1. NAME OF THE MEDICINAL PRODUCT

TIXXA (DICLOFENC SODIUM OPHTHALMIC SOLUTION)

2. QUALITATIVE AND QUANTITATIVECOMPOSITION

Label Claim:
Diclofenac Sodium USP.....0.1% w/v

Sorbic Acid NF .....0.2% w/v

Sterile aqueous base.....Q.S.

3. PHARMACEUTICAL FORM

Ophthalmic (Eye Drop)

4. Clinical particulars

4.1 Therapeutic indications

i. Inhibition of peroperative miosis during cataract surgery (Voltarol Ophtha has no intrinsic mydriatic properties and does not replace standard mydriatic agents).

ii. Treatment of post-operative inflammation in cataract surgery.

iii. Control of ocular pain and discomfort associated with corneal epithelial defects after excimer PRK surgery or accidental non-penetrating trauma.

iv. Control of inflammation after Argon Laser Trabeculoplasty (ALT).

v. The relief of the ocular signs and symptoms of Seasonal Allergic Conjunctivitis (SAC).

vi. Treatment of inflammation and discomfort after strabismus surgery

vii. Treatment of ocular pain and discomfort after radial keratotomy

4.2 Posology and method of administration

Voltarol Ophtha eye drop solution is for instillation into the conjunctival sac only. It should never be injected subconjunctivally, nor should it be directly introduced into the anterior chamber of the eye.

Adults:

Prophylaxis of preoperative miosis	Apply 1 drop four times during the 2 hours before surgery
Control of post-operative inflammation	Apply 1 drop 4 times daily for up to 28 days
Control of Post PRK pain and discomfort	Apply 1 drop 2 times in the hour prior to surgery, one drop 2 times five minutes apart immediately after PRK surgery and then post-operatively 1 drop every 2-5 hours while awake for up to 24 hours.
Control of ocular pain associated with	Apply one drop 4 times daily for up to 2 days.

corneal epithelial defects after non-penetrating accidental trauma.	
Control of post ALT inflammation	Apply one drop 4 times during the 2 hours before ALT, and then one drop 4 times daily for up to 7 days
The relief of the ocular signs and symptoms of Seasonal Allergic Conjunctivitis	Apply one drop 4 times daily for as long as required
Treatment of inflammation and discomfort after strabismus surgery	One drop 4 times daily in the 1st week, thrice daily in the 2nd week, twice daily in the 3rd week and as required in the 4th week.
Treatment of ocular pain and discomfort after radial keratotomy	Pre-operatively one drop before surgery Post-operatively one drop immediately after surgery and then one drop 4 times daily for up to 2 days

4.3 Contraindications

Patients with known hypersensitivity to any of the ingredients.

Like other non-steroidal anti-inflammatory agents, Voltarol Ophtha is also contraindicated in patients in whom attacks of asthma, urticaria or acute rhinitis are precipitated by acetylsalicylic acid or by other drugs with prostaglandin synthetase inhibiting activity. Intraocular use during surgical procedure is also contraindicated.

4.4 Special warnings and precautions for use

The anti-inflammatory activity of ophthalmic non-steroidal anti-inflammatory agents (NSAIDs) 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 (e.g. antibiotics) should be given concurrently with Voltarol 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 Voltarol Ophtha.

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).

Following instillation of the eye drops, nasolacrimal occlusion or closing the eyes for 3 minutes may reduce the systemic absorption. This may result in a decrease in systemic side effects and an increase in local activity.

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.

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.

4.6 Pregnancy and Lactation

Pregnancy

There are no clinical data from the use of Voltarol Ophtha or Voltarol Ophtha Multidose during pregnancy. Even if systemic exposure is lower compared with oral administration, it is not known if the systemic Voltarol Ophtha or Voltarol Ophtha Multidose exposure reached after topical administration can be harmful to an embryo/foetus.

During the first and second trimester of pregnancy, Voltarol Ophtha or Voltarol Ophtha Multidose should not be used unless clearly necessary. If used, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, systemic use of prostaglandin synthetase inhibitors including diclofenac may induce cardiopulmonary and renal toxicity in the foetus. At the end of the pregnancy prolonged bleeding time in both mother and child may occur, and labour can be delayed. Therefore, Voltarol Ophtha or Voltarol Ophtha Multidose is not recommended during the last trimester of pregnancy.

Lactation

Diclofenac is excreted in breast milk. However, at therapeutic doses of Voltarol Ophtha no effects on the suckling child are anticipated. 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 with blurred vision should refrain from driving a vehicle or operating machines.

4.8 Undesirable effects

Very frequent: Eye pain.

The other frequently observed adverse reaction is a transient, mild to moderate eye irritation.

Other less frequently observed reactions are 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, punctuate keratitis, corneal epithelium defect and corneal oedema, which might become sight-threatening. Most patients were treated for a prolonged period of time.

Allergic conditions have been reported for ocular reactions such as conjunctival hyperaemia, allergic conjunctivitis, eyelid erythema, oedema, and pruritus, and systemic hypersensitivity reactions such as urticaria, rash, eczema, erythema, pruritus, cough and rhinitis.

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

4.9 Overdose

There is practically no risk of adverse effects due to accidental oral ingestion, since the eye drop solution in a block of 10 units contains only 3mg of diclofenac sodium, corresponding to about 1.8% of the recommended maximum daily adult dose of Voltarol after oral administration. By way of comparison, the maximum oral daily dose for diclofenac sodium recommended in children is 2mg/kg body weight.

5.1 Pharmacodynamics properties

Voltarol Ophtha contains diclofenac sodium, a non-steroidal compound with pronounced 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, Voltarol Ophtha has been found to:

i. inhibit miosis during cataract surgery

ii. reduce inflammation following surgical interventions

iii. reduce ocular pain and discomfort associated with corneal epithelial defects after excimer PRK surgery or accidental non-penetrating trauma.

iv. reduce the incidence of angiographic cystoid macular oedema after cataract surgery but clinical significance remains to be established.

v. reduce ocular inflammation and discomfort more effectively than topical steroids after strabismus surgery whilst avoiding steroidal adverse effects such as delayed conjunctival wound healing and raised intraocular pressure

vi. reduce ocular inflammation, pain and discomfort (photophobia, burning/stinging, foreign body sensation, deep headache-like ocular pain and itching) more effectively than placebo eye drops after corneal incisional surgery such as radial keratotomy.

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

5.2 Pharmacokinetic properties

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. Elimination was fast and almost complete after 6 hours.

Penetration of diclofenac into the anterior chamber has been confirmed in humans. No measurable levels of diclofenac could be found in humans after ocular application of diclofenac sodium eye drops.

5.3 Preclinical safety data

Preclinical data of systemically applied diclofenac from acute and repeated dose toxicity studies, as well as from genotoxicity and carcinogenicity studies revealed no specific hazard for humans at the intended therapeutic doses.

In reproductive and developmental toxicity studies systemic diclofenac has been shown to cross the placental barrier in mice and rats. Whilst no teratogenic effects have been demonstrated, maternally toxic doses were associated with dystocia, prolonged gestation, decreased foetal survival, and intrauterine growth retardation. The effects of diclofenac on fertility and delivery as well as the constriction of the ductus arteriosus in utero are pharmacological consequences of this class of prostaglandin synthesis inhibitors

Local ocular tolerance and toxicity of Voltarol Ophtha and Voltarol Ophtha Multidose 0.1% eye drops (containing hydroxypropyl-gamma cyclodextrin) were investigated and no evidence of toxicity and local adverse effects was found.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbic Acid NF
Sodium Metabisulphite NF
Edetate Disodium NF
Propylene Glycol USP
Sodium Chloride NF
Sodium hydroxide pellets NF
Purified water BP/IH

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months for the date of manufacturing.

6.4 Special precautions for storage

Store at a temperature not exceeding 30ºC in a dry place. Protect from light. Keep out of reach of children.

6.5 Natureandcontentsofcontainer<andspecialequipmentforuse, administration

or implantation>

1 x 10 ml

6.6 Special precautions for disposal <and other handling>

There are no special storage precautions. Any unused product or waste material should be disposed of in accordance with local requirements.

7 <APPLICANT/MANUFACTURER>

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