ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 2 314 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 the 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 3 000 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 contents 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

1. NAME OF THE MEDICINAL PRODUCT

NEVANAC 3 mg/ml eye drops, suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of suspension contains 3 mg nepafenac.

Excipient with known effect

Each ml of suspension contains 0.05 mg benzalkonium chloride

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, suspension

Light yellow to dark orange uniform suspension, pH 6.8 (approximately).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NEVANAC 3 mg/ml eye drops, suspension 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) once a day 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.

In clinical trials, patients were treated for up to 21 days with NEVANAC 3 mg/ml eye drops, suspension (see section 5.1).

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) once 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.

Once-daily dosing with NEVANAC 3 mg/ml eye drops, suspension provides the same total daily dose of nepafenac as three-times-daily dosing with NEVANAC 1 mg/ml eye drops, suspension.

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 a tamper evident snap collar is present and is loose, remove before using product.

If more than one topical ophthalmic medicinal product is being used, the medicinal products 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 medicinal 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 anti-microbial 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 over 1 900 patients receiving NEVANAC 3 mg/ml eye drops, suspension, the most frequently reported adverse reactions were punctate keratitis, keratitis, foreign body sensation in eyes and eye pain which occurred in between 0.4% and 0.1% of patients.

Diabetic patients
In the two clinical studies involving 594 patients, diabetic patients were exposed to NEVANAC eye drops, suspension treatment for 90 days for the prevention of macular oedema post cataract surgery. The most frequently reported adverse reaction was punctate keratitis which occurred in 1% of patients, resulting in a frequency category of common. The other most frequently reported adverse reactions were keratitis and foreign body sensation in eyes which occurred in 0.5% and 0.3% of patients, respectively both adverse reactions with a frequency category of uncommon.

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 the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The adverse reactions were obtained from clinical trials or post-marketing reports with NEVANAC 3 mg/ml eye drops, suspension and NEVANAC 1 mg/ml eye drops, suspension.

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

Description of selected adverse reactions

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 1 mg/ml eye drops, suspension, 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.

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: Ophthalmologicals, 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 3 mg/ml eye drops, suspension 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 NEVANAC 3 mg/ml 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 1 339 patients. In these studies 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, NEVANAC 3 mg/ml eye drops, suspension demonstrated superior clinical efficacy compared to its vehicle in treating postoperative pain and inflammation.

Patients treated with NEVANAC were less likely to have ocular pain and measurable signs of inflammation (aqueous cells and flare) in the early postoperative period through to the end of treatment than those treated with its vehicle. In the two studies, NEVANAC 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 NEVANAC group were 89% and 91% compared to 40% and 50% of patients on vehicle.

Some patients received NEVANAC 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, NEVANAC 3 mg/ml eye drops, suspension dosed once a day was non-inferior to NEVANAC 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.

Reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients

Two studies in diabetic patients were conducted to assess the efficacy and safety of NEVANAC 3 mg/ml eye drops, suspension dosed once a day 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 both double-masked, randomised vehicle-controlled studies, conducted in diabetic retinopathy patients, a significantly greater percentage of patients in the vehicle group developed macular oedema (17.3% and 14.3%) compared to patients treated with NEVANAC 3 mg/ml (2.3% and 5.9%). The corresponding percentages in integrated analysis of the 2 studies were 15.9% in vehicle group and 4.1% in NEVANAC group, $p<0.001$). A significantly greater percentage of patients achieved improvement of 15 or more letters at Day 14 and maintained the improvement through Day 90 in NEVANAC 3 mg/ml group (61.7%) compared to vehicle group (43%) in one study; the percentage of subjects was similar in the 2 treatment groups for this endpoint in the second study (48.8% in NEVANAC group and 50.5% in vehicle group). In integrated analysis of the 2 studies, the percentage of subjects with 15 letter improvement at Day 14 and maintained to Day 90 was higher in NEVANAC 3 mg/ml group (55.4%) compared to vehicle group (46.7%, $p=0.003$).

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 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following one drop of NEVANAC 3 mg/ml eye drops, suspension 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 C_{max} 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 ^{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 3 000 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.

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

Boric acid
Propylene glycol
Carbomer
Sodium chloride
Guar
Carmellose sodium
Disodium edetate
Benzalkonium chloride
Sodium hydroxide and/or hydrochloric acid (for pH adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

18 months

Discard 4 weeks after first opening.

6.4 Special precautions for storage

Do not store above 25°C. Keep bottle in the outer carton in order to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3

6.5 Nature and contents of container

Round or oval low density polyethylene bottle with a dispensing plug and white polypropylene screw cap containing 3 ml suspension. The bottle may be presented in a pouch.

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/1/07/433/002
EU/1/07/433/003

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Novartis Manufacturing NV
Rijksweg 14
2870 Puurs-Sint-Amands
Belgium

Novartis Pharma GmbH
Roonstraβe 25
90429 Nuremberg
Germany

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR SINGLE BOTTLE 5 ml

1. NAME OF THE MEDICINAL PRODUCT

NEVANAC 1 mg/ml eye drops, suspension
nepafenac

2. STATEMENT OF ACTIVE SUBSTANCE

1 ml of suspension contains 1 mg nepafenac.

3. LIST OF EXCIPIENTS

Mannitol E421, carbomer, sodium chloride, tyloxapol, disodium edetate, benzalkonium chloride, sodium hydroxide and/or hydrochloric acid and purified water.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Eye drops, suspension

1 x 5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Shake well before use.
Read the package leaflet before use.
Ocular use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Discard 4 weeks after first opening.
Opened:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30˚C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/433/001 1 x 5 ml

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nevanac 1 mg/ml

17. UNIQUE IDENTIFIER-2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDATE PACKAGING UNITS

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NEVANAC 1 mg/ml eye drops
nepafenac
Ocular use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

Opened:

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR SINGLE BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

NEVANAC 3 mg/ml eye drops, suspension
nepafenac

2. STATEMENT OF ACTIVE SUBSTANCE

1 ml of suspension contains 3 mg nepafenac.

3. LIST OF EXCIPIENTS

Boric acid, propylene glycol, carbomer, sodium chloride, guar, carmellose sodium, disodium edetate, benzalkonium chloride, sodium hydroxide and/or hydrochloric acid and purified water.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Eye drops, suspension

1 x 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Shake well before use.
Read the package leaflet before use.
Ocular use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Once daily

8. EXPIRY DATE

EXP
Discard 4 weeks after first opening.
Opened:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25˚C. Keep the bottle in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/433/002	1 x 3 ml – round bottle
EU/1/07/433/003	1 x 3 ml – oval bottle

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nevanac 3 mg/ml

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

NEVANAC 3 mg/ml eye drops
nepafenac
Ocular use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POUCH

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NEVANAC 3 mg/ml eye drops
nepafenac
Ocular use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

Discard 4 weeks after first opening.

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

NEVANAC 1 mg/ml eye drops, suspension
nepafenac

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What NEVANAC is and what it is used for

NEVANAC contains the active substance nepafenac, and belongs to a group of medicines called nonsteroidal anti-inflammatory drugs (NSAIDs).

NEVANAC is to be used by adults:
- to prevent and relieve eye pain and inflammation following cataract surgery on the eye
- to reduce the risk of macular oedema (swelling in the back of the eye) following cataract surgery on the eye in diabetic patients.

2. What you need to know before you use NEVANAC

Do not use NEVANAC
- if you are allergic to nepafenac or any of the other ingredients of this medicine (listed in section 6),
- if you are allergic to other nonsteroidal anti-inflammatory drugs (NSAID)
- if you have experienced asthma, skin allergy, or intense inflammation in your nose when using other NSAIDs. Examples of NSAIDs are: acetylsalicylic acid, ibuprofen, ketoprofen, piroxicam, diclofenac.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using NEVANAC:
- if you bruise easily or have bleeding problems or have had them in the past.
- if you have any other eye disorder (e.g. an eye infection) or if you are using other medicines in the eye (especially topical steroids).
- if you have diabetes.
- if you have rheumatoid arthritis.
- if you have had repeated eye surgery within a short period of time.

Avoid sunlight during treatment with NEVANAC

Wearing contact lenses is not recommended after cataract surgery. Your doctor will advise you when you can use contact lenses again (see also "NEVANAC contains benzalkonium chloride")

Children and adolescents
Do not give this medicine to children and adolescents below 18 years old because the safety and efficacy in this population has not been established.

Other medicines and NEVANAC
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

NEVANAC can affect or be affected by other medicines you are using, including other eye drops for the treatment of glaucoma.

Also tell your doctor if you are taking medicines that reduce blood clotting (warfarin) or other NSAIDs. They may increase the risk of bleeding.

Pregnancy and breast-feeding
If you are pregnant, or might get pregnant, talk to your doctor before you use NEVANAC. Women who may become pregnant are advised to use effective contraception during NEVANAC treatment. The use of NEVANAC is not recommended during pregnancy. Do not use NEVANAC unless clearly indicated by your doctor.

If you are breast-feeding, NEVANAC may pass into your milk. However, no effects on breast-fed children are anticipated. NEVANAC can be used during breast-feeding.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Do not drive or use machines until your vision is clear. You may find that your vision is blurred for a time just after using NEVANAC.

NEVANAC contains benzalkonium chloride

This medicine contains 0.25 mg benzalkonium chloride in each 5 ml which is equivalent to 0.05 mg/ml.

The preservative in NEVANAC, benzalkonium chloride, may be absorbed by soft contact lenses and may change the colour of the contact lenses. You should remove contact lenses before using this medicine and put them back 15 minutes afterwards. Benzalkonium chloride may also cause eye irritation, especially if you have dry eyes or disorders of the cornea (the clear layer at the front of the eye). If you feel abnormal eye sensation, stinging or pain in the eye after using this medicine, talk to your doctor.

3. How to use NEVANAC

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Only use NEVANAC for your eyes. Do not swallow or inject.

The recommended dose is
One drop in the affected eye or eyes, three times a day - morning, midday, and evening. Use at the same time each day.

When to take and for how long
Begin 1 day before cataract surgery. Continue on the day of surgery. Then use it for as long as your doctor tells you to. This may be up to 3 weeks (to prevent and relieve eye pain and inflammation) or 60 days (to prevent the development of macular oedema) after your operation.

How to use
Wash your hands before you start.


1


2

- Shake well before use.
- Twist off the bottle cap.
- After cap is removed, if tamper evident snap collar is loose, remove before using product.
- Hold the bottle, pointing down, between your thumb and fingers.
- Tilt your head back.
- Pull down your lower eyelid with a clean finger, until there is a 'pocket' between the eyelid and your eye. The drop will go in here (picture 1).
- Bring the bottle tip close to the eye. Do this in front of a mirror if it helps.
- Do not touch your eye or eyelid, surrounding areas or other surfaces with the dropper. It could infect the drops.
- Gently press on the base of the bottle to release one drop of NEVANAC at a time.
- Do not squeeze the bottle: it is designed so that a gentle press on the bottom is all that it needs (picture 2).

If you use drops in both eyes, repeat the steps for your other eye. Close the bottle cap firmly immediately after use.

If a drop misses your eye, try again.

If you are using other eye drops, wait at least five minutes between using NEVANAC and the other drops.

If you use more NEVANAC than you should
Contact your doctor for detailed instructions. Do not put in any more drops until it is time for your next regular dose.

If you forget to use NEVANAC
Use a single dose as soon as you remember. If it is almost time for the next dose, leave out the missed dose and continue with the next dose of your regular routine. Do not use a double dose to make up for a forgotten dose. Do not use more than one drop in the affected eye(s) 3 times daily.

If you stop using NEVANAC
Do not stop using NEVANAC without speaking to your doctor first. You can usually carry on using the drops, unless you experience serious side effects. If you are worried talk to your doctor or pharmacist.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

There may be a higher risk of corneal side effects (eye surface problems) if you have:

- complicated eye surgery
- repeated eye surgery within a short period of time
- certain disorders of the surface of the eye, such as inflammation or dry eye
- certain general disease, such as diabetes or rheumatoid arthritis

Contact your doctor immediately if your eyes become more red or more painful whilst using the drops. This may be a result of inflammation on the eye surface with or without loss or damage of cells or an inflammation of the coloured part of the eye (iritis). These side effects have been observed in up to 1 in 100 people.

The following side effects have also been observed with NEVANAC 1 mg/ml eye drops, suspension or NEVANAC 3 mg/ml eye drops, suspension, or both.

Uncommon *(may affect up to 1 in 100 people)*

- **Effects in the eye:** eye surface inflammation with or without loss or damage of cells, foreign body sensation in the eyes, eyelid crusting or drooping.

Rare *(may affect up to 1 in 1 000 people)*

- **Effects in the eye**: iris inflammation, eye pain, eye discomfort, dry eye, eyelid swelling, eye irritation, itchy eye, eye discharge, allergic conjunctivitis (eye allergy), increased tear production, deposits on the eye surface, fluid or swelling at the back of the eye, eye redness.

- **General side effects:** dizziness, headache, allergic symptoms (eyelid allergic swelling), nausea, skin inflammation, redness and itching.

Not known *(frequency cannot be estimated from the available data)*

- **Effects in the eye**: damage on the surface of the eye such as thinning or perforation, impaired healing of the eye, eye surface scar, clouding, reduced vision, eye swelling, blurred vision.

- **General side effects:** vomiting, increased blood pressure.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store NEVANAC

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and the carton after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

Throw away the bottle 4 weeks after first opening, to prevent infections. Write the date of opening on the bottle and carton label in the space provided.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What NEVANAC contains
- The active substance is nepafenac. One ml of suspension contains 1 mg of nepafenac.
- The other ingredients are benzalkonium chloride (see section 2), carbomer, disodium edetate, mannitol, purified water, sodium-chloride and tyloxapol.
  Tiny amounts of sodium hydroxide and/or hydrochloric acid are added to keep acidity levels (pH levels) normal.

What NEVANAC looks like and the contents of the pack
NEVANAC is a liquid (light yellow to light orange suspension) supplied in a pack containing one 5 ml plastic bottle with a screw cap.

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

Manufacturer
Novartis Manufacturing NV
Rijksweg 14
2870 Puurs-Sint-Amands
Belgium

Novartis Pharma GmbH
Roonstraβe 25
90429 Nuremberg
Germany

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

България
Novartis Bulgaria EOOD
Тел.: +359 2 489 98 28

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Danmark
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

Deutschland
Cranach Pharma GmbH
Tel: +49 40 3803837-10

Eesti
SIA Novartis Baltics Eesti filiaal
Tel: +372 66 30 810

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Lietuva
SIA Novartis Baltics Lietuvos filialas
Tel: +370 5 269 16 50

Luxembourg/Luxemburg
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

Magyarország
Novartis Hungária Kft.
Tel.: +36 1 457 65 00

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Nederland
Novartis Pharma B.V.
Tel: +31 88 04 52 111

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

România
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Slovenská republika
Novartis Slovakia s.r.o.
Tel: + 421 2 5542 5439

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
SIA Novartis Baltics
Tel: +371 67 887 070

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Package leaflet: Information for the user

NEVANAC 3 mg/ml eye drops, suspension
nepafenac

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What NEVANAC is and what it is used for

NEVANAC contains the active substance nepafenac, and belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs).

NEVANAC is to be used by adults:
- To prevent and relieve eye pain and inflammation following cataract surgery on the eye.
- To reduce the risk of macular oedema (swelling in the back of the eye) following cataract surgery on the eye in diabetic patients.

2. What you need to know before you use NEVANAC

Do not use NEVANAC
- if you are allergic to nepafenac or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to other nonsteroidal anti-inflammatory drugs (NSAID)
- if you have experienced asthma, skin allergy, or intense inflammation in your nose when using other NSAIDs. Examples of NSAIDs are: acetylsalicylic acid, ibuprofen, ketoprofen, piroxicam, diclofenac.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using NEVANAC:
- if you bruise easily or have bleeding problems or have had them in the past
- if you have any other eye disorder (e.g. an eye infection) or if you are using other medicines in the eye (especially topical steroids)
- if you have diabetes
- if you have rheumatoid arthritis
- if you have had repeated eye surgery within a short period of time.

Avoid sunlight during treatment with NEVANAC.

Wearing contact lenses is not recommended after cataract surgery. Your doctor will advise you when you can use contact lenses again (see also "NEVANAC contains benzalkonium chloride").

Children and adolescents
Do not give this medicine to children and adolescents below 18 years old because the safety and efficacy in this population has not been established.

Other medicines and NEVANAC
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

NEVANAC can affect or be affected by other medicines you are using, including other eye drops for the treatment of glaucoma.

Also tell your doctor if you are taking medicines that reduce blood clotting (warfarin) or other NSAIDs. They may increase the risk of bleeding.

Pregnancy and breast-feeding
If you are pregnant, or might get pregnant, talk to your doctor before you use NEVANAC. Women who may become pregnant are advised to use effective contraception during NEVANAC treatment. The use of NEVANAC is not recommended during pregnancy. Do not use NEVANAC unless clearly indicated by your doctor.

If you are breast-feeding, NEVANAC may pass into your milk. However, no effects on breast-fed children are anticipated. NEVANAC can be used during breast-feeding.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Do not drive or use machines until your vision is clear. You may find that your vision is blurred temporarily just after using NEVANAC.

NEVANAC contains benzalkonium chloride

This medicine contains 0.15 mg benzalkonium chloride in each 3 ml which is equivalent to 0.05 mg/ml.

The preservative in NEVANAC, benzalkonium chloride, may be absorbed by soft contact lenses and may change the colour of the contact lenses. You should remove contact lenses before using this medicine and put them back 15 minutes afterwards. Benzalkonium chloride may also cause eye irritation, especially if you have dry eyes or disorders of the cornea (the clear layer at the front of the eye). If you feel abnormal eye sensation, stinging or pain in the eye after using this medicine, talk to your doctor.

3. How to use NEVANAC

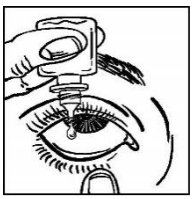
Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Only use NEVANAC for your eyes. Do not swallow or inject.

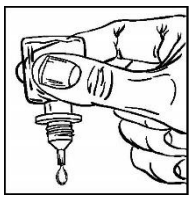
The recommended dose is
One drop in the affected eye or eyes, once a day. Use at the same time each day.

When to take and for how long
Begin 1 day before cataract surgery. Continue on the day of surgery. Then use it for as long as your doctor tells you to. This may be up to 3 weeks (to prevent and relieve eye pain and inflammation) or 60 days (to prevent the development of macular oedema and to improve vision) after your operation.

How to use
Wash your hands before you start.



1



2

- Shake well before use.
- Turn the closed bottle upside down and shake down once before each use.
- Twist off the bottle cap.
- After cap is removed, if a tamper evident snap collar is present and is loose, remove before using product.
- Hold the bottle, pointing down, between your thumb and fingers.
- Tilt your head back.
- Pull down your lower eyelid with a clean finger, until there is a 'pocket' between the eyelid and your eye. The drop will go in here (picture 1).
- Bring the bottle tip close to the eye. Do this in front of a mirror if it helps.
- Do not touch your eye or eyelid, surrounding areas or other surfaces with the dropper. It could infect the drops.
- Gently squeeze the sides of the bottle until one drop is released into your eye (picture 2).

If you use drops in both eyes, repeat the steps for your other eye. It is not necessary to close and shake the bottle between administrations for both eyes. Close the bottle cap firmly immediately after use.

If a drop misses your eye, try again.

If you are using other eye drops, wait at least five minutes between using NEVANAC and the other drops.

If you use more NEVANAC than you should
Contact your doctor for detailed instructions. Do not put in any more drops until it is time for your next regular dose.

If you forget to use NEVANAC
Use a single dose as soon as you remember. If it is almost time for the next dose, leave out the missed dose and continue with the next dose of your regular routine. Do not use a double dose to make up for a forgotten dose. Do not use more than one drop in the affected eye(s).

If you stop using NEVANAC
Do not stop using NEVANAC without speaking to your doctor first. You can usually carry on using the drops, unless you experience serious side effects.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

There may be a higher risk of corneal side effects (eye surface problems) if you have:

- complicated eye surgery
- repeated eye surgery within a short period of time
- certain disorders of the surface of the eye, such as inflammation or dry eye
- certain general diseases, such as diabetes or rheumatoid arthritis.

Contact your doctor immediately if your eyes become more red or more painful whilst using the drops. This may be a result of inflammation on the eye surface with or without loss or damage of cells or an inflammation of the coloured part of the eye (iritis). These side effects have been observed in up to 1 in 100 people.

The following side effects have been observed with NEVANAC 3 mg/ml eye drops, suspension or NEVANAC 1 mg/ml eye drops, suspension or both.

Uncommon (*may affect up to 1 in 100 people)*

- **Effects in the eye**: eye surface inflammation with or without loss or damage of cells, foreign body sensation in the eyes, eyelid crusting or drooping.

Rare (*may affect up to 1 in 1 000 people)*

- **Effects in the eye**: iris inflammation, eye pain, eye discomfort, dry eye, eyelid swelling, eye irritation, itchy eye, eye discharge, allergic conjunctivitis (eye allergy), increased tear production, deposits on the eye surface, fluid or swelling at the back of the eye, eye redness.

- **General side effects**: dizziness, headache, allergic symptoms (eyelid allergic swelling), nausea, skin inflammation, redness and itching.

Not known *(frequency cannot be estimated from the available data)*

- **Effects in the eye**: damage of the surface of the eye such as thinning or perforation, impaired healing of the eye, eye surface scar, clouding, reduced vision, eye swelling, blurred vision.

- **General side effects**: vomiting, increased blood pressure.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store NEVANAC

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and the carton after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C. Keep the bottle in the outer carton in order to protect from light.

Throw away the bottle 4 weeks after first opening, to prevent infections. Write the date of opening on the carton label in the space provided.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What NEVANAC contains
- The active substance is nepafenac. One ml of suspension contains 3 mg of nepafenac.
- The other ingredients are boric acid, propylene glycol, carbomer, sodium chloride, guar, carmellose sodium, disodium edetate, benzalkonium chloride (see section 2) and purified water. Tiny amounts of sodium hydroxide and/or hydrochloric acid are added to keep acidity levels (pH levels) normal.

What NEVANAC looks like and contents of the pack
NEVANAC eye drops, suspension (eye drops) is a liquid (light yellow to dark orange suspension) supplied in a plastic bottle with a screw cap. Each bottle may be placed in a pouch.

Each pack contains one bottle of 3 ml.

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

Manufacturer
Novartis Manufacturing NV
Rijksweg 14
2870 Puurs-Sint-Amands
Belgium

Novartis Pharma GmbH
Roonstraβe 25
90429 Nuremberg
Germany

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

България
Novartis Bulgaria EOOD
Тел.: +359 2 489 98 28

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Danmark
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

Deutschland
Cranach Pharma GmbH
Tel: +49 40 3803837-10

Eesti
SIA Novartis Baltics Eesti filiaal
Tel: +372 66 30 810

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Lietuva
SIA Novartis Baltics Lietuvos filialas
Tel: +370 5 269 16 50

Luxembourg/Luxemburg
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

Magyarország
Novartis Hungária Kft.
Tel.: +36 1 457 65 00

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Nederland
Novartis Pharma B.V.
Tel: +31 88 04 52 111

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

România
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Slovenská republika
Novartis Slovakia s.r.o.
Tel: + 421 2 5542 5439

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
SIA Novartis Baltics
Tel: +371 67 887 070

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu