

NEVANAC[®]

Nepafenac 0.1% Eye Drops

Presentation

NEVANAC[®] (nepafenac) 0.1% Eye Drops is a sterile, topical, nonsteroidal anti-inflammatory (NSAID) prodrug for ophthalmic use.

NEVANAC[®] is an isotonic suspension with an osmolality of approximately 305 mOsmol/kg. NEVANAC[®] has a physiologic pH of approximately 7.4.

Uses

Actions

NEVANAC[®] Eye Drops contains nepafenac (0.1%), a nonsteroidal anti-inflammatory and analgesic prodrug. After topical ocular dosing, nepafenac penetrates the cornea and is converted by ocular tissue hydrolases to amfenac, a potent nonsteroidal anti-inflammatory drug. Amfenac is thought to inhibit the action of prostaglandin H synthase (cyclooxygenase), an enzyme required for prostaglandin production. In rabbits, a single topical ocular dose of nepafenac (0.1%) leads to a uniform inhibition (80% to 100%) of prostaglandin formation by the iris/ciliary body. Suppression of prostaglandin E₂ synthesis is maintained for a period of greater than 6 hours and is accompanied by a nearly 8 hour suppression of trauma-induced vascular leakage of the blood aqueous barrier.

Pharmacokinetics

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

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

Low but quantifiable plasma concentrations of nepafenac and amfenac were observed in the majority of subjects 2 and 3 hours postdose, respectively, following bilateral topical ocular TID dosing of nepafenac 0.1% Eye Drops. 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.

Indications

NEVANAC[®] 0.1% Eye Drops is indicated for the inhibition and treatment of pain and inflammation associated with cataract surgery.

Dosage and administration

Shake well before use. One drop of NEVANAC[®] 0.1% Eye Drops 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.

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.

Contraindications

NEVANAC[®] 0.1% Eye Drops is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation or to other NSAIDs.

Warnings and precautions

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

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

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

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

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

Postmarketing experience with topical NSAIDs also suggests that use more than 1 day prior to surgery or use beyond 14 days post surgery may increase patient risk for

occurrence and severity of corneal adverse events.

It is recommended that NEVANAC[®] 0.1% Eye Drops be used with caution in patients with known bleeding tendencies or who are receiving medications which may prolong bleeding time.

Actions the health care professional should take

Systemic absorption can be minimised if patients are instructed to gently occlude the nasolacrimal ducts for two minutes immediately after instillation of the eye drop.

Use in 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[®] Eye Drops should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.

Use in Lactation

NEVANAC[®] Eye Drops is excreted in the milk of pregnant rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NEVANAC[®] 0.1% Eye Drops is administered to a nursing woman.

Paediatric use

The safety and effectiveness of NEVANAC[®] 0.1% Eye Drops in pediatric patients below the age of 10 years have not been established.

Use in the Elderly

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

Hepatic/Renal Impairment

No dosage alteration of NEVANAC[®] 0.1% Eye Drops is necessary in these patients.

Carcinogenicity

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

Genotoxicity

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 a 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.

Effects on fertility

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).

Adverse effects

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 1 to 5% included conjunctival oedema, corneal oedema, dry eye, lid margin crusting, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, photophobia, tearing and vitreous detachment.

Some of these events were the consequence of the cataract surgical procedure.

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

Interactions

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

Effects on ability to drive and use machines

As with other ophthalmic medications, patients should be advised to exercise caution if they experience transient blurred vision following instillation of eye drops. Patients should wait until their vision clears before driving or using machinery.

Overdosage

No data are available in humans regarding overdosage by accidental or deliberate ingestion. The risk of overdosage by ingestion of the suspension is minimal.

Pharmaceutical precautions

Store below 30 °C. Do not freeze.

Discard four weeks after opening.

Medicine classification

Prescription Medicine.

Package quantities

NEVANAC[®] (nepafenac) 0.1% Eye Drops 1.5 mL (sample) and 3 mL are 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.

Consumer Medicine Information is supplied with this product.

Further information**Clinical Studies**

In two double-masked, randomized clinical trials in which patients were dosed three-times-daily beginning one day prior to cataract surgery, and continued on the day of surgery and for the first two weeks of the postoperative period, NEVANAC[®] 0.1% Eye Drops demonstrated clinical efficacy, compared to its vehicle in treating postoperative inflammation.

Patients treated with NEVANAC[®] 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.

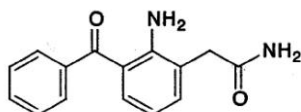
Contact lenses

NEVANAC[®] 0.1% Eye Drops should not be administered while wearing contact lenses. *If patients continue to wear soft (hydrophilic) contact lenses while under treatment with NEVANAC[®] they should remove their lens(es) prior to instilling NEVANAC[®] in the affected eye(s) and should not insert their lens(es) until 15 minutes after instillation of the eye drops.*

List of excipients

Active: Nepafenac (1 mg/mL) 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.

Nepafenac is a yellow crystalline or powder substance. Each mL of NEVANAC[®] Eye Drops contains 1 mg of nepafenac. The chemical structure is:



Molecular weight: 254.28

Empirical formula: C₁₅H₁₄N₂O₂

Chemical name: 2-amino-3-benzoylbenzeneacetamide

CAS Number: 78281-72-8

Name and address

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Date of preparation

April 2009

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