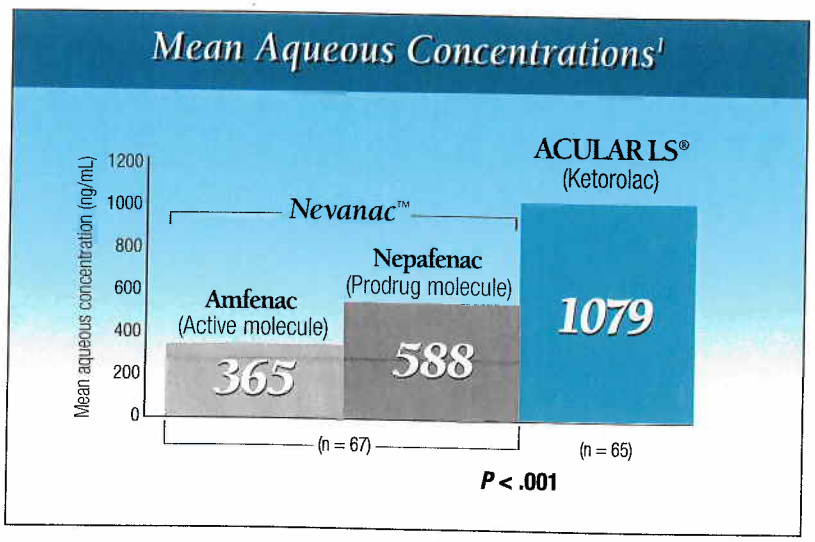
Human Data

ACULAR LS®: Outstanding Ocular

PENETRATION



Single-center, randomized, double-masked study of 132 patients undergoing phacoemulsification. Patients received either ACULAR LS® (ketorolac tromethamine ophthalmic solution) 0.4% or *Nevanac*™ (nepafenac ophthalmic suspension) 0.1% 4 times daily for 2 days preoperatively plus 4 drops in the 90 minutes prior to surgery.[1]

- In this study, ACULAR LS® achieved nearly **3-times greater penetration in patients** than the active metabolite of *Nevanac*™[1] (clinical significance unknown)
- In the same study, ACULAR LS® reduced prostaglandins below detectability in 62% of treated eyes vs 18% with *Nevanac*™ (N = 82)[1]

ACULAR LS® ophthalmic solution is indicated for the reduction of ocular pain and burning/stinging following corneal refractive surgery.

Important Safety Information: ACULAR LS® ophthalmic solution is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation. All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including ketorolac tromethamine ophthalmic solution, may slow or delay healing. The most frequently reported adverse events occurring in approximately 1% to 5% of the overall study population were conjunctival hyperemia, corneal infiltrates, headache, ocular edema, and ocular pain.

Please see brief prescribing information on the next page.

ACULAR LS® (ketorolac tromethamine ophthalmic solution) 0.4%

The #1 Choice Among Ophthalmologists[2]

ALLERGAN

1. Amico LM, Bucci FA Jr, Waterbury D. Aqueous PGE_2 inhibition of ketorolac 0.4% vs. nepafenac 0.1% in patients undergoing phacoemulsification. Poster presented at: Annual Meeting of the Association for Research in Vision and Ophthalmology; April 30-May 4, 2006; Fort Lauderdale, Fla. **2.** *Source™ Prescription Audit (SPA)*, Verispan, L.L.C., 9/8/2006.

ACULAR LS®
(ketorolac tromethamine ophthalmic solution) 0.4%
Sterile
BRIEF SUMMARY

INDICATIONS AND USAGE

ACULAR LS® ophthalmic solution is indicated for the reduction of ocular pain and burning/stinging following corneal refractive surgery.

CONTRAINDICATIONS

ACULAR LS® 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.

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: All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including ketorolac tromethamine ophthalmic solution, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDS and topical steroids may increase the potential for healing problems.

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.

Postmarketing experience with topical NSAIDs suggests that 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 may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Postmarketing 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.

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

Information for Patients: ACULAR LS® ophthalmic solution should not be administered while wearing contact lenses.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Ketorolac tromethamine was neither carcinogenic in rats given up to 5 mg/kg/day orally for 24 months (156 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in humans and animals) nor in mice given 2 mg/kg/day orally for 18 months (62.5 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in humans and animals).

Ketorolac tromethamine was not mutagenic *in vitro* in the Ames assay or in forward mutation assays. Similarly, it did not result in an *in vitro* increase in unscheduled DNA synthesis or an *in vivo* increase in chromosome breakage in mice. However, ketorolac tromethamine did result in an increased incidence in chromosomal aberrations in Chinese hamster ovary cells.

Ketorolac tromethamine did not impair fertility when administered orally to male and female rats at doses up to 280 and 499 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis, assuming 100% absorption in humans and animals.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Ketorolac tromethamine, administered during organogenesis, was not teratogenic in rabbits or rats at oral doses up to 112 times and 312 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis assuming 100% absorption in humans and animals. When administered to rats after Day 17 of gestation at oral doses up to 46 times the maximum recommended human topical ophthalmic dose on a mg/kg basis, assuming 100% absorption in humans and animals, ketorolac tromethamine resulted in dystocia and increased pup mortality. There are no adequate and well-controlled studies in pregnant women. ACULAR LS® ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Nursing Mothers: Caution should be exercised when ACULAR LS® ophthalmic solution is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of ketorolac tromethamine in pediatric patients 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.

ADVERSE REACTIONS

The most frequently reported adverse reactions for ACULAR LS® ophthalmic solution occurring in approximately 1 to 5% of the overall study population were conjunctival hyperemia, corneal infiltrates, headache, ocular edema and ocular pain.

The most frequent adverse events reported with the use of ketorolac tromethamine ophthalmic solutions have been transient stinging and burning on instillation. These events were reported by 20% - 40% of patients participating in these other clinical trials.

Other adverse events occurring approximately 1% - 10% of the time during treatment with ketorolac tromethamine ophthalmic solutions included allergic reactions, corneal edema, iritis, ocular inflammation, ocular irritation, ocular pain, superficial keratitis, and superficial ocular infections.

Clinical Practice: The following events have been identified during postmarketing use of ketorolac tromethamine ophthalmic solutions in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to topical ketorolac tromethamine ophthalmic solutions, or a combination of these factors, include corneal erosion, corneal perforation, corneal thinning and epithelial breakdown (see **PRECAUTIONS, General**).

Based on package insert 71654US10M revised May 2003.

Rx only

U.S. Pat. 5,110,493