

Nepacent™

1. Generic Names

Nepafenac

2. Qualitative and Quantitative Composition

Each ml of Nepacent eye drops contains:

Nepafenac0.1% w/v

Stabilized oxychloro complex01% w/v
(As preservative)

Sterile aqueous vehicle q.s

3. Dosage form and strength

Topical ophthalmic suspension containing Nepafenac 0.1%w/v

4. Clinical particulars

4.1 Therapeutic indication

For the treatment of pain and inflammation associated with cataract surgery.

4.2 Posology and method of administration

Posology

Use the medicine exactly as directed by the physician.

For the prevention and treatment of pain and inflammation, the recommended dose is to instil 1 drop of Nepacent eye drops in the conjunctival sac of the affected eye(s) 3 times daily beginning 1 day prior to cataract surgery, continued the day of surgery and for the first 2 weeks of the postoperative period. Treatment can be extended to the first 3 weeks of the postoperative period as directed by the clinician. An additional drop should be administered 30 to 120 minutes prior to surgery.

Method of administration

For ocular use only. Patients should be instructed to shake the bottle well before use. If more than one topical ophthalmic 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. Patients should be instructed to keep the bottle tightly closed when not in use.

4.3 Contraindication

Hypersensitivity to any active ingredient or to any of the ingredients in the formula or to other non-steroidal anti-inflammatory drugs (NSAIDs).

4.4 Special warnings and precautions for use

- Nepacent eye drops is for ocular use only. The product should not be injected OR swallowed.
- There is a potential for cross-sensitivity of nepafenac to acetylsalicylic acid, phenylacetic acid derivatives and other non-steroidal anti-inflammatory drugs (NSAIDs).
- 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 0.1% eye drops 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 report 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 the patient risk for occurrence and severity of corneal adverse reactions.
- With some ophthalmic NSAIDs including Nepafenac 0.1% eye drops, there exists 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. Therefore Nepafenac 0.1% eye drops should be used with caution in patients with bleeding tendencies or who are receiving other medicinal products which may prolong bleeding time.
- An acute ocular infection may be masked by topical use of anti-inflammatory medicinal products. NSAIDs do not have anti-microbial properties. In case of an ocular infection, their use with anti-infectives should be undertaken with care.
- Contact lens wear is not recommended during the postoperative period following cataract surgery. Therefore, patients should be advised not to wear contact lenses unless clearly indicated by their doctor.

4.5 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.

4.6 Use in special population

- Paediatric: The safety and effectiveness of Nepacent eye drops in children and adolescents have not been established. Its use is not recommended in these patients until further data becomes available.
- 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: 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 in non-pregnant women is negligible after treatment with Nepafenac 0.1% eye drops, 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. Nepacent eye drops are not recommended during pregnancy.

Lactation: Animal studies have shown excretion of nepafenac in the milk of rats. It is not known whether nepafenac is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Nepacent eye drops are administered to a nursing woman.

4.7 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 eye drops is known. Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

In a clinical study involving 2,314 patients receiving Nepafenac 0.1% 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.

Tabulated list of adverse reactions

The following adverse reactions are classified according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), very rare ($< 1/10\ 000$), or not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Classification	Frequency	Adverse Reactions
Immune system disorders	Rare	Hypersensitivity
Nervous system disorders	Rare	Dizziness, headache
Eye disorders	Uncommon	Keratitis, punctate keratitis, corneal epithelium defect, foreign body sensation in eyes, eyelid margin crusting
	Rare	Iritis, choroidal effusion, corneal deposits, eye pain, ocular discomfort, dry eye, blepharitis, eye irritation, eye pruritis, eye discharge, allergic conjunctivitis, increased lacrimation, conjunctival hyperaemia



	Not known	Corneal perforation, impaired healing (cornea), corneal opacity, corneal scar, reduced visual acuity, eye swelling, ulcerative keratitis, corneal thinning, blurred vision
Vascular disorders	Not known	Blood pressure increased
Gastrointestinal disorders	Rare	Nausea
	Not known	Vomiting
Skin and subcutaneous disorders	Rare	Cutis laxa (dermatochalasis), allergic dermatitis

Diabetic patients

In the two clinical studies involving 209 patients, diabetic patients were exposed to Nepafenac 0.1% eye drops, treatment for 60 days or greater for the prevention of macular oedema post cataract surgery. The most frequently reported adverse reaction was punctate keratitis which occurred in 3% of patients, resulting in a frequency category of common. The other reported adverse reactions were corneal epithelium defect and allergic dermatitis which occurred in 1% and 0.5% of patients, respectively both adverse reactions with a frequency category of uncommon.

Description of selected adverse reactions

Clinical trial experience for the long-term use of Nepafenac 0.1% ophthalmic eye drops, for the prevention of macular oedema post cataract surgery in diabetic patients is limited. Ocular adverse reactions in diabetic patients may occur at a higher frequency than observed in the general population.

Patients with evidence of corneal epithelial breakdown including corneal perforation should immediately discontinue use of Nepafenac 0.1% eye drops and should be monitored closely for corneal health.

From post-marketing experience with Nepafenac 0.1% 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. When nepafenac is prescribed to a diabetic patient post cataract surgery to prevent macular oedema, the existence of any additional risk factor should lead to reassessment of the foreseen benefit/risk and to intensified patient monitoring.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

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

5. Pharmacological properties

5.1 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. Stabilized oxychloro complex has been shown to be well tolerated by the ocular surface. The anti-microbial activity is broad even at very low concentrations of SOC (0.005%). SOC has been shown to lack cytotoxicity, in vivo. The antimicrobial effects are broad and include antibacterial, antifungal and antiviral effects. Chemically, SOC is a mixture of chlorine dioxide, chlorite and chlorate. When exposed to light, SOC dissociates into water, oxygen, sodium and chlorine free radicals. The chlorine free radicals inhibit microorganism protein synthesis, which cause microbial cell death.

5.2 Pharmacodynamic properties

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.

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.

5.3 Pharmacokinetic properties

Absorption

Following 3 times daily dosing of Nepafenac 0.1% eye drops in both eyes, 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 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.

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 C_{max}.



Excretion

After oral administration of ^{14}C -Nepafenac to healthy volunteers, urinary excretion was found to be the major route of radioactivity elimination, accounting for approximately 85% of the dose while faecal excretion represented approximately 6% of the dose. Nepafenac and Amfenac were not quantifiable in the urine.

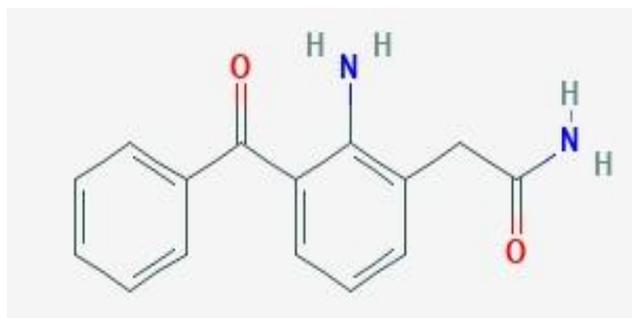
6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

NA

7. Description

Nepafenac is a monocarboxylic acid amide that is amfenac in which the carboxylic acid group has been converted into the corresponding carboxamide. It is a prodrug for amfenac, used in eye drops to treat pain and inflammation. Its chemical name is 2-(2-amino-3-benzoylphenyl)acetamide. The empirical formula and molecular weight is $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_2$ and 254.28 g/mol.



8. Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf-life

18 months.

8.3 Packaging Information

Nepacent is available in 5ml in plastic bottle.

8.4 Storage and handling instructions

Store below 25°C. Protect from light and moisture.

Do not freeze. Store in a cool and dry place.

9. Patient Counselling Information

9.1 Adverse Reactions

Refer part 4.8

9.2 Drug Interactions

Refer part 4.5

9.3 Dosage

Refer part 4.2

9.4 Storage

Refer part 8.4

9.5 Risk Factors

Refer part 4.4

9.6 Self-monitoring information

NA

9.7 Information on when to contact a health care provider or seek emergency help

Patient is advised to be alert for the emergence or worsening of the adverse reactions and contact the prescribing physician.

9.8 Contraindications

Refer part 4.3

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8/UA/LL/SC/P-2014

12. Date of revision: March 2026

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