AUSTRALIAN PRODUCT INFORMATION
ACULAR® (ketorolac trometamol) Eye Drops

1 NAME OF THE MEDICINE

Ketorolac trometamol

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ACULAR® contains ketorolac trometamol 5 mg/mL.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

ACULAR® eye drops is a clear, colourless to pale yellow, sterile, isotonic aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ACULAR® eye drops are indicated for the short term (2-4 weeks) relief of symptoms of seasonal allergic conjunctivitis.

ACULAR® eye drops are also indicated for the short term (2-4 weeks) prophylaxis and reduction in inflammation in patients undergoing cataract extraction.

4.2 Dose and method of administration

Seasonal allergic conjunctivitis

The recommended dose of ACULAR® eye drops for the relief of symptoms of seasonal allergic conjunctivitis is one drop (0.25 mg) instilled in the eye four times daily. Treatment may be continued for up to four weeks.

Post-operative inflammation

The recommended dose of ACULAR® eye drops for the prophylaxis and treatment of inflammation in patients who have undergone cataract extraction is one to two drops (0.25-0.5 mg) four times daily, starting 24 hours before surgery and continuing for 2-4 weeks.

4.3 Contraindications

ACULAR® eye drops are contraindicated in patients hypersensitive to any of the components of the medication.

The potential exists for cross sensitivity to acetylsalicylic acid, phenylacetic acid derivatives and other nonsteroidal anti-inflammatory medicines. ACULAR® eye drops are contraindicated in patients who have previously exhibited sensitivities to these drugs.

4.4 Special warnings and precautions for use

Patients with bleeding tendencies

With some nonsteroidal anti-inflammatory drugs a potential exists 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. ACULAR® eye drops should be used with care in patients with known bleeding tendencies, or in patients who are receiving other medications which may prolong bleeding time, or patients with a known history of peptic ulceration.

Cross-sensitivity

There exists 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®, which may be contributory. Caution is recommended in the use of ACULAR® in these individuals.

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.

Masking of Infections

In common with other anti-inflammatory drugs, ACULAR® eye drops may mask the usual signs of infections.

Use in the elderly

No data available.

Paediatric use

Safety and efficacy have not been demonstrated in children aged less than 12 years.

Effects on laboratory tests

No data available

Information for Patients

ACULAR® should not be administered while wearing contact lenses. ACULAR® 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® and may be reinserted 15 minutes following administration.

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

4.5 Interactions with other medicines and other forms of interactions

No specific clinical studies on interactions with other drugs have been conducted with ACULAR® eye drops. There were no reports in the controlled studies of interactions of ACULAR® eye drops with systemic and ophthalmic medications such as antibiotics, sedatives, beta blockers, carbonic anhydrase inhibitors, miotics, mydriatics, cycloplegics, local anaesthetics and corticosteroids.

Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems (see section 4.4. Special warnings and precautions for use - Delayed Healing).

4.6 Fertility, pregnancy and lactation

Effects on fertility

Impairment of fertility did not occur in male or female rats at oral doses of 9 mg/kg (1.2 times human parenteral AUC) and 16 mg/kg (2.1 times the human parenteral AUC) respectively.

Use in pregnancy – Pregnancy Category C

Ketorolac trometamol and its metabolites have been shown to pass into the foetus. Safety in human pregnancy has not been established. Not recommended in pregnancy.

Reproduction studies have been performed in rabbits and rats at oral doses of 3.6 and 10 mg/kg/day respectively. The results from these studies did not reveal any significant evidence of harm to the foetus. However, studies in rabbits have shown a small increase in the incidence of major vessel anomalies.

Use in lactation.

Ketorolac trometamol is excreted in the milk of lactating rats and rabbits, and has been detected in human breast milk. A peri/postnatal study in rats showed reductions in postnatal growth and survival of the offspring when ketorolac trometamol was administered to lactating rats at oral dose levels greater than 4.8 mg/kg/day. Thus, use of ketorolac trometamol in lactating mothers is not recommended.

4.7 Effects on ability to drive and use machines

As ACULAR® eye drops may cause transient blurring on instillation, caution is required with the use of hazardous machinery or driving, which are not recommended unless vision is clear. The patient should wait until their vision clears before driving or using machinery.

4.8 Adverse effects (Undesirable effects)

In controlled clinical studies, the most frequently reported adverse events with the use of ACULAR® eye drops have been transient stinging and burning on instillation (eye pain). These events were reported by up to 40% of subjects treated with ACULAR®. Other adverse events reported in controlled clinical studies (at an incidence of ≥1%) included conjunctivitis (scratching, foreign body sensation, itching, erythema), local allergic reactions, superficial keratitis, keratic precepitates (1%), haemorrhage retinal (1%), cystoid macular edema (1%), burning eye (1%), pruritus eye (1%), eye trauma (1%), intraocular pressure (2%), corneal oedema, eye infection, eye inflammation, eye irritation and hypersensitivity. Ptosis, blepharitis, photophobia, blurred vision, eye dryness, corneal lesion, iritis and glaucoma were also reported in >1% of patients in some studies. Uncommon (>0.1% and <1%) adverse events reported were eye dryness, corneal infiltrates, ulcerative keratitis, visual disturbance and headaches. (Note: The frequency of 1% represents 1 patient).

Post-marketing experience

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

In post-marketing experience ocular burning and stinging, Eye irritation, local allergic reactions, superficial ocular infections, superficial keratitis, Eye oedema, Ocular hyperaemia, Conjunctival hyperaemia, Eye swelling, Eye pain, Eye pruritus and Ulcerative Keratitis were the most frequently reported adverse reactions. Systemic allergic reactions have been reported very rarely. 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 (see section 4.4 Special warning and precautions for use).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

There is no experience of overdose by the ophthalmic route. If accidentally ingested, fluids should be taken to dilute the effects, if any.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class: Ketorolac trometamol is a member of the pyrrolo-pyrolle group of non-steroidal anti-inflammatory drugs for ophthalmic use.

Mechanism of action

Ketorolac trometamol is a nonsteroidal, anti-inflammatory agent demonstrating analgesic and anti-inflammatory activity. It is believed to inhibit the cyclo-oxygenase enzyme essential for prostaglandin biosynthesis. Ocular administration of ketorolac trometamol reduces prostaglandin E_2 levels in the aqueous humour. Ketorolac trometamol given systemically does not cause pupil constriction. Results from clinical studies indicate that ACULAR® eye drops have no significant effect upon intraocular pressure.

Clinical Trials

Allergic conjunctivitis

A total of 203 patients with seasonal allergic conjunctivitis were evaluable for efficacy in two randomised, controlled clinical trials of ACULAR® (ketorolac) eye drops against placebo. The patients who received ketorolac demonstrated significant decreases in itching, and conjunctival inflammation over the 7 day treatment period.

Post-operative inflammation

A total of 206 patients who had undergone cataract surgery participated in two randomised, controlled clinical trials of ACULAR® (ketorolac) eye drops against placebo. The patients who received ketorolac showed significantly greater decreases in anterior chamber cells and anterior chamber flare over the two weeks of treatment. 39% of ketorolac patients achieved a zero score for anterior cells and flare after 2 weeks of treatment compared to 12% of placebo patients.

5.2 Pharmacokinetic properties

Absorption

Two drops (0.1 mL) of 0.5% ACULAR® eye drops 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 concentrations 95 ng/mL aqueous humour, range 40-170 ng/mL). One drop (0.05 mL of 0.5% ketorolac trometamol solution was instilled into one eye and one drop of the vehicle into the other eye three times a day for 21 days in 26 normal subjects.

Distribution

Only 4 of 13 subjects had detectable amounts of ketorolac in their plasma (range 10.7 to 22.5 ng/mL) after 15 minutes at Day 10 during topical ocular treatment. Average peak plasma level

following intramuscular administration of 30 mg ketorolac trometamol was 2.2 μg/mL 50 minutes after administration.

5.3 Preclinical safety data

Genotoxicity

Ketorolac trometamol was not genotoxic in a series of assays for gene mutations and DNA damage. Ketorolac trometamol did not cause chromosome breakage in the mouse micronucleus test *in vivo* at 1590 μg/mL, approximately 1000 times the average human plasma levels, but increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells *in vitro* at higher concentrations.

Carcinogenicity

An 18-month study in mice at oral doses of ketorolac trometamol of 2 mg/kg/day (equal to 1.2 times the human systemic exposure at the maximum recommended IM dose of 90 mg/day, based on AUC) and a 24-month study in rats at oral doses of 5 mg/kg (0.7 times the human parenteral AUC) showed no evidence of tumours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride 0.01% (w/v), disodium edetate 0.1% (w/v), octoxinol 40, sodium chloride, sodium hydroxide/hydrochloric acid (to adjust pH) and purified water.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30 °C. Protect from light.

6.5 Nature and contents of container

ACULAR® (ketorolac trometamol) eye drops is supplied in white opaque plastic dropper bottles with dropper applicators.

Eye drops: 3 mL, 5 mL and 10 mL (3 mL and 10 mL pack sizes are not marketed)

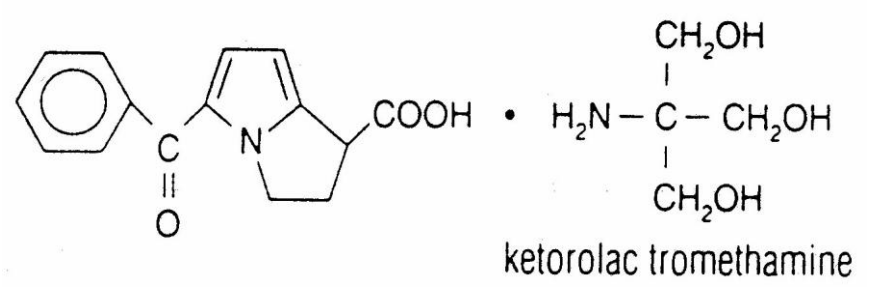
6.6 Special precautions for disposal

Discard any unused contents 28 days after opening the bottle.

6.7 Physicochemical properties

Chemical structure

Ketorolac trometamol is a white to off-white crystalline substance, which is a racemic mixture. It may exist in three crystalline forms, all of which are equally soluble in water.



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

Empirical Formula: C_{19} H_{24} N_2O_6
Molecular Weight: 376.41
pKa: 3.54

CAS number: 74103-07-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

6 March 1998

10 DATE OF REVISION

3 December 2025

Summary table of changes

Section Changed	Summary of new information
6.4	Update to Storage Temperature
8	Update to Sponsor contact phone number