CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-862

MEDICAL REVIEW(S)

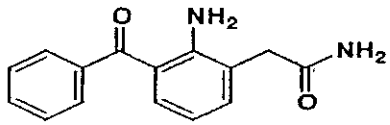
Medical Officer's Review of NDA 21-862
120-Day Safety Update
Labeling Amendment
Labeling for Carton and Container

NDA 21-862	Submission:	6/27/05
Medical Officer's Review	Submission:	8/05/05
	Submission:	8/12/05
	Review Completed:	8/15/05

Proposed Tradename: Nevanac

Established Name: nepafenac ophthalmic suspension, 0.1%

Chemical Name: 2-amino-3-benzoylbenzeneacetamide



Chemical Structure – Formula $C_{15}H_{14}N_2O_2$

Sponsor: Alcon Research, Ltd.
6201 South Freeway
Fort Worth, TX 76134

Pharmacologic Category: Nonsteroidal anti-inflammatory drug (NSAID)

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

Dosage Form and Route of Administration: Ophthalmic suspension for topical ocular administration

Submitted:

Submitted in the 120-Day Safety Update on 6/27/05 is a statement from Alcon Research, Ltd.:

Based upon a review of the additional safety data, there is no clinically relevant change in the side effect profile or risk/benefit ratio for nepafenac ophthalmic suspension, 0.1%.

Reviewer's Comments:

Concur. Original comments regarding the safety of nepafenac ophthalmic suspension, 0.1% are not altered.

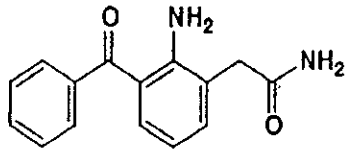
Submitted:

The sponsor has submitted on 8/05/05 a revised package insert incorporating all of the proposed agency labeling changes. The sponsor has modified the accepted label by eliminating some parentheses and correcting a numerical and spelling error as noted below.

Label:

NEVANAC™
(nepafenac ophthalmic suspension) 0.1%

DESCRIPTION
NEVANAC™ (nepafenac ophthalmic suspension) 0.1% is a sterile, topical, nonsteroidal anti-inflammatory (NSAID) prodrug for ophthalmic use. Each mL of NEVANAC™ suspension contains 1 mg of nepafenac. Nepafenac is designated chemically as 2-amino-3-benzoylbenzeneacetamide with an empirical formula of $C_{15}H_{14}N_2O_2$. The structural formula of nepafenac is:



Nepafenac is a yellow crystalline powder. The molecular weight of nepafenac is 254.28. NEVANAC™ ophthalmic suspension is supplied as a sterile, aqueous 0.1% suspension with a pH approximately of 7.4. The osmolality of NEVANAC™ ophthalmic suspension is approximately 305 mOsmol/kg. Each mL of NEVANAC™ contains: **Active:** nepafenac 0.1% **Inactives:** mannitol, carbomer 974P, sodium chloride, tyloxapol, edentate disodium benzalkonium chloride 0.005% (preservative), sodium hydroxide and/or hydrochloric acid to adjust pH and purified water, USP.

CLINICAL PHARMACOLOGY
Pharmacodynamics: NEVANAC™ suspension contains nepafenac (0.1%), a nonsteroidal anti-inflammatory and analgesic prodrug. After topical ocular dosing, nepafenac penetrates the cornea and is converted by ocular tissue hydrolases to amfenac, a nonsteroidal anti-inflammatory drug. Amfenac is thought to inhibit the action of

prostaglandin H synthase (cyclooxygenase), an enzyme required for prostaglandin production.

Pharmacokinetics:
Drug-Drug Interaction: Nepafenac at concentrations up to 300 ng/mL did not inhibit the *in vitro* metabolism of 6 specific marker substrates of cytochrome P450 (CYP) isozymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4). Therefore, drug-drug interactions involving CYP-mediated metabolism of concomitantly administered drugs are unlikely. Drug-drug interactions mediated by protein binding are also unlikely.

Gender: Data in healthy subjects indicate no clinically relevant or significant gender difference in the steady-state pharmacokinetics of amfenac following three-times-daily dosing of NEVANAC™.

Low but quantifiable plasma concentrations of nepafenac and amfenac were observed in the majority of subjects 2 and 3 hours postdose, respectively, following bilateral topical ocular TID dosing of nepafenac ophthalmic suspension, 0.1%. The mean steady-state C_{max} for nepafenac and for amfenac were 0.310 ± 0.104 ng/ml and 0.422 ± 0.121 ng/ml, respectively, following ocular administration.

Reviewer's comments:

Acceptable. The sponsor has eliminated parentheses and has corrected a numerical error in the C_{max}.

Clinical Studies: In two double-masked, randomized clinical trials in which patients were dosed three-times-daily beginning one day prior to cataract surgery, continued on the day of surgery and for the first two weeks of the postoperative period, NEVANAC™ ophthalmic suspension demonstrated clinical efficacy, compared to its vehicle in treating postoperative inflammation.

Patients treated with NEVANAC™ ophthalmic suspension were less likely to have ocular pain and measurable signs of inflammation (cells and flare) in the early postoperative period through the end of treatment than those treated with its vehicle.

For ocular pain in both studies a significantly higher percentage of patients (approximately 80%) in the nepafenac group reported no ocular pain on the day following cataract surgery (Day 1) compared to those in the vehicle group (approximately 50%).

Results from clinical studies indicated that NEVANAC™ has no significant effect upon intraocular pressure; however, changes in intraocular pressure may occur following cataract surgery.

INDICATIONS AND USAGE
NEVANAC™ ophthalmic suspension is indicated for the treatment of pain and inflammation associated with cataract surgery.

CONTRAINDICATIONS
NEVANAC™ ophthalmic suspension is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation or to other NSAIDs.

WARNINGS
There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory agents. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

With some nonsteroidal anti-inflammatory drugs including NEVANAC™, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

PRECAUTIONS
General: Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including NEVANAC™, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs including NEVANAC™ and should be closely monitored for corneal health.

Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Postmarketing experience with topical NSAIDs also suggests that use more than 1 day prior to surgery or use beyond 14 days post surgery may increase patient risk for occurrence and severity of corneal adverse events.

It is recommended that NEVANAC™ ophthalmic suspension be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Information for Patients: NEVANAC™ ophthalmic suspension should not be administered while wearing contact lenses.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nepafenac has not been evaluated in long-term carcinogenicity studies. Increased chromosomal aberrations were observed in Chinese hamster ovary cells exposed *in vitro* to nepafenac suspension. Nepafenac was not mutagenic in the Ames assay or in the mouse lymphoma forward mutation assay. Oral doses up to 5,000 mg/kg did not result in an increase in the formation of micronucleated polychromatic erythrocytes *in vivo* in the mouse micronucleus assay in the bone marrow of mice.

Nepafenac did not impair fertility when administered orally to male and female rats at 3 mg/kg (approximately 90 and 380 times the plasma exposure to the parent drug, nepafenac, and the active metabolite, amfenac, respectively, at the recommended human topical ophthalmic dose).

Reviewer's comments:

Acceptable. The sponsor has corrected the spelling of micronucleus.

Pregnancy: Teratogenic Effects.
Pregnancy Category C: Reproduction studies performed with nepafenac in rabbits and rats at oral doses up to 10 mg/kg/day have revealed no evidence of teratogenicity due to nepafenac, despite the induction of maternal toxicity. At this dose, the animal plasma exposure to nepafenac and amfenac was approximately 260 and 2400 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 80 and 680 times human plasma exposure for rabbits, respectively. In rats, maternally toxic doses $\geq$ 10 mg/kg were associated with dystocia, increased postimplantation loss, reduced fetal weights and growth, and reduced fetal survival.

Nepafenac has been shown to cross the placental barrier in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, NEVANAC™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects: Because of the known effects of prostaglandin biosynthesis inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of NEVANAC™ ophthalmic suspension during late pregnancy should be avoided.

Nursing Mothers: NEVANAC™ ophthalmic suspension is excreted in the milk of pregnant rats. It is not known whether this drug is excreted in human milk. Because many

drugs are excreted in human milk, caution should be exercised when NEVANAC™ ophthalmic suspension is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of NEVANAC™ in pediatric patients below the age of 10 years have not been established.

Geriatric Use: No overall differences in safety and effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS
In controlled clinical studies, the most frequently reported ocular adverse events following cataract surgery were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation. These events occurred in approximately 5 to 10% of patients.

Other ocular adverse events occurring at an incidence of 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 events may be the consequence of the cataract surgical procedure.

Nonocular adverse events reported at an incidence of 1 to 4% included headache, hypertension, nausea/vomiting, and sinusitis.

DOSAGE AND ADMINISTRATION
Shake well before use. One drop of NEVANAC™ ophthalmic suspension should be applied to the affected eye(s) 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.

NEVANAC™ ophthalmic suspension may be administered in conjunction with other topical ophthalmic medications such as beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics.

HOW SUPPLIED
NEVANAC™ (nepafenac ophthalmic suspension) is supplied in a natural, oval, low density polyethylene DROP-TAINER® dispenser with a natural low density polyethylene dispensing plug and gray polypropylene cap. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

3 mL in 4 mL bottle **NDC** 0065-0002-03

Storage: Store at 2 - 25°C (36 - 77°F).

Rx Only
[ALCON LOGO]®

Manufactured by:
Alcon Laboratories, Inc.
Fort Worth, TX 76134 USA

U.S. Patent No: 5,475,034

7 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Reviewer's comments:

The Chemist's concerns regarding the carton/container labeling (noted in original CMC review) have been adequately addressed. The carton and container labels are acceptable. Compared to the previous carton/container labeling submitted with the safety update on 6/27/05, Alcon has:

1) *revised the storage temperature;*
2) *revised the presentation of the ingredients on the carton labeling to be consistent with the package insert;*
3) *revised the presentation of the active ingredient on the container labeling to be consistent with the package insert;*
4) *deleted —— from the container labeling; and*
5) *increased the prominence of the established name on the container and carton labels to be commensurate with that of the proprietary name. Specifically, the text has been bolded and the color darkened.*

Conclusions:

NDA 21-862 is recommended for approval for the treatment of pain and inflammation associated with cataract surgery.

It is recommended that NDA 21-862 be approved with the revised package insert submitted.

Martin P. Nevitt, M.D., M.P.H.
Medical Officer

CLINICAL REVIEW

Application Type	NDA 21-862
Submission Number	000
Submission Code	Original
Letter Date	2/25/05
Stamp Date	2/27/05
PDUFA Goal Date	8/28/05 (Sunday); 8/26/05 (Friday)
Reviewer Name	Martin P. Nevitt, M.D., M.P.H.
Review Completion Date	7/21/05
Established Name	Nepafenac Ophthalmic Suspension, 0.1%
(Proposed) Trade Name	Nevanac
Therapeutic Class	Nonsteroidal Anti-Inflammatory Drug (NSAID)
Applicant	Alcon Research, Ltd. 6201 South Freeway Fort Worth, Texas 76134-2099 817-293-0450 FAX: 817-551-4630 Angela C. Kothe, OD, PhD 817-551-4933
Priority Designation	P

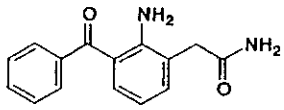
Structure	$C_{15}H_{14}N_2O_2$
	
Dosing Regimen	One drop in the affected eye three times daily beginning 1 day prior to cataract surgery, and continued on the day of surgery through the first 2 weeks of the postoperative period
Proposed Indication	[redacted] treatment of pain and inflammation associated with cataract surgery
Intended Population	Patients [redacted] years or older undergoing cataract surgery

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective, NDA 21-862 is recommended for approval for the treatment of pain and inflammation associated with cataract surgery when dosed three times a day beginning 1 day prior to cataract surgery and continued on the day of surgery through the first two post-operative weeks.

Reviewer's comments:

This NDA supports the use of nepafenac ophthalmic suspension, 0.1% for the treatment of pain and inflammation associated with cataract surgery. Nepafenac ophthalmic suspension 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. There are no new unexpected adverse events associated with the use of this product. The benefits of this drug outweigh the risks in the treatment of ocular inflammation and treatment of ocular pain following cataract surgery.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No additional clinical trials or postmarketing surveillance studies are required.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Established Name	nepafenac ophthalmic suspension, 0.1%
(Proposed) Trade Name	Nevanac
Therapeutic Class	Nonsteroidal Anti-Inflammatory Drug (NSAID)

There are currently no available topical treatments available for the treatment of pain and inflammation associated with cataract surgery.

Four clinical studies (C-95-93, C-97-30, C-02-53 and C-03-32) are pertinent to the demonstration of the safety and efficacy of nepafenac ophthalmic suspension, 0.1%. There are two dose-response studies (C-95-93 and C-97-30) in which nepafenac was dosed four-times-daily beginning the day after surgery and continuing through the first 2 weeks of the postoperative period. Concentrations of nepafenac range from 0.003% to 0.3%. Two additional studies (C-02-53 and C-03-32) use the final concentration (0.1%) and dosing regimen (three-

times-daily beginning 1 day prior to surgery, and continuing the day of surgery and through the first 2 weeks of the postoperative period). All 4 studies are placebo-controlled and conducted in adult patients requiring cataract extraction, the target patient population for the indication being pursued. The efficacy of nepafenac ophthalmic suspension, 0.1% for treatment of pain and inflammation following cataract surgery has not been investigated in pediatric patients.

1.3.2 Efficacy

Two adequate and well controlled clinical trials (C-02-53and C-03-32) demonstrate the efficacy of nepafenac ophthalmic suspension, 0.1%.

Reviewer's comments:

In determining nepafenac's efficacy results for inflammation and pain, the following criteria were utilized:

1.) For post-cataract inflammation at least a 1 unit or greater difference of the mean cell score during the post-operative period between the placebo and active group were required.

2.) For post-cataract pain the difference in the percentage of patients pain-free during the post-operative period between the active and placebo group was required to be statistically significant.

Nepafenac ophthalmic suspension, 0.1% (QD, BID and TID) in study C-02-53 was superior to placebo in the treatment of inflammation and pain associated with cataract surgery based upon clinical assessments of aqueous cells and pain. The TID dosing regimen was shown to be the optimal dosing regimen. Therefore in the final stage phase 3 study (C-03-32), all patients received TID dosing.

Nepafenac ophthalmic suspension, 0.1% dosed TID in study C-03-32 was superior to placebo in the treatment of inflammation and pain associated with cataract surgery based upon clinical assessments of aqueous cells and pain.

1.3.3 Safety

The most frequently reported adverse events among patients in the pertinent phase 3 post-cataract inflammation studies receiving nepafenac ophthalmic suspension, 0.1% (N=408) were decreased visual acuity (5.1%), capsular opacity (3.7%), headache (2.9%), foreign body sensation (1.7%), conjunctival edema (1.5%), and ocular pruritus (1.2%). All other adverse events among patients in the pertinent phase 3 post-cataract inflammation studies receiving nepafenac ophthalmic suspension, 0.1% occurred at an incidence of 1% (4 patients) or less.

The most frequently reported adverse events among patients in the pertinent phase 3 post-cataract inflammation studies receiving Vehicle (N=299) were photophobia (4.7%), decreased visual acuity (4.0%), capsular opacity (4.0%), ocular hyperemia (3.3%), foreign body sensation

(2.0%), headache (2.0%), conjunctival edema (1.7%), and ocular pruritus (1.3%). All other adverse events among patients in the pertinent phase 3 post-cataract inflammation studies receiving Vehicle occurred at an incidence of 1.0% (3 patients) or less.
All ocular events, with the exception of decreased visual acuity, occurred at a higher incidence among patients receiving Vehicle compared to patients receiving nepafenac ophthalmic suspension, 0.1%.

An analysis of ocular parameters (visual acuity, ocular signs, intraocular pressure, dilated fundus parameters, endothelial cell density, corneal thickness, and pupil diameter/response) and nonocular parameters (general physical examination, cardiovascular, and laboratory) revealed no safety concerns for the overall safety population, adult population, and elderly population.

Reviewer's Comments:

No safety concerns were identified based upon a review of the most common adverse events among patients in the pertinent phase 3 post-cataract inflammation studies.

1.3.4 Dosing Regimen and Administration

The recommended dosing schedule for nepafenac ophthalmic suspension, 0.1%, is one drop, applied topically to the affected eye, beginning 1 day prior to cataract surgery, and continued on the day of surgery through the first 2 postoperative weeks.

Reviewer's Comments:

The recommended dosing is appropriate based on the clinical data provided. Efficacy for this product was demonstrated, and there was an acceptable safety profile when dosed at this level. There are no recommended dose modifications for special populations.

1.3.5 Drug-Drug Interactions

Reviewer's Comments:

Additional drug-drug interaction studies were not conducted.

1.3.6 Special Populations

No overall differences in safety or effectiveness have been observed between elderly and adult patients.

There are no adequate and well-controlled studies in pregnant woman. No pediatric studies — — were conducted. Cataract development in the pediatric population is an orphan indication.

Reviewer's comments:

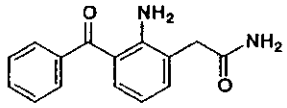
Nepafenac ophthalmic suspension should be labeled for patients 10 years or older.

There are no dosing modifications needed for any of the special populations (e.g. demographics, elderly, etc.). This is common for topical ophthalmic drugs due to the concentrations, dosing, amounts and the limited systemic availability.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Established Name nepafenac ophthalmic suspension, 0.1%
(Proposed) Trade Name Nevanac
Therapeutic Class Nonsteroidal Anti-Inflammatory Drug (NSAID)
Formulation $C_{15}H_{14}N_2O_2$



Proposed Indication — treatment of pain and inflammation associated with cataract surgery

Composition of Nepafenac Ophthalmic Suspension, 0.1%
FID[a] 105022

Component	Percent w/v	Function	Compendial Status
Nepafenac (AL-6515)	0.1	Active Ingredient	Non-compendial[b]
Benzalkonium Chloride	0.005	/	NF
Carbomer 974P	—	/	NF[c]
Tyloxapol		/	USP
Edetate Disodium	—	Preservative	USP
Mannitol	—	/	USP
Sodium Chloride	—	/	USP
Sodium Hydroxide and/or Hydrochloric Acid	QS for pH to —	pH adjustment	NF NF
Purified Water	QS 100	Vehicle	USP

a FID = Formulation Identification Number
b Meets in-house monograph
c Meets NF Monograph for Carbomer 934P

Reviewer's Comments:

Nepafenac ophthalmic suspension, 0.1% is a sterile, preserved, multi-dose aqueous suspension formulated for topical application.

2.2 Currently Available Treatment for Indications

There are currently no available single topical treatments available for the treatment of pain and inflammation associated with cataract surgery.

There are currently three topical nonsteroidal anti-inflammatory drugs (NSAIDs) and two topical ophthalmic steroids approved for the treatment of postoperative inflammation: 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.

Although nepafenac (amfenac amide) is a new molecular entity, 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.

Four clinical studies (C-95-93, C-97-30, C-02-53 and C-03-32) are pertinent to the demonstration of the safety and efficacy of nepafenac ophthalmic suspension, 0.1%. A table of these studies is provided in Section 2.4. There are 2 dose-response studies (C-95-93 and C-97-30) in which nepafenac is dosed four-times-daily beginning the day after surgery and continuing through the first 2 weeks of the postoperative period. Concentrations of nepafenac range from 0.003% to 0.3%. Two additional studies (C-02-53 and C-03-32) use the final concentration (0.1%) and dosing regimen (three-times-daily beginning 1 day prior to surgery, and continuing the day of surgery and through the first 2 weeks of the postoperative period). All 4 studies are placebo-controlled and conducted in adult patients requiring cataract extraction, the target patient population for the indication being pursued. The efficacy of nepafenac ophthalmic suspension, 0.1% for treatment of pain and inflammation following cataract surgery has not been investigated in pediatric patients.

2.4 Important Issues With Pharmacologically Related Products

Reviewer's comments:

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

2.5 Presubmission Regulatory Activity

An End-of-Phase 2 meeting was held with the U.S. Food and Drug Administration on August 11, 2003, at which Alcon presented a summary of completed clinical studies in order to obtain advice from the Agency for proceeding with the clinical development of nepafenac ophthalmic suspension, 0.1%. Alcon provided the Agency with data supporting the 0.1% concentration for marketing based on the stability of the formulation.

The Agency agreed that three-times-daily dosing regimen resulted in earlier efficacy (based on the percentage of patients cured) than the QD or BID regimen. The Agency also affirmed that acceptable efficacy endpoints for post-cataract inflammation are: 1) Statistically superior percentage of cured patients (i.e., cells + flare = 0) in the active vs. placebo group. The active group should also have a percentage of cured patients greater than 50%; or 2) Statistically superior mean cell score and at least 1 unit greater in the placebo group compared to the active group.

Following discussions with the Agency, clinical study C-03-32 was designed with cure rate as the primary efficacy endpoint.

Reviewer's comments:

Based on the information submitted at this EOP-2 meeting, the agency agreed that TID use of the 0.1% formulation appeared to demonstrate efficacy earlier than the QD or BID regimen based on the percentage of patients cured.

In determining nepafenac's efficacy results for inflammation and pain the following criteria were utilized:

1.) For post-cataract inflammation at least a 1 unit or greater difference of the mean cell score during the post-operative period between the placebo and active group were required.

2.) For post-cataract pain the difference in the percentage of patients pain-free during the post-operative period between the active and placebo group was required to be statistically significant.

2.6 Other Relevant Background Information

Nepafenac ophthalmic suspension, 0.1% is not currently approved in any country. There is no postmarketing experience.

Although nepafenac (amfenac amide) is a new molecular entity, 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.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

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

The application is recommended for approval from microbiology product quality standpoint.

Regulatory Acceptance Specifications for Nepafenac Ophthalmic Suspension, 0.1%

Test	Specification
Nepafenac (AL-6515) Identity[a]	
Nepafenac (AL-6515) Assay	
Impurites:[b]	
Nepafenac Specified Degradation Products:	
Any Single Unspecified Impurity	
Total Impurities	
pH	
Osmolality	
Appearance Suspension:	

Test	Specification
	Meets USP
	Meets USP

a Release test only
b Includes all impurities other than drug substance process impurities
c Tested initially and end of shelf-life
d Stability test only

Reviewer's comments:

Acceptable.

3.2 Animal Pharmacology/Toxicology

There were no significant findings from pre-clinical pharmacology or toxicology reviews that would affect the clinical outcome.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The submitted clinical study report and protocol for the four studies (C-95-93, C-97-30, C-02-53 and C-03-32) and relevant literature reports were reviewed. The submitted study report forms for studies C-02-53 and C-03-32 form the basis for the majority of this application.

The entire application was submitted in paper format with the proposed labeling submitted in paper and electronic format.

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

Reviewer's comments:

The proposed indication is for nepafenac 0.1%, TID, applied topically to the eye for the — treatment of pain and inflammation associated with cataract surgery (commencing the drug one day prior to surgery).

Studies C-02-53 and C-03-32 are the two adequate and well controlled clinical trials that form the basis of this review. In these studies the drug concentration was 0.1%, the drug was given 1 day prior to cataract surgery, and pain and inflammation data were collected.

Study C-02-53 for nepafenac 0.1% was a posology/safety and efficacy study with the patients randomized to a placebo group or to QD, BID or TID dosing. Those patients dosed TID specifically support the proposed indication.

Study C-03-32 for nepafenac 0.1%, with all patients dosed TID commencing the day prior to cataract surgery, was a safety and efficacy study. This study is an adequate and well controlled clinical trial that supports the proposed indication since the drug concentration was 0.1%, dosing was TID, and pain and inflammation data were collected.

Studies C-95-93 and C-97-30 were adequate and well controlled clinical trials (dose response studies) that provide supportive evidence for the proposed indication. In these studies the dosing was different, (QID not TID), the drug was not administered 1 day prior to cataract surgery, patients were randomized to drug concentrations of either 0.003%, 0.01%, 0.03%, 0.1% or 0.3% and to placebo, and only inflammation data was collected.

4.2 Tables of Clinical Studies

Listing of Clinical Studies for the Clinical Development of Nepafenac Ophthalmic Suspension, 0.1%

Study No.	Study Title / Objective	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Total Number of Enrolled Subjects /Patients	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
C-02-53	Topical preoperative and postoperative use of Nepafenac Ophthalmic Suspension 0.1% for treatment of anterior segment inflammation after cataract/IOL surgery	prospective, randomized, double-masked, placebo controlled, parallel group	AL-6515 0.1%: 1 drop once-daily in the affected eye beginning 1 day prior to surgery; topical ocular Placebo: 1 drop once-daily in the affected eye beginning 1 day prior to surgery; topical ocular AL-6515 0.1%: 1 drop twice-daily in the affected eye beginning 1 day prior to surgery; topical ocular Placebo: 1 drop twice-daily in the affected eye beginning 1 day prior to surgery; topical ocular AL-6515 0.1%: 1 drop three-times-daily in the affected eye beginning 1 day prior to surgery; topical ocular Placebo: 1 drop three-times-daily in the affected eye beginning 1 day prior to surgery; topical ocular	220	patients undergoing cataract extraction with implantation of a posterior chamber IOL	16 days

Listing of Clinical Studies for the Clinical Development of Nepafenac Ophthalmic Suspension, 0.1%

Study No.	Study Title / Objective	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Total Number of Enrolled Subjects /Patients	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
C-03-32	Preoperative and postoperative use of Nepafenac Ophthalmic Suspension, 0.1% for the treatment of ocular inflammation associated with cataract surgery	prospective, randomized, double-masked, placebo controlled, parallel group	AL-6515 0.1%: 1 drop three-times-daily in the affected eye beginning 1 day prior to surgery; topical ocular Placebo%: 1 drop three-times-daily in the affected eye beginning 1 day prior to surgery; topical ocular	487	patients undergoing cataract extraction with implantation of a posterior chamber IOL	16 days

AL-6515 = Nepafenac = Amfenac Amide
Placebo = Nepafenac Ophthalmic Suspension Vehicle
CNV = choroidal neovascularization
AMD = age-related macular degeneration
IOL = intraocular lens

Reviewer's Comments:

The design of the clinical trials and the number of centers are acceptable. See Section 4.1.

APPEARS THIS WAY
ON ORIGINAL

Listing of Clinical Studies for the Clinical Development of Nepafenac Ophthalmic Suspension, 0.1%

Study No.	Study Title / Objective	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Total Number of Enrolled Subjects /Patients	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
C-95-93	A dose-response placebo controlled clinical study of amfenac amide (AL-6515) 0.03%, 0.1% and 0.3% ophthalmic suspensions in controlling post-cataract surgical inflammation	prospective, randomized, double-masked, placebo controlled, parallel group	AL-6515 0.03%: 1 drop four-times-daily in the affected eye beginning 1 day after surgery; topical ocular AL-6515 0.1%: 1 drop four-times-daily in the affected eye beginning 1 day after surgery; topical ocular AL-6515 0.3%: 1 drop four-times-daily in the affected eye beginning 1 day after surgery; topical ocular Placebo: 1 drop four-times-daily in the affected eye beginning 1 day after surgery; topical ocular	280	patients having undergone cataract extraction with implantation of a posterior chamber IOL	14 days

APPEARS THIS WAY
ON ORIGINAL

Listing of Clinical Studies for the Clinical Development of Nepafenac Ophthalmic Suspension, 0.1%

Study No.	Study Title / Objective	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Total Number of Enrolled Subjects /Patients	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
C-97-30	A two-week, triple-masked, placebo-controlled dose-response study of AL-6515 0.003%, 0.01%, 0.03% and 0.1% ophthalmic suspensions in controlling postcataract surgical inflammation	prospective, randomized, double-masked, placebo controlled, parallel group	AL-6515 0.003%: 1 drop four-times-daily in the affected eye beginning 1 day after surgery; topical ocular AL-6515 0.01%: 1 drop four-times-daily in the affected eye beginning 1 day after surgery; topical ocular AL-6515 0.03%: 1 drop four-times-daily in the affected eye beginning 1 day after surgery; topical ocular AL-6515 0.1%: 1 drop four-times-daily in the affected eye beginning 1 day after surgery; topical ocular Placebo: 1 drop four-times-daily in the affected eye beginning 1 day after surgery; topical ocular	197	patients having undergone cataract extraction with implantation of a posterior chamber IOL	14 days

Reviewer's comments:

See Section 4.1.

APPEARS THIS WAY
ON ORIGINAL

4.3 Review Strategy

The submitted clinical study reports and protocols for the four trials (C-95-93, C-97-30, C-02-53 and C-03-32) and relevant literature reports were reviewed. The submitted study reports for studies C-02-53 and C-03-32 form the basis for the majority of this application.

The entire application was submitted in paper format with the proposed labeling submitted in paper and electronic format.

Reviewer's comments:

The sources of clinical data for safety and efficacy for this NDA include two phase 3 trials C-02-53 and C-03-32 with the safety data base including earlier studies, specifically C-95-93 and C-97-30. Each of the phase 3 trials were reviewed independently for the demonstration of overall efficacy for this product.

4.4 Data Quality and Integrity

The medical officer has reviewed all Case Report Forms for discontinued subjects in studies (C-95-93, C-97-30, and C-02-53). There were no problems noted with data quality and integrity.

4.5 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.

4.6 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.*

There is no evidence to suggest that the results of the studies were impacted by any financial payments.

5 CLINICAL PHARMACOLOGY (FROM THE CLINICAL PHARMACOLOGY REVIEW)

5.1 Pharmacokinetics

Nepafenac, an NSAID, is being developed for the — treatment of pain and inflammation associated with cataract surgery. Pharmacological studies showed that nepafenac rapidly penetrated the cornea and was converted to the active moiety amfenac by tissue

hydrolases. The cyclooxygenase inhibitory activity of nepafenac was weaker than that of amfenac. Topical administration of nepafenac significantly inhibited trauma-induced prostaglandin production and leakage of the ocular vasculature.

AL-6515 was hydrolyzed to amfenac in all species with all routes tested. Plasma exposures to amfenac were higher than that to AL-6515. The plasma half-life for amfenac amide and amfenac was short. The plasma half-lives of radioactivity were long, suggesting other uncharacterized metabolites. Following topical ocular administration of ^{14}C-AL-6515 to rabbits, radioactivity was absorbed into the eye with high concentrations of radioactivity in the conjunctiva and cornea. ^{14}C-AL-6515 or its radioactive drug equivalents did not bind to melanin pigmented tissues. Oral administration of ^{14}C-AL-6515 to pregnant rats resulted in distribution of radioactivity to maternal tissues and placental transfer of radioactivity into the developing fetus. Radioactivity was also found in the milk of lactating rats. ^{14}C-AL-6515 bound moderately to plasma proteins of rat, monkey, and human *in vitro* (73% to 84%) in a concentration-independent manner over the concentration range of 10 to 1000 ng/ml. Incubation of ^{14}C-amfenac amide in precision-cut human liver slices produced 12 metabolites. The major metabolite was amfenac with the remaining metabolites being present in relatively low amounts. Drug-derived radioactivity was rapidly excreted after iv administration to rats. The major route of excretion was via urine. Biliary excretion was also an important elimination pathway.

Several acute and repeated-dose oral systemic toxicity studies were conducted in rats with the duration up to 6 months. In the 2-week study, jejunal serositis and mesenteric lymphoid hyperplasia were noted in rats of 25 mg/kg/day group. The sponsor indicated that these changes were considered to be secondary to intra-abdominal trauma, possibly associated with gavage procedures. However, distinct gavage trauma was not observed grossly or microscopically in abdominal tissues, and a relationship between drug treatment and these findings could not be entirely ruled out. In the 3-month toxicity study in SD rats, histopathological examination showed renal papillary necrosis in two of ten females at 15 mg/kg only. GI and renal lesions were common findings in animals treated with high doses of NSAIDs. GI abnormalities including stomach or intestine distended with fluid or gas, abnormal mucoid contents in the stomach and small intestine, abnormal fluid, granular or gelatinous material in the abdominal cavity, abdominal adhesions, and perforated or eroded mucosa of the GI tract were noted in rats at $\geq$ 30 mg/kg doses in acute and reproductive studies, indicating that the GI tissues were the target organs of toxicity. TK evaluations showed that at 10 mg/kg/day dose (at which dose no GI toxicity was noted), systemic exposures to AL-6515 and AL-6295 were 500 and 1600 times human exposure under the proposed clinical dosage (see table below). Because of the great safety margin, GI toxicity is not a concern for this drug in this indication.

AUC (ng-hr/ml)	Rats (10 mg/kg)	Human (0.1%, tid x 4 days)	Animal/human
AL-6515	189±22	0.368±0.106	500
AL-6295	1550±106	0.976±0.284	1600
Cmax (ng/ml)			
AL-6515	49.5±21.9	0.310±0.104	160
AL-6295	388±99	0.422±0.121	900

In 6-month toxicity study in F344 rats, higher incidences of corneal mineralization (5 of 25 in males vs. 0 in control animals) and uterus hydrometra (5 of 25 in females vs. control's 1 of 25) were seen at 10 mg/kg/day. Similar changes were not seen in other studies including 6-month ocular toxicity in which 1.0% AL-6515 ophthalmic suspension was used. Corneal and uterus abnormalities were not listed in the common adverse events seen in clinical studies. In addition, the systemic exposure to AL-6515 and AL-6295 at 10 mg/kg/day was much higher than that in humans. These findings might not be toxicologically significant.

Several repeated dose ocular toxicity studies were conducted with durations up to 3 months in monkeys (concentrations up to 1.0%, qid) and NZW rabbits (concentrations up to 1.0%, qid), and 6 months in pigmented rabbits (concentrations up to 1.5%, tid). The drug was well tolerated. No drug-induced systemic and ocular toxicity was observed. In all studies, minimal to moderate conjunctival congestion and transient and sporadic incidences of minimal conjunctival discharge were seen in the eye treated with vehicle and drugs. Because of the similar incidences and severity between control and treated eyes, these changes were not considered as drug-related. In a rabbit study in which nepafenac ophthalmic suspension (up to 1.0%) was administered prior and subsequent to a corneal incision, no significant ocular and systemic toxicity as well as postoperative ocular complications were noted.

AL-6515 was nonmutagenic in the Ames test and in L5178Y/TK$^{+/-}$ mouse lymphoma mutagenesis assay. The drug was also negative in *in vivo* micronucleus assay. AL-6515 was positive for the induction of structural chromosome aberrations in CHO cells.

In a fertility and early embryonic development study conducted in SD rats. Male animals of the 15 mg/kg group showed lower sperm motility and sperm concentrations compared to the control males. Histological examination in the 15 mg/kg group showed slightly decreased spermatozoa in the duct of the epididymis, and slightly more intraluminal single necrotic cells in the epididymis in two of three animals examined. In females, there were no toxicologically significant differences in copulation and fertility indices between control and treated groups. However, a decrease in the number of viable fetuses and an increase in the early resorption and post-implantation loss were noted in animals at 10 and 15 mg/kg. Oral administration of AL-6515 in rats at 3.0 mg/kg showed no developmental toxicity in this study.

In the embryofetal development study in pregnant rats, a slight decrease in fetal body weight (3.3 $\pm$ 0.5 g vs. control's 3.5 $\pm$ 0.2 g) was seen in HD (30 mg/kg) group. One HD animal had 9 dead fetuses, 6 resorptions, and no viable fetuses. The observed malformations were not considered treatment-related due to the low incidence and lack of dose-dependence. Regarding developmental variations, the incidences of unossified 5th and 6th sternebrae and 7th cervical ribs were significantly higher in the HD group than in the control group. Based on the study results, the dose of 10 mg/kg was considered a NOEL for developmental toxicity in rats.

In the embryofetal development study in pregnant rabbits, abortion occurred in one MD (10 mg/kg) animal and one HD (30 mg/kg) animal. One HD animal had a premature delivery. HD animals showed a decrease in body weight gain and food consumption. Regarding reproductive evaluation, HD animals showed an increase in post-implantation loss which was mainly due to

an increase in early resorptions. There was a statistically significant increase in the number of litters with skeletal malformations and in the number of litters with total malformations in the 30 mg/kg/day group when compared to the controls. Low incidences of malformations were seen in the MD and LD groups and were not considered drug-related. Based on the study results, the dose of 3 mg/kg was considered a NOEL for maternal toxicity and a dose of 10 mg/kg was considered a NOEL for developmental toxicity in rats.

The dose of 10 mg/kg/day was the NOEL for both rat and rabbit segment 2 studies. The following table compares the plasma exposure to AL-6515 and AL-6295 between animals at 10 mg/kg/day and humans following multiple bilateral dosing of nepafenac ophthalmic suspension 0.1%.

AUC (ng-hr/ml)	Rats (10 mg/kg)	Rabbits	Human (0.1%, tid x 4 days)	Rat/human	Rabbit/human
AL-6515	97.0-207	28.4-62.5	0.368±0.106	260	77
AL-6295	2340-4190	663-3070	0.976±0 284	2400	680
Cmax (ng/ml)					
AL-6515	69.6-242	39 3-70.8	0.310±0 104	225	127
AL-6295	793-1710	666-2100	0.422±0.121	1900	1578

In the perinatal and postnatal study in pregnant F0 rats, AL-6515 produced dystocia and associated maternal mortality in F0 females at levels ≥ 3 mg/kg/day, and developmental toxicity in F1 offspring at levels ≥ 10 mg/kg/day. The developmental toxicity was characterized by decreased F 1 pup survival and decreased F1 pup body weights during lactation and growth phases. A no-observed-effect level (NOEL) for maternal effects in F0 females was not established in this study. The NOEL for developmental toxicity in F1 offspring was determined to be 3 mg/kg/day.

—, a known degradation product of AL-6515, was evaluated in a battery of genotoxicity studies. The compound was negative in the Ames test and *in vivo* mouse bone marrow micronucleus assay. In an *in vitro* mouse lymphoma TK assay, — was positive for inducing forward mutations under activation conditions. In an ocular toxicity study conducted in NZW rabbits, AL-6515 ophthalmic suspension (0.1%) containing the degradation product — at concentrations up to — (tid for one month) showed no local and systemic toxicity.

Conclusions: Nepafenac is a nonsteroidal anti-inflammatory agent. Nonclinical PK studies showed that following topical ocular administration of ^{14}C-AL-6515 to rabbits, radioactivity was absorbed into the eye with high concentrations of radioactivity in the conjunctiva and cornea. Nonclinical toxicity studies showed no unexpected toxicologically significant events.

5.2 Pharmacodynamics

No relevant studies.

5.3 Exposure-Response Relationships

There were 2 dose-response studies (C-95-93 and C-97-30) in which nepafenac was dosed four-times-daily beginning the day after surgery and continuing through the first 2 weeks of the postoperative period. Concentrations of nepafenac ranged from 0.003% to 0.3%. Two additional studies (C-02-53 and C-03-32) were conducted using the final concentration (0.1%) and dosing regimen (three-times-daily beginning 1 day prior to surgery, and continuing the day of surgery and through the first 2 weeks of the postoperative period).

Reviewer's comments:

Based on the information submitted by the sponsor at the End of Phase 2 meeting on August 11, 2003, the agency agreed that TID use of the 0.1% formulation appeared to demonstrate efficacy earlier than the QD or BID regimen based on the percentage of patients cured.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication for nepafenac ophthalmic suspension, 0.1 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 report and protocol for the four studies (C-95-93, C-97-30, C-02-53 and C-03-32) were reviewed. The submitted study reports for studies C-02-53 and C-03-32 form the basis for the majority of this application.

The entire application was submitted in paper format with the proposed labeling submitted in paper and electronic format.

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

6.1.2 General Discussion of Endpoints

In study C-02-53 the primary efficacy variable was the percent of patients declared treatment failures at the Day 14 Visit. Treatment failure was defined as an aqueous cells score ≥ 3, an aqueous flare score = 3, or an ocular pain score ≥ 4. Exploratory variables were the percentage of patients declared cured (cells + flare = 0) by visit, the percentage of patients who were pain free by visit, and the percentage of patients who were pain free at all visits.
In study C-03-32, the primary efficacy variable was percent cures (defined as cells + flare score = zero). Secondary efficacy variables were percent of patients declared treatment failures (cells score ≥ 3, flare score = 3, or ocular pain score ≥ 4), percent of patients with no ocular pain, and

clinically significant inflammation (cells + flare score ≥ 4). Exploratory variables were percent cures by visit (patients were considered cured at early postoperative visits only if they remained cured until study exit at Day 14), aqueous cells scores, flare scores, and inflammation (cells + flare) scores.

Reviewer's comments:

In determining nepafenac's efficacy results for inflammation and pain the following criteria were utilized:

1.) For post-cataract inflammation at least a 1 unit or greater difference of the mean cell score during the post-operative period between the placebo and active group were required.

2.) For post-cataract pain the difference in the percentage of patients pain-free during the post-operative period between the active and placebo group was required to be statistically significant.

6.1.3 Study Design

Studies C-02-53 and C-03-32 were multi-centered, prospective, randomized, double-masked, placebo controlled, parallel group clinical trials. For these studies information regarding the inclusion/exclusion criteria, the study plan, principle investigators, demographics, subject disposition, schedule of activities and evaluations, statistical analysis plan, and efficacy and safety endpoints are provided in this Medical Officer's review. The information from these clinical studies follows:

C-02-53

Listing of Principal Investigators and Numbers of Patients Who were Randomized, Enrolled and Received Therapy and Intent-to-Treat (ITT)

Inv. No.	Primary Investigator Name/Address	# Patients Randomized [a]	Enrolled and Received Therapy [b]	ITT [c]
1678	H. Dwight Cavanagh, MD University of Texas Southwestern Medical Center 5323 Harry Hines Blvd Dallas, Texas 75390-9057 214-648-2671 Zale Lipshy University Hospital 5151 Harry Hines Blvd Dallas, Texas 75235-7707	14	14	13
3725	Ezra Maguen, MD Ophthalmic Clinical Trials Center Cedars-Sinai Medical Center 444 S San Vicente Blvd, # 703 Los Angeles, California 90048 310-423-9517 Surgery Center Cedars-Sinai Medical Center 310 N San Vicente Blvd, Suite 703 Los Angeles, California 90048 American Eye Institute 8635 W 3rd Street, Suite 390W Los Angeles, California 90048	4	4	3
3747	Harvey J. Reiser, MD Eye Care Specialist of Northeast PA 703 Rutter Ave Kingston, Pennsylvania 18704 570-288-7405 Eye Care Specialist of Northeast PA 126 W Front Berwick, Pennsylvania 18603 Eye Care Specialist of Northeast PA 610 Wyoming Ave Kingston, Pennsylvania 18704 Eye Care Specialist of Northeast PA 390 Pierce (previous primary address) Kingston, Pennsylvania 18704	26	24	24

Inv. No.	Primary Investigator Name/Address	# Patients Randomized [a]	Enrolled and Received Therapy [b]	ITT [c]
1806	Kenneth Sall, MD Sall Eye Surgery Center 9604 Artesia Blvd, #203 Bellflower, California 90706 562-804-1974 Bellflower Medical Center 9542 E Artesia Blvd Bellflower, California 90706 562-925-8355	25	24	24
271	Robert H. Stewart, MD Houston Eye Associates 2855 Gramercy Drive Houston, Texas 77025 713-668-6828 Gramercy Surgery Center 2727 Gramercy Drive Houston, Texas 77027 Summit Surgery Center 4126 Southwest Blvd #108 Houston, Texas 77027	42	39	37
2631	William Colby Stewart, MD Middle Tennessee Eye Associates 345 N Washington Ave Cookeville, Tennessee 38501 931-372-1994 Cookeville Surgery Center 100 W 4th Street Cookeville, Tennessee 38501	17	16	15
1405	Stefan D. Trocme, MD University of Texas Medical Branch University Eye Center 700 University Blvd Galveston, Texas 77550 409-747-5425 University of Texas Medical Branch University Eye Center 301 University Blvd. Galveston, Texas 77555-1106	30	30	29
1007	Thomas R. Walters, MD Texan Eye Care, PA 1700 S. Mopac Expressway Austin, Texas 78746 512-314-1653	34	34	34

Inv. No.	Primary Investigator Name/Address	# Patients Randomized [a]	Enrolled and Received Therapy [b]	ITT [c]
	Texan Eye Care, PA 1020 W 34th Street Austin, Texas 78705 Texan Surgery Center 7000 N Mopac Expressway, #120 Austin, Texas 78731			
350	Arthur J. Weinstein, MD Eye Associates of New Mexico 809 Martin Luther King Blvd Albuquerque, New Mexico 87102 Phone: 505-883-6800 Eye Associates of New Mexico 101 Hospital Loop NE, Suite 203 Albuquerque, New Mexico 87109 Albuquerque Ambulatory Eye Surgery Center 5901 Harper Dr NE Albuquerque, New Mexico 87109	13	12	11
	Total	228	220	212

[a] Includes those patients who consented, were provided study medication and **did not dose** (i.e., 8 patients discontinued from the study prior to surgery and returned study medication bottles unopened and were excluded from the Safety and ITT analyses)

[b] All patients who received study medication as well as patients who discontinued from the study prior to the instructed time for use of the test article but either failed to return a test article bottle(s) or returned a test article bottle(s) with the tamper-evident seal broken (also denoted as the Safety data set)

[c] Includes all patients who received test article, completed cataract/IOL implant surgery and returned for at least one post-surgical follow-up visit

Study C-03-32

Listing of Principal Investigators and Numbers of Patients Who were Randomized, Enrolled and Received Therapy and Intent-to-Treat (ITT)

Inv. #	Primary Investigator Name/Address	# Patients Randomized [a]	Enrolled and Received Therapy [b]	ITT [c]
847	Stephen F. Brint, MD Brint Cataract Institute 3900 Veterans Memorial Blvd. Suite 203 Metairie, LA 70002 (504) 888-2020	16	15	15
970	Robert P. Lehmann, MD Lehmann Eye Center 5300 North Street Nacogdoches, TX 75965 (936) 569-8278	50	50	49
1204	Stephen S. Lane, MD Associated Eye Physicians and Surgeons, Ltd 232 N Main Street Stillwater, MN 55082 (651) 275-3000	16	15	14
1238	Stephen V. Scoper, MD Virginia Eye Consultants 400 Gresham Drive, Suite 403 Norfolk, VA 23507 (757) 622-2200	9	7	7
1908	E. Ronald Salvitti, MD Southwestern Pennsylvania Eye Center 750 East Beau Street Washington, PA 15301 (724) 228-2982	4	4	4
2435	Jeffrey C. Whitsett, MD Whitsett Vision Group 1237 Campbell Road Houston, TX 77055 (713) 365-9099	11	10	10
2666	Louis M. Alpern, MD The Cataract, Glaucoma and Refractive Surgery Center 2201 N. Stanton Street El Paso, TX 79902 (915) 545-2333	28	24	23

Inv. #	Primary Investigator Name/Address	# Patients Randomized [a]	Enrolled and Received Therapy [b]	ITT [c]
2678	Peter S. Dawson, MD Surgical Eye Associates 1631 N Loop W, Suite 500 Houston, TX 77008 (713) 869-6400	25	23	22
2902	Robert J. Cionni, MD Cincinnati Eye Institute 10494 Montgomery Road Cincinnati, OH 45242 (513) 984-5133	39	36	35
3025	Matthew D. Paul, MD Danbury Eye Physicians and Surgeons 69 Sand Pit Road Suite 101 Danbury, CT 06810 (203) 791-2020	21	21	20
3471	Robert J. Arleo, MD Arleo Eye Institute 10 Brentwood Drive, Suite A Ithaca, NY 14850 (607) 257-5599	25	25	25
3472	Edward J. Holland, MD Cincinnati Eye Institute 10494 Montgomery Road Cincinnati, OH 45242 (513) 984-5133 Main	12	12	12
3481	Jeffrey D. Horn, MD Vanderbilt University Medical Center Department of Ophthalmology and Visual Sciences 8000 Medical Center East-8808 Nashville, TN 37232-8808 (615) 936-2020	14	13	12
3807	Steven Silverstein, MD Silverstein Eye Centers 4240 Blue ridge Blvd Suite 1000 Kansas City, MO 64133 (816) 358-3633	20	18	17
3828	Satish S. Modi, MD 23 Davis Avenue Poughkeepsie, NY 12603 (845) 454-1025	51	50	50

Inv. #	Primary Investigator Name/Address	# Patients Randomized [a]	Enrolled and Received Therapy [b]	ITT [c]
3889	Henry M. Haley, Jr., MD Eye Surgery Center of Louisiana 5646 Read Boulevard, Suite 220 New Orleans, LA 70127 (504) 391-7545	32	27	27
3899	Arthur M. Fishman, MD Eye Surgery Associates 603 N Flamingo Road Suite 250 Pembroke Pines, FL 33028 (954) 431-2777	34	34	34
3900	Lisa Marie Cibik, MD Associates in Ophthalmology 500 N. Lewis Run Road Suite 218 Pittsburgh, PA 15122 (412) 466-8011	24	22	22
3901	Ronald A. Landry, MD Eye Care Associates 4324 Veterans Memorial Blvd. Suite 102 Metairie, LA 70006 (504) 455-4046	42	32	30
3903	Gary Foster, MD The Eye Center of Northern Colorado 1725 Prospect Road Fort Collins, CO 80525 (970) 221-2222	26	26	26
3904	Mike Caplan, MD Berkeley Eye Center 3100 Weslayan, Suite 400 Houston, TX 77027 (713) 526-1600	23	23	22
	Total	522	487	476

[a] Includes those patients who consented, were provided study medication and **did not dose** (i.e., 35 patients discontinued from the study prior to surgery and returned study medication bottles unopened and were excluded from the Safety and ITT analyses)

[b] All patients who received study medication as well as patients who discontinued from the study prior to the instructed time for use of the test article but either failed to return a test article bottle(s) or returned a test article bottle(s) with the tamper-evident seal broken (also denoted as the Safety data set)

[c] Includes all patients who received test article, completed cataract/IOL implant surgery and returned for at least one post-surgical follow-up visit

Reviewer's comments:

It is preferred to have at least 10 subjects per center to allow for an interaction analysis.

Patient Inclusion/Exclusion Criteria

Since ocular inflammation was the efficacy endpoint in these studies, the use of concomitant topical and systemic anti-inflammatory agents of any type were contraindicated in all protocols during the study and required a wash out period of these medications prior to entry into the study. A washout period of a minimum of 14 days for C-02-53 and C-03-32 was required for steroids. For NSAIDs, the washout period was a minimum of 7 days for C-02-53 and C-03-32. Patients who were taking a prophylactic daily dose of aspirin (81 mg) prior to the study were permitted to continue with their aspirin therapy during the study.

Only one eye of each patient was exposed to either nepafenac or placebo. Patients having bilateral cataract surgery were not eligible for participation in the study, nor were patients having surgery in their second eye and having previously participated in the study.

The general criteria for study inclusion / exclusion for the two studies C-02-53 and C-03-32 are presented below:

Inclusion/Exclusion Criteria for Nepafenac Ophthalmic Suspension, 0.1%
Efficacy Studies

C-02-53 and C-03-32
Inclusion Criteria
Men or women of any race and over the age of 18
Individuals who had a cataract, and were expected to undergo cataract extraction with the implantation of a posterior chamber intraocular lens
Exclusion Criteria
Any intraocular inflammation (cells or flare greater than Grade 0) or ocular pain greater than Grade 1 in the study eye that was present during the screening slit-lamp examination (operative eye)
Previous ocular trauma to the operative eye; planned multiple procedures during cataract/IOL implantation surgery; fellow eye of an individual currently or previously enrolled in the study; or patients who planned to have cataract surgery in their fellow, non-study eye prior to the 14 day postoperative study visit;
Congenital ocular anomaly (e.g., aniridia, congenital cataract); iris atrophy in the operative eye; any abnormality that prevented reliable Goldmann applanation tonometry
A nonfunctional fellow eye
History of chronic or recurrent inflammatory eye disease (e.g., iritis, scleritis, uveitis, iridocyclitis, rubeosis iritis) (operative eye); lens pseudoexfoliation syndrome with glaucoma or zonular compromise (operative eye);
Use of an investigational intraocular lens
Known or suspected allergy or hypersensitivity to nonsteroidal anti-inflammatory agents, or to any component of the study medication
Use of topical ocular or systemic steroids within 14 days prior to surgery
Use of topical ocular or systemic nonsteroidal anti-inflammatory drugs within 7 days of surgery, except an allowed daily dose of baby aspirin (81 mg)
Women of childbearing potential (those who were not surgically sterilized or post-menopausal) who were breast-feeding; had a positive urine pregnancy test at screening; were not willing to undergo a urine pregnancy test upon exiting the study; intended to become pregnant during the duration of the study; or, did not agree to using adequate birth control methods for the duration of the study
Proliferative diabetic retinopathy (operative eye); uncontrolled diabetes mellitus;
Participation in any other clinical study within 30 days before surgery

Inclusion/Exclusion Criteria for Nepafenac Ophthalmic Suspension, 0.1%
Efficacy Studies

C-02-53 and C-03-32
Exclusion Criteria (continued)
Use of a topical ophthalmic prostaglandin, (e.g. Travatan, Xalatan)
Patients with known bleeding tendencies, or who were receiving medications that might have prolonged bleeding time, could be enrolled at the physician's discretion
Patients, who in the opinion of the investigator, might have been at increased risk of complications from topical NSAIDs
The Alcon medical monitor could declare any patient ineligible for per-protocol evaluability based upon sound medical reason (e.g., significant surgical complications unrelated to the use of the study drug, such as difficult lens placement, zonular dehiscence, vitreous in the anterior chamber, etc.)

Reviewer's Comments:

Inclusion/exclusion criteria are acceptable.

Study Plans for Studies C-02-53 and C-03-32:

Study C-02-53

Title
Topical Preoperative and Postoperative Use of Nepafenac Ophthalmic Suspension, 0.1% for Treatment of Anterior Segment Inflammation after Cataract/IOL Surgery

This prospective, randomized, double-masked, placebo-controlled, parallel group posology study was designed to evaluate the safety and efficacy of nepafenac ophthalmic suspension, 0.1% (QD, BID and TID) in patients requiring cataract extraction with planned implantation of a posterior chamber intraocular lens.

Patients who met study entrance criteria were randomly assigned to receive nepafenac ophthalmic suspension, 0.1% or placebo as a QD, BID, or TID dosing regimen. Dosing in the affected eye began one day prior to surgery, and continued on the day of surgery and for the first two weeks of the postoperative period. Patients were assessed on postoperative Days 1, 3, 7, and 14.

The primary efficacy variable was the percent of patients declared treatment failures at the Day 14 Visit. Treatment failure was defined as an aqueous cells score ≥ 3, an aqueous flare score $= 3$, or an ocular pain score ≥ 4. Aqueous cells were graded on a 5-point scale, aqueous flare on a 4-point scale, and ocular pain on a 6-point scale. Secondary efficacy variables included aqueous

cells score, flare score, inflammation score, the percent of patients with clinically significant inflammation (cells score plus flare score ≥ 4) at each visit, and the percent of treatment responders (cells score ≤ 1 and flare score = 0). Exploratory variables were the percentage of patients declared cured (cells + flare = 0) by visit, the percentage of patients who were pain free by visit, and the percentage of patients who were pain free at all visits.

The percent of patients declared as treatment failures was compared independently between each of the nepafenac groups and placebo using a Fisher's exact test. Treatment comparisons for aqueous cells scores, flare scores, inflammation scores, the incidence of treatment failures by visit, the incidence of clinically significant inflammation, and the percent of responders were made with repeated measures analysis of variance or logistic regression, as applicable. Exploratory analyses on the percent of patients declared cured by visit, the percentage of patients pain free by visit, and the percent of patients pain free at all visits were conducted in a fashion similar to the planned analysis.

Reviewer's Comments:

Acceptable.

Study C-03-32

Title
Preoperative and Postoperative Use of Nepafenac Ophthalmic Suspension, 0.1% for the Treatment of Ocular Inflammation Associated with Cataract Surgery

This prospective, randomized, double-masked, placebo-controlled, parallel group study was designed to evaluate the safety and efficacy of nepafenac ophthalmic suspension, 0.1% in patients requiring cataract extraction with planned implantation of a posterior chamber intraocular lens.

Patients who met study entrance criteria were randomly assigned to receive nepafenac ophthalmic suspension, 0.1% or placebo dosed three-times-daily. Dosing in the affected eye began one day prior to surgery, and continued on the day of surgery and for the first two weeks of the postoperative period. Patients were assessed on postoperative Days 1, 3, 7, and 14. The primary efficacy variable was percent cures (defined as cells + flare score = zero). Aqueous cells were graded on a 5-point scale and flare on a 4-point scale. Secondary efficacy variables were percent of patients declared treatment failures (cells score ≥ 3, flare score = 3, or ocular pain score ≥ 4), percent of patients with no ocular pain, and clinically significant inflammation (cells + flare score ≥ 4). Exploratory variables were percent cures by visit (patients were considered cured at early postoperative visits only if they remained cured until study exit at Day 14), aqueous cells scores, flare scores, and inflammation (cells + flare) scores.

The percent of patients declared cured was compared between the nepafenac group and placebo using a Fisher's exact test. Treatment comparisons for the incidence of treatment failures, for the incidence of clinically significant inflammation, and the incidence of patients reporting no pain were made using logistic regression. Planned exploratory analyses of cures by visit, aqueous

cells scores, flare scores, and inflammation scores were conducted similarly to the secondary efficacy analysis or with a repeated measures analysis of variance.

Reviewer's Comments:

Acceptable.

Efficacy Endpoint for Studies C-02-53 and C-03-32

Assessment of Aqueous Cells and Flare

In each of the efficacy studies C-02-53 and C-03-32, aqueous cells and flare, which are the hallmark of ocular inflammation, served as the basis for evaluating the efficacy of the drug product. As is the standard in ophthalmic practice, aqueous cells and flare were evaluated using slit-lamp biomicroscopy. Aqueous cells were graded by the investigator on a 5-point scale and aqueous flare was graded by the investigator on a 4-point scale (Table follows). The aqueous cells and flare scales used to assess aqueous cells and flare have been used in previous post-cataract inflammation trials and have successfully demonstrated the clinical efficacy of currently marketed topical ocular anti-inflammatory products (e.g., ACULAR®). 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).

Table
Grading Scales for Aqueous Cells and Flare

Aqueous Cells	Determined using the narrowest 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 the narrowest 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.

In studies C-02-53 and C-03-32, patients began study medication the day prior to surgery and also took their medication on the day of surgery and continued through the first 2 weeks of the postoperative period. Patients began dosing one day preoperatively in order to benefit from the mechanism of action of nepafenac (i.e., inhibition of cyclooxygenase). Therefore, these studies allow for a comparison of the efficacy of nepafenac and placebo for the treatment of pain and inflammation associated with cataract surgery.

Assessment of Ocular Pain

Subjective assessment of ocular pain, rated on a 6-point scale (Table follows), was evaluated in the 2 efficacy studies (C-02-53 and C-03-32). 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.

Table
Grading Scales for Ocular Pain

Ocular Pain	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
	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

Efficacy Endpoints

In C-02-53, the primary efficacy endpoint was treatment failures which was based on aqueous cells and flare scores (i.e., a treatment failure was defined as a grade 3 or higher cells or flare score) and ocular pain scores (i.e., treatment failure was also defined as a Grade 4 or greater pain score). In C-03-32, the primary efficacy endpoint was percent cures, wherein cures were defined as the absence of inflammation (i.e., cells + flare = 0).

Data Analysis

The statistical objective for the efficacy studies was to demonstrate the superiority of nepafenac ophthalmic suspension over placebo. All hypothesis testing was conducted with a 0.05 probability of a type 1 error.

In accordance with ICH E9 (Statistical Principles for Clinical Trials), per protocol data and intent-to-treat results are provided for all safety/efficacy studies. As these studies were designed to demonstrate the superiority of nepafenac treatment over placebo, intent-to-treat data were considered primary. All patients who received study medication, had cataract surgery and returned for at least one scheduled postoperative visit were considered evaluable for the intent-to-treat analysis. All patients who received study medication, completed surgery, met study inclusion/exclusion criteria, and adhered to protocol guidelines were considered evaluable for the

per protocol analysis. In the ITT dataset, the last visit data for all discontinued patients or missed visits were carried forward.

The safety analysis is based upon an evaluation of the following: the extent of exposure to study drug, adverse events and other safety related parameters, which included visual acuity (best-corrected logMAR or Snellen), ocular signs (eyelids/conjunctiva, cornea, iris/anterior chamber, lens, aqueous cells, aqueous flare, corneal edema, conjunctival injection, and chemosis), intraocular pressure, dilated fundus parameters (retina/macula/choroid, vitreous, optic nerve, disc pallor, and cup/disc ratio), specular microscopy (endothelial cell density), pachymetry (corneal thickness), pupil diameter and pupillary response, fluorescein staining, laboratory evaluations (hematology, blood chemistry, and urinalysis), physical examination, and cardiovascular parameters (pulse rate, systolic blood pressure, and diastolic blood pressure).

Reviewer's Comments:

Acceptable.

Schedule of Visits and Measurements for C-02-53 and C-03-32

Study Activity	Preoperative	Preop.	Surgery	Postoperative				
	-6 wks. to -1 day	Day -1	(Day 0)	Day 1 (24 ± 8 hr.)	Day 3 (± 1 day)	Day 7 (± 2 day)	Day 14 (Day -1 to +5)	Early Exit[4,5]
Informed Consent	X							
Demographics	X							
BCVA logMar	X[1]			X[2]	X[2]	X[2]	X[1]	X[1]
Goldmann IOP	X[1]			X[2]	X[2]	X[2]	X[1]	X[1]
Slit-lamp	X[1]			X[2]	X[2]	X[2]	X[1]	X[1]
Ocular pain assessment	X[1]			X[2]	X[2]	X[2]	X[1]	X[1]
Dilated fundus exam.	X[1]							
Medication(s)	X							
Medical condition(s)	X							
Urine pregnancy[3]	X[3]						X[3]	X[3]
Begin dosing		X						
Change in medical condition(s)/medication(s)			X	X	X	X	X	X
Surgical data			X					
Surgery related meds.			X					
Change in surgically related medication(s)				X	X	X	X	X
Adverse Events			X	X	X	X	X	X
Exit form								

1 Both eyes
2 Study (operative) eye only
3 Urine pregnancy test were administered to women of childbearing potential

4 For study C-02-53: Day 14/Exit Form was completed upon study exit to capture safety data in the study eye and the non-treated fellow eye. Data from exit visits occurring at a day 1, 3, 7 or 14, or unscheduled visit were recorded on this form.
5For study C-03-32: if patient exits from study prior to the Day 14 visit, ocular procedures will be performed in both eyes where noted.

Reviewer's Comments:

Acceptable.

Patient Population for Nepafenac Ophthalmic Suspension, 0.1%, TID
Study C-02-53

Patient Group	Number of Patients Evaluable for Analysis		Number of Patients Excluded from Analysis	
	Vehicle	Nepafenac 0.1%, TID	Vehicle	Nepafenac 0.1%, TID
Intent –to-Treat (ITT):	58	56	1	2
Safety:	59	58	2	2
PPP:	54	54	4	2

Patient Population for Nepafenac Ophthalmic Suspension, 0.1%, TID
Study C-03-32

Patient Group	Number of Patients Evaluable for Analysis		Number of Patients Excluded from Analysis	
	Vehicle	Nepafenac 0.1%, TID	Vehicle	Nepafenac 0.1%, TID
Intent –to-Treat (ITT):	233	243	7	4
Safety:	240	247	20[a]	15[a]
PPP:	216	227	17	16

a Patients did not dose with randomized test article.

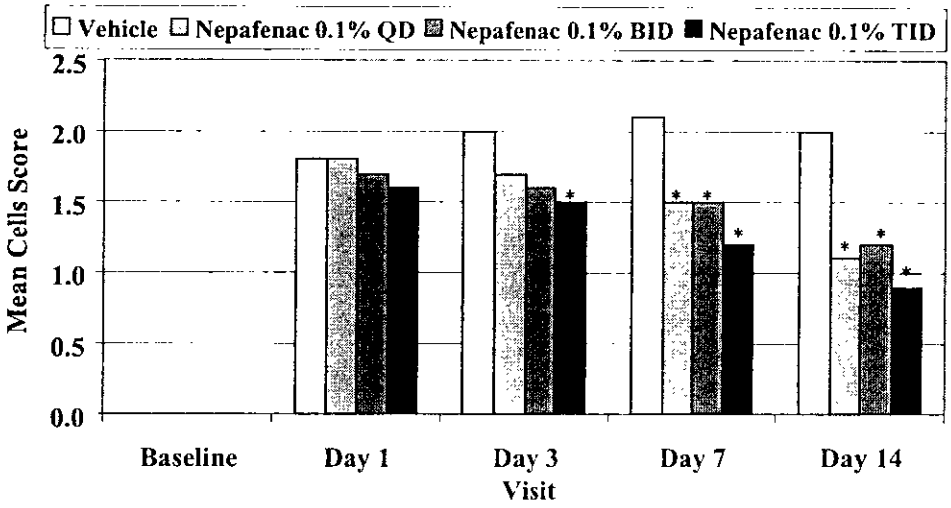
Reviewer's Comments:

The ITT population provides the basis for the primary efficacy data set. All case report forms for discontinued patients were reviewed by the medical officer. There are nearly equal numbers of patients discontinued for each population (ITT, Safety and PPP) and for each drug product.

APPEARS THIS WAY
ON ORIGINAL

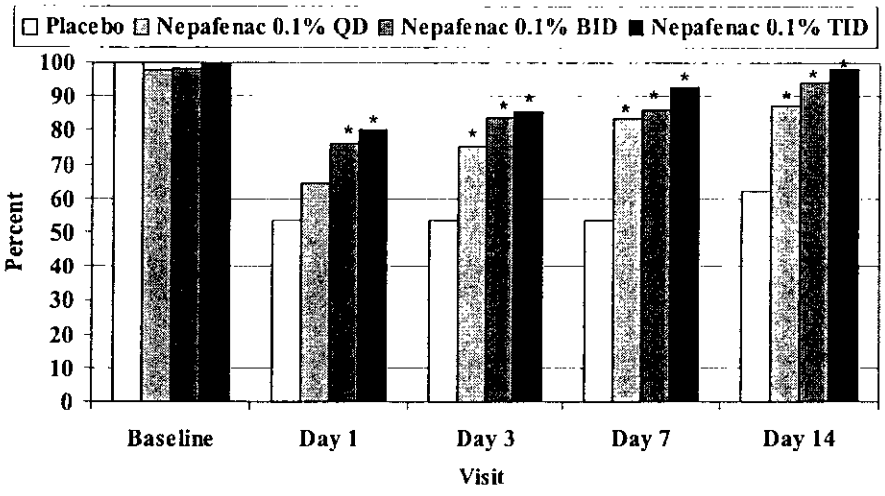
6.1.4 Efficacy Findings: based on studies C-02-53 and C-03-32, results follow:

Mean Aqueous Cells Scores by Visit
(C-02-53, Intent-to-Treat)



*LSMeans p-value ≤ 0.0098
RM ANOVA treatment by visit interaction p-value < 0.0001

Percent of Patients with No Ocular Pain by Visit
(C-02-53, Intent-to-Treat)



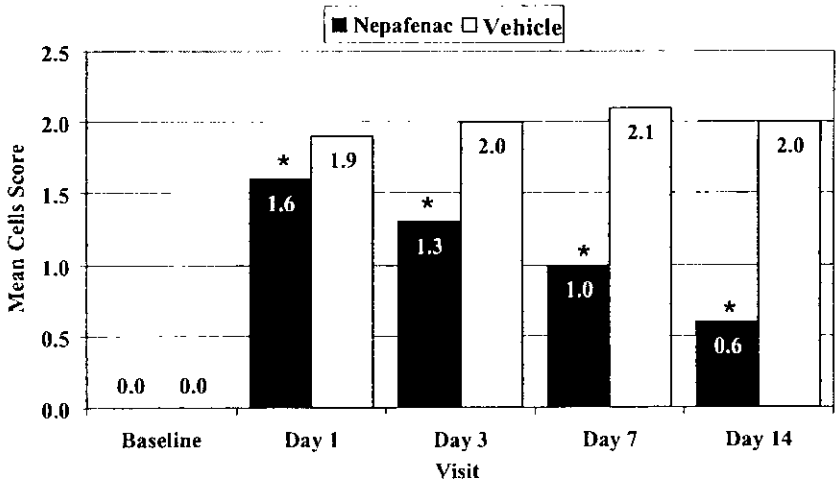
*Chi-square test p-value ≤ 0.0220

Reviewer's comments:

Nepafenac ophthalmic suspension, 0.1% (QD, BID and TID) in study C-02-53 was superior to placebo in the treatment of inflammation and pain associated with cataract surgery based upon clinical assessments of aqueous cells and pain. The TID use of the 0.1% formulation appeared to demonstrate efficacy earlier than then QD or BID regimen based on percentage of patients cured. This information was presented at the EOP-2 meeting.

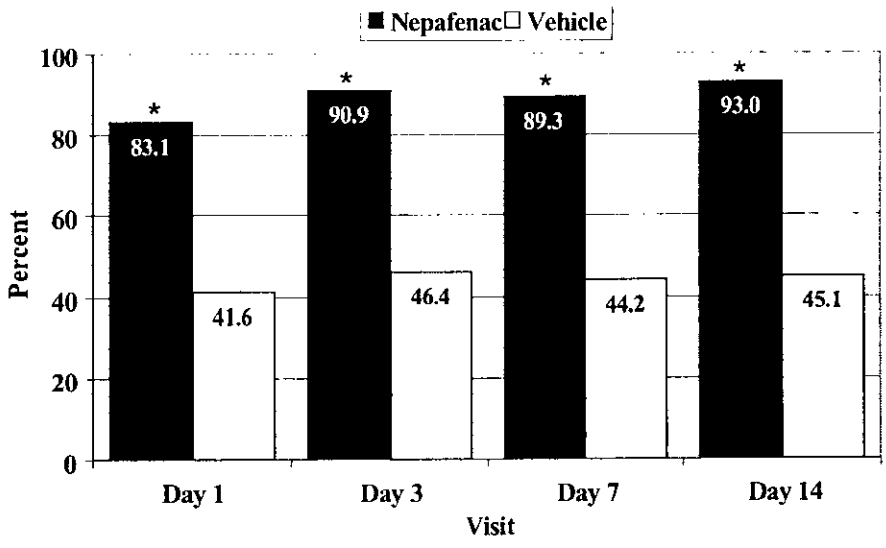
A clinically significant difference is demonstrated at Day 14 for treatment of inflammation.

Mean Aqueous Cells Score by Visit
(C-03-32, Intent-to-Treat)



Baseline t-test p-value not applicable
* LSMeans p-values < 0.0001

Percent of Pain-free Patients by Visit
(C-03-32, Intent-to-Treat)



* NLMixed Model treatment comparison p-values < 0.0001

Reviewer's comments:

Nepafenac ophthalmic suspension, 0.1% dosed TID in study C-03-32 was superior to placebo in the treatment of inflammation and pain associated with cataract surgery based upon clinical assessments of aqueous cells and pain.

APPEARS THIS WAY
ON ORIGINAL

Summary Results for Mean Cell Score
Nepafenac Studies C-02-53 and C-03-32
(Intent-to-Treat)

Efficacy Parameter	Postop Day	C-02-53			C-03-32		
		Nepafenac TID	Placebo	P value	Nepafenac TID	Placebo	P value
Mean Cells Score (units)	1	1.6	1.8	0.2121	1.6	1.9	<0.0001
	3	1.5	2.0	0.0071	1.3	2.0	<0.0001
	7	1.2	2.1	<0.0001	1.0	2.1	<0.0001
	14	0.9	2.0	<0.0001	0.6	2.0	<0.0001

Summary for Mean Cell Scores
Nepafenac Studies C-02-53 and C-03-32
(Per Protocol)

Efficacy Parameter	Postop Day	C-02-53			C-03-32		
		Nepafenac TID	Placebo	P value	Nepafenac TID	Placebo	P value
Mean Cells Score (units)	1	1.6	1.8	0.1198	1.5	1.9	<0.0001
	3	1.2	1.8	0.0016	1.2	1.8	<0.0001
	7	0.8	1.5	<0.0001	0.8	1.6	<0.0001
	14	0.4	0.9	0.0007	0.4	0.7	<0.0001

Reviewer's comments:

The efficacy of TID-dosed nepafenac ophthalmic suspension, 0.1% in treating ocular inflammation is demonstrated by the reduction in the mean cell scores over the postoperative period (above Table).

These analyses demonstrate approximately 1 unit difference between nepafenac and placebo after 1 week of treatment. Differences of this level served as the basis of approval for other products with this indication.

These data show replicated results demonstrating the efficacy of nepafenac in the absence of additional anti-inflammatory agents to treat ocular inflammation. These results are supportive of the primary efficacy analysis.

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

Summary of Pain Results from C-02-53 and C-03-32 (Intent-to-Treat)

Efficacy Parameter	Postop Day	C-02-53			C-03-32		
		Nepafenac TID	Placebo	P value	Nepafenac	Placebo	P value
% Pain-free	1	80.4%	53.4%	0.0023	83.1%	41.6%	<0.0001
	3	85.7%	53.4%	0.0002	90.9%	46.4%	<0.0001
	7	92.9%	53.4%	<0.0001	89.3%	44.2%	<0.0001
	14	98.2%	62.1%	<0.0001	93.0%	45.1%	<0.0001

Summary of Pain Results from C-02-53 and C-03-32 (Per Protocol)

Efficacy Parameter	Postop Day	C-02-53			C-03-32		
		Nepafenac TID	Placebo	P value	Nepafenac	Placebo	P value
% Pain-free	1	79.6%	53.7%	0.0043	82.6%	41.1%	<0.0001
	3	82.67%	47.7%	0.0005	92.1%	53.5%	<0.0001
	7	90.9%	50.0%	<0.0001	91.3%	63.1%	<0.0001
	14	97.7%	82.6%	<0.0254	95.1%	83.1%	0.0050

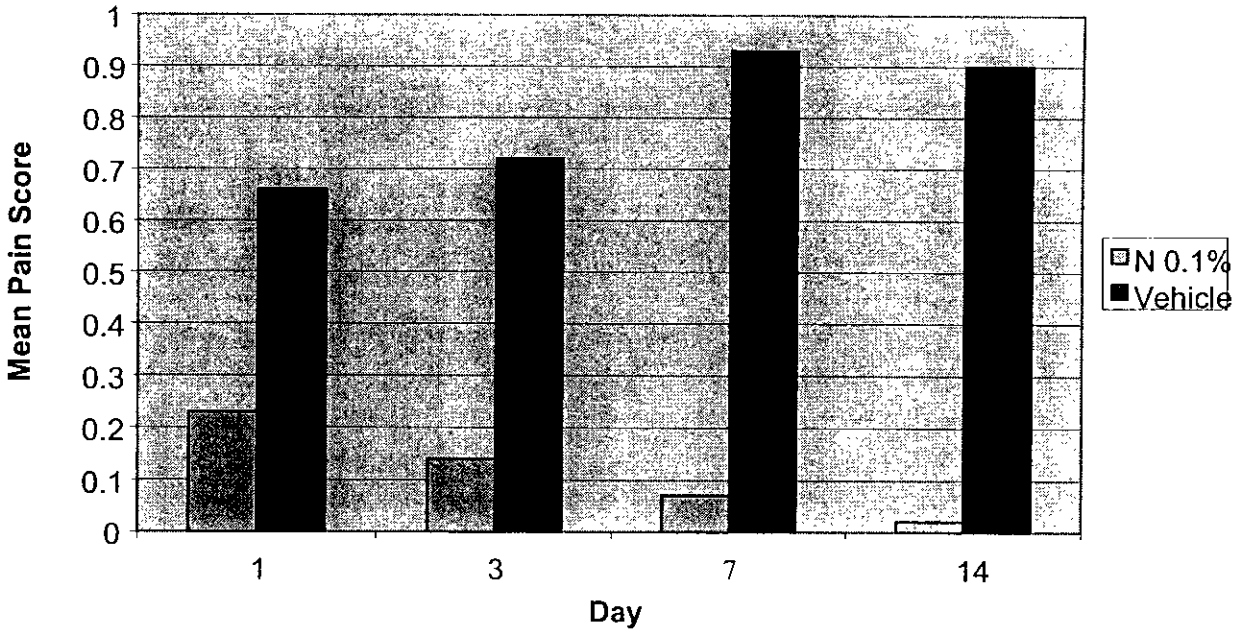
Reviewer's comments:

A significantly higher percentage of patients in the nepafenac treatment group reported no ocular pain on the day following cataract surgery (Day 1) compared to those in the placebo group for C-02-53 (80.4% vs. 53.4%, respectively; p=0.0023) and C-03-32 (83.1% vs. 41.6%, respectively; p<0.0001) (above Table). This statistically significant difference in proportions between the nepafenac and placebo treatment groups was maintained throughout the 14-day postoperative period in both studies. The clinical relevance of nepafenac's efficacy in treating ocular pain associated with cataract surgery is demonstrated by the finding that 1.5 to 2 times as many nepafenac vs. placebo-treated patients reported no ocular pain at any postoperative visit.

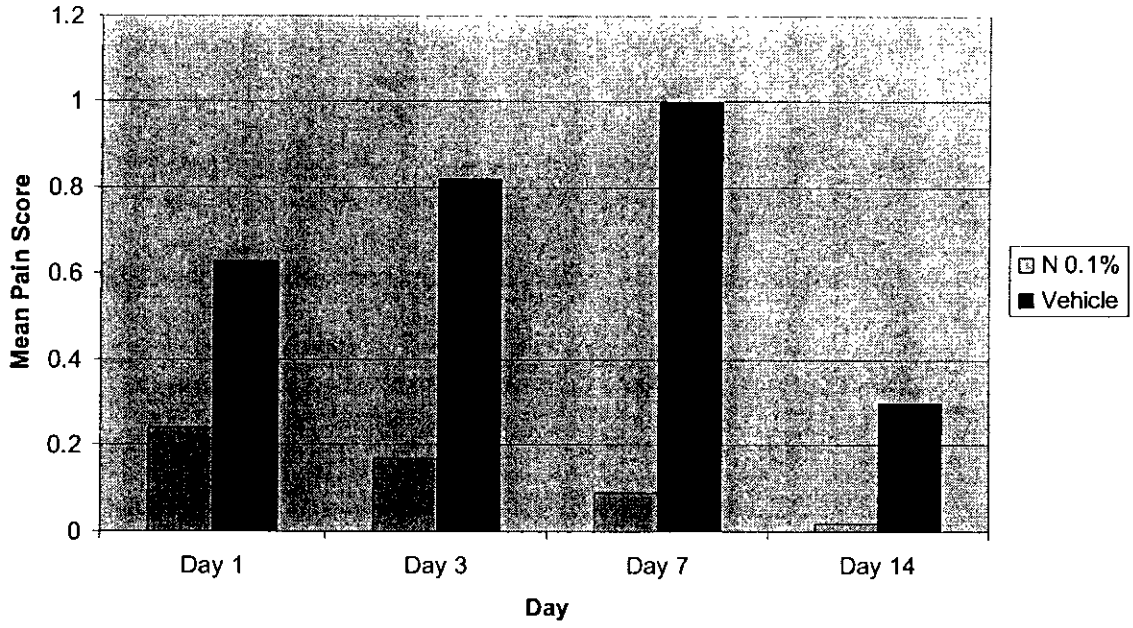
These data show replicated results demonstrating the efficacy of nepafenac in the absence of additional analgesic agents to treat ocular pain. These results are supportive of the primary efficacy analysis.

For the percent pain-free patients the per protocol analysis demonstrated similar results to the intent- to-treat analysis. The difference between treatments was statistically significant at all postoperative visits, though by Day 14 the difference was less pronounced.

Study C-02-53 Mean Pain Score (ITT)



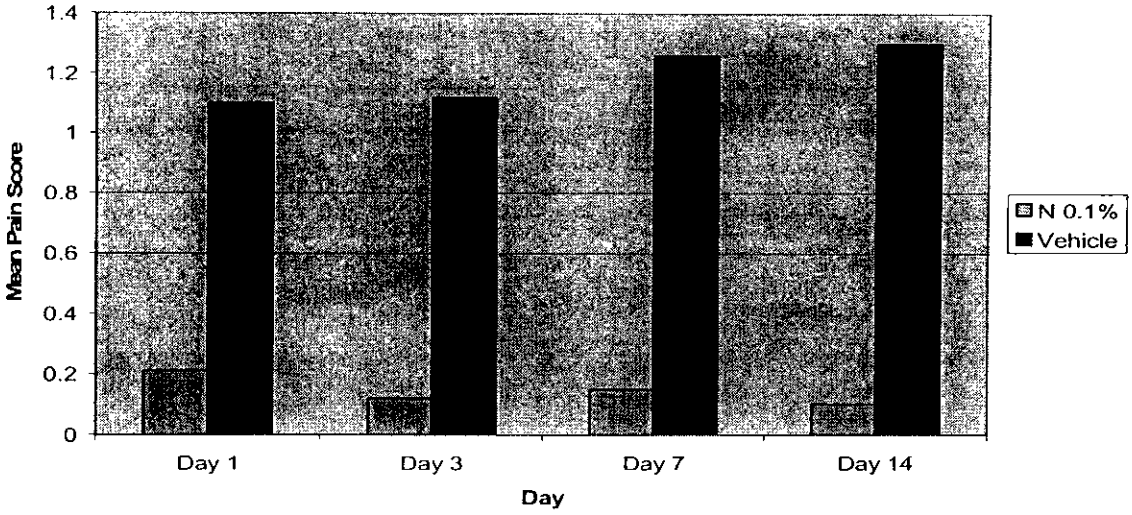
Study C-02-53 Mean Pain Score (Per Protocol)



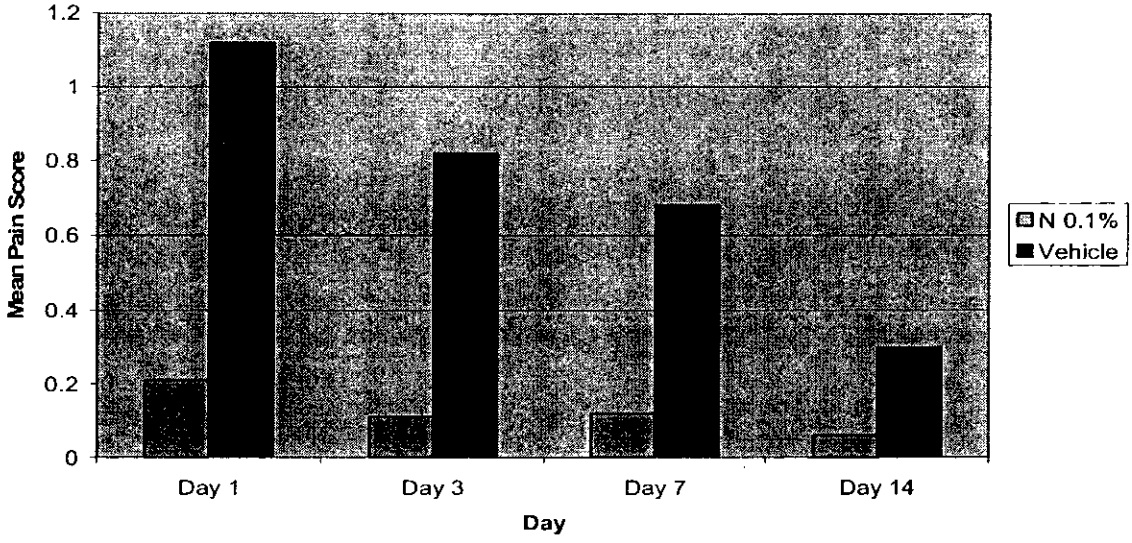
Reviewer's comments:

In study C-02-53 for the ITT population there were statistically significant differences in the mean ocular pain score between the two treatment groups (nepafenac 0.1% versus vehicle) at all postoperative visits (p-value from t-test <0.0001). The results from the Per Protocol population were similar.

Study C-03-32 Mean Pain Score (ITT)



Study C-03-32 Mean Pain Score (Per Protocol)



Reviewer's comments:

In study C-03-32 for the ITT and Per Protocol populations at all post-operative visits the nepafenac group had significantly lower mean ocular pain scores than those of vehicle. For both the ITT and Per Protocol population the p value was <0.0001 (based on the t-test) at all postoperative visits except at Day 14 for the Per Protocol group the p value was 0.015.

6.1.5 Clinical Microbiology

Not applicable. This drug is not an antimicrobial.

6.1.6 Efficacy Conclusions

Reviewer's comments:

Nepafenac ophthalmic suspension, 0.1% dosed three-times-daily beginning one day prior to surgery and continuing the day of surgery and through the first two weeks of the postoperative period is effective in the treatment of ocular inflammation and ocular pain.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The submitted clinical study reports and protocols for four studies (C-95-93, C-97-30, C-02-53 and C-03-32) and literature reports were reviewed. The submitted study reports were reviewed and form the basis of the review of safety for this application.

The medical officer has reviewed all Case Report Forms for discontinued subjects in the four studies (C-95-93, C-97-30, C-02-53 and C-03-32) as part of the safety review.

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 respective trials

7.1.1 Deaths

No deaths occurred during the studies.

7.1.2 Other Serious Adverse Events

Reviewer's comments:

Corneal ulcer and corneal perforation are known adverse events associated with this class of drugs.

Serious Adverse Events
Study C-03-32
Overall Safety Population

Adverse Event	Nepafenac 0.1%, TID N=247 N (%)	Vehicle N = 240 N (%)
Overall	0(0.0%)	1 (0.4%)
Encephalitis	0(0.0%)	1 (0.4%)

Serious Adverse Events
Study C-02-53
Overall Safety Population

Adverse Event	Nepafenac 0.1% (QD, BID, or TID) N=161 N (%)	Vehicle N = 59 N (%)
Overall	1(0.6%)	0 (0.0%)
Aphasia (BID dose)	1(0.6%)	0 (0.0%)

Reviewer's comments:

Few serious adverse events were reported in these clinical trials. None of the events were ocular, and none were considered by the investigators to be related to the study medications; there were no deaths.

Serious Adverse Events
Study C-95-93
Overall Safety Population

Adverse Event	Nepafenac 0.03%, 0.1% or 0.3% (All doses QID) N=208 N (%)	Vehicle N = 72 N (%)
Overall	7(3.3%)	1 (1.4%)
Hypopyon	0(0.0%)	1 (1.4%)
Pancreatitis (dose 0.3%)	1(0.5%)	0(0.0%)
Gastritis (dose 0.1%)	1(0.5%)	0(0.0%)
Nausea (dose 0.1%)	1(0.5%)	0(0.0%)
Vomit (dose 0.1%)	1(0.5%)	0(0.0%)
Decreased weight (dose 0.1%)	1(0.5%)	0(0.0%)
Intestinal obstruction (dose 0.1%)	1(0.5%)	0(0.0%)
Sepsis (dose 0.1%)	1(0.5%)	0(0.0%)

Reviewer's Comments:

In the Nepafenac group two patients each had 3 adverse events – one patient had gastritis, nausea and vomiting, and another patient had decreased weight, intestinal obstruction and sepsis.

Serious Adverse Events
Study C-97-30
Overall Safety Population

Adverse Event	Nepafenac 0.003%, 0.01%, 0.03%, or 0.1% (All doses QID) N=158 N (%)	Vehicle N = 39 N (%)
Overall	0(0.0%)	2(5.0%)
Ocular pain	0(0.0%)	1(2.5%)
Uveitis	0(0.0%)	1(2.5%)

Reviewer's comments:

No patients in the nepafenac group experienced a serious adverse event in this study.

7.1.3 Dropouts and Other Significant Adverse Events

Discontinued Patients

C-03-32 Listing of Patients by Investigator Who Discontinued the Study

(Nepafenac 0.1%, TID)

Investigator # Product	Reason Discontinued	Patient #	Evaluable for Safety*
847			
Nepafenac	Patient Decision - Withdrew consent, never used study drug.	2903	No
Vehicle	Treatment Failure**	2902	Yes
Vehicle	Treatment Failure	2904	Yes
Vehicle	Treatment Failure	2906	Yes
Vehicle	Treatment Failure	2907	Yes
Vehicle	Treatment Failure	2910	Yes
Vehicle	Treatment Failure	2911	Yes
970			
Vehicle	Treatment Failure	2629	Yes
Vehicle	Treatment Failure	2601	Yes
Vehicle	Treatment Failure	2604	Yes
Vehicle	Treatment Failure	2607	Yes
Vehicle	Treatment Failure	2610	Yes
Vehicle	Treatment Failure	2611	Yes
Vehicle	Treatment Failure	2615	Yes
Vehicle	Treatment Failure	2616	Yes
Vehicle	Treatment Failure	2617	Yes
Vehicle	Treatment Failure	2618	Yes
Vehicle	Treatment Failure	2622	Yes
Vehicle	Treatment Failure	2624	Yes
Vehicle	Treatment Failure	2626	Yes
Vehicle	Treatment Failure	2627	Yes
Vehicle	Treatment Failure	2631	Yes
Vehicle	Treatment Failure	2633	Yes
Vehicle	Treatment Failure	2634	Yes
Vehicle	Treatment Failure	2639	Yes
Vehicle	Treatment Failure	2640	Yes
Vehicle	Treatment Failure	2642	Yes
Vehicle	Treatment Failure	2643	Yes
Vehicle	Treatment Failure	2645	Yes
Vehicle	Treatment Failure	2647	Yes
Vehicle	Treatment Failure	2649	Yes
Vehicle	Treatment Failure	2650	Yes

1204			
Nepafenac	Patient Decision – Patient withdrew, returned medication unopened	2508	Yes
Vehicle	Patient Decision – Patient withdrew, returned medication unopened	2510	No
Vehicle	Treatment Failure	2503	Yes
Vehicle	Treatment Failure	2507	Yes
Vehicle	Treatment Failure	2509	Yes
Vehicle	Treatment Failure	2516	Yes
1238			
Vehicle	Other – Patient did not understand the directions, returned medication unopened	3201	No
Vehicle	Other – Patient decided not to participate, returned medication unopened	3208	No
Vehicle	Treatment Failure	3203	Yes
Vehicle	Treatment Failure	3205	Yes
1908			
Vehicle	Treatment Failure	3105	Yes
2435			
Vehicle	Other – Patient admitted to hospital, never had cataract surgery, medication returned unopened	3008	No
Vehicle	Treatment Failure	3002	Yes
Vehicle	Treatment Failure	3004	Yes
Nepafenac	Treatment Failure	3009	Yes
Vehicle	Treatment Failure	3010	Yes
Vehicle	Treatment Failure	3011	Yes
2666			
Nepafenac	Other – Withdrew consent, medication returned unopened	1215	No
Nepafenac	Other – Withdrew consent, medication returned unopened	1228	No
Vehicle	Other – Withdrew consent, medication returned unopened	1205	No
Vehicle	Other – Withdrew consent, medication returned unopened	1212	No
Nepafenac	Treatment Failure	1211	Yes
Nepafenac	Treatment Failure	1224	Yes
Vehicle	Treatment Failure	1203	Yes
Vehicle	Treatment Failure	1208	Yes
Vehicle	Treatment Failure	1209	Yes
Vehicle	Treatment Failure	1217	Yes
Vehicle	Treatment Failure	1222	Yes
Vehicle	Treatment Failure	1225	Yes
2678			

Nepafenac	Other - Patient was on a steroid (an excluded medicine) prior to surgery	1722	Yes
Vehicle	Other – Patient was on a steroid (an excluded medicine) 2 days prior to surgery	1706	No
Vehicle	Other – Patient could not return for follow up visits, medication returned unopened	1725	No
Nepafenac	Treatment Failure	1709	Yes
Nepafenac	Treatment Failure	1711	Yes
Nepafenac	Treatment Failure	1720	Yes
Vehicle	Treatment Failure	1710	Yes
Vehicle	Treatment Failure	1712	Yes
Vehicle	Treatment Failure	1714	Yes
Vehicle	Treatment Failure	1715	Yes
Vehicle	Treatment Failure	1717	Yes
Vehicle	Treatment Failure	1718	Yes
Vehicle	Treatment Failure	1721	Yes
2902			
Vehicle	Adverse Event - Photophobia	1636	Yes
Vehicle	Other – Patient never started medication	1610	No
Vehicle	Other – Patient used excluded medication (steroid) prior to surgery	1627	No
Vehicle	Patient Decision – After signing informed consent, patient declined to be in study	1607	No
Vehicle	Patient Decision – After signing informed consent, patient declined to be in study	1616	Yes
Nepafenac	Treatment Failure	1611	Yes
Nepafenac	Treatment Failure	1612	Yes
Vehicle	Treatment Failure	1601	Yes
Vehicle	Treatment Failure	1628	Yes
Vehicle	Treatment Failure	1629	Yes
Vehicle	Treatment Failure	1630	Yes
Vehicle	Treatment Failure	1633	Yes
3025			
Nepafenac	Patient Decision -- Patient stated after pre-op exam did not want to be in study. Patient did not use test article.	2817	Yes
Vehicle	Patient Decision – Patient chose to exit study at post-op day 3 and withdrew consent.	2808	Yes
Vehicle	Patient Decision – Patient requested to withdraw from study after day 7 exam for personal reasons.	2815	Yes
Vehicle	Treatment Failure	2801	Yes
Vehicle	Treatment Failure	2805	Yes
Nepafenac	Treatment Failure	2807	Yes

3471			
Nepafenac	Adverse Event Conjunctival edema / Ocular hyperemia	1309	Yes
Nepafenac	Treatment Failure	1304	Yes
Nepafenac	Treatment Failure	1305	Yes
Vehicle	Treatment Failure	1302	Yes
Vehicle	Treatment Failure	1306	Yes
Vehicle	Treatment Failure	1308	Yes
Vehicle	Treatment Failure	1316	Yes
Vehicle	Treatment Failure	1317	Yes
Vehicle	Treatment Failure	1320	Yes
3472			
Vehicle	Adverse Event -- Ocular hyperemia	2203	Yes
Nepafenac	Treatment Failure	2204	Yes
Vehicle	Treatment Failure	2202	Yes
Vehicle	Treatment Failure	2206	Yes
Vehicle	Treatment Failure	2212	Yes
3481			
Vehicle	Noncompliance – patient failed to take medication after surgery	2305	Yes
Nepafenac	Other Patient took NSAID 2 days prior to surgery, study medication never used.	2308	No
Nepafenac	Treatment Failure	2302	Yes
Vehicle	Treatment Failure	2301	Yes
Vehicle	Treatment Failure	2306	Yes
3807			
Nepafenac	Other – subject withdrew at preop visit, had not taken medication	3310	No
Nepafenac	Other – patient never took study medication	3319	No
Vehicle	Other – Exited after complicated surgery (vitreous prolapse)	3317	Yes
Vehicle	Treatment Failure	3301	Yes
Vehicle	Treatment Failure	3302	Yes
Vehicle	Treatment Failure	3305	Yes
Vehicle	Treatment Failure	3308	Yes
Vehicle	Treatment Failure	3312	Yes
Vehicle	Treatment Failure	3314	Yes
3828			
Vehicle	Patient Decision – Patient withdrew consent, never took medication	2704	No
Nepafenac	Treatment Failure	2737	Yes
Nepafenac	Treatment Failure	2742	Yes
Vehicle	Treatment Failure	2705	Yes
Vehicle	Treatment Failure	2711	Yes
Vehicle	Treatment Failure	2712	Yes

Vehicle	Treatment Failure	2713	Yes
Vehicle	Treatment Failure	2716	Yes
Vehicle	Treatment Failure	2717	Yes
Vehicle	Treatment Failure	2719	Yes
Vehicle	Treatment Failure	2721	Yes
Vehicle	Treatment Failure	2723	Yes
Vehicle	Treatment Failure	2726	Yes
Vehicle	Treatment Failure	2728	Yes
Vehicle	Treatment Failure	2729	Yes
Vehicle	Treatment Failure	2730	Yes
Vehicle	Treatment Failure	2733	Yes
Vehicle	Treatment Failure	2734	Yes
Vehicle	Treatment Failure	2738	Yes
Vehicle	Treatment Failure	2740	Yes
Vehicle	Treatment Failure	2741	Yes
Vehicle	Treatment Failure	2743	Yes
Vehicle	Treatment Failure	2746	Yes
Vehicle	Treatment Failure	2748	Yes
Vehicle	Treatment Failure	2751	Yes
3889			
Vehicle	Other – Patient had enrolled in another study without investigator's knowledge, no medication used	2105	No
Vehicle	Other – Patient changed their mind, did not take medication	2106	No
Nepafenac	Patient Decision - Patient changed their mind, returned medication unopened	2117	No
Nepafenac	Patient Decision - Patient changed their mind, returned medication unopened	2121	No
Vehicle	Patient Decision – Patient did not want to travel to different office for post-op	2113	Yes
Vehicle	Patient Decision – Patient changed mind, medication returned unopened	2132	No
Nepafenac	Treatment Failure	2108	Yes
Nepafenac	Treatment Failure	2111	Yes
Nepafenac	Treatment Failure	2120	Yes
Nepafenac	Treatment Failure	2123	Yes
Vehicle	Treatment Failure	2104	Yes
Vehicle	Treatment Failure	2112	Yes
Vehicle	Treatment Failure	2119	Yes
Vehicle	Treatment Failure	2124	Yes
Vehicle	Treatment Failure	2126	Yes
Vehicle	Treatment Failure	2128	Yes
3899			

Vehicle	Adverse Event - Patient developed corneal edema, dropped from study to start steroid drops (a protocol excluded medication)	1801	Yes
Vehicle	Adverse Event – Increased injection in study eye, dropped from study to start steroid drops (a protocol excluded medication)	1808	Yes
Vehicle	Treatment Failure	1803	Yes
Vehicle	Treatment Failure	1807	Yes
Vehicle	Treatment Failure	1826	Yes
3900			
Vehicle	Adverse Event – Injection (grade 4) in study eye, dropped from study to start steroid drops (a protocol excluded medication)	1510	Yes
Vehicle	Adverse Event – Injection (grade 4) in study eye, dropped from study to start steroid drops (a protocol excluded medication)	1516	Yes
Vehicle	Noncompliance - Patient did not use study drops the day prior to surgery and was exited from study	1521	No
Vehicle	Other – Patient was given steroid drop by mistake on pre-op day, was exited from study	1506	Yes
Nepafenac	Other - Discontinued at pre-op for health reasons	1524	No
Vehicle	Patient Decision – Patient decided to exit study due to other obligations	1507	Yes
Vehicle	Treatment Failure	1504	Yes
Vehicle	Treatment Failure	1512	Yes
Vehicle	Treatment Failure	1519	Yes
Vehicle	Treatment Failure	1522	Yes
3901			
Nepafenac	Other – Patient excluded during pre-op exam, was on excluded study	2435	No
Nepafenac	Other – Complicated surgery, patient required steroid post-op, an excluded protocol medication	2437	Yes
Vehicle	Other – Patient had incomplete washout of protocol excluded medication, exited from study at post-op day 1	2410	Yes
Vehicle	Other – Trabeculectomy performed, exited study per protocol	2423	Yes
Nepafenac	Patient Decision – Retinal specialist requested patient to withdraw from study after pre-op exam	2417	No

Nepafenac	Patient Decision – Patient withdrew from study after pre-op exam and prior to using study drops	2420	No
Nepafenac	Patient Decision - Patient withdrew from study after pre-op exam and prior to using study drops	2424	No
Nepafenac	Patient Decision - Patient withdrew from study after pre-op exam and prior to using study drops	2425	No
Nepafenac	Patient Decision – Patient did not use study drop day prior to surgery, exited from study	2436	No
Vehicle	Patient Decision -- Patient decided to withdraw from study at pre-op visit	2412	No
Vehicle	Patient Decision - Patient decided to withdraw from study at pre-op visit, no drops used	2432	No
Vehicle	Patient Decision - Patient decided to withdraw from study at pre-op visit, no drops used	2434	No
Vehicle	Patient Decision - Patient decided to withdraw from study at pre-op visit, no drops used	2442	No
Vehicle	Treatment Failure	2406	Yes
Vehicle	Treatment Failure	2415	Yes
Vehicle	Treatment Failure	2418	Yes
Vehicle	Treatment Failure	2419	Yes
Vehicle	Treatment Failure	2426	Yes
Vehicle	Treatment Failure	2428	Yes
Vehicle	Treatment Failure	2429	Yes
Vehicle	Treatment Failure	2433	Yes
Vehicle	Treatment Failure	2438	Yes
Vehicle	Treatment Failure	2439	Yes
3903			
Vehicle	Other – Patient inadvertently dispensed steroid drop in surgical recovery room by staff after surgery	1922	Yes
Vehicle	Treatment Failure	1901	Yes
Vehicle	Treatment Failure	1904	Yes
Vehicle	Treatment Failure	1905	Yes
Vehicle	Treatment Failure	1906	Yes
Vehicle	Treatment Failure	1910	Yes
Vehicle	Treatment Failure	1911	Yes
Vehicle	Treatment Failure	1919	Yes
Vehicle	Treatment Failure	1925	Yes
3904			

Vehicle	Other – Patient withdrew consent after per-op exam, drops not used	1407	Yes
Vehicle	Treatment Failure	1403	Yes
Vehicle	Treatment Failure	1404	Yes
Vehicle	Treatment Failure	1405	Yes
Vehicle	Treatment Failure	1409	Yes
Vehicle	Treatment Failure	1413	Yes
Vehicle	Treatment Failure	1416	Yes
Vehicle	Treatment Failure	1418	Yes
Vehicle	Treatment Failure	1419	Yes
Vehicle	Treatment Failure	1423	Yes

* Pts with Evaluable for Safety = 'No' were discontinued from the study prior to surgery and returned study medication bottles unopened

**Treatment failure = Subjects presenting at any postoperative visit with a cells score of Grade 3 or greater, OR flare score of Grade 3, OR with moderately severe to severe ocular pain (Grade 4 or 5) were exited from the study. Upon study exit, the Investigator treated these subjects as they deemed appropriate for resolution of the inflammation and/or pain.

Cumulative Percent Treatment Failures by Visit
(Intent –to-Treat)
C-03-32

	Total	Day 1		Day 3		Day 7		Day 14	
Treatment	**N**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Nepafenac 0.1%	243	11	4.5	15	6.2	19	17.8	20	8.2
Vehicle	233	52	22.3	100	42.9	133	57.1	142	60.9
p-value		<0.0001		<0.0001		<0.0001		<0.0001	

Failure defined as aqueous cells score ≥ 3 or aqueous flare = 3 or ocular pain score ≥ 4

Reviewer's comments:

Treatment failure rates are presented as a cumulative total at each visit. The incidences of treatment failure for nepafenac were significantly lower at all visits compared to Vehicle. At Day 1, the incidence of treatment failures was more than 4 times lower for nepafenac 0.1% treatment group (4.5%) compared to vehicle (22.3%). At Day 14 final study visit, the incidence of treatment failures was more than 7 times lower for the nepafenac 0.1% treatment group (8.2%) compared to Vehicle (60.9%).

C-02-53 Listing of Patients by Investigator Who Discontinued the Study

(Nepafenac 0.1%: QD, BID or TID)

Investigator # Product	Reason Discontinued	Patient #	Evaluable for Safety*
271			
Placebo	Other – Patient decision based on post-op pain/headache at unscheduled visit at day 9	1031	Yes
Nepafenac QD	Adverse Event – Patient exited day 3 visit after patient given protocol excluded drug (celebrex) for leg pain	1016	Yes
Nepafenac QD	Other – Patient cancelled surgery	1032	Yes
Placebo	Patient Decision – Patient did not return for surgery	1027	No
Nepafenac QD	Patient Decision - Patient did not return for surgery	1010	No
Nepafenac BID	Patient Decision - Patient did not return for surgery	1030	No
Nepafenac TID	Patient Decision – Patient decided not to participate in study prior to day of surgery	1003	Yes
Nepafenac TID	Patient Decision - Patient decided not to participate in study prior to day of surgery	1026	Yes
Placebo	Treatment Failure	1001	Yes
Placebo	Treatment Failure	1008	Yes
Placebo	Treatment Failure	1021	Yes
Placebo	Treatment Failure	1025	Yes
Nepafenac QD	Treatment Failure	1017	Yes
Nepafenac QD	Treatment Failure	1024	Yes
Nepafenac QD	Treatment Failure	1028	Yes
Nepafenac BID	Treatment Failure	1019	Yes
Nepafenac BID	Treatment Failure	1042	Yes
Nepafenac TID	Treatment Failure	1012	Yes
Nepafenac TID	Treatment Failure	1038	Yes
350			
Nepafenac QD	Adverse Event – Sinus infection, started Zithromax	2003	Yes
Placebo	Other – Patient developed UTI prior to surgery, surgery postponed.	2012	Yes
Placebo	Patient Decision – Patient signed informed consent and the next day withdrew from study	2001	No

Investigator # Product	Reason Discontinued	Patient #	Evaluable for Safety*
Nepafenac QD	Treatment Failure	2007	Yes
Nepafenac QD	Treatment Failure	2009	Yes
Nepafenac BID	Treatment Failure	2004	Yes
Nepafenac BID	Treatment Failure	2010	Yes
Nepafenac BID	Treatment Failure	2011	Yes
Nepafenac TID	Treatment Failure	2002	Yes
Nepafenac TID	Treatment Failure	2005	Yes
Nepafenac TID	Treatment Failure	2013	Yes
1007			
Placebo	Treatment Failure	1101	Yes
Placebo	Treatment Failure	1104	Yes
Placebo	Treatment Failure	1107	Yes
Placebo	Treatment Failure	1119	Yes
Placebo	Treatment Failure	1120	Yes
Placebo	Treatment Failure	1123	Yes
Placebo	Treatment Failure	1128	Yes
Nepafenac QD	Treatment Failure	1109	Yes
Nepafenac QD	Treatment Failure	1112	Yes
Nepafenac BID	Treatment Failure	1108	Yes
Nepafenac TID	Treatment Failure	1118	Yes
1405			
Nepafenac QD	Adverse Event – Sinusitis; patient did not take any study medication and cancelled surgery	1321	Yes
Nepafenac BID	Adverse Event – Post-op day 1; elevated IOP (45 mmHg); given timoptic, IOP to 18 mmHg	1303	Yes
Placebo	Other – Patient took protocol excluded medications (pred forte)	1307	Yes
Placebo	Treatment Failure	1317	Yes
Placebo	Treatment Failure	1318	Yes
Placebo	Treatment Failure	1319	Yes
Placebo	Treatment Failure	1327	Yes
Nepafenac QD	Treatment Failure	1328	Yes
Nepafenac BID	Treatment Failure	1315	Yes

Investigator # Product	Reason Discontinued	Patient #	Evaluable for Safety*
Nepafenac BID	Treatment Failure	1330	Yes
Nepafenac TID	Treatment Failure	1305	Yes
Nepafenac TID	Treatment Failure	1316	Yes
1434			
Nepafenac QD	Other – Patient required lens exchange, exited from study	1712	Yes
Nepafenac BID	Patient Decision	1702	Yes
Nepafenac BID	Patient Decision	1719	Yes
Placebo	Treatment Failure	1708	Yes
Placebo	Treatment Failure	1714	Yes
Placebo	Treatment Failure	1717	Yes
Nepafenac QD	Treatment Failure	1710	Yes
Nepafenac BID	Treatment Failure	1707	Yes
Nepafenac BID	Treatment Failure	1722	Yes
Nepafenac TID	Treatment Failure	1718	Yes
1678			
Nepafenac BID	Other – Exited from day of surgery because difficult to dilate	1508	Yes
Placebo	Treatment Failure	1501	Yes
Placebo	Treatment Failure	1503	Yes
Placebo	Treatment Failure	1513	Yes
Nepafenac QD	Treatment Failure	1505	Yes
Nepafenac QD	Treatment Failure	1512	Yes
Nepafenac TID	Treatment Failure	1502	Yes
Nepafenac TID	Treatment Failure	1510	Yes
1806			
Nepafenac QD	Other – patient ill before surgery; enrollment closed before patient regained health.	1217	No
Placebo	Treatment Failure	1207	Yes
Placebo	Treatment Failure	1218	Yes
Placebo	Treatment Failure	1219	Yes
Placebo	Treatment Failure	1221	Yes
Nepafenac QD	Treatment Failure	1210	Yes

Investigator # Product	Reason Discontinued	Patient #	Evaluable for Safety*
Nepafenac BID	Treatment Failure	1202	Yes
Nepafenac BID	Treatment Failure	1211	Yes
2631			
Nepafenac QD	Adverse Event – Corneal Edema; patient treated with protocol excluded medication (econopred)	1604	Yes
Nepafenac BID	Lost to Follow-Up – Patient did not return for surgery	1610	Yes
Nepafenac TID	Other – Patient did not have surgery withdrew at pre-op exam; surgery date was scheduled too far out	1615	No
Placebo	Treatment Failure	1607	Yes
Placebo	Treatment Failure	1617	Yes
Nepafenac BID	Treatment Failure	1609	Yes
3725			
Nepafenac TID	Other – Patient withdrawn from study prior to surgery; all study mediations returned	1803	Yes
3747			
Nepafenac QD	Adverse Event – Bilateral serous choroidal effusion	1915	Yes
Nepafenac TID	Other – Physician decided patient was not a good candidate; patient had history of retinoschisis, optic nerve drusen and mild dry macular degeneration	1904	No
Nepafenac BID	Patient Decision – Following pre-op visit patient decided not to be in study	1907	No
Placebo	Treatment Failure	1901	Yes
Placebo	Treatment Failure	1903	Yes
Placebo	Treatment Failure	1911	Yes
Placebo	Treatment Failure	1913	Yes
Placebo	Treatment Failure	1916	Yes
Placebo	Treatment Failure	1920	Yes
Nepafenac BID	Treatment Failure	1917	Yes

* Pts with Evaluable for Safety = 'No' were discontinued from the study prior to surgery and returned study medication bottles unopened

Cumulative Percent of Treatment Failures at Day 14 by Treatment (Intent-to-Treat)
C-02-53

	Total Patients	Treatment Failures		P-value
		N	%	
Nepafenac 0.1% QD	48	12	25.0	0.0004*
Nepafenac 0.1% BID	50	15	30.0	0/0020*
Nepafenac 0.1% TID	56	11	19.6	<0.0001*
Vehicle	58	35	60.3	

* P-values reflect treatment comparisons to Vehicle.

Reviewer's comments:

By the Day 14 visit, all nepafenac posology groups demonstrated significantly lower cumulative rates of treatment failures compared to the Vehicle group. The lowest treatment failure rate was observed in the nepafenac TID group (19.6%), followed by the nepafenac QD (25.0%) and nepafenac BID groups (30.0%), respectively. The highest treatment failure rate was observed in the Vehicle group (60.3%).

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C-95-93 Listing of Patients by Investigator Who Discontinued the Study

(All dosing QID)

Investigator # Product	Reason Discontinued	Patient #	Evaluable for Safety*
479			
Vehicle	Adverse Event - Ocular pain, photophobia	104	Yes
770			
Vehicle	Adverse Event - Corneal edema	703	Yes
Vehicle	Adverse Event - Iritis	708	Yes
847			
Nepafenac 0.3%	Lost to follow up	304	Yes
Vehicle	Treatment failure		
Vehicle	Treatment failure		
Vehicle	Treatment failure		
Nepafenac 0.1%	Treatment failure	314	Yes
1076			
Nepafenac 0.03%	Other – patient given protocol exclude drug (steroid)	201	Yes
1204			
Vehicle	Lost to Follow up	1011	Yes
1253			
Nepafenac 0.03%	Adverse event - Macular edema, retinal hemorrhage, decreased visual acuity	1401	Yes
1403			
Nepafenac 0.3%	Adverse event – Corneal edema	1707	Yes
1434			
Nepafenac 0.3%	Lost to follow up	1109	Yes
Nepafenac 0.03%	Treatment Failure	1114	Yes
1499			
Nepafenac 0.03%	Adverse event – Increased IOP	801	Yes
Nepafenac 0.1%	Treatment Failure	825	Yes
1806			
Nepafenac 0.1%	Adverse Event – Conjunctivitis	1632	Yes
Vehicle	Adverse event – Conjunctival hyperemia	1617	Yes
Vehicle	Lost to follow up	1655	Yes

Investigator # Product	Reason Discontinued	Patient #	Evaluable for Safety*
Nepafenac 0.03%	Other – patient withdrew	1615	Yes
Vehicle	Treatment Failure	1601	Yes
Vehicle	Treatment Failure	1610	Yes
Vehicle	Treatment Failure	1616	Yes
Vehicle	Treatment Failure	1633	Yes
Vehicle	Treatment Failure	1638	Yes
Vehicle	Treatment Failure	1642	Yes
Nepafenac 0.3%	Treatment Failure	1613	Yes
1971			
Vehicle	Adverse event – corneal edema	420	Yes
Vehicle	Treatment failure	423	Yes

Treatment Failure Rate by Treatment
C-95-93

	NO		Yes	
	N	%	N	%
Treatment				
Nepafenac, 0.03%	69	98.6	1	1.4
Nepafenac, 0.1%	68	97.1	2	2.9
Nepafenac, 0.1%	67	98.5	1	1.5
Nepafenac, 0.3%	67	98.5	1	1.5
Vehicle	62	86.1	10	13.9

Treatment failure was defined as a summed score for aqueous cells and flare that is equal to or greater than the patient's baseline score.
Fisher's exact test $p<0.0001$ (all active treatments combined).

Reviewer's comments:

The nepafenac treatment failure rate ranged from 1.4 to 2.9%, whereas 13.9% of the Vehicle treated patients were defined as treatment failures. A statistically significant treatment difference was observed based on Fisher's exact test.

C-97-30 Listing of Patients by Investigator Who Discontinued the Study

(All dosing QID)

Investigator # Product	Reason Discontinued	Patient #	Evaluable for Safety*
847			
Vehicle	Treatment failure	204	Yes
Vehicle	Adverse Event – Ocular pain, ocular hyperemia	210	Yes
970			
Nepafenac 0.03%	Patient decision - withdraw	615	Yes
Vehicle	Treatment failure	602	Yes
Vehicle	Treatment failure	610	Yes
Vehicle	Treatment failure	618	Yes
Nepafenac 0.003%	Treatment failure	614	Yes
Nepafenac 0.01%	Treatment failure	628	Yes
1007			
Vehicle	Adverse event -- Ocular hyperemia, tearing	927	Yes
Nepafenac 0.003%	Protocol violation	915	Yes
Vehicle	Missed day 15 (exit) visit	925	Yes
Vehicle	Treatment failure	918	Yes
Vehicle	Treatment failure	930	Yes
1300			
Nepafenac 0.01%	Lost to follow up	111	Yes
Vehicle	Treatment failure	106	Yes
1806			
Vehicle	Treatment failure	717	Yes

Treatment Failure Rate by Treatment
C-97-30

	Treatment Failure			
	No		Yes	
	N	%	N	%
Treatment				
Nepafenac, 0.003%	26	65.0	14	35.0
Nepafenac, 0.01%	25	62.5	15	37.5
Nepafenac, 0.03%	26	70.3	11	29.7
Nepafenac, 0.1%	27	67.5	13	32.5
Vehicle	17	43.6	22	56.4

Treatment failure was defined as a summed score for aqueous cells and flare at Day 8 or Day 15 that is equal to or greater than the patient's baseline score.
Fisher's exact test p=0.0159 (all active treatments combined).

Reviewer's Comments:

The nepafenac treatment failure rate ranged from 29.7% to 37.5% whereas 56.4% of the Vehicle treated patients were defined as treatment failures. Nepafenac ophthalmic suspension (0.003%, 0.01%, 0.03% and 0.1%) produced significantly lower treatment failure rates than did Vehicle.

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7.1.3.1 Overall profile of dropouts

Number of Patient Withdrawals from Study and Reason for Withdrawal (Intent-to-Treat)

Protocol	Treatment Group	N	Reason for Patient Withdrawal				
			Treatment Failure	Adverse Event	Patient Decision/ Withdrew Consent	Lost to Follow up	Other
C-95-93	Nepafenac 0.03%	70	1	1	0	0	2
	Nepafenac 0.1%	70	2	2	0	0	0
	Nepafenac 0.3%	68	1	1	0	2	0
	Placebo	72	10	5	0	2	0
C-97-30	Nepafenac 0.003%	40	1	0	0	0	1
	Nepafenac 0.01%	41	1	0	0	1	0
	Nepafenac 0.03%	37	0	0	1	0	0
	Nepafenac 0.1%	40	1	0	0	0	0
	Placebo	39	7	2	0	0	1
C-02-53	Nepafenac 0.1% QD	48	12	4	1	0	1
	Nepafenac 0.1% BID	50	14	1	4	0	0
	Nepafenac 0.1% TID	56	11	0	2	0	0
	Placebo	58	33	0	2	0	2
C-03-32	Nepafenac 0.1%	243	19	1	10	0	0
	Placebo	233	139	6	13	0	3

Patients could be withdrawn from the 4 efficacy studies if they were considered treatment failures. The dose-response studies (C-95-93 and C-97-30) were designed such that patients who experienced an increase in cells and flare from their baseline levels assessed at Day 1 could be withdrawn from the study as treatment failures. Likewise, studies C-02-53 and C-03-32 provided for the withdrawal of patients who experienced a cells score of ≥3 units or flare score =3 units or ocular pain ≥4 units during the postoperative period. Withdrawal of patients due to treatment failure by study visit is presented in the above table and in Section 7.1.3.

Reviewer's comments:

Adverse events in the overall safety population were predominantly nonserious, generally mild or moderate in intensity, and usually resolved with or without treatment. The incidence of adverse events was relatively higher among patients receiving Vehicle compared to patients receiving nepafenac ophthalmic suspension, 0.1%.

7.1.3.2 Adverse events associated with dropouts

Refer to Table in Section 7.1.3.1.

7.1.3.3 Other significant adverse events

Refer to section 7.1.2.

7.1.4 Other Search Strategies

Case Report Forms for all discontinued subjects due to adverse events were reviewed by the medical officer.

7.1.5 Common Adverse Events

Most Common Adverse Events Occurring at > 1.0%
Post-Cataract Inflammation Studies
(C-02-53 and C-03-32)

Treatment	Nepafenac 0.1% N=408		Vehicle N=299	
Coded Adverse Event	**N**	**%**	**N**	**%**
OCULAR				
Decreased Visual Acuity	21	5.1	12	4.0
Capsular Opacity	15	3.7	12	4.0
Photophobia	3	0.7	14	4.7
Foreign Body Sensation	7	1.7	6	2.0
Ocular Hyperemia	2	0.5	10	3.3
Conjunctival Edema	6	1.5	5	1.7
Ocular Pruritus	5	1.2	4	1.3
NONOCULAR				
Body as a Whole				
Headache	12	2.9	6	2.0

Most common adverse events represent all adverse events occurring at an incidence greater than 1% in any treatment group.

The most frequently reported adverse events among patients in the phase 3 pivotal post-cataract inflammation studies receiving nepafenac ophthalmic suspension, 0.1% (N=408) were decreased visual acuity (5.1%), capsular opacity (3.7%), headache (2.9%), foreign body sensation (1.7%), conjunctival edema (1.5%), and ocular pruritus (1.2%). All other adverse events among patients in the phase 3 pivotal post-cataract inflammation studies receiving nepafenac ophthalmic suspension, 0.1% occurred at an incidence of 1% (4 patients) or less.

Reviewer's Comments:

No safety concerns were identified based upon a review of the most common adverse events among patients in the pertinent phase 3 post-cataract inflammation studies.

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were assessed at each scheduled visit (Day 0 through Day 14) and at any unscheduled visits. Duration, investigator's perceived relationship between event and study drug, action(s) taken and outcome were recorded on the Adverse Event form.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The applicant's categorization of events is comparable to the investigators' categorization of events when case report forms are reviewed. Investigator recorded verbatim terms were coded to preferred terms and grouped by body system using a modified COSTART dictionary.

7.1.5.3 Incidence of common adverse events

Refer to section 7.1.5.

7.1.5.4 Common adverse event tables

Refer to section 7.1.5.

7.1.5.5 Identifying common and drug-related adverse events

Refer to Section 7.1.5.

7.1.5.6 Additional analyses and explorations

Not applicable. There were no additional analyses and explorations performed regarding adverse events.

7.1.6 Less Common Adverse Events

Refer to section 7.1.5.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

An analysis of the laboratory data (hematology, blood chemistry, and urinalysis) revealed no safety concerns for patients following exposure to nepafenac ophthalmic suspension.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values.

Refer to Section 7.1.7.1.

7.1.7.3 Standard analyses and explorations of laboratory data

No additional or special analyses were required.

7.1.7.4 Additional analyses and explorations

Refer to Section 7.1.7.1.

7.1.7.5 Special assessments

An analysis by intrinsic factors (age, gender, race, iris color, concomitant diseases, concomitant medications, and time of adverse event) revealed no safety concerns among nepafenac ophthalmic suspension.

An analysis of ocular parameters (visual acuity, ocular signs, intraocular pressure, dilated fundus parameters, endothelial cell density, corneal thickness, and pupil diameter/response) and nonocular parameters (general physical examination, cardiovascular, and laboratory) revealed no safety concerns for the overall safety population, adult population, and elderly population.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Nepafenac ophthalmic suspension is safe and well-tolerated based upon an assessment of cardiovascular parameters (pulse rate, systolic and diastolic blood pressure) with an analysis that includes a review of the ranges of change from baseline, mean changes from baseline, and shift table analysis of changes from baseline for the overall safety population, adult population and elderly population.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Refer to section 7.1.8.1.

7.1.8.3 Standard analyses and explorations of vital signs data

Refer to section 7.1.8.1.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Refer to Section 7.1.8.1.

7.1.10 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.

7.1.11 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.

7.1.12 Special Safety Studies

An analysis by intrinsic factors (age, gender, race, iris color, concomitant diseases, concomitant medications, and time of adverse event) revealed no safety concerns among nepafenac ophthalmic suspension.

An analysis of ocular parameters (visual acuity, ocular signs, intraocular pressure, dilated fundus parameters, endothelial cell density, corneal thickness, and pupil diameter/response) and nonocular parameters (general physical examination, cardiovascular, and laboratory) revealed no safety concerns for the overall safety population, adult population, and elderly population.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Not applicable. This is not a therapeutic class with known abuse potential or apparent withdrawal potential.

7.1.14 Human Reproduction and Pregnancy Data

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

7.1.15 Assessment of Effect on Growth

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

7.1.16 Overdose Experience

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

7.1.17 Postmarketing Experience

There have been no post-marketing clinical trials with nepafenac.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The clinical study reports, clinical protocols and literature reports were reviewed.

Refer to Section 4.2 for a table of the clinical studies.

7.2.1.2 Study type and design/patient enumeration

Data from two phase 3 clinical studies in support of efficacy has been submitted in support of this NDA. Refer to Section 4.2 for a table of the clinical studies submitted supporting the safety and efficacy of this product.

7.2.1.2 Demographics

Patient Demographics (Intent-to-Treat Dataset)

		C-02-53	C-03-32
Total Intent-to-Treat Dataset		212	476
Race	Caucasian	168	426
	Black	10	19
	Asian	3	4
	Hispanic	--[a]	25
	Other	31	2
Age	≥18 and <65 years	49	113
	≥ 65 years	163	363
Sex	Male	91	209
	Female	121	267
Eye Color	Brown	99	189
	Hazel	28	85
	Green	21	33
	Blue	57	159
	Grey	7	10

[a] racial category not evaluated in C-02-53

Reviewer's Comments:

Overall, the demographics of the patient population in these studies are representative of the population that would be expected to receive the drug product.

7.2.1.3 Extent of exposure (dose/duration)

Subject/Patient Exposure to Nepafenac at ≥ TID Dosing, ≥ 0.1% Concentration, and ≥ Two Weeks Duration (Safety Dataset)

Study	Nepafenac Conc.	Dosing Regimen	N per group	N per study	Total
C-95-92	0.1%	QID	10	20	536
	0.3%		10		
C-95-93	0.1%	QID	70	138	
	0.3%		68		
C-96-08	0.1%	QID	1	1	
C-97-30	0.1%	QID	40	40	
C-00-35	0.3%	QID	13	13	
C-00-60	0.3%	QID	7	7	
C-00-61	0.3%	QID	12	12	
C-02-53	0.1%	TID	58	58	
C-03-32	0.1%	TID	247	247	

In addition to the studies conducted to support the clinical development of nepafenac ophthalmic suspension, 0.1% for the treatment of pain and inflammation associated with cataract surgery, Alcon conducted several exploratory studies to assess the efficacy and safety of nepafenac for [redacted] (C-96-08), [redacted] C-00-35 and C-00-60), [redacted] (C-00-61), and [redacted] (C-97-52). These studies, which evaluated concentrations of nepafenac up to 0.3% dosed for up to 6 months, are included in the submission to support the safety of the drug product.

To date, 536 subjects/patients have been exposed to nepafenac ophthalmic suspension at or above the target concentration (0.1%) and dosing regimen (TID) for two or more weeks.

Reviewer's Comments:

These additional studies noted above as well as the 4 studies referenced throughout this review, support the efficacy and safety of the drug product. Some of these studies evaluated nepafenac 0.3% for up to 6 months duration.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

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

7.2.2.1 Other studies

Refer to section 7.1.18.3.

7.2.2.2 Postmarketing experience

There is no postmarketing data with this drug.

7.2.2.3 Literature

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

7.2.3 Adequacy of Overall Clinical Experience

An adequate number of subjects, including adequate demographic subsets, were exposed to the drug product in a well-controlled, randomized, clinical trial. The doses and durations of exposure were adequate to assess safety for the intended use.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable. Refer to Pharmacology/Toxicology review.

7.2.5 Adequacy of Routine Clinical Testing

The methods and ophthalmologic tests used and their frequency were adequate to effectively monitor the subject population.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Refer to Pharmacology/Toxicology review.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

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

7.2.8 Assessment of Quality and Completeness of Data

The submitted safety database appeared adequate and complete for the class of pharmacologic class of agents.

7.2.9 Additional Submissions, Including Safety Update

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Reviewer's Comments:

Refer to comments to section 7.1.5, Common adverse events.

7.4 General Methodology

Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1 Pooled data vs. individual study data

Reviewer's comments:

Pooled and individual data were used in this review to adequately address the safety profile of nepafenac. Data from studies C-95-93, C-97-30, C-02-53 and C-03-32 were used in the safety analysis; data from C-02-53 and C-03-32 were predominantly used in the efficacy analysis.

7.4.1.2 Combining data

Reviewer's comments:

Pooled and individual data were used in this review to adequately address the safety profile of nepafenac. Data from studies C-95-93, C-97-30, C-02-53 and C-03-32 were used in the safety analysis; data from C-02-53 and C-03-32 were predominantly used in the efficacy analysis.

7.4.2 Explorations for Predictive Factors

Reviewer's comments:

This review has not revealed specific drug-related adverse events or demographic effects on the safety profile.

7.4.2.1 Explorations for dose dependency for adverse findings

Reviewer's comments:

N/A – see section 7.4.2.

7.4.2.2 Explorations for time dependency for adverse findings

Reviewer's comments:

N/A – see section 7.4.2.

7.4.2.3 Explorations for drug-demographic interactions

Reviewer's comments:

N/A – see section 7.4.2.

7.4.2.4 Explorations for drug-disease interactions

Reviewer's comments:

N/A – see section 7.4.2.

7.4.2.5 Explorations for drug-drug interactions

Reviewer's comments:

N/A – see section 7.4.2.

7.4.3 Causality Determination

Reviewer's comments:

N/A – see section 7.4.2.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Reviewer's comments:

The recommended dosing of nepafenac ophthalmic suspension, 0.1%, (1 drop three times daily beginning one day pre-op and continued on day of surgery through 2 weeks post-op) is appropriate based on the clinical data provided. Efficacy for this product was demonstrated and there was an acceptable safety profile when dosed at this level. There are no recommended dose modifications for special populations.

8.2 Drug-Drug Interactions

None known.

8.3 Special Populations

No overall differences in safety or effectiveness have been observed between elderly and adult patients.

No patients with hepatic or renal impairment were studied; there is no significant systemic absorption.

re no adequate and well-controlled studies in pregnant woman.

8.4 Pediatrics

Cataract development in the pediatric population is an orphan indication.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

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

8.7 Postmarketing Risk Management Plan

Not applicable. The applicant did not submit a postmarketing risk management plan, nor is one needed.

8.8 Other Relevant Materials

DDMAC and ODS have been consulted and have provided comments.

Reviewer's comments:

Recommended changes will be reviewed and implemented where appropriate in the final label review. The phrase "known bleeding tendencies" raised as an issue in the ODS review is considered a recognized phrase in the class labeling, has been used without problems for over 10 years and is considered acceptable.

9 OVERALL ASSESSMENT

9.1 Conclusions

Reviewer's comments:

This NDA supports the use of nepafenac ophthalmic suspension, 0.1% for the treatment of pain and inflammation associated with cataract surgery. Nepafenac ophthalmic suspension has demonstrated superiority to vehicle in 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. There are no new unexpected adverse events associated with the use of this product. The benefits of this drug outweigh the risks in the treatment of ocular inflammation and the treatment of pain following cataract surgery.

9.2 Recommendation on Regulatory Action

From a clinical perspective, NDA 21-862 is recommended for approval for the treatment of pain and inflammation associated with cataract surgery when dosed three times a day beginning 1 day prior to cataract surgery and continued on the day of surgery through the first 2 weeks post-operatively.

9.3 Recommendation on Postmarketing Actions

Not applicable. Further postmarketing actions are not required.

9.4 Labeling Review

9.5 Comments to Applicant

There are currently no comments for the applicant. No postmarketing actions are recommended.

Reviewer's comments:

There are no deficiencies other than labeling recommendations to be conveyed to the sponsor.

4 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

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