

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Acular 0.5% w/v Eye Drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ketorolac trometamol 5 mg/ml.

Excipient(s) with known effect: Benzalkonium chloride 0.1 mg/ml

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution

Clear, colourless to pale yellow aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the prophylaxis and reduction of inflammation following cataract surgery.

Acular is indicated in adults.

4.2 Posology and method of administration

Posology

Post-operative inflammation:

One drop instilled into the eye three times daily starting 24 hours before surgery and continuing for three to four weeks.

Paediatric population

There is no relevant use of ACULAR in the paediatric population in the indication: For the prophylaxis and reduction of inflammation following cataract surgery.

Elderly Population

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

Method of administration

Ocular use.

Instil one drop of the solution into the inferior conjunctival sac of the eye to be treated, while pulling the lower eyelid gently downwards and looking upwards.

If ACULAR is used concomitantly with other topical eye medications there must be an interval of at least 5 minutes between the two medications.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

The potential exists for cross-sensitivity to acetylsalicylic acid and other non-steroidal anti-inflammatory drugs. ACULAR is contra-indicated in individuals who have previously exhibited sensitivities to these drugs.

4.4 Special warnings and precautions for use

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

In common with other anti-inflammatory drugs, ACULAR may mask the usual signs of infection.

All non-steroidal anti-inflammatory drugs (NSAIDs) may slow down or delay wound healing. Concomitant use of NSAIDs and topical steroids can increase the potential for healing problems. Concomitant use of ACULAR and topical corticosteroids should be exercised with caution in patients susceptible to corneal epithelial breakdown.

Use of topical NSAIDs may result in keratitis. In some 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.

The preservative in ACULAR, benzalkonium chloride, may cause eye irritation. Contact lenses must be removed prior to application, with at least a 15-minute wait before reinsertion. Benzalkonium chloride is known to discolour soft contact lenses. Contact with soft contact lenses must be avoided.

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 (see section 4.8).

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.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

4.5 Interaction with other medicinal products and other forms of interactions

No interaction studies have been performed.

ACULAR has been safely administered with systemic and ophthalmic medications such as antibiotics, sedatives, beta blockers, carbonic anhydrase inhibitors, miotics, mydriatics local anaesthetics and cycloplegics.

ACULAR may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical corticosteroids may increase the potential for healing problems (see section 4.4).

If ACULAR is used concomitantly with other topical eye medications there must be an interval of at least 5 minutes between the two medications.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of eye drops containing ketorolac in pregnant women. Studies in animals have shown reproductive toxicity. Inhibition of prostaglandin synthesis may negatively affect pregnancy and/or embryonal/foetal development and/or postnatal development. Although a very low systemic exposure is expected after the use of ketorolac eye drops. ACULAR is not recommended during pregnancy.

Breast-feeding

ACULAR should not be used during breast-feeding. Ketorolac trometamol is excreted in human milk after systemic administration.

Fertility:

There are no adequate data from the use of ketorolac trometamol on fertility in humans

4.7 Effects on ability to drive and use machines

Transient blurring of vision may occur on instillation of eye drops. Do not drive or use hazardous machinery unless vision is clear.

4.8 Undesirable effects

The frequency of adverse reactions documented during clinical trials of ketorolac trometamol and through post-marketing experience is given below and is defined as follows: Very Common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Very Rare ($< 1/10,000$); Not Known (cannot be estimated from available data).

Immune system disorders

Common: Hypersensitivity including localised allergic reactions

Nervous system disorders

Common: Headache

Eye Disorders

Very Common: Eye irritation (including burning sensation)
Eye pain (including stinging)

Common: Superficial (punctate) keratitis

Eye and/or eyelid oedema

Ocular pruritus

Conjunctival hyperaemia

Eye infection

Eye inflammation

Iritis

Keratic precipitates

Retinal haemorrhage

Cystoid macular oedema

Eye trauma

Increased intraocular pressure

Blurred and/or diminished vision

Uncommon: Corneal ulcer

Corneal infiltrates

Eye dryness

Epiphora

Not known: Corneal damage, e.g. thinning, erosion, epithelial breakdown and perforation*

Ulcerative keratitis

Eye swelling

Ocular hyperaemia

Face odema

Swelling face

Respiratory, thoracic and mediastinal disorders

Not known: Bronchospasm or exacerbation of asthma**

*Occasional post marketing reports of corneal damage including corneal thinning, corneal erosion, epithelial breakdown and corneal perforation have been received. These occurred mainly in patients using concomitant topical corticosteroids and/or with predisposing co-morbidity (see section 4.4).

**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.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: <http://www.hpra.ie/>; E-mail: medsafety@hpra.ie.

4.9 Overdose

No case of overdose has been reported. Overdose is unlikely to occur via the recommended method of administration. If accidentally ingested, drink fluids to dilute.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory agents, non-steroids
ATC code = *S01B C 05*.

ACULAR (ketorolac trometamol) is a non-steroidal anti-inflammatory agent demonstrating analgesic and anti-inflammatory activity. It is believed to inhibit the cyclo-oxygenase enzyme essential for biosynthesis of prostaglandins. ACULAR has been shown to reduce prostaglandin levels in the aqueous humour after topical ophthalmic administration.

Ketorolac trometamol given systemically does not cause pupil constriction. Results from clinical studies indicate that ACULAR has no significant effect on intraocular pressure.

5.2 Pharmacokinetic properties

Ketorolac trometamol solutions (0.1% or 0.5%) or vehicle were instilled into the eyes of patients approximately 12 hours and 1 hour prior to surgery. Concentrations of ketorolac in aqueous humour sampled at the time of surgery were at the lower limit of detection (40 ng/ml) in 1 patient and below the quantitation limit in 7 patients dosed with 0.1% ketorolac trometamol. The average aqueous humour level of ketorolac in patients treated with 0.5% ketorolac trometamol was 95 ng/ml. Concentrations of PGE₂ in aqueous humour were 80 pg/ml, 40 pg/ml and 28 pg/ml in patients treated with vehicle, 0.1% ketorolac trometamol and 0.5% ketorolac trometamol, respectively.

In the 21-day multiple dose (TID) tolerance study in healthy subjects, only 1 of 13 subjects had a detectable plasma level pre-dose (0.021 µg/ml). In another group of 13 subjects, only 4 subjects showed very low plasma levels of ketorolac (0.011 to 0.023 µg/ml) 15 minutes after the ocular dose.

Thus, higher levels of ketorolac in the aqueous humour and very low or no detectable plasma levels after ophthalmic doses, suggest that the use of ketorolac trometamol by the ophthalmic route in treatment of ocular disorders results in quite low systemic absorption in patients.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Acute, subacute and chronic studies of ACULAR in experimental animals have established the safety of the drug. In addition, octoxinol 40 was separately evaluated for its ocular safety. ACULAR was found to be non-irritating, it did not demonstrate a local anaesthetic effect, it did not influence the healing of experimental corneal wounds in rabbits, it did not enhance the spread of experimental ocular infections of *Candida albicans*, *Herpes simplex virus* type one, or *Pseudomonas aeruginosa* in rabbits, and it did not increase the ocular pressure of normal rabbit eyes.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Benzalkonium chloride
Disodium Edetate
Octoxinol 40
Sodium hydroxide or hydrochloric acid (dilute), to adjust pH to 7.3-7.5
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 2 years.

Use within 28 days of first opening.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Low density polyethylene dropper bottles (with LDPE dropper tips) containing 5ml or 10ml of solution. Each bottle has a high impact polystyrene (HIPS) screw-cap.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals Ireland
Castlebar Road
Westport
Co. Mayo
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0148/057/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 June 1995

Date of last renewal: 27 July 2006

10 DATE OF REVISION OF THE TEXT

June 2019