PRODUCT MONOGRAPH

Pr NEVANAC®

(Nepafenac) Ophthalmic Suspension
0.1% w/v

Nonsteroidal Anti-Inflammatory

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Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Ophthalmic (topical)	Suspension/ 0.1%	Benzalkonium chloride as preservative. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

NEVANAC® (nepafenac) ophthalmic suspension, 0.1% is indicated for management of pain and inflammation associated with cataract surgery.

Geriatrics (> 65 years of age):
No overall differences in safety and effectiveness have been observed between elderly and younger patients.

Pediatrics (< 18 years of age):
The safety and effectiveness of NEVANAC in pediatric patients have not been established. Its use is not recommended in these patients until further data become available.

CONTRAINDICATIONS

NEVANAC is contraindicated in patients who are:

- hypersensitive to nepafenac, to any ingredient in the formulation or component of the container (for a complete listing see the Dosage Forms, Composition and Packaging section of the Product Monograph).
- hypersensitive to other nonsteroidal anti-inflammatory drugs (NSAIDs).

WARNINGS AND PRECAUTIONS

General
Benzalkonium chloride, the preservative in NEVANAC, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Close monitoring is required with frequent and/or

prolonged use of this product. Benzalkonium chloride is also known to discolour soft contact lenses and may cause eye irritation.

There is a potential for cross-sensitivity of nepafenac to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Topical NSAIDs 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.

Carcinogenesis and Mutagenesis
See Toxicology section for animal data.

Hematologic
With some NSAIDs, including NEVANAC, the potential exists for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ophthalmic NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

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

Ophthalmologic
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 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. Post-marketing experience also suggests that prolonged use of topical NSAIDs may increase patient risk for occurrence and severity of corneal adverse reactions.

Contact lens wear is not recommended during the postoperative period following cataract surgery; therefore, contact lenses should not be worn during treatment with NEVANAC.

Sexual Function/Reproduction
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). There are no adequate data regarding the use of NEVANAC on human fertility.

Driving and Using Machinery
Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at application, the patient must wait until the vision clears before driving or using machinery.

Special Populations
Pregnant Women:
No adequate and well-controlled studies have been conducted in pregnant women. Because animal reproduction studies are not always predictive of human response, NEVANAC should not be used during pregnancy.

Because of the known effects of prostaglandin biosynthesis inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of NEVANAC during late pregnancy should be avoided.

Nursing Mothers: It is unknown whether nepafenac is excreted in human milk after topical ocular administration. Animal studies have shown excretion of nepafenac in the milk of pregnant rats after oral administration. Caution should be exercised when NEVANAC is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of NEVANAC in pediatric patients have not been established. Its use is not recommended in these patients until further data become available.

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview
In clinical studies with over 800 patients receiving NEVANAC, approximately 5% of patients experienced adverse reactions. These events led to discontinuation in 0.5% of patients, which was less than placebo-treated patients (1.3%) in these same studies. No serious adverse events related to NEVANAC were reported in these studies.

Clinical Trial Adverse Drug Reactions
Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In 11 clinical studies, NEVANAC was administered to 811 patients at a dose of one drop one, two, three or four times daily. The most frequent adverse drug reactions (>0.1%) in patients with exposure to NEVANAC are presented in Table 1. No treatment-related adverse drug reactions

were reported at a frequency of ≥1% in patients with exposure to NEVANAC.

Table 1: Treatment-Related Adverse Drug Reactions > 0.1%

MedDRA Preferred Term (Version 9.0)	NEVANAC 0.1% n= 811 (%)	Placebo n= 529 (%)	Ketorolac 0.5% n=73 (%)	Ketorolac 0.4% n=163 (%)	Diclofenac 0.1% n=44 (%)
Eye Disorders					
eyelid margin crusting	0.6		1.4		
eye pain	0.5	0.9		2.5	
punctate keratitis	0.5	0.6	1.4		
vision blurred	0.5	0.2			
foreign body sensation	0.4	1.5			
dry eye	0.4	0.2			
eye pruritus	0.4				
lacrimation increased	0.2	0.2			
Nervous System Disorders					
Headache	0.4				

Less Common Clinical Trial Adverse Drug Reactions (≤0.1%)

Eye disorders: allergic conjunctivitis, choroidal effusion, conjunctival hyperaemia, corneal deposits, eye discharge, eye irritation, eyelid disorder, iritis, keratitis, ocular discomfort, photophobia
Gastrointestinal disorders: dry mouth, nausea
Immune system disorders: hypersensitivity

Abnormal Hematologic and Clinical Chemistry Findings

NEVANAC had no clinically relevant effect on laboratory parameters.

Post Market Adverse Drug Reactions

Adverse reactions identified from post-marketing experience (i.e. spontaneous reporting and subsequent clinical trials) that have not been reported previously in clinical trials with NEVANAC include the following: corneal perforation, ulcerative keratitis, corneal epithelium defect/disorder, corneal abrasion, anterior chamber inflammation, impaired healing (cornea), reduced visual acuity, corneal scar, corneal opacity, blepharitis, corneal thinning, eye swelling, ocular hyperemia, dizziness, vomiting, dermatitis allergic and blood pressure increased.

DRUG INTERACTIONS

Overview
Neither nepafenac nor amfenac inhibits any of the major human cytochrome P450 (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) metabolic activities *in vitro* at concentrations up to 300 ng/mL. Therefore, drug-drug interactions involving CYP-mediated metabolism of concomitantly administered drugs are unlikely. Drug-drug interactions mediated by protein binding are also unlikely.

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

The administration of NEVANAC in conjunction with prostaglandin analogues was not evaluated in clinical trials. Interactions between NEVANAC and prostaglandin analogues are not anticipated following topical ocular administration.

There is a potential cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory agents.

Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems. Concomitant use of NEVANAC with medications that prolong bleeding time may increase the risk of haemorrhage.

Drug-Food Interactions
Interactions with food are not anticipated following topical ocular administration.

Drug-Herb Interactions
Interactions with herbal products are not anticipated following topical ocular administration.

Drug-Laboratory Interactions
Interactions with laboratory tests are not anticipated following topical ocular administration.

DOSAGE AND ADMINISTRATION

Dosing Considerations
NEVANAC has not been studied in patients with hepatic disease or renal impairment. Nepafenac is eliminated primarily through biotransformation and the systemic exposure is very low following topical ocular administration. No dose adjustment is warranted in these patients.

Recommended Dose and Dosage Adjustment
Shake well before use. One drop of NEVANAC should be applied to the affected eye(s) three-times-daily beginning 1 day prior to cataract surgery, and continued on the day of surgery and through the first 2 weeks of the postoperative period.

Missed Dose
If a dose is missed, a single drop should be applied as soon as possible before reverting to regular routine. Do not use a double dose to make up for the one missed.

Administration
NEVANAC has been safely administered in conjunction with other ophthalmic medications such as antibiotics, anesthetics, beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics. Because the administration of NEVANAC in conjunction with prostaglandin analogues has not been studied, use only if the benefit outweighs any potential risk.

If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

Contact lens wear is not recommended during the postoperative period following cataract surgery; therefore, contact lenses should not be worn during treatment with NEVANAC.

To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

OVERDOSAGE

A topical overdosage may be flushed from the eye(s) with warm tap water.

There is minimal risk of adverse effects due to accidental ingestion of a 5 ml bottle of NEVANAC (total dose of 5 mg) by a child. The recommended adult dose of amfenac sodium (FENAZOX), marketed in Japan since 1986, is one to four 50 mg tablets daily. This translates to 1 to 4 mg/kg per day for a 50 kg person. If a 20 kg child ingested the entire contents of a 5 ml bottle of NEVANAC, it would translate to a dose of 0.25 mg/kg or only 6% to 25% of the recommended adult dose.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Nepafenac is 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 inhibits the action of prostaglandin H synthase (cyclooxygenase), an enzyme required for prostaglandin production.

Pharmacodynamics
In rabbits, nepafenac has been shown to inhibit blood-retinal-barrier breakdown, concomitant with suppression of PGE_2 synthesis. *Ex vivo*, a single topical ocular dose of nepafenac was shown to

inhibit prostaglandin synthesis in the iris/ciliary body (85% - 95%) and the retina/choroid (55%) for up to 6 hours and 4 hours, respectively. Topical nepafenac inhibits choroidal neovascularisation and ischemia induced retinal neovascularisation. A decreased production of vascular endothelial growth factor was noted in these studies.

The majority of hydrolytic conversion is in the retina/choroid followed by the iris/ciliary body and cornea consistent with the degree of vascularised tissue. The enhanced permeability of nepafenac, combined with rapid bioactivation, make it a target-specific NSAID for inhibiting prostaglandin formation in the anterior and posterior segments of the eye.

Results from clinical studies indicate the NEVANAC has no significant effect on intraocular pressure.

Pharmacokinetics

	C_{max} (ng/mL)	**T_{max} (h)**	**AUC_{0-8}** (ng•h/mL)	**$t_{½}$ (h)**
Nepafenac	0.310 ± 0.104	0.25 ± 0.10	0.368 ± 0.106	0.9 ± 0.2
Amfenac	0.422 ± 0.121	0.55 ± 0.14	0.976 ± 0.284	1.6 ± 0.3

Absorption: Following bilateral topical ocular three-times-daily dosing of NEVANAC, low but quantifiable plasma drug concentrations were observed in the majority of subjects at 2 hours (nepafenac) and 5 hours (amfenac) post-dose. The mean steady-state plasma 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.

Distribution: Amfenac has high affinity toward serum albumin proteins. *In vitro,* the percent bound to human albumin and human serum was 95.4% and 99.1%, respectively.

Studies in rats have shown that radioactive drug-related materials distribute widely in the body following single and multiple oral doses of ^{14}C-nepafenac.

Metabolism: Nepafenac undergoes relatively rapid bioactivation to amfenac via intraocular hydrolases. Subsequently, amfenac undergoes extensive metabolism to more polar metabolites involving hydroxylation of the aromatic ring leading to glucuronide conjugate formation.
Radiochromatographic analyses before and after β-glucuronidase hydrolysis indicated that all metabolites were in the form of glucuronide conjugates, with the exception of amfenac. Amfenac was the major metabolite in plasma, representing approximately 13% of total plasma radioactivity. The second most abundant plasma metabolite was identified as 5-hydroxy nepafenac, representing approximately 9% of total radioactivity at C_{max}.

Excretion: After oral administration of ^{14}C-nepafenac to healthy volunteers, urinary excretion was found to be the major route of radioactivity elimination, accounting for approximately 85% of the dose while fecal excretion represented approximately 6% of the dose. Nepafenac and amfenac were not quantifiable in the urine.

Special Populations and Conditions

Pediatrics: NEVANAC has not been evaluated in the pediatric population.

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

Gender: Gender differences in the plasma pharmacokinetics of nepafenac and amfenac were small and not clinically relevant.

Race: A comparison of the single- and steady-state pharmacokinetic data for nepafenac and amfenac in healthy Japanese and non-Japanese subjects indicate that there are no clinically meaningful ethnic differences in the systemic exposure of either nepafenac or amfenac following topical ocular administration of NEVANAC.

Hepatic or Renal Insufficiency: NEVANAC has not been studied in patients with hepatic disease or renal impairment. The systemic exposure is very low following topical ocular administration and no dose adjustment is warranted in these patients.

STORAGE AND STABILITY

Store at 2ºC - 30°C. Discard 28 days after opening.

SPECIAL HANDLING INSTRUCTIONS

None.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NEVANAC contains the active ingredient nepafenac (1 mg/ml) 0.1%, the preservative benzalkonium chloride 0.005%, and the inactive ingredients mannitol, carbomer 974P, sodium chloride, tyloxapol, edetate disodium, sodium hydroxide and/or hydrochloric acid (to adjust pH) and purified water.

NEVANAC is supplied in an 8 mL round low density polyethylene bottle with a natural low density polyethylene dispensing plug and white polypropylene cap. Tamper evidence is provided by a closure with an extended skirt that locks to the bottle finish on application and breaks away from the closure on opening. After cap is removed: if tamper evident snap collar is loose, remove before using product.

Net contents are 5 mL supplied in an 8 mL bottle.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

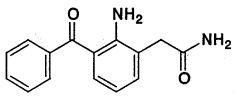
Drug Substance

Common name: nepafenac

Chemical name: 2-amino-3-benzoylbenzeneacetamide
2-(2-amino-3-benzoylphenyl)acetamide

Molecular formula and molecular mass: $C_{15}H_{14}N_2O_2$; 254.28

Structural formula:



Physicochemical properties: Nepafenac drug substance is provided as a yellow crystalline or powder material.

CLINICAL TRIALS

Study demographics and trial design

A summary of the patient demographics for each of the 4 pivotal studies relevant to the evaluation of the efficacy and safety of NEVANAC® (nepafenac) ophthalmic suspension, 0.1% is provided in Table 2. The study population consisted of patients, 18 years of age and older, requiring cataract extraction with planned implantation of a posterior chamber intraocular lens. Overall, the demographics of the patient population in these studies are representative of the population that would be expected to receive the drug product once on the market. Approximately 78% of the patients were over 65 years of age and about 86% were Caucasian. There was a slight predominance of female patients (~59%), which is typical of an elderly population.

Table 2: Summary of patient demographics for pivotal clinical trials in cataract surgery patients

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean Age (Range)	Gender	Race
C-02-53 Posology/ Safety & Efficacy	prospective, randomized, double-masked, placebo-controlled	One drop nepafenac 0.1% or placebo dosed QD, BID, or TID / topical ocular / 16 days[1]	n = 212 intent to treat patients	70.3 yrs (47–91 yrs)	91 M 121 F	A=3 B=10 C=168 H=n/a O=31
C-03-32 Safety & Efficacy	prospective, randomized, double-masked, placebo-controlled	One drop TID nepafenac 0.1% or placebo / topical ocular / 16 days[1]	n = 476 intent to treat patients	69.9 yrs (27–90 yrs)	209 M 267 F	A=4 B=19 C=426 H=25 O=2
C-04-65 Safety & Efficacy	prospective, randomized, double masked, active- and placebo-controlled	One drop TID nepafenac 0.1% or ketorolac 0.5% or placebo / topical ocular / 23 days[1]	n = 225 intent to treat patients	72.1 yrs (42-90 yrs)	90 M 135 F	A=3 B=3 C=217 H=2 O=0
C-04-41 Safety & Efficacy	prospective, randomized, observer and patient-masked, active-controlled	One drop TID nepafenac 0.1% or one drop QID ketorolac 0.4% / topical ocular / up to 30 days[1]	n = 264 intent to treat patients	69.4 yrs (32-89 yrs)	111 M 153 F	A=1 B=12 C=243 H=8 O=0

A=Asian; B=Black; C=Caucasian; H=Hispanic; O=Other
[1]Dosing started 1 day prior to surgery.

Study results

In each of the 4 pivotal efficacy studies (C-02-53, C-03-32, C-04-65 and C-04-41), aqueous cells and flare, which are the hallmark of ocular inflammation, served as the basis for evaluating the efficacy of the drug product. 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. 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).

Subjective assessment of ocular pain, rated by the investigator on a 6-point scale was evaluated as a secondary efficacy variable in all 4 of the efficacy studies. 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 3: Results of Study C-02-53

Endpoints	Associated value and statistical significance for Drug at specific dosages, placebo or active control.
C-02-53: The primary efficacy variable was the percentage of patients declared a treatment failure (aqueous cells score ≥ 3, aqueous flare score = 3 and/or ocular pain score ≥ 4) at Day 14. Secondary efficacy variables included the percentage of treatment responders (aqueous cell score ≤ 1 and aqueous flare score = 0), mean aqueous cells score, mean aqueous flare score and clinical cure rate (cells + flare = 0).	The lowest cumulative rate of treatment failure was nepafenac three times a day (19.6%) followed by nepafenac one time a day (25.0%), nepafenac two times a day (30.0%), and placebo (60.3%) at postoperative Day 14. Nepafenac three times a day was superior to placebo following surgery from Day 3 through study exit (Day 14), P≤0.0080. All nepafenac posologies resulted in numerically lower mean aqueous cells plus flare score compared to placebo at all post-surgical visits. Additonally, all nepafenac posologies were superior to placebo for the mean aqueous cells plus flare scores from Day 3 through study exit (Day 14), P≤0.0330. Three times a day dosing was associated with the lowest mean cells plus flare scores at Days 3, 7 and 14. All nepafenac posologies were associated with a greater percentage of treatment responders compared to placebo at all visits. Three times a day dosing with nepafenac resulted in statistically significant greater percentage of treatment responders at the Day 3 (41.1%, P=0.0081), Day 7 (53.6%, P=0.0001) and Day 14 (66.1%, P=0.0002) visits compared to placebo (19.0%, 20.7% and 32.8%, respectively, P≤0.0081). A patient was a treatment responder at a given visit only if he/she was a responder at that visit and all subsequent visits. Nepafenac three times a day was superior to placebo in treating inflammation as demonstrated by statistically significantly lower mean aqueous cells scores from postoperative Day 3 through study exit (Day 14), P≤0.0071. Nepafenac three times a day was superior to placebo in treating ocular inflammation as demonstrated by statistically significantly lower mean aqueous flare scores from postoperative Day 3 through study exit (Day 14), P≤0.0052. All nepafenac posologies (one, two and three times a day) demonstrated statistically significant higher cumulative cure rates at Day 14 compared to placebo (P≤0.0133). Nepafenac three times a day dosing resulted in an earlier significantly greater cure rate at Day 7 compared to placebo (P=0.0144). A patient was a cure at a given visit only if he/she was a cure at that visit and all subsequent visits.

Table 4: Results of study C-03-32

Endpoints:	**Associated value and statistical significance for Drug at specific dosages, placebo or active control.**
C-03-32: The primary efficacy variable was the percentage of patients declared a cure of ocular inflammation (aqueous cells score + flare score = 0) at Day 14. Secondary efficacy variables included the percentage of patients declared a treatment failure (cells score ≥ 3, flare score = 3, and/or ocular pain score ≥ 4) at each visit, the percentage of patients with clinically significant inflammation (aqueous cells + flare score ≥ 4), and the percentage of patients reporting no ocular pain.	Nepafenac 0.1% dosed three times a day was superior to placebo for percentage of patients cured at Day 14 (62.6% vs 17.2%, respectively; P<0.0001). Additionally, nepafenac 0.1% was superior to placebo for cures at all other postoperative visits (Day 1, 0.4%; Day 3, 6.6%; and Day 7, 29.6%) compared to placebo (0.0%, 3.0%, and 3.0%, respectively; P≤0.0050). A patient was considered cured at a given visit only if he/she was free of ocular inflammation at that visit and all subsequent visits. The use of nepafenac 0.1% resulted in statistically significantly lower percentages of treatment failures at all scheduled postoperative visits compared to placebo (P<0.0001). The use of nepafenac 0.1% resulted in statistically significantly higher percentages of patients with no ocular pain at all scheduled postoperative visits compared to placebo (P<0.0001). Nepafenac 0.1% resulted in statistically significantly lower incidences of patients with clinically significant inflammation at all scheduled post-operative visits compared to placebo (P<0.0001).

Table 5: Results of study C-04-65

Endpoints:	**Associated value and statistical significance for Drug at specific dosages, placebo or active control.**
C-04-65: The primary efficacy variable was the percentage of patients declared cured of ocular inflammation (aqueous cells score + flare scores = 0) at Day 14. Secondary efficacy variables included: • mean aqueous cells + flare scores (nepafenac 0.1% vs. ketorolac 0.5%) • percentage of patients who were treatment failures (cells score ≥3 or flare score = 3) • percentage of patients with clinically significant inflammation • investigator's assessment of ocular pain • mean comfort score at Day 7 (nepafenac 0.1% vs. ketorolac 0.5%)	Nepafenac dosed three times a day was superior to placebo and equal to ketorolac 0.5% for the prevention and treatment of ocular pain and inflammation associated with cataract surgery. At Day 14 there is a statistically significantly higher cure rate for patients treated with nepafenac dosed three times a day compared to placebo (76.3% vs 59.2%; P=0.0241). A patient was considered cured at a postoperative visit if they were free of ocular inflammation and remained free of ocular inflammation at all subsequent visits. Nepafenac dosed 3 times daily is non-inferior (equal) to ketorolac 0.5% dosed three times a day for the treatment of ocular inflammation associated with cataract extraction and IOL implantation surgery as evidenced by similar mean aqueous cells plus flare scores at Day 14. The use of nepafenac 0.1% resulted in statistically significantly lower percentages of treatment failures at Days 3 and 7 compared to placebo (P≤0.0496). The use of nepafenac 0.1% resulted in statistically significantly lower percentages of patients with significant postoperative inflammation at Day 3 and Day 7 compared to placebo (p≤0.0284). Nepafenac patients had a statistically significantly lower postoperative mean scores for patient reported and investigator rated ocular pain compared to placebo (P≤0.0103). Patients treated with nepafenac experienced significantly better comfort (less burning and stinging) upon instillation of their eye drops compared to those treated with ketorolac 5% (P=0.0158).

Table 6: Results of study C-04-41

Endpoints:	**Associated value and statistical significance for Drug at specific dosages, placebo or active control.**
C-04-41: The primary efficacy variable was the percentage of patients who were a clinical success [aqueous cells score = 0 (none) or 1 (1 to 5 cells) and flare score = 0] at Day 14. Secondary efficacy variables included: • percentage of patients declared cured of ocular inflammation (aqueous cells + flare score = 0), • patient evaluation of ocular study drop comfort/discomfort upon instillation (nepafenac 0.1% vs. ketorolac 0.4%) • patient satisfaction assessments (nepafenac 0.1% vs. ketorolac 0.4%)	Nepafenac 0.1% was statistically non-inferior for the incidence of patients declared a clinical success for ocular inflammation compared to ketorolac 0.4% at Day 14. Three times a day dosed nepafenac 0.1% resulted in similar percentages of cured patients when compared to four times a day dosed ketorolac 0.4% ($P>0.05$) at Day 14. Ocular discomfort to the study drop was rated by patients on a 5 point scale (0=none to 4=very severe) upon first application (1 day prior to surgery) and at 7 days following surgery. Nepafenac 0.1% was statistically significantly more comfortable upon instillation compared to Ketorolac 0.4% one day prior to and seven days following surgery ($P\leq0.0003$). Satisfaction with the study drop (nepafenac 0.1% or ketorolac 0.4%) was rated by patients on a 5 point scale (1-Strongly agree to 5-Strongly disagree). Nepafenac 0.1% was associated with significantly less burning ($P<0.0001$), stinging ($P<0.0001$), and redness ($P=0.0479$) and was significantly more soothing upon instillation ($P=0.0067$) compared to ketorolac 0.4%.

DETAILED PHARMACOLOGY

Human Pharmacodynamics

Nepafenac is an amide prodrug of amfenac, a potent nonsteroidal anti-inflammatory drug (NSAID). Following topical ocular administration, nepafenac undergoes amide hydrolysis by intraocular hydrolases to form the pharmacologically active amfenac. Amfenac inhibits both cyclooxygenase COX-1 and COX-2 activity.

Comparing aqueous humor levels at the time of maximum observed mean concentrations relative to cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) IC_{50} values, amfenac had higher mean ratios for both COX-1 and COX-2 than those for ketorolac and nepafenac. The concentration to COX-1 and COX-2 IC_{50} ratios for amfenac (0.649 and 1.07) were approximately 200% and 900% higher, respectively, than those for ketorolac (0.302 and 0.116). The ratio for nepafenac to COX-1 IC_{50} was much lower (>50-fold) than that for amfenac. These findings suggest superior anti-inflammatory activity with NEVANAC compared with Ketorolac Tromethamine Ophthalmic Solution, 0.4%.

Animal Pharmacodynamics
Following a single topical ocular dose, nepafenac distributes locally both to the iris/ciliary body and retina/choroid where, upon bioactivation (hydrolysis), it effectively suppresses *ex vivo* prostaglandin synthesis. Sustained suppression of prostaglandin synthesis is seen for a period of more than 6 hours in the iris/ciliary body. Similar inhibitory effects, although slightly lower in magnitude, are observed *ex vivo* in tissue of the retina/choroid. As a consequence of its unique ocular biodistribution and bioactivation by intraocular tissues, a single topical prophylactic dose of nepafenac effectively inhibits trauma-induced aqueous humor PGE2 accumulation and concomitant breakdown of the blood aqueous barrier. Maximum efficacy (60% inhibition) is noted with a single administration of a 0.3 mg/ml formulation of nepafenac that is maintained throughout the highest concentration tested (3 mg/ml). Drug efficacy is also observed in a more stringent Concanavalin A-induced panretinal inflammation model where topical nepafenac administration leads to significant reductions in retinal edema and blood-aqueous and blood-retinal barrier leakage.

Secondary pharmacology studies examined the ability of nepafenac to inhibit VEGF expression and signal transduction as well as VEGF-induced retinal vascular permeability in the rabbit. Further, the effect of topically administered nepafenac on the development of preretinal neovascularization was studied in several animal models, including a rat model of oxygen-induced retinopathy; a mouse model of laser-induced choroidal neovascularization; and a rabbit model of lipid peroxide induced choroidal neovascularization. Nepafenac's effect on diabetic retinopathy was examined in a rat streptozotocin-induced diabetes model.

Safety pharmacology studies investigated the effects of nepafenac on the central and autonomic nervous, cardiovascular, pulmonary, gastrointestinal, metabolic and renal systems. In *in vitro* studies, 1, 10 and 100 μM concentrations of nepafenac did not interact with 21 different receptors and binding sites including steroid receptors and 1 μM and 10 μM concentrations had no statistically significant effect on guinea pig ileum (smooth muscle) responses to acetylcholine, histamine and barium chloride. The active metabolite of nepafenac, amfenac, had no effect on the HERG tail current (a measure of cardiac repolarization) at concentrations up to 100 ng/ml.
In vivo studies showed that nepafenac (3 mg/kg) had no effect on general behavior, body temperature, or electroshock-induced convulsions (a measure of nepafenac's ability to alter CNS function). At the same concentration, nepafenac produced a statistically significant increase in barbiturate-induced sleep time, but, the increase was not considered clinically meaningful. Three mg/kg of nepafenac had no effect on phenylquinone-induced writhing (a measure of its analgesic activity) and 1 mg/kg administered subcutaneously had no effect on pulmonary or cardiovascular function including the lead II ECG. Likewise, the sodium salt of amfenac at 1.08 mg/kg IV (cumulative dose 1.55 mg/kg) had no effect on BP, HR or lead II ECG, including QTc interval, in anesthetized dogs. Nepafenac (0.1 to 3 mg/kg) also did not significantly affect gastrointestinal motility, urine output, pH or electrolyte concentrations. Oral doses of 3 mg/kg showed no gastric ulcer potential and topical ocular doses up to 500 μg showed no anesthetic activity in rabbits. These data suggest that Nepafenac Ophthalmic Suspension, 0.1% is unlikely to produce side effects when administered as recommended.

Human Pharmacokinetics
In Vitro Studies

Bioactivation of nepafenac to amfenac was demonstrated in the cornea, iris-ciliary body and retinal-choroidal tissues. In human ocular tissue preparations (obtained within 10 hours post-mortem), the specific activity of hydrolase in the iris-ciliary body was greater than that in the cornea. Bioactivation results showed that production of amfenac in target ocular tissues increases linearly in a concentration- and time-dependent manner. The rate of amide hydrolysis increases with increasing nepafenac concentrations.

Nepafenac protein binding was moderate and independent of concentration (range 10 to 1000 ng/mL). The mean protein binding of ^{14}C-nepafenac in human plasma was 83.5 ± 0.8%. Amfenac, on the other hand, exhibits high affinity binding to albumin. The percentages bound *in vitro* to human albumin and to human serum were 95.4% and 99.1%, respectively.

^{14}C-Amfenac partitioning into blood cells is minimal. The ratio of radioactivity in the blood to plasma was <0.09 and <0.04 at the 0.2 μg/mL and 2.0 μg/mL concentrations, respectively. The results indicate only slight distribution of radioactivity into blood cells. Given the limited ^{14}C-amfenac concentration range examined, slight partitioning of radioactivity into blood cells did not indicate concentration dependency.

Potential inhibitory effects of nepafenac on the metabolism of isozyme specific substrates of human cytochrome P450 (CYP) enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) were assessed. The results demonstrate that nepafenac up to 1000 ng/ml does not inhibit catalytic activities of the 6 major CYP isozymes studied. Based on these observations, nepafenac plasma concentrations up to 1000 ng/mL, approximately 3,000 fold greater than the mean steady state Cmax (0.310 ± 0.104 ng/ml) observed in subjects who received TID Nepafenac Ophthalmic Suspension, 0.1%, are unlikely to result in drug-drug interaction involving CYP mediated metabolism of concomitantly administered drugs.

In Vivo Studies

Single-Dose

Following topical ocular administration of nepafenac, quantifiable plasma concentrations of nepafenac (≥0.025 ng/mL) and amfenac (≥0.05 ng/mL) were observed at the first sampling time (10 min) in the majority of subjects, and plasma C_{max} was reached within 30 min. This indicated that the absorption of nepafenac is rapid (plasma C_{max} was reached within 30 min) after topical ocular administration. Following bilateral topical ocular TID administration of nepafenac 0.1% or nepafenac 0.3%, low but quantifiable plasma concentrations of nepafenac and amfenac were observed in the majority of subjects out to 2 and 5 hours post-dose, respectively. After the first dose in one study, nepafenac and amfenac reached plasma C_{max}, on average within 0.21 ± 0.08 hours and 0.48 ± 0.10 hours post-dose, respectively. The mean plasma C_{max} values were 0.276 ± 0.146 ng/mL and 0.293 ± 0.107 ng/mL for nepafenac and amfenac, respectively. The plasma concentrations declined with a mean $t_{1/2}$ of 1.1 ± 0.4 hours for nepafenac and 1.5 ± 0.5 hours for amfenac.

Steady-State

Pharmacokinetic steady state was achieved by Day 2 post-dose and there was no unexpected plasma accumulation of nepafenac or amfenac after TID administration of nepafenac 0.1% or nepafenac 0.3%. The mean AUC and C_{max} values for nepafenac and amfenac increased in a dose-

proportional manner following a single or multiple TID administration of nepafenac 0.1% and 0.3%. At steady-state, nepafenac and amfenac reached plasma C_{max}, on average at 0.25 ± 0.10 hours and 0.55 ± 0.14 hours post-dose, respectively. The mean plasma C_{max} values were 0.310 ± 0.104 ng/mL and 0.422 ± 0.121 ng/mL for nepafenac and amfenac, respectively. After the peak, plasma concentrations of nepafenac and amfenac declined with a mean $t_{1/2}$ of 0.9 ± 0.2 hours and 1.6 ± 0.3 hours, respectively. The mean steady-state amfenac C_{max} (0.422 ± 0.121 ng/mL) following bilateral topical TID dosing of nepafenac 0.1% is approximately 1600 times lower than the mean C_{max} (700 ng/mL) observed in subjects who received multiple 50-mg oral doses of amfenac sodium.

Animal Pharmacokinetics

Nepafenac and amfenac plasma levels decline rapidly with half-lives of approximately 1 hour or less following intravenous doses to rats, rabbits and monkeys. The absolute oral bioavailability of nepafenac is relatively low, approximately 6%, and is likely the result of first pass metabolism. However, the percent of dose reaching the systemic circulation as amfenac is higher, estimated to be in the range of 30% to 40%. The percent of a radiolabeled dose of nepafenac absorbed is substantially higher at approximately 85%.

Topical ocular administration of a ^{14}C-nepafenac ophthalmic suspension to non-pigmented New Zealand white rabbits and pigmented Dutch belted rabbits found both C_{max} levels and half-lives in corresponding tissues, such as iris-ciliary body, choroid and retina to be similar between the two rabbit strains, indicating that nepafenac and its metabolites do not bind to melanin pigmented tissues.

Multiple dosing (3 mg/kg daily oral doses for 14 days) show minimal accumulation in normal male rats. Systemic tissue distribution studies in normal male and pregnant female rats show that radioactive drug equivalents distribute widely in the body, including to the fetus.

In rats, approximately 90% of the dose is excreted within the first 24 hours following intravenous administration.

Radioactivity was found in the milk of lactating rats. However, the milk:plasma ratios were less than unity and the concentrations of radioactivity in milk and plasma declined with similar half-lives.

Nepafenac is metabolized to amfenac and to more polar metabolites involving hydroxylations of the aromatic ring and glucuronide conjugate formation. Except for nepafenac and amfenac, the circulating plasma metabolites in human and monkey are primarily in the form of glucuronide conjugates whereas those in rats are not conjugated. The most abundant plasma metabolite in all species is amfenac. In humans, amfenac represented approximately 13% of total plasma radioactivity whereas all other metabolites were <10%. Apart from amfenac, the most abundant human plasma metabolite has been identified as 5-hydroxy amfenac amide which represents about 9.5% of total radioactivity at C_{max}. This metabolite is also observed in rat and monkey plasma. In rat plasma the 5-hydroxy metabolite is not conjugated whereas in monkeys and humans it is conjugated.

In no observed adverse effect level (NOAEL) toxicokinetic studies with rats dosed orally 10 mg/kg/day for 6 months and with monkeys dosed four times a day for 3 months by the topical ocular route, maximal plasma levels of 5-hydroxy amfenac amide are estimated to be 31 ng/ml and 7.5 ng/ml, respectively. In humans dosed three times per day for 14 days by the topical ocular route with Nepafenac Ophthalmic Suspension, 0.1%, the maximal level of 5- hydroxy amfenac amide is estimated to be about 0.07 ng/ml. These estimated levels indicate safety margins in humans to be about 450-fold compared to rats and 110-fold compared to monkeys based on the NOAEL doses.

In all toxicokinetic studies, a substantial margin of safety was demonstrated by both C_{max} and AUC pharmacokinetic parameters. Safety margins based on C_{max} and AUC were 56-fold and 96-fold, respectively, for nepafenac and 63-fold and 49-fold, respectively, for amfenac in monkeys administered NOAEL doses of 10 mg/ml nepafenac suspension QID for 3 months.

MICROBIOLOGY
Not applicable.

TOXICOLOGY
Single Dose Studies
Single dose toxicity studies using the Up and Down procedure to approximate the LD_{50} were conducted in mice and rats by the oral and intraperitoneal routes (see Table 7). Rats showed greater lethality than mice and the LD_{50} in this species was similar for the PO and IP routes of administration. Systemic exposure to high dose nepafenac (greater than 50,000-fold the maximum proposed clinical dose) resulted in no evidence of toxicity.

Table 7: Single-Dose Toxicity of Nepafenac

Species	Route / Doses (mg/kg)	LD_{50} (mg/kg)	Findings
Mouse/ICR	Oral 1000 mg/kg 2000 mg/kg	> 2000	None of the animals treated orally with 2.0 g/kg of nepafenac were noted with any significant signs of toxicity during the study.
	Intraperitoneal 1000 mg/kg 2000 mg/kg	> 1000	Clinical signs included decreased activity, hunched gait, and swollen abdomen.
Rat/Sprague Dawley	Oral 100 mg/kg 500 mg/kg 1000 mg/kg	Male LD_{50} > 100 Female LD_{50} > 500	Clinical signs noted include swollen abdomens, red exudates on face, little or no stool and less active behavior.
	Intraperitoneal 100 mg/kg 250 mg/kg 500 mg/kg	Male LD_{50} > 250 mg/kg; Female LD_{50} > 100 mg/kg;	Clinical signs noted include swollen abdomens, red exudates on face, little or no stool and less active behavior.

Repeat-Dose Oral Studies: Oral repeat-dose studies conducted with nepafenac are summarized in Table 8. The daily dose levels of nepafenac evaluated in these studies are significantly higher

than the recommended daily dose of NEVANAC.

Table 8: Repeat-Dose Systemic Studies of Nepafenac

Species/No. per Group	Dose/Route[a]	Duration of Treatment	Findings
Sprague-Dawley rats/ 10 male, 10 female	0, 2.5, 7.5, 25 mg/kg/day orally by gavage.	2 weeks	Decreases in RBC, hemoglobin and hematocrit were noted in the 25 mg/kg group. There was no evidence that oral dose levels of 25 mg/kg/day of the test material resulted in histomorphological changes usually associated with NSAID's toxicity.
Sprague Dawley rats/ 10 male, 10 female	0,1 (male), 5 (female), 15 mg/kg/day orally by gavage	3 months	Renal papillary necrosis (a common finding with NSAID) was observed in 2 of 10 females receiving 15 mg/kg/day. For males, a slight decrease in the mean body weight was noted in the mid- and high-dose groups (<10%). The 5 and 1 mg/kg/day were considered to represent the NOEL in female and male Sprague Dawley rats.
Fischer F344 rats / 25 male, 25 female	Vehicle, 1, 3, and 10 mg/kg/day orally by gavage	6 months	The most common finding was alopecia of the forelimbs, discoloration around the nose, eyes, paws and mouth and inguinal area. Red blood cell parameters (red cell counts, haemoglobin and hematocrit) were slightly reduced in the high dose males after 26 weeks of treatment compared to controls, but were within the normal range. Absolute kidney and liver weights were elevated in the high dose female rats compared to vehicle controls. Thymus weights (absolute and relative) were significantly reduced in the low and mid dose females, compared to vehicle controls. No differences in male organ weights. The no observable adverse effect level for nepafenac was greater than 10 mg/kg/day.

[a] Underlined values indicate the no observed adverse effect level or the no observable effect level

Repeat-Dose Ocular Studies: Ophthalmic solutions of nepafenac were evaluated in repeat-dose topical ocular studies in rabbits (NZW/pigmented) and Cynomolgus monkeys (see Table 9).

Table 9: Results of Topical Ocular Repeat-Dose Studies of Nepafenac

Species/No. per Group	Dose/Route	Duration of Treatment	Findings
Rabbits (New Zealand white) / 4 male, 4 female	Vehicle, 0.1%, 0.3%, 1.0% or sham. Four drops unilateral per day / topical ocular.	7 days prior to corneal incision and 27 days post incision.	Low ocular irritation potential; no postoperative ocular complications, no ocular irritation or delayed wound healing.
Rabbits (New Zealand white) / 4 male, 4 female	Untreated control, vehicle, 0.1%, 0.3%, 1.0%. Four daily doses bilateral (1 drop/dose) / topical ocular.	1 month	Minimal conjunctival congestion (hyperemia) was noted in all treatment and control groups.
Rabbits (New Zealand white) / 4 male, 4 female	Untreated control, vehicle, 0.1%, 0.3%, 1.0%. Four daily doses bilateral (1 drop/dose) / topical ocular.	3 months	Minimal conjunctival congestion (hyperemia) was noted in all treatment and control groups.
Rabbits (Pigmented) / 7 male, 7 female	Untreated control, vehicle, 0.3%, 1.0% or 1.5%. Three daily doses unilateral (2 drops/dose) / topical ocular.	6 months	Low ocular irritation potential; and did not elicit any signs of ocular or systemic toxicity.
Cynomolgus monkeys / 4 male, 4 female	Vehicle, 0.1%, 0.3% or 1.0% unilateral. Four daily doses (2 drops/dose) / topical ocular.	3 months	Low ocular irritation potential; and did not elicit any signs of ocular or systemic toxicity.

[a] Underlined values indicate the no observed adverse effect level or the no observable effect level

Toxicokinetic Studies

The toxicokinetics of nepafenac and amfenac were characterized in repeat dose oral and topical ocular studies. Maximal plasma concentrations (C_{max}), areas under the concentration-time curves (AUC) and exposure margins were determined (see Table 10 and Table 11).

Table 10: Nepafenac Plasma C_{max} and AUC Values from Highest NOAEL Doses in Toxicology Studies

Species	Route, Frequency, Duration	Dose (Nepafenac)	C_{max} (ng/ml)	AUC_{0-t} (ng*h/ml) (Interval 0-t)	C_{max} Exposure Margin [a]	AUC Exposure Margin [b]
Rat	Oral, QD, 6 months	10 mg/kg/day	118 ± 32	189 ± 22 (0 – 4 hours)	381	509
Rat Segment II	Oral, QD, Gestation days 6-17	10 mg/kg/day (NOEL dose)[c] Data from Day 17	242 ± 196	207 ± 51 (0 - 6 hours)	781	558
Rabbit Segment II	Oral, QD, Gestation days 6-18,	10 mg/kg/day (NOEL dose)[c] Data from Day 18	40.2 ± 59.6	28.4 ± 40.9 (0 – 6 hours)	130	77
Rabbit	Topical Ocular, TID, 6 months	Nepafenac 1.5% Ophthalmic Suspension (3.6 mg/day)	6.01 ± 6.03	6.01 ± 5.98 (0 - 2.25 hours)	19	16
Monkey	Topical Ocular, QID, 3 months (97 days)	Nepafenac 1.0% Ophthalmic Suspension (3.2 mg/day)	17.4 ± 5.8	35.7 ± 12.7 (0 – 3 hours)	56	96

[a] C_{max} divided by clinical C_{max} of 0.310 ng/ml observed at the end of 4 days of TID dosing of Nepafenac 0.1% Ophthalmic Suspension.

[b] AUC divided by clinical AUC_{0-inf} estimated at the end of 4 days of TID dosing of Nepafenac 0.1% Ophthalmic Suspension.

[c] Retrospective TK, no toxicological evaluations were performed during this study.

Table 11: Amfenac Plasma C_{max} and AUC Values from Highest NOAEL Doses in Toxicology Studies

Species	Route, Frequency, Duration	Dose (Nepafenac)	C_{max} (ng/ml)	AUC $_{0-t}$ (ng*h/ml) (interval 0-t)	C_{max} Exposure Margin [a]	AUC Exposure Margin [b]
Rat	Oral, QD, 6 months	10 mg/kg/day	670 ± 137	1550 ± 106 (0 – 4 hours)	1,588	1,505
Rat Segment II	Oral, QD, Gestation Days 6-17	10 mg/kg/day (NOEL dose) [c] Data from Day 17	1710 ± 1620	4190 ± 620 (0 – 6 hours)	4,052	4,068
Rabbit Segment II	Oral, QD, Gestation Days 6-18	10 mg/kg/day (NOEL dose) [c] Data from Day 18	666 ± 608	663 ± 453 (0 – 6 hours)	1,578	644
Rabbit	Topical Ocular, TID, 6 months	Nepafenac 1.5% Ophthalmic Suspension (3.6 mg/day)	45.4 ± 18.0	50.6 ± 21.2 (0 - 2.25hours)	146	49
Monkey	Topical Ocular QID, 3 months (97 days)	Nepafenac 1.0% Ophthalmic Suspension (3.2 mg/day)	26.4 ± 14.5	45.5 ± 16.1 (0 – 3 hours)	63	44

[a] C_{max} divided by clinical C_{max} of 0.422 ng/ml observed at the end of 4 days of TID dosing of Nepafenac 0.1% Ophthalmic Suspension (C-04-08).
[b] AUC divided by clinical AUC_{0-inf} of 1.03 ng*h/ml estimated at the end of 4 days of TID dosing of Nepafenac 0.1% Ophthalmic Suspension (C-04-08).
[c] Retrospective TK, no toxicological evaluations were performed during this study.

Mutagenicity: Increased chromosomal aberrations were observed in Chinese hamster ovary cells exposed *in vitro* to nepafenac suspension. However, nepafenac was not mutagenic *in vitro* in the Ames assay or in a forward mutation assay. Additionally, 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.

Carcinogenicity: Nepafenac has not been evaluated in long-term carcinogenicity studies.

Reproduction and Teratology: 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 ≥ 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.

PART III: CONSUMER INFORMATION

Pr NEVANAC®
Nepafenac Ophthalmic Suspension, 0.1% w/v

This leaflet is part III of a three-part "Product Monograph" published when NEVANAC® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NEVANAC. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
NEVANAC is used to manage eye pain and inflammation following cataract surgery on the eye.

What it does:
NEVANAC, as a nonsteroidal anti-inflammatory drug (NSAID), can reduce the substances produced by your body, such as prostaglandins, which cause pain and swelling in your eye.

When it should not be used:
NEVANAC should not be used if you are:

- allergic (*hypersensitive*) to nepafenac or any of the other ingredients in NEVANAC (see What the important nonmedicinal ingredients are).
- Allergic to other NSAIDs.

Tell your doctor if you have allergies.

What the medicinal ingredient is:
Nepafenac

What the important nonmedicinal ingredients are:
Preservative: benzalkonium chloride.
Other ingredients: carbomer 974P, edetate disodium, mannitol, purified water, sodium chloride and tyloxapol. Tiny amounts of hydrochloric acid or sodium hydroxide are sometimes added during the manufacture of the product to adjust to the proper pH.

What dosage forms it comes in:
NEVANAC contains tiny yellow particles suspended in a clear liquid. It is supplied as 5 mL of suspension in an 8 mL plastic bottle with a screw cap.

WARNINGS AND PRECAUTIONS

BEFORE you use NEVANAC, talk to your doctor or pharmacist if you:

- have any allergies to NEVANAC or any of its ingredients (see What the important nonmedicinal ingredients are).
- bruise easily or have bleeding problems.
- take any medicines that may make you bleed more like acetylsalicylic acid or warfarin.
- have an eye disorder called dry eye syndrome, a corneal ulcer, a corneal denervation or a corneal epithelial defect.
- have diabetes.
- have rheumatoid arthritis.
- have had many eye surgeries within a short period of time.
- have had complicated eye surgeries.
- wear contact lenses.
- apply other NSAID or steroid medications to your eye since these may slow the healing of your eye.
- are using any other medications in the eye.
- have ever had an allergic reaction to nonsteroidal anti-inflammatory drugs including acetylsalicylic acid, as you may be allergic to NEVANAC.

Pregnancy or breast-feeding
If you are pregnant, or might get pregnant, talk to your doctor before you use NEVANAC. You should not use NEVANAC if you are pregnant. If you are breast-feeding, do not use NEVANAC since it may get into your milk.

Other Medications
Please tell your doctor or pharmacist if you are taking (or recently took) any other medicines. Remember to mention also medicines that you bought without prescription, over the counter.

While taking NEVANAC
Tell your doctor if you are not getting any relief or if problems develop.

If you wear contact lenses
There is a preservative in NEVANAC (benzalkonium chloride) that can discolour soft lenses and may cause eye irritation. Wearing contact lenses is not recommended after cataract surgery. Do not wear contact lenses while using NEVANAC.

Driving and using machines
You may find that your vision is blurred for a time just after you use NEVANAC. Do not drive or use machines until your vision is clear.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmactist about all the medications you are taking, recently took or planning to use, including those without a prescription.

Do not use acetylsalicylic acid, phenylacetic acid or other nonsteroidal anti-inflammatories with NEVANAC if you have previously developed reactions to the use of these products (see When it should not be used).

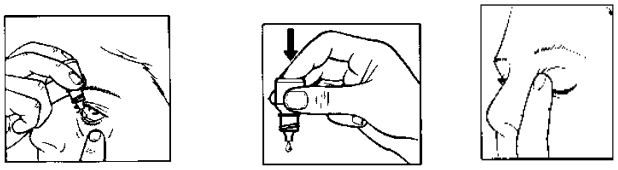
Taking a topical NSAID, like NEVANAC, at the same time with a topical steroid may delay healing. Taking NEVANAC at the same time as other drugs that prolong bleeding time may also increase the risk of bleeding problems.

PROPER USE OF THIS MEDICATION

Always use NEVANAC exactly as your doctor has told you.

Usual adult dose:
One drop of NEVANAC should be applied to the affected eye(s) three times a day – morning, mid-afternoon, and prior to bed. Use at the same time each day. Begin 1 day before cataract surgery. Continue on the day of surgery. Then use it for as long as your doctor told you to. This may be up to 2 weeks after your operation.

How to Use:



1 2 3

- Get the NEVANAC bottle and a mirror.
- Wash your hands.
- Shake well before use.
- Twist off the bottle cap.
- After cap is removed: if security snap collar is loose, remove before using product.
- Hold the bottle, pointing down, between your thumb and fingers.
- Tilt your head back.
- Pull down your lower eyelid with a clean finger until there is a 'pocket' between the eyelid and your eye. The drop will go in here (picture 1).
- Bring the bottle tip close to the eye. Do this in front of a mirror if it helps.
- Do not touch your eye or eyelid, surrounding areas or other surfaces with the dropper. It could infect the drops.
- Gently press on the base of the bottle to release one drop of NEVANAC at a time.
- Do not squeeze the bottle: it is designed so that a gentle press on the bottom is all that it needs (picture 2).
- After using NEVANAC, press a finger into the corner of your eye, by the nose (picture 3). This helps to stop NEVANAC getting into the rest of the body.
- If you use drops in both eyes, repeat the steps for your other eye.
- Close the bottle cap firmly immediately after use.
- Use up one bottle before opening the next bottle
  If a drop misses your eye, try again.

If you use drops in both eyes, repeat the steps for your other eye. Close the bottle cap firmly immediately after use.

If you are using other eye drops wait at least 5 minutes between putting in NEVANAC and the other drops.

Overdose:

If you use more NEVANAC than you should, rinse it all out with warm water. Don't put in any more drops until it's time for your next regular dose. If accidentally ingested, contact your local poison control centre or doctor.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to use NEVANAC, use a single dose as soon as you remember. If it is almost time for the next dose, leave out the missed dose and continue with the next dose of your regular routine. Do not use a double dose to make up for a missed dose. Do not use more than one drop in the affected eye(s) 3 times daily.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

A small number of people who use NEVANAC may get side effects. They can be unpleasant, but most of them disappear rapidly.

Do not stop taking NEVANAC without speaking to your doctor. You can usually continue using the drops, unless the effects are serious. If you're worried, talk to a doctor or pharmacist.

The most common side effects include eye pain, blurred vision, eye itching, dry eye, increased tear production, abnormal sensation in the eye, crusty eyelids, inflammation inside the eye, and headache.

Less common side effects include deposits on the eye surface, fluid in the back of the eye, eye discharge, sensitivity to light, eye irritation, eye allergy, eyelid swelling or drooping, eye redness, increased skin allergy, nausea, dry mouth and allergy.

Additional side effects may also affect people using NEVANAC including inflammation (pain, redness, swelling) of the eye or eyelid, reduced vision, dizziness, vomiting and increased blood pressure.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
	Only if severe	**In all cases**	
Eyes get redder or more painful		✓	
Cornea (protective outer layer of the eye) disorders including ulcers, surface changes, injury and damage including thinning or perforation and impaired healing, scarring, clouding: blurred vision, eye pain and redness.		✓	

This is not a complete list of side effects. For any unexpected effects while taking NEVANAC, contact your doctor or pharmacist.

HOW TO STORE IT

Store at 2ºC - 30°C. Keep out of reach and sight of children. Discard 28 days after opening.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:
www.novartis.ca or by contacting the sponsor, Novartis Pharmaceuticals Canada Inc., at: 1-800-363-8883.

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