ACULAR ®

ketorolac tromethamine
0.5% sterile ophthalmic
solution

DESCRIPTION

Each mL contains: ketorolac tromethamine 5 mg with: benzalkonium chloride 0.1 mg, edetate disodium 1 mg, octoxynol 40, sodium chloride and purified water.

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 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 tromethamine reduces prostaglandin E_2 levels in aqueous humor. The mean concentration of PGE_2 was 80 pg/mL in the aqueous humor of eyes receiving vehicle and 28 pg/mL in the 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 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 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% 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% 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 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 temporary relief of ocular itching due to seasonal allergic conjunctivitis. ACULAR® is also indicated for the treatment of postoperative inflammation in patients who have undergone cataract extraction.

CONTRAINDICATIONS

ACULAR® ophthalmic solution is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation.

WARNINGS

Cross-Sensitivity: 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 ACULAR® ophthalmic solution, which may be contributory. Caution is recommended in the use of ACULAR® ophthalmic solution in these individuals (Refer to section **Post-Marketing Experience**).

Bleeding: With 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 surgery.

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.

Delayed Healing: All topical nonsteroidal anti-inflammatory drugs (NSAIDs) may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids 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.

Contact Lens Wear: ACULAR® should not be administered to patients wearing contact lenses.

ACULAR® ophthalmic solution 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 ACULAR® ophthalmic solution and may be reinserted 15 minutes following administration.

Eye Injury and Contamination: 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 (Standard Medical Practice).

DRUG INTERACTIONS

There have been no reports of interactions of ketorolac tromethamine (trometamol) ophthalmic solution 0.5% with topical or injectable drugs used in ophthalmology used 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), 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 above sections **Bleeding, Delayed Healing**).

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 rats at oral doses 2.5 times 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 9 mg/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 fetus. 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. ACULAR® ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic effects: Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system of rats (closure of the ductus arteriosus), the use of ACULAR® ophthalmic solution during late pregnancy should be avoided.

NURSING MOTHERS

Because many drugs are excreted in human milk, caution should be exercised when ACULAR® is administered to a nursing woman.

PEDIATRIC USE

Safety and efficacy in children have not been established.

GERIATRIC USE

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

ABILITY TO DRIVE

No effect is expected with the ophthalmic formulations, although patients should be warned of the potential of experiencing blurred vision when using 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.

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%).

Clinical Studies Experience: Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared with the rates in the clinical studies of another drug and may not reflect the rates observed in practice.

For the indications, the frequency of adverse reactions documented during clinical trials is given below and is defined as follows: Very Common (≥ 1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very Rare (<1/10,000).

In up to 40% of patients participating in clinical trials for the indication of seasonal allergic conjunctivitis, the following adverse reactions occurred:

Eye Disorders	
Very Common	Eye pain and eye irritation upon instillation, transient (between 9.7 and 49%)
Common	Blurred vision (1-3%), conjunctivitis (1-3%)

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%), retinal hemorrhage (1%), cystoid macular edema (1%), burning eye (1%), pruritus eye (1%), eye trauma (1%), increased intraocular pressure (2%)
Nervous System Disorders	
Common	Headaches (3.9%)

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

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 adverse reactions have been observed following the use of ACULAR®: Eye irritation, eyelid oedema, ocular hyperaemia, conjunctival hyperaemia, 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 ACULAR® which may be contributory (Refer to sections **Warnings, Precautions**).

OVERDOSE

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

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. For the treatment of postoperative inflammation in patients who have undergone cataract extraction, one drop of ACULAR® ophthalmic solution should be applied to the affected eye(s) four times daily beginning 24 hours after cataract surgery and continuing through the first 2 weeks of the postoperative period.

HOW SUPPLIED

ACULAR® (ketorolac tromethamine) 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 sizes: 3 mL, 5 mL, 10 mL. **Note:** Store between 15° - 25°C; protect from light. On prescription only.
Keep out of the reach of children.
Discard contents one month after opening.

Manufactured by:
Allergan Pharmaceuticals
Ireland, Westport, Ireland.

Date of revision: April 2018

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