

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
203491Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review NDA 203491

Date	October 16, 2012
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA	203491
Applicant	Alcon Research Ltd.
Date of Submission	December 15, 2011
PDUFA Goal Date	October 16, 2012
Established (USAN) name	Nepafenac ophthalmic suspension, 0.3%
Dosage forms / Strength	Topical ophthalmic suspension
Indication(s)	treatment of pain and inflammation associated with cataract surgery
Recommended:	Recommended for Approval

1. Introduction

Nepafenac is a member of the nonsteroidal anti-inflammatory drug (NSAID) class. The drug is presented as a suspension formulation applied by the topical ocular route, and is proposed for use for the treatment of pain and inflammation associated with cataract surgery.

Nepafenac, also known as amfenac amide, is a prodrug that penetrates the cornea and is converted to the active moiety amfenac by intraocular hydrolases.

Nepafenac at a concentration of 0.1% (NEVANAC) was approved for marketing in the U.S. in 2005. It is also approved for marketing in the European Union (EU) and Japan as well as over 60 other countries for the treatment of postoperative pain and inflammation associated with cataract surgery. Nevanac is intended to be dosed 3 times daily.

Post-marketing experience with this class of drugs has shown that use of topical NSAIDs for more than 24 hours prior to surgery or use beyond 14 days post surgery may increase the risk for the occurrence and severity of corneal adverse events such as epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration and corneal perforation which are potentially sight threatening.

Class labeling that addresses this issue has been added to all existing topical NSAID labels and should be included in the label for this drug product.

2. Background

An End-of-Phase 2 meeting was held between Alcon and the Agency on October 5, 2009. The Agency gave Alcon advice regarding its proposal for the nepafenac ophthalmic suspension, 0.3%

clinical development program. Alcon presented evidence that nepafenac had the potential to be as effective when administered once daily as when administered 3 times daily. The Agency agreed that a single clinical study using Alcon's proposed study design, if successful, would be sufficient to demonstrate noninferiority of nepafenac ophthalmic suspension, 0.3% to Nevanac for the safety and efficacy of the product. Additionally, the Agency provided the following response to an Alcon question:

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

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

This concern was reiterated during the meeting and in an email in October 2010.

A meeting was held between the Agency and Alcon to obtain additional clarification regarding the Agency's concern about a potential increased safety risk due to the higher concentration of active ingredient in the proposed formulation on January 10, 2011. Following this meeting, Protocol C-11-003 was designed to demonstrate a clinical benefit of Nepafenac 0.3% dosed once daily relative to Nevanac dosed once daily with primary inference at the day 7 visit.

3. Product Quality

From the ONDQA CMC Review finalized 9/13/2012:

The drug product contains nepafenac as the drug substance. Nepafenac was previously approved by the FDA for its use in NEVANAC® (nepafenac ophthalmic suspension, 0.1%) for the NDA# 21-862. The approved NEVANAC is also marketed by Alcon Research, Ltd., Fort Worth, TX. The applicant proposed the same drug substance manufacturers (b) (4) that are currently used for the manufacturing of NEVANAC and the CMC information for the drug substance was cross-referenced to the DMFs (b) (4) and (b) (4) respectively, which are currently adequate. In addition, some CMC information was also directly provided in the NDA.

Nepafenac drug substance is a yellow crystalline solid or powder with a melting point of 184°C to 184.9°C and it has a molecular formula of C₁₅H₁₄N₂O₂ and molecular weight of 254.28. It has a solubility of 0.014 mg/mL in water. It does not exhibit polymorphism. The manufacturing of the drug substance was cross-referenced to (b) (4) DMF# (b) (4) and (b) (4) DMF# (b) (4) and the applicant provided LOAs for the cross-reference of the information in those DMFs. Both the DMFs were previously reviewed by the ONDQA

reviewers and were found to be adequate. Later, amendments and annual reports to those DMFs were submitted by the Holders, therefore, those DMFs were again reviewed by this reviewer and they are found to be adequate as of the date of this review.

COMPOSITION OF DRUG PRODUCT

<u>Component</u>	<u>Percent w/v</u>	<u>Function</u>		
Nepafenac	0.3	Active ingredient		
Benzalkonium Chloride	0.005*	Microbial preservative		
Carboxymethylcellulose	(b) (4)			
Guar Gum				
Carbomer 974P**				
Boric Acid				
Edetate Disodium				
Propylene Glycol				
Sodium Chloride				
NaOH/HCl			qs for pH adjustment	pH Adjuster
Purified Water			(b) (4)	

(b) (4)

REGULATORY ACCEPTANCE SPECIFICATIONS

<u>Test</u>	<u>Specification</u>
Nepafenac Identity (TLC)	(b) (4)
Nepafenac Identity (HPLC)	
Nepafenac Assay	
(b) (4)	
Impurity @ (b) (4)	
Any single unspecified impurity	
Total impurities	
Benzalkonium Chloride Assay	
Edetate disodium Assay	
pH	
Osmolality	
Redispersibility	
Viscosity @ 12 rpm	
Particulate Size, Suspension	

Endoxin
Sterility



INSPECTIONS

All the drug substance and drug product manufacturing and testing sites were submitted for evaluation in EES. The OC issued an Overall Recommendation of Acceptable for this NDA on 4/23/2012. A copy of the report is provided below:

**FDA CDER EES
 ESTABLISHMENT EVALUATION REQUEST
 SUMMARY REPORT**

Application:	NDA 203491/000	Sponsor:	ALCON PHARMA
Org. Code:	590		8201 SOUTH FREEWAY
Priority:			FORT WORTH, TX 761342099
Stamp Date:	16-DEC-2011	Brand Name:	nepafenac ophthalmic suspension 0.3%
PDUFA Date:	16-OCT-2012	Estab. Name:	
Action Goal:		Generic Name:	nepafenac ophthalmic suspension 0.3%
District Goal:	17-APR-2012	Product Number; Dosage Form; Ingredient; Strengths	001; SUSPENSION, NEPAFENAC, .3%
FDA Contacts:	A. CUFF	Project Manager	(HF-01) 3017964061
	R. KAMBHAMPATI	Review Chemist	(HFD-830) 3017961382
	B. SHANMUGAM	Team Leader	3017961457
Overall Recommendation:	ACCEPTABLE	on 23-APR-2012	by M. STOCK (HFD-320) 3017964753
	PENDING	on 23-JAN-2012	by EES_PROD
	PENDING	on 23-JAN-2012	by EES_PROD
Establishment:	CFN: 1610267	FEI: 1610267	
	ALCON LABORATORIES INC		
	FORT WORTH, UNITED STATES 761342001		
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	STERILE LIQUID (b) (4)	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	23-APR-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		
Establishment:	CFN: (b) (4)	FEI: (b) (4)	
	(b) (4)		
DMF No:		AADA:	
Responsibilities:			
Profile:			OAI Status: NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	24-JAN-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

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

DMF No: AADA:
Responsibilities:
Profile: OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 24-JAN-2012
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

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

DMF No: AADA:
Responsibilities:
Profile: OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 27-JAN-2012
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review finalized 9/13/2012:

“The applicant has submitted an NDA for nepafenac 0.3% for the treatment of pain and inflammation associated with cataract surgery. Nepafenac 0.3% differs from Nevanac (nepafenac 0.1%) in content of the active pharmaceutical ingredient (API) and excipient formulation. All excipients are similar except nepafenac 0.3% contains the novel excipient guar gum (b) (4) and the previously qualified excipient carboxymethylcellulose (b) (4). The applicant conducted a one-month (35-day) toxicity/bridging study and an ocular distribution study to support qualification of the excipients. In the 35-day toxicity/bridging study, no treatment-related toxicities were reported in any dose group (0.3% to 1.5% QD, bilateral), and toxicokinetic results showed a less than dose proportional increase in exposure (amfenac and nepafenac) across doses. As such, no new toxicities were associated with the increased strength and additional excipients in the formulation, and the NDA is approvable from a pharmacology/toxicology standpoint.”

No carcinogenicity studies were conducted on for nepafenac. A waiver for carcinogenicity studies is considered appropriate.

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review finalized 8/28/2012:

Following bilateral topical ocular dosing of 1 drop of Nepafenac 0.3% Ophthalmic Suspension once daily for 4 days, the mean nepafenac and active metabolite (amfenac) plasma concentration versus time profiles on Day 1 and Day 4 were similar, indicating no accumulation. The mean steady-state C_{max} for nepafenac and amfenac were 0.847 ± 0.269 ng/ml and 1.13 ± 0.491 ng/ml, respectively, following topical ocular administration of Nepafenac 0.3% Ophthalmic Suspension.

In vitro studies suggested that nepafenac at concentrations up to 3000 ng/mL did not inhibit in vitro metabolism of CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. Similarly, in vitro studies suggested that amfenac at concentrations up to 1000 ng/mL did not inhibit the metabolism of CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. Therefore, drug-drug interactions involving CYP mediated metabolism of concomitantly administered drugs are unlikely following topical ocular administration of Nepafenac 0.3% Ophthalmic Suspension.

6. Sterility Assurance

From the original Product Quality Microbiology Review dated 10/2/2012:

The container/closure system includes a plastic bottle with a plastic dispensing plug and plastic closure. The bottle and the dispensing plug are made of low density polyethylene (LDPE) and the closure is made of polypropylene. (b) (4)



The finished product specification and stability specification for Benzalkonium Chloride (BAC) and edetate disodium is (b) (4) product label. Antimicrobial effectiveness testing performed at (b) (4) BAC label claim. Testing was based on UPS<51> methodology using compendial organisms. All test samples show a 4 to 6 log reduction in microorganisms at day 7 through day 28. Results are acceptable.



7. Clinical/Statistical - Efficacy

From the original Medical Officer Review finalized 9/14/2012:

Summary of All Completed Clinical Studies with Nepafenac Ophthalmic Suspension, 0.3%

Study Identifier / Study Type	Study Design	Study Population	Treatment Group	Number of Patients ^a	Dosing Regimen	Dosing Duration
Safety / Clinical Pharmacology Studies						
C-09-053	Randomized, double masked, placebo-controlled, parallel group	Healthy subjects 18 years of age and older	<ul style="list-style-type: none"> • Nepafenac 0.3% QD • Vehicle QD 	12 8	1 drop in both eyes once daily for 4 days	4 days
Post-cataract Inflammation Safety and Efficacy Studies						
C-11-003 Safety and Efficacy / Post-Cataract Inflammation	Randomized, double masked, active- and placebo-controlled, parallel group	Patients, 18 years of age and older, requiring cataract extraction with implantation of a posterior chamber intraocular lens	<ul style="list-style-type: none"> • Nepafenac 0.3% QD • Nepafenac 0.1% QD • Vehicle QD 	522 506 254	1 drop in study eye QD beginning 1 day before surgery. An additional drop was administered 30 to 120 min prior to surgery	16 days
C-09-055 Safety and Efficacy / Post-Cataract Inflammation	Randomized, double masked, active- and placebo-controlled, parallel group	Patients, 18 years of age and older, requiring cataract extraction with implantation of a posterior chamber intraocular lens	<ul style="list-style-type: none"> • Nepafenac 0.3% QD • Nevanac TID • Vehicle QD • Vehicle TID 	807 813 197 205	1 drop in study eye QD or TID, as assigned, beginning 1 day before surgery. An additional drop was administered 30 to 120 minutes prior to surgery	16 days

^a Safety Dataset

Analysis of Primary Endpoint(s)

In Study C-09-055 and Study C-11-003, the primary efficacy variable was a binary variable for cure of inflammation. The variable is composite, requiring a score of 0 for both cells (0 cells present) and flare (no flare present). The primary efficacy endpoint was the Percent Cures at Day 14 in both studies.

STUDY 09-055

For comparison of the two nepafenac groups, a two-tailed 95% confidence interval was calculated for the difference in cure rates (Nepafenac 0.3% minus Nevanac) using a test-based confidence interval. The non-inferiority margin used was 10 percentage points, meaning that the lower limit of the two-sided 95% confidence interval must have been greater than -10% to establish non-inferiority. The margin is supported by the comparison with the vehicle in this trial.

Table 6.1.4.1-1
Primary Efficacy Results - Percent of Patients Cured at Day 14
Vehicle Comparison (Superiority) Study C-09-055

	Nepafenac 0.3% N=807 n(%)	Nepafenac Vehicle 0.3% N=197 n(%)	Nevanac N=811^a n(%)	Nevanac Vehicle N=205 n(%)
ITT Population	552 / 807 (68.4)	67 / 197 (34.0)	568 (70.0)	73 (35.6)
	p value ^b <0.0001		p value ^c <0.0001	
PP Population	531 / 761 (69.8)	63 / 175 (36.0)	546 / 760 (71.8)	69 / 176 (39.2)
	p value ^b <0.0001		p value ^c <0.0001	

p value is based upon Cochran-Mantel-Haenszel test controlling data
 a ITT population - 2 patients were randomized but did not have on-study data
 b Nepafenac 0.3% versus Nepafenac Vehicle 0.3%
 c Nevanac versus Nevanac Vehicle

The study also demonstrates that Nepafenac 0.3% is superior to Nepafenac Vehicle 0.3% and Nevanac is superior to Nevanac vehicle each comparison achieving statistical significance with $p < 0.0001$, for the percentage of patients cured at postoperative Day 14. See Table 6.1.4.1-1 above.

Table 6.1.4.1-2
Primary Efficacy - Percent of Patients Cured at Day 14
Active Comparison (Noninferiority) Study C-09-055

	Nepafenac 0.3% N=807 n(%)	Nevanac N=811 n(%)	Confidence Interval^a
ITT Population	552 / 761 (68.4)	568 / 760 (70.0)	(-5.73, 3.17)
PP Population	531 / 761 (69.8)	546 / 760 (71.8)	(-6.42, 2.64)

a Test based confidence interval for difference of treatment proportions (Nepafenac 0.3% QD - NEVANAC TID) (PP Population). If the lower bound of the confidence interval (CI) for (Nepafenac 0.3% QD - NEVANAC TID) is greater than the non-inferiority margin -10%, then the data supports the non-inferiority of Nepafenac 0.3% QD vs NEVANAC TID.

The study achieved its primary noninferiority efficacy endpoint since the lower bound of the 95% two-sided confidence interval (-5.73, 3.17) is greater than -10%. The study demonstrates that Nepafenac 0.3% dosed once daily is noninferior to Nevanac dosed 3 times daily for the treatment of ocular inflammation 14 days after cataract extraction. See Table 6.1.4.1-2 above.

The study maintained its primary noninferiority efficacy success using the Per Protocol population since the lower bound of the 95% two-sided confidence interval (-6.42, 2.64) is greater than -10%.

STUDY C-11-003

The difference between Nepafenac 0.3% and Nepafenac Vehicle 0.3% with respect to the proportion of patients considered to be a cure at Day 14 was assessed using the Cochran-Mantel-Haenszel test controlling for investigative site.

**Table 6.1.4.2-1
Primary Efficacy Results
Percent of Patients Cured at Day 14**

	Nepafenac 0.3% n(%) N=512	Nepafenac Vehicle 0.3% n(%) N=252	p value
ITT Population	331 / 512 (64.6)	63 / 252 (25.0)	p < 0.0001

Cure was defined as a patient having a score of 0 for both cells and flare at the visit (LOCF). N is the number of patients with non-missing post surgery data. n is the number of patients cured. p value is based upon Cochran-Mantel-Haenszel test controlling data

The study met its primary efficacy endpoint by demonstrating that the difference in the proportions of patients who achieved cure in the treatment of ocular inflammation at Day 14 in the Nepafenac 0.3% group was statistically superior (p<0.0001) to that in the Nepafenac Vehicle 0.3% group.

Analysis of Secondary Endpoints(s)

Secondary Efficacy Endpoint

STUDY 09-055

The secondary efficacy variable was the percent of patients with no ocular pain at Day 14 as assessed by the Investigator on a 5-point scale. Pain-free is defined as a score of 0.

Investigators assessed ocular pain at each post surgical visit – Days 1, 3, 7 and 14, as well as at the Early Exit Visit and any unscheduled visits.

Table 6.1.5.1-1
Secondary Efficacy Results - Percent Pain-Free Patients at Day 14
Vehicle Comparison (Superiority) Study C-09-055

	Nepafenac 0.3% n (%)	Nepafenac Vehicle 0.3% n (%)	Nevanac n (%)	Nevanac Vehicle n (%)
ITT Population	734 / 807 (91.0)	98 / 197 (49.7)	737 / 811 (90.9)	115 / 205 (56.1)
	p value ^b <0.0001		p value ^c <0.0001	
PP Population	701 / 761 (92.1)	86 / 175 (49.1)	699 / 760 (92.0)	102 / 176 (58.0)
	p value ^b <0.0001		p value ^c <0.0001	

p value is based upon Cochran-Mantel-Haenszel test controlling data

a ITT population - 2 patients were randomized but did not have on-study data

b Nepafenac 0.3% versus Nepafenac Vehicle 0.3%

c Nevanac versus Nevanac Vehicle

Both Nepafenac 0.3% and Nevanac are statistically superior to their respective vehicles in the percent of pain free patients at Day 14. See Table 6.1.5.1-1 above.

Table 6.1.5.1-2
Secondary Efficacy Results - Percent of Pain-free Patients at Day 14
Active Comparison (Non-Inferiority) Study C-09-055

	Nepafenac 0.3% n(%)	Nevanac n(%)	Confidence Interval ^a
ITT Population	734 / 807 (91.0)	737 / 811 (90.9)	(-3.08, 2.70)
PP Population	701 / 761 (92.1)	699 / 760 (92.0)	(-3.63, 2.34)

p value is based upon Cochran-Mantel-Haenszel test controlling data

a ITT population - 2 patients were randomized but did not have on-study data

a Test based confidence interval for difference of treatment proportions (Nepafenac 0.3% QD -NEVANAC TID) using the method of Yanagawa, Tango and Hiejima. (PP Population): If the lower bound of the confidence interval (CI) for (Nepafenac 0.3% QD - NEVANAC TID) is greater than the non-inferiority margin -10%, then the data supports the non-inferiority of Nepafenac 0.3% QD vs NEVANAC TID.

The study achieved its secondary noninferiority efficacy endpoint since the lower bound of the 95% two-sided confidence interval (-3.08, 3.17) is greater than -10%. The study demonstrates that Nepafenac 0.3% dosed once daily is noninferior to Nevanac dosed 3 times daily for the treatment of ocular pain as assessed by the Investigator on Day 14 days post cataract extraction. See Table 6.1.5.1-1 above.

The study maintained its secondary noninferiority efficacy success in the Percent of Pain-Free Patients in the Per Protocol population as well since the lower bound of the 95% two-sided confidence interval (-3.63, 2.34) is greater than -10%.

STUDY C-11-003

The secondary efficacy variable was the percent of patients cured at Day 7. Cure is defined as a score of zero for both cells and flare. A “cumulative” cure required that a patient who was judged to be a cure must have remained a cure at all subsequent visits.

**Table 6.1.5.2-1 Secondary Efficacy Results
Cumulative Percent Cures at Day 7 - Study C-11-003**

	Nepafenac 0.3% n(%)	Nepafenac 0.1% n(%)	Nepafenac 0.3% vs. Nepafenac 0.1% p value
ITT Population	160 / 512 (31.3)	152 / 493 (30.8)	p = 0.9805

p value is based upon Cochran-Mantel-Haenszel test stratified by site.

Summary Efficacy Statement

Nepafenac ophthalmic suspension 0.3% has demonstrated superiority to vehicle in two adequate and well controlled trials in its ability to clear ocular inflammation and treat pain following cataract surgery.

8. Safety

From the original Medical Officer Review finalized 9/14/2012:

Data from Study C-09-053 a Pharmacokinetic Study in healthy subjects and Studies C-09-055 and C-11-003, the two Phase 3 studies of Post-Cataract Inflammation are included in this section. The safety population thus included 3344 patients, 1351 of who were exposed to Nepafenac Ophthalmic Suspension, 0.3%.

DEATHS

There were no deaths reported for patients exposed to any test article in any of the studies. However, in Study C-09-055, two patients enrolled in the study died prior to exposure to test article. Both patients died more than one week prior to the date that they were scheduled to begin dosing with the study medication.

EXPOSURE

Table 7.2.1 – Exposure to Nepafenac 0.3% Ophthalmic Suspension by Protocol

	Safety Population	Nepafenac 0.3% N=1351	Nevanac TID N=819	Nepafenac 0.1% QD N=506	Nepafenac 0.3% Vehicle N=463	Nevanac Vehicle N=205
Protocol C-09-053 Pharmacokinetic Study	20	12	--	--	8	--
Protocol C-09-055 Post Cataract Inflammation Study	2042	817	819	--	201	205
Protocol C-11-003 Post Cataract Inflammation Study	1282	522	--	506	254	--
TOTALS	3344	1351	819	506	455	205

NONFATAL SERIOUS ADVERSE EVENTS

Table 7.3.2 Nonfatal Serious Adverse Events

Study	Patient Number	Treatment	Coded Event	Outcome
C-11-003	3630	Nepafenac 0.3%	Angle closure glaucoma	Resolved w/ Tx
C-09-055	3351	Nepafenac 0.3%	Appendicitis	Resolved w/ Tx
C-09-055	2034	Nepafenac 0.3%	Brain edema	Continuing w/ Tx
C-11-003	1514	Nepafenac 0.3%	Congestive Cardiac Failure	Resolved w/ Tx
C-09-055	9049	Nepafenac 0.3%	Cerebrovascular Accident	Resolved w/o Tx
C-11-003	1008	Nepafenac 0.3%	Corneal abrasion	Resolved w/ Tx
C-11-003	2814	Nepafenac 0.3%	Endophthalmitis	Resolved w/ Tx
C-09-055	3306	Nepafenac 0.3%	Hyperkalemia	Resolved w/ Tx
C-11-003	2112	Nepafenac 0.3%	Hypopyon	Resolved w/ Tx
C-09-055	7910	Nepafenac 0.3%	Injury	Resolved w/ Tx
C-09-055	4456	Nepafenac 0.3%	Injury	Resolved w/ Tx
C-11-003	3630	Nepafenac 0.3%	Lens dislocation	Resolved w/ Tx
C-09-055	9049	Nepafenac 0.3%	Stage IV Lung CA	Continuing w/ Tx
C-09-055	4527	Nepafenac 0.3%	Myocardial infarction	Resolved w/ Tx
C-11-003	3630	Nepafenac 0.3%	Retinal detachment	Resolved w/ Tx
C-09-055	5014	Nevanac	Atrial fibrillation	Resolved w/ Tx
C-09-055	3545	Nevanac	Cerebrovascular accident	Continuing w/ Tx

Study	Patient Number	Treatment	Coded Event	Outcome
C-09-055	3307	Nevanac	Sepsis	Resolved w/ Tx
C-11-003	4138	Nepafenac 0.1%	Viral gastritis	Resolved w/ Tx
C-11-003	3416	Nepafenac 0.1%	Hypertensive encephalopathy	Resolved w/ Tx
C-11-003	1303	Nepafenac 0.1%	Injury	Resolved w/ Tx
C-11-003	3717	Nepafenac 0.1%	Visual acuity reduced	Resolved w/ Tx

No new safety signal was identified by the reported non-serious adverse events.

The most common reason for treatment discontinuation was treatment failure in either vehicle group. There was no safety signal raised regarding treatment discontinuation in either nepafenac group.

COMMON ADVERSE EVENTS

Table 7.4.1 Adverse Events Occurring at a Rate of $\geq 1\%$ Safety Population

	Nepafenac 0.3% N=1339	Nevanac N=819	Nepafenac 0.1% N=506	Nepafenac 0.3% Vehicle N=455	Nevanac Vehicle N=205
Eye Disorders					
Eye pain	2 (0.1%)	1 (0.1%)	1 (0.2%)	5 (1.1%)	7 (3.4%)
Posterior capsule rupture	8 (0.6%)	4 (0.5%)	1 (0.2%)	1 (0.2%)	2 (1.0%)
Corneal edema	6 (0.4%)	0	1 (0.2%)	6 (1.3%)	2 (1.0%)
Photophobia	0	0	0	7 (1.5%)	5 (2.4%)
Eye inflammation	1 (0.1%)	0	0	4 (0.9%)	2 (1.0%)
Vision blurred	0	0	0	2 (0.4%)	2 (1.0%)
Ocular hyperemia	0	0	0	0	3 (1.5%)
Investigations					
Intraocular pressure increased	15 (1.1%)	7 (0.9%)	1 (0.2%)	1 (0.2%)	0
Nervous System Disorders					
Headache	27 (2.0%)	13 (1.6%)	6 (1.2%)	5 (1.1%)	3 (1.5%)

Headache and intraocular pressure increased were the most common adverse events reported in patients who received nepafenac. The adverse event profile was similar for patients with a

history of diabetes mellitus and dry eye, conditions that might compromise the corneal epithelium.

POSTMARKET EXPERIENCE

The first Alcon product containing nepafenac for ocular use was approved in the US in August 2005. In December 2007, this product was approved by the European Medicines Agency (EMA). So far, Alcon has registered nepafenac-containing products for ocular use in a total of 84 countries world-wide. These nepafenac-containing products are indicated for treatment and prevention of inflammation and postoperative pain secondary to cataract surgery and refractive surgery, pre- and postoperative prophylaxis of cystoid macular edema, as well as non-infectious inflammations of the cornea, iris, ciliary body, retina and choroid.

According to Alcon’s database (b) (4) units (equivalent to (b) (4) patients) containing nepafenac were sold worldwide from September 1 2010 to August 31 2011. During the same time period, 2,345 patients were exposed to nepafenac in four Alcon-sponsored clinical studies.

During this time period, Alcon received a total of 87 cases (17 serious, 70 nonserious) worldwide associated with the use of nepafenac.

Nepafenac (1 mg/ml, eye drops, suspension)	Medically confirmed		Non-medically confirmed		TOTAL
	Serious	Non-serious	Serious	Non-serious	
	8	32	9	38	87

Adverse events possibly associated with the ocular use of nepafenac were generally non-serious and related to local eye disorders.

Alcon’s analysis of information received for ocular use of nepafenac during the period of time covered by this report does not indicate any new or potentially important safety findings for the ocular use of this product that could change the safety information included in the current reference safety information. Safety data for Alcon products containing nepafenac for ocular use remain in concordance with the previous cumulative experience, and with the reference safety information. No specific areas of concern were identified by this safety update and therefore no change in the pharmacovigilance activities is planned.

The postmarketing experience data submitted revealed no new safety signals and required no additional revisions to the current labeling.

Summary Safety Statement

The safety profile of this drug product is consistent with other products in the topical NSAID class. No new unexpected adverse events associated with the use of this product were observed.

Headache and intraocular pressure increased were the most common adverse events reported in patients who received nepafenac. The adverse event profile was similar for patients with a history of diabetes mellitus and dry eye, conditions that might compromise the corneal epithelium.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

Nepafenac has not been studied in clinical trials in pediatric patients.

This application was presented at the Pediatric Regulatory Committee (PeRC) on April 25, 2012. PeRC agreed with the applicant's request a full waiver. The drug does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in the 0-16 age group and is not likely to be used by a substantial number of pediatric patients in this age group.

11. Other Relevant Regulatory Issues

BIostatISTICS

Per the original Biostatistics review finalized 9/21/2012:

Efficacy results for the endpoints of complete resolution of inflammation (primary endpoint) and complete resolution of ocular pain (secondary endpoint) are summarized in Table 1 and Table 2 below.

We see in Table 1 that the test drug is superior to vehicle for both resolution of inflammation and resolution of ocular pain with a very large treatment effect. We see in Table 2 that Study C09055 was successful in showing non-inferiority of test drug to NEVANAC for both inflammation resolution and pain resolution at Day 7 and Day 14 visits with a non-inferiority margin of 10%.

Table 1: Inflammation and Ocular Pain Resolution Results of Nepafenac 0.3% versus Vehicle at Day 14 post-surgery

Study	Treatment	Inflammation Resolution	Ocular Pain Resolution
C0905 5	Nepafenac 0.3% (n/N*)	552/851 (65%)	734/851 (86%)
	Vehicle (n/N*)	67/211 (32%)	98/211 (46%)
	Difference (95% CI)**	33% (26%, 40%)	40% (32%, 47%)
C1100 3	Nepafenac 0.3% (n/N*)	331/540 (61%)	456/540 (84%)
	Vehicle (n/N*)	63/268 (24%)	101/268 (38%)
	Difference (95% CI)**	38% (31%, 45%)	47% (40%, 54%)

* n/N is the ratio of those with no treatment failure prior to Day 14 post-surgery visit and complete resolution by Day 14 post-surgery visit over all randomized subjects prior to cataract surgery. Treatment failure is defined as cells score of grade 3 or greater, a flare score of grade 3 or greater, or an ocular pain score of grade 4 or greater.

** Difference is (test drug – vehicle). The 95% confidence interval is derived using asymptotic approximation.

Table 2: Inflammation and Ocular Pain Resolution of Nepafenac 0.3% versus Active Control Comparators at Day 7 and Day 14

Study	Visit	Treatment	Inflammation Resolution	Ocular Pain Resolution
C0905 5	Day 7	Nepafenac 0.3% (n/N*)	295/851 (35%)	717/851 (84%)
		NEVANAC (n/N*)	330/845 (39%)	733/845 (87%)
		Difference (95% CI)**	4% (0%, 9%)	2% (-1%, 6%)
	Day 14	Nepafenac 0.3% (n/N*)	552/851 (65%)	734/851 (86%)
		NEVANAC (n/N*)	568/845 (67%)	737/845 (87%)
		Difference (95% CI)**	2% (-2%, 7%)	1% (-2%, 4%)
C1100 3	Day 7	Nepafenac 0.3% (n/N*)	174/540 (32%)	453/540 (84%)
		Nepafenac 0.1% Once Daily (n/N*)	172/534 (32%)	425/534 (80%)
		Difference (95% CI)**	0% (-6%, 6%)	-4% (-9%, 1%)
	Day 14	Nepafenac 0.3% (n/N*)	331/540 (61%)	456/540 (84%)
		Nepafenac 0.1% Once Daily (n/N*)	322/534 (60%)	439/534 (82%)
		Difference (95% CI)**	-1% (-7%, 5%)	-2% (-7%, 2%)

* n/N is the ratio of those with no treatment failure prior to Day 14 post-surgery visit and complete resolution by Day 14 post-surgery visit over all randomized subjects prior to cataract surgery.

** Difference is (active control – test drug). The 95% confidence interval is derived using asymptotic approximation.

DMEPA

As of the date of this review, the Division of Medication Error Prevention and Analysis has not approved a proprietary name for this drug product.

In a letter to the applicant dated August 17, 2012, DMEPA found the name [REDACTED] (b) (4) unacceptable.

In a letter to the applicant dated June 14, 2012, DMEPA found the name [REDACTED] (b) (4) unacceptable.

After a teleconference with DMEPA on October 12, 2012, where the applicant was informed that the name, [REDACTED] (b) (4) was not acceptable, the applicant withdrew the name.

DMEPA provided labeling comments in a review dated June 29, 2012. At that time the proposed tradename was [REDACTED] (b) (4). The carton and container labeling has been modified since the June 2012 review because DMEPA has not approved a proprietary name for this drug product.

DMEPA has suggested revisions to the labeling including removing information on the active ingredient and usual dosage from the container labels. The Clinical group disagrees with the suggestion to remove the information on the active ingredient and usual dosage from the container labels. All ophthalmic labels are small by nature. Although not required under 21 CFR 201.10(i), this is relevant information for the patient and prescriber. The revised container label is easily legible. The strength statement is prominent in the redesigned label without a tradename. The blue shading and teardrop on the carton labeling do not interfere with the legibility of the revised carton label. The manufacturer's name is not overly prominent on the revised carton label. The strength statement is prominent in the redesigned label without a tradename.

DPDP

As of the date of this review, the Division of Professional Drug Promotion (DPDP) has not provided formal labeling comments for the package insert or carton and container labeling.

The carton and container labeling and package insert are consistent with the similar Alcon product, Nevanac, in format, layout, and content (NDA 21-862).

FINANCIAL DISCLOSURE

Alcon has adequately disclosed financial arrangements with the clinical investigators who participated in the clinical studies for nepafenac ophthalmic suspension 0.3% which include: C-09-053, C-09-055 and C-11-003. There were no financial disclosures for Study C-09-053.

**Study C-09-055:
 Description of Financial Interests and Arrangements Reporting Period:
 June 23, 2010 to June 14, 2011**

Investigator and Payment Description	Total Monies by Investigators
(b) (6)	\$389,124
(b) (6)	\$55,254
(b) (6)	> \$50,000
(b) (6)	\$64,400
(b) (6)	\$197,494
(b) (6)	\$88,809
(b) (6)	\$118,510
(b) (6)	\$81,636
(b) (6)	\$136,641
(b) (6)	\$27,165
(b) (6)	\$29,316

**Study C-11-003:
 Description of Financial Interests and Arrangements Reporting Period:
 June 23, 2010 to June 14, 2011**

Investigator and Payment Description	Total Monies by Investigators
(b) (6)	\$270,130
(b) (6)	\$68,301
(b) (6)	\$71,094
(b) (6)	> \$50,000
(b) (6)	\$32,022
(b) (6)	\$106,916
(b) (6)	\$48,552
(b) (6)	\$50,255

A review of these arrangements did not raise questions about the integrity of the data.

OSI

An Office of Scientific Investigations (OSI) audit was requested; OSI completed their review on 8/8/2012. Per the DSI review:

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.

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.

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.

12. Labeling

NDA 203491 for Nepafenac ophthalmic suspension, 0.3% is recommended for approval for the treatment of pain and inflammation associated with cataract surgery with the package insert and with carton and container labeling received from the applicant on 10/16/12 and found in the Appendix of this CDTL memo.

In a teleconference on October 16, 2013, with Alcon representative Norma Schafer, Alcon committed to two minor editorial revisions to the labeling:

- 1) Alcon will renumber the subsections under Section 6 in the Highlights to correspond to the text of the label (i.e. 6.1, 6.2, 6.3).
- 2) Alcon will revise the usage statement on the carton labeling to correspond with the package insert (i.e. Shake Well Before Use).

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

NDA 203491 for Nepafenac ophthalmic suspension, 0.3% is recommended for approval for the treatment of pain and inflammation associated with cataract surgery with the package insert and with carton and container labeling found in this CDTL review (see Appendix).

RISK BENEFIT ASSESSMENT:

This NDA supports the use of nepafenac ophthalmic suspension, 0.3% for the treatment of pain and inflammation associated with cataract surgery. Nepafenac ophthalmic suspension 0.3% has demonstrated superiority to vehicle in two adequate and well controlled trials in its ability to clear ocular inflammation and treat pain following cataract surgery. The safety profile of this drug product is consistent with other products in the topical NSAID class. No new unexpected adverse events associated with the use of this product were observed. The benefits of this drug outweigh the risks in the treatment of ocular inflammation and treatment of ocular pain following cataract surgery.

Clinical, Biostatistics, Pharmacology/Toxicology, Clinical Pharmacology, and CMC, and Product Quality Microbiology have recommended approval for this application.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

APPENDIX

NDA 203491 for Nepafenac ophthalmic suspension, 0.3% is recommended for approval for the treatment of pain and inflammation associated with cataract surgery with the package insert and with carton and container labeling received from the applicant on 10/16/12 and found in this Appendix.

In a teleconference on October 16, 2013, with Alcon representative Norma Schafer, Alcon committed to two minor editorial revisions to the labeling:

- 3) Alcon will renumber the subsections under Section 6 in the Highlights to correspond to the text of the label (i.e. 6.1, 6.2, 6.3).
- 4) Alcon will revise the usage statement on the carton labeling to correspond with the package insert (i.e. Shake Well Before Use).

13 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

WILLIAM M BOYD
10/16/2012

WILEY A CHAMBERS
10/16/2012