SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DETOFEN 0.025% Eye Drops, Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
1 ml solution contains;
Ketotifen hydrogen fumarate…..345 mcg (equivalent to 250 mcg ketotifen)

Excipients:
1 ml solution contains;
Benzalkonium chloride 0.1 mg
Sodium hydroxide q.s.(for pH 5.2-5.5)

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile eye drops, solution
Clear and colorless, particle-free solution.

4. CLINICAL PARTICULARS

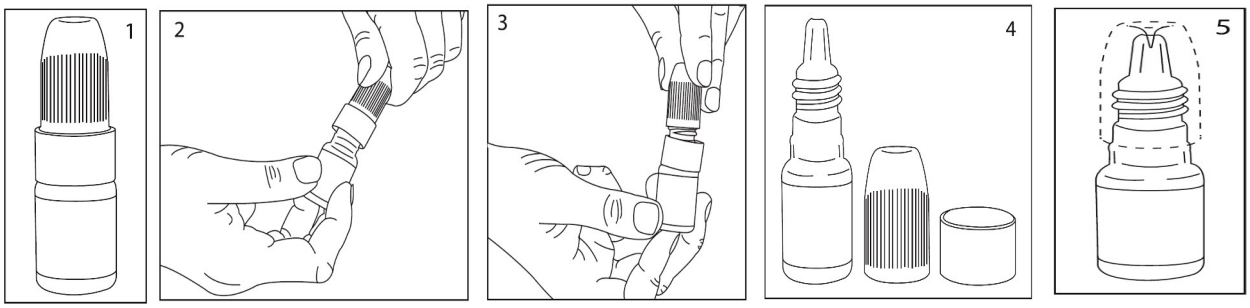
4.1 Therapeutic indications

It is indicated for the treatment of symptoms of allergic conjunctivitis.

4.2 Posology and method of administration

Posology/frequency and duration of administration:
Adults, elderly and children (age 3 and older): One drop is instilled into the conjunctival sac twice a day.

Method of administration
For ophthalmic use only. It is applied by instilling into the eyes.
It remains sterile until the original closure is opened. Patients should be warned that touching the dropper tip may contaminate the solution.



Wash your hands.
- Open the cap of the bottle.

- Remove the ring under the cap (see Figure 3 and Figure 4).
- Close the cap again without the ring. The plastic pin in the cap pierces the tip of the bottle (See Figure 5).

Apply it to your eyes as follows

1. Lean your head back; form a pouch between your eye and your eyelid by pulling down your lower eyelid with your finger.

2. Hold the bottle upside down with your other hand, upright above your eye. Squeeze the bottle gently so that one drop falls into the eye. Be careful not to let the tip of the dropper touch your hand or eye.

3. After instilling, press the tip of one finger on the inner corner of your eye for 1–2 minutes. This will prevent the drop running through the tear duct into your nose.

Additional information on special populations
Renal/Hepatic impairment:
The efficacy and safety of ketotifen in renal or hepatic impairment have not been studied.

Pediatric population:
The safety and efficacy of ketotifen in children under 3 years have not yet been established.

Geriatric population:
No dosage adjustment is required in the elderly.

4.3 Contraindications

It is contraindicated in patients with known hypersensitivity to ketotifen or any of the excipients.

4.4 Special warnings and precautions for use

DETOFEN contains benzalkonium chloride as a preservative, which may be deposited in soft contact lenses; therefore there should be no contact lenses in the eye during instillation of the drug. The contact lenses can be put back at least 15 minutes afterwards.
All eye drops preserved with benzalkonium chloride may possibly discolour soft contact lenses.

4.5 Interaction with other medicinal products and other forms of interaction

If DETOFEN is used concomitantly with other eye medications there must be an interval of at least 5 minutes between the two medications.

The use of oral ketotifen fumarate may potentiate the effect of CNS depressants, antihistamines and alcohol. The significance of this for ophthalmic products containing ketotifen fumarate is unknown.

4.6 Fertility, pregnancy and lactation

General recommendation
Pregnancy category: C

Women of child-bearing potential/Contraception
There is no recommendation for the use of this medicine in women of childbearing potential and those using contraception.

Pregnancy
There are no adequate data from the use of ketotifen in pregnant women. Animal studies using maternally toxic oral doses showed increased pre- and postnatal mortality, but not teratogenicity (see section 5.3). Systemic levels after ocular administration are generally lower than limits. DETOFEN should not be used during pregnancy unless necessary.

Breast-feeding
Although the medicine has been reported to pass into breast milk based on animal data following oral administration, it has not been found in detectable amounts in human breast milk following topical administration. Nevertheless, caution should be exercised when using DETOFEN during breastfeeding.

Reproduction ability / Fertility
The effect of ketotifen on fertility was studied in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Any patient who experiences blurred vision or somnolence should not drive or use machines.

4.8 Undesirable effects

The following side effects were observed at the recommended dose. Undesirable effect are listed as 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).

Ocular side effects:
Eye disorders
Common: Eye burning/stinging, punctate corneal epithelial erosion
Uncommon: Vision blurred during instillation, dry eye, eyelid disorder, conjunctivitis, eye pain, photophobia, subconjunctival hemorrhage

Systemic side effects:
Immune system disorders
Uncommon: Allergic reaction, dry mouth

Nervous system disorders
Uncommon: Headache, somnolence

Skin and subcutaneous tissue disorders
Uncommon: Rash, eczema, urticaria

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 via the national reporting system.

4.9 Overdose

No case of overdose has been reported.
Oral ingestion of the contents of a 5 ml bottle would be equivalent to 1.25 mg of ketotifen which is 60% of a recommended oral daily dose for a 3 year old child. Clinical results have shown no serious signs or symptoms after oral ingestion of up to 20 mg of ketotifen.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, other antiallergics
ATC code: S01GX08

Mechanism of action:
Ketotifen is a histamine H_1-receptor antagonist. Ketotifen also inhibits the release of mediators (e.g. histamine, leukotrienes and prostaglandins, and PAF) from cells involved in immediate type I allergic reactions (mast cells, eosinophils, basophils and neutrophils). Increased cAMP levels by phosphodiesterase inhibition may contribute to the cell stabilising effect of ketotifen.

5.2 Pharmacokinetic properties

General properties
Absorption:
In a pharmacokinetic study conducted in 18 healthy volunteers with ketotifen eye drops, plasma levels of ketotifen after repeated ocular administration for 14 days were in most cases below the limit of quantitation (20 pg/ml).

Distribution:
After oral administration, ketotifen is eliminated biphasically with an initial half-life of 3 to 5 hours and a terminal half-life of 21 hours.

Biotransformation:
The main metabolite is the practically inactive ketotifen-N-glucuronide.

Elimination:
About 1% of the substance is excreted unchanged in the urine within 48 hours and 60 to 70% as metabolites.

Linearity/non-linearity:
There is no data on linearity/non-linearity.

Characteristics in patients
There are no known significant pharmacokinetic changes in different patient groups.

5.3 Preclinical safety data

Preclinical data reveal no special hazard in humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

Carcinogenesis, Mutagenesis, Fertility Disorder

A number of *in vitro* and *in vivo* studies have shown that ketotifen fumarate is not mutagenic. These studies are: Ames test, *in vitro* chromosomal aberration test with V79 Chinese hamster cells, *in vivo* micronucleus test in mice and mouse dominant lethal test.

Treatment of male rats with oral ketotifen doses > 10 mg/kg/day (6,667 times the maximum recommended human ocular dose of 0.0015 mg/kg/day (MRHOD)) for 70 days prior to mating resulted in mortality and decreased fertility. Administration of ketotifen did not adversely affect fertility in female rats given 50 mg/kg/day (33.333 times the MRHOD) oral ketotifen for up to 15 days prior to mating.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Glycerol
Sodium hydroxide
Water for injections

6.2 Incompatibilities

There is not any known incompatibility.

6.3 Shelf life

24 months.
Once the bottle is opened, the medicine should be used within 28 days.

6.4 Special precautions for storage

Store at room temperature below 25°C.

6.5 Nature and contents of container

The primary packaging material consists of a 5 mL, opaque, white low-density polyethylene bottle with dropper, closed with white screw cap. It is supplied in a printed cardboard box with a package leaflet.

6.6 Special precautions for disposal and other handling

There are no special instructions for use.
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-ISTANBUL/TURKEY

8. MARKETING AUTHORIZATION NUMBER

2015/295

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

Date of first authorization: 02.04.2015
Date of renewal:

10. DATE OF REVISION OF THE TEXT

21.06.2021