SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

NEVANAC® Eye drops, suspension

COMPOSITION

1 ml of suspension contains 1 mg nepafenac.

Preservatives: benzalkonium chloride 0.005 % (m/v) and disodium edetate 0.01 % (m/v).

Excipients are: Carbomer 974P, tyloxapol, mannitol, sodium chloride, sodium hydroxide, hydrochloric acid.

Contains sugar: mannitol

PHARMACOLOGICAL CLASSIFICATION

A.15.4 Ophthalmic preparations, Anti-inflammatory agents, non-steroids

ATC code: S01BC10

PHARMACOLOGICAL ACTION

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 non-steroidal anti-inflammatory drug. Amfenac inhibits the action of prostaglandin H synthase (cyclooxygenase), an enzyme required for prostaglandin production.

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.

Pharmacokinetic properties

Absorption

Following three-times-daily dosing of nepafenac 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 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 a high affinity toward serum albumin proteins. In vitro, 98,4 %, 95,4 % and 99,1 % was bound to rat albumin, human albumin and human serum, respectively.

Metabolism

Nepafenac undergoes 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 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/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. Nepafenac and amfenac were not quantifiable in the urine.

Following a single dose of 0.1% nepafenac in 25 cataract surgery patients, aqueous humour concentrations were measured at 15, 30, 45 and 60 minutes post-dose. The maximum mean aqueous humour concentrations

were observed at the 1 hour time-point (nepafenac 177 ng/ml, amfenac 44, 8 ng/ml). These findings indicate rapid corneal penetration.

INDICATIONS

Prevention and treatment of pain and inflammation associated with cataract surgery and reduction in the risk of macular oedema associated with cataract surgery.

CONTRA-INDICATIONS

Hypersensitivity to the active substance, to any of the excipients, or to other non-steroidal anti-inflammatory drugs (NSAIDs).

Cardiovascular:

Heart failure.

Gastrointestinal:

History of gastrointestinal bleeding or perforation (PUB's) related to previous NSAIDs, including NEVANAC®.

Active or history of recurrent ulcer / haemorrhage / perforations.

NEVANAC® Eye drops is also contra-indicated in patients in whom attacks of asthma, urticaria or acute rhinitis are precipitated by aspirin or other NSAIDs.

WARNINGS AND SPECIAL PRECAUTIONS

Use of topical NEVANAC® Eye drops may result in keratitis. Continued use of topical NEVANAC® Eye drops 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 NEVANAC® Eye drops and should be monitored closely for corneal health.

Topical NEVANAC® Eye drops may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of NEVANAC® Eye drops and topical steroids may increase the potential for healing problems.

In view of the product's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

Post-marketing experience with topical NSAIDs such as NEVANAC® 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. NEVANAC® Eye drops should be used with caution in these patients. Prolonged use of NEVANAC® Eye drops may increase patient risk for occurrence and severity of corneal adverse reactions.

NEVANAC® may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. NEVANAC® Eye drops should be used with caution in patients with known bleeding tendencies or who are receiving other medicines which may prolong bleeding time.

NEVANAC® Eye drops contains benzalkonium chloride which may cause irritation and is known to discolour soft contact lenses. Additionally, contact lens wear is not recommended during the postoperative period following cataract surgery. Therefore, patients should be advised not to wear contact lenses during treatment with NEVANAC® Eye drops.

Benzalkonium chloride, used as a preservative in NEVANAC®, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since NEVANAC® Eye drops contains benzalkonium chloride, close monitoring is required with frequent or prolonged use.

An acute ocular infection may be masked by the topical use of NEVANAC®. NEVANAC® does not have antimicrobial properties. In case of ocular infection, NEVANAC® should be used with care with anti-infectives.

Cardiovascular: Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NEVANAC® Eye drops therapy. In view of NEVANAC's ® inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

Gastrointestinal: Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation (PUBs) which may be fatal. The risk of gastrointestinal bleeding or perforation is higher with increasing doses of NEVANAC® Eye drops, in patients with a history of ulcers and the elderly. When gastrointestinal bleeding or ulceration occurs in patients receiving NEVANAC® Eye drops, treatment with NEVANAC® Eye drops should be stopped. NEVANAC® Eye drops should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated.

Skin Reactions: Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. NEVANAC® Eye drops should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Cross-sensitivity
There is a potential for cross-sensitivity of NEVANAC® Eye drops to aspirin, phenylacetic acid derivatives, and other NSAIDs.

Effects on ability to drive and use machines

If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machinery.

INTERACTIONS

Interactions with other medicines: 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 300 ng/ml. Therefore, interactions involving CYP-mediated metabolism of concomitantly administered medicines are unlikely.

In vitro studies have demonstrated a low potential for interactions. Interactions mediated by protein binding are also unlikely.

Use of NEVANAC® with another NSAID concomitantly could result in an increase in side effects.

Gastrointestinal

Corticosteroids: increased risk of gastrointestinal perforation ulceration or bleeding (PUBs).

Anti-coagulants: NEVANAC® Eye drops may enhance the effects of anti-coagulants such as warfarin.

Anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs): increased risk of intestinal bleeding.

NEVANAC eye drops may be administered in conjunction with other topical ophthalmic medicines such as beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics and mydriatics.

PREGNANCY AND LACTATION

Pregnancy

NEVANAC® Eye drops should not be used during pregnancy.

NEVANAC® is contraindicated in the third trimester of pregnancy.

There are no adequate data from the use of NEVANAC® Eye drops in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. As inhibition of prostaglandin synthesis may negatively affect pregnancy and/or embryonal/foetal development and/or parturition and/or postnatal development.

Regular use of non-steroidal anti-inflammatory drugs during the 3rd trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus in utero and possibly in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed and its duration increased.

Lactation

It is unknown whether NEVANAC® Eye drops is excreted in human milk. Animal studies have shown excretion of NEVANAC® Eye drops in the milk of lactating rats. NEVANAC® Eye drops should not be used in women breastfeeding their infants.

DOSAGE AND DIRECTIONS FOR USE

Use in adults

Use the lowest effective dose for the shortest possible duration of treatment.

Instill one drop of NEVANAC® Eye drops in the conjunctival sac of the affected eye(s) three times daily, beginning 1 day prior to cataract surgery, continued on 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 30-120 minutes prior to surgery.

Treatment can be extended for up to 60 days to reduce the risk of macular oedema associated with cataract surgery.

Paediatric patients

The efficacy and safety of NEVANAC® Eye drops in patients below the age of 18 years has not been established.

Geriatric patients

No dose adjustment is warranted in these patients as no overall difference in safety and efficacy have been observed in this population.

Use in hepatic and renal impairment

NEVANAC® Eye drops 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.

Shake well before use.

If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

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.

Keep the bottle tightly closed when not in use.

SIDE EFFECTS

In clinical studies involving over 800 patients receiving NEVANAC® Eye drops, approximately 5 % of patients experienced adverse reactions. These events led to discontinuation in 0,5 % of patients, which was less than placebo-treated patients (1,3 %) in these same studies. No serious adverse events related to NEVANAC® Eye drops were reported in these studies.

The following undesirable effects were assessed to be treatment-related and are 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 <1/1000) or very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Immune system disorders

Rare: hypersensitivity.

Nervous system disorders

Rare: headache, dizziness

Eye disorders

Uncommon: keratitis, allergic conjunctivitis, punctate keratitis, eye pain, foreign body sensation in eyes, eyelid margin crusting.

Rare: Blurred vision, eye pruritus, dry eye, eye discharge, photophobia, eye irritation, increased lacrimation, blepharitis.

Gastrointestinal disorders

Rare: nausea,

Skin and subcutaneous tissue disorders

Rare: Allergic dermatitis

Post marketing

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data. Within each System Organ Class adverse reactions are presented in order of decreasing seriousness.

System Organ Classification	Adverse reactions MedDRA Preferred Term (v. 18.0)

Eye disorders	corneal perforation, ulcerative keratitis, corneal thinning, corneal opacity, corneal abrasion, corneal scar, impaired healing (cornea), visual acuity reduced, eye swelling, ocular hyperaemia
Gastrointestinal disorders	vomiting
Investigations	blood pressure increased

Data obtained from package inserts of other Non-Steroidal Anti-Inflammatory medicines (NSAIDs):

Cardiovascular:

Oedema, hypertension and cardiac failure.

Gastrointestinal disorders:

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, malaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis.

Skin and subcutaneous tissue disorders:

Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Adverse reactions identified from post-marketing experience that have not been reported previously in clinical trials with NEVANAC® Eye drops include the following. The frequency category in which these adverse reactions occur is not known and cannot be estimated from the available data.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

There is no experience of overdose with ocular use. The application of more than one drop per eye is unlikely to lead to unwanted side-effects. There is practically no risk of adverse effects due to accidental oral ingestion.

IDENTIFICATION

Light yellow to light orange uniform suspension.

PRESENTATION

8 ml round, colourless low density polyethylene bottle and dispensing plug with white polypropylene screw cap containing 5 ml suspension.

STORAGE INSTRUCTIONS

Keep the container well-closed after opening. Discard four weeks after first opening.

KEEP OUT OF SIGHT AND REACH OF CHILDREN.

Do not store above 30°C.

REGISTRATION NUMBER

42/15.4/1006

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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DATE OF PUBLICATION OF THE PACKAGE INSERT

Date on the registration certificate of the medicine: 11 April 2011

Date of the most recent revised package insert approved by council: 20 March 2018