

# DATA SHEET

## ZADITEN<sup>®</sup> Ketotifen 0.25mg/ml, eye drops, solution

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### Qualitative and Quantitative Composition

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Zaditen: One ml contains 0.345 mg ketotifen hydrogen fumarate corresponding to 0.25 mg ketotifen.

For excipients, see List of excipients.

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### Pharmaceutical Form

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**Multidose Formulation:** Eye drops, solution.

**Unpreserved Single Dose Units:** Eye drops, solution in single-dose containers.

Clear, colourless to faintly yellow solution.

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### Clinical Particulars

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#### ***Therapeutic indications***

Treatment and prevention of signs and symptoms of seasonal allergic conjunctivitis.

#### ***Dosage and method of administration***

Adults, elderly and children (age 3 and older): one drop of ZADITEN into the conjunctival sac twice a day.

Safety and effectiveness in paediatric patients below the age of 3 years have not been established.

**Multidose Formulation:** The contents and dispenser remain sterile until the original closure is broken. To avoid contamination do not touch any surface with the dropper tip.

**Unpreserved Single Dose Units:** The contents remain sterile until the original closure is broken. To avoid contamination do not touch any surface with the tip of the container.

#### ***Contraindications***

Hypersensitivity to ketotifen or to any of the excipients.

#### ***Special warnings and special precautions for use***

**Multidose Formulation:** The formulation of ZADITEN eye drops contains benzalkonium chloride as a preservative, which may be deposited in soft contact lenses; therefore ZADITEN eye drops should not be instilled while the patient is wearing these lenses. The lenses should

be removed before application of the drops and not reinserted earlier than 15 minutes after use.

All eye drops preserved with benzalkonium chloride may possibly discolour soft contact lenses.

**Unpreserved Single Dose Units:** No special warning.

### ***Interaction with other medicinal products and other forms of interaction***

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

### ***Pregnancy and lactation***

There are no adequate data from the use of ketotifen eye drops in pregnant women. Animal studies using maternally toxic oral doses showed increased pre- and postnatal mortality, but no teratogenicity. Systemic levels after ocular administration are much lower than after oral use. Caution should be exercised when prescribing to pregnant women.

Although animal data following oral administration show excretion into breast milk, topical administration to human is unlikely to produce detectable quantities in breast milk. ZADITEN eye drops can be used during lactation.

Oral treatment of pregnant rabbits during organogenesis with 45 mg/kg/day of ketotifen (30,000 times the Maximum Recommended Human Oral Dose) resulted in an increased incidence of retarded ossification of the sternbrae. However, no effects were observed in rabbits treated with up to 15 mg/kg/day (10,000 times the MRHOD). Similar treatment of rats during organogenesis with 100 mg/kg/day of ketotifen (66,667 times the MRHOD) did not reveal any biologically relevant effect.

Oral treatment of pregnant rats (up to 100 mg/kg/day or 66,667 times the MRHOD) and rabbits (up to 45 mg/kg/day or 30,000 times the MRHOD) during organogenesis did not reveal any biologically relevant embryofetal toxicity. In the offspring of the rats that received ketotifen orally from day 15 of pregnancy to day 21 post partum at 50 mg/kg/day (33,333 times the MRHOD), a maternally toxic treatment protocol, the incidence of postnatal mortality was slightly increased, and body weight gain during the first four days post partum was slightly decreased.

### ***Effects on ability to drive and use machines***

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

### ***Adverse effects***

At the recommended dose, the following adverse effects have been reported.

#### **Ocular side effects:**

between 1% and 2%: burning/stinging, punctate corneal epithelial erosion.

<1%: blurring of vision upon drug instillation, dry eyes, eyelid disorder, conjunctivitis, eye pain, photophobia, subconjunctival haemorrhage.

#### **Systemic side effects:**

<1%: headache, somnolence, skin rash, eczema, urticaria, dry mouth and allergic reaction.

## Overdose

No case of overdose has been reported.

**Multidose Formulation:** 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.

**Unpreserved Single Dose Units:** Oral ingestion of the contents of a single-dose container would be equivalent to 0.1 mg of ketotifen which is 5% 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.

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## Pharmacological Properties

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### ***Pharmacodynamic properties***

Pharmacotherapeutic group: Ophthalmologicals, other antiallergics ATC code: S01GX08

Ketotifen is a histamine H<sub>1</sub>-receptor antagonist. *In vivo* and *in vitro* ketotifen 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). Ketotifen also decreases chemotaxis, activation and degranulation of eosinophils. Increased cAMP levels by phosphodiesterase inhibition may contribute to the cell stabilising effect of ketotifen.

### ***Pharmacokinetic properties***

In a pharmacokinetic study conducted in 18 healthy volunteers with ZADITEN 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).

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. About 1% of the substance is excreted unchanged in the urine within 48 hours and 60 to 70% as metabolites. The main metabolite is the practically inactive ketotifen-N-glucuronide.

### ***Preclinical safety data***

Preclinical data reveal no special hazard which is considered relevant in connection with use of ZADITEN eye drops in humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

### **Carcinogenesis, Mutagenesis, Impairment of Fertility:**

Ketotifen fumarate was determined to be non-mutagenic in a battery of *in vitro* and *in vivo* mutagenicity assays including: Ames test, *in vitro* chromosomal aberration test with V79 Chinese hamster cells, *in vivo* micronucleus assay in mouse, and mouse dominant lethal test.

Treatment of male rats with oral doses of ketotifen  $\geq 10$  mg/kg/day orally [6,667 times the maximum recommended human ocular dose of 0.0015 mg/kg/day on a mg/kg basis (MRHOD)] for 70 days prior to mating resulted in mortality and a decrease in fertility. Treatment with ketotifen did not impair fertility in female rats receiving up to 50 mg/kg/day of ketotifen orally (33,333 times the MRHOD) for 15 days prior to mating.

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## Pharmaceutical Particulars

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### ***List of excipients***

#### **Multidose Formulation:**

Benzalkonium chloride  
Glycerol (E422)  
Sodium hydroxide (E524)  
Water for injections

#### **Unpreserved Single Dose Units:**

Glycerol (E422)  
Sodium hydroxide (E524)  
Water for injections

### ***Incompatibilities***

Not applicable

### ***Shelf life***

**Multidose Formulation:** In unopened bottle: 2 years.

The product remains within specifications for 4 weeks after opening.

**Unpreserved Single Dose Units:** In unopened blister: 2 years.

Opened blister: 28 days.

Single-dose containers stored without blister in the outer carton: 3 months.

After opening, the contents of a single-dose container should be used immediately.

### ***Special precautions for storage***

**Multidose Formulation** and **Unpreserved Single Dose Units:** Do not store above 25 °C.

### ***Nature and contents of container***

**Multidose Formulation:** The container is a white-coloured Low Density PolyEthylene (LDPE) bottle with a transparent LDPE dropper and a white HDPE screw cap with an integrated safety ring. One bottle contains 5 ml of the solution.

**Unpreserved Single Dose Units:** The container is a transparent 0.4 ml LDPE single-dose container. Blocks of 5 single-dose containers are each packed in a blister made of PVC, aluminium, polyamide tray sealed with an aluminium foil cover and paper layer. Carton boxes of 20 single-dose containers.

### ***Instructions for use and handling***

**Unpreserved Single Dose Units:** Single-dose containers must be discarded after use.

After opening a blister, any unused single-dose containers should be discarded after 4 weeks unless they have been stored in the outer carton, in which case they should be discarded after 3 months.

**Medicine classification**

Pharmacy Medicine  
Except when sold in practice by a registered optometrist.

**Sponsor**

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