Nepacent™

1. Composition

Each ml of Nepacent eye drops contains:

Nepafenac	0.1% w/v
Stabilized oxychloro complex	0.01% w/v

2. Dosage form and strength

Nepacent is available in 5ml in plastic bottle.

3. Clinical particulars

3.1 Therapeutic indication

- In pain and inflammation
- Post cataract surgery
- Cystoid macular edema (CME)
- Retinal inflammation control

3.2 Posology and method of administration

As directed by physician.

3.3 Contraindication

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

3.4 Special warnings and precautions for use

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.

3.5 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.

3.6 Use in special population

- Paediatric: The safety and effectiveness of Nepacent (Nepafenac ophthalmic suspension), 0.1% in paediatric patients below the age of 10 years have not been established.
- Geriatric: No overall differences in safety and effectiveness have been observed between elderly and younger patients
- Liver impairment: No data found.
- Renal failure: No data found.
- Pregnancy and lactation: 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 70 and 630 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 20 and 180 times human plasma exposure for

rabbits, respectively. In rats, maternally toxic doses ≥ 10 mg/kg were associated with dystocia, increased post implantation 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, Nepacent (Nepafenac ophthalmic suspension), 0.1% should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

3.7 Effects on ability to drive and use machine

Patients should be cautioned against engaging in activities requiring complete mental alertness, and motor coordination such as operating machinery until their response to Nepacent is known.

3.8 Undesirable effects

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

3.9 Overdose

There is limited experience of overdose with Nepacent. Initiate general symptomatic and supportive measures in all cases of overdosages where necessary.

4. Pharmacological properties

4.1 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. As prostaglandins sensitize pain receptors, inhibition of their synthesis is responsible for the analgesic effects of nepafenac.

- Stabilized oxychloro complex

It is mild, non-sensitizing preservative that when used, ultimately changes into components of natural tears (sodium chloride and water).

4.2 Pharmacodynamic properties

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 for amfenac were 0.310 ± 0.104 ng/ml and 0.422 ± 0.121 ng/ml, respectively, following ocular administration.

4.3 Pharmacokinetic properties

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.

5. Nonclinical properties

5.1 Animal Toxicology or Pharmacology

Not required.

6. Description

Already mentioned and covered in the above points.

7. Pharmaceutical particulars

7.1 Incompatibilities

There are no known incompatibilities.

7.2 Shelf-life

18 months.

7.3 Storage and handling instructions

Store in cool and dry place.