CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203491Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products[1]
Subject	Division Director Summary Review
BLA Number	NDA 203491
Related INDs	IND 49924
Review type	Standard
Applicant Name	Alcon Pharmaceuticals, Ltd.
Date of Submission **Date of Receipt**	December 15, 2011 December 16, 2011
PDUFA Goal Date	October 16, 2012
Proprietary Name / **Established (USAN) Name**	pending nepafenac
Formulation **Concentration** **Dosing Regimen**	Topical ophthalmic suspension 0.3% 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 post-operative period. An additional drop should be administered 30 to 120 minutes prior to surgery (total up to 16 days)
Proposed Indication	For the treatment of pain and inflammation associated with cataract surgery
Action for NME	*Approval*

[1] The Office of Antimicrobial Products was reorganized effective May 2011; specifically the Division of Special Pathogen and Transplant Products (DSPTP) and Division of Anti-Infective and Ophthalmology Products (DAIOP) were reorganized into the Division of Transplant and Ophthalmology Products (DTOP) and the Division of Anti-Infective Products (DAIP).

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Rhea Lloyd, Bill Boyd 9/14/2012, 10/9/2012
CDTL Review	Bill Boyd 10/16/2012
Deputy Director Review	Wiley Chambers 10/16/2012
Statistical Review	Rima Izem, Yan Wang 9/12/2012
Pharmacology/Toxicology Review	Aaron Ruhland, Lori Kotch 9/13/2012
Clinical Pharmacology Review	Yongheng Zhang, Philip Colangelo 8/28/2012
CMC – ONDQA, Division II, Branch V Review	Rao Kambhampati, Rapti Madurawe 9/13, 2012,9/19/2012, 10/11/2012, 10/12/2012
CMC-Biopharmaceutics	Tapash Ghosh, Angelica Dorantes 9/14/2012
Quality Microbiology Review	Steven Donald, Bryan Riley 5/28/2012
OC/Facilities Inspection	M Stock 4/23/2012 Acceptable
OSI/DGCPC	Kassa Ayalew, Susan Leibenhaut, Susan Thompson 7/2/2012, 10/8/2012
OSE/DMEPA Proprietary Name Letters	Jung Lee, Jamie Wilkins Parker, Kellie Taylor, Carol Holquist 6/14/2012, 8/9/2012 Carol Holquist 6/14/2012, 8/17/2012
OSE/OMEPARM/DMEPA Label, Labeling and Packaging Review	Jung Lee, Jamie Wilkins Parker, Carol Holquist 6/29/2012
Pediatric Review Committee	Pediatric studies waived 4/25/2012

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
ONDQA=Office of New Drug Quality Assessment
OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance (formerly Division of Scientific Investigation (DSI)
OMEPARM=Office of Medication Error Prevention and Risk Management
DMEPA=Division of Medication Error Prevention and Analysis
OPDP/DPDP=Office of Prescription Drug Promotion/Division of Professional Drug Promotion; formerly, DDMAC=Division of Drug Marketing, Advertising and Communication

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1. Summary and Recommendations

Nepafenac ophthalmic suspension, 0.3% has been shown to be effective and safe for the treatment of pain and inflammation associated with cataract surgery based on superiority to vehicle and non-inferiority to the approved NEVANAC control arms. The treatment regimen evaluated in two Phase 3 trials and recommended for approval is 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 post- operative period. An additional drop should be administered 30 to 120 minutes prior to surgery (total up to 16 days).

Inflammation and Ocular Pain Resolution Results of Nepafenac 0.3% versus Vehicle at Day 14 Post-surgery (All-Randomized Population)

Studies	Treatment	Inflammation Resolution at Postop Day 14	Ocular Pain Resolution at Postop Day 14
Study 1	TRADENAME (n/N) [1]	552/851 (65%)	734/851 (86%)
	NEVANAC (n/N) [1]	568/845 (67%)	737/845 (87%)
	Vehicle (n/N) [1]	67/211 (32%)	98/211 (46%)
	Difference (95% CI) [2]	33% (26%, 40%)	40% (32%, 47%)
Study 2	TRADENAME (n/N) [1]	331/540 (61%)	456/540 (84%)
	Nepafenac 0.1% QD*	322/534 (60%)*	439/534 (82%)*
	Vehicle (n/N) [1]	63/268 (24%)	101/268 (38%)
	Difference (95% CI) [2]	38% (31%, 45%)	47% (40%, 54%)

(b) (4)

The safety of the 0.3% nepafenac formulation was evaluated in over 1300 patients treated with this product, and no new adverse reactions were identified in these trials or from post-marketing information.

Alcon currently markets a 0.1% nepafenac ophthalmic suspension under the trade name NEVANAC which is given three times daily for the same indication; therefore this represents a new concentration and a once-daily regimen.

The labeling will state that after cataract surgery, approximately 5 to 10% of patients experienced re: capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation, and approximately 1 to 5% included conjunctival edema, corneal edema, dry eye, lid margin crusting, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, photophobia, tearing and vitreous detachment. Some of these adverse reactions may also be the consequence of the cataract surgical procedure.

All reviewers recommend approval. OSI recommends that clinical site data are considered reliable. OC recommends that manufacturing facilities are recommended acceptable. Multiple trade names have been reviewed and rejected by DMEPA for reasons summarized in their reviews, (b) (4) and there is no approved trade name at this time; however, new drug applications can be approved without a trade name. Product labeling has been reviewed and is acceptable, the package insert is similar to the approved NEVANAC labeling, except where specific differences are present, including product characteristics and results of new studies.

The application will be issued an *Approval* letter.

1.1 Deficiencies
None

1.2 Post-Marketing Studies:
None

1.3 Other Issues
There is no approved tradename for this product at this time.

2. Background

Nepafenac is a non-steroidal anti-inflammatory drug (NSAID). The active ingredient was first approved August 19, 2005 as NEVANAC (nepafenac ophthalmic suspension) 0.1% under NDA 21862 for the same indication. The recommended treatment regimen of NEVANAC is one drop applied to the affected eye three-times-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. The product is supplied in a 4 mL bottle containing 3 mL of suspension. Labeling was revised and approved in the PLR format on May 8, 2008.

The applicant developed the current product with the goal of having a higher concentration (0.3%) that could be administered once-daily (QD).

As noted by Dr. Lloyd, there are currently four NSAIDs and two corticosteroids approved for the treatment of postoperative inflammation (and pain for some): 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).

2.1 Application History
IND 49924 for nepafenac (AL-6515, amfenac) was originally submitted February 2, 1996. This IND includes developmental work on both the 0.1% and 0.3% formulations. The earlier studies evaluated (b) (4) nepafenac ophthalmic suspension 0.1% formulation for prevention and treatment of ocular inflammation associated with anterior segment surgery, including cataract extraction.

An end-of-phase 2 meeting was held August 11, 2003 for the 0.1% formulation there was discussion of the cataract surgery indication. (b) (4)

Another end-of-phase 2 meeting was held October 5, 2009 during which the 0.3% suspension dosed once daily for treatment of postoperative pain and inflammation associated with cataract surgery was discussed, along with CMC, nonclinical and clinical/statistical issues. The Division agreed that one controlled trial would be adequate to support filing the application. A Type B meeting was held January 10, 2011 during which the protocol comparing nepafenac

0.3% and approved TID NEVANAC were discussed.[2, 3] There is no record of a pre-NDA meeting for this indication. The most recent meeting was a Type B meeting on July 24, 2012 during which (b) (4)

On August 10, 2011, the applicant notified the FDA that sponsorship had changed from Alcon, Inc. to Alcon Pharmaceuticals, Ltd.

3. CMC/Product Quality Microbiology

For complete details, see the reviews by the product quality, quality microbiology and CMC biopharmaceutics reviewers. The following summary is excerpted from these reviews:

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The proposed labeling and labels have adequate information as required. The inspection of the manufacturing and testing facilities was complete and the Office of Compliance issued an Overall Acceptable Recommendation for this NDA on April 23, 2012.

Comments:
The Product Quality and Microbiology Sterility reviewers recommend approval of the application. There are no outstanding deficiencies and no post-marketing commitments requested.

The drug product, nepafenac ophthalmic suspension, 0.3% is a sterile, preserved, multi-dose aqueous suspension for topical ophthalmic application. Each 100 mL of the suspension contains 0.3 g (w/v) of nepafenac as the active ingredient and the following compendial grade (USP or NF) excipients: benzalkonium chloride (0.005 g; preservative, antimicrobial agent), carboxymethylcellulose sodium (b) (4) guar gum (b) (4) carbomer 974P (b) (4) boric acid (b) (4) edetate disodium (b) (4) propylene glycol (b) (4) sodium chloride (b) (4) sodium hydroxide and/or hydrochloric acid (QS for pH adjustment), and purified water (b) (4) The suspension is packaged in 4-mL size oval, LDPE Drop-Tainer® dispenser (bottle) with a LDPE dispensing plug and gray polypropylene cap filled with either 1.7 mL (for trade) or with 0.8 mL (for professional sample) of the suspension. The proposed packaging system (Drop-Tainer®) is already in the market and the gray cap color is consistent with AAO recommendation for NSAIDS. The applicant requested an expiration dating period of 18 months, which is acceptable according to the reviewer. The post-approval stability commitment to place the commercial lots on stability is acceptable.

A drop size study to simulate patient use of the product was conducted for Nepafenac Ophthalmic Suspension, 0.3%. The drop size data indicate an average drop size of approximately 40 microliters.

[2] IND 49924, Statistical review, March 17, 2011 and April 20, 2011. In DARRTS, item 127 sent January 24, 2011 is listed as sponsor submitted meeting minutes.
[3] IND 49924, entry March 25, 2011 states, "Alcon has requested to cancel the EOP2 meeting currently scheduled for March 25, 2011 for IND 49924 Nepafenac (b) (4) ."

Table 2.1.1-1: Composition of the Nepafenac Ophthalmic Suspension, 0.3% FID 115535

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

Note: FID = Formulation Identification Number
[a] Meets in-house monograph
(b) (4)

The drug product is manufactured by Alcon Laboratories Inc., Fort Worth, TX and the manufacturing process consists of (b) (4) Key process variables and control strategy (Quality by Design, QbD) were provided for the manufacture of the drug product. The specification for the drug product was finalized after negotiation with the reviewer.

The manufacturing and sterilization process is found to be acceptable by the product quality microbiologist (OPS). (b) (4)

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

A bio-waiver is not required and in-vitro drug release data are not necessary for this product.

Product specifications are listed in the following table from the applicant:

Table 3.2.P.5.1–1 Regulatory Acceptance Specifications for Nepafenac Ophthalmic Suspension, 0.3%

Test	Specification
Nepafenac (AL-6515) Identity (TLC)[a]	(b) (4)
Nepafenac (AL-6515) Identity (HPLC)[a]	
Nepafenac (AL-6515) Assay	
Impurities:	
(b) (4	
Benzalkonium Chloride Identity[a]	
Benzalkonium Chloride Assay	
Edetate Disodium Identity[a]	
Edetate Disodium Assay	
pH	
Osmolality	
Appearance Suspension: Color Uniformity	
Redispersibility	
Viscosity @ 12 rpm, CP-52 LVT	
Particle Size, Suspension (b) (4)	
Endotoxin[a]	
Sterility	

[a] Release test only

Guar gum, a well-known and characterized compendial material, is a naturally occurring material consisting primarily of guar galactomannan. The main components of guar galactomannan are polysaccharides composed of D-galactose and D-mannose. Additionally, a derivative of guar gum, commonly known as HP guar (hydroxypropyl guar), has been used in Alcon's topical over-the-counter (OTC) SYSTANE® family of lubricant eye drops. These ophthalmic products, SYSTANE® Lubricant Eye Drops and SYSTANE® ULTRA have been on the US market for up to six years.

Environmental Assessment: The applicant is granted categorical exclusion for marketing under 21 CFR 25.31(c).

4. Nonclinical Pharmacology/Toxicology

For detailed information, see Pharmacology/Toxicology (P/T) reviews.

The applicant relies on their previous systemic and ocular nonclinical studies of nepafenac, and the 1-month bridging study and ocular distribution study submitted in this application.

The proposed formulation is similar to the marketed NEVANAC (nepafenac 0.1% TID) product and differs in the concentration of nepafenac and excipients. The current product contains the novel excipient guar gum (b) (4) and the previously qualified excipient carboxymethylcellulose (CMC) (b) (4) In the FDA inactive ingredients database, CMC is qualified for ophthalmic use in solution up to 0.5%. The applicant conducted a one-month (35-day) toxicity/bridging study and an ocular distribution study to qualify the excipients; no treatment-related toxicities were reported in any dose group (0.3% to 1.5% QD, bilateral), and toxicokinetic results showed a less than dose proportional increase in exposure (amfenac and nepafenac) across doses. No new toxicities were associated with the increased strength and additional excipients.

The P/T reviewer recommends updating the exposure calculations for animal and human as shown in blue font, and provided the applicant with details of the calculation how these values were obtained:

> "At this dose, the animal plasma exposure to nepafenac and amfenac was approximately *70 and 630 times* human plasma exposure at the recommended human topical ophthalmic dose for rats and *20 and 180 times* human plasma exposure for rabbits, respectively. In rats, maternally toxic doses ≥ 10 mg/kg were associated with dystocia, increased postimplantation loss, reduced fetal weights and growth, and reduced fetal survival."

Cataracts

The P/T reviewer noted that drug levels in rabbits in the anterior segment tissues (bulbar conjunctiva, cornea, iris-ciliary body) are ~2 to 3-fold higher with Nepafenac 0.3% dosed QD compared to levels achieved following nepafenac 0.1% dosed TID. The exposure to nepafenac in the lens is similar following 0.1% nepafenac TID and 0.3% nepafenac QD dosing regimens, but exposure to amfenac in the lens was higher with nepafenac 0.1% TID than nepafenac 0.3% QD. Given that in previous studies of monkeys and rabbits cataract formation was seen, and the potential accumulation of amfenac/nepafenac in the lens tissues, the possibility that the cataracts are treatment-related cannot be ruled out.

Comment:
The application is recommended for approval from a pharmacology/toxicology standpoint. Labeling recommendations have been finalized. The applicant asked for clarification on the animal to human plasma exposure calculations in the pregnancy section, and these were provided.

The potential for nepafenac to have a role in cataract formation would be important to consider for indication that would seek longer duration of therapy for an indication that does not include cataract removal.

5. Clinical Pharmacology/Biopharmaceutics

For complete information, see clinical pharmacology review.

Nepafenac (amfenac amide) is a prodrug that penetrates the cornea and is converted to the active moiety amfenac by intraocular hydrolases. Nepafenac has very weak cyclooxygenase inhibitory activity whereas amfenac exhibits more potent cyclooxygenase activity.

The systemic PK of nepafenac and its pharmacologically active metabolite (amfenac) following single and multiple doses of nepafenac 0.3% in healthy subjects were assessed in a Phase 1 study (C-09-053). Following bilateral topical ocular dosing of 1 drop of nepafenac 0.3% once daily for 4 days, the mean nepafenac and amfenac plasma concentration were similar on Day 1 and Day 4, indicating no accumulation. The mean steady-state Cmax for nepafenac and amfenac were 0.847 ± 0.269 ng/ml and 1.13 ± 0.491 ng/ml, respectively.

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

Comment:
The reviewer recommends approval from the clinical pharmacology perspective; labeling revisions have been made and no phase 4 studies are requested.

6. Clinical Microbiology/Immunology

Not applicable

7. Clinical/Statistical-Efficacy

For complete details, see clinical and statistical reviews.

7.1 Phase 3 clinical trials

The following table from Dr. Lloyd's review provides a summary of the clinical trials, including two large Phase 3 controlled trials which compared nepafenac 0.3% QD to NEVANAC 0.1% TID, NEVANAC 0.1% QD, and vehicle QD and TID.

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

Study Identifier / Study Type	Study Design	Study Population	Treatment Group	Number of Patients[a]	Dosing Regimen	Dosing Duration
Safety / Clinical Pharmacology Studies						
C-09-053	Randomized, double masked, placebo-controlled, parallel group	Healthy subjects 18 years of age and older	• Nepafenac 0.3% QD • Vehicle QD	12 8	1 drop in both eyes once daily for 4 days	4 days
Post-cataract Inflammation Safety and Efficacy Studies						
C-11-003 Safety and Efficacy / Post-Cataract Inflammation	Randomized, double masked, active- and placebo-controlled, parallel group	Patients, 18 years of age and older, requiring cataract extraction with implantation of a posterior chamber intraocular lens	• Nepafenac 0.3% QD • Nepafenac 0.1% QD • Vehicle QD	522 506 254	1 drop in study eye QD beginning 1 day before surgery. An additional drop was administered 30 to 120 min prior to surgery	16 days
C-09-055 Safety and Efficacy / Post-Cataract Inflammation	Randomized, double masked, active- and placebo-controlled, parallel group	Patients, 18 years of age and older, requiring cataract extraction with implantation of a posterior chamber intraocular lens	• Nepafenac 0.3% QD • Nevanac TID • Vehicle QD • Vehicle TID	807 813 197 205	1 drop in study eye QD or TID, as assigned, beginning 1 day before surgery. An additional drop was administered 30 to 120 minutes prior to surgery	16 days

a Safety Dataset

There were 49 US and 16 European sites in study C-09-055 and 37 US investigators in Study C-11-003; of these 35 US investigators actually participated in both studies and 26 of these participated in the two trials concurrently.

There were 2120 patients randomized 4:4:1:1 in study C-09-055 (with Europe accounting for 268/2120 [13%] of randomized subjects) and 1342 patients were randomized 2:2:1 in study C-11-003.

Efficacy Endpoints:

Dr Lloyd notes that: Aqueous cells and flare are the hallmark of ocular inflammation and have been the basis of evaluating the primary efficacy and, 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. 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).

Aqueous cells and flare and ocular pain were grading using the scales provided in the tables below:

Grading Scales for Aqueous Cells and Flare

Aqueous Cells	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
Aqueous Flare	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.

Grading Scales for Ocular Pain

Ocular Pain (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 of 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 *other than* 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

Cure was defined as a score of 0 for both aqueous cells and flare and a score of 0 for ocular pain. [Clinical success was defined as cells score ≤ 1 (0-5 cells) and flare score = 0. This was an unplanned analysis.]

Primary Efficacy Endpoint

The primary endpoint in C-11-003 was to demonstrate that nepafenac 0.3% QD is superior to nepafenac vehicle 0.3% QD for the prevention and treatment of ocular inflammation with respect to cure rate 14 days after cataract extraction.

The primary endpoint in C-09-055 was to demonstrate that nepafenac 3% dosed QD was non-inferior to NEVANAC 0.1% dosed TID, and each of these was superior to vehicle dosed at the same frequency.

Secondary Efficacy Endpoints

The secondary in C-11-003 To demonstrate that nepafenac 0.3% dosed QD is superior to nepafenac 0.1% dosed QD, for the prevention and treatment of ocular inflammation with respect to cure rate 7 days after cataract extraction.

Safety Endpoints
Information was collected on best-corrected visual acuity (BCVA), IOP, slit-lamp parameters (chemosis, bulbar conjunctival injection, corneal edema), dilated fundus parameters (retina/macula/choroid, optic nerve).

Study Schedule
Patients were assessed at baseline, surgery, Days 1, 3, 7 and 14, and at the Early Exit Visit and any unscheduled visit.

7.2 Efficacy Results

The following two table show how many patients were randomized, treated, completed and discontinued.

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)

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)

By far the main reason for discontinuation in the vehicle arms was treatment failure; patients received rescue medication (details of discontinuations are listed in the CDTL review).

The demographic characteristics were similar in both trials and in all treatment groups within each study. Median age in both studies and all treatment groups was around 70 years of age. More females (56% to 61%) were in these studies than males (39% to 45%). The large majority of subjects in these studies are white (84% to 87%), then Black (7% to 9%) and Asian (5% to 7%).

The statistical reviewer notes that the FDA conclusions regarding efficacy are the same as the applicant's, but the numerical results are different due to differences in definition of Intent to Treat population (ITT). FDA considers all randomized patients to be part of the ITT population, whereas the application only included all treated patients in the analysis. This had the effect of lowering the applicant's denominators and thus yielding higher effect rates. However, the treatment effect (active minus vehicle) is generally similar, and efficacy is concluded from the applications and FDA's analyses.

The tables below provide the FDA-calculated rates of inflammation resolution and ocular pain resolution for each of the studies. Table 1 provides the outcome compared to the vehicle control, showing in both trials nepafenac 3% is superior to vehicle, and Table 2 provides information on the active controls, showing nepafenac 3% is non-inferior to the NEVANAC regimen.

NDA 203491 nepafenac ophthalmic suspension, 0.3%
Indication: For the treatment of pain and inflammation associated with cataract surgery

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

Study	Treatment	Inflammation Resolution	Ocular Pain Resolution
C09055	Nepafenac 0.3% (n/N*)	552/851 (65%)	734/851 (86%)
	Vehicle (n/N*)	67/211 (32%)	98/211 (46%)
	Difference (95% CI)**	33% (26%, 40%)	40% (32%, 47%)
C11003	Nepafenac 0.3% (n/N*)	331/540 (61%)	456/540 (84%)
	Vehicle (n/N*)	63/268 (24%)	101/268 (38%)
	Difference (95% CI)**	38% (31%, 45%)	47% (40%, 54%)

* n/N is the ratio of those with no treatment failure prior to Day 14 post-surgery visit and complete resolution by Day 14 post-surgery visit over all randomized subjects prior to cataract surgery. Treatment failure is defined as cells score of grade 3 or greater, a flare score of grade 3 or greater, or an ocular pain score of grade 4 or greater.
** Difference is (test drug – vehicle). The 95% confidence interval is derived using asymptotic approximation.

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

Study	Visit	Treatment	Inflammation Resolution	Ocular Pain Resolution
C09055	Day 7	Nepafenac 0.3% (n/N*)	295/851 (35%)	717/851 (84%)
		NEVANAC (n/N*)	330/845 (39%)	733/845 (87%)
		Difference (95% CI)**	4% (0%, 9%)	2% (-1%, 6%)
	Day 14	Nepafenac 0.3% (n/N*)	552/851 (65%)	734/851 (86%)
		NEVANAC (n/N*)	568/845 (67%)	737/845 (87%)
		Difference (95% CI)**	2% (-2%, 7%)	1% (-2%, 4%)
C11003	Day 7	Nepafenac 0.3% (n/N*)	174/540 (32%)	453/540 (84%)
		Nepafenac 0.1% Once Daily (n/N*)	172/534 (32%)	425/534 (80%)
		Difference (95% CI)**	0% (-6%, 6%)	-4% (-9%, 1%)
	Day 14	Nepafenac 0.3% (n/N*)	331/540 (61%)	456/540 (84%)
		Nepafenac 0.1% Once Daily (n/N*)	322/534 (60%)	439/534 (82%)
		Difference (95% CI)**	-1% (-7%, 5%)	-2% (-7%, 2%)

* n/N is the ratio of those with no treatment failure prior to Day 14 post-surgery visit and complete resolution by Day 14 post-surgery visit over all randomized subjects prior to cataract surgery.
** Difference is (active control – test drug). The 95% confidence interval is derived using asymptotic approximation.

The applicant's analyses are provided below: Table 6.1.4.1-1 below shows that nepafenac 0.3% was superior to vehicle when the ITT and PP populations were analyzed, Table 6.1.4.1-2 shows that nepafenac 0.3% QD is non-inferior to NEVANAC 0.1% given TID.

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

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

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

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

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

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

Table 6.1.4.2-1 for study C-11-03 shows that Nepafenac 0.3% is superior to its vehicle.

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

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

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

7.3 Non-Inferiority Margin

The 10% non-inferiority (NI) margin was justified from two previously conducted studies for the approval of NEVANAC 0.1% (C-03-32 and C-04-65) in which a combined cure rates were 65.8% (210/319) for NEVANAC and 27.5% (85/309) for vehicle. The treatment effect was 38.4% (95% CI = 31.3% to 45.5%). The proposed 10% NI margin is less than one-third the lower confidence limit for the observed treatment difference between NEVANAC and NEVANAC vehicle.

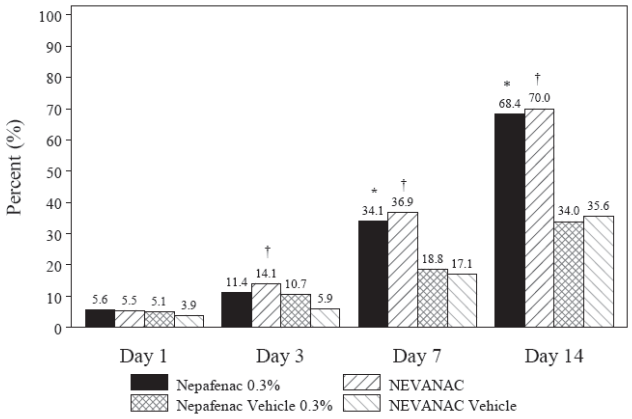
7.4 Additional Analyses

Cumulative cure rates and cumulative resolution of ocular pain are provided below, showing incremental improvement over the course of the 14 day follow-up.

Cumulative cure rates:

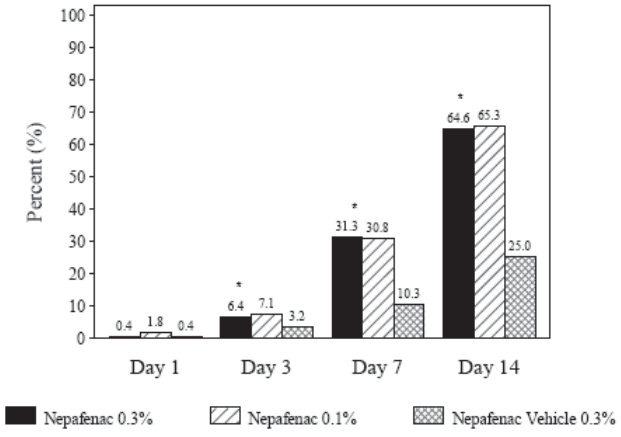
Cumulative cure rates at each of the four post-cataract surgery visits are shown in the figures below. By Day 14, 64.4% and 68.4% of patients on nepafenac 3% had complete resolution of inflammation and pain as seen in Figure 6.1.6.1.1 and 6.1.6.2.1.

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

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

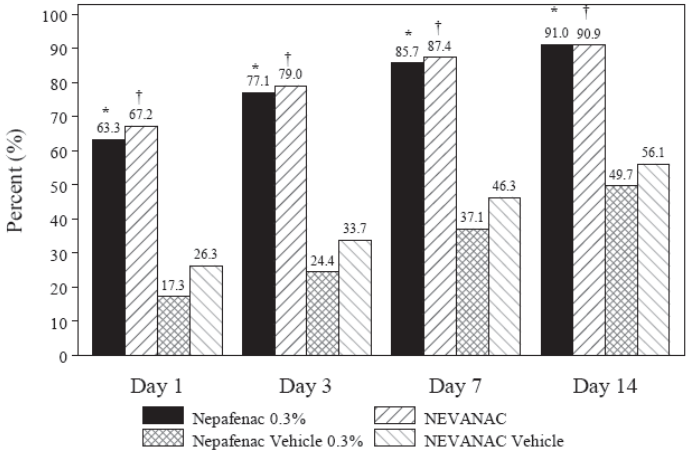


*p-value < 0.05: Nepafenac 0.3% versus Nepafenac Vehicle 0.3%

Resolution of Ocular Pain:

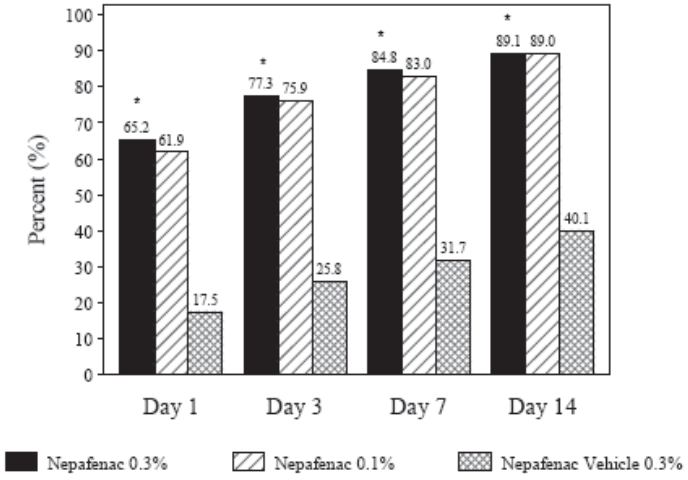
Resolution of ocular pain was a secondary endpoint: both nepafenac 0.3% and NEVANAC were statistically superior to their respective vehicles in the percent of pain free patients at Day 14 and Nepafenac 0.3% QD was non-inferior to NEVANAC 0.1% TID.

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

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



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

Comment:

The clinical and statistical reviewers concluded that nepafenac 0.3% given once daily at the recommended regimen was effective for the treatment of pain and inflammation associated with cataract surgery. A summary of the efficacy findings is included in Section 14 of the labeling.

8. Safety

The details on the safety evaluation are included in the clinical and statistical reviews.

Safety was evaluated in 1351patients from the two large controlled studies submitted in the application who received nepafenac 0.3% once daily. There were no deaths, most subjects who discontinued were in the vehicle control arm and were given rescue therapy and classified as treatment failure. Six patients with serious ocular adverse reactions resolved with treatment, some systemic diseases (cancer, brain edema, CVA) continued.

Adverse reactions reported in ≥ 1% of the safety population are shown below, and the rates associated with nepafenac are generally as low as for the vehicle (sometimes lower).

Table 7.4.1 Adverse Events Occurring at a Rate of ≥ 1%
Safety Population

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

In addition to information on the adverse reactions reported during trials, the labeling includes warning and precautions about adverse reactions associated with NEVANAC and other approved NSAIDs.

- Increased bleeding time
- Delayed healing
- Corneal effects-epithelial breakdown, corneal thinning, erosion, ulceration and perforation
- Contact lens wear – risks with Benzalkonium chloride, possibly product absorption into contact
- Advice to patients about potential contamination of product

8.1 Post Marketing Experience

Since the approval of NEVANAC in the US in August 2005, Alcon has registered nepafenac-containing products for ocular use in a total of 84 countries world-wide. 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 and Alcon received a total of 87 cases (17 serious, 70 nonserious) worldwide associated with the use of nepafenac. Based on the medical officer's review of this information, no new of potentially important safety findings that have not already been included in the NEVANAC and draft nepafenac 0.3% labeling were identified.

Comment:
The adverse reactions were reviewed. The reviewers concluded that the benefits outweigh the risks and recommend approval of the application. The adverse reaction findings and class labeling will be included in the warnings, precautions and adverse reactions section of labeling, as appropriate. Although the ADR rates in these trials are lower than those seen in the previous trials of NEVANAC, the applicant has chosen to have consistent rates reported in this PLR, this approach is more conservative and acceptable.

9. Advisory Committee Meeting

The application did not raise new scientific issues that needed input from the Advisory Committee.

10. Pediatrics

The application is subject to PREA because it represents a new dosage regimen. It was presented before the Pediatric Review Committee on August 25, 2012 and the recommendation was made to waive pediatric studies, the cited reason is that pediatric patients develop amore acute and pronounced pain after surgery and corticosteroids are considered the standard of care and the most effective therapy. (b) (4)

11. Other Relevant Regulatory Issues

11.1 Compliance Inspection - Facilities

The Office of Compliance issued an overall recommendation of "Acceptable" on April 23, 2012, as document in the FDA CDER EES establishment evaluation request summary report.

11.2 Office of Scientific Investigation (OSI) Audits

OSI inspected two investigators from Studies C-09-055 and C-11-003, who enrolled 160 and 171 patients, respectively. One investigator was given a classification of NAI and the other investigator was classified VAI, the violations were isolated (two subjects were given steroids). The overall conclusion and recommendation from OSI/DGCPC is that based on the inspectional findings above, efficacy and safety data obtained from these sites can be considered reliable in support of the application.

11.3 Debarment Certification

Alcon certified that they did not and will not use in any capacity the service of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in the connection of this application.

11.4 Financial Disclosure

The medical officer notes that the applicant provided disclosure of financial arrangements with the clinical investigators who participated in C-09-055 and C-11-003 and concluded that these arrangements did not raise questions about the integrity of the data.

11.5 Other Regulatory Issues

None identified.

12. Labeling

The package insert and carton and container labeling were reviewed as applicable by the Division, DMEPA, OPDP/DPDP, labeling recommendations were discussed and labeling finalized.

- **Package insert (PI):** The PI is written in PLR format, similar to the currently approved NEVANAC PI. Any discussion and resolution of different recommendation is included in the CDTL review.

- **Carton and Container Labels**: The labels have been reviewed by the Division, CMC and DMEPA and agreement reached or any differences in recommendations documented in the CDTL review.

- **Proprietary Name**: The proposed proprietary names of (b) (4) were found unacceptable by DMEPA. There is no approved trade name of this product at this time. However, an application can be approved without a trade name, and the applicant can work with DMEPA on getting an acceptable trade name after approval.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

The NDA will be issued an *Approval* letter given that two large controlled Phase 3 trials showed the product is safe and effective for the treatment of pain and inflammation associated with cataract surgery. All disciplines recommend approval, the facilities are acceptable and investigator site inspections recommend the clinical trial data are reliable. Labeling has been finalized.

13.2 Risk Benefit Assessment

Two large controlled clinical trials demonstrated that nepafenac ophthalmic suspension 0.3% was superior to vehicle and complete resolution of ocular inflammation and 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.

13.3 Recommendation for other Postmarketing Requirements and Commitments

None

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

/s/

RENATA ALBRECHT
10/16/2012