140.00 mm

260.00 mm

Nepafenac

Optanep

3 mg/mL (0.3% w/v) Sterile Ophthalmic Suspension
Non-Steroidal Anti-Inflammatory Drug

℞

FORMULATION:
Each ml contains:
Nepafenac ..... 3 mg
Benzalkonium chloride ..... 0.05 mg
Propylene glycol ..... 8.00 mg

PRODUCT DESCRIPTION:
Yellow coloured suspension (Eye drops)

PHARMACODYNAMIC PROPERTIES:
Pharmacotherapeutic group: Non-steroidal Anti-inflammatory agents.

Mechanism of action
Nepafenac is 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 nonsteroidal anti-inflammatory drug. Amfenac inhibits the action of prostaglandin H synthase (cyclooxygenase), an enzyme required for prostaglandin production.

Secondary pharmacology
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.

Pharmacodynamic effects
The majority of hydrolytic conversion is in the retina/choroid followed by the iris/ciliary body and cornea, consistent with the degree of vascularised tissue.

Results from clinical studies indicate that nepafenac eye drops have no significant effect on intraocular pressure.

Clinical efficacy and safety
Prevention and treatment of postoperative pain and inflammation associated with cataract surgery:

The efficacy and safety of nepafenac in the prevention and treatment of postoperative pain and inflammation associated with cataract surgery has been demonstrated in two masked, double blind, placebo-controlled clinical trials in a total of 1351 patients. In this study in which patients were dosed daily beginning one day prior to cataract surgery, continued on the day of surgery and for the first 14 days of the postoperative period. Nepafenac 3 mg/ml eye drops, suspension demonstrated superior clinical efficacy compared to its vehicle in treating postoperative pain and inflammation.

Patients treated with Nepafenac were less likely to have ocular pain and measurable signs of inflammation in the early postoperative period through to the end of treatment than those treated with its vehicle. In the two studies, Nepafenac cleared inflammation at day 14 post operation in 65% and 68% of patients compared to 25% and 35% of patients on vehicle. Pain free rates in the Nepafenac group were 89% and 91% compared to 40% and 50% of patients on vehicle. Some patients received nepafenac 3 mg/ml eye drops, suspension for up to 21 days post operation. However, efficacy beyond day 14 post operation was not measured.

In addition, in one of the two clinical trials, nepafenac 3 mg/ml eye drops, suspension dosed once a day showed similar effect with nepafenac 1 mg/ml eye drops, suspension dosed three times a day for the prevention and treatment of postoperative pain and inflammation following cataract surgery. Inflammation clearing and pain free rates were similar for both products at all postoperative evaluations.

PHARMACOKINETIC PROPERTIES:
General Properties
Absorption
Following one drop of nepafenac 3 mg/ml eye drops, in both eyes once daily for four days, low but quantifiable plasma concentrations of nepafenac and amfenac were observed in the majority of subjects 2 and 3 hours post-dose, respectively. The mean steady-state plasma Cmax for nepafenac and for amfenac were 0.847 ± 0.269 ng/ml and 1.13 ± 0.491 ng/ml, respectively, following ocular administration.

Distribution
Amfenac has a high affinity toward serum albumin proteins. In vitro, the percent bound to rat albumin, human albumin and human serum was 98.4%, 95.4% and 99.1%, respectively.

Studies in rats have shown that radioactive labelled active substance-related materials distribute widely in the body following single and multiple oral doses of 14C-nepafenac.

Biotransformation
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.

Radiochromatographic analyses before and after -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.

Interactions with other medicinal products: Neither nepafenac nor amfenac inhibit any of the major human cytochrome P450 (CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4) metabolic activities *in vitro* at concentrations up to 3000 ng/ml. Therefore, interactions involving CYP-mediated metabolism of concomitantly administered medicinal products are unlikely. Interactions mediated by protein binding are also unlikely.

Elimination
After oral administration of 14C-nepafenac to healthy volunteers, urinary excretion was found to be the major route of radioactive excretions, accounting for approximately 85% while faecal excretion represented approximately 6% of the dose.

Preclinical safety data
Non-clinical data reveal no special hazard for humans based upon conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

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

In reproduction studies performed with nepafenac in rats, maternally toxic doses ≥ 10 mg/kg were associated with dystocia, increased postimplantation loss, reduced foetal weights and growth, and reduced foetal survival. In pregnant rabbits, a maternal dose of 30 mg/kg that produced slight toxicity in the mothers showed a statistically significant increase in the incidence of litter malformations.

INDICATION:
Nepafenac is indicated in adults for prevention and treatment of postoperative pain and inflammation associated with cataract surgery.

DOSAGE AND ADMINISTRATION:
Posology/frequency and duration of administration
Using in adults, including the elderly
For the prevention and treatment of pain and inflammation, the dose is 1 drop of Nepafenac in the conjunctival sac of the affected eye(s) 1 time daily beginning 1 day prior to cataract surgery, continued on the day of surgery and up to 21 days of the postoperative period, as directed by the clinician. An additional drop should be administered 30 to 120 minutes prior to surgery.
In clinical studies, 3 mg/ml nepafenac has been administered to patients up to 21 days.
The dose with administration of 1 drop of Nepafenac 0.3% Ophthalmic Suspension 1 time daily provides same total daily nepafenac dose with administration of 1 drop of nepafenac 1 mg/ml eye drops 3 times daily.

Method of administration
For ocular use.

Instruct your patients to shake the bottle well before use.

If more than one topical ophthalmic medicinal product is being used, the medicinal product must be administered at least 5 minutes apart. Eye ointments should be administered last.

To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle. The bottle should be kept tightly closed when not in use.

ADDITIONAL DATA FOR SPECIAL POPULATIONS:
Renal or hepatic impairment:
Nepafenac has not been studied in patients with hepatic disease or renal impairment. Nepafenac is eliminated primarily through biotransformation and the systemic exposure is very low following topical ocular administration. No dose adjustment is warranted in these patients.

Paediatric population:
The safety and efficacy of Nepafenac in children have not been established. No data are available. Its use is not recommended in these patients.

Geriatric Population:
It has the same usage as in adults.

CONTRAINDICATIONS
It is contraindicated in patients have hypersensitivity to the active substance, any of the excipients or to other nonsteroidal anti-inflammatory drugs (NSAIDs).

Like other NSAIDs, Nepafenac is contraindicated in patients with urticaria, acute rhinitis or asthma attacks precipitated by acetylsalicylic acid or other NSAIDs.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Do not inject. Instruct your patients not to swallow Nepafenac.

Instruct your patients to avoid sunlight during treatment with Nepafenac.

Nepafenac 3 mg/mL eye drops should not be used for reducing postoperative macular oedema risk associated with cataract surgery because the safety and efficacy of this dose have not been studied.

Ocular 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. In patients with evidence of corneal epithelial breakdown, Nepafenac use should be immediately discontinued and should be monitored closely for corneal health.

Topical NSAIDs may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids increase the potential for healing problems. For this reason, caution is advised when Nepafenac is used concomitantly with corticosteroids, especially in patients with high risk for the side effects described below.

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 reactions which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Prolonged use of topical NSAIDs may increase risk for occurrence and severity of corneal adverse reactions in patients.
There have been reports that ophthalmic NSAIDs may cause increased bleeding of ocular tissues (including blooding in the front chamber of the eye) in conjunction with ocular surgery. Nepafenac should be used with caution in patients with known bleeding tendencies or who are receiving other medicinal products which prolong bleeding time.

An acute ocular infection may be masked by the topical use of anti-inflammatory medicines. NSAIDs do not have any antimicrobial properties. Caution is advised during concomitant use with anti-infectives in case of ocular infection.

Contact lenses
Contact lens wear is not recommended during the postoperative period following cataract surgery. Therefore, contact lenses should not be worn during treatment with Nepafenac.

Benzalkonium Chloride
Benzalkonium chloride is widely used as preservative in ophthalmic products and has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since Nepafenac contains benzalkonium chloride, close monitoring is required with frequent or prolonged use.

Benzalkonium chloride may cause eye irritation. Avoid contacting with soft contact lenses. Remove contact lenses before administration and wait at least 15 minutes to wear them. It is known that it cause discolour soft contact lenses.

Nepafenac contains propylene glycol. Propylene glycol may cause eye irritation.
Cross-sensitivity
There is a potential for cross-sensitivity of nepafenac to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs.

DRUG INTERACTIONS:
In vitro studies have demonstrated a very low potential for interaction with other medicinal products and protein binding interactions.

Prostaglandin analogues
There is very limited data about using concomitantly Nepafenac and analogues of prostaglandin. When their action mechanisms are taken into consideration, concomitantly usage of these medicinal drugs should not be recommended.

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

Additional data for special populations:
Interaction studies have not been performed.

Pediatric population:
Interaction studies have not been performed.

PREGNANCY AND LACTATION:
General recommendation
Pregnancy category: C, D at 3rd trimester

Women of childbearing potential/Contraception
It is recommended that women with childbearing potential to use a medically appropriate contraceptive method during their treatment with Nepafenac.

Pregnancy Period
There are no adequate data regarding the use of Nepafenac in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Since the systemic exposure is expected as negligible after treatment with Nepafenac, the risk during pregnancy could be considered low. Nevertheless, as inhibition of prostaglandin synthesis may negatively affect pregnancy and/or embryonal/foetal development and/or parturition and/or postnatal development, it is not recommended to use during pregnancy.

Lactation Period
It is unknown whether Nepafenac is excreted in human milk or not. Animal studies have shown excretion of Nepafenac in the milk of rats. However, no effects on the suckling child are anticipated since the systemic exposure of the breastfeeding woman to Nepafenac is negligible. Nepafenac can be used during lactation period.

Fertility
There is no data on the effect of Nepafenac on reproductive ability.

Effects on ability to drive and use machines
Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines, as usage of any eye drop. If blurred vision occurs after administration, the patients must wait until the vision clears before driving or using machines.

ADVERSE DRUG REACTIONS:
Summary of the safety profile
In clinical studies involving 1300 patients using nepafenac 3 mg/ml eye drops, 3 side effects (eye pain, punctate keratitis, hypersensitivity) have been observed in 3 patients (0.2%). One patient (0.1%) discontinued due to an adverse reaction (hypersensitivity), while no placebo-treated patients in these same studies discontinued due to an adverse reaction.

Observed adverse reactions with the use of Nepafenac 1 mg/ml eye drops, suspension and may also be observed with the use of Nepafenac 3 mg/ml eye drops, suspension. In clinical studies involving 2314 patients receiving Nepafenac 1 mg/ml eye drops, the most common adverse reactions were punctate keratitis, foreign body sensation, and eyelid margin crusting which occurred in between 0.4% and 0.2% of patients.

The following adverse reactions are evaluated according to the treatment and classified according to the following 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), very rare (<1/10,000), or not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The adverse reactions were obtained from clinical trials and post-marketing reports.

Immune system disorders
Rare: Hypersensitivity

Nervous system disorders
Rare: Dizziness, headache

Eye disorders
Uncommon: keratitis, punctate keratitis, corneal epithelium defect, foreign body sensation in eye, eyelid margin crusting
Rare: Iritis, choroidal effusion, corneal deposits, eye pain, ocular discomfort, dry eye, blepharitis, eye irritation, eye pruritus, watering of eyes, allergic conjunctivitis, increased lacrimation, conjunctival hyperemia.
Not known: impaired healing (cornea), corneal opacity, corneal scar, reduced visual acuity, eye irritation, eye swelling, ulcerative keratitis, corneal thinning, blurred vision.

Vascular disorders
Not known: Increase in blood pressure

Gastrointestinal disorders
Rare: Nausea
Not known: Vomiting

Skin and subcutaneous tissue disorders
Rare: Cutis laxa (as a result of thickening, skin shows sagging in the form of folds) allergic dermatitis
Not Known: Increase in blood pressure

Description of selected adverse effects
Patients with evidence of corneal epithelial breakdown should immediately discontinue use of Nepafenac and should be monitored closely for corneal health.
From post-marketing experience with Nepafenac 1 mg/mL eye drops, cases reporting corneal epithelium defect/disorder have been identified. Severity of these cases vary from non-serious effects on the epithelial integrity of the corneal epithelium to more serious events where surgical interventions and/or medical therapy are required to regain clear vision.

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 reactions which may become sight threatening.

Pediatric population
The safety and efficacy of Nepafenac in children and adolescents have not been established.

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

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

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph. Seek medical attention immediately at the first sign of any adverse drug reaction.

STORAGE CONDITION:
Store at temperatures not exceeding 30˚C.

AVAILABILITY:
5 mL White Opaque LDPE Bottle with LDPE/HDPE cap and LDPE Dropper (Box of 1's)

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING:
Any unused product or waste material should be disposed of in accordance with local requirements.

Shake before use.

After opening the bottle, avoid contamination and the tip of the bottle should not be touched anywhere. After use, the cap should be closed.

4 weeks after opening the bottle, discard the remaining solution.

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