KETOROLAC TROMETAMOL

ACULAR®
5 mg/mL (0.5% w/v)
Sterile Ophthalmic Solution (Drops)

FORMULATION

Each mL contains:
Ketorolac trometamol 5 mg
Benzalkonium chloride 0.1 mg
Edetate sodium 1 mg
Octoxynol 40
Sodium chloride
Purified water

ANIMAL PHARMACOLOGY
Ketorolac trometamol 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 trometamol 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 trometamol is a nonsteroidal anti-inflammatory drug which, when administered systemically, has demonstrated analgesic, anti-inflammatory and anti-pyretic activity. The mechanism of its action is thought to be due, in part, to its ability to inhibit prostaglandin biosynthesis. Ocular administration of ketorolac trometamol reduces prostaglandin E_2 levels in aqueous humor. The mean concentration of PGE was 80 pg/mL in the aqueous humor of eyes receiving vehicle and 28 pg/mL in the eyes receiving 0.5% ketorolac trometamol (ACULAR®) ophthalmic solution.

Ketorolac trometamol given systemically does not cause pupil constriction.

Results from clinical studies indicate that ketorolac trometamol (ACULAR®) ophthalmic solution has no significant effect upon intraocular pressure.

Two controlled clinical studies showed that ketorolac trometamol (ACULAR®) ophthalmic solution was significantly more effective than its vehicle in relieving ocular itching caused by seasonal allergic conjunctivitis. Two controlled clinical studies showed that patients treated for two weeks with ketorolac trometamol (ACULAR®) ophthalmic solution were less likely to have measurable signs of inflammation (cell and flare) than patients treated with its vehicle.

Two drops (0.1 mL) of 0.5% of ketorolac trometamol (ACULAR®) ophthalmic solution instilled into 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% ketorolac trometamol (ACULAR®) ophthalmic solution was instilled into one eye and one drop of vehicle into the other eye tid 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 trometamol 10 mg is administered systemically every 6 hours, peak plasma levels at steady state are around 960 ng/mL.

Ketorolac trometamol (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
Ketorolac trometamol (ACULAR®) ophthalmic solution is indicated for the relief of ocular itching due to seasonal allergic conjunctivitis and for the prophylaxis and reduction of inflammation and associated symptoms following ocular surgery.

CONTRAINDICATIONS
Ketorolac trometamol (ACULAR®) ophthalmic solution is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation.

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. There have been post-marketing reports of bronchospasm or exacerbation of asthma in patients, who have either a known hypersensitivity to aspirin/non-steroidal anti-inflammatory drugs or a past medical history of asthma associated with the use of ketorolac trometamol (ACULAR®), which may be contributory. Caution is recommended in the use of ketorolac trometamol (ACULAR®) in these individuals (Refer to ADVERSE REACTIONS, Post-Marketing Experience section). 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.

PRECAUTIONS
General: It is recommended that ketorolac trometamol (ACULAR®) ophthalmic solution be used in caution with patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.
Delayed Healing: All topical nonsteroidal anti-inflammatory drugs (NSAIDs) may slow or delay healing. Concomitant use of topical NSAIDs and topical steroid may increase the potential for healing problems.
Corneal Effects: Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored for corneal health. Topical NSAIDs should be used with caution in patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time as they may be at increased risk for corneal adverse events which may become sight threatening. Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.
Information for patients: Ketorolac trometamol (ACULAR®) ophthalmic solution should not be administered to patients wearing contact lenses. Ketorolac trometamol (ACULAR®) contains the preservative benzalkonium chloride, which may be absorbed and cause discoloration to soft contact lenses. Contact lenses should be removed prior to administration of ketorolac trometamol (ACULAR®) and may be reinserted 15 minutes following administration. Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures to avoid injury and contamination of eye drops.
Carcinogenesis, Mutagenesis, and Impairment of Fertility: An 18-month study in mice at oral doses of ketorolac trometamol equal to the parenteral MRHD (Maximum Recommended Human Dose) and a 24-month study in rats at oral doses 2.5 times the parenteral MRHD, showed no evidence of tumorigenicity.

Ketorolac trometamol 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 trometamol 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 9 mg/kg (53.1 mg/m^2) and 16 mg/kg (94.4 mg/m^2) respectively.

Pregnancy: Reproduction studies have been performed in rabbits, using daily oral doses at 3.6 mg/kg (42.35 mg/m^2) and in rats at 10 mg/kg (59 mg/m^2) during organogenesis. Results of these studies did not reveal evidence of teratogenicity to the fetus. Oral doses of ketorolac trometamol at 1.5 mg/kg (8.8 mg/m^2), 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 trometamol (ACULAR®) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system of rats (closure of the ductus arteriosus), the use of ketorolac trometamol (ACULAR®) ophthalmic solution during late pregnancy should be avoided.

Nursing Mothers: Because may drugs are excreted in human milk, caution should be exercised when ketorolac trometamol (ACULAR®) is administered to a nursing woman.

Pediatric Use: Safety and efficacy in children below the age of 3 have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

Effects on Ability to Drive and Use Machines: No effect is expected with the ophthalmic formulations, although patients should be warned of the potential of experiencing blurred vision when using ketorolac trometamol (ACULAR®) which could compromise driving performance and the ability to use machines. The patient should wait until their vision clears before driving or using machinery.

DRUG INTERACTION

There have been no reports of interactions of ketorolac trometamol (trometamol) ophthalmic solution 0.5% with topical or injectable drugs used in ophthalmology used pre-, intra-, or postoperatively including antibiotics (e.g., gentamicin, tobramycin, neomycin, polymyxin), sedatives (e.g., diazepam, hydroxyzine, lorazepam, promethazine HCl), miotics, mydriatics, cycloplegics (e.g., acetylcholine, atropine, epinephrine, physostigmine, phenylephrine, timolol maleate), hyaluronidase, local anesthetics (e.g., bupivacaine HCl, cyclopentolate HCl, lidocaine HCl, tetracaine), or corticosteroids. Concomitant use of topical NSAIDs and topical corticosteroids may increase the potential for healing problems (Refer to PRECAUTIONS section).

ADVERSE REACTIONS

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

The most common adverse reactions reported in clinical trials for post-operative inflammation (in patients who have undergone cataract extraction) are as follows:

Eye Disorders	
Common	iritis (1%), keratic precipitates (1%), hem retinal (1%), cystoid macular edema (1%), burning eye (1%), pruritus eye (1%), eye trauma (1%), intraocular pressure (2%)
Nervous System Disorders	
Common	Headaches (3.9%)

Note: The frequency of 1% only represents 1 patient.

There were no significant adverse reactions reported in patients treated for the indications of intraoperative miosis (in patients undergoing cataract extraction) and cystoid macular edema in aphakic or pseudophakic eyes. The adverse reactions in clinical trials for these indications were comparable between the treated group and placebo.

Post-marketing Experience
The following adverse reactions have been identified during postmarketing use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Since marketed, the following drug reactions have been observed following the use of ketorolac trometamol (ACULAR®), Eye irritation, Eyelid edema, Eye edema, Ocular hyperemia, Conjunctival hyperemia, Eye swelling, Eye pain, Eye pruritus and Ulcerative Keratitis.

There have been post-marketing reports of bronchospasm or exacerbation of asthma, in patients, who have either a known hypersensitivity to aspirin/non-steroidal anti-inflammatory drugs or a past medical history of asthma, associated with the use of ketorolac trometamol (ACULAR®) which may be contributory (Refer to WARNINGS section).

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

DOSAGE AND ADMINISTRATION
The recommended dose of ketorolac trometamol (ACULAR®) ophthalmic solution is one drop (0.25 mg) four times a day for relief of ocular itching due to seasonal allergic conjunctivitis. For the prophylaxis and reduction of inflammation and associated symptoms following ocular surgery, the recommended dose is one drop three times daily starting 24 hours pre-operatively and continuing up to 3 weeks post- operatively.
FOR EXTERNAL USE ONLY

AVAILABILITY
Ketorolac trometamol (ACULAR®) ophthalmic solution is available for topical ophthalmic administration as a 0.5% sterile solution, and is supplied in white opaque plastic bottles in the following size: 5 mL.

Store at temperatures not exceeding 25°C.

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Caution: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription. For suspected adverse drug reaction, report to FDA: www.fda.gov.ph
Seek medical attention at the first sign of ADR.

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