NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Diclofenac Devatis 0.1% (1 mg/ml) Eye Drops, Single Dose

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 1 mg diclofenac sodium

Excipient with known effect:
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drop, solution.
Clear and colorless solution. Free of particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Post-operative inflammation in cataract surgery and other surgical interventions.
- Prevention of cystoid macular oedema after cataract extraction with lens implantation.
- Post-traumatic inflammation in non-penetrating wounds.
- Inhibition of miosis in cataract surgery.
- Relief of pain and photophobia.
- Non-infected inflammatory conditions of the anterior segment of the eye.

4.2 Dose and Method of Administration

Adults
a) Ocular surgery and its complications
Preoperatively, up to 1 drop 5 times during the 3 hours before surgery.
Postoperatively, 1 drop 3 times on the day of surgery, followed by 1 drop 3 to 5 times daily for as long as required.
b) Relief of pain and photophobia; post-traumatic inflammation
One drop 4 to 6 hourly.
When pain is due to a surgical procedure (e.g. refractive surgery), 1 to 2 drops in the hour preceding surgery, 1 to 2 drops within the first 15 minutes after intervention and 1 drop 4 to 6 hourly for 3 days thereafter.

Elderly
There is no indication that the dosage needs to be modified for the elderly.

Paediatric use
Diclofenac Devatis Eye Drops is not indicated for use in children. Pediatric experience is limited to a few published clinical studies in strabismus surgery.

Instructions for use and handling
The dispenser remain sterile until the original closure is broken. Patients must be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures as this may contaminate the solution.

4.3 Contraindications

Known hypersensitivity to the active substance or to any of the excipients listed under section 6.1.

As with other non-steroidal anti-inflammatory agents, Diclofenac Devatis Eye Drops is contraindicated in patients in whom attacks of asthma, urticaria or acute rhinitis are precipitated by aspirin or by other drugs with prostaglandin synthesis inhibiting activity. There is the potential for cross- sensitivity to aspirin, phenylacetic acid derivatives, and other non-steroidal anti-inflammatory agents.

4.4 Special warning and precautions for use

The anti-inflammatory activity of ophthalmic non-steroidal anti-inflammatory agents (NSAIDs) including diclofenac may mask the onset and/or progression of ocular infections. In the presence of an infection or if there is a risk of infection, appropriate therapy should be given concurrently with Diclofenac Devatis Eye Drops. Although there have been no reported adverse events, there is a theoretical possibility that patients receiving other medications which may prolong bleeding time, or with known haemostatic defects may experience exacerbation with Diclofenac Devatis Eye Drops.

Topical NSAIDs are known to slow or delay healing. Topical ophthalmic corticosteroids may slow corneal wound healing. Caution should be exercised when topical NSAIDs such as diclofenac are used concomitantly with topical steroids (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Eye drops are not for injection. They should never be injected subconjunctivally, nor should they be directly introduced into the anterior chamber of the eye.

Patients with evidence of corneal epithelial breakdown should immediately discontinue use of Diclofenac Devatis Eye Drops and should be monitored closely for corneal health.

Diclofenac Devatis Eye Drops should not be used while wearing soft contact lenses. The lenses must be removed before application of the drops and not reinserted earlier than 15 minutes after use.

The wearing of contact lenses is discouraged during treatment of an ocular inflammation.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of topical NSAIDs such as diclofenac and topical steroids in patients with significant pre-existing corneal inflammation may increase the risk of developing corneal complications including slow or delay corneal healing, therefore caution should be used.

Concomitant use of Diclofenac Devatis Eye Drops with medications that prolong bleeding time may increase the risk of hemorrhage.

Ocular diclofenac at 0.1% has been used safely in clinical studies in combination with antibiotics and beta-blocking agents for ocular use.

4.6 Fertility, Pregnancy and lactation

Pregnancy
Category C

Risk summary
No reproductive toxicity studies have been conducted with Diclofenac Devatis Eye Drops. There are insufficient data on the use of diclofenac in pregnant women.

Diclofenac has been shown to cross the placental barrier in humans.

Diclofenac Devatis Eye Drops should not be used during the third trimester of pregnancy, due to possible risk of premature closure of the ductus arteriosus and possible inhibition of contractions.

Diclofenac Devatis Eye Drops should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the fetus.

In addition, data from epidemiological studies suggest an increased risk of miscarriage after the use of prostaglandin synthesis inhibitors in early pregnancy.

Animal fertility and reproductive studies are included in Section 5.3. Preclinical safety data.

Breast-feeding
There is insufficient information on the excretion of diclofenac in human milk after the use of Diclofenac Devatis Eye Drops. Following oral administration of 50 mg coated tablets only traces of the active substance were detected in breast milk and in quantities so small that no undesirable effects on the infant are to be expected. Use of ocular diclofenac is not recommended during breast-feeding unless the expected benefits outweigh the possible risks.

Fertility
Studies have not been performed to evaluate the effect of topical ocular administration of Diclofenac Devatis Eye Drops on human fertility.

Diclofenac administered to male and female rats at 4 mg/kg/day (41 times the MROHD based on BSA comparison) did not affect fertility.

As with other NSAIDs, the use of Diclofenac Devatis Eye Drops may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Diclofenac Devatis Eye Drops should be considered. Diclofenac has negligible absorption after administration, compared to oral administration.

4.7 Effects on ability to drive and use machines
Patients experiencing blurred vision or other visual disturbances should refrain from driving a vehicle or operating machines until vision clears.

4.8 Undesirable effects
The most frequently observed adverse reaction is a transient, mild to moderate eye irritation.

Other less frequently observed reactions are eye pain, eye pruritus, ocular hyperemia and blurred vision immediately after instillation of the eye drops.

Punctate keratitis or corneal disorders have been observed, usually after frequent application. In patients with risk factors of corneal disorders such as during the use of corticosteroids or with concomitant diseases such as infections or rheumatoid arthritis, diclofenac has been associated, in rare cases, with ulcerative keratitis, corneal thinning, punctate keratitis, corneal epithelium defect and corneal edema, which might become sight-threatening. Most patients were treated for a prolonged period of time.

In rare cases dyspnea and exacerbation of asthma have been reported.

Allergic conditions has been reported such as conjunctival hyperemia, allergic conjunctivitis, eyelid erythema, eye allergy, eyelid oedema, eyelid pruritus, urticaria, rash, eczema, erythema, pruritus, hypersensitivity, cough and rhinitis.

Post Marketing Experience
The following adverse reactions have been reported during clinical studies with diclofenac sodium 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.

Eye disorders
Common (≥ 1% to < 10%): punctate keratitis, eye pain, eye irritation, eye pruritus, conjunctival hyperemia.
Uncommon (≥ 0.1% to < 1%): keratitis, intraocular pressure increased, corneal oedema, conjunctival oedema, corneal deposits, conjunctival follicles, ocular discomfort, eye discharge, eyelid margin crusting, lacrimation increased, eyelid irritation, ocular hyperemia.

Immune system disorders
Uncommon (≥ 0.1% to < 1%): hypersensitivity

General disorders and administration site conditions
Uncommon (≥ 0.1% to < 1%): impaired healing

The following adverse reactions have been identified from post-marketing surveillance following administration of Diclofenac sodium. Frequency cannot be estimated from the available data. Within each System Organ Class adverse reactions are presented in order of decreasing seriousness.

Eye disorders
Not known: corneal perforation, ulcerative keratitis, corneal epithelium defect, corneal opacity, corneal thinning, allergic conjunctivitis, eye allergy, eyelid erythema, eyelid oedema, eyelid pruritus, vision blurred.

Infections and infestations
Not known: rhinitis

Respiratory, thoracic and mediastinal disorders
Not known: asthma exacerbations, dyspnoea, cough

Skin and subcutaneous tissue disorders
Not known: urticaria, rash, eczema, erythema, pruritus

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.

4.9 Overdose
There is no experience of overdose with Diclofenac Devatis Eye Drops. However, inadvertent oral ingestion carries a minimal risk of adverse effects as a single dose unit of Diclofenac Devatis Eye Drops contains only 0.3 mg diclofenac sodium, corresponding to about 0.2% of the recommended maximum oral daily dose for an adult.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Ophthalmologicals; anti-inflammatory agents, non-steroids,
ATC code: S01BC03

Mechanism of Action
Diclofenac Devatis Eye Drops contains diclofenac sodium, a non-steroidal anti-inflammatory agent with analgesic properties. It has marked prostaglandin synthesis inhibitory activity and this is thought to have an

important bearing on its mechanism of action.

Pharmacodynamic effects
Clinical trials have demonstrated that diclofenac inhibits miosis during cataract surgery and reduces ocular inflammation and pain associated with corneal epithelial defects after some types of surgical intervention.

There is no indication that diclofenac has any adverse effects on wound healing.

Clinical efficacy and safety
Not available.

5.2. Pharmacokinetic properties

In rabbits, peak concentrations of ^{14}C-labeled diclofenac could be demonstrated in the cornea and conjunctiva 30 minutes after application. Elimination was rapid and almost complete after 6 hours.

Concentrations of HP-gamma-CD in plasma and aqueous humor were below detection limits (1 nMol/ml) in rabbits after single or four times daily (q.i.d.) ocular administration for 28 days. Low concentrations of HP-gamma-CD were detected in the aqueous humor of two rabbits (1 after single instillation, 1 after q.i.d. instillation for 28 days).

Penetration of diclofenac into the anterior chamber has been confirmed in humans. No measurable plasma levels of diclofenac could be found after ocular application of Diclofenac Devatis Eye Drops, which contains 0.1% diclofenac.

Absorption
Aqueous humor C_{max} value was reported as 82 ng/mL at 2.4 hours after ocular instillation and remained above 20 ng/mL for 4 hours with a mean residence time of 7.4 hours. No measurable plasma levels of diclofenac were observed after ocular application of 0.1% diclofenac over 4 hours.

Distribution
The volume of distribution after oral dosing for diclofenac has been reported between 0.1 to 0.2 L/kg. The high plasma protein binding (>99%) and low volume distribution suggests that diclofenac is largely confined to the central compartment.

Biotransformation
Diclofenac is metabolized by both phase I and phase II enzymes. The principal human phase I metabolite is 4-hydroxy diclofenac, primarily metabolized by cytochrome P450 2C9.

But no relationship between phenotypic expression of CYP2C9 and diclofenac's elimination has been established. A smaller percentage of other hydroxyl metabolites has been detected and phase II conjugates have been identified in the urine. Only a small percentage (<10%) of diclofenac is excreted unchanged in the urine. The reported half-life after intravenous and oral administration is only 1 to 2 hours.

Elimination
Elimination was rapid and nearly complete after 6 hours. Ocular inflammation changes diclofenac disposition in the rabbit with decreases in exposure to specific ocular tissues. Penetration of diclofenac into the anterior chamber was confirmed in humans.

5.3 Preclinical safety data
Preclinical data of systemically applied diclofenac from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, teratogenicity, carcinogenicity and reproductive performance studies revealed no specific hazard for humans at the intended therapeutic doses. Systemic diclofenac has been shown to cross the placental barrier in mice and rats, but had no influence on the fertility of parent animals in rats. In rats, maternally toxic doses were associated with dystocia, prolonged gestation, decreased fetal

survival, and intrauterine growth retardation. The slight effects of diclofenac on fertility and delivery as well as constriction of the ductus arteriosus in utero are pharmacological consequences of this class of prostaglandin synthesis inhibitors.

Local ocular tolerance and toxicity of different formulations of Diclofenac Devatis Eye Drops were investigated and no evidence of toxicity and local adverse effects was found.

Pregnancy
Systemic diclofenac has been shown to cross the placental barrier in mice and rats, but had no influence on the fertility of parent animals in rats. There was no evidence that diclofenac had a teratogenic potential in routine mice, rat or rabbit embryo-fetal development studies. In rats, maternally toxic doses were associated with dystocia, prolonged gestation, decreased fetal survival, and intrauterine growth retardation. The slight effects of diclofenac on fertility and delivery as well as constriction of the ductus arteriosus in utero are pharmacological consequences of this class of prostaglandin synthesis inhibitors.

The prenatal, perinatal and postnatal development of the offspring were not affected.

Animal studies have so far shown no risk to the fetus during the first and second trimesters of pregnancy, but no controlled studies in pregnant women are available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Macrogolglycerol ricinoleate
Boric acid (E284)
Trometamol
Water for injection

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months
After first opening of the sachet: 28 days. Store the containers in the outer carton to protect from light.
After first opening of the single-dose container: the product must be used immediately and the remaining content discarded after use.

6.4 Special precautions for storage
Do not store above 25°C.
Store in the original package in order to protect from light.
For storage conditions of the opened medicinal product, see section 6.3.

6.5 Nature and contents of container
0.3 ml transparent low density polyethylene single-dose containers in pre-formable PET/ Aluminum/ PE peelable sachets containing 5 single-dose containers.
Pack-sizes: 10 x 0.3 ml, 20 x 0.3 ml, 30 x 0.3 ml or 60 x 0.3 ml single dose containers.
Sachets are packed into carton boxes accompanied by Consumer Medicine Information.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal
No special requirements for disposal.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

DEVATIS LIMITED
Findex, 173 Spey Street,
Invercargill 9810, New Zealand
Toll Free Number: 0800 887750
www.devatis.nz

9. DATE OF FIRST APPROVAL

Date of first authorization: 09 April 2020
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

October 2024