Nepafenac

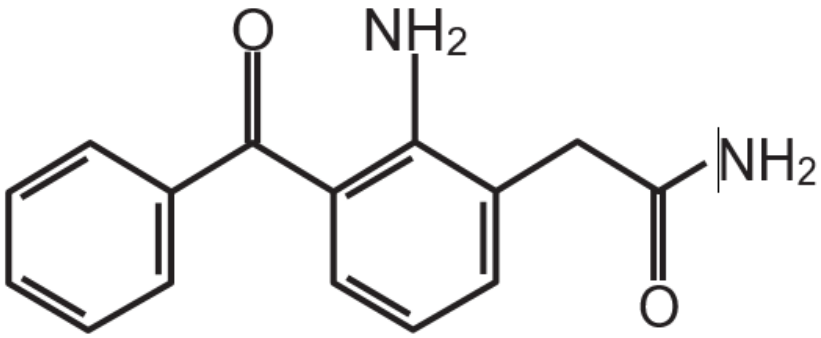
Nevanac®

1 mg/mL (0.1% w/v)

Sterile Ophthalmic Suspension

Non-Steroidal Anti-Inflammatory Drug

DESCRIPTION:
Nepafenac (Nevanac®) Sterile Ophthalmic Suspension 0.1% is a sterile, topical, non-steroidal anti-inflammatory (NSAID) prodrug for ophthalmic use. Each mL of nepafenac (Nevanac®) *Sterile Ophthalmic Suspension* contains 1 mg of nepafenac. Nepafenac is designated chemically as 2-amino-3-benzoylbenezenacetamide 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. *Nepafenac (Nevanac®) Sterile Ophthalmic Suspension* is supplied as a sterile, aqueous 0.1% suspension with a pH approximately of 7.4. The osmolality of *nepafenac (Nevanac®) Sterile Ophthalmic Suspension* is approximately 305 mOsmol/kg.

FORMULATION:
Active: 1 mL of suspension contains 1 mg nepafenac.
Preservative: Benzalkonium chloride 0.005%
Excipients: Mannitol, carbomer 974P, sodium chloride, tyloxapol, edetate disodium, sodium hydroxide and/or hydrochloric acid (for pH adjustment), purified water.

CLINICAL PHARMACOLOGY:
Pharmacodynamics:
Mechanism of action: *Nepafenac (Nevanac®) Sterile Ophthalmic Suspension* contains nepafenac (0.1%), a non-steroidal anti-inflammatory and analgesic prodrug. After topical ocular dosing, nepafenac penetrates the cornea and is converted by ocular tissue hydrolases to amfenac, a non-steroidal anti-inflammatory drug.

Amfenac is thought to inhibit action of prostaglandin H synthase (cyclooxygenase), an enzyme required for prostaglandin production.

Pharmacokinetics:

Absorption

Following 3-time daily dosing of nepafenac 0.1% Eye Drops in both eyes for four days, maximal steady-state plasma concentrations (Cmax) of nepafenac (0.310 + 0.104 ng/mL) and amfenac (0.422 + 0.121 ng/mL) were attained within 0.5 hours. Steady-state plasma levels were achieved by day 2. Based on the steady-state/single dose ration of individual Cmax values, the mean accumulation index was 1.34 + 0.58 for nepafenac and 1.61 + 0.66 for amfenac.

Distribution

Nepafenac and amfenac distributed to ocular tissues in rabbits after single topical dose with either 0.1% or 0.3% suspension. Higher concentrations were observed as site of dosing, cornea and conjunctiva and lower concentrations in posterior tissues, retina and choroid. Concentrations in ocular tissues increased with increased dose. When anterior ocular tissues concentrations were compared from a single dose of 0.3% nepafenac to that after three doses of 0.1% nepafenac in a single day, only the lens did not have higher concentrations after the 0.3% nepafenac once a day dosing.

In cataract surgical patients, maximal aqueous humor concentrations were observed 1 hour following single dose of 0.1% nepafenac with a concentration 177 ng/mL and 44.8 ng/mL for nepafenac and amfenac, respectively.

Plasma protein binding of nepafenac is moderate, ranging from 72.8% in rat plasma to 83.5% in human plasma. Protein binding was found to be concentration independent in rat, monkey, and human plasma over a wide concentration range (10 to 1000 ng/mL). Amfenac is more highly bound at approximately 99%.

Biotransformation

Nepafenac undergoes relatively rapid in vivo hydrolysis to amfenac. After oral administration, unconjugated amfenac and nepafenac, and eight other metabolites were detected in plasma with amfenac, a pharmacological active metabolite having the highest concentration. Several of the metabolites were glucuronide conjugates based chromatographic shift after β-glucuronidase treatment. Nepafenac was detected in plasma but at relatively low levels (3.2% of total radioactivity). Amfenac was the major metabolite in plasma, representing approximately 13% of total plasma radioactivity. The second most abundant plasma metabolite was 5-hydroxy nepafenac in the form of a glucuronide, representing approximately 9.5% of total radioactivity at Cmax.

Neither nepafenac nor amfenac inhibit any of the major human cytochrome P-450 isozymes (CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4) in vitro at concentrations up to 3000 and 1000 ng/mL, respectively.

After 14 days of oral administration, nepafenac does not increase CYP1A, CYP2B, CYP3A activities or total P450 content in rats, therefore, no potential induction was observed for rats.

Elimination

After oral administration of ^{14}C-nepafenac to healthy human volunteers, urinary excretion was found to be the major route of excreted radioactivity, accounting for approximately 85%, while fecal represented approximately 6% of the dose out to 7 days.

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 *nepafenac (Nevanac®) Sterile Ophthalmic Suspension.*

Low but quantifiable plasma concentrations of nepafenac and amfenac were observed in the majority of subjects 2 and 3 hours post-dose, respectively, following bilateral topical ocular TID dosing of nepafenac ophthalmic suspension, 0.1%.

The mean steady-state Cmax for nepafenac and amfenac were 0.310 ± 0.104 ng/mL and 0.422 ± 0.121 ng/mL, respectively, following ocular administration.

Clinical Studies: In two double-masked, randomized clinical trials in which patients were dose three times daily beginning one day prior to cataract surgery, continued on the day of the surgery and for the first two weeks of the postoperative period, *nepafenac (Nevanac®) Sterile Ophthalmic Suspension* demonstrated clinical efficacy, compared to its vehicle in treating postoperative inflammation.

Patients treated with *nepafenac (Nevanac®) Sterile 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 *nepafenac (Nevanac®) Sterile Ophthalmic Suspension* has no significant effect upon intraocular pressure; however, changes in intraocular pressure may occur following cataract surgery.

INDICATIONS AND USAGE:
Nepafenac (Nevanac®) Sterile Ophthalmic Suspension is indicated for the treatment of pain and inflammation associated with cataract surgery.

CONTRAINDICATIONS:
Nepafenac (Nevanac®) Sterile Ophthalmic Suspension is contraindicated in patients with previously demonstrated hypersensitivity to the active substance, or to any of the excipients, or to other non-steroidal anti-inflammatory drugs (NSAIDs).

WARNINGS:
There is a potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other non-steroidal anti-inflammatory agents.

Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs. With some non-steroidal anti-inflammatory drugs including *Nepafenac (Nevanac®) Sterile Ophthalmic Suspension,* there exists the potential 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. *Nepafenac (Nevanac®) Sterile Ophthalmic Suspension* should be used with caution in patients with known bleeding tendencies or who are receiving other medicinal products which may prolong bleeding time.
Nepafenac (Nevanac®) Sterile Ophthalmic Suspension contains benzalkonium chloride which may cause eye irritation and is known to discolor soft contact lenses. Patients should be advised not to wear contact lenses during treatment with *nepafenac (Nevanac®) Sterile Ophthalmic Suspension.* Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Close monitoring is required with frequent and/or prolonged use.

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

PRECAUTIONS:
General: Topical non-steroidal anti-inflammatory drugs (NSAIDs), including *nepafenac (Nevanac®) Sterile Ophthalmic Suspension*, 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 *nepafenac (Nevanac®) Sterile Ophthalmic Suspension* and should be closely monitored for corneal health.

Post-marketing 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 with topical NSAIDs also suggests that patients with repeat and/or complex ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases, dry eye or rheumatoid arthritis may be at increased risk for corneal adverse reactions which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Prolonged use of topical NSAIDs may increase patient risk for occurrence and severity of corneal adverse reactions.

Information for Patients: *Nepafenac (Nevanac®) Sterile Ophthalmic Suspension* should not be administered while wearing contact lenses.

Interaction with other medicinal products and other forms of interaction: Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
Concomitant use of *nepafenac (Nevanac®) Sterile Ophthalmic Suspension* with medications that prolong bleeding time may increase the risk of hemorrhage.

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).

There are no adequate data regarding the use of *nepafenac (Nevanac®) Sterile Ophthalmic Suspension* on human fertility. No significant fertility effects were seen in studies in rats at doses up to 2500 times greater than the maximum recommended human ocular dose.

Pregnancy: Teratogenic Effects.
Pregnancy Category C: There are no adequate data regarding the use of *nepafenac (Nevanac®)* on human pregnancy. No significant teratogenic effects were observed in rats and rabbits orally administered with doses of nepafenac up to 2500 times greater than the maximum recommended human ocular dose. Since human systemic exposure is negligible (< 1 ng/mL) after treatment with *nepafenac (Nevanac®)*, the

risk during pregnancy could be considered low. Nevertheless, inhibition of prostaglandin synthesis may negatively affect pregnancy and/or embryonal/fetal development and/or parturition and/or postnatal development.

Nepafenac (Nevanac®) is not recommended during pregnancy unless the benefit outweighs the potential risk.

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 *nepafenac (Nevanac®) Sterile Ophthalmic Suspension* during late pregnancy should be avoided.

Nursing Mothers: *Nepafenac (Nevanac®) Sterile Ophthalmic Suspension* is excreted in the milk of pregnant rats. It is unknown whether nepafenac is excreted in human milk after topical administration. Because many drugs excreted in human milk, caution should be exercised when *nepafenac (Nevanac®) Sterile Ophthalmic Suspension* is administered to a nursing woman. Animal studies have shown excretion of nepafenac in the milk of rats after oral administration. While no effects on the suckling child are anticipated since the systemic exposure of the breastfeeding woman to nepafenac is negligible (<1 ng/mL), caution should be exercised when *nepafenac (Nevanac®)* is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of *nepafenac (Nevanac®) Sterile Ophthalmic Suspension* in pediatric patients below the age of 10 years have not been established. Its use is not recommended in these patients until further data become available.

Use in hepatic and renal impairment: Nepafenac has not been studied in patients with hepatic disease or renal impairment. No dose adjustment is warranted in these patients, as the systemic exposure is very low following topical ocular administration.

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

Effects on ability to drive and use machines: 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.

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

The following adverse reactions have been reported during clinical trials with *nepafenac (Nevanac®) Sterile Ophthalmic Suspension* and are classified according to the subsequent convention: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Classification	MedDRA Preferred Term (v.18.0)
Nervous system disorders	Rare: dizziness, headache
Eye disorders	Uncommon: Keratitis, punctate keratitis, corneal epithelium defect, conjunctivitis allergic, eye pain, foreign body sensation in the eye,

	eyelid margin crusting Rare: Blurred vision, photophobia, dry eye, blepharitis, eye irritation, eye pruritus, eye discharge, lacrimation increased
Immune system disorders	Rare: Hypersensitivity
Gastrointestinal disorders	Rare: Nausea
Skin and subcutaneous tissue disorders	Rare: Dermatitis allergic

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data. Within each System Organ Class, adverse reactions are presented in order of decreasing seriousness.

System Organ Classification	**MedDRA Preferred Term (v.18.0)**
Eye disorders	Corneal perforation, ulcerative keratitis, corneal thinning, corneal opacity, corneal scar, impaired healing (cornea), visual acuity reduced, eye swelling, eye irritation, ocular hyperaemia
Gastrointestinal disorders	Vomiting
Investigations	Blood pressure increased

DOSAGE AND ADMINISTRATION:
Shake well before use. One drop of *nepafenac (Nevanac®) Sterile 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 the surgery and through the first 2 weeks of postoperative period. An additional drop should be administered 30-120 minutes prior to surgery. Treatment can be extended to the first 3 weeks (21 days) of the postoperative period, as directed by the clinician.

Nepafenac (Nevanac®) Sterile Ophthalmic Suspension may be administered in conjunction with other topical ophthalmic medications such as beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics.

FOR OCULAR USE ONLY. After cap is removed, if tamper evident snap collar is loose, remove before using the product. If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 5 minutes apart. Eye ointments should be administered last.

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.

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

OVERDOSE:
No toxic effects are likely to occur in case of overdose with ocular use, nor in the event of accidental oral ingestion.

AVAILABILITY:
Nepafenac (Nevanac®) Sterile Ophthalmic Suspension is supplied in a natural, round, low-density polyethylene DROPTAINER 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. 5 mL in an 8 mL bottle.

STORAGE: Store at a temperature not exceeding 30°C.

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: **www.fda.gov.ph**
The patient is advised to seek IMMEDIATE medical attention at the first sign of adverse drug reaction.

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Rx Only.

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