PRODUCT MONOGRAPH

Pr**ACULAR®**

ketorolac tromethamine ophthalmic solution 0.5% w/v

with benzalkonium chloride 0.01% w/v as preservative

Pr**ACULAR LS®**

ketorolac tromethamine ophthalmic solution 0.4% w/v

with benzalkonium chloride 0.006% w/v as preservative

Topical Non-steroidal Anti-inflammatory Agent

Allergan Inc.
Markham, ON
L6G 0B5

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Ophthalmic	Solution, ketorolac tromethamine, 0.5% w/v	Benzalkonium chloride 0.01% w/v as preservative *For a complete listing see Dosage Forms, Composition and Packaging section.*
	Solution, ketorolac tromethamine, 0.4% w/v	Benzalkonium chloride 0.006% w/v as preservative *For a complete listing see Dosage Forms, Composition and Packaging section*

INDICATIONS AND CLINICAL USE

ACULAR® (ketorolac tromethamine) ophthalmic solution 0.5% is indicated for the prophylaxis and the relief of postoperative ocular inflammation in patients undergoing cataract extraction with or without implantation of an intraocular lens.

ACULAR LS® (ketorolac tromethamine) ophthalmic solution 0.4% is indicated for the reduction of ocular pain and ocular symptoms of foreign body sensation, burning/stinging, tearing, and photophobia following refractive surgery.

Pediatrics (< 18 years of age):
Safety and effectiveness of ketorolac tromethamine ophthalmic solutions in pediatric patients have not been established.

Geriatrics (>65 years of age): No overall differences in safety or effectiveness have been observed between elderly and younger patients.

CONTRAINDICATIONS

ACULAR® and ACULAR LS® is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

General
There have been post-marketing reports of bronchospasm or exacerbation of asthma, in patients, who have either a known hypersensitivity to acetylsalicylic acid/nonsteroidal anti-inflammatory drugs (NSAIDs) or a past medical history of asthma, associated with the use of ACULAR® or ACULAR LS®, which may be contributory. Caution is recommended in the use of ACULAR® or ACULAR LS® in these individuals.

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

Hematologic
With some NSAIDs, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

Occupational Hazards
Based on the pharmacodynamic profile, ketorolac is not expected to influence a patient's ability to drive or operate machinery. As with any ocular medication, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machinery.

Ophthalmologic
All topical NSAIDs may slow or delay wound healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Postmarketing experiences suggest that topical NSAIDs used by patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface disease (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short

period of time may be at an increased risk of corneal adverse events which may become sight threatening. These adverse events may include keratitis, epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored for corneal health. It is also suggested that if used more than 24 hours prior to surgery or used beyond 14 days post-surgery, the patient risk for the occurrence and severity of corneal adverse events increases.

Blurred and/or diminished vision has been reported with the use of ketorolac tromethamine ophthalmic solution and other NSAIDs. These symptoms should diminish over time. However, if they persist, this drug should be discontinued and an ophthalmic examination should be performed.

ACULAR® and ACULAR LS® should not be administered while wearing contact lens(es).

Contact lenses should be removed prior to instillation of ACULAR® or ACULAR LS®, and may be re-inserted 15 minutes following administration. Patients should be advised that ACULAR® and ACULAR LS® both contain benzalkonium chloride, which may discolour soft contact lenses.

Peri-Operative Considerations

It is recommended that ketorolac tromethamine ophthalmic solutions be used with caution in surgical patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Respiratory

There have been post-marketing reports of bronchospasm or exacerbation of asthma in patients, who have either a known hypersensitivity to acetylsalicylic acid/NSAIDs or a past medical history of asthma associated with the use of ACULAR® or ACULAR LS®, which may be contributory. Caution is recommended in the use of ACULAR® or ACULAR LS® in these individuals (Refer to Post-Market Adverse Drug Reactions section).

Special Populations

Pregnant Women: Use of ketorolac tromethamine ophthalmic solutions is not recommended during pregnancy, labour or delivery due to no adequate and well controlled studies.

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 tromethamine ophthalmic solutions during late pregnancy should be avoided.

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

Pediatrics (< 18 years of age):
Safety and effectiveness of ketorolac tromethamine ophthalmic solutions in pediatric patients have not been established.

Geriatrics (>65 years of age): No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Since other NSAIDs have been known to irritate the eye upon topical application, ketorolac tromethamine was studied for its ocular irritation potential in animals and man.

In two multi-dose studies in healthy volunteers, one drop of 0.5% ketorolac tromethamine ophthalmic solution was applied three times daily for 21 days. Mild to moderate transient ocular burning/stinging was reported. Most ocular complaints reported in clinical studies with ACULAR® could not be distinguished from adverse events caused by the trauma of cataract surgery and the insertion of an intraocular lens.

Up to two 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.

The most frequent adverse reactions in patients using ACULAR®, 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 elevated intraocular pressure were each reported with a prevalence of 2%.

The frequency of adverse reactions observed during two multi-center, randomized, double-masked, vehicle-controlled, parallel-group studies involving patients treated ACULAR LS® in post-photorefractive keratectomy patients is presented below in Table 1, using MedDRA System Organ Class.

Table 1 - Number (%) of Patients with Treatment-Related Adverse Reactions, Reported by > 1% of Patients, During Treatment Period in the Pooled Phase 3 Studies

System Organ Class Preferred Term[a]	Ketorolac n= 156 (%)	Vehicle n= 157 (%)
Eye disorders		
Pain eye	2 (1.3%)	4 (2.5%)
Nervous system disorders		
Headache	1 (0.6%)	3 (1.9%)

None of the typical adverse reactions reported with the systemic non-steroidal anti-inflammatory agents or ketorolac tromethamine have been observed at the doses used in topical ophthalmic therapy.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Eye disorders: conjunctival hyperaemia (NOS), corneal infiltrates, edema eye, irritation
Gastrointestinal: nausea, vomiting

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during postmarketing use of ACULAR®. 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.

Eye disorders: eye irritation, eyelid oedema, ocular hyperaemia, eye swelling, eye pruritus and ulcerative keratitis
Respiratory disorders: bronchospasm or exacerbation of asthma

The following adverse reactions have been identified during postmarketing use of ACULAR LS®. 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.

Eye disorders: eye swelling, eyelid oedema, ocular hyperaemia and ulcerative keratitis
Respiratory disorders: bronchospasm or exacerbation of asthma

DRUG INTERACTIONS

Drug-Drug Interactions

There have been no reports of interactions of ketorolac tromethamine ophthalmic solution 0.5% with topical or injectable drugs used in ophthalmology pre-, intra, or post-operatively, 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., bupivicaine HCl, cyclopentolate HCl, lidocaine HCl, tetracaine), or corticosteroids.

The potential for cross sensitivity to acetylsalicylic acid, and other NSAIDs exists. Ketorolac tromethamine ophthalmic solutions therefore should be used with caution in patients who have previously exhibited sensitivities to these drugs.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

There are no data specific for patients with hepatic or renal impairment and therefore specific dosage recommendations cannot be made.

Recommended Dose and Dosage Adjustment

The recommended dose of ACULAR® is one to two drops (0.25 mg - 0.5 mg) every six to eight hours beginning 24 hours before surgery and continuing for three to four weeks for prophylaxis and relief of postoperative ocular inflammation.

The recommended dose of ACULAR LS® is one drop four times a day for up to four days in the affected eye.

Missed Dose

NOTE: If you forget to apply your eye drops at your normal time, simply apply them as soon as you remember. Then go back to the original schedule as directed by your doctor. **Don't try to catch up on missed drops by applying more than one dose at a time.**

Administration

ACULAR® and ACULAR LS® is administered topically to the eye.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid eye injury and contamination of the solution by common bacteria known to cause ocular infections.

ACULAR® and ACULAR LS® should not be administered while wearing contact lens(es).

Contact lenses should be removed prior to instillation of ketorolac tromethamine ophthalmic solutions and may be re-inserted 15 minutes following administration. Patients should be advised that ACULAR® and ACULAR LS® both contain benzalkonium chloride, which may discolour soft contact lenses. (see WARNINGS and PRECAUTIONS, Ophthalmologic).

If more than one topical ophthalmic medication is being used, each one should be administered at least 5 minutes apart**.**

OVERDOSAGE

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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Ketorolac tromethamine is a non-steroidal, anti-inflammatory agent demonstrating analgesic and anti-inflammatory activity mediated by peripheral effects. Ketorolac inhibits the synthesis of prostaglandins through inhibition of the cyclo-oxygenase enzyme system. Prostaglandins play a critical role in many inflammatory processes of the eye and appear to play a role in the miotic response during ocular surgery. At concentrations of 0.02% - 0.5%, ketorolac tromethamine solution did not irritate the eyes of rats, dogs or monkeys. Up to 4.0% concentrations were nonirritating in albino rabbits.

Ketorolac tromethamine has demonstrated anti-inflammatory activity when applied topically in several animal models of ocular inflammation. The compound significantly inhibited the inflammatory responses 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 *Candida albicans*, *Herpes simplex virus type one*, or *Pseudomonas aeruginosa*.

Pharmacodynamics

Ketorolac tromethamine given systemically does not cause pupil constriction. Results from clinical studies indicate that ketorolac tromethamine ophthalmic solution has no significant effect upon intraocular pressure, although changes in intraocular pressure may occur following refractive surgery.

Pharmacokinetics

Absorption: In human studies, penetration of the drug is rapid after application to the eye. The relationship between the concentrations of solution administered and the amount of drug that penetrates the cornea is roughly linear.

Two drops (0.1 mL) of 0.5% ketorolac tromethamine 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 ng/mL 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 tromethamine ophthalmic solution.

One drop (0.05 mL) of 0.5% ketorolac tromethamine ophthalmic solution was instilled into one

eye and one 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 amount of ketorolac in their plasma (range 10.7 ng/mL 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.

Distribution: Animal studies have shown that ^{14}C-labelled ophthalmic solution 0.5% was found to be extensively distributed in ocular tissues with major portions retained in the cornea and sclera.

Metabolism: Although no studies have been conducted regarding the sites of metabolism for ophthalmic ketorolac, studies of systemic administration have shown that the drug is metabolized in the liver.

Excretion: Results of studies in rabbits and cynomolgus monkeys suggest that the major route of drug elimination from the eye is probably through intraocular blood flow after distribution from the aqueous humor to the iris-ciliary body.

STORAGE AND STABILITY

Store in the original container at 25ºC, with excursions to 15ºC - 30 ºC. Protect from light. DISCARD 28 days after opening.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ACULAR® is supplied in a white opaque plastic bottle with a controlled dropper tip. ACULAR® is available in 5 mL and 10 mL.

ACULAR LS® is supplied in a white opaque plastic bottle with a controlled dropper tip. ACULAR LS® is available in 5 mL.

ACULAR® contains ketorolac tromethamine 0.5% w/v as the active ingredient, with benzalkonium chloride 0.01% w/v NF as the preservative. Inactive ingredients in the preserved multi dose bottles are sodium chloride, USP; edetate disodium, USP; octoxynol 40; sodium hydroxide and/or hydrochloric acid solution to adjust to pH 7.4; and purified water. Product is supplied sterile.

ACULAR LS® contains ketorolac tromethamine 0.4% w/v as the active ingredient, with benzalkonium chloride 0.006% w/v as the preservative. Inactive ingredients include edetate disodium, octoxynol 40, purified water, sodium chloride, hydrochloric acid and/or sodium hydroxide to adjust the pH to 7.4. Product is supplied sterile.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

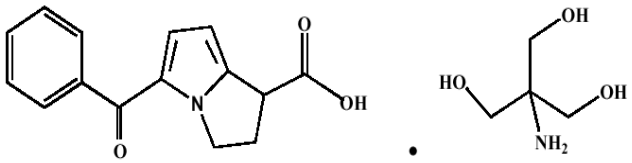
Drug Substance

Proper name: ketorolac tromethamine (USAN)
ketorolac trometamol (BAN)
ketorolac (INN)

Chemical name: (±)-5-Benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1) 1*H*-Pyrrolizine-1-carboxylic acid, 5-benzoyl-2,3-dihydro, (±)-, compound with 2-amino-2-(hydroxymethyl) 1,3-propanediol (1:1)

Molecular formula and molecular mass: $C_{19}H_{24}N_2O_6$ and 376.41

Structural formula:



Molecular Weight: 376.41

Physicochemical properties: Ketorolac tromethamine is an off-white to white crystalline powder that melts at about 162ºC with decomposition. It is freely soluble in water and methanol, slightly soluble in tetrahydrofuran, 190 proof and 200 proof ethanol and practically insoluble or insoluble in acetone, dichloromethane, toluene, ethyl acetate, dioxane, hexane, butanol and acetonitrile.

CLINICAL TRIALS

Data is not available because ACULAR® was approved as a C-REF NDS and no data was submitted.

In two double-masked, multi-centered, parallel-group studies, 313 patients who had undergone photorefractive keratectomy received ACULAR LS® (ketorolac tromethamine) ophthalmic solution 0.4% or its vehicle four times daily for up to 4 days. Significant differences favored ACULAR LS® for the treatment of ocular pain and the ocular symptoms of foreign body sensation, burning/stinging, tearing, and photophobia.

Study demographics and trial design

Table 2 - Phase 3 Controlled Clinical Trials of Ketorolac Tromethamine Ophthalmic Solution 0.4% in Post-Photorefractive Keratectomy Patients

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)		Mean age (Range)	Gender
191578-002	Multicenter, double-masked, randomized, parallel, vehicle control	1 drop in study eye 4 times daily Up to 4 days	**No. Enrolled** 156	**No. Completed** 147	39.9 (18-66) years	M: 55.8% (87/156) F: 44.2% (69/156)
191578-003	Multicenter, double-masked, randomized, parallel, vehicle control	1 drop in study eye 4 times daily Up to 4 days	**No. Enrolled** 157	**No. Completed** 157	38.9 (20-66) years	M: 42.0% (66/157) F: 58.0% (91/157)

Study results

Ketorolac tromethamine ophthalmic solution 0.4% is safe and effective in the treatment of ocular pain, when used 4 times daily for up to 4 days following photorefractive keratectomy (PRK) surgery.

DETAILED PHARMACOLOGY

Animal Pharmacology

Several studies have been conducted in animals with ketorolac acid or ketorolac tromethamine solutions demonstrating: minimal eye irritation; anti-inflammatory activity in several models of ocular inflammation; prevention of arachidonic acid induced increases in intraocular pressure with no affect on normal intraocular pressure; no impairment of corneal wound healing; no potentiation of ocular infections; and no effects on the proliferation of endothelial cells.

Metabolism and Pharmacokinetics

A series of studies were conducted with ophthalmic formulations of ketorolac acid and ketorolac tromethamine in rabbits and cynomolgus monkeys. Two different preservatives were used throughout these studies, namely a thimerosal (THIM) or a benzalkonium chloride (BAC) system. The benzalkonium chloride system was the final form selected for development due to its greater preservative efficacy and acceptability.

Single dose studies were performed using topical application, intracameral injection or intravenous administration in rabbits and/or cynomolgus monkeys. In the rabbit studies topical doses of 0.5% ketorolac tromethamine were delivered via microliter syringe drop-wise onto the eye (50 µL (0.25 mg) per eye). Intracameral injections consisted of 20 µL (0.25 mg) of the dose

solution injected directly into the anterior chamber. Intravenous doses were delivered via the marginal ear vein.

In those studies involving monkeys the target dose for intravenous administration was 0.25 mg/kg. The topical ocular dose consisted of 100 µL per eye of 0.5% ketorolac tromethamine.

Ocular Absorption and Kinetics
Ocular absorption studies were conducted in female New Zealand white rabbits. Each topical formulation (50 µL, 0.25 mg), containing either BAC or THIM preservative systems, was applied to both eyes of six rabbits. An equivalent dose (0.25 mg per eye) was injected intracamerally to both eyes of six additional rabbits. The rabbits were kept anesthetized throughout the study.

Peak concentrations of ^{14}C-ketorolac were 100-fold greater after intracameral injection compared with topical administration. The ocular absorption of the BAC formulation was 93% relative with the thimerosal formulation. The ocular bioavailability of the topical formulations averaged 4%.

After topical ocular doses, the half-life of total radioactivity in aqueous humor using the BAC formulation (3.8 - 6.4 hours) was longer than after intracameral injection (2.1 hours). This suggests that topical dosing may lead to a "reservoir" effect in the corneal epithelium and continued flux of drug from the reservoir into the aqueous humor. In the anterior chamber, clearance of ^{14}C-ketorolac averaged 11 µL/min while the apparent volume of distribution averaged 1.93 mL.

Systemic Absorption
The extent of systemic absorption of the ocular dose in the rabbit was estimated using both plasma AUC and urinary excretion data. Plasma concentrations of total radioactivity and intact ketorolac were measured in the rabbit after topical (n=6), intracameral (n=6), and intravenous (n=3) administration of ^{14}C-ketorolac tromethamine.

After a single ophthalmic dose (50 µL) in the rabbit, intact ketorolac was absorbed rapidly into the systemic circulation (T_{max}, 15 minutes). The plasma half-life after ophthalmic doses (6.9 hours) was longer than after i.v. administration (1.1 hour), suggesting that removal of drug from the eye into the venous circulation may be rate-limiting. By comparison of drug levels in aqueous humor after intracameral injection vs. plasma levels after i.v. administration, ketorolac was shown to clear more rapidly in plasma (6 mL/min) than in the anterior chamber (11 µL/min).

In a study involving 3 cynomolgus monkeys, ^{14}C-ketorolac tromethamine solution was administered intravenously and in a topical ocular solution. Peak plasma levels of ketorolac occurred at 1.1 hour after the ophthalmic dose. The plasma half-life of ketorolac was similar after ophthalmic (1.8 hours) and i.v. doses (1.6 hours).

The majority of the ophthalmic dose was excreted in urine (66% in rabbit (n=24) and 75% in monkey (n=3)) and a small amount in feces (11% in rabbit (n=24) and 2% in monkey (n=3)). The extent of systemic absorption based upon urinary data after ophthalmic dosing averaged 73% (n=3) and 74% (n=24) in rabbit and 76% (n=3) in the cynomolgus monkey. The systemic

absorption estimated from the AUC data were 40% (n=3) and 64% (n=24) in rabbit and 73% in the cynomolgus monkey.

Concentrations of ketorolac tromethamine in aqueous humor and plasma were determined in a six-month ocular toxicity study in the cynomolgus monkey. Two drops (100µL) per eye of the ophthalmic solution were applied 3, 6 and 9 times daily over 8 hours to groups of 12 cynomolgus monkeys. Plasma concentrations of ketorolac tromethamine were determined on day 1 and at the end of 3 and 6 months. Aqueous humor was also assayed at 3 and 6 months. Concentrations of ketorolac in the aqueous humor confirmed drug absorption in the eye of monkeys and were directly proportional to the administered dose. Relative to the 3X/day dose, concentrations of ketorolac in the aqueous humor after the 6X and 9X daily dose averaged 2.1 and 3.1 times higher respectively at the end of 3 months, and 1.8 and 2.7 fold higher levels respectively at the end of 6 months. A dose-proportional increase in plasma trough levels was demonstrated at the end of 6 months. Mean plasma levels of ketorolac were 2.2-fold and 3.3-fold higher after the 6X and 9X daily dose, respectively, compared with the 3X daily dose. The results indicted that there was no accumulation of drug levels in aqueous humor and in plasma with repeated ophthalmic dosing.

In a similar study two drops (100 µL) per eye of the ophthalmic solution were applied 3 or 9 times daily over 8 hours for one month to groups of 4 cynomolgus monkeys. Plasma concentrations were determined on day 1 and at the end of the study, and aqueous humor concentrations of ketorolac were measured at 1 month. Relative to the 3X/day dose, concentrations of ketorolac in the aqueous humor after the 9X/dose averaged 5.3-fold higher at the end of 1 month. Plasma levels a 1 month were 5-fold higher in the 9X/day dose relative to the 3X/day dose. The results of the one-month study also showed a low degree of systemic exposure and relatively higher levels in the aqueous humor compared to plasma levels of ketorolac.

Ocular Distribution

The intraocular distribution of ^{14}C-ketorolac tromethamine was determined in the rabbit (n=24) after topical application of 50 µL of 0.5% ^{14}C-ketorolac tromethamine optical solution containing benzalkonium chloride as the preservative. Peak concentrations of radioactivity were achieved within 1 hour in the ocular tissues and were highest in the cornea (6.06 µg-eg/mL). At 1 hour, the majority of the radioactivity (0.9% of administered dose) was recovered in the sclera (0.58%) and cornea (0.26%), vitreous humor (0.023%), retina-choroid (0.018%), iris-ciliary body (0.007%) and lens (0.002%).

Relative to plasma AUC values, the AUCs were higher for cornea (104-fold), sclera (27-fold), iris-ciliary body (5.8-fold), retina-choroid (5.6-fold), aqueous humor (3.3-fold) and approximately one-half in the vitreous humor and lens . When compared with an intravenous dose equivalent to twice the ophthalmic dose of ^{14}C-ketorolac tromethamine administered via the marginal ear vein (n=3), concentrations of drug-related radioactivity were higher in the ocular tissues and lower in plasma after ophthalmic administrations.

Animal Metabolism

The metabolite profile in aqueous humor was determined in the rabbit, while plasma and urinary metabolite profiles were determined in both the rabbit and cynomolgus monkey after

ophthalmic and i.v. dosing.

After ophthalmic administration in rabbits, ketorolac represented the major component (>90%) of radioactivity in aqueous humor and plasma and the p-hydroxy metabolite accounted for 5% of radioactivity in plasma. Ketorolac was also the major component (96%) of plasma radioactivity after ophthalmic dosing in monkeys (n=3).

After ophthalmic dosing in the rabbit, 72%, 17% and 6% of the total radioactivity in urine was comprised of intact ketorolac, p-hydroxy ketorolac and other polar metabolites. After i.v. dosing, the relative proportions of total radioactivity averaged 6% as intact ketorolac, 68% as p-hydroxy ketorolac an ~ 22% as polar metabolites.
In the monkey, intact ketorolac and its polar metabolite (possibly the glucuronide conjugate of ketorolac) accounted for 32% and 65% of the total radioactivity in urine, respectively after ophthalmic dosing, and 50% and 49% of the radioactivity in urine, respectively after i.v. dosing. Thus, the metabolism of ketorolac was qualitatively very similar after ophthalmic and i.v. administration in the monkey.

Clinical Studies
Pharmacokinetics

The penetration of ketorolac ophthalmic solution into the anterior chamber of the eye was studied in patients undergoing unilateral cataract extraction with intra-ocular lens implantation. The average concentration of ketorolac in the aqueous humor was 95 ng/mL following the instillation of two drops of the 0.5% solution approximately 12 hours and 1 hour before surgery. The concentration of ketorolac in the aqueous humor was below the detection limit of the assay (40 ng/mL) when 2 drops of 0.1% solution were instilled into the eyes of another group of patients undergoing the same surgical procedure.

Concentrations of PGE2 in the aqueous humor were depressed following the instillation of both the 0.1% and 0.5% ketorolac solutions. However, compared to the vehicle-treated group, the depression of PGE was not statistically significant.

In a 21-day multiple (t.i.d.) dose study in healthy volunteers, five of the 26 subjects had detectable (>10 ng/mL) plasma levels of ketorolac (11 ng/mL to 22 ng/mL) following 10 days of instillation of one 0.5% ketorolac ophthalmic solution. One subject had detectable levels before the first morning dose on Day 10 and the other 4 subjects had detectable levels when tested 15 minutes after the morning dose on Day 10. None of the volunteers had detectable levels on Day 24, three days after the end of dosing.

To put these plasma levels into perspective, when 10 mg of ketorolac was given a single intramuscular or oral dose or as multiple doses, the plasma level of ketorolac was approximately 850 mg/mL 30 minutes after dosing.

TOXICOLOGY

Acute Toxicity

Species Strain Regimen Group Size Preservative	***Route Concentration*(mg/mL)***	***Mortality***	***Clinical Ophthalmology***
Rabbit New Zealand One dose in right eye followed by a 72-hour observation 3 females 0.01% BAC	Ocular 2.5 5.0 10.0 20.0 40.0	 0/3 0/3 0/3 0/3 0/3	 NDE NDE NDE NDE NDE
Rabbit New Zealand One dose every one-half hour for a total of 12 doses to both eyes. Eyes were examined after the last dose and on days 1, 2, 3 and 6 following dosing 6 males 0.01% BAC	Ocular Saline control Vehicle control 5.0	 0/6 0/6 0/6	 NDE

*Volume = 0.1 mL/eye
NDE: No drug effect (no indications of irritation or toxicity)
BAC: Benzalkonium chloride

Long-term Toxicity

Ketorolac ophthalmic solution was evaluated in rabbits (pigmented and non-pigmented) in studies up to 6 weeks, and in monkeys in studies lasting up to 12 months.

The results of the preclinical toxicology studies indicate no adverse drug-related effects to ketorolac tromethamine. No adverse effects were observed in monkeys following 6 months of treatment with a thimerosal-preserved formulation. However, in studies with the BAC (benzalkonium chloride) formulation, corneal fluorescein staining, accompanied by thinning of the epithelium, was seen in vehicle-treated and drug-treated animals. The Dutch Belted rabbit was most sensitive to these effects, with the New Zealand rabbit and the monkey showing decreasing sensitivities. Since the effects were seen primarily in vehicle and low-dose groups and since similar effects have been reported for BAC, the corneal changes were attributed to the preservative. The difference in sensitivity shown by the rabbit compared to the primate may be

explained physiologically because of the greater blinking rate and lacrimal response to irritation in primates, including humans. In fact, formulations containing 0.01% BAC are well tolerated by humans and are approved as over-the-counter ophthalmic medications.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICAL INFORMATION

PrACULAR®

Ketorolac tromethamine 0.5%, w/v

PrACULAR LS®

Ketorolac tromethamine 0.4%, w/v

Read this carefully before you start using ACULAR® or ACULAR LS® and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about ACULAR® or ACULAR LS®.

What are ACULAR® or ACULAR LS® used for:
ACULAR® eye drops are used to prevent and treat inflammation in your eyes after having cataracts removed. A cataract is the clouding of the lens of the eye.

ACULAR LS® eye drops are used to manage eye pain and other symptoms that may occur after vision correction surgery. It may reduce eye pain, burning, stinging, sensitivity to light and the feeling that something is in your eye.

How ACULAR® or ACULAR LS® work:
ACULAR® and **ACULAR LS®** belong to a family of drugs known as non-steroidal anti-inflammatory drugs (NSAIDs). These drugs reduce certain substances (called prostaglandins). When prostaglandin levels are reduced, the intensity of pain, and inflammation is reduced as well.

What are the ingredients in ACULAR® and ACULAR LS®:
Medicinal ingredients: Ketorolac tromethamine
Non-medicinal ingredients:
ACULAR®: Benzalkonium chloride 0.01% w/v as the preservative, sodium chloride, edetate disodium, octoxynol 40, purified water, and sodium hydroxide and/or hydrochloric acid solution to adjust the pH to 7.4.
ACULAR LS®: Benzalkonium chloride 0.006% w/v as the preservative, edetate disodium, octoxynol 40, purified water, sodium chloride, hydrochloric acid and/or sodium hydroxide to adjust the pH to 7.4.

ACULAR® and ACULAR LS® come in the following dosage forms:
ACULAR® ophthalmic solution 0.5%, w/v
ACULAR LS® ophthalmic solution 0.4%, w/v

Do not use ACULAR® or ACULAR LS® if:
- you are allergic to ketorolac tromethamine or any of the other ingredients (see "What are the ingredients in **ACULAR®** and **ACULAR LS®**", above)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you use ACULAR® or ACULAR LS®. Talk about any health conditions or problems you may have, including if you:
- are allergic to acetylsalicylic acid (e.g. Aspirin®) or to any of the other non-steroidal anti-inflammatory drugs (NSAID).
- have a past medical history of asthma.
- are pregnant or are planning to become pregnant. **ACULAR®** and **ACULAR LS®** are not recommended during

pregnancy.
- breast-feeding, or are planning to be breast-feeding. **ACULAR®** and **ACULAR LS®** are not recommended for nursing mothers.
- have had recent eye surgery or are planning for eye surgery.
- have medical conditions such diabetes mellitus, dry eye syndrome, rheumatoid arthritis or any issues with your cornea (the front part of your eye).
- have bleeding problems, as **ACULAR®** may cause bleeding in the eyes when associated with eye surgery.

Other warnings you should know about:
ACULAR® and **ACULAR LS®** may cause blurred vision. Do not drive or use heavy machinery until your vision clears.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to use ACULAR® or ACULAR LS®:
Remove your contact lenses before using **ACULAR®** or **ACULAR LS®**. You may re-insert them 15 minutes after taking **ACULAR®** or **ACULAR LS®**.

ACULAR® and **ACULAR LS®** both contain benzalkonium chloride, which may discolour soft contact lenses.

Always use **ACULAR®** and **ACULAR LS®** exactly as your doctor has instructed you.

If you use **ACULAR®** or **ACULAR LS®** with another eye drop, leave at least five minutes between putting in **ACULAR®** or **ACULAR LS®** and then the other drops.

To help prevent infections, do not let the tip of the bottle touch your eye or anything else. Put the cap back on and close the bottle immediately after you have used it.

ACULAR® and **ACULAR LS®** should only be applied to the eye.

You must not use the bottle if the tamper-proof seal on the bottle neck is broken before you first use it.

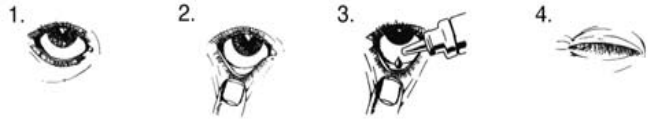
Follow the following steps to help you use **ACULAR®** and **ACULAR LS®** properly:

1. Wash your hands. Tilt your head back and look at the ceiling.

2. Gently pull down the lower eyelid to create a small pocket.

3. Turn the bottle upside down and squeeze it gently to release one drop into each eye that needs treatment.

4. Let go of the lower lid and close your eye for 30 seconds.



If a drop misses your eye, try again.

Usual dose:
ACULAR®
Instill 1 or 2 drops in your affected eye 3 or 4 times daily or as directed by your doctor.

ACULAR LS®
Instill 1 drop in your affected eye 4 times daily for up to 4 days.

Overdose:
If ingested accidentally, drink a lot of fluids.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to apply **ACULAR®** or **ACULAR LS®** at your normal time, simply apply them as soon as you remember, and then go back to your regular routine. Do not take two doses to make up for the one that you missed.

What are possible side effects from using ACULAR® or ACULAR LS®?
These are not all the possible side effects you may feel when taking **ACULAR®** or **ACULAR LS®**. If you experience any side effects not listed here, contact your healthcare professional.

Common with **ACULAR®**:
- Irritation of the eye (stinging, burning, redness)
- Itchy and/or swollen eye
- Blurred vision after instillation of the eye drops
- Eye pain
- Conjunctivitis (pink eye)

Common with **ACULAR LS®**:
- Eye pain

Uncommom with **ACULAR LS®**:
- Headache

Serious side effects and what to do about them

Symptom / effect	Talk with your healthcare professional		Stop taking drug and get immediate medial help
	Only if severe	In all cases	
Rare delay wound healing in those with serious eye conditions including corneal thinning, erosion, perforation or ulceration, and cause these conditions to worsen and may affect sight		√	
bronchospasm (shortness of breath) and worsen asthma symptoms		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
ACULAR® and **ACULAR LS®** should be stored in the original container at room temperature (25ºC). **DISCARD** unused solution 28 days after opening.

Keep out of reach and sight of children.

If you want more information about ACULAR® and ACULAR LS®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.allergan.ca, or by calling 1-800-668-6424.

This leaflet was prepared by Allergan Inc.

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