Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

ACULAR 0.5% w/v eye drops, solution.

2. Qualitative and quantitative composition

One mL of solution contains:
Ketorolac tromethamine..... 5mg
Excipients with known effect:
Acular eye drops solution contains up to 0.1 mg per mL of benzalkonium chloride.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Eye drops, solution.
Clear solution.
pH: 6.8 – 7.6
Osmolality: 260 - 320 mOsmol/kg

4. Clinical particulars

4.1 Therapeutic indications

Ketorolac tromethamine is a drug that belongs to the group of non-steroidal anti-inflammatory drugs (NSAIDs). It is indicated in adults for the prevention and reduction of inflammation and associated symptoms after eye surgery.

4.2 Posology and method of administration

Posology

For topical use in the eye only.
Adults and the elderly (over 65 years):
Post-operative inflammation:
One drop of solution is instilled in the eye/eyes three times a day. The treatment starts 24 hours before surgery and lasts for up to three weeks after surgery.
Paediatric population:
There is no applicable use of Ketorolac tromethamine in the paediatric population for the indication: Prevention and reduction of inflammation after cataract surgery.
Method of administration:
The drops are applied by instillation into the conjunctival sac.
To prevent contamination, avoid the bottle dropper tip touching the eye or other surfaces.
To prevent absorption of the drug through the nasal mucosa, the nasolacrimal canal should be pressed with the fingers for 2-3 minutes after the drops have been applied. This may reduce systemic side effects and increase local activity.
If more than one medicinal product is used in the eye, the interval between the individual applications should not be shorter than 5 minutes.

4.3 Contraindications

Hypersensitivity to Ketorolac tromethamine to any of the excipients listed in section 6.1 There is a risk of cross-sensitivity to acetylsalicylic acid and other NSAIDs. This product is contraindicated in subjects with a history of hypersensitivity to medicines from this group.

4.4 Special warnings and precautions for use

It is recommended that Ketorolac tromethamine be used with caution in patients with a known predisposition to bleeding or taking medication that may prolong bleeding time.

Like other anti-inflammatory drugs, Ketorolac tromethamine can mask the usual signs of infection.

All NSAIDs may delay wound healing. Concomitant use of NSAIDs and topical steroids may increase this risk.

The use of Ketorolac tromethamine together with topical corticosteroids requires caution in patients suspected of having epithelial corneal damage.

The use of local NSAIDs may cause keratitis. In some patients the prolonged use of topical NSAIDs may lead to epithelial damage, corneal thinning, corneal erosion, ulceration or corneal perforation. These conditions can be dangerous for the vision. Patients with known corneal epithelial disorder should immediately stop using local NSAIDs and be closely monitored.

Local NSAIDs should be used with caution in patients with complications following eye surgery, corneal denervation, corneal epithelial defects, diabetes mellitus, eye diseases (e.g. Dry Eye Syndrome), rheumatoid arthritis or repeated eye surgery over a short period of time, as these conditions increase the risk of corneal adverse reactions that may be dangerous for the eyesight.

Post-marketing experience with topical NSAIDs suggests that using them more than 24 hours before surgery or over 14 days postoperatively may increase the risk of cornea side effects and their severity.

Ketorolac tromethamine contains benzalkonium chloride that can cause eye irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses. Patients should be instructed to remove contact lenses before Ketorolac tromethamine and wait for at least 15 minutes before re-insertion.

Bronchospasm or asthma exacerbation have been reported post-marketing in patients who have a known hypersensitivity to aspirin/NSAIDs or a history of asthma associated with the use of Ketorolac tromethamine. Caution is advised with the use of Ketorolac tromethamine in these patients (see section 4.8).

Adverse reactions can be minimized with the administration of the lowest effective dose and for the shortest duration of treatment sufficient to control the symptoms.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Ketorolac tromethamine can be safely used in combination with systemic and ophthalmic drugs such as antibiotics, sedatives, beta-blockers, carbonic anhydrase inhibitors, miotics, mydriatics, local anaesthetics

and cycloplegics.
Ketorolac tromethamine may delay or prolong the healing process. Local corticosteroids are also known to delay or prolong healing. Concomitant use of topical NSAIDs and topical corticosteroids may increase the risk of problems with the healing process (see section 4.4).

4.6 Pregnancy and Lactation

Pregnancy

There are insufficient data on the use of Ketorolac tromethamine tromethamine in pregnant women. Animal studies have shown reproductive toxicity. Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo/foetal development and/or postnatal development. Although very low systemic exposure is expected, Ketorolac tromethamine is not recommended during pregnancy.

Breast-feeding

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

Fertility

There are insufficient data on the effect on fertility in humans.

4.7 Effects on ability to drive and use machines

Ketorolac tromethamine may affect the ability to drive and use machines. Transient blurred vision may occur after instillation of the drops. Patients should not drive or operate machines while they have blurred vision.

4.8 Undesirable effects

The most common adverse reactions reported with the ocular use of Ketorolac tromethamine are transient burning and stinging sensations. Adverse reactions observed in clinical trials with ketorolac tromethamine are listed by system organ class (MedDRA) and are presented by frequency. The appropriate frequency category for each adverse drug reaction is based on the following convention: 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 (≥1/1000); not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse Reactions
Immune system disorders	Common	Hypersensitivity, including local allergic reactions
Nervous system disorders	Common	Headache
Eye disorders	Very common	Irritation (including burning sensation); pain (including stinging)
	Common	Superficial (punctate) keratitis, ocular and/or eyelid oedema, pruritus, conjunctival hyperaemia, eye

		infection, inflammation, iritis, corneal precipitation, retinal haemorrhage, cystoid macular oedema, eye trauma, increased intraocular pressure, blurred or reduced vision.
	Common	Corneal ulcer, corneal infiltration, dry eye, epiphora
	Not known	Corneal damage (e.g. thinning), erosion, epithelial damage and perforation*
Respiratory, thoracic and mediastinal disorders	Not known	Bronchospasm or asthma exacerbation**

* There have been unsolicited post-marketing reports of corneal damage, including thinning, erosion, epithelial damage and corneal perforation. These occur mainly in patients using concomitant topical corticosteroids and/or predisposing concomitant morbidity (see section 4.4).
** There are post-marketing reports of bronchospasm or asthma exacerbation in patients who have either a known hypersensitivity to aspirin/non-steroidal anti-inflammatory drugs or a history of asthma associated with Ketorolac tromethamine use.
None of the typical adverse reactions reported with systemic NSAIDs (including ketorolac tromethamine) were observed after dosing used for topical ophthalmic therapy.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 Pharmacy and Poisons Board- Pharmacovigilance Electronic Reporting System (PvERS); *https://pv.pharmacyboardkenya.org* .

4.9 Overdose
No cases of overdose have been reported. Overdose is unlikely to occur under the recommended method of administration. In case of accidental ingestion, it is recommended to take a large amount of liquids.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Ophthalmologicals. Anti-inflammatory agents, nonsteroids, ATC code: S01BC05
Ketorolac tromethamine belongs to the group of non-steroidal anti-inflammatory drugs. It has analgesic and anti-inflammatory activity.

Inhibits the enzyme cyclooxygenase, which plays a major role in the process of prostaglandin biosynthesis.
Ketorolac tromethamine has been shown to reduce prostaglandin levels in the aqueous humour following topical administration. Ketorolac tromethamine, administered systemically, does not cause mydriasis. Results from clinical studies have shown that Ketorolac tromethamine has no significant effect on intraocular pressure.

5.2 Pharmacokinetic properties

A) General characteristics:

Absorption

Bioavailability in rabbit aqueous humour:

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 eye bioavailability	3.7%

Following topical application in a rabbit, the half-life of total radioactivity in the aqueous humour is longer than after intra-chamber injection. This suggests that topical application may result in a reservoir effect in the corneal epithelium and a prolonged flow of drug from the reservoir into the aqueous humour.

Distribution

Following topical administration in rabbits, peak radioactivity concentrations were achieved within 1 hour in the ophthalmic tissues and were highest in the cornea (6.06 mcg-eq/ml). After 1 hour most of the radioactivity (0.9% of the administered dose) was recovered from the sclera (0.58%) and the cornea (0.24%), and smaller amounts were recovered from the aqueous humour (0.026%, retina-choroid (0.018%), irisciliary body (0.007%) and lens (0.002%).
Plasma AUC in rabbits was higher in the cornea (104 times), sclera (27 times), irisciliary body (5.8 times), retino-choroid (5.6 times), aqueous humour (3, 3 times) and half the vitreous body and lens. After ocular administration, the concentrations of drug-related radioactivity were higher in the ocular tissues and lower in plasma compared to those after intravenous administration.

Systemic absorption

Following administration of ketorolac to the rabbit eye, it is rapidly absorbed in the systemic circulation (Tmax, 15 min). Plasma half-life after ocular administration (6.6- 6.9 hours) is longer than that after intravenous administration (1.1 hours), suggesting that drug penetration from the eye into the venous circulation may be rate-limiting. When comparing drug levels in intraocular fluid after intra-chamber injection to plasma levels following intravenous administration, Ketorolac tromethamine clears faster than plasma (6 ml/min) than the anterior

chamber (11 mcl/min).
In the cynomolgus monkey peak plasma levels of Ketorolac tromethamine occur 1.1 hours after ophthalmic administration. The plasma half-life of Ketorolac tromethamine is similar after ocular administration (1.8 hours) and after intravenous (1.6 hours).
Most of the ocular dose is excreted in the urine (66% in the rabbit and 75% in the monkey) and a small amount in the faeces (11% in the rabbit and 2% in the monkeys). The mean rate of systemic absorption after ocular administration is 73% in the rabbit and 76% in the cynomolgus monkey.

Metabolism

Following ocular administration in rabbits, Ketorolac tromethamine is the major component (more than 90%) of radioactivity in the aqueous humour and plasma, and the polyhydroxy metabolite represents 5% of the plasma radioactivity. Ketorolac tromethamine is the major component (96%) of plasma radioactivity after topical administration in monkeys. Following ocular administration in the rabbit, 72%, 17% and 6% of the total radioactivity in the urine consists of intact Ketorolac tromethamine, p-hydroxy Ketorolac tromethamine and other polar metabolites. Following intravenous administration, the relative proportions of total radioactivity in urine were approximately 6% as intact Ketorolac tromethamine, 68% as p-hydroxy Ketorolac tromethamine and 22% as polar metabolites.
In the monkey, the intact Ketorolac tromethamine and its polar metabolite represent respectively 32% and 65% of the total radioactivity in the urine after ocular administration and 50% and 49%, respectively, of urine radioactivity after intravenous administration. Thus, the metabolism of Ketorolac tromethamine is qualitatively similar after ocular and intravenous administration in monkey and rabbit

B) Characteristics in patients:

Solutions of ketorolac tromethamine (0.1% or 0.5%) or vehicle were instilled into the eyes of patients approximately 12 hours and 1 hour before surgery. Concentrations of Ketorolac tromethamine in the intraocular fluid measured during the surgery were at the lower detection limit (40 ng/ml) in 1 patient and below the quantification limit in 7 patients who received 0.1% ketorolac tromethamine. The mean serum level of Ketorolac tromethamine in intraocular fluid of patients treated with 0.5% ketorolac tromethamine was 95 ng/ml. PGE2 concentrations in the aqueous humour are 80 pg/ml, 40 pg/ml and 28 pg/ml in vehicletreated patients, 0.1% ketorolac tromethamine and 0.5% ketorolac tromethamine.
In the 21-day repeated dose tolerability (TID) study in healthy volunteers, only 1 in 13 patients had a detectable pre-dose plasma level (0.021 µg/ml). In another group of 13 patients, only 4 patients showed very low plasma levels of Ketorolac tromethamine (0.011 to 0.023 µg/ml) 15 minutes after ocular administration.
Therefore, higher levels of Ketorolac tromethamine in the aqueous humour and very low or undetectable plasma levels after ocular

administration suggest that the use of ketorolac tromethamine ophthalmologically in the treatment of vision problems results in rather low systemic absorption in patients.

5.3 Preclinical safety data

Non-clinical data reveal no particular risk for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, reproductive and developmental toxicity. Acute, subacute and chronic studies of Ketorolac tromethamine in experimental animals have established the safety of the drug. In addition, octoxynol 40 was evaluated separately for its ocular safety. Ketorolac tromethamine has been shown to be non-irritating, has no local anaesthetic effect, has no effect on the cure of experimental corneal wounds in rabbits, does not improve the incidence of experimental Candida albicans, Herpes simplex virus type I or Pseudomonas aeruginosa infections in rabbits and does not increase the ocular pressure in rabbits with normal vision.

6. Pharmaceutical Particulars

6.1 List of Excipients

Benzalkonium chloride (10% aqueous solution)
Disodium edetate
Octoxynol 40
Sodium chloride
Sodium hydroxide
1N Hydrochloric acid
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

24 months,
30 days after first opening of the bottle.

6.4 Special Precautions for storage

Store bottle upright, below 25°C, and in the original carton in order to protect from light.

6.5 Nature and Content of container

White low-density polyethylene (LDPE) bottle with dropper tip and closed with a tamper-evident screw cap in a unit carton.
Pack size: 5 mL

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder

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8. **Marketing Authorization Number**
   14501
9. **Date of first authorization/renewal of the authorization**
   24th February, 2003
10. **Date of revision of the text**
    24th February, 2026