2012 to April, 06, 2012	NAI
Thomas Walters, M.D. Texas Eye, PA 5717 Balcones Drive Austin, TX 78731 Phone #: 512-327-7000 Site # 1007	Study C-09-055/ Site 1007/ n=100 Study C-11-003/ Site 1007/ n=71	April 11, 2012 to April 19, 2012	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Raymond Fong, M.D.109 Lafayette Street, 4th Floor
New York, NY 10013

- a. What was inspected:** This inspection was conducted in accordance with Compliance Program 7348.811 between March 27 and March 29, 2012. There were five INDs associated with the inspected entity in CDER's database, and the CI had no prior inspection history.

For Study C-09-055, at this site, 91 subjects were screened, 90 subjects were randomized, and 68 subjects completed the study. A total of 22 subjects discontinued the study due to treatment failure, not using study medication, or an adverse event. There were no deaths or SAEs reported. For study C-09-055, an audit of 31 subjects' records was conducted.

For study C-11-003, at this site, 70 subjects were screened, 70 subjects were randomized, and 40 subjects completed the study. Fifteen (15) subjects discontinued the study either due to treatment failure or not using study medication. There were no deaths or SAEs reported. For study C-11-003, an audit of 27

subjects' records was conducted.

For both protocols, study subject files were reviewed for verification of: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, and 4) adequate adverse experience reporting. All primary efficacy endpoint data were compared with the line listings. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

- b. General observations/commentary:** In general, the study was conducted appropriately. There was no evidence of under reporting of adverse events. All primary efficacy endpoint data were verified by comparison of the source documents with the line listings submitted in the NDA. No regulatory violations were noted and no Form FDA 483 was issued at the conclusion of the inspection.
- c. Assessment of data integrity:** Based on the inspectional findings above, efficacy and safety data obtained from this site can be considered reliable in support of the application.

2. Thomas Walters, M.D.

Texas Eye, PA
5717 Balcones Drive
Austin, TX 78731

- a. What was inspected:** This inspection was conducted in accordance with compliance Program 7348.811 between April 11 and April 19, 2012. [REDACTED] (b) (4), and the CI had one previous inspection that was classified NAI.

At this site, for Study C-09-055, 100 subjects were screened, 99 subjects were randomized, and 76 subjects completed the study. One subject failed screening. Of the 99 patients randomized, 21 were treatment failures per protocol definition. An audit of 25 subjects' records was conducted.

For Study C-11-003, at this site, 71 subjects were screened, 70 subjects were randomized, 14 were treatment failures, and 56 subjects completed the study. One subject withdrew consent before surgery and was a considered screen failure. There were no deaths or SAEs reported. An audit of 35 subjects' records was conducted.

- b. General observations/commentary:** For both protocols, there was no evidence of under reporting of adverse events. The primary efficacy endpoint data was verifiable. The inspection of Dr. Thomas Walters's site revealed that the study was not conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was issued to this investigator for failure to ensure that the investigation was conducted

according to the investigational plan [21 CFR 312.60]. For example, the following regulatory violations were observed during the inspection:

1. Subject 9057 used rhinocort nasal spray until 9/12/2010 which was within 14 days of surgery on 9/21/2010. The protocol excludes use of topical steroids within 14 days prior to surgery.
2. Subject 9088 took a Medrol Dose-pak from 1/27/2011 through 2/2/2011. The protocol excludes the use of systemic steroids throughout the period of the study.

OSI Reviewer Comments: The two subjects who received steroid treatment in violation of the protocol completed the study. The above observation is a regulatory violation; however, it is isolated in nature and unlikely to impact data reliability, nor did it compromise the rights, safety, and welfare of subjects in the study.

- c. Assessment of data integrity:** Although regulatory violations were noted at Dr. Walters's site, the violations appear isolated and the nature of the findings appears unlikely to significantly impact reliability of the data. The violations did not compromise the safety and welfare of subjects in the study.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The final classification of the Clinical Investigator inspection of Dr. Raymond Fong is No Action Indicated (NAI). Based on the inspectional findings at this site, efficacy and safety data obtained from this site can be considered reliable in support of the application.

The final classification of Clinical Investigator inspections of Dr. Thomas Walters is Voluntary Action Indicated (VAI). Although regulatory violations were noted, these were not considered to have a significant impact on data reliability. Based on the inspectional findings at this site, efficacy and safety data obtained from this site can be considered reliable in support of the application.

Overall, the data submitted from these sites are considered acceptable in support of the pending application.

{See appended electronic signature page}

Kassa Ayalew, M.D.
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CONCURRENCE:

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/s/

KASSA AYALEW
08/08/2012

SUSAN LEIBENHAUT
08/08/2012

SUSAN D THOMPSON
08/08/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: June 29, 2012

Reviewer: Jung Lee, RPh
Division of Medication Error Prevention and Analysis

Acting Team Leader: Jamie Wilkins Parker, PharmD
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: (b) (4) (Nepafenac Ophthalmic Suspension), 0.3%

Application Type/Number: NDA 203491

Applicant: Alcon, Inc

OSE RCM #: 2012-684

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

Contents

1	Introduction.....	1
1.1	Background and Regulatory History.....	1
1.2	Product Information	1
2	Methods and Materials Reviewed.....	1
2.1	Selection of Medication Error Cases.....	2
2.2	Labels and Labeling	2
3	Medication Error Risk Assessment	2
3.1	Medication Error Cases.....	2
4	Recommendations.....	3
4.1	Comments to the Division.....	4
4.2	Comments to the Applicant.....	4
	Appendices.....	5
	Appendix A. Database Descriptions.....	5

1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for (b) (4) (Nepafenac Ophthalmic Suspension), 0.3% (NDA 203491) for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND AND REGULATORY HISTORY

The currently marketed product with the (b) (4) name Nevanac (Nepafenac Ophthalmic Suspension), 0.1% (NDA 021862) was approved on August 19, 2005. (b) (4) 0.3% is also an ophthalmic suspension that is intended to be a once daily alternative to Nevanac which is dosed three times daily.

1.2 PRODUCT INFORMATION

The following product information is provided in the March 15, 2012 proprietary name submission.

- Active Ingredient: Nepafenac
- Indication of Use: For the treatment of pain and inflammation associated with cataract surgery
- Route of Administration: Ophthalmic
- Dosage Form: Ophthalmic Suspension
- Strength: 0.3%
- Dose and Frequency: One drop to the affected eye one time daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.
- How Supplied: 1.7 mL in a 4 mL bottle
- Storage: Store at 2°C to 25°C (36°F to 77°F)
- Container and Closure Systems: 1.7 mL in a 4 mL oval, LDPE Drop-Tainer dispenser with a LDPE dispensing plug and gray polypropylene cap. The gray cap color is consistent with the American Academy of Ophthalmology's policy statement "Color Code for Ocular Medications" which recommends a gray cap color for nonsteroidal anti-inflammatories (NSAIDS).

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS database for Nevanac medication error reports (b) (4) (b) (4) We also reviewed the (b) (4) container labels, carton and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) database using the strategy listed in Table 1.

Table 1: AERS Search Strategy	
Date	June 25, 2012
Drug Names	Active Ingredient: Nepafenac Trade Name: Nevanac Verbatim Term: Nevan% Verbatim Term: Nepaf%
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues (HLT) Product Label Issues (HLT) Product Quality Issues NEC (HLT)

The AERS database search strategy identified 12 reports. Each report was reviewed for relevancy and duplication. After individual review, 11 reports were not included in the final analysis for the following reasons:

- Adverse drug reactions not related to a medication error
- Product quality complaints not related to the labels and labeling of the product
- Accidental overdose due to repeat administration of Nevanac and other concomitant medications because patient forgot they had already administered them and took them again

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted March 16, 2012 (Appendix A)
- Carton Labeling submitted March 16, 2012 (Appendix B)
- Insert Labeling submitted February 13, 2012

3 MEDICATION ERROR RISK ASSESSMENT

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, one Nevanac medication error case remained for our detailed analysis (ISR # 5894414-4).

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This case reported a possible wrong drug error between Nevanac and Vigamox in which the patient may have received two bottles of Nevanac instead of one bottle of Nevanac and one bottle of Vigamox from either the ophthalmologist's office or from the pharmacy. The outcome of this event was not reported in the narrative.

Since the drug names are not phonetically or orthographically similar, we evaluated the container label, carton labeling and packaging for Nevanac and Vigamox to determine if the labeling of either product could have contributed to the wrong drug error. We note that the two products share a similar package size of 3 mL and are both manufactured by Alcon. However, we found there was adequate differentiation between the container label and carton labeling of Nevanac and Vigamox. Nevanac's carton is a tan and grey color with a grey circular graphic above the name while Vigamox's carton is a solid burgundy color with a gold teardrop graphic above the name. The container labels for each product also share the same color scheme as their respective cartons.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

4.1 COMMENTS TO THE DIVISION

A. Insert Labeling

1. Under Dosage Forms and Strengths in the Highlights of Prescribing and Full Prescribing Information sections, remove the statement "1.7 mL in a 4 mL bottle" as this is already included in the How Supplied Section.
2. During clinical trials, (b) (4)
Therefore, in section 17.6 under the Patient Counseling Information section, revise the statement (b) (4)
to read "Before each use, patients should be instructed to shake the bottle well".

4.2 COMMENTS TO THE APPLICANT

A. Container Label

1. Due to the small size of the label, it appears crowded. Therefore, the information included on the side panel of the label should be limited. Remove the following information not required under 21 CFR 201.10(i) to improve readability:
 - a. Each mL contains: Active nepafenac 0.3%
 - b. Usual dosage statement
2. Increase the prominence of the strength statement on the principal display panel (PDP).

3. The proposed product is a suspension that requires shaking prior to use. After removing the statements above, add the statement “Shake Well” to the side panel of the label.
4. Debold and decrease the prominence of the net quantity statement so it does not have greater prominence than that of the strength statement and the established name.

B. Carton Labeling

1. Remove the blue shading under the proprietary name as it interferes with the readability of the proprietary name.
2. Remove the (b) (4) to ensure there is no intervening matter between the proprietary and established names on the principal display panel.
3. Increase the prominence of the strength statement on the principal display panel (PDP).
4. Relocate the route of administration statement, “For Topical Ophthalmic Use Only” to the PDP directly below the dosage form and strength statements.
5. Relocate the “Rx Only” statement to the PDP.
6. Decrease the prominence of the manufacturer’s name on the PDP as it appears overly prominent and distracts from the most important information on the label.
7. (b) (4) to read “Shake Well Before Using”.

If you have further questions or need clarifications, please contact Karen Townsend, project manager, at 301-796-5413.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

Appendix B: Container Labels



Appendix C: Carton Labeling

(b) (4)



Appendix D: ISR numbers of cases discussed in this review (n=1)

<u>ISR Number</u>	<u>Medication Error Type</u>	<u>Narrative</u>
5894414-4	Wrong Drug	<p>I received 2 rx's, one for Vigamox, one for Nevanac and dispensed them 9/20. Pt's daughter discovered that Nevanac was in both bottles, both brought in containing Nevanac. I redispensed Vigamex and gave to patient's daughter I double check with invoices 1 (one) Vigamox and 1 (one) Nevanac were ordered and history of rx's were that only 1 (one) Vigamox rx was written for and order and dispensed match I do not know how 2 bottles got dispensed of Nevanac when only 1 (one) on shelf</p> <p>Patient's daughter brought in 2 rx bottles, one labeled Nevanac, one labeled Vigamox. Nevanac was in both bottles. Patient did not receive drugs per daughter.</p> <p>-We only had 1 (one) vial of Nevanac on shelf. It had not been ordered for over one year</p> <p>-Drug usage for Nevanac and Vigamox attached-only 1 rx of each ordered 9/20/08. See McKesson order attached-1 bottle of each received from that order</p> <p>-The Nevanac that she brought back to me-expired 9/08. We boxed up and pulled all our expired meds through 9/08 for send back.</p> <p>-Daughter works at an ophthalmologist's office. Perhaps she got a sample and didn't realize it and it got mixed up. I would never dispense an expired medication we all make mistakes but I do not believe this was my error</p> <p>Please see ordering history of Nevanac-we order 1 at a time-we use it so little.</p>

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/s/

JUNG E LEE
06/29/2012

JAMIE C WILKINS PARKER
06/29/2012

CAROL A HOLQUIST
06/29/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 203491 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: NA/none submitted with original NDA Established/Proper Name: nepafenac Dosage Form: suspension Strengths: 0.3%		
Applicant: Alcon Research, Ltd Agent for Applicant (if applicable):		
Date of Application: 12/15/11 Date of Receipt: 12/16/11 Date clock started after UN:		
PDUFA Goal Date: 10/16/12		Action Goal Date (if different):
Filing Date: 2/14/12		Date of Filing Meeting: 1/27/12
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication(s)/Proposed change(s): treatment of pain and inflammation associated with cataract surgery		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 49924				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			No proprietary name submitted with original NDA
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			Sent email to doc room regarding date correction from Standard to Priority review on January 26, 2012
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 3</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			See section 1.4.4 of the original NDA submission
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with	X			

authorized signature?				
<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA 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...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			Victor Ng sent an email to the Pediatric and Maternal Health Staff on February 10, 2012 notifying them that this application triggers PREA.

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			Applicant requested a full waiver
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		Comments to the sponsor regarding the proprietary name was sent on 2/6/12
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted. From original submission, carton and container mock-ups were not included. These mock-ups were received on 2/10/12.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<p>If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request?</p> <p><i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i></p>				
<p>All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?</p>	X			<p>Alcon is in the process of finalizing a proprietary name. A decision is expected by March 16, 2012 and a submission to the NDA will be made with the proposed name.</p> <p>The submitted carton/container labels currently utilize Nepafenac as a proprietary name.</p> <p>Consult to DDMAC after the proposed proprietary name is submitted.</p>
<p>MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)</p>		X		
<p>Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?</p>		X		
<p>OTC Labeling</p>	<input checked="" type="checkbox"/> Not Applicable			
<p>Check all types of labeling submitted.</p>	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample			

	<input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>			X	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		X		
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 12/31/09 Meeting Minutes <i>If yes, distribute minutes before filing meeting</i>	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		X		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 1/27/12

BLA/NDA/Supp #: 203491

PROPRIETARY NAME: NA/none submitted with original NDA

ESTABLISHED/PROPER NAME: nepafenac

DOSAGE FORM/STRENGTH: suspension 0.3%

APPLICANT: Alcon Research, Ltd

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): treatment of pain and inflammation associated with cataract surgery

BACKGROUND: Alcon Research, Inc submitted their NDA on December 15, 2011 for the treatment of pain and inflammation associated with cataract surgery. It was received on December 16, 2011. The NDA will be standard review and the PDUFA Goal Date is October 16, 2012.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Victor Ng	Y
	CPMS/TL:	Diana Willard	Y
Cross-Discipline Team Leader (CDTL)	Bill Boyd		Y
Clinical	Reviewer:	Rhea Lloyd	Y
	TL:	Bill Boyd	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		

	TL:		
Clinical Pharmacology	Reviewer:	Eric Yongheng Zhang	Y
	TL:	Phil Colangelo	Y
Biostatistics	Reviewer:	Rima Izem	Y
	TL:	Yan Wang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Conrad Chen	Y
	TL:	Terry Miller	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Rao Kambhampati	Y
	TL:	Bala Shanmugam	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Steven Donald	Y
	TL:	Stephen Languille	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Kassa Ayalew	N
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Jung Lee	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: none</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments: Proposed carton and container mock-ups were not included in original application submitted on December 15, 2011.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the</i></p>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<p>reason. For example:</p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • 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? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

Comments:	
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility Inspection</u> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Renata Albrecht, MD, Division Director</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <p><u>Review Classification:</u></p> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Regulatory Project Manager

Date

Chief, Project Management Staff

Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

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

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

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

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

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

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

for approval on published literature based on data to which the applicant does not have a right of reference).

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

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

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

VICTOR F NG
03/06/2012

DIANA M WILLARD
03/06/2012

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

Application: NDA 203491
Name of Drug: nepafenac ophthalmic suspension, 0.3%
Applicant: Alcon Research, Ltd.

Labeling Reviewed

Submission Date: December 15, 2011
Receipt Date: December 16, 2011

Background and Summary Description

This original New Drug Application (NDA) provides for the following indication: the treatment of pain and inflammation associated with cataract surgery.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

In addition, the following labeling issues were identified:

- A Patient Package Insert (PPI) was not submitted for this application. As a result, the words, [REDACTED] ^{(b) (4)} should be removed from the Patient Counseling Information statement in the Highlights. The Patient Counseling Information statement should now read, “**See 17 for PATIENT COUNSELING INFORMATION.**”
- The carton and container labeling submitted is in text form only; there are no graphics, font size, or color choice provided. The applicant should submit proposed carton and container mock-ups which include color, font size, graphics, etc., so that they can be preliminarily reviewed prior to the Filing deadline.
- No request for proprietary name review has been submitted. The sponsor should be contacted to inquire if they intend to submit a proprietary name.

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies by February 17, 2012. The resubmitted labeling will be used for further labeling discussions.

Leanna M. Kelly	December 27, 2011
Consumer Safety Officer	Date
Judit Milstein	January 30, 2012
Chief, Project Management Staff	Date

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)

• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**

- Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**

- Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- All text in the boxed warning is **bolded**.
- Summary of the warning must not exceed a length of 20 lines.
- Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- Removal of a section or subsection should be noted. For example, “Dosage and

Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.
- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
 - “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/

LEANNA M KELLY
02/01/2012

JUDIT R MILSTEIN
02/01/2012
NDA 203491-Initial Labeling review