

DESCRIPTION:

Each ml contains:

- Ketorolac Tromethamine USP 5 mg
- Benzalkonium Chloride USP 0.1 mg

ANIMAL PHARMACOLOGY:

Ketorolac Tromethamine prevented the development of increased intraocular pressure induced in rabbits with topically applied arachidonic acid. Ketorolac did not inhibit rabbit lens aldose reductase *in vitro*.

Ketorolac Tromethamine ophthalmic solution did not enhance the spread of ocular infections induced in rabbits with *Candida albicans*, *Herpes simplex* virus type one, or *Pseudomonas aeruginosa*.

CLINICAL PHARMACOLOGY:

Ketorolac Tromethamine is a nonsteroidal anti-inflammatory drug which, when administered systemically, has demonstrated analgesic, anti-inflammatory and antipyretic activity. The mechanism of its action is thought to be due, in part, to its ability to inhibit prostaglandin biosynthesis. Ocular administration of Ketorolac Tromethamine reduces prostaglandin E₂ levels in aqueous humor. The mean concentration of PGE₂ was 80 pg/ml in the aqueous humor of eyes receiving vehicle and 28 pg/ml in eyes receiving 0.5% ACULAR™ ophthalmic solution.

Ketorolac Tromethamine given systemically does not cause pupil constriction.

Results from clinical studies indicate that ACULAR™ ophthalmic solution has no significant effect upon intraocular pressure.

Two controlled clinical studies showed that ACULAR™ ophthalmic



ACULAR™
(KETOROLAC TROMETHAMINE 0.5%)

solution was significantly more effective than its vehicle in relieving ocular.

itching caused by seasonal allergic conjunctivitis. Two drops (0.1 ml) of 0.5% ACULAR™ ophthalmic solution instilled in the eyes of patients 12 hours and 1 hour prior to cataract extraction achieved measurable levels in 8 of 9 patients eyes (mean Ketorolac concentration 95 ng/ml aqueous humor, range 40 to 170 ng/ml).

One drop (0.05 ml) of 0.5% ACULAR™ ophthalmic solution was instilled in one eye and one drop of vehicle in the other eye in 26 normal subjects. Only 5 of 26 subjects had a detectable amount of Ketorolac in their plasma (range 10.7 to 22.5 ng/ml) at day 10 during topical ocular treatment. When Ketorolac Tromethamine 10 mg is administered systemically every 6 hours, peak plasma levels at steady state are around 960 ng/ml.

ACULAR™ ophthalmic solution has been safely administered in conjunction with other ophthalmic medications, such as antibiotics, beta blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics.

INDICATIONS AND USAGE:

ACULAR™ ophthalmic solution is indicated for the relief of ocular itching due to seasonal allergic conjunctivitis.

CONTRAINDICATIONS:

ACULAR™ ophthalmic solution is contraindicated in patients while wearing soft contact lenses and in patients who are hypersensitive to the drug.

WARNINGS:

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.

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.

NOT FOR INJECTION. Do not touch the nozzle tip to any surface since this may contaminate solution. If irritation persists or increases discontinue use and consult physician.

PRECAUTIONS:

General: It is recommended that ACULAR™ ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

An 18-month study in mice at oral doses of Ketorolac Tromethamine equal to the parenteral MRHD (Maximum Recommended Human Dose) and a 24-month study in Tromethamine equal to the parenteral MRHD, showed no evidence of tumorigenicity.

Ketorolac Tromethamine was not mutagenic in Ames test, unscheduled DNA synthesis and repair, and in forward mutation assays. Ketorolac did not cause chromosome breakage in the in vivo mouse micronucleus assay. At 1590 µg/ml (approximately 1000 times the average human plasma levels) and at higher concentrations, Ketorolac Tromethamine increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells.

Impairment of fertility did not occur in male or female rats at oral doses of 9mg/kg (53.1 mg/m²) and 16 mg/kg (94.4 mg/m²) respectively.

Pregnancy: Reproduction studies have been performed in rabbits, using daily oral doses at 3.6 mg/kg (42.35 mg/m²) and in rats at 10 mg/kg (59 mg/m²) during organogenesis. Results of

these studies did not reveal evidence of teratogenicity to the foetus. Oral doses of Ketorolac tromethamine at 1.5 mg/kg (8.8 mg/m²) which was half of the human oral exposure, administered after gestation day 17 caused dystocia and higher pup mortality in rats. There are no adequate and well-controlled studies in pregnant women. Ketorolac Tromethamine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Nursing Mothers: Caution should be exercised when ACULAR™ is administered to a nursing woman.

Paediatric use: Safety and efficacy in children have not been established.

ADVERSE REACTIONS:

In patients with allergic conjunctivitis, the most frequent adverse events reported with the use of ACULAR™ ophthalmic solution have been transient stinging and burning on instillation. These events were reported by approximately 40% of patients treated with ACULAR™ ophthalmic solution. In all development studies conducted, other adverse events reported during treatment with ACULAR™ include ocular irritation (3%), allergic reactions (3%), superficial ocular infections (0.5%) and superficial keratitis (1%).

DOSAGE AND ADMINISTRATION:

The recommended dose of ACULAR™ ophthalmic solution is one drop (0.25 mg) four times a day for relief of ocular itching due to seasonal allergic conjunctivitis. The efficacy of ACULAR™ ophthalmic solution has not been established beyond one week of therapy.

HOW SUPPLIED:

ACULAR™ (Ketorolac Tromethamine) ophthalmic solution is available for topical ophthalmic administration as a 0.5% sterile solution, and is supplied in 5 ml plastic dropper bottles.

Note: Store in a cool place, protect from light. On prescription only:

DESCRIPTION:

Each ml contains:

- Flurbiprofen Sodium USP 0.3 mg
- Hydroxypropyl Methylcellulose 2.5 mg
- Phenyl Mercuric Nitrate IP 0.02 mg
- Aqueous buffered vehicle

CLINICAL PHARMACOLOGY:

Flurbiprofen Sodium is one of a series of phenylalkanoic acids that have shown analgesic antipyretic and anti-inflammatory activity in animal inflammatory diseases. Its mechanism of action is believed to be through inhibition of the cyclo-oxygenase enzyme that is essential in the biosynthesis of prostaglandins.

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

Prostaglandins also appear to play a role in the miotic response produced during ocular surgery by constricting the iris sphincter independently of cholinergic mechanisms. In clinical studies, FLUR™ has been shown to inhibit the miosis induced during the course of cataract surgery.

Results from clinical studies indicate that Flurbiprofen Sodium has no significant effect upon intraocular pressure.

INDICATIONS AND USAGE:

FLUR™ is indicated for the inhibition of intraoperative miosis. FLUR™ is also indicated for



FLUR™
(Flurbiprofen Sodium 0.03%) Eye Drops

treatment of postoperative and postlaser trabeculoplasty inflammation of the anterior segment of the eye.

CONTRAINDICATIONS:

FLUR™ is contraindicated in epithelial herpes simplex keratitis (dendritic keratitis) and in individuals who are hypersensitive to the drug.

WARNINGS/PRECAUTIONS:

There exists the potential for cross sensitivity to acetylsalicylic acid and other non-steroidal anti-inflammatory and histidine drugs. Therefore caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Acute infections of the eye may be masked by the use of topical anti-inflammatory agents.

Flurbiprofen Sodium possesses no inherent antimicrobial activity. Use of Flurbiprofen Sodium with an anti-infective drug in the presence of ocular infections should be monitored closely.

Patients with histories of herpes simplex keratitis should be monitored closely.

Wound healing may be delayed with the use of Flurbiprofen Sodium.

Drug Interaction: Although clinical studies with Acetylcholine Chloride and animal studies with Acetylcholine Chloride or Carbachol revealed no interference and there is no known pharmacological basis for an interaction, they have been ineffective when used in surgical patients treated with Flurbiprofen Sodium.

NOT FOR INJECTION. Use the solution within one month after opening the container. Do not touch the nozzle tip to any surface since this may contaminate solution.

If irritation persists or increases discontinue use and consult physician.

ADVERSE REACTIONS:

The most frequent adverse reactions reported with the use of Flurbiprofen Sodium are transient burning and stinging upon instillation and other minor symptoms of ocular irritation.

It is known that some systemic absorption does occur with ocularly applied drugs, and that nonsteroidal anti-inflammatory drugs have been shown to increase bleeding time by interference with thrombocyte aggregation. There have been reports that ocularly applied Flurbiprofen Sodium may cause an increased bleeding tendency of ocular tissues in conjunction with surgery. It is recommended that Flurbiprofen Sodium be used with caution in surgical patients with known bleeding tendencies or who are receiving other medication which may prolong bleeding time.

OVER DOSAGE:

Overdosage will not ordinarily cause acute problems. If accidentally ingested, drink fluids to dilute.

DOSAGE & ADMINISTRATION:

For inhibition of intraoperative miosis, a total of four drops of FLUR™ should be administered in the eye(s) by instilling one drop approximately every half hour beginning two hours before surgery. One drop should be instilled into the conjunctival sac every four hours for one week following laser trabeculoplasty or two to three weeks after other surgical procedures.

HOW SUPPLIED:

FLUR™ is supplied 5ml plastic dropper bottles.

Note: Store in a cool place. On prescription only.