

CENTAGESIC Eye Drops

Composition –

Each mL of **CENTAGESIC** ophthalmic solution contains Ketorolac tromethamine 0.5%.

Description –

CENTAGESIC (ketorolac tromethamine ophthalmic solution) is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs) for ophthalmic use. **CENTAGESIC** ophthalmic solution is supplied as a sterile isotonic aqueous 0.5% solution, with a pH of 7.4.

CENTAGESIC ophthalmic solution is a racemic mixture of R- (+) and S- (-)- ketorolac tromethamine.

Clinical pharmacology –

CENTAGESIC [Ketorolac tromethamine] is a nonsteroidal anti-inflammatory drug which, when administered systemically, has demonstrated analgesic, anti-inflammatory, and anti-pyretic activity. The mechanism of its action is thought to be due to its ability to inhibit prostaglandin biosynthesis. Ketorolac tromethamine given systemically does not cause pupil constriction.

Prostaglandins have been shown in many animal models to be mediators of certain kinds of intraocular inflammation. In studies performed in animal eyes, prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilation, increased vascular permeability, leukocytosis, and increased intraocular pressure.

Prostaglandins also appear to play a role in the miotic response produced during ocular surgery by constricting the iris sphincter independently of cholinergic mechanisms.

Concentration of CENTAGESIC in aqueous humor –

Mean concentration 95ng/mL aqueous humor; range 40 to 170 ng/mL.

The post-dose PGE₂ concentration of CENTAGESIC –

Ocular administration of ketorolac tromethamine reduces prostaglandin E₂ (PGE₂) levels in aqueous humor. The mean concentration of PGE₂ was 80 pg/mL in the aqueous humor of eyes receiving vehicle and 28 pg/mL in the eyes receiving **CENTAGESIC** 0.5% ophthalmic solution.

The post-dose systemic concentration of CENTAGESIC –

One drop (0.05 mL) of 0.5% **CENTAGESIC** ophthalmic solution was instilled into one eye and one drop of vehicle into the other eye TID in 26 normal subjects. Only 5 of 26 subjects had a detectable amount of ketorolac in their plasma (range 10.7 to 22.5 ng/mL) at day 10 during topical ocular treatment. When ketorolac tromethamine 10 mg is administered systemically every 6 hours, peak plasma levels at steady state are around 960 ng/mL.

Indications and usage

CENTAGESIC ophthalmic solution is indicated for the treatment of postoperative pain and inflammation in patients who have undergone cataract extraction.

CENTAGESIC ophthalmic solution is indicated for the prevention of cystoid macular edema [CME] after cataract surgery.

Contraindications

CENTAGESIC ophthalmic solution is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation.

Warnings

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory agents. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs. With some nonsteroidal anti-inflammatory drugs, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

PRECAUTIONS

General: All topical nonsteroidal anti-inflammatory drugs (NSAIDs) may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems. Use of topical NSAIDs may result in keratitis. In some susceptible 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.

Postmarketing experience with topical NSAIDs suggests that 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 may be at increased risk for corneal adverse events which may become sight threatening. **Topical NSAIDs should be used with caution in these patients.**

Postmarketing experience with topical NSAIDs also suggests 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.

It is recommended that **CENTAGESIC** ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications, which may prolong bleeding time.

Information for Patients: **CENTAGESIC** ophthalmic solution should not be administered while wearing contact lenses.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Ketorolac tromethamine was not carcinogenic in rats given up to 5 mg/kg/day orally for 24 months. [151 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in humans and animals] nor in mice given 2

mg/kg/day orally for 18 months [60 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in humans and animals].

Ketorolac tromethamine was not mutagenic *in vitro* in the Ames assay or in forward mutation assays. Similarly, it did not result in an *in vitro* increase in unscheduled DNA synthesis or an *in vivo* increase in chromosome breakage in mice. However, ketorolac tromethamine did result in an increased incidence in chromosomal aberrations in Chinese hamster ovary cells.

Ketorolac tromethamine did not impair fertility when administered orally to male and female rats at doses up to 272 and 484 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis, assuming 100% absorption in humans and animals.

Pregnancy:

CENTAGESIC ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of **CENTAGESIC** ophthalmic solution during late pregnancy should be avoided.

Nursing Mothers: Caution should be exercised when **CENTAGESIC** ophthalmic solution is administered to a nursing woman.

Pediatric Use: Safety and efficacy in pediatric patients below the age of 3 have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

Adverse Reactions

The most frequent adverse events reported with the use of ketorolac tromethamine ophthalmic solutions have been transient stinging and burning on instillation. These events were reported by up to 40% of patients participating in clinical trials.

Other adverse events occurring approximately 1 to 10% of the time during treatment with ketorolac tromethamine ophthalmic solutions included allergic reactions, corneal edema, iritis, ocular inflammation, ocular irritation, superficial keratitis and superficial ocular infections.

Other adverse events reported rarely with the use of ketorolac tromethamine ophthalmic solutions included: corneal infiltrates, corneal ulcer, eye dryness, headaches, and visual disturbance (blurry vision).

Dosage and Administration

For the treatment of postoperative inflammation in patients who have undergone cataract extraction, one drop of **CENTAGESIC** ophthalmic solution should be applied to the affected eye(s) four times daily beginning 24 hours before cataract surgery and continuing through the first 2 weeks of the postoperative period.

CENTAGESIC ophthalmic solution has been safely administered in conjunction with other ophthalmic medications such as antibiotics, beta-blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics.

How Supplied: **CENTAGESIC** is supplied sterile in transparent lupolen 10 mL bottle.

Store at room temperature 15°C – 30°C (59°F- 86°F) with protection from light.

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