SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Acular®.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ketorolac trometamol 5 mg/ml.

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

For the 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

ACULAR is indicated for the prophylaxis and reduction of inflammation and associated symptoms following ocular 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 pre-operatively and continuing for up to three weeks post-operatively.

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.

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 contraindicated in individuals who have previously exhibited sensitivities to these drugs.
sensitivities to these drugs.

4.4 Special warnings and precautions for use

It is recommended that ACULAR be 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 suggest 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 interaction

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).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of eye drops containing ketorolac trometamol 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 most frequent adverse events reported with the use of ACULAR are transient stinging and burning on instillation.

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 (≥ 1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥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

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:

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

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.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory agents, non-steroids
ATC code: *S01BC* 05.

ACULAR (ketorolac trometamol) is a non-steroidal anti-inflammatory agent demonstrating analgesic and anti-inflammatory activity. Ketorolac trometamol inhibits 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 intra-ocular pressure.

5.2 Pharmacokinetic properties

a) <u>General characteristics</u>

Absorption

Rabbit aqueous humor bioavailability:

Mean concentration of total radioactivity	0.856 µg-equiv./ml @ 0.5 hr 1.607 µg-equiv./ml @ 2 hr
T_{max}	3.38 hr
C_{max}	1.905 µg-equiv./ml
AUC (0-8 hr)	9.39 µg-equiv. hr/ml
Total AUC	13.53 µg-equiv. hr/ml
Half-life	3.77 hr
Absolute ocular bioavailability	3.7%

After topical ocular doses in the rabbit the half life of total radioactivity in aqueous humor was longer than after intracameral injection. 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.

Distribution

After ophthalmic doses were administered to rabbits, peak concentrations of radioactivity were achieved within 1 hour in the ocular tissues and were highest in the cornea (6.06 mcg-eq/ml). At 1 hour, the majority of the radioactivity (0.9% of administered dose) was recovered from the sclera (0.58%) and cornea (0.24%), and smaller amounts were recovered from the aqueous humor (0.026%), vitreous humor (0.023%), retina-choroid (0.018%), iris-ciliary body (0.007%) and lens (0.002%).

Relative to plasma AUC values, the AUC's in rabbits 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. After ophthalmic administration, concentrations of drug-related radioactivity were higher in the ocular tissues and lower in plasma compared with those after IV dosing.

Systemic Absorption

After ophthalmic doses in the rabbit, ketorolac was absorbed rapidly into the systemic circulation (T_{max}, 15 min). Plasma half-lives after ophthalmic doses (6.6 - 6.9 hr) were longer than those after IV administration (1.1 hr), suggesting that removal of drug from eye into the venous circulation may be rate-limiting. By comparison of drug levels in aqueous humor after intracameral injection vs. plasma levels after IV administration, ketorolac was shown to clear more rapidly from plasma (6 ml/min) than from the anterior chamber (11 mcl/min).

In the cynomolgus monkey, peak plasma levels of ketorolac occurred at 1.1 hr after the ophthalmic dose. The plasma half-life of ketorolac was similar after ophthalmic (1.8 hr) and IV doses (1.6 hr).

The majority of the ophthalmic dose was excreted in urine (66% in rabbit and 75% in monkey) and a small amount in faeces (11% in rabbit and 2% in monkey). The extent of systemic absorption after ophthalmic dosing averaged 73% in the rabbit and 76% in the cynomolgus monkey.

Metabolism

After ophthalmic administration in rabbits, ketorolac represented the major component (more than 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.

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, respectively. After IV dosing, the relative proportions of total radioactivity in urine averaged 6% as intact ketorolac, 68% as p-hydroxy ketorolac and 22% as polar metabolites.

In the monkey, intact ketorolac and its polar metabolite 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 IV dosing. Thus, the metabolism of ketorolac was qualitatively similar after ophthalmic and IV administration in the monkey and rabbit.

b) Characteristics in patients

Ketorolac tromethamine 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 humor 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 tromethamine. The average aqueous humor level of ketorolac in patients treated with 0.5% ketorolac tromethamine was 95 ng/ml. Concentrations of PGE_2 in aqueous humor were 80 pg/ml, 40 pg/ml and 28 pg/ml in patients treated with vehicle, 0.1% ketorolac tromethamine and 0.5% ketorolac tromethamine, 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 humor and very low or no detectable plasma levels after ophthalmic doses, suggest that the use of ketorolac tromethamine 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, sub-acute 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
1N Sodium hydroxide or 1N Hydrochloric acid, to adjust pH
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^{o} C

6.5 Nature and contents of container

Low density polyethylene dropper bottles (with LDPE dropper tips) containing 3 ml, 5 ml or 10 ml of solution. The drop size is 35 microlitres. Each bottle has a medium impact polystyrene (MIPS) screw-cap.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Allergan Ltd.

Marlow International
The Parkway
Marlow
Bucks SL7 1YL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00426/0082

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/07/2006

10 DATE OF REVISION OF THE TEXT

07/06/2019