NEVANAC®

1 mg/ml eye drops, suspension

1. NAME OF THE MEDICINAL PRODUCT

NEVANAC® eye drops 1 mg/ml eye drops, suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of suspension contains 1 mg nepafenac.
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, suspension
Light yellow to light orangeuniform suspension, pH 7.4 (approximately).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nevanac is indicated in adults for:

- Prevention and treatment of postoperative pain and inflammation associated with cataract surgery.
- Reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients (see section 5.1).

4.2 Posology and method of administration

Use in adults, including the elderly

For the prevention and treatment of postoperative pain and inflammation associated with cataract surgery, the dose is one drop of NEVANAC eye drops in the conjunctival sac of the affected eye(s) 3 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. An additional drop should be administered 30to 120 minutes prior to surgery.
For the reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients, the dose is 1 drop of NEVANAC eye drops in the conjunctival sac of the affected eye(s) 3 times daily beginning 1 day prior to cataract surgery, continued on the day of surgery and up to 60 days of the postoperative period as directed by the clinician. An additional drop should be administered 30 to 120 minutes prior to surgery.

Paediatric patients

The safety and efficacy of Nevanacin paediatric patients have not been established. Its use is not

recommended in this age group until further data become available. There is no relevant use of NEVANAC eye drops in the paediatric population in the indications.

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.

Geriatric population

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

Method of administration

- For ocular use.
- After cap is removed, if tamper evident snap collar is loose, it should be removed before using the product.
- Instruct patients to shake the bottle well before use.
- If more than one topical ophthalmic medicinal product is being used, the medicines must be administered at least 5 minutes apart. Eye ointments should be administered last.
- If a dose is missed, a single drop should be applied as soon as possible before reverting to regular routine. No double dose should be used to make up for the one missed.
- To avoid contamination, the dropper tip should not touch any surface. The dropper tip should also not come into contact with the eye as this may cause injury to the eye. Patients should be instructed to keep the bottle tightly closed when not in use.

4.3 Contraindications

Hypersensitivity to the active substance, to any of the excipients, or to other nonsteroidal anti inflammatory drugs (NSAIDs).
Like other NSAIDs, NEVANAC eye drops is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs.

4.4 Special warnings and precautions for use

- NEVANAC eye drops, suspension is for topical use only and not for injection or oral use.
- Instruct patients to avoid sunlight during treatment with NEVANAC eye drops.
- Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued and prolonged use may increase patient risk for occurrence and severity of corneal adverse reactions which may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. Post-marketing experience with topical NSAIDs suggests that patients with repeat and/or complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes

mellitus, ocular surface diseases, dry eye or rheumatoid arthritis may be at increased risk for corneal adverse reactions. These events may be sight threatening. Topical NSAIDs should be used with caution in these patients. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of NEVANAC eye drops 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 may increase the potential for healing problems.

- There have been reports that ophthalmic NSAIDs may cause increased bleeding of ocular tissues (including hyphaemas) in conjunction with ocular surgery. NEVANAC should be used with caution in patients with known bleeding tendencies or who are receiving other medicinal products which may prolong bleeding time.

- There are very limited data on the concomitant use of prostaglandin analogues and NEVANAC® eye drops. Considering their mechanisms of action, the concomitant use of these medicinal products is not recommended.Contact lens wear is not recommended during the postoperative period following cataract surgery and during treatment with NEVANAC eye drops.

- An acute ocular infection may be masked by the topical use of anti-inflammatory medicines. NSAIDs do not have any antimicrobial properties. In case of ocular infection, their use with anti-infectives should be undertaken with care.
- There is a potential for cross-sensitivity of nepafenac to acetylsalicylic acid, phenylacetic acid derivatives, and other non steroidal anti-inflammatory agents.

Special Excipients

- Nevanac Eye drops suspension contains benzalkonium chloride which may cause eye irritation and may possibly discolor soft contact lenses. Avoid contact with soft contact lenses during treatment. In case patients are allowed to wear contact lenses, they must be removed before administration of Nevanac Eye drops and reinserted at least 15 minutes later.
- Benzalkonium chloride has been reported to cause punctuate keratopathy and/or toxic ulcerative keratopathy. Close monitoring is required with frequent and/or prolonged use.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies have demonstrated a very low potential for interaction with other medicinal products and protein binding interactions (see section 5.2).

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

4.6 Fertility, Pregnancy and Lactation

Fertility

There are no adequate data regarding the use of NEVANAC eye drops on human fertility. No significant fertility effects were seen in studies in rats at doses up to 3 mg/kg/day (17 and 351 times higher than the human exposure to nepafenac and amfenac at the maximum recommended ocular human dose respectively).

In a fertility study, rats were orally dosed with 3, 10, 15 and 30 mg/kg/day. Animals at 30 mg/kg/day were euthanized early due to excessive toxicity. At 15 mg/kg/day, sperm motility and concentration were affected in males in the absence of any microscopic findings in the testes and epididymides. No significant differences in copulation or fertility indices were noted. Decreased number of viable fetuses and increased early resorptions were observed at 10 and 15 mg/kg/day. The NOEL for male and female reproductive toxicity was 3 mg/kg/day (17 and 351 times higher than the human exposure to nepafenac and amfenac at the MROHD, respectively) .

Pregnancy

Risk Summary

There are no adequate and well-controlled studies in pregnant women to inform a product-associated risk. There are limited data with the use of Nevanac in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

In embryofetal studies in rats and rabbits, oral administration of nepafenac during the period of organogenesis did not produce embryofetal toxicity at 10 mg/kg/day (20 times and 179 times higher than human exposures based on AUC of nepafenac and amfenac at the maximum recommended ocular human dose (MROHD) of one drop of 0.3 % nepafenac ophthalmic suspension in each eye, respectively).

Oral administration of nepafenac to pregnant rats during gestation and lactation produced maternal lethality at all doses, including the lowest dose tested, 3 mg/kg/day.

A no-observed effect-level (NOEL) for maternal toxicity was not established in this study. Doses ≥3 mg/kg/day were associated with dystocia and doses ≥10 mg/kg/day increased the death rate of the offspring, especially during the early neonatal period.

Since human systemic exposure is negligible (< 1ng/mL) after treatment with Nevanac, the risk during pregnancy could be considered low. Nevertheless, inhibition of prostaglandin synthesis may negatively affect pregnancy and/or embryo/fetal development and/or parturition and/or postnatal development.

NEVANAC eye drops is not recommended during pregnancy and in women of childbearing potential not using contraception unless the benefit outweighs the potential risk.

Clinical Considerations

Fetal/Neonatal adverse reactions

Because of the known effects of prostaglandin biosynthesis inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of Nevanac during late pregnancy should be avoided.

Data

Animal data

In rats, oral administration of 3, 10 or 30 mg/kg/day nepafenac during the period of organogenesis (gestational days 6 to 17) caused significant maternal toxicity at 10 mg/kg/day and maternal lethality

at 30 mg/kg/day. The NOEL for maternal toxicity was 3 mg/kg/day (17 and 351 times higher than human exposure to nepafenac and amfenac at MROHD, respectively. A dose of 30 mg/kg/day produced embryofetal toxicity (embryofetal lethality and increased incidence of minor skeletal anomalies). The NOEL for embryofetal toxicity was 10 mg/kg/day (212 and 1,432 times higher than human exposure to nepafenac and amfenac at MROHD, respectively).

In rabbits, oral administration of 3, 10 or 30 mg/kg/day nepafenac during the period of organogenesis (gestational days 6 to 18) caused abortion at ≥10 mg/kg/day. The NOEL for abortion and maternal toxicity was 3 mg/kg/day (0.6 and 41 times higher than human exposure to nepafenac and amfenac at MROHD, respectively). Embryofetal toxicity, including external, visceral and skeletal malformations (omphalocele, malformations of the heart/great vessels; and skull, vertebrae, sternebrae and costal cartilage anomalies) was produced at 30 mg/kg/day. The NOEL for embryofetal toxicity was 10 mg/kg/day (20 and 179 times higher than human exposure to nepafenac and amfenac at MROHD, respectively).

In a peri- and postnatal study in rats, oral administration of 3, 10, 15 or 30 mg/kg/day nepafenac during organogenesis and through lactation (gestational days 6 through lactation day 20) caused treatment-related maternal lethality at all doses, with deaths generally following initiation of parturition. A NOEL for maternal toxicity was not established in this study. Maternally toxic doses ≥3 mg/kg/day were associated with dystocia, while doses ≥10 mg/kg/day increased post-implantation loss, reduced fetal growth/weight, and reduced fetal survival. At 15 mg/kg/day, pup viability continued to decrease during the first four days of lactation. No further spontaneous pup mortality occurred after lactation day 4. Nepafenac caused no developmental toxicity in surviving F1 offspring and did not elicit adverse effects with respect to F1 reproductive parameters or F2 viability and growth. The NOEL for developmental toxicity was 3 mg/kg/day (17 and 351 times higher than human exposure to nepafenac and amfenac at MROHD, respectively).

Breast-feeding

Risk summary

There is no information regarding the presence of nepafenac in human milk, the effects on breast-fed infants, or on milk production. Nepafenac is transferred into the milk of lactating rats after oral administration with a milk to plasma ratio of <0.6. It is not known whether measurable levels of nepafenac would be present in maternal milk following topical ocular administration.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Nevanac and any potential adverse effects on the breast-fed child from Nevanac.

4.7 Effects on ability to drive and use machines

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 machinery.

4.8 Undesirable effects

Adverse drug reactions from clinical trials (Table 7-1) are listed by MedDRA system organ class. Within

each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

System Organ Classification	**Adverse reactions MedDRA Term (v. 18.0)**
Nervous system disorders	*Rare*: dizziness, headache
Eye disorders	*Uncommon*: iritis, choroidal effusion, keratitis, punctate keratitis, corneal epithelium defect, corneal deposits, conjunctivitis allergic, eye pain, ocular discomfort, foreign body sensation in eye, eyelid margin crusting, conjunctival hyperaemia. *Rare:* blurred vision, photophobia, dry eye, blepharitis, eye irritation, eye pruritus, eye discharge, lacrimation increased
Immune system disorders	*Rare:* hypersensitivity
Gastrointestinal disorders	*Uncommon:* cutis laxa (dermatochalasis) *Rare:* nausea
Skin and subcutaneous tissue disorders	*Rare:* Allergic dermatitis

Description of selected adverse events

Clinical trial experience for the long-term use of NEVANAC 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 (see Section 4.4).

Patients with evidence of corneal epithelial breakdown should immediately discontinue use of NEVANAC eye drops and should be monitored closely for corneal health (see section 4.4).

From post-marketing experience with NEVANAC 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 (eg, 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.

The following adverse drug reactions have been derived from post-marketing experience with Nevanac via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system Organ Class adverse reactions are presented in order of decreasing seriousness.

System Organ Classification	**Adverse reactions MedDRA Term (v. 18.0)**
Eye disorders	Corneal perforation, ulcerative keratitis, corneal thinning, corneal opacity, corneal scar, impaired healing (Cornea), visual acuity reduced, eye swelling, eye irritation, ocular hyperaemia.
Gastrointestinal disorders	Vomiting
Investigation	Blood pressure increased

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : Antiinflammatory agents, non-steroids, ATC code : S01BC10

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.
No significant effect on intraocular pressure have been reported in clinical trials (Section 4.8).

Clinical Effects

Prevention and treatment of postoperative pain and inflammation associated with cataract surgery.
Three pivotal studies were conducted to assess the efficacy and safety of NEVANAC eye drops dosed 3 times daily as compared to vehicle and/or ketorolac trometamol in the prevention and treatment of postoperative pain and inflammation in patients undergoing cataract surgery. In these studies, study medication was initiated the day prior to surgery, continued on the day of surgery and for up to 2 -4 weeks of the postoperative period. Additionally, nearly all patients received prophylactic treatment with antibiotics, according to clinical practice at each of the clinical trial sites.

In two double-masked, randomised vehicle-controlled studies, patients treated with NEVANAC eye drops had significantly less inflammation (aqueous cells and flare) from the early postoperative period through the end of treatment than those treated with vehicle.

In one double-masked, randomised, vehicle-and active-controlled study, patients treated with NEVANAC eye drops had significantly less inflammation than those treated with vehicle. Additionally, NEVANAC eye drops was non-inferior to ketorolac 5 mg/ml in reducing inflammation and ocular pain, and was slightly more comfortable upon instillation.

A significantly higher percentage of patients in the NEVANAC eye drops group reported no ocular pain following cataract surgery compared to those in the vehicle group.

Reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.
Three studies (one in diabetic patients and two in non-diabetic patients) were conducted to assess the efficacy and safety of NEVANAC eye drops for the prevention of postoperative macular oedema associated with cataract surgery. In these studies, study medication was initiated the day prior to surgery, continued on the day of surgery and for up to 90 days of the postoperative period.

In 1 double-masked, randomised vehicle-controlled study, conducted in diabetic retinopathy patients, a significantly greater percentage of patients in the vehicle group developed macular oedema (16.7 %) compared to patients treated with NEVANAC eye drops (3.2 %). A greater percentage of patients treated with vehicle experienced a decrease in BCVA of more than 5 letters from day 7 to day 90 (or early exit) (11.5 %) compared with patients treated with Nepafenac (5.6 %). More patients treated with NEVANAC

eye drops achieved a 15 letter improvement in BCVA compared to vehicle patients, 56.8 % compared to 41.9 % respectively, p=0.019.

Pediatric population

Nepafenac has not been studied in pediatric populations.

5.2 Pharmacokinetic properties

Absorption

Following three-times-daily dosing of NEVANAC eye drops in both eyes for four days maximal steady-state plasma concentrations (C_{max}) for nepafenac (0.310 ± 0.104 ng/ml) and for amfenac (0.422 ± 0.121 ng/ml) were achieved within 0.5 hours. Steady-state plasma levels were achieved by day 2. The mean nepafenac and amfenac AUC0-∞ were 0.371 ng.h/mL and 1.03 ng.h/mL, respectively. Based on the steady-state/single dose ratio of individual Cmax values, the mean accumulation index was 1.34 + 0.58 for nepafenac and 1.61 + 0.66 for amfenac.

Distribution

Nepafenac and amfenac distributed to ocular tissues in rabbits after single topical dose with either 0.1% or 0.3% suspension. Higher concentrations were observed at site of dosing, cornea and conjunctiva and lower concentrations in posterior tissues, retina and choroid. Concentrations in ocular tissues increased with increased dose. When anterior ocular tissues concentrations were compared from a single dose of 0.3% nepafenac to that after three doses of 0.1% nepafenac in a single day, only the lens did not have a higher concentrations after the 0.3% nepafenac once a day dosing.

In cataract surgical patients, maximal aqueous humor concentrations were observed 1 hour following single dose of 0.1% nepafenac with a concentration of 177 ng/mL and 44.8 ng/mL for nepafenac and amfenac, respectively.

Plasma protein binding of nepafenac is moderate, ranging from 72.8% in rat plasma to 83.5% in human plasma. Protein binding was found to be concentration independent in rat, monkey and human plasma over a wide concentration range (10 to 1000 ng/mL). Amfenac is more highly bound at approximately 99%.

Biotransformation

Nepafenac undergoes relatively rapid *in vivo* hydrolysis to amfenac. After oral administration, unconjugated amfenace and nepafenac, and eight other metabolites were detected in plasma with amfenac, a pharmacological active metabolite having the highest concentration. Several of the metabolites were glucuronide conjugates based chromatographic shift after β-glucuronidase treatment. Nepafenac was detected in plasma but at relatively low levels (3.2% of total radioactivity). Amfenac was the major metabolite in plasma, representing approximately 13 % of total plasma radioactivity. The second most abundant plasma metabolite was 5-hydroxy nepafenac in the form of a glucuronide, representing approximately 9.5 % of total radioactivity at C_{max}.

Neither nepafenac nor amfenac inhibit any of the major human cytochrome P-450 isozymes (CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4) *in vitro* at concentrations up to 3000 and 1000 ng/ml, respectively. After 14 days of oral administration, nepafenac does not increase CYP1A, CYP2B, CYP3A activities or total P450 content in rat, therefore no potential induction

was observed for rat.

Elimination

After oral administration of ^{14}C-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 up to 7 days. Nepafenac and amfenac were not quantifiable in the urine. Following a single dose of NEVANAC eye drops 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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based upon conventional studies of single dose toxicity, repeated dose toxicity, genotoxicity and topical ocular irritation studies.
Nepafenac has not been evaluated in long-term carcinogenicity studies.
For information on reproductive and developmental toxicity, see section 4.6 **Fertility, Pregnancy and Lactation**.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipient with known effect: 1mL of the eye drop suspension contains 0.05mg of benzalkonium chloride.
Other excipients: mannitol, carbomer, sodium chloride, tyloxapol, disodium edetate, sodium hydroxide and/or hydrochloric acid (for pH adjustment), purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years.
Discard 4 weeks after first opening.

6.4 Special precautions for storage

Do not store above 30º C.
Nevanac must be kept out of the reach and sight of children.

6.5 Nature and content of container

8 ml bottle with a dispensing plug and a screw cap containing 5 ml suspension.
Carton containing 1 bottle.

6.6 Special precautions for disposal

No special requirements.

6.7 Manufacturer

See folding box.

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Novartis Pharma AG, Basel, Switzerland