PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]ACULAR®

ketorolac tromethamine ophthalmic solution

Solution, 0.5% w/v, for ophthalmic use

with benzalkonium chloride 0.01% w/v as preservative

[Pr]ACULAR LS®

ketorolac tromethamine ophthalmic solution

Solution, 0.4% w/v, for ophthalmic use

with benzalkonium chloride 0.006% w/v as preservative

Topical Non-Steroidal Anti-Inflammatory Agent
ATC code: S01BC05

AbbVie Corporation

8401 Trans-Canada Highway

St-Laurent, Quebec

H4S 1Z1

Date of Initial Authorization:
FEB 12, 1992

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RECENT MAJOR LABEL CHANGES

None at the time of the most recent authorization.

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ACULAR® (ketorolac tromethamine ophthalmic solution 0.5% w/v) 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% w/v) is indicated for:

- the reduction of ocular pain and ocular symptoms of foreign body sensation, burning/stinging, tearing, and photophobia following refractive surgery.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

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

2 CONTRAINDICATIONS

ACULAR and ACULAR LS is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of ACULAR is one to two drops (0.25 mg to 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.

Health Canada has not authorized an indication for pediatric use.

4.4 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 (BAC), which may discolour soft contact lenses. See 7 WARNING AND PRECAUTIONS, Ophthalmologic.

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

4.5 Missed Dose

A missed dose should be applied as soon as the patient remembers. The regular dosing schedule should then be resumed with the next dose. Patients should not apply more than one dose at a time in an effort to catch up on missed doses.

5 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Ophthalmic	Solution Ketorolac tromethamine 0.5% w/v	Edetate disodium, octoxynol 40, sodium chloride, sodium hydroxide and/or hydrochloric acid to adjust pH to 7.4 and purified water. Benzalkonium chloride 0.01% w/v as preservative.
Ophthalmic	Solution Ketorolac tromethamine 0.4% w/v	Edetate disodium, octoxynol 40, sodium chloride, sodium hydroxide and/or hydrochloric acid to adjust pH to 7.4 and purified water. Benzalkonium chloride 0.006% w/v as preservative.

ACULAR and ACULAR LS are sterile solutions and are supplied in a white opaque plastic bottle with a controlled dropper tip. ACULAR is available in 5 mL and 10 mL, and ACULAR LS is available in 5 mL.

7 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. See 8.5 Post-Market Adverse Reactions.

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.

Driving and Operating Machinery

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.

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.

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.

Post-marketing 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.

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.

7.1 Special Populations

7.1.1 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.

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

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

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, 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 reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use. 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 (t.i.d) 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 post-surgically.

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 2, using MedDRA System Organ Class.

Table 2 – Number (%) of Patients with Treatment-Related Adverse Reactions, Reported by > 1% of Patients, During Treatment Period in the Pooled Phase 3 Studies

	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.

8.3 Less Common Clinical Trial Adverse Reactions

Eye disorders: conjunctival hyperaemia (NOS), corneal infiltrates, edema eye, irritation.

Gastrointestinal: nausea, vomiting.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-marketing 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, ulcerative keratitis.

Respiratory disorders: bronchospasm or exacerbation of asthma.

The following adverse reactions have been identified during post-marketing 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, ulcerative keratitis.

Respiratory disorders: bronchospasm or exacerbation of asthma.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No interaction studies were conducted.

9.3 Drug-Behavioural Interactions

No formal drug-behavioural interaction studies were conducted.

9.4 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.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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.

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 prostaglandin E2 (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*.

10.2 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.

10.3 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 was 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.

Ocular Distribution

The intraocular distribution of ^{14}C-ketorolac tromethamine was determined in rabbit (n=24) after topical application of 50 mcL of 0.5% ^{14}C-ketorolac tromethamine optical solution containing BAC as the preservative. Peak concentrations of radioactivity were achieved within 1 hour in the ocular tissues and were highest in the cornea (6.06 mcg-eg/mL). At 1 hour, the majority of the radioactivity (0.9% of administered dose) was recovered in 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.

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.

Animal

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 THIM or a BAC system. The BAC 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 mcL (0.25 mg) per eye). Intracameral injections consisted of 20 mcL (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 mcL per eye of 0.5% ketorolac tromethamine.

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 and ~ 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.

Elimination
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.

11 STORAGE, STABILITY AND DISPOSAL

ACULAR and ACULAR LS: Store in the original container at 25°C, with excursions to 15 – 30 °C. Protect from light. Discard 28 days after opening.

12 SPECIAL HANDLING INSTRUCTIONS

Patients should be advised to avoid touching the tip of the bottle to the eye or any surface, as this may contaminate the solution. Refer to 4.4 Administration for more detailed information.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: ketorolac tromethamine (USAN)

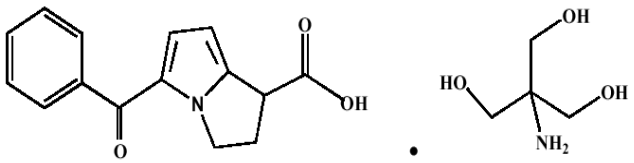
ketorolac trometamol (BAN)

ketorolac (INN)

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



Physicochemical properties: Ketorolac tromethamine is an off-white to white crystalline powder that melts at about 162°C 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.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Prophylaxis and relief of postoperative ocular inflammation

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

Reduction of ocular pain and ocular symptoms of foreign body sensation, burning/stinging, tearing, and photophobia

Table 3 – Summary of patient demographics for clinical trials in Post-Photorefractive Keratectomy Patients

Study #	Study design	Dosage, route of administration and duration	Study subjects (n=number)		Mean age (Range)	Sex
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)

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 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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Table 4 – 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 THIM-preserved formulation. However, in studies with the BAC 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.

Carcinogenicity: Ketorolac tromethamine (trometamol) was not carcinogenic in rats given up to 5 mg/kg/day orally for 24 months (151 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 (60 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in humans and animals).

Genotoxicity: 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.

Reproductive and Developmental Toxicology: Ketorolac tromethamine, administered during organogenesis, was not teratogenic in rabbits and rats at oral doses up to 109 times and 303 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 45 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis, assuming 100% absorption in humans and animals, ketorolac tromethamine resulted in dystocia and increased pup mortality.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrACULAR® / PrACULAR LS®

ketorolac tromethamine ophthalmic solution

Read this carefully before you start taking **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 is 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 is 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 does 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 ingredient: Ketorolac tromethamine

Non-medicinal ingredients:

ACULAR: Benzalkonium chloride 0.01% w/v as the preservative, edetate disodium, octoxynol 40, purified water, sodium chloride 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 and sodium hydroxide and/or hydrochloric acid 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 section above **What are the ingredients in ACULAR and ACULAR LS?**).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take 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.
- are breast-feeding, or are planning to breast-feed. 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 as 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.

The following may interact with ACULAR or ACULAR LS:

- Non-steroidal anti-inflammatory drugs (NSAID) such as aspirin.

How to take 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 these steps to use ACULAR and ACULAR LS properly:

- Wash your hands. Tilt your head back and look at the ceiling. (See illustration 1)
- Gently pull down the lower eyelid to create a small pocket. (See illustration 2)
- Turn the bottle upside down and squeeze it gently to release one drop into the eyelid pocket. If a drop misses your eye, try again. (See illustration 3)
- Let go of the lower lid and close your eye for 30 seconds. (See illustration 4)

Repeat steps 1 – 4 in the other eye if both eyes need treatment.

Usual dose:

ACULAR**:** Instill 1 or 2 drops in your affected eye(s) 3 or 4 times daily or as directed by your doctor.

ACULAR LS**:** Instill 1 drop in your affected eye(s) 4 times daily for up to 4 days.

Overdose:

If ingested accidentally, drink a lot of fluids.

If you think you, or a person you are caring for, have taken too much ACULAR or ACULAR LS, contact a healthcare professional, 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 have when taking ACULAR or ACULAR LS. If you experience any side effects not listed here, tell 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

Uncommon with ACULAR LS:

- Headache

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical 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, tell 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) 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 (15 – 30 °C) and protected from light. Discard unused solution 28 days after opening.

Keep out of reach and sight of children.

If you want more information about ACULAR or 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: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.abbvie.ca, or by calling 1-888-704-8271.

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