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RESEARCH**

*APPLICATION NUMBER:*  
**203491Orig1s000**

**MEDICAL REVIEW(S)**

**Medical Officer's Review #2**  
**NDA 203-491**

Submission Date: September 17, 2012  
Receipt Date: September 17, 2012

Review Completed: September 18, 2012

Reviewer: Rhea Lloyd, MD  
Medical Officer

Established Name: Nepafenac ophthalmic suspension, 0.3%

Proprietary Name: None

Sponsor: Alcon Research, Ltd.  
6201 South Freeway  
Fort Worth, TX 76134-2099  
(817) 551-8568  
Norma Schaefer

**Submitted:**

The applicant has submitted a response to the Agency's September 14, 2012, clinical information request for clarification regarding investigators who had enrolled subjects in both studies. In this submission, the sponsor also states that there is no new safety information to be reported regarding nepafenac ophthalmic suspension.

### Agency Information Request

It is noted that 35 of the 37 investigators in Study C-11-003 were also investigators in Study C-09-055. Twenty-six of the 35 investigators participated in the studies concurrently (concurrent time period ranging from 1 day to 41 days).

Please clarify if investigators were actually concurrently enrolling in both studies. If so, please provide an explanation of how it was decided in to which study a patient would be enrolled.

### Applicant Response:

Although the conduct of patient visits in the C-09-055 study did overlap with conduct of patient visits in the C-11-003 study at some of the 35 sites, the C-09-055 enrollment at each site was completed prior to the initiation of enrollment for C-11-003.

The spreadsheet below illustrates the date of the last patient first visit on the C-09-055 study and the first patient visit for the C-11-003 study for each site. It was required that each site finish enrollment on the first study to beginning enrollment in the second study.

Site #	PI Last Name	Last Patient First Visit C-09-055	First Patient First Visit C-11-003
C11003T001	Christie	8-Mar-11	1-Apr-11
C11003T002	Cionni	11-Mar-11	13-Apr-11
C11003T003	Fisher	30-Mar-11	4-Apr-11
C11003T004	Fishman	25-Mar-11	8-Apr-11
C11003T005	Fong	21-Mar-11	4-Apr-11
C11003T006	Foster	31-Mar-11	28-Apr-11
C11003T007	Kloess	9-Mar-11	11-Apr-11
C11003T008	Lehmann	24-Mar-11	5-Apr-11
C11003T009	Lozier	4-Apr-11	24-May-11
C11003T010	Malhotra	2-Mar-11	31-Mar-11
C11003T011	Modi	30-Mar-11	4-Apr-11
C11003T012	Nethery	23-Mar-11	6-Apr-11
C11003T013	Cable	31-Mar-11	11-Apr-11
C11003T014	Maxwell	8-Apr-11	6-May-11
C11003T015	Panzo	18-Mar-11	18-Apr-11
C11003T016	Pennell	5-Apr-11	5-May-11
C11003T017	Rauchman	29-Mar-11	31-May-11

Site #	PI Last Name	Last Patient First Visit C-09-055	First Patient First Visit C-11-003
C11003T018	Reiser	30-Mar-11	7-Apr-11
C11003T019	Rice	31-Mar-11	12-Apr-11
C11003T020	Roel	16-Mar-11	4-Apr-11
C11003T021	Sandor Jr	23-Mar-11	7-Apr-11
C11003T023	Segal	30-Mar-11	14-Apr-11
C11003T024	Seidenberg	29-Mar-11	2-May-11
C11003T025	Silverstein	23-Mar-11	4-Apr-11
C11003T026	Smith	30-Mar-11	22-Apr-11
C11003T027	Tepedino	14-Mar-11	11-Apr-11
C11003T028	Thorne	21-Mar-11	4-Apr-11
C11003T029	Vold	21-Mar-11	4-Apr-11
C11003T030	Walters	24-Feb-11	30-Mar-11
C11003T031	Wood	29-Mar-11	11-Apr-11
C11003T032	Johnson	31-Mar-11	25-Apr-11
C11003T033	Jong	25-Mar-11	8-Apr-11
C11003T034	Katzman	11-Mar-11	22-Apr-11
C11003T035	Shulman	22-Mar-11	13-Apr-11
C11003T038	Thompson	17-Mar-11	26-May-11

**Reviewer's Comment:**

*Acceptable.*

**Recommended Regulatory Action:**

From a clinical perspective, it is recommended that NDA 03-491 be approved for the treatment of pain and inflammation associated with cataract surgery when dosed once a day beginning 1 day prior to cataract surgery and continued on the day of surgery through the first two postoperative weeks. An additional drop should be administered 30-120 minutes before surgery.

Final labeling is pending. Please see the CDTL memo for final package insert, carton and container labeling.

Rhea A. Lloyd, MD  
Medical Officer

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RHEA A LLOYD  
10/09/2012

WILLIAM M BOYD  
10/09/2012

## CLINICAL REVIEW

Application Type NDA  
Application Number(s) 203-491  
Priority or Standard Standard

Submit Date(s) December 15, 2011  
Received Date(s) December 16, 2011  
PDUFA Goal Date October 12, 2012  
Division / Office DTOP / OAP

Reviewer Name(s) Rhea A. Lloyd, MD  
Review Completion Date

Established Name nepafenac ophthalmic  
suspension, 0.3%  
(Proposed) Trade Name  
Therapeutic Class non-steroidal anti-inflammatory  
agent  
Applicant Alcon Research Ltd.  
6201 South Freeway  
Fort Worth, TX 76134-2099  
817-293-0450  
  
Norma Schaefer  
817-551-8568

Formulation(s) ophthalmic suspension  
Dosing Regimen One drop in the affected eye

one time daily beginning 1 day prior to cataract surgery, and continued on the day of surgery through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

Indication(s) For the treatment of pain and inflammation associated with cataract surgery.

Intended Population(s) Patients 18 or older undergoing cataract surgery.

Template Version: March 6, 2009

## Table of Contents

<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>	<b>6</b>
1.1	Recommendation on Regulatory Action .....	6
1.2	Risk Benefit Assessment.....	6
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	6
1.4	Recommendations for Postmarket Requirements and Commitments .....	6
<b>2</b>	<b>INTRODUCTION AND REGULATORY BACKGROUND .....</b>	<b>6</b>
2.1	Product Information .....	6
2.2	Tables of Currently Available Treatments for Proposed Indications .....	7
2.3	Availability of Proposed Active Ingredient in the United States .....	7
2.4	Important Safety Issues With Consideration to Related Drugs.....	7
2.5	Summary of Presubmission Regulatory Activity Related to Submission .....	8
2.6	Other Relevant Background Information .....	9
<b>3</b>	<b>ETHICS AND GOOD CLINICAL PRACTICES.....</b>	<b>9</b>
3.1	Submission Quality and Integrity .....	9
3.2	Compliance with Good Clinical Practices .....	9
3.3	Financial Disclosures.....	9
<b>4</b>	<b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES .....</b>	<b>11</b>
4.1	Chemistry Manufacturing and Controls .....	11
4.2	Clinical Microbiology.....	12
4.3	Preclinical Pharmacology/Toxicology .....	12
4.4	Clinical Pharmacology .....	12
4.4.1	Mechanism of Action.....	12
4.4.2	Pharmacodynamics.....	13
4.4.3	Pharmacokinetics.....	13
<b>5</b>	<b>SOURCES OF CLINICAL DATA.....</b>	<b>14</b>
5.1	Tables of Studies/Clinical Trials .....	14
5.2	Review Strategy .....	15
5.3	Discussion of Individual Studies/Clinical Trials.....	15
<b>6</b>	<b>REVIEW OF EFFICACY .....</b>	<b>42</b>
	Efficacy Summary.....	42
6.1	Indication .....	42
6.1.1	Methods .....	42
6.1.2	Demographics.....	42
6.1.3	Subject Disposition.....	45
6.1.4	Analysis of Primary Endpoint(s) .....	49
6.1.5	Analysis of Secondary Endpoints(s) .....	53
6.1.6	Other Endpoints .....	55

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6.1.7	Subpopulations .....	67
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations ....	67
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	67
6.1.10	Additional Efficacy Issues/Analyses .....	67
<b>7</b>	<b>REVIEW OF SAFETY.....</b>	<b>68</b>
	Safety Summary .....	68
7.1	Methods.....	68
7.1.1	Studies/Clinical Trials Used to Evaluate Safety .....	68
7.1.2	Categorization of Adverse Events.....	68
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	68
7.2	Adequacy of Safety Assessments .....	68
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations .....	68
7.2.2	Explorations for Dose Response.....	69
7.2.3	Special Animal and/or In Vitro Testing .....	69
7.2.4	Routine Clinical Testing .....	69
7.2.5	Metabolic, Clearance, and Interaction Workup .....	69
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..	69
7.3	Major Safety Results .....	70
7.3.1	Deaths.....	70
7.3.2	Nonfatal Serious Adverse Events .....	70
7.3.3	Dropouts and/or Discontinuations .....	72
7.3.4	Significant Adverse Events .....	91
7.3.5	Submission Specific Primary Safety Concerns .....	91
7.4	Supportive Safety Results .....	92
7.4.1	Common Adverse Events .....	92
7.4.2	Laboratory Findings .....	92
7.4.3	Vital Signs .....	92
7.4.4	Electrocardiograms (ECGs) .....	92
7.4.5	Special Safety Studies/Clinical Trials.....	92
7.4.6	Immunogenicity.....	93
7.5	Other Safety Explorations.....	93
7.5.1	Dose Dependency for Adverse Events .....	93
7.5.2	Time Dependency for Adverse Events.....	93
7.5.3	Drug-Demographic Interactions .....	93
7.5.4	Drug-Disease Interactions.....	93
7.5.5	Drug-Drug Interactions.....	93
7.6	Additional Safety Evaluations .....	94
7.6.1	Human Carcinogenicity.....	94
7.6.2	Human Reproduction and Pregnancy Data.....	94
7.6.3	Pediatrics and Assessment of Effects on Growth .....	94
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	94
7.7	Additional Submissions / Safety Issues.....	94

<b>8</b>	<b>POSTMARKET EXPERIENCE</b> .....	<b>94</b>
<b>9</b>	<b>APPENDICES</b> .....	<b>96</b>
9.1	Literature Review/References .....	96
9.2	Advisory Committee Meeting.....	96
9.3	Labeling Recommendations .....	96

## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

From a clinical perspective, NDA 203-491 is recommended for approval for the treatment of pain and inflammation associated with cataract surgery when dosed once a day beginning 1 day prior to cataract surgery and continued on the day of surgery through the first two post-operative weeks. An additional drop should be administered 30 – 120 minutes prior to surgery.

### 1.2 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.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

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

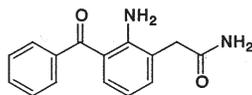
### 1.4 Recommendations for Postmarket Requirements and Commitments

No additional clinical trials or postmarketing surveillance studies are required.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

<b>Established Name</b>	nepafenac ophthalmic suspension, 0.3%
<b>(Proposed) Trade Name</b>	
<b>Therapeutic Class</b>	Nonsteroidal Anti-Inflammatory Drug (NSAID)
<b>Formulation</b>	C <sub>15</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>



**Proposed Indication** Treatment of pain and inflammation associated with cataract surgery

## 2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently four topical nonsteroidal anti-inflammatory drugs (NSAIDs) and two topical ophthalmic steroids approved for the treatment of postoperative inflammation: nepafenac 0.1% (Nevanac), bromfenac sodium 0.1% (Xibrom), ketorolac tromethamine ophthalmic solution 0.5% (Acular), diclofenac sodium ophthalmic solution 0.1% (Voltaren), loteprednol etabonate ophthalmic solution 0.5% (Lotemax), and rimexolone ophthalmic suspension 1% (Vexol).

## 2.3 Availability of Proposed Active Ingredient in the United States

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. The prodrug has very weak cyclooxygenase inhibitory activity whereas amfenac exhibits more potent cyclooxygenase activity.

Amfenac sodium (AHR 5850) has been on the Japanese market since 1986 (as FENAZOX®, Meiji) in an oral dosage form (50 mg, four-times-daily) indicated for the treatment of pain and inflammation associated with rheumatoid and osteoarthritis and low back pain, as well as the treatment of pain and inflammation following surgery, injury or tooth extraction.

Nepafenac at a concentration of 0.1% (NEVANAC) was approved for marketing in the US 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.

## 2.4 Important Safety Issues With Consideration to Related Drugs

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.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

October 5, 2009: An End-of-Phase 2 meeting was held between Alcon and the Agency. 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.*

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

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

January 10, 2011: 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. 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.

## 2.6 Other Relevant Background Information

There is no additional relevant background information.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

This submission was of sufficient quality to allow for a substantive review without requiring additional clinical information requests for the sponsor.

### 3.2 Compliance with Good Clinical Practices

The data was reviewed for consistency with other applications in this class. No special methods were used.

All trials were conducted under the review of approved Institutional Review Board committees. Investigators used an informed consent form that was appropriate for the trial.

### 3.3 Financial Disclosures

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
	\$55,254

Clinical Review  
 Rhea A. Lloyd, MD  
 NDA 203-491  
 Nepafenac ophthalmic suspension 0.3%

(b) (6)	> \$50,000
	\$64,400
	\$197,494
	\$88,809
	\$118,510
	\$81,636
	\$136,641
	\$27,165
	\$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
	\$68,301
	\$71,094
	> \$50,000
	\$32,022
	\$106,916
	\$48,552
	\$50,255

**Reviewer's Comment:**

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

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

There are no clinically relevant CMC issues at this time based on a preliminary evaluation from the chemistry reviewer.

**Composition of Nepafenac Ophthalmic Suspension, 0.3%**

Component	Percent w/v	Function	Compendial Status
Nepafenac (AL-6515)	0.3	Active Ingredient	Non-compendial <sup>b</sup>
Benzalkonium Chloride	0.005 <sup>b</sup>	Antimicrobial agent	NF
Carboxymethylcellulose Sodium <sup>(b) (4)</sup>	(b) (4)		USP
Guar Gum			NF
Carbomer 974P			NF <sup>c</sup>
Boric Acid			NF
Edetate Disodium			USP
Propylene Glycol			USP
Sodium Chloride			USP
Sodium Hydroxide and/or Hydrochloric Acid			QS for pH adjustment
Purified Water			USP

<sup>a</sup> Meets in-house monograph

<sup>(b) (4)</sup>

## 4.2 Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

## 4.3 Preclinical Pharmacology/Toxicology

The results of a repeated-dose topical ocular evaluation conducted in pigmented rabbits with concentrations of nepafenac as high as five-fold the proposed marketed concentration of 0.3% for one month demonstrated a low potential for ocular irritation with no signs of systemic toxicity. Similarly, repeated daily oral administration of nepafenac for six months in rats resulted in an NOAEL of 10mg/kg/day. At this dose, both  $C_{max}$  and  $AUC_{0-t}$  for nepafenac (amfenac amide) were determined to be over 130-fold higher in rat plasma compared to human plasma after multiple topical ocular dosing. The  $C_{max}$  and  $AUC_{0-t}$  for amfenac were over 460-fold greater in rat plasma compared to human plasma following multiple topical ocular dosing. Nepafenac did not show evidence of genotoxicity in the Ames assay, the mouse lymphoma forward mutation assay or the mouse micronucleus test. Nepafenac showed no evidence of reproductive or developmental toxicity at doses up to 3 mg/kg/day and 10 mg/kg/day, respectively. At doses which exceeded the human therapeutic exposure, effects observed in the nonclinical safety evaluations of nepafenac were consistent with those observed with other non-steroidal anti-inflammatory drugs.

Nepafenac administered subcutaneously and intravenously produced no hemodynamic or ECG effects in anesthetized dogs or airway resistance or dynamic lung compliance effects in anesthetized guinea pigs at 277-fold the theoretical maximum therapeutic dose (TMTD). The TMTD is based on bilateral topical ocular dosing of a 50 kg person once daily with Nepafenac 0.3% and assumes that the volume of the eye drops is 30  $\mu$ L, that there is 100% systemic absorption of the ocular dose, and that there is complete bioavailability of the absorbed dose. The TMTD under these conditions would be 3.6  $\mu$ g/kg. Nepafenac did not affect renal function in rats, peristalsis in mice, produce ulcers in rats, show pro- or anti-convulsant effects in mice or alter the writhing response of mice at 833-fold the TMTD. Amfenac, the metabolite of nepafenac, at 100 ng/mL had no effect on the hERG tail current of stably transfected HEK293 cells. No significant interactions were evident in a battery of receptor binding assays.

## 4.4 Clinical Pharmacology

### 4.4.1 Mechanism of Action

Primary pharmacology studies discussed in NDA 21-862 [Nevanac (nepafenac ophthalmic suspension, 0.1%)] examined the anti-inflammatory activity of nepafenac (AL-6515, amfenac amide) in both in vitro and in vivo models. Initial evaluations centered on the in vitro characterization of nepafenac's intrinsic cyclooxygenase inhibitory activity and that of its metabolite, amfenac. Other ex vivo studies addressed

nepafenac's ability to suppress prostaglandin synthesis by ocular tissues and its duration of action when administered by the topical ocular route.

The latter studies were enhanced with in vitro evaluations of nepafenac's corneal permeability and hydrolytic conversion to its active metabolite by ocular tissues. In vivo anti-inflammatory efficacy and duration of action assessments were conducted in a rabbit model of trauma (paracentesis)-induced ocular inflammation monitoring blood aqueous barrier leakage and accumulation of PGE<sub>2</sub> in the aqueous humor. A Concanavalin A-induced pan-retinal inflammation model was used to assess nepafenac's ability to suppress posterior ocular inflammation when administered topically. Drug efficacy was also determined by assessing vitreal and aqueous humor PGE<sub>2</sub> accumulation, evaluation of changes in retinal thickness (edema), and determination of blood retinal and blood aqueous barrier leakage.

#### 4.4.2 Pharmacodynamics

Nonclinical pharmacodynamic data indicate that nepafenac is effective in suppressing PGE<sub>2</sub> synthesis for over 30 hours following a single dose. Its topical anti-inflammatory activity was established in in vivo models of ocular inflammation of both the anterior and posterior section of the eye where it effectively suppresses prostaglandin synthesis and concomitant development of leakage of the blood-aqueous and blood-retinal barriers including retinal edema. In addition to nepafenac's effective suppression of prostaglandin synthesis and vascular leakage, in vivo and ex vivo studies demonstrate a long duration of anti-inflammatory action. These findings served as guidance for the selection of the appropriate dose-frequency in the clinical efficacy trials, C-09-55 and C-11-003.

#### 4.4.3 Pharmacokinetics

Because of the low plasma levels following topical ocular doses, the systemic pharmacokinetics of both nepafenac and amfenac following administration of Nepafenac 0.3% are not expected to be different than those previously submitted for registration Nevanac. In addition, the ocular tissue elimination kinetics for both nepafenac and amfenac with Nepafenac 0.3% are similar to those with Nevanac.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

**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 <sup>a</sup>	Dosing Regimen	Dosing Duration
<b>Safety / Clinical Pharmacology Studies</b>						
C-09-053	Randomized, double masked, placebo-controlled, parallel group	Healthy subjects 18 years of age and older	<ul style="list-style-type: none"> <li>• Nepafenac 0.3% QD</li> <li>• Vehicle QD</li> </ul>	12 8	1 drop in both eyes once daily for 4 days	4 days
<b>Post-cataract Inflammation Safety and Efficacy Studies</b>						
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"> <li>• Nepafenac 0.3% QD</li> <li>• Nepafenac 0.1% QD</li> <li>• Vehicle QD</li> </ul>	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"> <li>• Nepafenac 0.3% QD</li> <li>• Nevanac TID</li> <li>• Vehicle QD</li> <li>• Vehicle TID</li> </ul>	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

<sup>a</sup> Safety Dataset

**Reviewer's Comments:** *The design of the clinical trials and the number of centers are acceptable.*

## 5.2 Review Strategy

## 5.3 Discussion of Individual Studies/Clinical Trials

### **C-09-055: Clinical Evaluation of Nepafenac Ophthalmic Suspension, 0.3% for Prevention and Treatment of Ocular Inflammation and Pain after Cataract Surgery**

#### **Primary Efficacy Objectives:**

- Nepafenac Ophthalmic Suspension, 0.3% (Nepafenac 0.3%) dosed once daily is non-inferior to Nepafenac Ophthalmic Suspension, 0.1% (Nevanac) dosed 3 times daily for the prevention and treatment of ocular inflammation 14 days after cataract extraction.
- Nepafenac 0.3% dosed once daily is superior to Nepafenac Ophthalmic Suspension, 0.3% Vehicle (Nepafenac Vehicle 0.3%) dosed once daily for the prevention and treatment of ocular inflammation 14 days after cataract extraction.
- Nevanac dosed 3 times daily is superior to Nevanac Vehicle dosed 3 times daily for the prevention and treatment of ocular inflammation 14 days after cataract extraction.

#### **Secondary Efficacy Objectives:**

- Nepafenac 0.3% dose once daily is non-inferior to Nevanac dosed 3 times daily for the prevention and treatment of ocular pain as assessed by the Investigator 14 days after cataract extraction.
- Nepafenac 0.3% dosed once daily is superior to Nepafenac Vehicle 0.3% dosed once daily for the prevention and treatment of ocular pain as assessed by the Investigator 14 days after cataract extraction.
- Nevanac dosed 3 times daily is superior to Nevanac Vehicle dosed 3 times daily for the prevention and treatment of ocular pain as assessed by the Investigator 14 days after cataract extraction.

#### **Supportive Efficacy Objectives:**

- To further characterize the efficacy of Nepafenac 0.3% relative to the comparator groups at days 1, 3, and 7 for the primary and secondary endpoints, and at all on-therapy visits for assessment of treatment failures.

#### **Safety Objectives:**

- To demonstrate that topical ocular use of Nepafenac 0.3% dosed once daily for up to 14 days after cataract extraction is safe and well tolerated, consistent with the established safety profile of Nevanac.

### General Study Design

This was a double-masked, parallel-group, multicenter, vehicle and active-controlled, randomized study. Patients who met the entrance criteria were randomized 4:1 to Nepafenac 0.3% or Nepafenac Vehicle 0.3%, and 4:1 to Nevanac or Nevanac Vehicle.

Treatment	Enrollment by Treatment Group
Nepafenac 0.3% QD	800
Nevanac TID	800
Nepafenac Vehicle 0.3% QD	200
Nevanac Vehicle TID	200
<b>Total Enrollment</b>	2000

All patients had a preoperative Screening/Baseline examination prior to cataract surgery. Patients were eligible for surgery within 2 days of the baseline evaluation if they had neither used topical ocular or systemic NSAIDs within the 7 days before surgery nor topical ocular or systemic steroids within the 14 days before surgery. Patients were instructed not to use systemic NSAIDs and steroids until after the Day 14 postoperative examination/Exit Visit. Patients were allowed to use acetaminophen (paracetamol) for analgesia during the study.

After receiving the test article at the Baseline Visit (2 days to 6 weeks) prior to surgery, patients were dosed in the operative eye 1 day before surgery, on the day of surgery, and daily for 14 days postoperatively. An additional dose (1 drop) was administered between 30 to 120 minutes prior to surgery by an individual who was not required to be masked to study treatment. Postoperative examinations were conducted on Day 1, Day 3, Day 7, and Day 14.

Patients underwent cataract extraction by phacoemulsification with implantation of posterior chamber intraocular lens into the capsular bag. Investigators used their standard surgical methods, regimen of preoperative, operative, and postoperative medications with the exception of NSAID or steroid usage. Any other medications that were used and their frequency of use remained standard and were not modified except as necessary for the patient's safety. Surgical techniques and medications were recorded for each study patient.

**Reviewer's Comments:** *The study design is acceptable.*

### **C-11-003: 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 after Cataract Surgery**

#### **Primary Efficacy Objectives:**

- To demonstrate that Nepafenac 0.3% is superior to Nepafenac vehicle 0.3% each used once daily, for the prevention and treatment of ocular inflammation with respect to cure rate 14 days after cataract extraction.

#### **Secondary Efficacy Objectives:**

- To demonstrate that Nepafenac 0.3% is superior to Nepafenac 0.1% each used once daily, for the prevention and treatment of ocular inflammation with respect to cure rate 7 days after cataract extraction.

#### **Supportive Efficacy Objectives:**

- To describe ocular inflammation and pain 1, 3, 7, and 13 days after cataract extraction for Nepafenac 0.3%, Nepafenac 0.1%, and Nepafenac Vehicle 0.3% each used once daily.

#### **General Study Design**

This was a prospective, double-masked, parallel-group, multicenter, vehicle and active-controlled, randomized study. Patients who met the entrance criteria were randomized 2:2:1 to Nepafenac 0.3%, Nepafenac 0.1%, or Nepafenac Vehicle 0.3%, dosed once daily.

<b>Treatment</b>	<b>Enrollment by Treatment Group</b>
Nepafenac 0.3% QD	500
Nepafenac 0.1% QD	500
Nepafenac Vehicle 0.3% QD	250
<b>Total Enrollment</b>	1250

All patients had a preoperative Screening/Baseline examination prior to cataract surgery. Patients were eligible for surgery within 2 days of the baseline evaluation if they had neither used topical ocular or systemic NSAIDs within the 7 days before surgery nor topical ocular or systemic steroids within the 14 days before surgery. Patients were instructed not to use systemic NSAIDs and steroids until after the Day 14 postoperative examination/Exit Visit. Patients were allowed to use acetaminophen (paracetamol) for analgesia during the study.

After receiving the test article at the Baseline Visit (2 days to 6 weeks) prior to surgery, patients were dosed in the operative eye 1 day before surgery, on the day of surgery, and daily for 14 days postoperatively. An additional dose (1 drop) was administered

between 30 to 120 minutes prior to surgery by an individual who was not required to be masked to study treatment. Postoperative examinations were conducted on Day 1, Day 3, Day 7, and Day 14. The Day 3 and Day 7 slit lamp examinations were to be performed after 10:00 am to ensure that patients' dosing had occurred at least 12 hours prior to their examination.

Patients underwent cataract extraction by phacoemulsification with implantation of posterior chamber intraocular lens into the capsular bag. Investigators used their standard surgical methods, regimen of preoperative, operative, and postoperative medications with the exception of NSAID or steroid usage. Any other medications that were used and their frequency of use remained standard and were not modified except as necessary for the patient's safety. Surgical techniques and medications were recorded for each study patient.

### Investigational Products

Test Article	Lot Numbers	Formulation Identification Numbers
Nepafenac 0.3%	11-501256-1	115535
Nepafenac 0.1%	11-501263-1	105022
Nepafenac Vehicle 0.3%	10-501165-1	104285

**Reviewer's Comments:** *The study design is acceptable.*

### Studies C-09-055 and C-11-003

#### Choice of Endpoints

##### Assessment of Aqueous Cells and Flare

Aqueous cells and flare are the hallmark of ocular inflammation and have been the basis of evaluating the primary efficacy of this class of medicinal product. As is the standard in ophthalmic practice, inflammation was evaluated using slit-lamp biomicroscopy. Aqueous cells were graded by the investigator using a 5-point scale and aqueous flare was graded on a 4-point scale. These are the same scales used previously for clinical trials in the development of Nevanac, as well as, in previous post-cataract inflammation trials. Currently marketed topical ocular anti-inflammatory products have successfully demonstrated clinical efficacy using these scales for aqueous cells and flare. The scales were designed to distinguish between the various degrees of anterior segment inflammation encountered following cataract surgery and to describe when inflammation is cured (i.e., a score of 0 for cells indicates that no cells are observed and a score of 0 for flare indicates that no flare is observed).

#### Efficacy Endpoints

In the submitted efficacy studies (C-09-055 and C-11-003), the primary and secondary efficacy endpoints were based on clinical evaluations of the following variables: aqueous cells, aqueous flare, aqueous cells + flare score, and ocular pain. Aqueous

cells and flare scores served as the basis for the primary efficacy endpoint, cure when it was defined as the absence of inflammation (i.e., cells score + flare score = 0).

**Grading Scales for Aqueous Cells and Flare**

<b>Aqueous Cells</b>	Determined using a narrow slit beam (0.5 width at least 8 mm length) at maximum luminance. Pigment and red blood cells are to be ignored. 0   None 1   1 to 5 cells 2   6 to 15 cells 3   16 to 30 cells 4   Greater than 30 cells
<b>Aqueous Flare</b>	Determined using a narrow slit beam (0.5 mm width at least 8 mm length) at maximum luminance. 0   No visible flare when compared with the normal eye. 1   Mild – Flare visible against dark pupillary background but not visible against iris background. 2   Moderate – Flare is visible with the slit-lamp beam aimed onto the iris surface as well as the dark pupillary background. 3   Severe – Very dense flare. May also present as a “hazy” appearance of anterior segment structures when viewed with low power magnification of the slit-lamp. Presents as pronounced Tyndall effect.

**Assessment of Ocular Pain**

Subjective assessment of ocular pain, rated on a 6-point scale, was evaluated in the two efficacy studies (C-09-055 and C-11-003). The scales were designed to differentiate between the various degrees of ocular pain that may be encountered following cataract surgery and also served as an element in determining treatment failures.

### Grading Scales for Ocular Pain

<b>Ocular Pain</b> (Investigator's Assessment)	A positive sensation of the eye, including foreign body sensation, stabbing, throbbing or aching.
	0 None – absence of positive sensation
	1 Patient reports presence of mild sensation or discomfort typical of postoperative ocular surgery (e.g., diffuse or focal foreign body sensation, mild transient burning or stinging, etc.
	2 Mild – mild, tolerable aching of the eye
	3 Moderate – moderate or more prolonged aching sufficient to require the use of over-the-counter analgesics (e.g., acetaminophen)
	4 Moderately Severe – more prolonged aching requiring the use of an over-the-counter analgesic <i>other than</i> acetaminophen/paracetamol
5 Severe – Patient reports intense ocular, periocular or radiating pain (e.g., constant or nearly constant sharp stabbing pain, throbbing or aching, etc.) requiring prescription analgesics	

### Primary Efficacy Variable

The primary efficacy variable was the proportion of patients with cure at Day 14 in both studies.

Inflammation was assessed at each post surgical visit, scheduled for Days 1, 3, 7 and 14, and at the Early Exit Visit and any unscheduled visit. Cure was defined as a score of 0 for both aqueous cells and flare, where the 5-unit aqueous cells score ranged from 0 (none) to 4 (> 30 cells), and the 4-unit aqueous flare score ranged from 0 (no visible flare when compared with normal eye) to 3 (severe – very dense flare). It was possible for a patient to be considered a treatment failure for ocular pain and still have zero cells and zero flare; therefore, patients with pain scores of 4 or greater were not considered to be a cure even if they had a cells score and flare score = 0.

### Efficacy Variables

- The proportion of patients who were declared a cure, defined as a score of 0 for aqueous cells and a score of 0 for aqueous flare.
- The proportion of patients who were pain free, defined by ocular pain assessment score equals zero.
- The proportion of patients who were declared a treatment failure, defined as aqueous cells score  $\geq 3$  ( $\geq 16$  cells), aqueous flare score = 3 (severe), and/or ocular pain score  $\geq 4$  (moderately severe)
- The proportion of patients who were a clinical success, defined as cells score  $\leq 1$  (0-5 cells) and flare score = 0. This was an unplanned analysis.

### **Safety Variables**

- Adverse events (incidence of adverse events)
- Best-corrected visual acuity
- IOP
- Slit-lamp parameters (chemosis, bulbar conjunctival injection, corneal edema)
- Dilated fundus parameters (retina/macula/choroid, optic nerve)

The inclusion and exclusion criteria were the same in both clinical efficacy studies, C-09-055 and C-11-003.

### **Study Population**

#### **Inclusion Criteria**

1. Written protocol-specific informed consent was obtained prior to conducting any study procedures by patient or legally authorized representative of patient.
2. Men or women of any race, 18 years or older who were undergoing cataract extraction by phacoemulsification with the implantation of a posterior chamber intraocular lens.
3. Study eye of patient, in the Investigator's opinion, would have improvement in best-corrected visual acuity after surgery.

#### **Exclusion Criteria**

The key exclusion criteria utilized in the studies were implemented to ensure that patients had no baseline inflammation and that they did not receive any anti-inflammatory medication other than the assigned therapy.

1. Planned multiple procedures during cataract/IOL implantation surgery (e.g., trabeculectomy, corneal transplant). Note: A planned limbal relaxing incision may have been performed for the correction of astigmatism.
2. Use of topical, topical ocular, inhaled or systemic steroids within 14 days prior to surgery and through study exit.
3. Use of topical, topical ocular, inhaled or systemic steroids within 14 days prior to surgery and through study exit.
4. Use of a topical ophthalmic prostaglandin in the operative eye (e.g., travoprost, latanoprost, bimatoprost, tafluprost); Patients with a previous history of topical ophthalmic prostaglandin use must have discontinued at least 4 days prior to surgery and through study exit.
5. Any intraocular inflammation (aqueous cells or flare greater than Grad 0) or ocular pain greater than Grad 1 in the study eye that was present during the Baseline Visit
6. Previous ocular trauma to the operative eye (this included cataract and previous intraocular surgery, where a wound was created to gain access to the anterior or posterior segments; this did not include previous laser therapy without use of an incision)
7. A history of chronic or recurrent inflammatory eye disease (e.g., iritis, scleritis, uveitis, iridocyclitis, rubeosis iridis) in the operative eye

8. Patients who, in the opinion of the Investigator, were at increased risk of developing postoperative macular edema (e.g., diabetic retinopathy) in the operative eye
9. Uncontrolled glaucoma in the operative eye
10. Lens pseudoexfoliation syndrome with glaucoma or zonular compromise in the operative eye
11. Congenital ocular anomaly (e.g., aniridia, congenital cataract) in the operative eye
12. A visually nonfunctional fellow eye defined as a best-corrected visual acuity  $\leq$  35 ETDRS letters (20/200 Snellen equivalent) or worse
13. Participation in any other investigational drug or device study within 30 days before cataract surgery
14. Known or suspected allergy or hypersensitivity to NSAIDs, or to any component of the test article
15. Women of childbearing potential (those who were not surgically sterilized or post menopausal) may not have participated in the study if any of the following conditions existed:
  - a. they were breast-feeding;
  - b. they had a positive urine pregnancy test at screening;
  - c. they were not willing to undergo a urine pregnancy test upon entering or exiting the study;
  - d. they intended to become pregnant during the duration of the study, or;
  - e. they did not agree to use adequate birth control methods for the duration of the study (adequate birth control methods were: hormonal – oral, implantable, or injectable contraceptives; mechanical – spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device; or surgical sterilization of partner.

In addition, the Alcon Medical Monitor may have declared any patient ineligible for a valid medical reason.

**Reviewer's Comments:** *The Inclusion and Exclusion Criteria are acceptable.*

#### **Removal of Patients from Therapy or Assessment**

A discontinued patient was a study patient who received test article but did not complete the study. If a patient discontinued the study, all efforts were made to perform the exit procedures.

Patients may have been withdrawn in the following circumstances:

- Investigator determined that continuing in the study was not in the best interest of the patient; Alcon was notified of any decision by the Investigator to discontinue a patient for medical reasons; or patient chose to withdraw from the study at any time.
- If a patient returned on the day of surgery with an unopened bottle of test article, reported that he/she had not used the assigned test article, and his/her surgery could not be rescheduled, the patient was immediately exited

from the study. Patients who experienced a significant complication during surgery that, in the Investigator's opinion required the use of additional anti-inflammatory therapy, were discontinued from the study. If a patient used the assigned study medication and withdrew consent prior to a postoperative study visit, the patient was discontinued from the study.

- A patient presenting at any postoperative visit with a 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 was considered a treatment failure. Patients who were considered treatment failures at the Day 1 Visit or later discontinued using the investigational product and were discontinued from the study. Patients were then dispensed therapy (rescue medication) as deemed appropriate by the Investigator.

**Reviewer's Comments:** *Thus, patients who received rescue medication were counted as treatment failures. No separate accounting of patients who received rescue medication was made.*

### **Analysis**

Studies C-09-055 and C-11-003 were vehicle- and active comparator-controlled studies designed to demonstrate the efficacy of Nepafenac 0.3% dosed once daily for the prevention and treatment of pain and inflammation associated with cataract surgery. All patients who received study medication, had cataract surgery and returned for at least 1 scheduled postoperative visit were considered evaluable for the intent-to-treat (ITT) population of subjects.

### **Study C-09-055**

The statistical hypotheses tested in support of the primary efficacy objectives were:

- Nepafenac 0.3% dosed once daily is noninferior to Nevanac dosed 3 times daily for the prevention and treatment of ocular inflammation 14 days after cataract extraction.
- Nepafenac 0.3% dosed once daily is superior to Nepafenac Vehicle 0.3% dosed once daily for the prevention and treatment of ocular inflammation 14 days after cataract extraction.
- Nevanac dosed 3 times daily is superior to Nevanac vehicle dosed 3 times daily for the prevention and treatment of ocular inflammation 14 days after cataract extraction.

For comparison of the two nepafenac groups, a 2-tailed 95% confidence interval was calculated for the difference in cure rates (Nepafenac 0.3% minus Nevanac) using a test-based confidence interval based on the method of Yanagawa, Tango and Hiejima, a stratified version of the method Farrington and Manning. Differences in proportion that did not result in rejecting the null hypothesis that there is no treatment difference ( $\alpha= 0.05$ ) were included in the confidence interval. The noninferiority 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 noninferiority. Stratification was by Investigator to match the stratification used in the randomization process.

Statistical analyses, in general, utilized site as a stratification variable or as a parameter within the analysis model. Investigative sites with a small number of enrolled subjects were combined by geography (i.e., with other sites in the same state or region). For analysis purposes pseudo-site was used in place of investigative site.

Although the primary inference for noninferiority was based upon the ITT analysis data set, similar results from the PP analysis data set were used to assess the impact of protocol deviations.

#### *Justification of Non-Inferiority Margin*

The basis for the 10% margin was both statistical and clinical. This study was conducted in both the US and Europe; therefore, data from 2 previously conducted, confirmatory, vehicle-controlled Nevanac clinical trials conducted in the US and EU (C-03-32 and C-04-65, respectively) were used to obtain estimated cure rates for Nevanac and Nevanac vehicle and a 95% confidence interval for the difference.

Data from these two studies were used since they represented both a large vehicle-controlled confirmatory study (C-03-32) as well as a study with both vehicle and active controls (C-04-65). The cure rates observed in the combined studies were 65.8% (210/319) and 27.5% (85/309), respectively, for Nevanac and Nevanac vehicle, yielding a difference of 38.4% and a 95% confidence interval of 31.3% to 45.5%. The proposed noninferiority margin of 10 percentage points was less than one-third the lower confidence limit for the observed treatment difference between Nevanac and Nevanac vehicle. In addition, the proposed margin of 10 percentage points can be interpreted that to obtain 1 excess noncure, more than 10 patients must be treated. The margin is also justified by noting that the difference between Nevanac and Nevanac vehicle in prior comparisons is generally much greater than 10 percentage points. Thus, the choice of 10 percentage points was considered justified.

The analyses of the secondary variable, the Investigator's assessment of ocular pain, were analogous to the analyses described above for the primary endpoint, and included a noninferiority comparison of Nepafenac 0.3% to Nevanac, as well as comparisons of each nepafenac group to vehicle (same dosing frequency) to establish assay sensitivity and the efficacy of the investigational product. The noninferiority margin was 10 percentage points.

The supportive efficacy analyses of this study were to further characterize the efficacy of Nepafenac 0.3% relative to the comparator groups at Days 1, 3, and 7 for the primary and secondary endpoints, and at all on-therapy visits for assessment of treatment failures. The statistical hypotheses to be tested in support of the supportive efficacy objectives are analogous to those already reported for primary and secondary objectives.

**Reviewer's Comment:**

*Since this study includes vehicle arms, it is more appropriate to use the actual vehicle results instead of a cross study comparison.*

**Study C-11-003**

The primary efficacy objective of this study was to demonstrate the Nepafenac 0.3% is superior to Vehicle used once daily for the prevention and treatment of ocular inflammation with respect to cure 14 days after cataract extraction. The secondary objective of this study was to demonstrate that Nepafenac 0.3% is superior to Nepafenac 0.1% used once daily for the prevention and treatment of ocular inflammation with respect to cure 7 days after cataract extraction.

These analyses used Cochran-Mantel-Haenszel (CMH) tests controlling for investigative site to assess differences between treatment groups at alpha of 0.05. Stratification was by investigative site to match the stratification used in the randomization process. The cumulative percentage of patients with a cure at Day 7 was examined, with "cumulative" requiring that a patient who was judged to be cured at Day 7 must have remained cured at all subsequent visits. Additionally, the cumulative percentage of patients with a cure was summarized by treatment group at each scheduled visit, with "cumulative" requiring that a patient who was judged to be cured must have remained cured at all subsequent visits. In the event that a patient was a cure prior to day 14 and missed subsequent visits, a last observation carried forward (LOCF) approach was used; therefore, the patient was considered a cure at subsequent visits. The cumulative percentage with a score of 0 by component (cells and flare) was also summarized at each scheduled visit.

Statistical analyses, in general, utilized site as a stratification variable or as a parameter within the analysis model. Investigative sites with a small number of enrolled subjects were combined by geography (i.e., with other sites in the same state or region). For analysis purposes pseudo-site was used in place of investigative site. There were 4 sites in this study that enrolled a small number of patients. For analysis purposes, these sites were combined into 2 pseudo-sites as follows: 2449/1710 and 4734/1434.

Supportive efficacy included:

- proportion of patients who were declared a cure by visit
- proportion of patients who were pain-free by visit
- proportion of patients who were declared to be a treatment failure
- aqueous cells score at Days 1, 3, 7, and 14 (as a continuous variable)
- aqueous flare score at Days 1, 3, 7, and 14 (as a continuous variable)
- aqueous cells score plus aqueous flare score at Days 1, 3, 7, and 14 (as a continuous variable)

The supportive analyses of binomial data used CMH tests controlling for investigative site to assess differences between pairs of treatment groups. Stratification was by investigative site to match the stratification used in the randomization process.

#### **Determination of Sample Size**

A Fisher's exact test with a 0.05 two-sided significance level had 99% power to detect the difference between Nepafenac 0.3% Day 7 cure rate of 0.43 and Nepafenac 0.3% Vehicle Day 14 cure rate of 0.24 with sample sizes of 500 and 250, respectively. A Fisher's exact test with a 0.05 two-sided significance level had 91% power to detect the difference between Nepafenac 0.3% Day 7 cure rate of 0.38 and Nepafenac 0.1% Day 7 cure rate of 0.28 with the sample size in each group of 500.

Previous studies of Nepafenac in the same indication were used to predict cure rates in this study. In study C-02-53:

- Nepafenac 0.1% TID Day 14 cure rate was 46.4%
- Vehicle Day 14 cure rate was 24.1%
- Nepafenac 0.1% TID Day 7 cure rate was 37.5%
- Nepafenac 0.1% QD Day 7 cure rate was 18.8%

In several other studies (C-07-03, C-04-41, and C-04-65), cure rates were similar for Nepafenac 0.1% TID at Days 7 and 14, compared to those observed in study C-02-53. the assumptions above were consistent, or conservative, with these observed rates. Additionally, presuming that the cure rate for Nepafenac 0.1% TID and Nepafenac 0.3% QD were equal completed the assumptions.

**Schedule of Visits and Measurements for C-09-055 and C-11-003**

Study Activity	Screening /Baseline Examination -6 wks. to -2 days	Surgery (Day 0)	Postoperative				
			Day 1 (24 ± 8 hr.)	Day 3 (± 1 day)	Day 7 (± 2 day)	Day 14 (Day -1 to +5)	Early Exit <sup>4,5</sup>
Informed Consent Process	X						
Demographics	X						
Best Corrected Visual Acuity	X <sup>1</sup>		X <sup>2</sup>	X <sup>2</sup>	X	X	X
Slit-lamp Examination (corneal edema, bulbar conj. injxn, chemosis, inflammatory cells and flare)	X <sup>1</sup>		X	X	X	X	X
Ocular Pain Assessment	X		X	X	X	X	X
Goldmann Intraocular Pressure	X <sup>1</sup>		X	X	X	X	X
Dilated Fundus Exam	X <sup>1</sup>					X	X
Urine Pregnancy Test	X					X	X
Dispense Study Medication <sup>3</sup>	X						
Record Change in Concomitant Medications		X	X	X	X	X	X
Collect Study Medications						X	X
Record Adverse Events		X	X	X	X	X	X
Assess for Treatment Failure			X	X	X	X	X
Complete Exit Form <sup>4</sup>						X	X

1 Both eyes

2 A pinhole-corrected visual acuity may have been performed at Day 1 and Day 3.

3 Patient administered assigned study medication on Day -1 (1 day before surgery).

4 An Early Exit form was completed if the patient discontinued from the study at an earlier date.

**Reviewer's Comment:**            *Acceptable.*

**Study C-09-055: Listing of Principal Investigators and Numbers of Patients Randomized, and Included in the Intent-to-Treat (ITT) and Per Protocol (PP) Populations**

Inv. #	Primary Investigator Name/Address	# Patients Randomized <sup>a</sup>	ITT <sup>b</sup>	PP
5967	Ács, Tamás, MD Bács-Kiskun megyei Önkormányzat Hospital Nyíri út 38 H-6000, Kecskemét, Hungary	33	32	32
5920	Ahlberg, Peter, MD Department of Ophthalmology Falun Hospital SE-791 82, Falun, Sweden	23	23	22
5003	Andersen, Bo, MD CaphoMedocular Ostra Hamngatan 52 SE-411 09, Goteborg, Sweden	3	3	3
5442	Cable, Melissa, MD Discover Vision Centers 4741 S. Cochise Drive Independence, MO 64055	27	25	25
5921	Campos, Emilio C. MD Policlinico S. Orsola Malpighi Via Palagi, 9 Bologna, 40138, Italy	5	5	5
3904	Caplan, Michael, MD Berkeley Eye Center 3100 Wesleyan, Suite 400 Houston, TX 77027	8	6	6
3712	Christie, William, MD Scott & Christie & Assoc. PC 105 Brandt Drive, Suite 201, 202, & 204 Cranberry Township, PA 16066	80	75	75

<b>Inv. #</b>	<b>Primary Investigator Name/Address</b>	<b># Patients Randomized <sup>a</sup></b>	<b>ITT <sup>b</sup></b>	<b>PP</b>
2902	Cionni, Robert, MD The Eye Institute of Utah 755 East 3900 South Salt Lake City, UT 84107	39	38	38
5901	De La Chapa, Jorge, DO Medical Center Ophthalmology Associates 9157 Huebner Road San Antonio, TX78240	19	17	15
1931	Dirks, Monte, MD Black Hills Regional Eye Institue 2800 3 <sup>rd</sup> Street Rapid City, SD 57701	2	2	1
5303	Dixon, El-Roy, MD Dixon Eye Care 806 N. Jefferson Street Albany, GA 31701	30	30	26
1927	DuBiner, Harvey, MD Eye Care Centers Management Inc. Clayton Eye Center 1000 Corporate Center Drive, Suites 100 & 120 Morrow, GA 30260	44	41	37
5127	Fisher, Bret, MD The Eye Center of North Florida 2500 Martin Luther King Jr., Blvd. Panama City, FL 32405	60	57	57
3899	Fishman, Arthur, MD Eye Surgery Associates 603 North Flamingo Road, Suite 250 Pembroke Pines, FL 33028	46	45	43
5758	Fong, Raymond, MD Raymond Fong MD PC 109 Lafayette Street, 4 <sup>th</sup> Floor New York, NY 10013	90	84	83

<b>Inv. #</b>	<b>Primary Investigator Name/Address</b>	<b># Patients Randomized <sup>a</sup></b>	<b>ITT <sup>b</sup></b>	<b>PP</b>
3903	Foster, Gary, MD Eye Center of Northern Colorado PC 1725 East Prospect Road Fort Collins, CO 80525	46	43	42
3695	Grosinger, Les, MD Grosinger & Spigelman Grey Eye Surgeons PC 1750 Telegraph Road, Suite 205 Bloomfield Hills, MI 48302	2	2	2
5548	Johnson, Stark, MD Glaucoma Consultants of Colorado dba Specialty Eye Care 11960 Lioness Way, Suite 190 Parker, CO 80134	24	23	23
5848	Jong, Kevin, MD Houston Eye Associates 1919 N. Loop West, Suite 220 Houston, TX 77008	51	50	50
2449	Katzman, Barry, MD West Coast Eye Care Associates 6945 El Cajon Blvd San Diego, CA 92115	26	25	25
4702	Kerenyi, Agnes, MD Fovarosi Onkormanyzat Bajcsy Zsilinszky Hospital Maglodi ut 89-91 H-1106 Budapest, Hungary	15	11	9
4988	Kloess, Price, MD Alabama Vision Center 790 Montclair Road, Suite 100 Birmingham, AL 35213	50	50	49
5953	Kloos, Patrik, MD Kantonsspital St. Gallen Augenklini Rorschachertr 95 9700, St. Gallen, Switzerland	2	2	2

Clinical Review  
Rhea A. Lloyd, MD  
NDA 203-491  
Nepafenac ophthalmic suspension, 0.3%

<b>Inv. #</b>	<b>Primary Investigator Name/Address</b>	<b># Patients Randomized <sup>a</sup></b>	<b>ITT <sup>b</sup></b>	<b>PP</b>
1980	Kraff, Colman, MD Kraff Eye Institute 25 E. Washington, Suite 606 Chicago, IL 60602	16	15	15
970	Lehmann, Robert, MD Lehmann Eye Center 5300 North Street Nacodoches, TX 75965	90	89	88
5776	Logan, Andrew, MD Logan Ophthalmic Research LLC 7401 N. University Drive, Suite 201 Tamarac, FL 33321	20	19	17
3678	Lozier, Jeffrey, MD Physicians Independent Medical Group Arch Health Partners 15611 Pomerado Road, Suite 400 Poway, CA 92064	50	46	42
5962	Lundberg, Bjorn, MD Department of Ophthalmology Norrlands University Hospital, SE-901 85, Umea, Sweden	28	27	26
4824	Malhotra, Ranjan, MD Ophthalmology Associates 12990 Manchester Road, Suite 200 St. Louis, MO 63131	30	26	26
2034	Mauger, Thomas, MD Ohio State University Dept of Ophthalmology 915 Olentangy River Road, Suite 5000 Columbus, OH 43212	10	10	10
1434	Maxwell, W. Andrew, MD California Eye Institute 1360 Herndon, Suite 401 Fresno, CA 93720	27	26	25

<b>Inv. #</b>	<b>Primary Investigator Name/Address</b>	<b># Patients Randomized <sup>a</sup></b>	<b>ITT <sup>b</sup></b>	<b>PP</b>
3828	Modi, Satish, MD Alterman, Modi & Wolter 23 Davis Avenue Poughkeepsie, NY 12603	80	72	71
4526	Nardi, Marco, MD U.O. Oculistica Universitaria A.O.U.P. Nuovo Ospedale S. Chiara Presidio Ospedaliero di Cisanello Edificio 30 Via Paradisa 2 Pisa-Cisanello, 56124, Italy	4	4	4
4119	Nethery, David, MD Nethery Eye Associates 6551 Harris Parkway, Suite 200 Fort Worth, TX 76132	80	76	71
3844	Ori, Zsolt, MD Vaszary Kolos Hospital Ear-Nose and Throat-Ophthalmology Petofi Sandor u. 26-28 H-2500 Esztergom, Hungary	11	11	11
5727	Panzo, Gregory, MD Mid Florida Eye Center, PA 17560 West US Highway 441 Mt. Dora, FL 32757	23	19	17
5966	Papp, Andras, MD Semmelweis University Tomo u. 25-29 H-1083, Budapest, Hungary	5	4	4
3025	Paul, Matthew, MD Danbury Eye Physicians & Surgeons PC 69 Sand Pit Road, Suite 101 Danbury, CT 06810	3	3	3
5161	Pennell, Jeffrey, MD Eye Care Assoc. of East Texas 2440 E. Fifth Street Tyler, TX 75701	22	22	21

<b>Inv. #</b>	<b>Primary Investigator Name/Address</b>	<b># Patients Randomized <sup>a</sup></b>	<b>ITT <sup>b</sup></b>	<b>PP</b>
4865	Perkins, Scott, MD Barnet Dulaney Perkins Eye Center 4800 N. 22 <sup>nd</sup> Street Phoenix, AZ 85016	20	20	19
5954	Philipson, Bo, MD Valihallas Eyeclinic AB Odengatan 1 SE-114 24, Stockholm, Sweden	20	20	20
1440	Raizman, Michael, MD Ophthalmic Consultants of Boston 50 Staniford Street, Suite 600 Boston, MA 02114	13	13	13
3839	Ratiglia, Roberto, MD Clinica Oculistica, Fondazione IRCCS Ca Granda – Ospedale Maggiore Policlinico Via Manfredo Fanti 6 20122 – Milano, Italy	9	9	9
5180	Rauchman, Steven, MD North Valley Eye Medical Group, Inc. 11550 Indian Hills Road, Suite 341 Mission Hills, CA 91345	26	22	21
3747	Reiser, Harvey, MD Eye Care Specialists 703 Rutter Ave. Kingston, PA 18704	80	79	75
3733	Rice, Robert, MD R&R Eye Research LLC 5430 Fredericksburg Road, Suite 100 San Antonio, TX 78229	29	27	23
5541	Roel, Lawrence, MD Eastside Westside Research Center 1413 John B. White, Sr., Blvd., Suite D Spartanburg, SC 29306	80	77	77

<b>Inv. #</b>	<b>Primary Investigator Name/Address</b>	<b># Patients Randomized <sup>a</sup></b>	<b>ITT <sup>b</sup></b>	<b>PP</b>
1806	Sall, Kenneth, MD Sall Eye Research Medical Center Inc. 11423 187 <sup>th</sup> Street, Suite 200 Artesia, CA 90701	24	23	23
5957	Sandor Jr., Charles, MD Clinical Research Center of Wheaton Eye Clinic, LLC 2015 N. Main Street Wheaton, IL 60187	46	46	46
1238	Scoper, Stephen, MD Virginia Eye Consultants 241 Corporate Boulevard Norfolk, VA 23502	18	18	18
5444	Segal, Zachary, MD MedEye Associates 5950 Sunset Drive Miami, FL 33143	40	35	34
3435	Seidenberg, Jonathan, MD Seidenberg Protzko Eye Associates 520 Upper Chesapeake Drive, Suite 401 Bel Air, MD 21014	24	24	23
5922	Sharkawi, Eamon, MD Hopital Ophtalmique Jules-Gonin Universite de Lausanne Av. de France 15 1004 Lausanne, Switzerland	16	14	13
1710	Shulman, David, MD David G. Shulman, MD, PA 999 E. Basse, Suite 127 San Antonio, TX 78209	14	13	1
3807	Silverstein, Steven, MD Silverstein Eye Centers 4140 Blue Ridge Boulevard, Suite 1000 Kansas City, MO 64133	60	58	56

<b>Inv. #</b>	<b>Primary Investigator Name/Address</b>	<b># Patients Randomized <sup>a</sup></b>	<b>ITT <sup>b</sup></b>	<b>PP</b>
3988	Smith, Stephen, MD Eye Associates of Fort Myers 4225 Evans Ave. Fort Myers, FL 33901	27	27	26
4915	Sohajda, Zoltan, MD Kenezy Hospital Bartok Belau t 2-26 H-4043, Debrecen, Hungary	32	30	28
3626	Tepedino, Michael, MD Cornerstone Eye Care 307 N. Lindsay Street Highpoint, NC 27262	50	48	47
3351	Thompson, Vance, MD Vance Thompson Vision 1310 West 22 <sup>nd</sup> Street Sioux Falls, SD 57105	20	20	20
2353	Thorne, George, MD Eye Physicians of Austin 5011 Burnet Road Austin, TX 78756	40	38	37
5955	Traverso, Carlo Enrico, MD Azienda Opedaliero Univesitaria San Martino V. le Benedetto XV, 5 Genova, 16132, Italy	15	15	14
5660	Tsorbatzoglou, Alexis, MD Josa Andras Hospital Ophthalmology Department Szent Istvan str. 68 11-4400, Nyiregyhaza, Hungary	47	45	45
4734	Vold, Steven, MD Boozman-Hof Regional Clinic, PA 3737 West Walnut Street Rogers, AR 72756	30	29	29

Inv. #	Primary Investigator Name/Address	# Patients Randomized <sup>a</sup>	ITT <sup>b</sup>	PP
1007	Walters, Thomas, MD Texan Eye, PA 5717 Balcones Drive Austin, TX 78731	100	99	98
3865	Wood, John, MD Vistar Eye Center 375 Hernbarger Rd. Roanoke, VA 24012	16	15	14
	Total	2120	2022	1962

<sup>a</sup> Includes those patients who were consented, provided study medication and **did not dose** (i.e., 78 patients were excluded from the Safety, ITT and PP analyses because the test article was not used)

<sup>b</sup> All patients who were randomized with at least 1 on therapy postoperative assessment (including those who discontinued as treatment failures).

<sup>c</sup> Includes all patients included in the ITT analysis set who met all inclusion/exclusion criteria that may have affected efficacy assessments, took test article according to treatment assignment, and had a visit at Day 14 or discontinued study as a treatment failure.

**Study C-11-003: Listing of Principal Investigators and Numbers of Patients Randomized, and Included in the Intent-to-Treat (ITT) and Per Protocol (PP) Populations**

Inv. #	Primary Investigator Name/Address	# Patients Randomized <sup>a</sup>	ITT <sup>b</sup>
5442	Cable, Melissa, MD Discover Vision Centers 4741 S. Cochise Drive Independence, MO 64055	37	33
3712	Christie, William, MD Scott & Christie, MD 105 Brandt Drive, Suite 201 Cranberry Township, PA 16066	69	68

<b>Inv. #</b>	<b>Primary Investigator Name/Address</b>	<b># Patients Randomized <sup>a</sup></b>	<b>ITT <sup>b</sup></b>
2902	Cionni, Robert, MD The Eye Institute of Utah 755 East 3900 South Salt Lake City, UT 84107	23	20
5127	Fisher, Bret, MD The Eye Center of North Florida 2500 Martin Luther King Jr. Blvd Panama City, FL 32405	60	58
3899	Fishman, Arthur, MD Eye Surgery Associates 603 North Flamingo Road, Suite 250 Pembroke Pines, FL 33028	27	25
5758	Fong, Raymond, MD 109 Lafayette Street, 4 <sup>th</sup> Floor New York, NY 10013	70	62
3903	Foster, Gary, MD Eye Center of Northern Colorado 1725 East Prospect Road Fort Collins, CO 80525	26	22
5548	Johnson, Stark, MD Glaucoma Consultants of Colorado DBA Specialty Eye Care 11960 Lioness Way, Suite 190 Parker, CO 80134	12	12
5848	Jong, Kevin, MD Houston Eye Associates 2855 Gramercy Street Houston, TX 77025	51	49
2449	Katzman, Barry, MD West Coast Eye Care Associates 6945 El Cajon Blvd. San Diego, CA 92115	8	6

<b>Inv. #</b>	<b>Primary Investigator Name/Address</b>	<b># Patients Randomized <sup>a</sup></b>	<b>ITT <sup>b</sup></b>
4988	Kloess, Price, MD Alabama Vision Center 790 Montclair Road, Suite 100 Birmingham, AL 35213	33	32
970	Lehmann, Robert, MD Lehmann Eye Center 5300 North Street Nacogdoches, TX 75965	73	68
3678	Lozier, Jeffrey, MD Arch Health Partners 15611 Pomerado Road, Suite 400 Poway, CA 92064	25	23
4824	Malhotra, Ranjan, MD Ophthalmology Associates 12990 Manchester Road, Suite 200 St. Louis, MO 63131	49	46
1434	Maxwell, W. Andrew, MD PhD California Eye Institute 1360 East Herndon Avenue, Suite 401 Fresno, CA 93720	10	10
6192	Milstein, Bernard, MD The Eye Clinic of Texas 1100 Gulf Freeway, Suite 114 League City, TX 77573	45	39
6216	Mitchell, Paul, MD Marietta Eye Clinic 895 Canton Rd. Marietta, GA 30060	32	31
3828	Modi, Satish, MD Alterman, Modi & Wolter 23 Davis Avenue Poughkeepsie, NY 12603	60	56

<b>Inv. #</b>	<b>Primary Investigator Name/Address</b>	<b># Patients Randomized <sup>a</sup></b>	<b>ITT <sup>b</sup></b>
4119	Nethery, David, MD Nethery Eye Associates 6551 Harris Parkway, Suite 200 Fort Worth, TX 76132	70	64
5727	Panzo, Gregory, MD Mid Florida Eye Center, PA 17560 West US Highway 441 Mt. Dora, FL 32757	24	22
5161	Pennell, Jeffrey, MD EyeCare Associates of East Texas 2440 E. Fifth Street Tyler, TX 75701	12	11
5180	Rauchman, Steven, MD North Valley Eye Medical Group, Inc. 11550 Indian Hills Road, Suite 341 Mission Hills, CA 91345	19	17
3747	Reiser, Harvey, MD Eye Care Specialists 703 Rutter Avenue Kingston, PA 18704	55	55
3733	Rice, Robert, MD Rand R Eye Research, LLC 5430 Fredericksburg Road, Suite 100 San Antonio, TX 78229	28	27
5541	Roel, Lawrence, MD, PhD Eastside Westside Research Center 1413 John B. White Sr. Blvd Suite G Spartanburg, SC 29306	68	65
5957	Sandor, Charles, MD Clinical Research Center of Wheaton Eye Clinic, LLC 2015 N. Main Street Wheaton, IL 60187	49	43

<b>Inv. #</b>	<b>Primary Investigator Name/Address</b>	<b># Patients Randomized <sup>a</sup></b>	<b>ITT <sup>b</sup></b>
5444	Segal, Zachary, MD MedEye Associates 5950 Sunset Drive Miami, FL 33143	53	47
3435	Seidenberg, Jonathan, MD Seidenberg Protzko Eye Associates 520 Upper Chesapeake Drive, Suite 401 Bel Air, MD 21014	19	19
1710	Shulman, David, MD, PA 999 E. Basse, Suite 127 San Antonio, TX 78209	8	8
3807	Silverstein, Steven, MD Silverstein Eye Centers 4240 Blue Ridge Blvd., Suite 1000 Kansas City, MO 64133	32	29
3988	Smith, Stephen, MD Eye Associates of Fort Myers 4225 Evans Ave. Fort Myers, FL 33901	13	12
3626	Tepedino, Michael, MD Cornerstone Eye Care 307 N. Lindsay Street Highpoint, NC 27262	38	37
3351	Thompson, Vance, MD Sanford Clinic Vance Thompson Vision 1310 West 22 <sup>nd</sup> Street Sioux Falls, SD 57105	21	20
2353	Thorne, George, MD Eye Physicians of Austin 5011 Burnet Road Austin, TX 78756	18	18

Inv. #	Primary Investigator Name/Address	# Patients Randomized <sup>a</sup>	ITT <sup>b</sup>
4734	Vold, Steven, MD Boozman Hof Regional Eye Center 3737 West Walnut Street Rogers, AR 72756	8	8
1007	Walters, Thomas, MD Texas Eye, PA 5717 Balcones Drive Austin, TX 78731	71	70
3865	Wood, John, MD Vistar Eye Center 375 Hershberger Rd. Roanoke, VA 24012	26	25
	<b>Total</b>	<b>1342</b>	<b>1257</b>

**Reviewer's Comment:**

*Thirty-five of the 37 investigators in Study C-11-003 were also investigators in Study C-09-055. Twenty-six of the 35 investigators participated in the studies concurrently (concurrent time period ranging from 1 day to 41 days).*

## 6 Review of Efficacy

### Efficacy Summary

#### 6.1 Indication

The proposed indication for nepafenac ophthalmic suspension, 0.3% is for the treatment of pain and inflammation associated with cataract surgery.

##### 6.1.1 Methods

All submitted clinical study reports, clinical protocols and relevant literature reports were reviewed. The submitted clinical study reports and protocols for the studies (C-09-055 and C-11-003) were reviewed. The submitted study reports for studies C-09-055 and C-11-003 form the basis for the majority of this application.

The entire application was submitted in eCTD format.

An electronic literature search was performed to supplement the review, and no new information was found.

##### 6.1.2 Demographics

###### 6.1.2.1 Study C-09-055

**Table 6.1.2-1 Baseline Demographics and Characteristics  
Intent to Treat Population  
Study C-09-055**

Demographic	Nepafen. 0.3% N=807 n (%)	Nevanac N=813 n (%)	Nepafen. vehicle 0.3% N=197 n(%)	Nevanac Vehicle N=205 n (%)	Total N=2022 n (%)
Age (yr)					
Mean	68.7	68.8	69.8	68.9	68.9
SD	9.08	9.31	9.31	9.37	9.22
Min	32	20	38	38	20
Max	89	90	92	90	92

Demographic	Nepafen. 0.3% N=807 n (%)	Nevanac N=813 n (%)	Nepafen. vehicle 0.3% N=197 n(%)	Nevanac Vehicle N=205 n (%)	Total N=2022 n (%)
< 65	233 (28.9)	220 (27.1)	51 (25.9)	55 (26.8)	559 (27.6)
≥ 65	574 (71.1)	593 (72.9)	146 (74.1)	150 (73.2)	1463 (72.4)
<b>Age group (yr)</b>					
< 65	233 (28.9)	220 (27.1)	51 (25.9)	55 (26.8)	559 (27.6)
≥ 65 - < 75	355 (44.0)	361 (44.4)	77 (39.1)	91 (44.4)	884 (43.7)
≥ 75 - < 85	204 (25.3)	217 (26.7)	64 (32.5)	54 (26.3)	539 (26.7)
≥ 85 - < 95	15 (1.9)	15 (1.8)	5 (2.5)	5 (2.4)	40 (2.0)
<b>Sex</b>					
Male	342 (42.4)	355 (43.7)	79 (40.1)	90 (43.9)	866 (42.8)
Female	465 (57.6)	458 (56.3)	118 (59.9)	115 (56.1)	1156 (57.2)
<b>Race</b>					
White	708 (87.7)	702 (86.3)	170 (86.3)	175 (85.4)	1755 (86.8)
Black or African American	59 (7.3)	59 (7.3)	17 (8.6)	17 (8.3)	152 (7.5)
Asian American	36 (4.5)	48 (5.9)	10 (5.1)	12 (5.9)	106 (5.2)
American Indian or Alaska Native	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Multiracial	1 (0.1)	2 (0.2)	0 (0.0)	1 (0.5)	4 (0.2)
Other	2 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)	4 (0.2)
<b>Iris Color</b>					
Brown	379 (47.0)	373 (45.9)	83 (42.1)	93 (45.4)	928 (45.9)
Hazel	105 (13.0)	97 (11.9)	26 (13.2)	23 (11.2)	251 (12.4)
Green	67 (8.3)	61 (7.5)	15 (7.6)	13 (6.3)	156 (7.7)
Blue	236 (29.2)	267 (32.8)	70 (35.5)	73 (35.6)	646 (31.9)
Grey	14 (1.7)	12 (1.5)	1 (0.5)	2 (1.0)	29 (1.4)
Other	6 (0.7)	3 (0.4)	2 (1.0)	1 (0.5)	12 (0.6)

N is the number of patients with non-missing postsurgery data.  
n is the number of patients with the demographic characteristic  
% is calculated as (n/N)\*100

6.1.2.2 Study C-11-003

**Table 6.1.2-2 Baseline Demographics and Characteristics  
Intent to Treat Population  
Study C-11-003**

Demographic	Nepafenac 0.3% N=512 n (%)	Nepafenac 0.1% N=493 n (%)	Nepafenac vehicle 0.3% N=252 n(%)	Total N=1257 n (%)
Age (yr)				
Mean	69.3	69.4	69.3	69.3
SD	9.26	9.15	9.60	9.28
Min	35	21	27	21
Max	92	91	94	94
< 65	130 (25.4)	120 (24.3)	72 (28.6)	322 (25.6)
≥ 65	382 (74.6)	373 (75.7)	180 (71.4)	935 (74.4)
Age group (yr)				
< 65	130 (25.4)	120 (24.3)	72 (28.6)	322 (25.6)
≥ 65 - < 75	220 (43.0)	230 (46.7)	108 (42.9)	558 (44.4)
≥ 75 - < 85	149 (29.1)	131 (26.6)	63 (25.05)	343 (27.3)
≥ 85 - < 95	13 (2.5)	12 (2.4)	9 (3.6)	34 (2.7)
Sex				
Male	230 (44.9)	192 (38.9)	110 (43.7)	532 (42.3)
Female	282 (55.1)	301 (61.1)	142 (56.3)	725 (57.7)
Race				
White	446 (87.1)	416 (84.4)	219 (86.9)	1081 (86.0)
Black or African American	40 (7.8)	37 (7.5)	17 (6.7)	94 (7.5)
Asian American	26 (5.1)	37 (7.5)	15 (6.0)	78 (6.2)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
American Indian or Alaska Native	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Other	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.2)
Iris Color				

Demographic	Nepafenac 0.3% N=512 n (%)	Nepafenac 0.1% N=493 n (%)	Nepafenac vehicle 0.3% N=252 n(%)	Total N=1257 n (%)
Brown	237 (46.3)	226 (45.8)	121 (48.0)	584 (46.5)
Hazel	67 (13.1)	73 (14.8)	37 (14.7)	177 (14.1)
Green	32 (6.3)	41 (8.3)	20 (7.9)	93 (7.4)
Blue	170 (33.2)	146 (29.6)	70 (27.8)	386 (30.7)
Grey	4 (0.8)	7 (1.4)	4 (1.6)	15 (1.2)
Other	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.2)

N is the number of patients with non-missing postsurgery data.  
n is the number of patients with the demographic characteristic  
% is calculated as (n/N)\*100

### 6.1.3 Subject Disposition

#### Data Sets Analyzed

**Safety Data Set** – all patients who received exposure to study medication or potential exposure to study medication (i.e., patients who discontinued the study before the surgery visit but returned an opened study medication bottle or who failed to return study medication). No imputation was performed for missing data due to patient discontinuation or missed visits.

**Intent-to-Treat Data Set** – all randomized patients with at least 1 on-therapy postoperative assessment (including those who discontinued due to treatment failure).

**Per Protocol Data Set** – all patients who received study medication, had at least 1 scheduled on-therapy visit, satisfied pre-randomization inclusion /exclusion criteria, and did not have protocol deviations that, in the opinion of the Medical Monitor, would impact the efficacy data.

Patient evaluability was established prior to breaking the code for masked treatment assignment. Primary inferences were based upon the ITT data set.

6.1.3.1 Study C-09-055

**Study C-09-055 – All Enrolled**

Patient Status	Nepafenac 0.3% N=851 n(%)	Nevanac N=845 n(%)	Nepafenac Vehicle 0.3% N=211 n(%)	Nevanac Vehicle N=213 n(%)	Total N=2120 n(%)
Randomized	851 (100.0)	845 (100.0)	211 (100.0)	213 (100.0)	2120 (100)
Completed	763 (89.7)	759 (89.8)	110 (52.1)	120 (56.3)	1752 (82.6)
Discontinued	88 (10.3)	86 (10.2)	101 (47.9)	93 (43.7)	368 (17.4)

**Analysis Data Sets - Study C-09-055**

Patient Group	Number of Patients Evaluable for Analysis				Number of Patients Excluded from Analysis			
	Nepafen. 0.3%	Nevanac	Nepafen. 0.3% vehicle	Nevanac vehicle	Nepafen. 0.3%	Nevanac	Nepafen. 0.3% vehicle	Nevanac vehicle
Safety:	817	819	200	206	34	26	11	7
Intent -to-Treat (ITT):	807	813	197	205	10	6	4	0
Per Protocol (PP):	788	787	193	194	19	26	4	11

**Reviewer's Comment:** *Seventy eight patients were excluded from the Safety, ITT and PP analysis populations because the study drug was not used. Twenty additional patients were excluded from the ITT and PP data sets because they were dispensed study drug, but were discontinued on the day of surgery. Thus, there was no on-therapy follow up efficacy data collected.*

6.1.3.2 Study C-11-003

**Study C-11-003 – All Enrolled**

Patient Status	Nepafenac 0.3% N=540 n(%)	Nepafenac 0.1% N=534 n(%)	Nepafenac Vehicle 0.3% N=268 n(%)	Total N=1342 n(%)
Randomized	540 (100.0)	534 (100.0)	268 (100.0)	1342 (100)
Treated	522 (96.7)	506 (94.8)	254 (94.8)	1282 (95.5)
Completed	475 (88.0)	458 (85.8)	121 (45.1)	1054 (78.5)
Discontinued	65 (12.0)	76 (14.2)	147 (54.9)	288 (21.5)

**Patient Population for Study C-11-003**

Patient Group	Number of Patients Evaluable for Analysis			Number of Patients Excluded from Analysis		
	Nepafenac 0.3%	Nepafenac 0.1%	Nepafenac 0.3% vehicle	Nepafenac 0.3%	Nepafenac 0.1%	Nepafenac 0.3% vehicle
<b>Safety:</b>	522	506	254	18	28	14
<b>Intent –to-Treat (ITT):</b>	512	493	252	10	13	2

**Reviewer’s Comment:** *No Per Protocol population was analyzed for Study C-11-003.*

**Reasons for Study Discontinuation  
All Enrolled - Study C-09-055**

Primary Reason for Study Discontinuation	Nepafenac 0.3% N=851	Nevanac N=845	Nepafenac Vehicle 0.3 % N=211	Nevanac Vehicle N=213	Total N=2120
<b>Total n(%)</b>	<b>88 (10.3)</b>	<b>86 (10.2)</b>	<b>101 (47.9)</b>	<b>93 (43.7)</b>	<b>368 (17.4)</b>
Adverse event	15 (1.8)	17 (2.0)	9 (4.3)	6 (2.8)	<b>47 (2.2)</b>
Lost to follow-up	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	<b>1 (0.0)</b>
Patient's Decision Unrelated to an Adverse Event	5 (0.6)	0 (0.0)	2 (0.9)	0 (0.0)	<b>7 (0.3)</b>
Noncompliance	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	<b>1 (0.0)</b>
Treatment failure	25 (2.9)	32 (3.8)	69 (32.7)	64 (30.0)	<b>190 (9.0)</b>
Protocol Violation	4 (0.5)	5 (0.6)	1 (0.5)	2 (0.9)	<b>12 (0.6)</b>
Patient Did Not Use Study Medication	34 (4.0)	26 (3.1)	11 (5.2)	7 (3.3)	<b>78 (3.7)</b>
Other	5 (0.6)	4 (0.5)	9 (4.3)	14 (6.6)	<b>32 (1.5)</b>

**Reasons for Study Discontinuation  
All Enrolled - Study C-11-003**

Primary Reason for Study Discontinuation	Nepafenac 0.3% N=540	Nepafenac 0.1% N=534	Nepafenac Vehicle 0.3 % N=268	Total N=1342
<b>Total n(%)</b>	<b>65 (12.0)</b>	<b>76 (14.2)</b>	<b>147 (54.9)</b>	<b>288 (21.5)</b>
Adverse event	16 (3.0)	11 (2.1)	6 (2.2)	<b>33 (2.5)</b>
Patient's Decision Unrelated to an Adverse Event	1 (0.2)	1 (0.2)	2 (0.7)	<b>4 (0.3)</b>
Noncompliance	2 (0.4)	3 (0.6)	0 (0.0)	<b>5 (0.4)</b>
Treatment failure	19 (3.5)	19 (3.6)	101 (37.7)	<b>139 (10.4)</b>
Protocol Violation	2 (0.4)	4 (0.7)	2 (0.7)	<b>8 (0.6)</b>
Patient Did Not Use Study Medication	18 (3.3)	28 (5.2)	14 (5.2)	<b>60 (4.5)</b>
Other	75 (1.3)	10 (1.9)	22 (8.2)	<b>39 (2.9)</b>

**Reviewer's Comment:** *Approximately 50% of patients in the vehicle groups discontinued the study prior to study completion.*

*Treatment failure was the most frequent reason for study discontinuation in both studies. Treatment failure included patients who received rescue medication at any post-operative visit.*

**Protocol Deviations - Study C-09-055  
Randomized Subjects**

Deviation	Nepafenac 0.3% N=851	Nevanac N=845	Nepafenac Vehicle 0.3% N=211	Nevanac Vehicle N=213
Medication was not used. There was no postoperative efficacy data available	33	27	11	7
Dispensed study drug, but discontinued on day of surgery. No on-therapy follow-up. <sup>1</sup>	10	6	3	1
Use of disallowed medication	19	25	5	11
Not compliant with study drug dosing regimen	7	10	1	1
Clinical Study Monitor / Study Staff inadvertently unmasked	8	5	0	0
Day 14/ Early Exit Visit performed outside protocol window	7	4	0	1
Inclusion/ exclusion criteria not met	3	1	0	0

<sup>1</sup> Two patients were excluded because they were enrolled twice. Patient 4915.9802 was later enrolled again as 4915.9811. Patient 4915.9810 later enrolled into the study a second time as 4915.9825. Each patient was excluded from efficacy analyses for the 2<sup>nd</sup> enrollment (i.e., 9811 and 9825).

**Reviewer's Comments:** *The most frequent protocol deviations were that the study medication was not used and that disallowed medications were used.*

**Protocol Deviations - Study C-11-003  
Randomized Subjects**

Deviation	Nepafenac 0.3% N=540	Nepafenac Vehicle 0.3% N=534	Nevanac Vehicle N=268
Did not receive study medication	18	28	14
No on therapy follow-up data	10	13	2

**Reviewer's Comments:** *The only patients excluded from the efficacy analyses were those that did not receive study medication or did not have an on therapy follow-up visit.*

6.1.4 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.

6.1.4.1 Study C-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 noninferiority 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 noninferiority. Stratification was by Investigator to match the stratification used in the randomization process.

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

	<b>Nepafenac 0.3% N=807 n(%)</b>	<b>Nepafenac Vehicle 0.3% N=197 n(%)</b>	<b>Nevanac N=811<sup>a</sup> n(%)</b>	<b>Nevanac Vehicle N=205 n(%)</b>
<b>ITT Population</b>	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	
<b>PP Population</b>	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	

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

**Reviewer's Comment:** *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.*

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

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

<sup>a</sup> 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.

**Reviewer's Comment:** *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.*

*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%.*

#### 6.1.4.2 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**

	<b>Nepafenac 0.3%</b> <b>n(%)</b> <b>N=512</b>	<b>Nepafenac</b> <b>Vehicle 0.3%</b> <b>n(%)</b> <b>N=252</b>	<b>p value</b>
<b>ITT Population</b>	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

**Reviewer's Comment:** *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.*

## 6.1.5 Analysis of Secondary Endpoints(s)

### 6.1.5.1 Study C-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**

	<b>Nepafenac 0.3%</b> n (%)	<b>Nepafenac Vehicle 0.3%</b> n (%)	<b>Nevanac</b> n (%)	<b>Nevanac Vehicle</b> n (%)
<b>ITT Population</b>	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	
<b>PP Population</b>	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	

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

**Reviewer's Comment:** *Both Nepafenac 0.3% and Nevanac are statistically superior to their respective vehicles in the percent of pain free patients at Day 14.*

**Table 6.1.5.1-1  
 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 <sup>a</sup>
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.

**Reviewer's Comment:** *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.*

*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%.*

#### 6.1.5.2 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

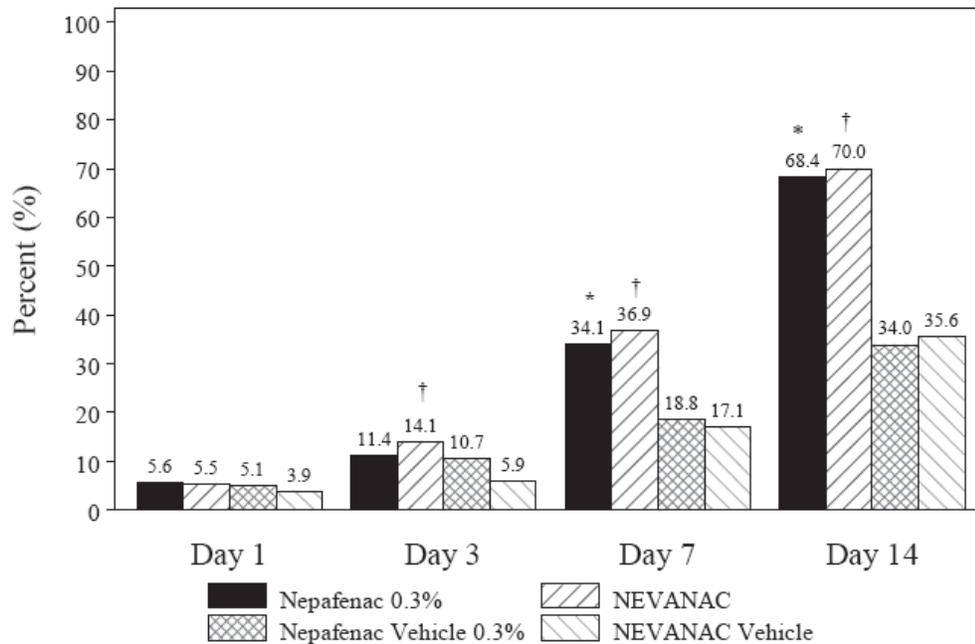
p value is based upon Cochran-Mantel-Haenszel test stratified by site.

**Reviewer's Comment:** *There was no significant difference between Nepafenac 0.3% and Nepafenac 0.1% for cumulative percent cures at the Day 7 visit following cataract surgery.*

### 6.1.6 Other Endpoints

#### 6.1.6.1 Study C-09-055

**Figure 6.1.6.1-1 Percent Cumulative Cures by Visit  
 ITT Population - Study C-09-055**



\* p-value < 0.05: Nepafenac 0.3% versus Nepafenac Vehicle 0.3%

† p-value < 0.05: NEVANAC versus NEVANAC Vehicle

**Reviewer's Comment:** *A statistically significant difference in the cumulative percent of patients cured for Nepafenac 0.3% compared with Nepafenac vehicle 0.3% was demonstrated beginning on Day 7 postoperatively (p<0.0001).*

*Nevanac had a statistically significant difference in the percentage of patients cured at the Day 3 Visit (p<0.0001) compared with Nevanac vehicle.*

*Both findings were confirmed in the Per Protocol data set.*

“Pain-free” patients were not necessarily pain-free over the entire study.

**Table 6.1.6.1-1  
Percent of Patients Pain Free at Each Visit  
ITT Population - Study C-09-055**

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

a 3 patients missed the Day 1 visit

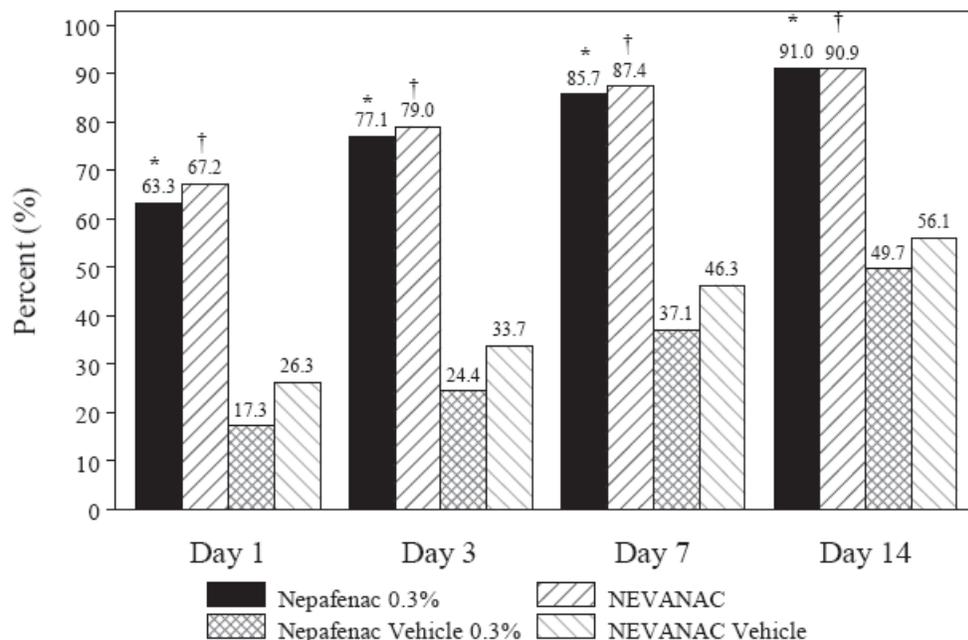
b 2 patients were randomized but did not have on-study data

c 1 patient missed the Day 1 visit

**Reviewer’s Comment:** *A statistically significant difference in the percent of pain-free patients was noted beginning at Day 1 postoperatively (p<0.0001) continuing throughout the study.*

Cumulative pain-free patients were those who were pain-free and remained pain-free at all subsequent visits. This is the more conservative and appropriate assessment of pain data.

**Figure 6.1.6.1-2 Percent Cumulative Pain-Free by Visit  
 ITT Population - Study C-09-055**



\*p-value < 0.05: Nepafenac 0.3% versus Nepafenac Vehicle 0.3%

†p-value < 0.05: NEVANAC versus NEVANAC Vehicle

**Reviewer's Comment:** A statistically significant difference in the cumulative percent of patients who were pain-free was demonstrated at all postoperative visits between Nepafenac 0.3% compared with Nepafenac vehicle 0.3% ( $p < 0.0001$ ).

Similarly, the treatment group difference was demonstrated between Nevanac and Nevanac vehicle at all postoperative visits ( $p < 0.0001$ ).

Both findings were confirmed in the Per Protocol data set.

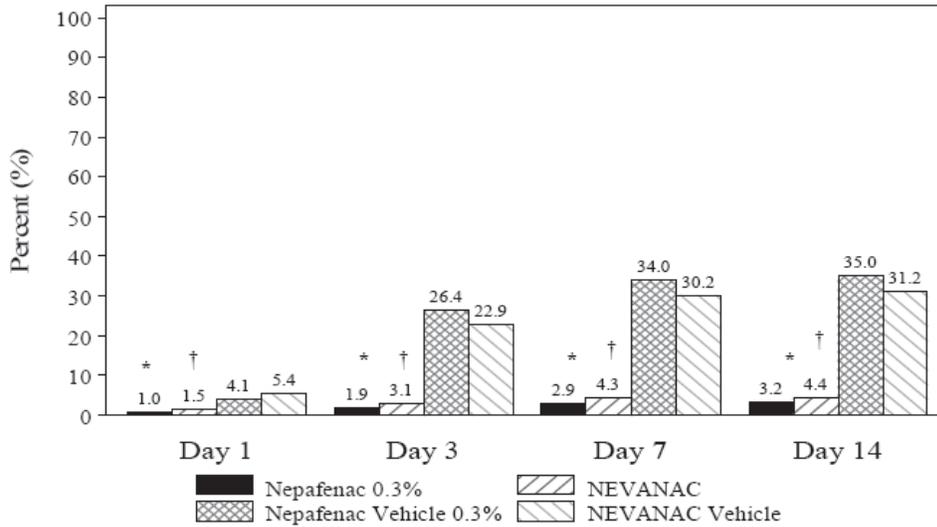
A patient was designated a treatment failure if at any postoperative timepoint the patient had cells score  $\geq 3$ , or flare score = 3, or ocular pain score  $\geq 4$  (Investigator assessed). Though patients who were designated treatment failures were discontinued from the study, they were included in the primary and secondary endpoint analyses as not having been a cure (primary endpoint) and as having ocular pain (secondary endpoint).

**Table 6.1.6.1-2 Percent Treatment Failures during the Study  
ITT Population – Study C-09-055**

	<b>Nepafenac 0.3%</b> n (%)	<b>Nepafenac Vehicle 0.3%</b> n (%)	<b>Nevanac</b> n (%)	<b>Nevanac Vehicle</b> n (%)
<b>ITT Population</b>	26 / 807 (3.2)	69 / 197 (35.0)	36 / 811 (4.4)	64 / 205 (31.2)
	p value <sup>b</sup> <0.0001		p value <sup>c</sup> <0.0001	
<b>PP Population</b>	25/787 (3.2)	69 / 193 (35.8)	30/785 (3.8)	62/194 (32.0)
	p value <sup>b</sup> <0.0001		p value <sup>c</sup> <0.0001	

**Reviewer’s Comment:** *There were a statistically significant differences between both active treatments compared to their respective vehicles in the percentage of patients who were treatment failures at any time during the study ( $p < 0.0001$ ) for each comparison in the ITT and PP populations.*

**Figure 6.1.6.1-3 Percent Cumulative Treatment Failures by Visit  
 ITT Population - Study C-09-055**



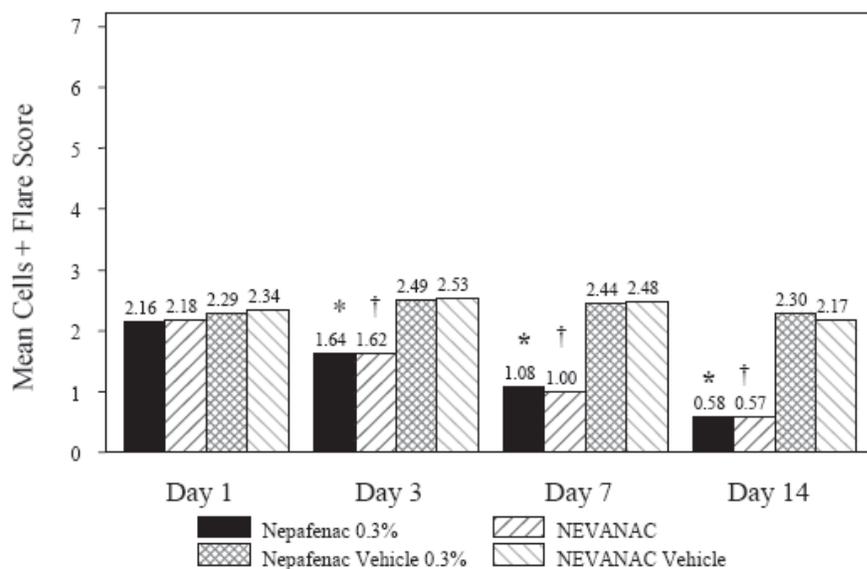
\* p-value < 0.05: Nepafenac 0.3% versus Nepafenac Vehicle 0.3%

† p-value < 0.05: NEVANAC versus NEVANAC Vehicle

**Reviewer’s Comment:**

*There were fewer subjects who were treatment failures at all postoperative visits during the study in the Nepafenac 0.3% group compared to Nepafenac 0.3% vehicle. The treatment group difference was statistically significant at all postoperative visits (p=0.0012 Day 1, p<0.0001 Days 3, 7 and 14). Similar differences were observed in the Nevanac group compared with the Nevanac Vehicle group.*

**Figure 6.1.6.1-3**  
**Mean Cell + Flare Scores Results by Visit**  
**ITT Population - Study C-09-055**



\* p-value < 0.05: Nepafenac 0.3% versus Nepafenac Vehicle 0.3%

† p-value < 0.05: NEVANAC versus NEVANAC Vehicle

**Table 6.1.6.1-3**  
**Mean Cell + Flare Scores Results by Visit**  
**Study C-09-055**  
**(Intent-to-Treat)**

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

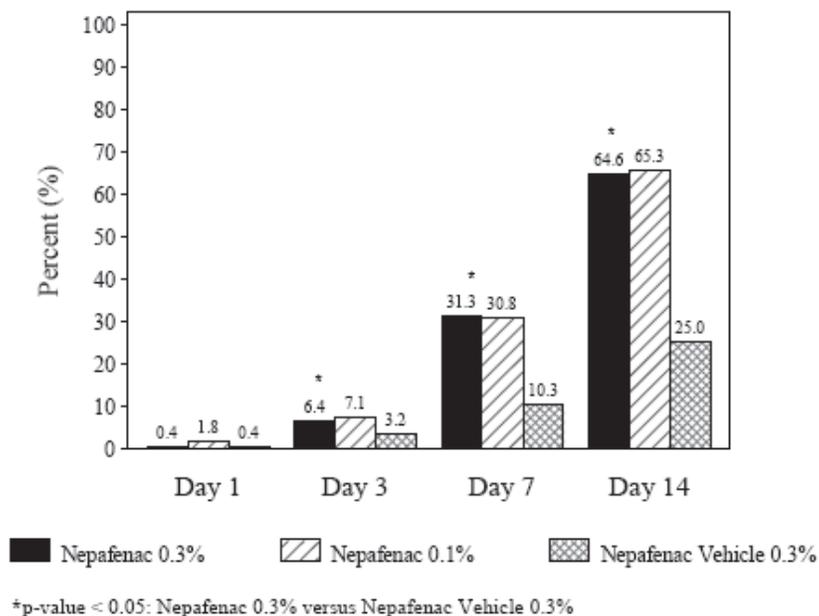
**Reviewer’s Comment:** *The efficacy of QD-dosed Nepafenac 0.3% in treating ocular inflammation is demonstrated by the reduction in the mean cell + flare scores beginning at Day 3 over the postoperative period compared to Nepafenac 0.3% vehicle.*

*These analyses demonstrate approximately 1 unit difference between Nepafenac 0.3% and Nepafenac 0.3% vehicle after Day 7 of treatment. Differences of this level served as the basis of approval for other products with this indication.*

*The per protocol analysis demonstrated similar results to the intent- to-treat analysis.*

6.1.6.2 Study C-11-003

**Figure 6.1.6.2-1– Cumulative Percent Cures by Visit  
ITT Population – Study C-11-003**

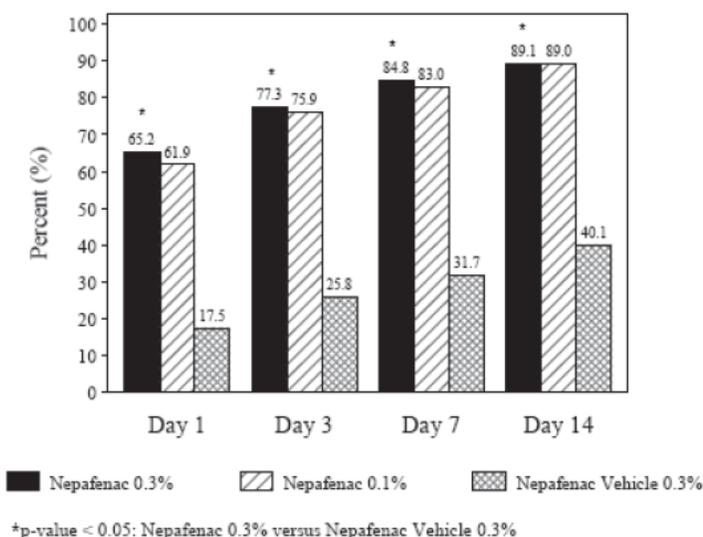


**Reviewer's Comment:** *The cumulative percent cures by visit were similar in the Nepafenac 0.3% and Nepafenac 0.1% QD treatment groups. There was a statistically significant difference between the Nepafenac 0.3% and Nepafenac 0.3% vehicle groups beginning postoperative Day 3 ( $p=0.0367$  Day 3, and  $p<0.0001$  Days 7 and 14).*

**Table 6.1.6.2-1**  
**Cumulative Percent of Patients Pain Free at Each Visit**  
**Study C-11-003**  
**(Intent-to-Treat)**

Efficacy Parameter	Post-op Day	Nepafenac 0.3% N=512	Nepafenac 0.1% N=493	Nepafenac vehicle 0.3% N=252	p value active comparison	p value Nepafenac 0.3% vehicle comparison
Cumulative Percent Pain Free	1	334 (65.2)	305 (61.9)	44 (17.5)	0.3385	<0.0001
	3	396 (77.3)	374 (75.9)	65 (25.8)	0.7769	<0.0001
	7	434 (84.8)	409 (83.0)	80 (31.7)	0.5954	<0.0001
	14	456 (89.1)	439 (89.0)	101 (40.1)	0.7365	<0.0001

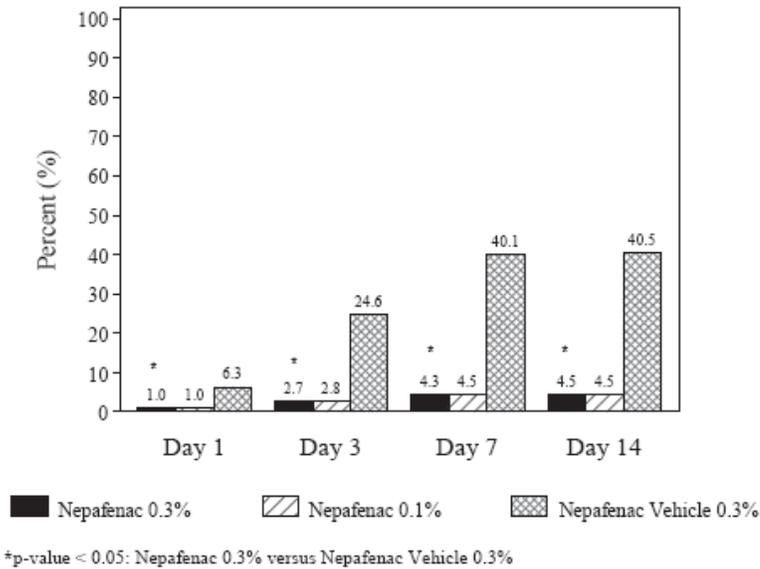
**Figure 6.1.6.2-2 Cumulative Percent Pain Free by Visit**  
**ITT population - Study C-11-003**



**Reviewer's Comment:** *The cumulative percent pain-free by visit were those patients who were assessed pain-free by the Investigator and remained pain-free at all subsequent visits. There was a statistically significant difference between the Nepafenac 0.3% and Nepafenac 0.3% vehicle groups at all postoperative visits (p=0.0001).*

Treatment failure was defined as aqueous cells score  $\geq 3$ , aqueous flare score  $=3$ , and/or ocular pain score  $\geq 4$ .

**Figure 6.1.6.2-3 Percent Treatment Failures by Visit  
ITT Population - Study C-11-003**

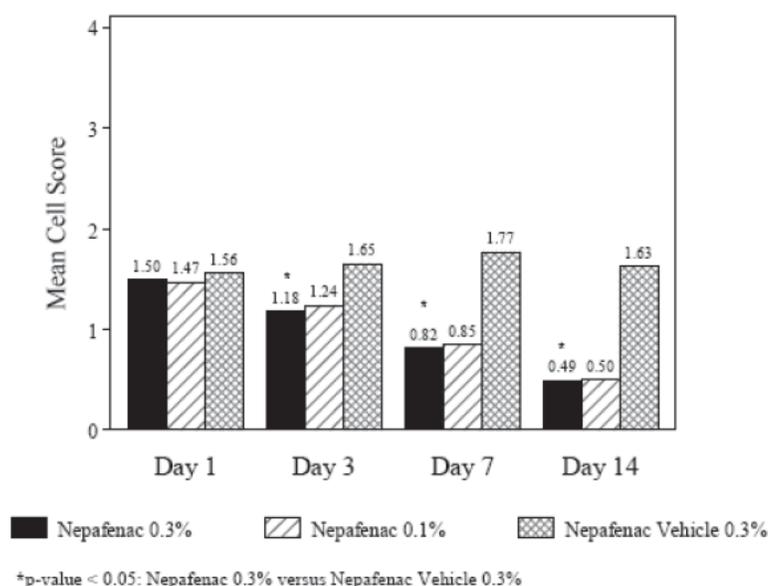


**Reviewer's Comment:** *There were fewer subjects who were treatment failures at all postoperative visits during the study in the Nepafenac 0.3% group compared to Nepafenac 0.3% vehicle. This treatment group difference was statistically significant at all postoperative visits ( $p < 0.0001$ ).*

**Table 6.1.6.2-2**  
**Mean Cells Scores Results by Visit**  
**ITT Population - Study C-11-003**

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
Mean Cells (units)	1	1.50	1.47	1.56	0.5634	0.2503
	3	1.18	1.24	1.65	0.2634	<0.0001
	7	0.82	0.85	1.77	0.4717	<0.0001
	14	0.49	0.50	1.63	0.7924	<0.0001

**Figure 6.1.6.2-4 Mean Cells Score by Visit**  
**ITT Population - Study C-11-003**

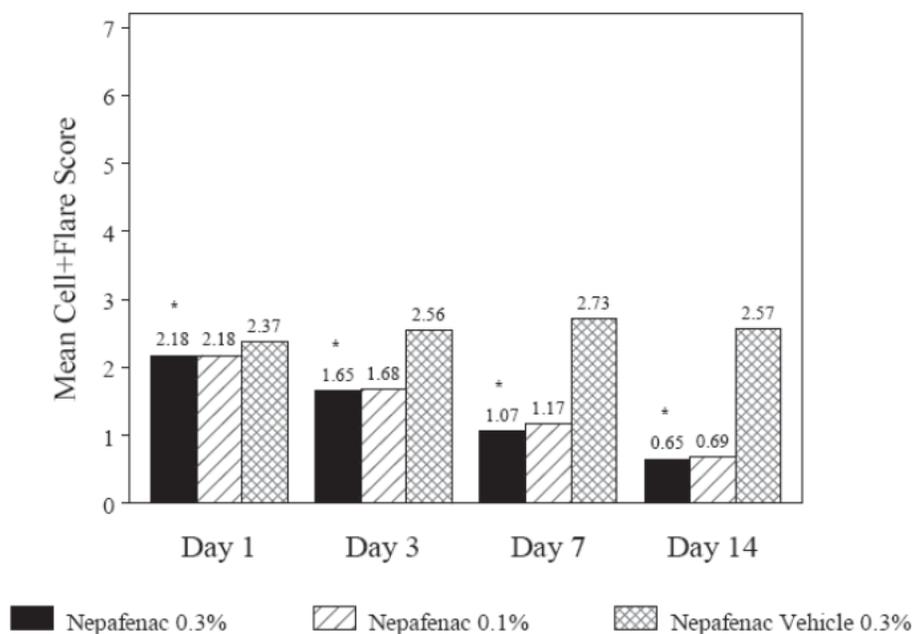


**Reviewer's Comment:** *The mean cells score decreased at each postoperative visit for patients in the Nepafenac 0.3% and Nepafenac 0.1% treatment groups. This treatment group difference between Nepafenac 0.3% and the Nepafenac 0.3% vehicle was statistically significant beginning at postoperative Day 3 (p<0.0001).*

**Table 6.1.6.2-4**  
**Mean Cell + Flare Scores Results by Visit**  
**ITT Population - Study C-11-003**

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
Sum of Cells and Flare (units)	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

**Figure 6.1.6.2- 6**  
**Mean Cell + Flare Scores Results by Visit**  
**ITT Population - Study C-11-003**



\*p-value < 0.05: Nepafenac 0.3% versus Nepafenac Vehicle 0.3%

**Reviewer's Comment:** *The mean cell + flare score decreased at each postoperative visit for patients in the Nepafenac 0.3% and Nepafenac 0.1% treatment groups. This treatment group difference between Nepafenac 0.3% and the Nepafenac 0.3% vehicle was statistically significant at each postoperative visit.*

### 6.1.7 Subpopulations

There were no statistically significant differences in demographic data, diagnoses, or baseline characteristics between treatment groups within each study.

The number of patients within any particular demographic group was too small to draw definitive conclusions regarding safety and efficacy. There do not appear to have been any race or ethnicity effects.

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The applicant performed adequate dose ranging studies during the drug development program.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No evidence of tolerance or withdrawal effects has been detected in any of the trials submitted.

### 6.1.10 Additional Efficacy Issues

There were no additional efficacy issues.

## **7 Review of Safety**

### **Safety Summary**

#### **7.1 Methods**

##### **7.1.1 Studies/Clinical Trials Used to Evaluate Safety**

This review of safety describes the safety profile of nepafenac ophthalmic suspension 0.3% for the treatment of pain and inflammation associated with cataract surgery. 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%.

##### **7.1.2 Categorization of Adverse Events**

The protocols adequately defined an adverse event. Each investigator evaluated study participants for adverse events, volunteered and elicited, at each study visit. An Adverse Event Form was completed to document a description of the event, onset, severity, treatment required, outcome and relatedness to the use of the study medication.

The study utilized the MedDRA preferred terms for adverse event recording. The terms were sufficiently descriptive to assess adverse events expected to be experienced by the study population.

##### **7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence**

The safety population thus included 3344 patients, 1351 of who were exposed to Nepafenac Ophthalmic Suspension, 0.3%.

#### **7.2 Adequacy of Safety Assessments**

##### **7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations**

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

### 7.2.2 Explorations for Dose Response

The dose response profile for nepafenac has been adequately studied throughout the drug's development including as submitted in NDA 21-862 Nevanac (nepafenac ophthalmic suspension) 0.1% submitted and approved in 2005.

### 7.2.3 Special Animal and/or In Vitro Testing

Not applicable. There was no special animal or in vitro testing performed. Refer to the Pharmacology/Toxicology review for additional details.

### 7.2.4 Routine Clinical Testing

Routine clinical testing and monitoring of study subjects was adequate to elicit adverse events.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

The metabolic, clearance and interaction profiles of nepafenac and amfenac have been adequately described and reviewed in NDA 21-862 for Nevanac submitted in February 2005. Refer to the Pharmacology / Toxicology and Clinical Pharmacology reviews for details.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The applicant's evaluation of potential adverse effects for this pharmacological class of drug is adequate.

## 7.3 Major Safety Results

### 7.3.1 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.

### 7.3.2 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
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

**Reviewer's Comment:** *No new safety signal was identified by the reported non-serious adverse events.*

### 7.3.3 Dropouts and/or Discontinuations

**Table 7.3.3-1  
Subjects Discontinued from Treatment or Study  
Study C-09-055: Safety Population**

Investigator No. Product	Patient Number	Reason for Discontinuation
<b>970</b>		
Vehicle 0.1%	2201	Treatment failure
Vehicle 0.3%	2207	Treatment failure
Vehicle 0.3%	2214	Treatment failure
Vehicle 0.1%	2216	Treatment failure
Vehicle 0.3%	2228	Treatment failure
Vehicle 0.1%	2230	Treatment failure
Vehicle 0.3%	2233	Treatment failure
Vehicle 0.1%	2240	Treatment failure
Vehicle 0.1%	2242	Treatment failure
Vehicle 0.3%	2246	Treatment failure
Nevanac	2248	AE – post procedural complication
Vehicle 0.3%	2252	Treatment failure
Vehicle 0.1%	2256	Treatment failure
Nevanac	2263	AE - herpes keratitis
Vehicle 0.1%	2264	Treatment failure
Vehicle 0.3%	2267	Treatment failure
Vehicle 0.3%	2273	Treatment failure
Vehicle 0.1%	2277	Treatment failure
Nepafenac 0.3%	2281	Subject did not use Study Medication
Vehicle 0.3%	2287	Treatment failure
Vehicle 0.1%	2289	Treatment failure
<b>1007</b>		
Nepafenac 0.3%	9001	AE – atopic dermatitis
Vehicle 0.3%	9002	Treatment Failure
Nepafenac 0.3%	9003	AE – eye inflammation
Vehicle 0.3%	9013	Treatment failure
Vehicle 0.1%	9018	Treatment failure
Nepafenac 0.3%	9020	Treatment failure
Vehicle 0.3%	9027	Treatment failure
Vehicle 0.1%	9030	Treatment failure

Investigator No. Product	Patient Number	Reason for Discontinuation
Vehicle 0.1%	9032	Treatment failure
Vehicle 0.3%	9035	Treatment failure
Nevanac	9042	Treatment failure
Vehicle 0.3%	9047	Treatment failure
Nepafenac 0.3%	9048	Subject did not use Study Medication
Vehicle 0.1%	9050	Treatment Failure
Vehicle 0.1%	9058	Treatment failure
Vehicle 0.3%	9060	Treatment failure
Vehicle 0.1%	9067	Treatment failure
Nevanac	9068	Treatment failure
Vehicle 0.3%	9071	Treatment failure
Vehicle 0.1%	9077	Treatment failure
Nepafenac 0.3%	9081	Treatment failure
Vehicle 0.1%	9084	Treatment failure
Vehicle 0.3%	9090	Treatment failure
Vehicle 0.3%	9099	Treatment failure
<b>1238</b>		
Nepafenac 0.3%	6201	Treatment failure
Nevanac	6204	Treatment failure
Nevanac	6205	Treatment failure
Vehicle 0.1%	6206	Treatment failure
Vehicle 0.3%	6207	Treatment failure
Nepafenac 0.3%	6212	Treatment failure
Nevanac	6215	Treatment failure
Vehicle 0.1%	6217	Treatment failure
<b>1434</b>		
Vehicle 0.3%	6807	Other
Nevanac	6808	Treatment failure
Nepafenac 0.3%	6810	Treatment failure
Nevanac	6813	Treatment failure
Vehicle 0.3%	6814	Treatment failure
Vehicle 0.1%	6821	Treatment failure
Nevanac	6824	Treatment failure
<b>1440</b>		
Nevanac	7901	Treatment failure
Nevanac	7902	Treatment failure
Vehicle 0.1%	7903	Treatment failure
Nevanac	7905	Treatment failure
Vehicle 0.3%	7907	Treatment failure

Investigator No. Product	Patient Number	Reason for Discontinuation
Nevanac	7908	Treatment failure
Nepafenac 0.3%	7910	AE – injury
<b>1710</b>		
Vehicle 0.3%	8802	Subject did not use Study Medication
Nevanac	8806	AE – cystoid macular edema
<b>1806</b>		
Nevanac	1709	Other
Vehicle 0.1%	1721	Treatment failure
<b>1927</b>		
Nepafenac 0.3%	4009	Treatment failure
Nepafenac 0.3%	4018	Subject did not use Study Medication
Nepafenac 0.3%	4019	Subject did not use Study Medication
Vehicle 0.1%	4024	Treatment failure
Vehicle 0.3%	4025	Subject did not use Study Medication
Nevanac	4028	Treatment failure
Vehicle 0.3%	4033	Treatment failure
Nevanac	4039	Treatment failure
Nevanac	4043	Treatment failure
<b>1980</b>		
Nevanac	9512	Subject did not use Study Medication
Vehicle 0.1%	9514	Treatment failure
<b>2034</b>		
Vehicle 0.1%	2104	Other
Nepafenac 0.3%	2107	AE – Brain edema
<b>2353</b>		
Vehicle 0.1%	7102	Treatment failure
Vehicle 0.3%	7108	AE – Cataract surgery complication
Vehicle 0.1%	7113	Subject did not use Study Medication
Nevanac	7121	Treatment failure
Vehicle 0.1%	7122	Treatment failure
Nevanac	7135	Subject did not use Study Medication
<b>2449</b>		
Vehicle 0.1%	6707	Other
Nevanac	6709	Subject did not use Study Medication
Vehicle 0.3%	6711	Other
Vehicle 0.1%	6719	Other
Vehicle 0.3%	6724	Other
Nevanac	6726	AE – Cataract surgery complication
<b>2902</b>		

Investigator No. Product	Patient Number	Reason for Discontinuation
Nevanac	3307	AE – Sepsis
Nevanac	3308	AE – Corneal abrasion
Nevanac	3326	Subject did not use Study Medication
<b>3025</b>		
Nepafenac 0.3%	6001	Treatment failure
<b>3351</b>		
Vehicle 0.3%	9614	AE – Iritis
<b>3435</b>		
Nepafenac 0.3%	9704	Treatment failure
Vehicle 0.1%	9714	Other
<b>3626</b>		
Vehicle 0.3%	6409	Treatment failure
Nepafenac 0.3%	6410	Treatment failure
Nevanac	6412	Treatment failure
Nevanac	6413	AE – Posterior capsule rupture
Nepafenac 0.3%	6417	Treatment failure
Vehicle 0.3%	6418	Treatment failure
Nevanac	6422	Treatment failure
Vehicle 0.1%	6423	Treatment failure
Nepafenac 0.3%	6424	AE – Posterior capsule rupture
Nepafenac 0.3%	6435	AE – Posterior capsule rupture
Vehicle 0.3%	6437	Treatment failure
Vehicle 0.1%	6440	Treatment failure
Nevanac	6442	Treatment failure
Nepafenac 0.3%	6443	Hypersensitivity
Vehicle 0.3%	6444	Treatment failure
Nepafenac 0.3%	6450	Treatment failure
<b>3678</b>		
Nepafenac 0.3%	2506	Subject did not use Study Medication
Vehicle 0.1%	2507	Treatment failure
Nevanac	2510	Subject did not use Study Medication
Vehicle 0.3%	2517	Treatment failure
Vehicle 0.1%	2519	Treatment failure
Nevanac	2526	Subject did not use Study Medication
Nevanac	2527	Subject did not use Study Medication
Vehicle 0.3%	2530	Treatment failure
Vehicle 0.1%	2531	Treatment failure
Vehicle 0.3%	2539	Treatment failure
Vehicle 0.1%	2544	Treatment failure

Investigator No. Product	Patient Number	Reason for Discontinuation
Vehicle 0.3%	2546	Treatment failure
<b>3712</b>		
Nevanac	9401	Subject did not use Study Medication
Vehicle 0.1%	9405	Subject did not use Study Medication
Vehicle 0.3%	9422	Subject did not use Study Medication
Nepafenac 0.3%	9442	Subject did not use Study Medication
Vehicle 0.3%	9459	Treatment failure
Nepafenac 0.3%	9466	Subject did not use Study Medication
<b>3733</b>		
Vehicle 0.1%	4202	AE – Posterior capsule rupture
Nepafenac 0.3%	4207	Subject did not use Study medication
Vehicle 0.3%	4208	AE – Iritis
Nevanac	4210	Treatment failure
Nevanac	4212	Subject did not use Study Medication
Nevanac	4222	Protocol violation – Use of disallowed medication
Vehicle 0.1%	4223	Protocol violation – Use of disallowed medication
Nepafenac 0.3%	4229	Patient's decision – Unrelated to AE
<b>3747</b>		
Vehicle 0.1%	4405	Treatment failure
Vehicle 0.3%	4413	AE – Visual acuity reduced
Nevanac	4416	Treatment failure
Nevanac	4435	Subject did not use Study Medication
Nepafenac 0.3%	4455	Treatment failure
Vehicle 0.1%	4457	Treatment failure
Nepafenac 0.3%	4459	Treatment failure
Vehicle 0.3%	4465	Treatment failure
<b>3807</b>		
Vehicle 0.1%	3101	Treatment failure
Nepafenac 0.3%	3103	Treatment failure
Vehicle 0.3%	3104	Treatment failure
Nevanac	3108	Other
Nepafenac 0.3%	3111	AE – Post procedural complication
Vehicle 0.3%	3113	Other
Nevanac	3117	Other
Vehicle 0.1%	3122	Other
Vehicle 0.3%	3123	Treatment failure
Nepafenac 0.3%	3125	AE – Corneal abrasion
Nepafenac 0.3%	3132	Other
Vehicle 0.1%	3133	Other

Investigator No. Product	Patient Number	Reason for Discontinuation
Vehicle 0.3%	3139	Other
Vehicle 0.1%	3150	Other
Nepafenac 0.3%	3154	Subject did not use Study Medication
Nevanac	3158	Other
Vehicle 0.3%	3160	Treatment failure
<b>3828</b>		
Nepafenac 0.3%	9101	Treatment failure
Nevanac	9103	Treatment failure
Vehicle 0.1%	9107	Treatment failure
Nepafenac 0.3%	9109	Subject did not use Study Medication
Vehicle 0.1%	9112	Treatment failure
Nepafenac 0.3%	9115	Subject did not use Study Medication
Nepafenac 0.3%	9121	Patient's decision unrelated to AE
Vehicle 0.3%	9123	Treatment failure
Nevanac	9127	Treatment failure
Nepafenac 0.3%	9128	AE – Posterior capsule rupture
Nepafenac 0.3%	9132	Subject did not use Study Medication
Vehicle 0.1%	9139	Treatment failure
Vehicle 0.3%	9141	Treatment failure
Vehicle 0.1%	9143	Treatment failure
Nepafenac 0.3%	9153	Subject did not use Study Medication
Nevanac	9154	Subject did not use Study Medication
Nepafenac 0.3%	9159	Subject did not use Study Medication
Vehicle 0.3%	9162	AE – Visual acuity reduced
Vehicle 0.1%	9169	Treatment failure
Vehicle 0.1%	9178	Treatment failure
Vehicle 0.3%	9180	Subject did not use Study Medication
<b>3865</b>		
Vehicle 0.1%	1101	AE – Visual acuity reduced
Nevanac	1107	Protocol violation – D/C at surgery; No on therapy follow-up data
Vehicle 0.3%	1108	Treatment failure
Vehicle 0.1%	1115	Treatment failure
<b>3899</b>		
Nevanac	2302	Protocol violation – Use of disallowed medication.
Vehicle 0.1%	2305	Treatment failure
Nepafenac 0.3%	2307	Subject did not use Study Medication
Vehicle 0.3%	2324	Treatment failure
Nevanac	2325	AE – Posterior capsule rupture

Investigator No. Product	Patient Number	Reason for Discontinuation
Vehicle 0.3%	2334	Treatment failure
<b>3903</b>		
Vehicle 0.3%	4501	Treatment failure
Nevanac	4510	Treatment failure
Vehicle 0.3%	4511	Subject did not use Study Medication
Nevanac	4519	Treatment failure
Nepafenac 0.3%	4521	Treatment failure
Vehicle 0.3%	4526	Subject did not use Study Medication
Nevanac	4530	Treatment failure
Vehicle 0.1%	4536	Other
Vehicle 0.3%	4541	Treatment failure
Vehicle 0.1%	4542	Treatment failure
Nevanac	4544	Treatment failure
<b>3904</b>		
Nevanac	7002	Subject did not use Study Medication
Vehicle 0.3%	7004	Subject did not use Study Medication
<b>3988</b>		
Vehicle 0.3%	5501	Protocol violation – Use of disallowed medication
Nevanac	5508	AE – Cataract operation complication
Vehicle 0.1%	5514	Treatment failure
<b>4119</b>		
Nepafenac 0.3%	1912	Subject did not use Study Medication
Vehicle 0.1%	1919	Subject did not use Study Medication
Vehicle 0.3%	1932	Treatment failure
Vehicle 0.3%	1946	Treatment failure
Vehicle 0.1%	1948	Treatment failure
Nepafenac 0.3%	1949	AE – IOP increased
Nevanac	1952	Subject did not use Study Medication
Vehicle 0.1%	1959	Treatment failure
Vehicle 0.1%	1966	Subject did not use Study Medication
Vehicle 0.1%	1975	Treatment failure
<b>4702</b>		
Vehicle 0.1%	5401	AE – Eye inflammation
Nevanac	5405	Subject did not use Study Medication
Vehicle 0.3%	5407	Treatment failure
Nevanac	5409	Subject did not use Study Medication
Nepafenac 0.3%	5412	Subject did not use Study Medication
Nepafenac 0.3%	5413	Subject did not use Study Medication
Vehicle 0.1%	5415	Treatment failure

Investigator No. Product	Patient Number	Reason for Discontinuation
<b>4734</b>		
Nepafenac 0.3%	4904	Other
Nevanac	4906	Treatment failure
Vehicle 0.3%	4910	Treatment failure
Vehicle 0.1%	4913	AE – Corneal edema
<b>4824</b>		
Nepafenac 0.3%	7509	Subject did not use Study Medication
Vehicle 0.1%	7519	Subject did not use Study Medication
Nevanac	7526	Subject did not use Study Medication
Vehicle 0.1%	7527	Treatment failure
Vehicle 0.3%	7530	Other
<b>4865</b>		
Nevanac	5104	Treatment failure
Vehicle 0.3%	5108	Patient's Decision unrelated to an AE
Vehicle 0.1%	5111	Other
<b>4988</b>		
Vehicle 0.1%	1617	Other
Vehicle 0.3%	1619	Patient's Decision unrelated to an AE
Vehicle 0.3%	1633	Treatment failure
Vehicle 0.1%	1644	Treatment failure
Vehicle 0.3%	1648	Treatment failure
<b>5003</b>		
Vehicle 0.3%	7303	AE – Eye inflammation
<b>5127</b>		
Vehicle 0.1%	3806	Treatment failure
Nepafenac 0.3%	3808	Subject did not use Study Medication
Vehicle 0.3%	3812	Treatment failure
Nevanac	3817	AE – Posterior capsule rupture
Nepafenac 0.3%	3825	Treatment failure
Vehicle 0.3%	3826	Treatment failure
Nepafenac 0.3%	3833	Treatment failure
Nevanac	3848	Protocol violation – D/C at surgery; No on therapy follow-up data
Vehicle 0.3%	3855	Treatment failure
Vehicle 0.1%	3860	Other
<b>5161</b>		
Nepafenac 0.3%	5815	Protocol violation – Use of disallowed medication
<b>5180</b>		
Nevanac	1201	Subject did not use Study Medication

Investigator No. Product	Patient Number	Reason for Discontinuation
Vehicle 0.3%	1202	Subject did not use Study Medication
Vehicle 0.1%	1209	Treatment failure
Vehicle 0.3%	1211	Subject did not use Study Medication
Nepafenac 0.3%	1214	Treatment failure
Nevanac	1216	AE – Vitreous loss
Vehicle 0.1%	1218	AE – Photophobia
Vehicle 0.3%	1225	Treatment failure
<b>5303</b>		
Nepafenac 0.3%	8203	Protocol violation – Use of disallowed medication
Vehicle 0.1%	8204	Protocol violation – Use of disallowed medication
Nepafenac 0.3%	8229	Protocol violation – Use of disallowed medication
<b>5442</b>		
Nepafenac 0.3%	5906	Subject did not use Study Medication
Vehicle 0.3%	5907	Treatment failure
Vehicle 0.1%	5910	Other
Nevanac	5911	Treatment failure
Vehicle 0.1%	5914	Treatment failure
Nepafenac 0.3%	5918	Patient's Decision unrelated to an AE
<b>5444</b>		
Nevanac	1302	Subject did not use Study Medication
Vehicle 0.3%	1313	Subject did not use Study Medication
Nepafenac 0.3%	1328	Subject did not use Study Medication
Nevanac	1333	Subject did not use Study Medication
Nevanac	1337	Subject did not use Study Medication
<b>5541</b>		
Vehicle 0.1%	1805	Subject did not use Study Medication
Vehicle 0.3%	1822	Other
Nevanac	1840	Lost to follow-up
Nepafenac 0.3%	1856	Treatment failure
Nevanac	1861	AE – Gout
Vehicle 0.1%	1868	Treatment failure
Nevanac	1870	Subject did not use Study Medication
Nepafenac 0.3%	1873	Subject did not use Study Medication
<b>5548</b>		
Nepafenac 0.3%	6602	Treatment failure
Nepafenac 0.3%	6607	Subject did not use Study Medication
Vehicle 0.3%	6616	Treatment failure
Nevanac	6620	Treatment failure
<b>5660</b>		

Investigator No. Product	Patient Number	Reason for Discontinuation
Vehicle 0.3%	5310	Other
Nepafenac 0.3%	5339	Subject did not use Study Medication
Vehicle 0.3%	5341	Treatment failure
<b>5727</b>		
Vehicle 0.1%	5606	Treatment failure
Nepafenac 0.3%	5608	Patient's decision unrelated to an AE
Nepafenac 0.3%	5612	Treatment failure
Nepafenac 0.3%	5615	Treatment failure
Vehicle 0.3%	5616	Treatment failure
Vehicle 0.1%	5618	Subject did not use Study Medication
Nepafenac 0.3%	5620	Subject did not use Study Medication
Nevanac	5621	Subject did not use Study Medication
Nevanac	5622	Treatment failure
Vehicle 0.1%	5623	Treatment failure
<b>5758</b>		
Nepafenac 0.3%	2611	Treatment failure
Nepafenac 0.3%	2612	Subject did not use Study Medication
Vehicle 0.3%	2616	AE – Corneal edema
Nevanac	2619	AE – Asthma
Vehicle 0.3%	2627	Treatment failure
Vehicle 0.1%	2632	Other
Vehicle 0.3%	2637	Treatment failure
Vehicle 0.1%	2648	Other
Vehicle 0.3%	2649	Treatment failure
Nepafenac 0.3%	2653	Subject did not use Study Medication
Nepafenac 0.3%	2655	Subject did not use Study Medication
Vehicle 0.3%	2656	Treatment failure
Vehicle 0.1%	2660	Treatment failure
Vehicle 0.3%	2664	Treatment failure
Nepafenac 0.3%	2667	Subject did not use Study Medication
Nepafenac 0.3%	2671	Subject did not use Study Medication
Nepafenac 0.3%	2672	AE – Ciliary zonular dehiscence
Nepafenac 0.3%	2677	Treatment failure
Vehicle 0.3%	2680	Treatment failure
Vehicle 0.1%	2684	Treatment failure
Nepafenac 0.3%	2686	Other
Vehicle 0.3%	2689	Other
<b>5776</b>		
Nepafenac 0.3%	5002	Subject did not use Study Medication

Investigator No. Product	Patient Number	Reason for Discontinuation
Nepafenac 0.3%	5011	AE – Lens dislocation
Nevanac	5014	Protocol violation – Use of disallowed medication
Nepafenac 0.3%	5017	AE – Ciliary zonular dehiscence
<b>5848</b>		
Vehicle 0.3%	3507	AE – Anterior chamber cell
Nepafenac 0.3%	3509	Other
Nepafenac 0.3%	3521	Other
Nevanac	3524	AE – Retinal tear
Nevanac	3539	Subject did not use Study Medication
Vehicle 0.3%	3541	Treatment failure
Vehicle 0.1%	3544	Treatment failure
Nevanac	3545	AE – Cerebrovascular accident
<b>5901</b>		
Nevanac	4605	Subject did not use Study Medication
Nepafenac 0.3%	4612	Protocol violation – Use of disallowed medication
Nevanac	4616	Subject did not use Study Medication
<b>5920</b>		
Nevanac	1005	Treatment failure
Vehicle 0.3%	1010	Treatment failure
Vehicle 0.3%	1016	Treatment failure
Nevanac	1017	Treatment failure
Vehicle 0.1%	1020	Treatment failure
<b>5922</b>		
Nevanac	1401	Subject did not use Study Medication
Nevanac	1402	AE – Keratopathy
Nepafenac 0.3%	1405	Subject did not use Study Medication
<b>5953</b>		
Vehicle 0.1%	8901	AE – Vitreous fibrin, iris adhesions
<b>5954</b>		
Vehicle 0.3%	2408	Treatment failure
<b>5955</b>		
Nepafenac 0.3%	8614	Patient's decision unrelated to AE
<b>5957</b>		
Nevanac	8512	AE – Atrial fibrillation
Vehicle 0.3%	8513	Treatment failure
<b>5962</b>		
Nepafenac 0.3%	5703	AE – Panic attack
Vehicle 0.1%	5706	Treatment failure
Vehicle 0.3%	5712	Treatment failure

Investigator No. Product	Patient Number	Reason for Discontinuation
Vehicle 0.1%	5723	Treatment failure
Nepafenac 0.3%	5725	Treatment failure
Vehicle 0.3%	5727	AE – Corneal edema
<b>5966</b>		
Nepafenac 0.3%	4801	Subject did not use Study Medication
<b>5967</b>		
Vehicle 0.3%	4108	Subject did not use Study Medication

**Table 7.3.3-2  
Subjects Discontinued from Treatment or Study  
Study C-11-003: Safety Population**

Investigator No. Product	Patient Number	Reason for Discontinuation
<b>970</b>		
Vehicle 0.3%	1005	Treatment failure
Vehicle 0.3%	1007	Treatment failure
Nepafenac 0.3%	1008	AE – Corneal abrasion
Vehicle 0.3%	1013	Treatment failure
Vehicle 0.3%	1016	Treatment failure
Vehicle 0.3%	1024	Treatment failure
Vehicle 0.3%	1026	Patient's decision unrelated to an AE
Nepafenac 0.1%	1028	Subject did not use study medication
Vehicle 0.3%	1031	Treatment failure
Vehicle 0.3%	1038	Treatment failure
Vehicle 0.3%	1045	Treatment failure
Nepafenac 0.1%	1048	Subject did not use study medication
Vehicle 0.3%	1050	Treatment failure
Vehicle 0.3%	1053	Treatment failure
Vehicle 0.3%	1058	Treatment failure
Nepafenac 0.1%	1060	Subject did not use study medication
Nepafenac 0.3%	1064	AE - Hypertension
Vehicle 0.3%	1065	Treatment failure
Nepafenac 0.1%	1066	Subject did not use Study Medication
Vehicle 0.3%	1070	Treatment failure
<b>1007</b>		
Vehicle 0.3%	1105	Treatment Failure
Vehicle 0.3%	1110	Treatment Failure
Vehicle 0.3%	1115	Treatment failure

Investigator No. Product	Patient Number	Reason for Discontinuation
Vehicle 0.3%	1120	Treatment failure
Vehicle 0.3%	1121	Treatment failure
Nepafenac 0.1%	1123	Subject did not use Study Medication
Vehicle 0.3%	1131	Treatment failure
Vehicle 0.3%	1138	Treatment failure
Vehicle 0.3%	1143	Treatment failure
Vehicle 0.3%	1147	Treatment failure
Vehicle 0.3%	1152	Treatment failure
Vehicle 0.3%	1160	Treatment failure
Nepafenac 0.1%	1162	Treatment Failure
Vehicle 0.3%	1165	Treatment failure
Vehicle 0.3%	1166	Treatment failure
<b>1434</b>		
Nepafenac 0.3%	1202	Treatment failure
Vehicle 0.3%	1203	Treatment failure
<b>2449</b>		
Nepafenac 0.3%	1401	Other
Vehicle 0.3%	1402	Other
Nepafenac 0.1%	1403	Subject did not use Study Medication
Nepafenac 0.1%	1404	Other
Vehicle 0.3%	1407	Other
<b>2902</b>		
Vehicle 0.3%	1501	Treatment failure
Vehicle 0.3%	1508	Subject did not use Study Medication
Nepafenac 0.3%	1509	Treatment failure
Nepafenac 0.3%	1510	Subject did not use Study Medication
Nepafenac 0.1%	1516	Noncompliance
Nepafenac 0.3%	1519	Noncompliance
<b>3351</b>		
Vehicle 0.3%	4403	Other
Vehicle 0.3%	4406	Treatment failure
Nepafenac 0.3%	4408	Other
Nepafenac 0.1%	4418	Other
Nepafenac 0.1%	4419	Subject did not use study medication
Vehicle 0.3%	4420	Treatment failure
<b>3435</b>		
Nepafenac 0.3%	1603	AE – Corneal edema
Nepafenac 0.3%	1611	Treatment failure
Vehicle 0.3%	1616	Treatment failure

Investigator No. Product	Patient Number	Reason for Discontinuation
<b>3626</b>		
Nepafenac 0.1%	1706	Subject did not use study medication
Vehicle 0.3%	1707	Treatment failure
Nepafenac 0.3%	1709	Other
Nepafenac 0.3%	1710	Other
Nepafenac 0.3%	1714	Treatment failure
Vehicle 0.3%	1715	Treatment failure
Nepafenac 0.1%	1718	Treatment failure
Vehicle 0.3%	1720	Other
Vehicle 0.3%	1722	Other
Vehicle 0.3%	1729	Other
Vehicle 0.3%	1734	Treatment failure
<b>3678</b>		
Vehicle 0.3%	1803	Treatment failure
Vehicle 0.3%	1807	Treatment failure
Nepafenac 0.1%	1808	Subject did not use Study Medication
Vehicle 0.3%	1811	Treatment failure
Vehicle 0.3%	1819	Treatment failure
Nepafenac 0.1%	1824	Subject did not use Study Medication
<b>3712</b>		
Nepafenac 0.1%	1903	Subject did not use Study Medication
Vehicle 0.3%	1905	Treatment failure
Nepafenac 0.1%	1906	Treatment failure
Nepafenac 0.1%	1907	Treatment failure
Vehicle 0.3%	1913	Treatment failure
Nepafenac 0.3%	1916	Treatment failure
Nepafenac 0.1%	1923	Treatment failure
Nepafenac 0.3%	1927	Treatment failure
Vehicle 0.3%	1928	Treatment failure
Nepafenac 0.1%	1933	Treatment failure
Vehicle 0.3%	1940	Treatment failure
Nepafenac 0.1%	1944	Treatment failure
Vehicle 0.3%	1948	Treatment failure
Nepafenac 0.1%	1950	Treatment failure
Nepafenac 0.3%	1953	Treatment failure
Nepafenac 0.3%	1966	Treatment failure
<b>3733</b>		
Vehicle 0.3%	2006	Other
Nepafenac 0.1%	2007	Other

Investigator No. Product	Patient Number	Reason for Discontinuation
Nepafenac 0.1%	2010	AE – Blepharitis
Vehicle 0.3%	2011	Other
Nepafenac 0.1%	2018	AE – Iritis
Nepafenac 0.1%	2019	Protocol violation – No on therapy follow-up data
Nepafenac 0.3%	2027	Other
Vehicle 0.3%	2028	Other
<b>3747</b>		
Nepafenac 0.3%	2101	Treatment failure
Nepafenac 0.3%	2112	AE – Hypopyon
Vehicle 0.3%	2116	Treatment failure
Vehicle 0.3%	2123	Other
Vehicle 0.3%	2155	Other
<b>3807</b>		
Nepafenac 0.3%	2203	AE – Corneal abrasion
Vehicle 0.3%	2205	Subject did not use study medication
Vehicle 0.3%	2206	Other
Nepafenac 0.3%	2208	Other
Nepafenac 0.1%	2213	Other
Nepafenac 0.1%	2214	Other
Vehicle 0.3%	2215	Other
Nepafenac 0.1%	2218	Other
Vehicle 0.3%	2220	Treatment failure
Vehicle 0.3%	2222	Treatment failure
Nepafenac 0.1%	2227	Other
Vehicle 0.3%	2228	Treatment failure
Nepafenac 0.1%	2230	Other
<b>3828</b>		
Vehicle 0.3%	2311	Treatment failure
Nepafenac 0.1%	2319	AE – Floppy iris syndrome
Nepafenac 0.3%	2320	Treatment failure
Vehicle 0.3%	2322	Treatment failure
Vehicle 0.3%	2330	Treatment failure
Nepafenac 0.3%	2337	Subject did not use study medication
Nepafenac 0.1%	2340	AE – Floppy iris syndrome
Vehicle 0.3%	2354	Treatment failure
Nepafenac 0.3%	2356	Subject did not use study medication
<b>3865</b>		
Vehicle 0.3%	2402	Treatment failure
Vehicle 0.3%	2408	Treatment failure

Investigator No. Product	Patient Number	Reason for Discontinuation
Vehicle 0.3%	2411	Treatment failure
Nepafenac 0.3%	2415	Treatment failure
Vehicle 0.3%	2418	AE – Vision blurred
Vehicle 0.3%	2423	Protocol violation – No on-therapy follow-up data
<b>3899</b>		
Vehicle 0.3%	2510	Treatment failure
Nepafenac 0.1%	2511	Subject did not use study medication
Nepafenac 0.1%	2512	Subject did not use study medication
Vehicle 0.3%	2516	Treatment failure
Vehicle 0.3%	2523	Treatment failure
<b>3903</b>		
Nepafenac 0.1%	2602	Subject did not use study medication
Nepafenac 0.1%	2603	AE - Arrhythmia
Vehicle 0.3%	2612	Treatment failure
Nepafenac 0.1%	2615	Subject did not use study medication
Vehicle 0.3%	2619	Treatment failure
Nepafenac 0.3%	2620	Protocol violation – Did not receive study medication
Vehicle 0.3%	2625	Treatment failure
Vehicle 0.3%	2626	Treatment failure
<b>3988</b>		
Nepafenac 0.1%	2703	AE – Cataract operation complication
Nepafenac 0.3%	2713	Noncompliance
<b>4119</b>		
Vehicle 0.3%	2802	Other
Nepafenac 0.1%	2803	Subject did not use study medication
Vehicle 0.3%	2807	Other
Vehicle 0.3%	2812	Other
Nepafenac 0.3%	2814	AE - Endophthalmitis
Vehicle 0.3%	2816	Treatment failure
Nepafenac 0.1%	2826	Subject did not use study medication
Vehicle 0.3%	2828	Treatment failure
Vehicle 0.3%	2834	Treatment failure
Vehicle 0.3%	2836	Other
Nepafenac 0.1%	2837	Subject did not use study medication
Vehicle 0.3%	2842	Treatment failure
Vehicle 0.3%	2849	Treatment failure
Nepafenac 0.1%	2852	Noncompliance
Vehicle 0.3%	2855	Subject did not use study medication

Investigator No. Product	Patient Number	Reason for Discontinuation
Vehicle 0.3%	2856	Other
Nepafenac 0.1%	2857	Subject did not use study medication
Vehicle 0.3%	2868	Other
<b>4824</b>		
Vehicle 0.3%	3003	AE – Photophobia
Nepafenac 0.3%	3004	Subject did not use study medication
Vehicle 0.3%	3011	AE – Eye inflammation
Nepafenac 0.3%	3012	Subject did not use study medication
Vehicle 0.3%	3021	Treatment failure
Vehicle 0.3%	3036	Subject did not use study medication
Vehicle 0.3%	3045	Treatment failure
Nepafenac 0.1%	3046	Treatment failure
<b>4988</b>		
Vehicle 0.3%	3104	Treatment failure
Vehicle 0.3%	3108	Subject did not use study medication
Vehicle 0.3%	3118	Treatment failure
Vehicle 0.3%	3125	Patient's decision unrelated to an AE
Vehicle 0.3%	3132	Treatment failure
<b>5127</b>		
Nepafenac 0.1%	3201	Other
Nepafenac 0.3%	3211	Subject did not use study medication
Vehicle 0.3%	3219	Treatment failure
Vehicle 0.3%	3226	Treatment failure
Nepafenac 0.1%	3230	Treatment failure
Vehicle 0.3%	3239	Treatment failure
Vehicle 0.3%	3255	Treatment failure
Nepafenac 0.3%	3257	AE – Posterior capsule rupture
<b>5161</b>		
Nepafenac 0.3%	3312	Protocol violation – No on-therapy follow-up data
<b>5180</b>		
Nepafenac 0.3%	3404	Patient's decision unrelated to an AE
Nepafenac 0.3%	3406	AE – Cataract operation complication
Nepafenac 0.1%	3409	Treatment failure
Vehicle 0.3%	3410	AE – Eye pain
Vehicle 0.3%	3412	AE – Eye inflammation
Nepafenac 0.1%	3416	AE – Hypertensive encephalopathy
Vehicle 0.3%	3419	Other
<b>5442</b>		
Nepafenac 0.3%	3502	Subject did not use study medication

Investigator No. Product	Patient Number	Reason for Discontinuation
Vehicle 0.3%	3513	Treatment failure
Nepafenac 0.3%	3517	Subject did not use study medication
Nepafenac 0.3%	3518	AE – Cataract surgery complication
Vehicle 0.3%	3519	Subject did not use study medication
Nepafenac 0.3%	3521	AE – IOP increased
Nepafenac 0.1%	3522	Subject did not use Study Medication
Vehicle 0.3%	3524	Treatment failure
Vehicle 0.3%	3526	Treatment failure
<b>5444</b>		
Vehicle 0.3%	3609	Subject did not use study medication
Vehicle 0.3%	3613	AE – Corneal edema
Nepafenac 0.3%	3617	Subject did not use study medication
Nepafenac 0.3%	3630	AE – Lens dislocation
Vehicle 0.3%	3644	Subject did not use study medication
Nepafenac 0.1%	3647	Subject did not use study medication
Nepafenac 0.1%	3650	Subject did not use study medication
Nepafenac 0.1%	3653	Subject did not use study medication
<b>5541</b>		
Vehicle 0.1%	3713	Treatment failure
Nepafenac 0.3%	3716	AE – Corneal edema
Nepafenac 0.1%	3717	AE – Visual acuity reduced
Nepafenac 0.3%	3722	Treatment failure
Nevanac	3733	Treatment failure
Vehicle 0.1%	3738	Treatment failure
Nepafenac 0.3%	3739	AE – Posterior capsule rupture
Nepafenac 0.3%	3740	Treatment failure
Nepafenac 0.3%	3748	Subject did not use study medication
Nepafenac 0.1%	3751	AE – Posterior capsule rupture
Nepafenac 0.1%	3760	Subject did not use study medication
Nepafenac 0.1%	3766	Treatment failure
<b>5548</b>		
Vehicle 0.3%	3810	Treatment failure
Nepafenac 0.3%	3811	AE – Corneal edema
<b>5727</b>		
Vehicle 0.3%	3918	Treatment failure
Nepafenac 0.3%	3919	Subject did not use study medication
Nepafenac 0.3%	3920	AE – Posterior capsule rupture
<b>5758</b>		
Nepafenac 0.3%	4002	Subject did not use study medication

Investigator No. Product	Patient Number	Reason for Discontinuation
Vehicle 0.3%	4005	Treatment failure
Vehicle 0.3%	4010	Treatment failure
Nepafenac 0.3%	4013	Treatment failure
Vehicle 0.3%	4015	Subject did not use study medication
Vehicle 0.3%	4017	Treatment failure
Nepafenac 0.3%	4018	Treatment failure
Nepafenac 0.1%	4019	Other
Nepafenac 0.1%	4023	Treatment failure
Nepafenac 0.3%	4024	Treatment failure
Vehicle 0.3%	4025	Subject did not use study medication
Vehicle 0.3%	4027	Treatment failure
Nepafenac 0.1%	4028	Treatment failure
Nepafenac 0.1%	4029	Treatment failure
Vehicle 0.3%	4031	Treatment failure
Nepafenac 0.3%	4033	AE – Corneal abrasion
Vehicle 0.3%	4037	Treatment failure
Nepafenac 0.3%	4038	Treatment failure
Vehicle 0.3%	4042	Treatment failure
Nepafenac 0.1%	4043	Treatment failure
Nepafenac 0.3%	4044	Subject did not use study medication
Nepafenac 0.3%	4045	Treatment failure
Vehicle 0.3%	4046	Treatment failure
Nepafenac 0.3%	4047	Treatment failure
Vehicle 0.3%	4051	Treatment failure
Nepafenac 0.3%	4052	Subject did not use study medication
Nepafenac 0.1%	4053	Treatment failure
Nepafenac 0.3%	4054	Treatment failure
Nepafenac 0.3%	4056	Subject did not use study medication
Nepafenac 0.3%	4057	Subject did not use study medication
<b>5848</b>		
Vehicle 0.3%	4103	Treatment failure
Nepafenac 0.1%	4109	AE – Retinal tear
Vehicle 0.3%	4114	Treatment failure
Nepafenac 0.1%	4116	Patient's decision unrelated to an AE
Vehicle 0.3%	4126	Subject did not use study medication
Vehicle 0.3%	4131	Treatment failure
Nepafenac 0.3%	4141	Subject did not use study medication
<b>5957</b>		
Nepafenac 0.1%	4201	Subject did not use study medication

Investigator No. Product	Patient Number	Reason for Discontinuation
Nepafenac 0.1%	4204	AE – Corneal edema
Vehicle 0.3%	4209	Protocol violation – No on-therapy follow-up data
Vehicle 0.3%	4212	Subject did not use study medication
Vehicle 0.3%	4244	Subject did not use study medication
Nepafenac 0.3%	4245	Subject did not use study medication
Vehicle 0.3%	4246	Subject did not use study medication
<b>6192</b>		
Vehicle 0.3%	4501	Treatment failure
Nepafenac 0.1%	4513	Protocol violation – No on-therapy follow-up data
Nepafenac 0.1%	4515	Protocol violation – No on-therapy follow-up data
Nepafenac 0.1%	4516	Protocol violation – No on-therapy follow-up data
Nepafenac 0.3%	4521	Subject did not use study medication
Nepafenac 0.1%	4526	Subject did not use study medication
Nepafenac 0.1%	4540	Treatment failure
Nepafenac 0.1%	4543	Noncompliance
<b>6216</b>		
Vehicle 0.3%	4601	Treatment failure
Vehicle 0.3%	4606	Treatment failure
Vehicle 0.3%	4615	Other
Nepafenac 0.3%	4618	Other
Vehicle 0.3%	4619	Treatment failure
Nepafenac 0.1%	4620	Subject did not use study medication
Vehicle 0.3%	4621	Treatment failure
Nepafenac 0.1%	4628	Treatment failure
Vehicle 0.3%	4630	Other

**Reviewer’s Comment:** *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.*

#### 7.3.4 Significant Adverse Events

Refer to Section 7.3.2.

#### 7.3.5 Submission Specific Primary Safety Concerns

*No specific primary safety concerns were identified for the submission.*

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

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

	<b>Nepafenac 0.3% N=1339</b>	<b>Nevanac N=819</b>	<b>Nepafenac 0.1% N=506</b>	<b>Nepafenac 0.3% Vehicle N=455</b>	<b>Nevanac Vehicle N=205</b>
<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%)

**Reviewer's Comment:** *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.*

### 7.4.2 Laboratory Findings

Laboratory evaluations were not performed in either Study C-09-055 or C-11-003.

### 7.4.3 Vital Signs

Vital signs were not evaluated in either Study C-09-055 or Study C-11-003.

### 7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not obtained in either Study C-09-055 or Study C-11-003.

### 7.4.5 Special Safety Studies/Clinical Trials

No special safety studies or clinical trials were conducted in support of this application.

#### 7.4.6 Immunogenicity

Nepafenac ophthalmic suspension is contraindicated in patients with previously demonstrated hypersensitivity to any ingredients in the formulation or to other NSAIDs. There is no known potential to cause immunogenicity.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

Various dosing regimens were studied in support of this application and during the clinical development of nepafenac. The known safety profile of non-steroidal anti-inflammatory drugs indicates that the frequency of adverse events increases with repeated instillation. No clinical evidence of dose dependent adverse events was submitted in this application.

#### 7.5.2 Time Dependency for Adverse Events

Various dosing regimens were studied in support of this application and during the clinical development of nepafenac. The known safety profile of non-steroidal anti-inflammatory drugs indicates that the frequency of adverse events increases with repeated instillation and higher concentrations. No clinical evidence of time dependent adverse events during the proposed treatment duration (15 days) was submitted in this application.

#### 7.5.3 Drug-Demographic Interactions

The safety profiles of both nepafenac formulations were similar in the subgroup analyses performed by age, race, gender, and iris color. The sample sizes for each subgroup were small making interpretation difficult.

There were no significant new findings. Drug-disease interactions are sufficiently described in the current labeling for Nevanac (nepafenac ophthalmic suspension) 0.1%.

#### 7.5.4 Drug-Disease Interactions

There were no significant new findings. Drug-disease interactions are sufficiently described in the current labeling for Nevanac (nepafenac ophthalmic suspension) 0.1%.

#### 7.5.5 Drug-Drug Interactions

There were no significant new findings in either study. Drug-drug interactions are sufficiently described in the current labeling for Nevanac (nepafenac ophthalmic suspension) 0.1%.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

Nepafenac has not been evaluated in long-term carcinogenicity studies; however the active metabolite of nepafenac, amfenac, was evaluated in a 2-year carcinogenicity bioassay. Amfenac sodium was administered to mice at doses up to 30 mg/kg/day and was shown to be non-carcinogenic.

### 7.6.2 Human Reproduction and Pregnancy Data

The drug was not studied in pregnancy. No pregnancies were reported during the clinical trial.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

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

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No information is available on overdosage of nepafenac during clinical trials in adults.

## 7.7 Additional Submissions / Safety Issues

No clinical studies evaluating Nepafenac Ophthalmic Suspension, 0.3% are ongoing or have been initiated or completed since the NDA was submitted in December 2011. Nepafenac Ophthalmic Suspension, 0.3% is not marketed in any country. There is no new safety information available for Nepafenac Ophthalmic Suspension, 0.3% per the 120-Day Safety Update submitted on April 6, 2012.

## 8 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.

**Reviewer's Comment:** *The postmarketing experience data submitted revealed no new safety signals and required no additional revisions to the current labeling.*

## 9 Appendices

### 9.1 Literature Review/References

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

### 9.2 Advisory Committee Meeting

No Advisory Committee meeting was held for this application.

### 9.3 Labeling Recommendations

The applicant submitted updated draft labeling on February 17, 2012.

Following is that draft labeling

The applicant's additions are noted by underline and deletions by ~~\_\_\_\_\_~~

The reviewer's additions are noted by underline and deletions by ~~\_\_\_\_\_~~

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RHEA A LLOYD  
09/14/2012

WILLIAM M BOYD  
09/14/2012



## CLINICAL FILING CHECKLIST FOR NDA 203-491

	Content Parameter	Yes	No	NA	Comment
	Indication: Treatment of pain and inflammation associated with cataract surgery  Pivotal Study #2: C-09-055 Indication: Treatment of pain and inflammation associated with cataract surgery				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product ( <i>e.g.</i> , QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested	X			

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

## CLINICAL FILING CHECKLIST FOR NDA 203-491

	Content Parameter	Yes	No	NA	Comment
	by the Division)?				
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Full waiver requested
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?   YES**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

# CLINICAL FILING CHECKLIST FOR NDA 203-491

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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Reviewing Medical Officer

Date

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Clinical Team Leader

Date

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

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RHEA A LLOYD  
01/30/2012

WILLIAM M BOYD  
01/30/2012