

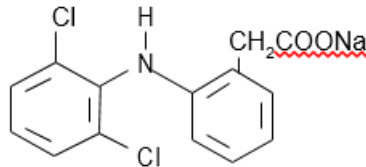
VOLTAREN* OPHTHA

Eye Drops

(diclofenac sodium)

NAME OF THE MEDICINE

Active ingredient:	diclofenac sodium
Chemical name:	sodium [2-(2,6-dichloroanilino)phenyl] acetate, a phenylacetic acid derivative
Molecular formula:	C ₁₄ H ₁₀ Cl ₂ NNaO ₂
CAS number:	15307-79-6
Molecular weight:	318.1
Structural formula:	



DESCRIPTION

Diclofenac sodium is a yellowish-white, odourless, crystalline powder sparingly soluble in water.

Excipients:

Multidose bottle: Benzalkonium chloride 50µg/mL as preservative, disodium edetate, hydroxypropyl gamma cyclodextrin, hydrochloric acid, propylene glycol, trometamol, tyloxapol and water for injections.

Single dose units: PEG-35 castor oil, boric acid, trometamol and water for injections.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: anti-inflammatory agents, ATC code: S01BC03

VOLTAREN* Ophtha eye drops contain diclofenac sodium, a non-steroidal compound with anti-inflammatory and analgesic properties.

Inhibition of prostaglandin biosynthesis, which has been demonstrated experimentally, is regarded as having an important bearing on its mechanism of action. Prostaglandins play a major role in the causation of inflammation and pain.

In clinical trials VOLTAREN* Ophtha has been found to inhibit miosis during cataract surgery and to reduce inflammation following surgical interventions.

The effective daily dose after ocular application of VOLTAREN Ophtha eye drops (approx. 0.25-0.5 mg diclofenac sodium) corresponds less than 1% of the daily dose recommended for VOLTAREN in rheumatic indications.

The benzalkonium chloride containing formulation of VOLTAREN Ophtha multidose bottle contains a cyclodextrin, hydroxypropyl gamma cyclodextrin. Cyclodextrins (CDs) increase

the aqueous solubility of some lipophilic water-soluble 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.

Pharmacokinetics

In rabbits peak concentrations of ¹⁴C-labelled diclofenac could be demonstrated in the cornea and conjunctiva 30 minutes after application. The highest amounts are found in these two tissues and in the choroid and retina.

Penetration of diclofenac into the anterior chamber has been confirmed in humans. No measurable plasma levels of diclofenac (limit of detection 10 ng/mL) could be found in 22 human subjects after ocular application of a multidose formulation of 0.1% diclofenac sodium eye drops preserved with sorbic acid.

The pharmacokinetics of the reformulated multidose product were not studied in humans and were not compared with the pharmacokinetics of the original multidose formulation.

CLINICAL TRIALS

The safety and efficacy of the reformulated multidose product were compared to the original multidose formulation in a prospective, 2:1 randomised, double-masked, parallel group trial in 299 patients undergoing cataract phacoemulsification and intraocular lens implantation. The study medications were instilled in the operated eye 4 times in the 30 minutes leading to surgery followed by 4 times daily for 4 weeks post-operatively. Equivalence of the two formulations was demonstrated with respect to anterior chamber flare (primary efficacy criterion) in ITT and PP populations. Results for the primary efficacy criterion are summarised in Table 1.

Table 1: Anterior chamber flare measured by flare meter

Timepoint	New Formulation Mean (Change from Day 1) (n=164*)	Original Formulation Mean (Change from Day 1) (n=87*)	Between Patient Difference and 95% CI (New - Original Formulation)
Day 1	16.98	15.97	
Day 6-8	12.87 (-4.21)	13.23 (-2.78)	-1.15 (-3.03, 0.73)
Day 24-32	9.58 (-7.50)	9.21 (-6.75)	0.35 (-1.13, 1.82)

* Per protocol population including all subjects who completed the study without any systemic NSAID, glucocorticosteroids or latanoprost.

A negative difference indicates that the new formulation had a greater mean decrease in anterior chamber flare than did the original formulation.

INDICATIONS

Reduction of post-operative inflammation in cataract surgery and other surgical interventions.

The single dose units can also be used to inhibit operative miosis during cataract surgery.

CONTRAINDICATIONS

Patients with known hypersensitivity to diclofenac or other components of the medication.

Like other non-steroidal anti-inflammatory agents, VOLTAREN* Ophtha eye drops is also

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

PRECAUTIONS

As with other topically applied ophthalmic drugs, this drug may be absorbed systemically. However, in considering potential systemic toxicity, it should be noted that the effective daily dose of VOLTAREN Ophtha eye drops after ophthalmic administration corresponds to less than 1% of the daily dose recommended for VOLTAREN in rheumatic indications. In addition, application of 2 drops of 0.1% diclofenac sodium solution to each eye of healthy humans resulted in blood levels below the detection limit (10 ng/mL).

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 infection, or if there is a risk of infection, appropriate therapy (eg. antibiotics) should be given concurrently with VOLTAREN Ophtha eye drops.

Patients with evidence of corneal epithelial breakdown should immediately discontinue use of VOLTAREN* Ophtha eye drops and should be monitored closely for corneal health.

Administer with caution in the presence of active gastrointestinal lesions or a history of recurrent gastrointestinal lesions.

There is a potential for increased bleeding time due to interference with thrombocyte aggregation with non-steroidal anti-inflammatory drugs. There have been reports (with other NSAIDs) of increased bleeding of ocular tissues in conjunction with ocular surgery. Caution should be used in surgical patients with known bleeding tendencies or who are receiving other medications that may prolong bleeding time.

There is a possibility that patients receiving other medications which may prolong bleeding time, or with known haemostatic defects may experience exacerbation with VOLTAREN Ophtha 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 **Interactions with Other Medicines**).

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.

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 multidose product contains benzalkonium chloride as a preservative; benzalkonium chloride may cause irritation and is known to discolour soft contact lenses. 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 wearing of contact lenses is discouraged during treatment of an ocular inflammation.

Carcinogenicity and Mutagenicity

Dietary administration of diclofenac to mice and rats at doses up to 0.5 mg/kg/day revealed no carcinogenic activity. However, the plasma concentration of diclofenac at this dose level

was 20 to 100 times lower than that in humans after oral administration. Administration of higher doses to rats and mice resulted in increased mortality due to gastrointestinal ulceration. Diclofenac showed no mutagenic effects in the studies conducted.

Effects on Fertility

Studies have not been performed to evaluate the effect of topical ocular administration of VOLTAREN* Ophtha on human fertility. Animal studies suggest that prostaglandins are necessary for implantation. Therefore, long-term use of NSAIDs by prescription for chronic non-reproductive disorders and continuing use of over-the-counter NSAIDs preparations, while trying to conceive, could potentially adversely affect the peri-implantation process and outcome.

Use in Pregnancy (Category C)

NSAIDs inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, and delay labour and birth. VOLTAREN Ophtha 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. During the last few days before expected birth, agents with an inhibitory effect on prostaglandin synthesis should be avoided.

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

Safety of diclofenac sodium in human pregnancy has not been established. Therefore VOLTAREN Ophtha should not be used in pregnant women or in those likely to become pregnant unless the expected benefits are likely to outweigh any possible risk.

Use in Lactation

No measurable amounts of active substance are to be expected in the breast milk of nursing mothers. However, since no experience has been acquired with VOLTAREN Ophtha during lactation, it is not recommended for use in this circumstance.

Paediatric use

VOLTAREN Ophtha is not indicated for use in children as safety and effectiveness have not been demonstrated in children.

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.

INTERACTIONS WITH OTHER MEDICINES

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.

A previous formulation of this product, which also contained 0.1% diclofenac sodium, has been used safely in clinical studies in combination with antibiotics and beta-blocking agents for ocular use.

Concomitant administration of voriconazole with diclofenac may increase plasma diclofenac levels.

Concomitant use of VOLTAREN* Ophtha eye drops with medications that prolong bleeding time may increase the risk of haemorrhage.

ADVERSE EFFECTS

In clinical studies with VOLTAREN Ophtha eye drops, the following adverse events have been reported:

Incidence greater than 10 %	- a mild to moderate eye irritation (approximately 13%).
Incidence 1 to 10 %	- keratitis/punctate keratitis/ulceration (approximately 2%). - elevated intraocular pressure, particularly in patients post-surgery, but not at a frequency consistently higher than placebo-treated patients.
Incidence less than 1%	- blurred vision immediately after instillation of the eye drops; hypersensitivity reactions with pruritis and ocular hyperaemia; photosensitivity. - permanent post-operative mydriasis has been reported (a causality has not been established). - systemic reactions have been reported at a rate (1%) not significantly higher than in placebo-treated patients.

Corneal disorders have also been reported 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 epithelial defect or corneal oedema which may 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 such as conjunctival hyperaemia, allergic conjunctivitis, eyelid erythema, eye allergy, eyelid oedema, eyelid pruritis, urticaria, rash, eczema, erythema, pruritis, hypersensitivity, cough and rhinitis have been reported. Another less frequently observed reaction is eye pain.

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

DOSAGE AND ADMINISTRATION

Adults Pre-operatively: up to 5 drops during 3 hours before surgery.

Post-operatively: 1 drop 3 times on the day of surgery, followed by 1 drop 3 to 5 times daily.

The preservative free formulation should be used if patients have shown previous sensitivity to benzalkonium chloride or when product is used pre-operatively for operative miosis.

Although systemic absorption of diclofenac sodium has been found to be minimal following ocular application, as a general precaution to reduce systemic absorption, pressure should be applied to the tear-duct immediately after application.

In clinical studies, effectiveness was demonstrated in patients treated throughout the first two weeks of the post-operative period. In some patients with persisting signs of inflammation, treatment continued for up to four weeks for the multidose bottle and sixty days for the single dose units post-operatively.

To prevent the active substances from being washed out when additional ophthalmic medication is used, an interval of at least 5 minutes between each application should be adhered to.

Instructions for Use and Handling

Multidose bottle: Store below 25°C. Protect from light. Do not freeze. The dispenser remains sterile until the original closure is broken. Discard contents four weeks after opening. Patients must be instructed to avoid allowing the tip of the dispensing container to contact the eye as this may contaminate the solution.

Single dose units: Store in the refrigerator (2-8°C) until opening an inner blister. Once the blister is open, the contents are stable for one month at room temperature (below 25°C). The contents of the single dose unit remain sterile until the original closure is broken. Discard each single dose unit immediately after use. Do not save unused contents.

OVERDOSAGE

There is no experience of overdose with VOLTAREN* Ophtha eye drops. However, accidental oral ingestion carries a minimal risk of adverse effects, since the eye drop solution in a 5mL multidose bottle contains only 5mg diclofenac sodium corresponding to about 3% of the maximum recommended daily adult dose of VOLTAREN Ophtha for oral administration. Similarly a block of 5 units contains only 1.5mg diclofenac sodium, corresponding to about 0.9% of the recommended maximum daily adult dose of VOLTAREN Ophtha for oral administration.

PRESENTATION AND STORAGE CONDITIONS

A slightly opalescent, slightly yellowish sterile aqueous solution containing diclofenac sodium 1.0mg/mL (0.1% w/v).

Multidose bottle: 3mL and 5mL (preserved with benzalkonium chloride 0.05 mg/mL).

Single dose units: Four pack sizes containing 1 x 5, 6 x 5, 8 x 5 or 20 x 5 single dose units, i.e. packs of 5, 30, 40 or 100. Each single dose unit contains 0.3mL of solution (preservative free).

NAME AND ADDRESS OF THE SPONSOR

Alcon Laboratories (Australia) Pty Ltd

25 Frenchs Forest Road East

Frenchs Forest NSW 2086

In New Zealand this product is distributed by:

Pharmaco (NZ) Ltd

4 Fisher Crescent

Auckland 1060

New Zealand

Free Phone: 0800 101 106

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4)

DATE OF FIRST INCLUSION IN THE ARTG

20 July 2005

DATE OF MOST RECENT AMENDMENT

24 October 2017

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