

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Voltaren Ophtha Eye Drops 0.1%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Voltaren Multi Dose Unit Eye Drops contains diclofenac sodium 1.0mg per 1 mL.

Excipient with known effect

Benzalkonium chloride 50µg per 1 mL as a preservative.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

Slightly opalescent, slightly yellowish sterile aqueous solution.

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

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.

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

Voltaren Ophtha is not indicated for use in children. Paediatric experience is limited to a few published clinical studies in strabismus surgery.

Instructions for use and handling

The dispenser remains 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, Voltaren Ophtha 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 warnings 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 Voltaren Ophtha. 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 Voltaren Ophtha.

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 Interactions with other medicinal products and other forms of interactions).

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 Voltaren Ophtha eye drops and should be monitored closely for corneal health.

Voltaren Ophtha 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 Voltaren Ophtha Eye Drops contain benzalkonium chloride as a preservative which may cause eye irritation and is known to discolour soft contact lenses.

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

4.5 Interactions with other medicinal products and other forms of interactions

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 Voltaren Ophtha eye drops with medications that prolong bleeding time may increase the risk of haemorrhage.

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 Voltaren Ophtha. There are insufficient data on the use of diclofenac in pregnant women.

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

Voltaren Ophtha 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.

Voltaren Ophtha 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 Voltaren Ophtha. Following oral administration of 50 mg coated tablets (content of 10 x 5 mL bottles of Voltaren Ophtha) 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 Voltaren Ophtha 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 Voltaren Ophtha 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 Voltaren Ophtha should be considered. Voltaren Ophtha has negligible absorption after administration, compared to oral administration.

4.7 Effects on ability to drive or 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 hyperaemia 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 oedema, which might become

sight-threatening. Most patients were treated for a prolonged period of time.

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

Allergic conditions has been reported such as conjunctival hyperaemia, 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 Alcon clinical studies with Voltaren Ophtha and are classified according to the subsequent convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $<1/10$), uncommon ($\geq 1/1,000$ to $<1/100$), rare ($\geq 1/10,000$ 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 ($\geq 1\%$ to $< 10\%$): punctate keratitis, eye pain, eye irritation, eye pruritus, conjunctival hyperaemia.

Uncommon ($\geq 0.1\%$ 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 hyperaemia.

Immune system disorders

Uncommon ($\geq 0.1\%$ to $< 1\%$): hypersensitivity.

General disorders and administration site conditions

Uncommon ($\geq 0.1\%$ to $< 1\%$): impaired healing.

The following adverse reactions have been identified from post-marketing surveillance following administration of Voltaren Ophtha. 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 Voltaren Ophtha. However, inadvertent oral ingestion carries a minimal risk of adverse effects as a multiple dose unit of Voltaren Ophtha contains only 5 mg diclofenac sodium, corresponding to about 3%, respectively, 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

Voltaren Ophtha 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. Voltaren Ophtha multiple dose unit contains a cyclodextrin, hydroxypropyl gamma- cyclodextrin (HPgamma-CD). Cyclodextrins (CDs) increase the aqueous solubility of some lipophilic water-insoluble drugs. It is believed that CDs act as true carriers by keeping hydrophobic drug molecules in solution and delivering them to the surface of biological membranes.

Clinical efficacy and safety

Not available.

5.2 Pharmacokinetic properties

In rabbits, peak concentrations of ¹⁴C-labelled 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 Voltaren Ophtha, 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 Voltaren Ophtha were investigated and no evidence of toxicity and local adverse effects was found.

The potential for local ocular toxicity and associated systemic toxicity of Voltaren Ophtha multiple dose unit (MDU) and HPgamma-CD were investigated in a series of ocular tolerance studies in rabbits. In these studies the rabbits received up to 8 instillations of 25 microlitres of solution into the conjunctival sac of the right eye each day for up to 13 weeks. The left eye was untreated and provided a control for local effects in the treated right eye. The animals received either Voltaren Ophtha MDU with or without benzalkonium chloride or a formulation containing all of the excipients in Voltaren Ophtha MDU but containing 0.1% diclofenac potassium (instead of 0.1% diclofenac sodium) as the active ingredient or a 2% solution of HPgamma-CD in saline solution. In none of the studies was there any evidence of local adverse effects detectable by detailed ophthalmological and ocular histological examinations. There was no evidence of systemic effects in the haematology, clinical chemistry, urinalysis parameters or in the histological examination of the liver, lungs and kidneys.

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

Benzalkonium chloride
Disodium edetate
Hydroxypropyl gamma-cyclodextrin
Hydrochloric acid
Propylene glycol
Trometamol
Tyloxapol
Water for injections.

6.2 Incompatibilities

Not known.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 25° C. Do not freeze. Store upright.

Discard container 4 weeks after opening.

6.5 Nature and contents of container

5 mL white-coloured LDPE bottle fitted with a LDPE dropper and a HDPE closure.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Only Medicine.

8. SPONSOR

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9. DATE OF FIRST APPROVAL

19 October 2006

10. DATE OF REVISION OF THE TEXT

2 November 2022

Summary Table of Changes

Section changed	Summary of new information
4.6 Fertility, pregnancy and lactation	Changes include: text about crossing of placental barrier, fertility, use in first two trimesters of pregnancy.
5.2 Pharmacokinetic properties	Added sub sections Absorption, Distribution, Biotransformation, Elimination

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