NDA 20-809 Draft Labeling

Diclofenac Sodium Ophthalmic Solution, 0.1%

DESCRIPTION

Diclofenac Sodium Ophthalmic Solution, 0.1% is a sterile, topical, nonsteroidal, anti-inflammatory product for ophthalmic use. Diclofenac sodium is designated chemically as 2-[(2,6-dichlorophenyl)amino] benzeneacetic acid, monosodium salt, with an empirical formula of $C_{14}H_{10}C_{l2}NO_2Na$. The structural formula of diclofenac sodium is:

[Structure]

Diclofenac Sodium Ophthalmic Solution, 0.1% is available as a sterile solution which contains diclofenac sodium 0.1% (1 mg/mL).

Inactive Ingredients: POLYQUAD® (polyquaternium-1) (0.05 mg/mL), tocophersolan, boric acid, mannitol, hydrochloric acid and/or sodium hydroxide (to adjust pH to 6.7) and purified water.

Diclofenac sodium is a faintly yellow-white to light-beige, slightly hygroscopic crystalline powder. It is freely soluble in methanol, sparingly soluble in water, very slightly soluble in acetonitrile, and insoluble in chloroform and in 0.1 N hydrochloric acid. Its molecular weight is 318.14. Diclofenac Sodium Ophthalmic Solution, 0.1 % is an iso-osmotic solution with an osmolality of about 300 mOsmol/1000g.

CLINICAL PHARMACOLOGY

Animal Studies

Prostaglandins have been shown in many animal models to be mediators of certain kinds of intraocular inflammation. In studies performed in animal eyes, prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilation, increased vascular permeability, leukocytosis, and increased intraocular pressure.

Pharmacodynamics

Diclofenac sodium is one of a series of phenylacetic acids that has demonstrated anti-inflammatory and analgesic properties in pharmacological studies. It is thought to inhibit the enzyme cyclooxygenase, which is essential in the biosynthesis of prostaglandins.

Pharmacokinetics

Results from a bioavailability study of another formulation of diclofenac sodium ophthalmic solution established that plasma levels of diclofenac following ocular instillation of two drops of diclofenac sodium ophthalmic solution, 0.1 % to each eye were below the limit of quantitation (10 ng/mL) over a 4-hour period. This study suggests that limited, if any, systemic absorption occurs with diclofenac sodium ophthalmic solution, 0.1%.

Clinical Trials: Postoperative Anti-Inflammatory Effects
In a clinical therapeutic equivalence study, Diclofenac Sodium Ophthalmic Solution, 0.1% was found to be therapeutically equivalent to Voltaren Ophthalmic® (diclofenac sodium ophthalmic solution) [CIBA Vision Ophthalmics®] in the treatment of signs and symptoms of inflammation resulting from cataract surgery.

INDICATIONS AND USAGE
Diclofenac Sodium Ophthalmic Solution, 0.1% is indicated for the treatment of postoperative inflammation in patients who have undergone cataract extraction.

CONTRAINDICATIONS
Diclofenac Sodium Ophthalmic Solution, 0.1% is contraindicated in patients who are hypersensitive to any component of the medication.

WARNINGS
With some nonsteroidal anti-inflammatory drugs, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory agents. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

PRECAUTIONS
General: It is recommended that Diclofenac Sodium Ophthalmic Solution, 0.1%, like other NSAIDs, be used with caution in surgical patients with known bleeding tendencies or who are receiving other medications that may prolong bleeding time.

Diclofenac Sodium Ophthalmic Solution, 0.1% may slow or delay healing.

Results from clinical studies indicate that Diclofenac Sodium Ophthalmic Solution, 0.1% has no significant effect upon intraocular pressure, however, elevations in intraocular pressure may occur following cataract surgery.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term carcinogenicity studies in rats given oral diclofenac sodium up to 2 mg/kg/day (approximately the human oral dose) revealed no significant increases in tumor incidence. There was a slight increase in benign rat mammary fibroadenomas in mid-dose females (high dose females had excessive mortality) but the increase was not significant for this common rat tumor. A 2-year carcinogenicity study conducted in mice employing oral diclofenac sodium up to 2 mg/kg/day did not reveal any oncogenic potential. Diclofenac sodium did not show mutagenic potential in various mutagenicity studies including the Ames test. Diclofenac sodium administered to male and female rats at 4 mg/kg/day did not affect fertility.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Reproduction studies performed in mice at oral doses up to 5000 times (20 mg/kg/day) and in rats and rabbits at oral doses up to 2500 times (10 mg/kg/day) the human topical dose have revealed no evidence of teratogenicity due to diclofenac sodium, despite the induction of maternal toxicity and fetal toxicity. In rats, maternally toxic doses were associated with dystocia, prolonged gestation, reduced fetal weights and growth, and reduced fetal survival. Diclofenac sodium has been shown to cross the placental barrier in mice and rats.

There are however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic effects: Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of Diclofenac Sodium Ophthalmic Solution, 0.1% during late pregnancy should be avoided.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Ocular: Transient burning and stinging has been reported in approximately 15% of patients with the use of topical diclofenac sodium ophthalmic solution, 0.1%. In cataract studies, keratitis occurred in 28% of patients receiving diclofenac sodium ophthalmic solution, 0.1%, however, most of the cases of keratitis occurred prior to drug therapy. Elevated intraocular pressure following cataract surgery was reported in 15% of patients receiving diclofenac sodium ophthalmic solution, 0.1%. The following adverse reactions were reported in approximately 5% or less of the patients: abnormal vision, anterior chamber reaction, blurred vision, conjunctivitis, corneal deposits, corneal edema, corneal lesions, corneal opacity, discharge, injection, iritis, irritation, itching and ocular allergy.

Systemic: The following adverse reactions were reported in 3% or less of the patients: abdominal pain, asthenia, chills, dizziness, facial edema, fever, headache, insomnia, nausea, pain, rhinitis, viral infection, and vomiting.

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OVERDOSAGE
Overdosage will not ordinarily cause acute problems. If accidentally ingested, fluids should be taken to dilute the medication.

DOSAGE AND ADMINISTRATION
One drop of Diclofenac Sodium Ophthalmic Solution, 0.1% should be applied to the affected eye four times daily beginning 24 hours after cataract surgery and continuing throughout the first 2 weeks of the postoperative period.

How Supplied: Diclofenac Sodium Ophthalmic Solution, 0.1% is supplied in opaque, plastic 5 mL DROP-TAINER® dispenser (NDC 0065-0231-05).

Store between 59°-86°F (15°-30°C). Protect from light. *Dispense in original, unopened container only.*

Alcon Ophthalmic Logo
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