

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

TOROLAC EYE DROPS

Ketorolac Trometamol Ophthalmic, Solution 0.5% w/v

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 colorless to pale yellow liquid, practically free from particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ketorolac Trometamol Ophthalmic Solution is indicated for the prophylaxis and reduction of inflammation and associated symptoms following ocular surgery.

Ketorolac Trometamol Ophthalmic Solution 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 preoperatively and continuing for up to three weeks post-operatively.

Paediatric population

There is no relevant use of Ketorolac Trometamol Ophthalmic Solution 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 Ketorolac Trometamol Ophthalmic Solution 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 nonsteroidal anti-inflammatory drugs. Ketorolac Trometamol Ophthalmic Solution is contraindicated in individuals who have previously exhibited sensitivities to these drugs. sensitivities to these drugs.

4.4 Special warnings and special precautions for use

It is recommended that Ketorolac Trometamol Ophthalmic Solution 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, Ketorolac Trometamol Ophthalmic Solution 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 Ketorolac Trometamol Ophthalmic Solution 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 Ketorolac Trometamol Ophthalmic Solution, 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/nonsteroidal anti-inflammatory drugs or a past medical history of asthma associated with the use of Ketorolac Trometamol Ophthalmic Solution, which may be contributory. Caution is recommended in the use of Ketorolac Trometamol Ophthalmic Solution 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 FPPs and other forms of interaction

No interaction studies have been performed.

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

Ketorolac Trometamol Ophthalmic Solution 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, Ketorolac Trometamol Ophthalmic Solution is not recommended during pregnancy.

Breast-feeding

Ketorolac Trometamol Ophthalmic Solution 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 Ketorolac Trometamol Ophthalmic Solution 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 ($\geq 1/10$); 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 mKetorolac Trometamol Ophthalmic Solution 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/nonsteroidal anti-inflammatory

drugs or a past medical history of asthma, associated with the use of Ketorolac Trometamol Ophthalmic Solution 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.

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: S01BC 05.

Ketorolac Trometamol Ophthalmic Solution (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. Ketorolac Trometamol Ophthalmic Solution 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 Ketorolac Trometamol Ophthalmic Solution has no significant effect on intra-ocular pressure.

5.2 Pharmacokinetic properties

a) General characteristics

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 drugrelated 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 ml/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 PGE₂ 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 Ketorolac Trometamol Ophthalmic Solution in experimental animals have established the safety of the drug. In addition, octoxinol 40 was separately evaluated for its ocular safety. Ketorolac Trometamol Ophthalmic Solution was found to be nonirritating, 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:

Benzalkonium chloride

Sodium chloride

Disodium Edetate

Octoxynol 40

Sodium hydroxide for pH adjustment

Hydrochloric acid for pH adjustment

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

36 Months

Use solution within one month after opening the vial.

6.4 Special precautions for storage:

Store below 30°C.

Protect from light.

Keep out of reach of children.

6.5 Nature and contents of container:

5 ml filled in 5 ml 3-Piece container and packed in a single carton.

6.6 Instructions for use and handling and disposal

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

7. MARKETING AUTHORISATION HOLDER

Micro Labs Limited, No. 31, Race Course Road, Bangalore-560 001, India.

8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

07395/07282/NMR/2019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/05/2022

10. DATE OF REVISION OF THE TEXT

July 2023