

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**203491Orig1s000**

**OFFICE DIRECTOR MEMO**

## Deputy Division Director Review for NDA 203491

<b>Date</b>	October 16, 2012
<b>From</b>	Wiley A. Chambers, M.D.
<b>NDA Number</b>	NDA 203-491
<b>Applicant</b>	Alcon Research Ltd.
<b>Date of Submission</b>	December 15, 2011
<b>Name</b>	Nepafenac ophthalmic suspension, 0.3%
<b>Dosage forms / Strength</b>	Topical ophthalmic suspension
<b>Indication(s)</b>	For the treatment of pain and inflammation associated with cataract surgery
<b>Recommended:</b>	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 as opposed this NDA in which nepafenac ophthalmic suspension is proposed to be dosed once 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

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 non-inferiority of nepafenac ophthalmic suspension, 0.3% to Nevanac for the safety and efficacy of the product. During the development of the product, the Agency expressed concern about whether a lower concentration could instead be administered once a day or whether the 0.3% was needed to maintain efficacy. Between the two applications (nepafenac 0.1% and nepafenac 0.3%) there are studies which provide comparisons between different concentrations and different dosing regimens justifying the use of the 0.3% concentration administered once per day.

### 3. Product Quality

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 C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> 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/y</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

Test	Specification
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 rmp	
Particulate Size, Suspension	
Endoxin	
Sterility	

#### CONTAINER CLOSURE SYSTEM

The primary package system for Nepafenac Ophthalmic Suspension, 0.3% consists of 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. Both the trade and sample sizes are filled into this container.

#### INSPECTIONS

All the drug substance and drug product manufacturing and testing sites were found to be acceptable.

### 4. Nonclinical Pharmacology/Toxicology

Nepafenac ophthalmic suspension 0.3% differs from Nevanac (nepafenac ophthalmic suspension, 0.1%) with respect to the excipient guar gum (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

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<sub>max</sub> for nepafenac and amfenac were  $0.847 \pm 0.269$  ng/ml and  $1.13 \pm 0.491$  ng/ml, respectively, following topical ocular administration of Nepafenac 0.3% Ophthalmic Suspension.

## 6. Sterility Assurance

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)

(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.

(b) (4)

## 7. Clinical/Statistical - Efficacy

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. Pain was a secondary endpoint.

**Primary Efficacy Results - Percent of Patients Cured at Day 14- C-09-055**

	Nepafenac 0.3% N=807 n(%)	Nepafenac Vehicle 0.3% N=197 n(%)	Nevanac N=811 n(%)	Nevanac Vehicle N=205 n(%)	Confidence Interval between 0.3% qd and 0.1% tid
ITT Population	552 / 807 (68.4)	67 / 197 (34.0)	568 (70.0)	73 (35.6)	
	p value <sup>b</sup> <0.0001		p value <sup>c</sup> <0.0001		(-5.73, 3.17)
PP Population	531 / 761 (69.8)	63 / 175 (36.0)	546 / 760 (71.8)	69 / 176 (39.2)	
	p value <sup>b</sup> <0.0001		p value <sup>c</sup> <0.0001		(-6.42, 2.64)

Efficacy Parameter	Post-op Day	Nepafenac 0.3%	Nevanac	Nepafenac vehicle 0.3%	Nevanac Vehicle	p value active comparison	p value Nepafenac 0.3% vehicle comparison	p value Nevanac vehicle comparison
Sum of Cells and Flare (units)	1	2.16	2.18	2.29	2.34	0.7018	0.1109	0.1280
	3	1.64	1.62	2.49	2.53	0.7635	<0.0001	<0.0001
	7	1.08	1.00	2.44	2.48	0.1635	<0.0001	<0.0001
	14	0.58	0.57	2.30	2.17	0.8525	<0.0001	<0.0001

Efficacy Parameter	Post-op Day	Nepafenac 0.3% <sup>a</sup> n (%)	Nevanac <sup>b</sup>	Nepafenac vehicle 0.3% <sup>c</sup>	Nevanac Vehicle	p value Nepafenac 0.3% vehicle comparison	p value Nevanac vehicle comparison
Cumulative Percent Pain Free	1	592 (73.6%)	614 (75.7%)	81 (41.3%)	89 (43.4%)	<0.0001	<0.0001
	3	668 (82.8%)	687 (84.7%)	72 (36.5%)	87 (42.4%)	<0.0001	<0.0001
	7	717 (88.8%)	733 (90.4%)	80 (40.6%)	98 (47.8%)	<0.0001	<0.0001
	14	734 (91.0%)	737 (90.9%)	98 (49.7%)	115 (56.1%)	<0.0001	<0.0001

	Nepafenac 0.3% n (%)	Nepafenac Vehicle 0.3% n (%)	Nevanac n (%)	Nevanac Vehicle n (%)	Confidence Interval <sup>a</sup>
ITT Population	734 / 807 (91.0)	98 / 197 (49.7)	737 / 811 (90.9)	115 / 205 (56.1)	
	p value <sup>b</sup> <0.0001		p value <sup>c</sup> <0.0001		(-3.08, 2.70)
PP Population	701 / 761 (92.1)	86 / 175 (49.1)	699 / 760 (92.0)	102 / 176 (58.0)	
	p value <sup>b</sup> <0.0001		p value <sup>c</sup> <0.0001		(-3.63, 2.34)

**STUDY C-11-003**

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

Efficacy Parameter	Post-op Day	Nepafenac 0.3%	Nepafenac 0.1%	Nepafenac vehicle 0.3%	p value active comparison	p value Nepafenac 0.3% vehicle comparison
<b>Sum of Cells and Flare (units)</b>	1	2.18	2.18	2.37	0.8711	0.0312
	3	1.65	1.68	2.56	0.7140	<0.0001
	7	1.07	1.17	2.73	0.2054	<0.0001
	14	0.65	0.69	2.57	0.7109	<0.0001

Efficacy Parameter	Post-op Day	Nepafenac 0.3% <sup>a</sup> n (%)	Nevanac <sup>b</sup>	Nepafenac vehicle 0.3% <sup>c</sup>	Nevanac Vehicle	p value Nepafenac 0.3% vehicle comparison	p value Nevanac vehicle comparison
<b>Cumulative Percent Pain Free</b>	1	592 (73.6%)	614 (75.7%)	81 (41.3%)	89 (43.4%)	<0.0001	<0.0001
	3	668 (82.8%)	687 (84.7%)	72 (36.5%)	87 (42.4%)	<0.0001	<0.0001
	7	717 (88.8%)	733 (90.4%)	80 (40.6%)	98 (47.8%)	<0.0001	<0.0001
	14	734 (91.0%)	737 (90.9%)	98 (49.7%)	115 (56.1%)	<0.0001	<0.0001

## 8. Safety

### EXPOSURE

#### 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	--
<b>TOTALS</b>	<b>3344</b>	<b>1351</b>	<b>819</b>	<b>506</b>	<b>455</b>	<b>205</b>

### NONFATAL SERIOUS ADVERSE EVENTS

#### 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

Study	Patient Number	Treatment	Coded Event	Outcome
C-09-055	5014	Nevanac	Atrial fibrillation	Resolved w/ Tx
C-09-055	3545	Nevanac	Cerebrovascular accident	Continuing w/ Tx
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

##### Adverse Events Occurring at a Rate of $\geq 1\%$

	Nepafenac 0.3% N=1339	Nevanac N=819	Nepafenac 0.1% N=506	Nepafenac 0.3% Vehicle N=455	Nevanac Vehicle N=205
<b>Eye Disorders</b>					
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%)
<b>Investigations</b>					
Intraocular pressure increased	15 (1.1%)	7 (0.9%)	1 (0.2%)	1 (0.2%)	0
<b>Nervous System Disorders</b>					
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. Alcon has registered nepafenac-containing products for ocular use in a total of 84 countries worldwide. According to Alcon's database (b) (4) units containing nepafenac were sold worldwide. Adverse events possibly associated with the ocular use of nepafenac were generally non-serious and related to local eye disorders. The postmarketing experience data submitted revealed no new safety signals and required no additional revisions to the current labeling.

## 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. Biostatistics

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.

**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 cell 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
C09055	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%)
C11003	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.

## 12. Other

### 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. 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. 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.

## 13. 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.

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

## 14. 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.

### **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.

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WILEY A CHAMBERS  
10/16/2012