SUMMARY OF PRODUCT CHARACTERISTICS

BROWN & BURK UK LTD
MODULE 1 ADMINISTRATIVE AND PRESCRIBING INFORMATION
MODULE 1.3 PRODUCT INFORMATION
KETOROLAC TROMETAMOL 0.5%w/v EYE DROPS, SOLUTION

1. NAME OF THE MEDICINAL PRODUCT

Ketorolac trometamol 0.5% w/v eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 5 mg of ketorolac trometamol (0.5 % w/v)

Excipients(s): contains benzalkonium chloride 0.1 mg/ml (0.01 %w/v)

For a the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye Drops, Solution.

Clear, colourless to pale yellow solution practically free from particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ketorolac trometamol 0.5% w/v eye drops, solution are indicated for the prophylaxis and reduction of inflammation and associated symptoms following ocular surgery.

4.2 Posology and method of administration

Posology
Adults and elderly:

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

Ketorolac trometamol 0.5% w/v eye drops, solution is not recommended for use in children or adolescents under the age of 18 years as there is no relevant experience with the medication in this age group.

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 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 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. Ketorolac trometamol 0.5% w/v eye drops, solution are contra-indicated in individuals who have previously exhibited hypersensitivity to these drugs.

4.4 Special warnings and precautions for use

It is recommended that Ketorolac trometamol 0.5% w/v eye drops, 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 0.5% w/v eye drops, solution may mask the usual signs of infection.

All non-steroidal ant-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 0.5% w/v eye drops, 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 undergoing complicated ocular surgery, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g. dry eye syndrome), rheumatoid arthritis, or repeat ocular surgery 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 0.5% w/v eye drops, 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/non steroidal anti-inflammatory drugs or a past medical history of asthma associated with the use of Ketorolac trometamol 0.5% w/v eye drops, solution, which may be contributory. Caution is recommended in the use of Ketorolac trometamol 0.5% w/v eye drops, solution in these individuals (see section 4.8)

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Ketorolac trometamol 0.5% w/v eye drops, solution have been safely administered with systemic and ophthahnic medications such as antibiotics, sedatives, beta blockers, carbonic anhydrase inhibitors, miotics, mydriatics and cycloplegics.

Ketorolac trometamol 0.5% w/v eye drops, 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).
If Ketorolac trometamol 0.5% w/v eye drops, solution are 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 or a limited amount of data from the use of ketorolac trometamol in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. Ketorolac trometamol 0.5% w/v eye drops are not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

Ketorolac trometamol 0.5% w/v eye drops, 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

Ketorolac trometamol 0.5% w/v eye drops, solution has no or negligible influence on the ability to drive and use machines.

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

4.8 Undesirable effects

The most frequent adverse events reported with the use of Ketorolac trometamol 0.5% w/v eye drops, solution are transient stinging and burning on instillation.

The frequency of adverse reactions 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 the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:

Immune system disorders

Common: Hypersensitivity including localised allergic reactions

Nervous system disorders

Uncommon: 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

Uncommon: Corneal ulcer

Corneal infiltrates

Blurred and/or diminished vision

Eye dryness

Epiphora

Iritis

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

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 Ketorolac trometamol 0.5% w/v eye drops, 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

There is no experience of overdose by the ophthalmic route. 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

Mechanism of action

Ketorolac trometamol is a non-steroidal anti-inflammatory agent demonstrating analgesic and anti-inflammatory activity.

Pharmacodynamic effects

Ketorolac trometamol inhibits the cyclo-oxygenase enzyme essential for biosynthesis of prostaglandins. Ketorolac 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 has no significant effect on intra-ocular pressure.

5.2 Pharmacokinetic properties

a) General characteristics

Absorption

Rabbit aqueous humour 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 corrnealcorneal 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 corrneacornea (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 ophthalamicophthalmic 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 (Tmax, 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 excreled 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.

Biotransformation

After ophthalmic administration in rabbits, ketorolac represented the major component (more than 90%) of radioactivity in aqueous humor and plasma and the p-hydroxy melabolitemetabolite 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 kelorolacketorolac 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 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 humor 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 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 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, or toxicity to reproduction and development.

Acute, sub-acute and chronic studies of ketorolac in experimental animals have established the safety of the drug. In addition, octoxynol 40 was separately evaluated for its ocular safety. Ketorolac 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
Octoxynol 40
Sodium hydroxide and / or Hydrochloric acid (for pH adjustment)
Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 36 Months

Use within 28 days of first opening.

6.4 Special precautions for storage

This product does not require any special storage conditions.

6.5 Nature and contents of container

White low density polyethylene (LDPE) container with translucent LDPE block nozzle and white high density polyethylene (HDPE) screw caps. Bottles are available as 3 ml, 5 ml and 10 ml eye drops. Each pack contains either 1 bottle of 3ml, 1 bottle of 5ml, 3 bottles of 5ml or 1 bottle of 10ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

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

Using the drops for the first time: These eye drops come in a bottle with a coned shaped nozzle and screw cap. The inside of the screw cap contains a spike. The screw cap is fitted to the bottle in such a way that there is no contact between the spike and the top of the nozzle of the bottle. In order to open the bottle it is necessary to tighten the screw cap further, so that the edge of the screw cap and the nozzle edge are totally aligned. At this point the screw cap spike will pierce the top of the nozzle of the bottle which will open the bottle. Once the bottle has been opened in this way, unscrew the screw cap fully to remove it from the bottle and apply the eye drops.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

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