NEW ZEALAND DATA SHEET

1. PRODUCT NAME

NEVANAC™ (nepafenac) Eye Drops 0.1%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nevanac contains 1 mg in 1 mL of nepafenac.

Excipient with known effect

Benzalkonium chloride 0.05 mg in 1 mL as a preservative.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, suspension. Physiological pH of approximately 7.4.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Nevanac Eye Drops 0.1% are indicated for:

- inhibition and treatment of pain and inflammation associated with cataract surgery
- reduction in the risk of post-operative macular oedema associated with cataract surgery in diabetic patients.

4.2. Dose and method of administration

For ocular use only.

Shake well before use. One drop of Nevanac Eye Drops 0.1% should be applied to the affected eye(s) three-times-daily beginning 1 day prior to cataract surgery and continued on the day of surgery and through the first 2 weeks of the postoperative period.

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.

If more than one topical ophthalmic medical product is being used, the medicinal products must be administered at least 5 minutes apart. Eye ointments should be administered last.

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

After the cap is removed, if the tamper evident snap collar is loose, remove before using Nevanac Eye Drops 0.1%.

To prevent contamination of the dropper tip and solutions, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle. Instruct patients to keep the bottle tightly closed when not in use.

Nevanac has been safely administered in conjunction with other ophthalmic medications such as antibiotics, anaesthetics, beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics and mydriatics.

Contact lenses

Nevanac Eye Drops 0.1% should not be administered while wearing contact lenses. If
patients continue to wear soft (hydrophilic) contact lenses while under treatment with Nevanac they should remove their lens(es) prior to instilling Nevanac in the affected eye(s) and should not insert their lens(es) until 15 minutes after instillation of the eye drops.

4.3. **Contraindications**

Nevanac Eye Drops 0.1% are contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation or to other NSAIDs.

See Section 6.1. List of excipients.

4.4. **Special warnings and precautions for use**

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives and other nonsteroidal anti-inflammatory agents. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

With some nonsteroidal anti-inflammatory drugs including Nevanac, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ophthalmic NSAIDs may cause increased bleeding of ocular tissues (including hyphaemas) in conjunction with ocular surgery.

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including Nevanac, 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.

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs including Nevanac and should be closely monitored for corneal health.

Postmarketing 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 events 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.

Postmarketing experience with topical NSAIDs also suggests that use more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk for occurrence and severity of corneal adverse events.

It is recommended that Nevanac Eye Drops 0.1% be used with caution in patients with known bleeding tendencies or who are receiving medications which may prolong bleeding time.

Nevanac contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Patients should be advised not to wear contact lenses during treatment with Nevanac. Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Close monitoring is required with frequent and/or prolonged use.
Actions the health care professional should take
Systemic absorption can be minimised if patients are instructed to gently occlude the nasolacrimal ducts for two minutes immediately after instillation of the eye drop.

Paediatric use
The safety and effectiveness of Nevanac Eye Drops 0.1% in paediatric patients below the age of 10 years have not been established. Its use is not recommended in these patients until further data become available.

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

Hepatic/Renal Impairment
Nepafenac has not been studied in patients with hepatic disease or renal impairment. No dosage alteration of Nevanac Eye Drops 0.1% is necessary in these patients.

4.5 Interactions with other medicinal products and other forms of interactions
Nepafenac at concentrations up to 300 ng/mL did not inhibit the in vitro metabolism of 6 specific marker substrates of cytochrome P450 (CYP) isozymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4). Therefore, drug-drug interactions involving CYP-mediated metabolism of concomitantly administered drugs are unlikely. Drug-drug interactions mediated by protein binding are also unlikely.

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

Drug-Drug Interaction
Nepafenac at concentrations up to 300 ng/mL did not inhibit the in vitro metabolism of 6 specific marker substrates of cytochrome P450 (CYP) isozymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4). Therefore, drug-drug interactions involving CYP-mediated metabolism of concomitantly administered drugs are unlikely. Drug-drug interactions mediated by protein binding are also unlikely.

4.6 Fertility, pregnancy and lactation
Pregnancy
There are no adequate data regarding the use of Nepafenac on human pregnancy.

Since the systemic exposure in non-pregnant women is negligible after treatment with Nevanac, the risk during pregnancy could be considered low. Inhibition of prostaglandin synthesis may negatively affect pregnancy and/or embryonal/fetal development and/or parturition and/or postnatal development.

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

See Section 5.3. Preclinical safety studies for reproduction studies in animals

Breast-feeding
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Nevanac 0.1% Eye Drops is administered to a nursing woman. However, no effects on the nursing child are anticipated.
since the systemic exposure of the breastfeeding woman to nepafenac is negligible.

See Section 5.3. Preclinical safety studies for lactation studies in animals

**Fertility**

There are no adequate data regarding the use of Nepafenac on human fertility.

See Section 5.3. Preclinical safety studies for fertility studies in animals.

### 4.7 Effects on ability to drive or use machines

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at application, the patient must wait until their vision clears before driving or using machinery.

### 4.8 Undesirable effects

The following adverse reactions have been reported during clinical trials with Nevanac and are classified according to the subsequent 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) and very rare (< 1/10,000). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>System Organ Classification</th>
<th>MedDRA Term (v. 15.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Rare: dizziness, headache.</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Uncommon: keratitis, punctate keratitis, corneal epithelium defect, conjunctivitis allergic, eye pain, foreign body sensation in eye, eyelid margin crusting. Rare: blurred vision, photophobia, dry eye, blepharitis, eye irritation, eye pruritus, eye discharge, lacrimation.</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Rare: hypersensitivity.</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Rare: nausea.</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rare: dermatitis allergic.</td>
</tr>
</tbody>
</table>

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.

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

<table>
<thead>
<tr>
<th>System Organ Classification</th>
<th>MedDRA Preferred Term (v. 15.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye disorders</td>
<td>corneal perforation, ulcerative keratitis, corneal thinning, corneal opacity, corneal scar, impaired healing (cornea), visual acuity reduced, eye swelling, eye irritation, ocular hyperaemia.</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Vomiting.</td>
</tr>
<tr>
<td>Investigations</td>
<td>blood pressure increased.</td>
</tr>
</tbody>
</table>
Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions [https://nzphvc.otago.ac.nz/reporting](https://nzphvc.otago.ac.nz/reporting).

4.9 Overdose

No data are available in humans regarding overdosage by accidental or deliberate ingestion. The risk of overdosage by ingestion of the suspension is minimal. No toxic effects are likely to occur in the case of overdose with ocular use, nor in the event of accidental oral ingestion.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties


Mechanism of action

Nevanac Eye Drops contains nepafenac (0.1%), a nonsteroidal anti-inflammatory and analgesic prodrug. After topical ocular dosing, nepafenac penetrates the cornea and is converted by ocular tissue hydrolases to amfenac, a potent nonsteroidal anti-inflammatory drug.

Pharmacodynamic effects

Amfenac is thought to inhibit the action of prostaglandin H synthase (cyclooxygenase), an enzyme required for prostaglandin production. In rabbits, a single topical ocular dose of nepafenac (0.1%) leads to a uniform inhibition (80% to 100%) of prostaglandin formation by the iris/ciliary body. Suppression of prostaglandin E2 synthesis is maintained for a period of greater than 6 hours and is accompanied by a nearly 8 hour suppression of trauma-induced vascular leakage of the blood aqueous barrier.

Clinical efficacy and safety

In two double-masked, randomized clinical trials in which patients were dosed three-times-daily beginning one day prior to cataract surgery, and continued on the day of surgery and for the first two weeks of the postoperative period, Nevanac 0.1% Eye Drops demonstrated clinical efficacy, compared to its vehicle in treating postoperative inflammation.

Patients treated with Nevanac were less likely to have ocular pain and measurable signs of inflammation (cells and flare) in the early postoperative period through the end of treatment than those treated with its vehicle.

For ocular pain in both studies a significantly higher percentage of patients (approximately 80%) in the nepafenac group reported no ocular pain on the day following cataract surgery (day 1) compared to those in the vehicle group (approximately 50%).

Results from clinical studies indicated that Nevanac has no significant effect upon intraocular pressure; however, changes in intraocular pressure may occur following cataract surgery.

5.2 Pharmacokinetic properties
Data in healthy subjects indicate no clinically relevant or significant gender difference in the steady-state pharmacokinetics of amfenac following three-times-daily dosing of Nevanac.

Low but quantifiable plasma concentrations of nepafenac and amfenac were observed in the majority of subjects 2 and 3 hours postdose, respectively, following bilateral topical ocular TID dosing of nepafenac 0.1% Eye Drops. The mean steady-state Cmax for nepafenac and for amfenac were 0.310 ± 0.104 ng/mL and 0.422 ± 0.121 ng/mL, respectively, following ocular administration.

5.3 Preclinical safety data

Pregnancy

Reproduction studies performed with nepafenac in rabbits and rats at oral doses up to 10 mg/kg/day have revealed no evidence of teratogenicity due to nepafenac, despite the induction of maternal toxicity. At this dose, the animal plasma exposure to nepafenac and amfenac was approximately 260 and 2,400 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 80 and 680 times human plasma exposure for rabbits, respectively. In rats, maternally toxic doses ≥ 10 mg/kg were associated with dystocia, increased post-implantation loss, reduced fetal weights and growth, and reduced fetal survival.

Nepafenac has been shown to cross the placental barrier in rats. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Breast-feeding

Nevanac Eye Drops is excreted in the milk of pregnant rats.

Fertility

Nepafenac did not impair fertility when administered orally to male and female rats at 3 mg/kg (approximately 90 and 380 times the plasma exposure to the parent drug, nepafenac, and the active metabolite, amfenac, respectively, at the recommended human topical ophthalmic dose).

Carcinogenicity

Nepafenac has not been evaluated in long-term carcinogenicity studies.

Mutagenicity

Increased chromosomal aberrations were observed in Chinese hamster ovary cells exposed in vitro to nepafenac suspension. Nepafenac was not mutagenic in the Ames assay or in the mouse lymphoma forward mutation assay. Oral doses up to 5,000 mg/kg did not result in an increase in the formation of micronucleated polychromatic erythrocytes in vivo in the mouse micronucleus assay in the bone marrow of mice.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Benzalkonium chloride as a preservative
Carbomer
Disodium edetate dehydrate
Mannitol
Sodium chloride
Tyloxoapol
Hydrochloric acid and sodium hydroxide to adjust pH
Purified water.

6.2 Incompatibilities
Not known.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store below 30°C. Do not freeze.
Discard container 4 weeks after opening.

6.5 Nature and contents of container
4 mL Drop-Tainer™ dispenser with a natural low density polyethylene dispensing plug and grey polypropylene cap. Tamper evidence is provided with a shrink band around the closure and neck area of the package. The bottle contains 3 mL of solution.

6.6 Special precautions for disposal
No special requirements for disposal.

7. MEDICINE SCHEDULE
Prescription Only Medicine.

8. SPONSOR
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PO Box 99102
Newmarket
Auckland 1149
New Zealand.
Free Phone: 0800 354 335.

9. DATE OF FIRST APPROVAL
6 August 2009.

10. DATE OF REVISION OF THE TEXT

Summary Table of Changes

<table>
<thead>
<tr>
<th>Data Sheet – all.</th>
<th>Updated to Summary of Product Characteristics format.</th>
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<tr>
<td>8. Sponsor.</td>
<td>Change in sponsor from Pharmaco to</td>
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</table>
TM trademark of Novartis.