NOVARTIS

Drug Regulatory Affairs

VOLTAREN® OPHTHA / VOLTAREN® OPHTHA CD

(diclofenac sodium)

0.1% Eye drops, solution

Basic Prescribing Information

NOTICE

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to the characterisation of risks and benefits.

Author(s):	Clemence Clouet-Foraison, Ariane Falconnier
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1 Name of the medicinal product

VOLTAREN® OPHTHA and VOLTAREN® OPHTHA CD, 0.1%, eye drops, solution.

2 Qualitative and quantitative composition

Voltaren® Ophtha and Voltaren® Ophtha CD: one mL contains 1 mg of diclofenac sodium.

For a full list of excipients, see section 6.1 List of excipients.

3 Pharmaceutical form

Eye drops, solution.

4 Clinical particulars

4.1 Therapeutic indications

- Post-operative inflammation in cataract surgery and other surgical interventions [1,3,7,11,12,14,17,23,28,29,32-34,47,48,57-60,63,65,70,75].
- Prevention of cystoid macular oedema after cataract extraction with lens implantation [5,62,29,51,52,56].
- Post-traumatic inflammation in non-penetrating wounds [4,69].
- Inhibition of miosis in cataract surgery [2,6,16,60,64,72,76].
- Relief of pain and photophobia [8,15,18,20,24,25,27,31,39,50,53,54,71,74,78].

4.2 Posology 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 dosage needs to be modified for the elderly.

Paediatric use: Voltaren Ophtha and Voltaren Ophtha CD are not indicated for use in children. Paediatric experience is limited to a few published clinical studies in strabismus surgery [3,70,82,83,84].

Multiple Dose Unit (MDU): 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 [85].

Single Dose Unit (SDU): The contents remain sterile until the original closure is broken. Patients must discard residual contents after use.

If more than one medication needs to be instilled in the eye, an interval of at least 5 minutes between application of the different medicinal products must be allowed.

Following instillation of the eye drops, nasolacrimal occlusion or closing the eyes for 5 minutes may reduce systemic absorption. This may result in a decrease in systemic side effects and an increase in local activity [~~87,~~88].

4.3 Contraindications

- Known hypersensitivity to the active substance or to any of the excipients (see section 6.1 List of excipients).
- As with other non-steroidal anti-inflammatory agents, both Voltaren Ophtha and Voltaren Ophtha CD are contraindicated in patients in whom attacks of asthma, urticaria or acute rhinitis are precipitated by acetylsalicylic acid or by other drugs with prostaglandin synthesis inhibiting activity. There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other non-steroidal anti-inflammatory agents [19].

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 or Voltaren Ophtha CD [89].

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 both Voltaren Ophtha and Voltaren Ophtha CD.

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) [90].

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 and Voltaren Ophtha CD 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 CD formulation contains benzalkonium chloride as a preservative which may cause eye irritation and is known to discolour soft contact lenses [91].

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, therefore caution should be used [90].

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 Pregnancy and lactation

Pregnancy

No reproductive toxicity studies have been conducted with Voltaren Ophtha or Voltaren Ophtha CD.

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-foetal development studies. In rats, maternally toxic doses were associated with dystocia, prolonged gestation, decreased foetal 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 [86].

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

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

Voltaren Ophtha and Voltaren Ophtha CD 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.

Lactation

Following oral administration of 50 mg coated tablets (content of 10 5 mL bottles of Voltaren Ophtha or Voltaren Ophtha CD) 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.

4.7 Effects on ability to drive and use machines

Patients experiencing blurred vision should refrain from driving a vehicle or operating machines.

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 [92], eye pruritus, ocular hyperaemia and blurred vision immediately after instillation of the eye drops.

Punctate keratitis or corneal disorders [68] 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, punctuate keratitis, corneal epithelium defect and corneal oedema, which might become sight-threatening [9,22,44,61,79-81,90]. Most patients were treated for a prolonged period of time.

In rare cases dyspnoea and exacerbation of asthma have been reported [66].

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 [90].

4.9 Overdose

There is no experience of overdose with Voltaren Ophtha or Voltaren Ophtha CD. However, inadvertent oral ingestion carries a minimal risk of adverse effects as a single dose unit of Voltaren Ophtha contains only 0.3 mg diclofenac sodium and a 5 mL bottle of Voltaren Ophtha CD contains only 5 mg diclofenac sodium, corresponding to about 0.2% and 3%, respectively, of the recommended maximum oral daily dose for an adult.

5 Pharmacological properties

5.1 Pharmacodynamic properties [30,73]

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

Voltaren Ophtha and Voltaren Ophtha CD contain 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 [36,37].

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 [21,46,49].

Voltaren Ophtha CD 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 [45].

5.2 Pharmacokinetic properties [10,13,35,55]

In rabbits, peak concentrations of ^{14}C-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) [86].

Penetration of diclofenac into the anterior chamber has been confirmed in humans [10]. No measurable plasma levels of diclofenac could be found after ocular application of Voltaren Ophtha, which, like Voltaren Ophtha CD, contains 0.1% diclofenac.

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 foetal 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 [86].

Local ocular tolerance and toxicity of different formulations of Voltaren Ophtha were investigated and no evidence of toxicity and local adverse effects was found.

Voltaren Ophtha CD: The potential for local ocular toxicity and associated systemic toxicity of Voltaren Ophtha CD and HPgamma-CD were investigated in a series of ocular tolerance studies in rabbits [40-43]. In these studies the rabbits received up to 8 instillations of 25 microliters of solution into the conjuctival 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 CD with or without benzalkonium chloride or a formulation containing all of the excipients in Voltaren Ophtha CD 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.

6 Pharmaceutical particulars

6.1 List of excipients

Voltaren Ophtha:

US multidose formulation (DIC 0.1%)

Macrogolglycerol ricinoleate, Boric acid, Tromethamine, Sorbic acid, Edetate disodium, Water for injections.

Unpreserved single dose units (DR 1201/1)

Macrogolglycerol ricinoleate, Boric acid, Trometamol, Water for injections.

Voltaren Ophtha CD:

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

Information might differ in some countries.

6.2 Incompatibilities

None known.

6.3 Shelf life

Voltaren Ophtha:

US multidose formulation (DIC 0.1%)

2 years.

Unpreserved single dose units (DR 1201/1)

2 years.

Voltaren Ophtha CD:

3 years.

Information might differ in some countries.

6.4 Special precautions for storage

Voltaren Ophtha:

US multidose formulation (DIC 0.1%)

Store between 59° - 86°F (15° - 30°C). Protect from light.

Unpreserved single dose units (DR 1201/1)

Do not store above 25°C.

Voltaren Ophtha CD:

Climatic zone I and II countries: No special precautions for storage.

Climatic zone III and IV countries: Do not store above 25°C.

Voltaren Ophtha and Voltaren Ophtha CD must be kept out of the reach and sight of children.

Information might differ in some countries.

6.5 Nature and contents of container

Voltaren Ophtha:

US multidose formulation (DIC 0.1%)

2.5 mL, white LDPE bottle with LDPE dropper-tip.

5.0 mL, white LDPE bottle with LDPE dropper-tip.

10.0 mL, white LDPE bottle with LDPE dropper-tip and white HDPE cap.

Unpreserved single dose units (DR 1201/1)

LDPE block containing 5 Single Dose Units filled with 0.3 ml of eye drops each.

Voltaren Ophtha CD:

The product is presented in a 5 mL white-coloured LDPE bottle fitted with a LDPE dropper and a HDPE closure.

Information might differ in some countries.

6.6 Instructions for use and handling, and disposal

No special requirements.

This is a non-referenced document.