NEPACENT® Eye Drops

Composition:

Each ml of drop contains:

Nepafenac… 0.1%

SOC (Sodium Oxychloro Complex)… 0.01%

(as Preservative)

PHARMACEUTICAL INFORMATION –

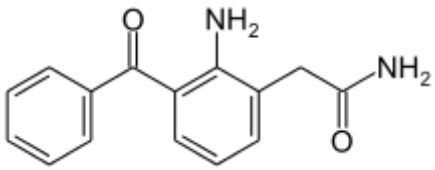
NEPAFENAC

Generic name: Nepafenac

Chemical name: 2-amino-3-benzoylbenzeneacetamide

Molecular mass: 254.28 g/mol

Structural formula:



Empirical formula – $C_{15}H_{14}N_2O_2$

Storage and Stability:

Mechanism of Action

NEPAFENAC

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.

SODIUM OXYCHLORO COMPLEX

It is mild, non-sensitizing preservative that when used, ultimately changes into components of natural tears (sodium chloride and water). The viscolizing properties of carboxymethylcellulose combined with sodium chloride have been shown to increase the tear film break-up time in animal models, whilst also acting as a lubricating agent for dry eyes.

Pharmacokinetics

Absorption: Following bilateral topical ocular three-times-daily dosing of NEPAFENAC* , 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 Cmax 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 14C-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. Radio chromatographic 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 Cmax.

Excretion: After oral administration of 14C-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.

Pharmacodynamics

In rabbits, Nepafenac has been shown to inhibit blood-retinal-barrier breakdown, concomitant with suppression of PGE2 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 neovascularization and ischemia induced retinal neovascularization. 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 vascularized 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 Nepafenac has no significant effect on intraocular pressure.

Indications

Treatment of pain and inflammation associated with cataract surgery.

Dosage and Administration

1-2 drops on each eye, thrice daily.

Contraindications

- Hypersensitivity to any active ingredient or to any of the ingredients in the formula or to other NSAID.

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 Nepafenac, 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 hyphaemas) in conjunction with ocular surgery. Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including Nepafenac, 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 Nepafenac 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. Prolonged use of topical NSAIDS may increase patient risk for occurrence and severity of corneal adverse reactions. Post-marketing 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 Nepafenac 0.1% Eye

Drops be used with caution in patients with known bleeding tendencies or who are receiving medications which may prolong bleeding time.

Adverse Effects

- Vision problems
- Crusting or drainage of your eyes
- Swollen eyelids
- Severe eye pain

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

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

SHELF-LIFE -

PACKAGING INFORMATION -