For the use of a Registered Medical Practitioner or a Hospital or a Laboratory

Ketorolac Tromethamine 0.4% w/v Ophthalmic Solution

# KETSENZ®

For the use of Registered Medical Practitioner only

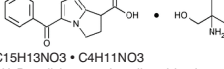
**Composition:**

Ketorolac Tromethamine USP …….... 0.4% w/v

Benzalkonium Chloride Solution USP ..... 0.02% v/v (as preservative)

Water for Injection USP ……..…….. q.s

**Chemical Structure & Name**



C15H13NO3 • C4H11NO3

1*H* -Pyrrolizine-1-carboxylic acid, 5-benzoyl-2,3-dihydro, (±)-, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1). (±)-5-Benzoyl-2,3-dihydro-1*H* -pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)

**Category**

*Pharmacotherapeutic group:* Anti-inflammatory agents, non-steroids

*ATC code:* S01BC 05.

**Description**

A clear colourless solution filled in 5mL Sterile Gamma-irradiated white opaque LDPE bottle sealed with Sterile Gamma-irradiated natural transparent LDPE open nozzle and Sterile Gamma-irradiated white HDPE tamp safe cap.

**Pharmacology**

Ketorolac Tromethamine is a non-steroidal anti-inflammatory agent demonstrating analgesic and anti-inflammatory activity. Ketorolac Tromethamine inhibits the cyclo-oxygenase enzyme essential for biosynthesis of prostaglandins. Ketorolac Tromethamine has been shown to reduce prostaglandin levels in the aqueous humour after topical ophthalmic administration.

Ketorolac Tromethamine given systemically does not cause pupil constriction. Results from various clinical studies indicate that Ketorolac Tromethamine 0.4% w/v Ophthalmic Solution has no significant effect on intra-ocular pressure.

**Pharmacokinetic:**

***Absorption and Distribution***

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.

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 (11mcl/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.

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 mcgeq/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%), irisciliary 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.

**Metabolism and Excretion**

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.

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% ketorolactromethamine 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.

**Indications**

Ketorolac Tromethamine 0.4% w/v Ophthalmic Solution is indicated for the prophylaxis and reduction of inflammation and associated symptoms following ocular surgery. Ketorolac Tromethamine 0.4% w/v Ophthalmic Solution is indicated in adults.

**Dosage & Administration**

**Dosage**

**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 Ketorolac Tromethamine 0.4% w/v Ophthalmic Solution in thepaediatric population as the indication is for the prophylaxis and reduction of inflammation following cataract surgery.

**Method of Administration:**

Ocular use.

Instill 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 Tromethamine 0.4% w/v Ophthalmic Solution is used concomitantly with other topical eye medications there must be an interval of at least 5 minutes between the two medications.

**Contraindications**

Hypersensitivity to the active substance or to any of the excipients.

The potential exists for cross-sensitivity to acetylsalicylic acid and other non-steroidal antiinflammatory drugs. Ketorolac Tromethamine 0.4% w/v Ophthalmic Solution is contraindicated in individuals who have previously exhibited sensitivities to these drugs.

**Warning and Precaution**

It is recommended that Ketorolac Tromethamine 0.4% w/v 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 Tromethamine 0.4% w/v Ophthalmic Solution masks 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 Tromethamine 0.4% w/v 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 of Ketorolac Tromethamine 0.4% w/v 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/non-steroidal anti inflammatory drugs or a past medical history of asthma, associated with the use of Ketorolac Tromethamine 0.4% w/v Ophthalmic Solution, which may be contributory. Caution is recommended in the use of Ketorolac Tromethamine 0.4% w/v Ophthalmic Solution in such individuals. 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. Transient blurring of vision may occur on instillation of eye drops. Do not drive or use hazardous machinery unless vision is clear.

**Interactions**

No interaction studies have been performed.

Ketorolac Tromethamine 0.4% w/v 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 Tromethamine 0.4% w/v 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.

**Pregnancy & Lactation**

**Pregnancy**

There are no adequate data from the use of eye drops containing Ketorolac Tromethamine 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 Tromethamine 0.4% w/v Ophthalmic Solution is not recommended during pregnancy.

**Lactation**

Ketorolac Tromethamine 0.4% w/v Ophthalmic Solution should not be used during lactation. Ketorolac Tromethamine is excreted in human milk after systemic administration.

**Adverse reaction**

The most frequent adverse events reported with the use of Ketorolac Tromethamine 0.4% w/v Ophthalmic Solution are transient stinging and burning on instillation.

The frequency of adverse reactions documented during clinical trials of Ketorolac Tromethamine 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, Conjunctivalhyperaemia, 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

***Respiratory, thoracic and mediastinal disorders***

*Not known:* Bronchospasm or exacerbation of asthma

None of the typical adverse reactions reported with the systemic non-steroidal antiinflammatory agents (including Ketorolac Tromethamine) have been observed at the doses used in topical ophthalmic therapy.

**Overdosage**

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

**Storage**

Store between 15°C - 30 °C. Protect from light

Keep out of reach of children.

**Shelf life**

24 Months from the date of manufacture.

**Presentation**

5mL of clear colourless solution filled in Sterile Gamma-irradiated white opaque LDPE bottle sealed with Sterile Gammairradiated natural transparent LDPE open nozzle and Sterile Gamma-irradiated white HDPE tamp safe cap.

**Directions for use :**

Turn the tamper proof cap anti-clockwise to break the seal.

Remove the cap, dispense drops with gentle pressure.

Replace the cap immediately after every use.

Manufactured in INDIA by :

**Senses Pharmaceuticals Pvt. Ltd.,**

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EKTPI-02

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