ACULAR®
Allergan
Ketorolac Tromethamine
Topical Anti-inflammatory

**Action And Clinical Pharmacology:** Ketorolac is a nonsteroidal, anti-inflammatory agent demonstrating analgesic and anti-inflammatory activity. At concentrations of 0.02 to 0.5%, ketorolac solution did not irritate the eyes of rats, dogs and monkeys. Up to 4% concentrations were nonirritating in albino rabbits.

Ketorolac has demonstrated anti-inflammatory activity when applied topically in several animal models of ocular inflammation. The compound significantly inhibited the inflammatory response to silver nitrate-induced cauterization of the corneas of rat eyes at concentrations of 0.25 and 0.5%. Concentrations of ketorolac ranging from 0.02 to 0.5% blocked vascular permeability changes caused by endotoxin-induced uveitis in the eyes of rabbits. Using the same model, ketorolac also blocked endotoxin-induced elevation of aqueous humor PGE2. It 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.

Applications of a 0.5% ketorolac solution did not delay the healing of experimental corneal wounds in rabbits. This solution did not enhance the spread of experimental ocular infections induced in rabbits with C. albicans, Herpes simplex virus type one, or P. aeruginosa.

Two drops (0.1 mL) of 0.5% ketorolac 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. The mean ketorolac concentration was 95 ng/mL in the aqueous humor and the range was 40 to 170 ng/mL. The mean concentration of PGE2 was 80 pg/mL in the aqueous humor of eyes receiving vehicle and 28 pg/mL in the eyes receiving 0.5% ketorolac ophthalmic solution.

One drop (0.05 mL) of 0.5% ketorolac ophthalmic solution was instilled into one eye and 1 drop of the vehicle into the other eye t.i.d. for 21 days in 26 healthy subjects. Only 5 of 26 subjects had detectable amounts of ketorolac in their plasma (range 10.7 and 22.5 ng/mL) when tested 15 minutes after the morning dose on day 10.
When ketorolac is given systemically to relieve pain, the average plasma level following chronic systemic treatment was approximately 850 ng/mL.

The recommended daily dose for ophthalmic use topically is from 1/20th to 1/50th of the recommended oral daily dose used to relieve pain.

Ketorolac given systemically does not cause pupil constriction. Results from clinical studies indicate that Acular ophthalmic solution has no significant effect upon intraocular pressure.

**Indications And Clinical Uses:** For the prophylaxis and the relief of postoperative ocular inflammation in patients undergoing cataract extraction with or without implantation of an intraocular lens.

**Contra-Indications:** In patients who have previously exhibited hypersensitivity to any of the ingredients in the formulation.

The potential for cross-sensitivity to ASA and other nonsteroidal anti-inflammatory drugs exists although it has not been reported. Ketorolac ophthalmic solution therefore should not be used in patients who have previously exhibited sensitivities to these drugs.

**Manufacturers' Warnings In Clinical States:** Pregnancy: Ketorolac is not recommended during pregnancy, labor or delivery.

Lactation: Ketorolac is not recommended for treatment of nursing mothers. Secretion of ketorolac in human milk after systemic administration is limited. The milk-to-plasma ratio of ketorolac concentrations ranged between 0.015 and 0.037 in a study of 10 women.

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

Children: Safety and efficacy in children have not been established.

**Drug Interactions:** There have been no reports in the controlled trials of interactions of ketorolac ophthalmic solution with topical or injectable drugs 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, phystostigmine, phenylephrine, timolol maleate), hyaluronidase, local anesthetics (e.g., bupivacaine HCl, cyclopentolate HCl, lidocaine HCl, tetracaine) or corticosteroids.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies in mice and rats have shown no evidence of carcinogenicity, teratogenicity or impairment of fertility, with ketorolac. No mutagenic potential of ketorolac was found in the Ames bacterial or the micronucleus test for mutagenicity.

Infection: In common with other anti-inflammatory drugs, ketorolac may mask the usual signs of infection.

Ophthalmology: Blurred and/or diminished vision has been reported with the use of ketorolac and other nonsteroidal anti-inflammatory drugs. If such symptoms develop this drug should be discontinued and an ophthalmologic examination performed. Ophthalmic examination should be carried out at periodic intervals in any patient receiving this drug for an extended period of time.

Adverse Reactions: Since other nonsteroidal anti-inflammatory drugs have been known to irritate the eye upon topical application, ketorolac was studied for its ocular irritation potential in animals and man.

In 2 multidose studies in healthy volunteers, 1 drop of 0.5% ketorolac ophthalmic solution was applied 3 times daily for 21 days. Mild to moderate transient ocular burning/stinging was reported.

Most ocular complaints reported in clinical studies could not be distinguished from adverse events caused by the trauma of cataract surgery and the insertion of an intraocular lens.

The most frequent adverse reactions were conjunctivitis (redness, scratchiness, foreign body sensation, 10%) eye pain (pain, ache and burn, 6%), ptosis (5%) and keratitis (corneal edema, 3%). Iritis, corneal lesion, eye disorder, photophobia pupillary disorder, blepharitis and glaucoma were each reported with a prevalence of 2%.

Up to 2 drops (0.1 mL or 0.5 mg) of 0.5% ketorolac ophthalmic solution per eye every 6 to 8 hours have been administered postsurgically.
None of the typical adverse reactions reported with the systemic nonsteroidal anti-inflammatory agents or ketorolac have been observed at the doses used in topical ophthalmic therapy.

**Symptoms And Treatment Of Overdose:** Symptoms and Treatment: The absence of experience with acute overdosage systemically or topically precludes characterization of sequelae and assessment of antidotal efficacy at this time. If ingested accidentally, drink fluids to dilute.

**Dosage And Administration:** The recommended dose is 1 to 2 drops (0.25 to 0.5 mg) every 6 to 8 hours beginning 24 hours before surgery and continuing for 3 to 4 weeks for prophylaxis and relief of postoperative ocular inflammation.

**Availability And Storage:** Multidose Bottles: Each mL contains: ketorolac tromethamine 5 mg. Nonmedicinal ingredients: benzalkonium chloride, edetate disodium, octoxynol 40, purified water, sodium chloride and sodium hydroxide and/or hydrochloric acid to adjust to pH 7.4. White opaque plastic multidose bottles of 5 and 10 mL with a controlled dropper tip.

Unit Dose Vials: Each mL contains: ketorolac tromethamine 5 mg. Nonmedicinal ingredients: purified water, sodium chloride, sodium hydroxide and/or hydrochloric acid to adjust to pH 7.4. Preservative-free. Unit dose vials of 0.4 mL, boxes of 24.

When stored at room temperature (15 to 30°C), has a 24-month expiry date with protection from light.