SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
ACUFIX 0.4% Eye Drops, Solution
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml solution contains:
Active substance(s):
Ketorolac trometamol_____4 mg
Excipient(s) with known effect:
Benzalkonium chloride_____0.06 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Eye drops.
Clear and colorless solution free from visible particles.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
ACUFIX is indicated for the reduction of ocular symptoms such as ocular pain and foreign body sensation, photophobia, burning/stinging and tearing following corneal refractive surgery.

4.2. Posology and method of administration
Posology/frequency and duration of administration
The recommended dose of ACUFIX is one drop four times a day in the operated eye as needed for pain and burning/stinging for 4 days following corneal refractive surgery.

Method of administration
It is instilled into the eye(s). Once opened, it should be used within 4 weeks provided that it is stored below 25°C.

Patients should be advised not to allow the tip of the bottle to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Additional information on special populations
- **Hepatic/Renal impairment:**

There is no report on ophthalmic use in hepatic/renal impairment.

- **Pediatric population:**

The safety and efficacy of ketorolac trometamol in pediatric patients under 3 years of age have not yet been established.

- **Geriatric population:**

Dose adjustment is not necessary for elderly. No differences in safety and efficacy were observed between young and elderly patients.

4.3. Contraindications

ACUFIX is contraindicated in individuals with a known history of hypersensitivity to ketorolac trometamol or any of its ingredients (see section 4.8 'Undesirable Effects').

4.4. Special warning and precautions for use

Cross-sensitivity or Hypersensitivity:

There is potential of cross-sensitivity in acetylsalicylic acid, phenylacetic acid and its derivatives and other nonsteroidal anti-inflammatory agents. There have been 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 ophthalmic solution. Caution is recommended in the individuals who demonstrated hypersensitivity to these drugs.

Increased Bleeding Time:

There is potential for increased bleeding time due to interactions of some nonsteroidal anti-inflammatory drugs with thrombocyte aggregation. There have been reports that ocularly administered nonsteroidal anti-inflammatory drugs can cause increased bleeding in ocular tissues (including hyphemas) associated with ocular surgery.

Delayed Healing:

All topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ketorolac trometamol ophthalmic solution can slow or delay healing. Topical corticosteroids are also known to delay or slow healing. Concomitant use of topical NSAIDs and topical steroids can increase the potential for problems with healing.

Corneal Effects:

Topical NSAID use can result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial damage, corneal thinning, corneal erosion, corneal ulceration and perforation. These events can threaten vision. In patients with proven corneal epithelial damage, topical NSAID use should be discontinued immediately and corneal health should be closely monitored.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface disease (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.

Post-marketing 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 to use ACUFIX with caution in patients with known bleeding tendencies or who are receiving other medications, which may prolong bleeding time.

ACUFIX should not be used while wearing contact lenses.

The efficacy and safety of ketorolac trometamol in pediatric patients under 3 years of age have not been established.

ACUFIX may cause eye irritation as it contains benzalkonium chloride as a preservative. Avoid contact with soft lenses. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Benzalkonium chloride is known to discolor soft contact lenses.

4.5. Interaction with other medicinal products and other forms of interaction
Concomitant use of topical NSAID and topical steroids may increase the potential for issues related to healing.

There should be an interval of at least 5 minutes between two drugs if it is to be used together with other topical eye drops.

It is recommended to use ACUFIX with caution in patients who have bleeding tendency or are taking other medications that prolong bleeding time.

Ketorolac trometamol ophthalmic solutions has been safely administered with other ophthalmic drugs such as alpha agonists, antibiotics, beta-blockers, carbonic anhydrase inhibitors, cycloplegics and mydriatics. There have been no reports of interactions of ketorolac tromethamine (trometamol) ophthalmic solution 0.5% with topical or injectable drugs used in ophthalmology pre□, intra, or post□operatively, including antibiotics (e.g., gentamicin, tobramycin, neomycin, polymyxin), sedatives (e.g., diazepam, hydroxyzine, lorazepam, promethazine HCl), miotics, mydriatics, cycloplegics (e.g., acetylcholine, atropine, epinephrine, physostigmine, phenylephrine, timolol maleate), hyaluronidase, local anesthetics (e.g., bupivicaine HCl, cyclopentolate HCl, lidocaine HCl, tetracaine), or corticosteroids.

Additional information on specific populations:
No interaction studies have been conducted.

Pediatric population:
No interaction studies have been conducted.

Geriatric population:
No interaction studies have been conducted.

4.6. Fertility, pregnancy and lactation
General recommendation
Pregnancy category is C.

Women of childbearing potential / Contraception
There is no special warning for women of childbearing potential.

Pregnancy
The use of the drug should be decided by the physician by evaluating the possible risk/benefit ratio on the fetus. ACUFIX should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Studies on animals are insufficient in terms of effects on pregnancy / and-or / embryonal / fetal development / and-or / birth / and-or / postpartum development. Potential risks on humans are not known.

Due to the known effects of prostaglandin inhibitor drugs on the fetal cardiovascular system of rats (closure of the ductus arteriosus), ACUFIX should not be used in late pregnancy.

Lactation
It is not known whether ketorolac is excreted in milk following topical application. Since many drugs are excreted in milk, ACUFIX should be used with caution in lactating women.

Reproductive ability / Fertility
No effect on human fertility/reproductive ability has been reported for topical ophthalmic use.

4.7. Effects on ability to drive and use machines
No information has been reported regarding the effects of topical ophthalmic use on driving or using machines. However, caution should be exercised. If temporary blurring of vision occurs during instillation, the patients should wait until their vision becomes clear before driving or operating machinery.

4.8. Undesirable effects
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).

Immune system disorders
Common: Allergic reaction (eye swelling, eyelid edema and hyperemia)

Nervous system disorders
Common: Headache

Eye disorders
Very common: Temporary burning and stinging following instilling the drug, conjunctival hyperemia, corneal infiltrates, ocular edema, ocular pain
Common: Corneal edema, iritis, ocular inflammation, superficial keratitis and superficial ocular infections
Rare: Corneal ulcer, eye dryness and vision disorders (blurred vision)

For the following serious adverse reactions, see section 4.4 'Special warnings and precautions for use':
- Delayed Healing
- Cross-sensitivity and hypersensitivity
- Increased Bleeding Time
- Corneal Effects

The following side effects have been identified during post-marketing use of ketorolac trometamol ophthalmic solution in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to topical ketorolac trometamol ophthalmic solution or a combination of these factors, include bronchospasm or exacerbation of asthma, corneal erosion, corneal perforation, corneal thinning and corneal melt, and epithelial breakdown.

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 in accordance with local requirements.

4.9. Overdose
No overdose cases associated with administration ocularly have been reported. In case of overdose, symptomatic and supportive treatment should be administered and diluted by applying plenty of fluids.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic group: Ophthalmologicals, Antiinflammatory agents, non-steroids
ATC code: S01BC05

Ketorolac trometamol is a nonsteroidal anti-inflammatory drug with analgesic, anti-inflammatory and antipyretic effects when administered systemically. Its mechanism of action is thought to be due to its inhibition of prostaglandin biosynthesis. Prostaglandins have been shown to be mediators of various types of intraocular inflammation. Ketorolac trometamol administered systemically does not cause pupillary constriction.

5.2. Pharmacokinetic properties
General properties
In 26 healthy volunteers, one drop of 0.5% ketorolac trometamol ophthalmic solution was instilled in one eye and one drop of carrier in the other eye three times daily. During topical ocular therapy, ketorolac was found in detectable concentrations (range 11-23 ng/mL) in the plasma of 5 of 26 volunteers on day 10.
When two drops of 0.5% ketorolac trometamol ophthalmic solution were instilled in the eyes of patients 12 hours and 1 hour prior to cataract extraction, the mean ketorolac concentration in the aqueous humor of 8 of 9 eyes tested was 95 ng/mL (range 40 – 170 ng/mL). .

Ocular pharmacokinetics:
The available data on the ocular pharmacokinetics of ketorolac trometamol is as follows:

Absorption:
^{14}C-labeled ketorolac trometamol was rapidly absorbed into the eye after a single dose in rabbits. While T_{max} was 0.5 hours after intracameral application; T_{max} was 1 hour in humoral aqueous in non-anesthetized and an average of 3.4 hours in in anesthetized rabbits following topical application. In unanesthetized rabbits, drug half-lives in the humoral aqueous and cornea were 7.1 and 8.2 hours, respectively.

Distribution:
It is widely distributed to ocular tissues, mainly cornea and sclera. Maximum tissue concentrations were seen 0.5 - 1 hour after administration, with the exception of the iris-ciliary body, which required 4 hours to reach T_{max}. Peak drug concentration (C_{max}) is 6.06 mcg µgEq/g in the cornea and 1.73 mcg µgEq/g in the sclera. The humoral aqueous peak concentration is 0.22 mcg µgEq/mL.

Biotransformation:
In systemic administration studies, the drug has been shown to be metabolized in the liver.

Elimination:
The route of drug removal from the eye is thought to be intraocular blood flow. According to results from clinical studies, ketorolac trometamol has no significant effect on intraocular pressure.

Linearity / Non-linearity
In human studies, penetration of the drug was rapid after application to the eye. The relationship between the applied solution concentrations and the amount of drug penetrating the cornea is roughly linear.

5.3. Preclinical safety data

Acute and Chronic Toxicity
In 12 preclinical toxicology studies with ketorolac trometamol in rabbits and cynomolgus monkeys at three time intervals (acute (1 day), subchronic (10 to 42 days), and chronic (6 and 12 months)); Dutch Belted Rabbits, one of the two rabbit species in the subchronic study with ketorolac trometamol were susceptible to the benzalkonium chloride (BAC) preservative system used in the vehicle. This rabbit breed is assumed to be sensitive due to its low blink rate and tear response to irritation. There were no other ocular irritation or toxicity associated with ketorolac administration in these animal studies.

Carcinogenesis, Mutagenesis, Fertility Disorder
Ketorolac trometamol was not found to be carcinogenic in rats given orally at doses up to 5 mg/kg/day for 24 months (151 times the maximum recommended human topical ophthalmic dose on a mg/kg basis, assuming 100% absorption in humans and animals) and in mice given orally at a dose of 2 mg/kg/day 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 trometamol was not mutagenic *in vitro* in the Ames test or forward mutation tests. Similarly, it did not result in an increase in unscheduled DNA synthesis *in vitro* or an increase in chromosome breakage in mice *in vivo*. However, ketorolac trometamol has led to an increased incidence of chromosomal aberrations in Chinese hamster ovary cells.

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

Ketorolac trometamol was not teratogenic when administered orally to rabbits and rats at up to 109 and 303 times the maximum recommended human topical ophthalmic dose during organogenesis, respectively, assuming 100% absorption in humans and animals on a mg/kg basis. Ketorolac trometamol caused dystocia and increased pup mortality when administered

orally to rats up to 45 times the maximum recommended human topical ophthalmic dose after day 17 of gestation, assuming 100% absorption on a mg/kg basis in humans and animals.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Benzalkonium chloride
Sodium chloride
Octoxinol 40
Disodium EDTA
Sodium hydroxide
Hydrochloric acid
Water for injections

6.2. Incompatibilities

Not reported.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at room temperature below 25°C.
Once the bottle has been opened, the solution should be used within 4 weeks provided that it is stored below 25°C.

6.5. Nature and contents of container

The primary packaging materials consist of an opaque, white, low-density polyethylene bottle (LDPE) containing 5 ml eye drops, LDPE dropper tip and pink HDPE screw cap. Each cardboard box includes 1 bottle and a package leaflet.

6.6. Special precautions for disposal and other handling

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

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER

2017/627

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

Date of first authorization : 24.08.2017
Date of renewal :

10. DATE OF REVISION OF THE TEXT

29.09.2023