

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NEVANAC[®] safely and effectively. See full prescribing information for NEVANAC[®].

NEVANAC[®] (nepafenac ophthalmic suspension) 0.1%, topical ophthalmic

Initial U.S. Approval: 2005

INDICATIONS AND USAGE

NEVANAC ophthalmic suspension is a nonsteroidal, anti-inflammatory prodrug indicated for the treatment of pain and inflammation associated with cataract surgery (1).

DOSAGE AND ADMINISTRATION

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. (2)

DOSAGE FORMS AND STRENGTHS

Sterile ophthalmic suspension: 0.1% (3)
3 mL in a 4 mL bottle

CONTRAINDICATIONS

Hypersensitivity to any of the ingredients in the formula or to other NSAIDs. (4)

WARNINGS AND PRECAUTIONS

Increased bleeding time due to increased thrombocyte aggregation (5.1)

Delayed healing (5.2)

Corneal effects including keratitis (5.3)

ADVERSE REACTIONS

Most common adverse reactions (5 to 10%) are capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Alcon Laboratories, Inc. at 1-800-757-9195 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 9/2007

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NEVANAC[®] ophthalmic suspension is indicated for the treatment of pain and inflammation associated with cataract surgery.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

One drop of NEVANAC[®] 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.

2.2 Use with Other Topical Ophthalmic Medications

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

3 DOSAGE FORMS AND STRENGTHS

Sterile ophthalmic suspension: 0.1%

3 mL in a 4 mL bottle

4 CONTRAINDICATIONS

NEVANAC[®] is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in

the formula or to other NSAID.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Bleeding Time

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.

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.

5.2 Delayed Healing

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.

5.3 Corneal Effects

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 and severity of corneal adverse events.

5.4 Contact Lens Wear

NEVANAC[®] should not be administered while using contact lenses.

6 ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to the rates in the clinical studies of another drug and may not reflect the rates observed in practice.

6.1 Ocular Adverse Reactions

The most frequently reported ocular adverse reactions 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 reactions 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.

6.2 Non-Ocular Adverse Reactions

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

8 USE IN SPECIFIC POPULATIONS

8.1 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 ≥ 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[®] during late pregnancy should be avoided.

8.3 Nursing Mothers

NEVANAC[®] is excreted in the milk of lactating 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.

8.4 Pediatric Use

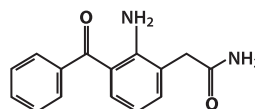
The safety and effectiveness of NEVANAC[®] in pediatric patients below the age of 10 years have not been established.

8.5 Geriatric Use

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

11 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, edetate disodium, benzalkonium chloride 0.005% (preservative), sodium hydroxide and/or hydrochloric acid to adjust pH and purified water, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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.

12.3 Pharmacokinetics

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 three-times-daily 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.

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.

13 NONCLINICAL TOXICOLOGY

13.1 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).

14 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

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).

17 PATIENT COUNSELING INFORMATION

17.1 Slow or Delayed Healing

Patients should be informed of the possibility that slow or delayed healing may occur while using nonsteroidal anti-inflammatory drugs (NSAIDs).

17.2 Avoiding Contamination of the Product

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

17.3 Contact Lens Wear

NEVANAC[®] should not be administered while wearing contact lens.

17.4 Intercurrent Ocular Conditions

Patients should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multi-dose container.

17.5 Concomitant Topical Ocular Therapy

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

17.6 Shake Well Before Use

Patients should be advised to shake the bottle well.

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Alcon[®]

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