1. NAME OF THE MEDICINAL PRODUCT

NEVANAC 1 mg/ml eye drops, suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of suspension contains 1 mg nepafenac.

Excipient with known effect

Each ml of suspension contains 0.05 mg of benzalkonium chloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, suspension

Light yellow to light orange uniform suspension, pH 7.4 (approximately).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NEVANAC 1 mg/ml 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

Posology

Adults, including the elderly
For the prevention and treatment of pain and inflammation, the dose is 1 drop of NEVANAC 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. 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.

For the reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients, the dose is 1 drop of NEVANAC 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.

Special populations
Patients with renal or hepatic impairment
NEVANAC 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 NEVANAC in children and adolescents have not been established. No data are available. Its use is not recommended in these patients until further data become available.

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

Method of administration

For ocular use.

Patients should be instructed to shake the bottle well before use. After cap is removed, if tamper evident snap collar is loose, remove before using product.

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. Patients should be instructed to keep the bottle tightly closed when not in use.

If a dose is missed, a single drop should be applied as soon as possible before reverting to regular routine. Do not use a double dose to make up for the 1 missed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to other nonsteroidal anti-inflammatory drugs (NSAIDs).

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

The product should not be injected. Patients should be instructed not to swallow NEVANAC.

Patients should be instructed to avoid sunlight during treatment with NEVANAC.

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 (see section 4.8). These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of NEVANAC 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. Therefore, it is recommended that caution should be exercised if NEVANAC is administered concomitantly with corticosteroids, particularly in patients at high risk for corneal adverse reactions 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 patient risk for occurrence and severity of corneal adverse reactions.

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.

An acute ocular infection may be masked by the topical use of anti-inflammatory medicinal products. NSAIDs do not have any antimicrobial properties. In case of ocular infection, their use with anti-infectives should be undertaken with care.

Contact lenses

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.

Benzalkonium chloride

NEVANAC contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. If contact lenses need to be used during treatment, patients should be advised to remove contact lenses prior to application and wait at least 15 minutes before reinsertion.

Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since NEVANAC contains benzalkonium chloride, close monitoring is required with frequent or prolonged use.

Cross-sensitivity

There is a potential for cross-sensitivity of nepafenac to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs.

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).

Prostaglandin analogues

There are very limited data on the concomitant use of prostaglandin analogues and NEVANAC. Considering their mechanism of action, the concomitant use of these medicinal products is not recommended.

Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems. Concomitant use of NEVANAC with medications that prolong bleeding time may increase the risk of haemorrhage (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

NEVANAC should not be used by women of child bearing potential not using contraception.

Pregnancy

There are no adequate data regarding the use of nepafenac in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Since the systemic exposure in non-pregnant women is negligible after treatment with NEVANAC, 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. NEVANAC is not recommended during pregnancy.

Breast-feeding

It is unknown whether nepafenac is excreted in human milk. 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 breast-feeding woman to nepafenac is negligible. NEVANAC can be used during breast-feeding.

Fertility

There are no data on the effect of NEVANAC on human fertility.

4.7 Effects on ability to drive and use machines

NEVANAC has no or negligible influence on the 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 machines.

4.8 Undesirable effects

Summary of the safety profile

In clinical studies involving 2314 patients receiving NEVANAC 1 mg/ml 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 (≥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.

System organ classification	**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 pruritus, 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 tissue disorders	*Rare:* cutis laxa (dermatochalasis), allergic dermatitis

Diabetic patients
In the two clinical studies involving 209 patients, diabetic patients were exposed to NEVANAC 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 NEVANAC 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 including corneal perforation should immediately discontinue use of NEVANAC and should be monitored closely for corneal health (see section 4.4).

From post-marketing experience with NEVANAC, 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.

Paediatric population

The safety and efficacy of NEVANAC in children and adolescents have not been established.

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 via the national reporting system listed in Appendix V.

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: Opthalmologicals, Anti-inflammatory 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 PGE_2 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 NEVANAC 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
Three pivotal studies were conducted to assess the efficacy and safety of NEVANAC 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 had significantly less inflammation (aqueous cells and flare) in the early postoperative period through the end of treatment than those treated with its vehicle.

In one double-masked, randomised, vehicle and active-controlled study, patients treated with NEVANAC had significantly less inflammation than those treated with vehicle. Additionally, NEVANAC 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 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
Four studies (two in diabetic patients and two in non-diabetic patients) were conducted to assess the efficacy and safety of NEVANAC 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 (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 achieved a 15 letter improvement in BCVA compared to vehicle patients, 56.8% compared to 41.9%. respectively, p=0.019.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with NEVANAC in all subsets of the paediatric population in prevention and treatment of post operative pain and inflammation associated with cataract surgery and prevention of post surgical macular oedema (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following 3 times daily dosing of NEVANAC 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 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 ^{14}C-nepafenac.

Studies in rabbits demonstrated that the topically administered nepafenac is distributed locally from the front of the eye to the posterior segments of the eye (retina and choroid).

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 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}.

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 ^{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. Nepafenac and amfenac were not quantifiable in the urine.

Following a single dose of NEVANAC 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 on 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Carbomer
Sodium chloride
Tyloxapol
Disodium edetate
Benzalkonium chloride
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 30˚C.
For storage conditions after first opening of the medicinal product, see section 6.3

6.5 Nature and content of container

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

Carton containing 1 bottle.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/433/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 December 2007
Date of latest renewal: 24 September 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu