

PRODUCT MONOGRAPH

^{Pr}**ZADITOR***

Ketotifen Fumarate Ophthalmic Solution
(0.025% as ketotifen)

Anti-allergy Agent

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*ZADITOR is a registered trademark

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ZADITOR*

Ketotifen Fumarate Ophthalmic Solution

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Topical (instillation)	Ophthalmic Solution 0.025% as ketotifen	Preservative benzalkonium chloride 0.01% <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

ZADITOR* (ketotifen fumarate ophthalmic solution) is indicated for:

- treatment of allergic conjunctivitis.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

General

For topical use only. Not for injection or oral use.

As with all ophthalmic preparations containing benzalkonium chloride, patients are advised not to instill ZADITOR* (ketotifen fumarate ophthalmic solution) while wearing soft (hydrophilic) contact lenses. Wearers of soft contact lenses should be instructed to remove lenses prior to instillation of drops and to wait at least ten minutes after instilling ZADITOR™ before they insert their contact lenses.

To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep the bottle tightly closed when not in use.

Special Populations

Pregnant Women: There are no clinical trials on the use of ZADITOR* (ketotifen fumarate ophthalmic solution) in pregnant or nursing women, therefore, ZADITOR* should not be used during pregnancy, except if the benefit justifies the potential risk to the foetus.

Pediatrics (> 3 years of age): ZADITOR* is indicated for use in pediatric patients over the age of 3 years.

ADVERSE REACTIONS

In controlled clinical studies with ZADITOR* (ketotifen fumarate ophthalmic solution), conjunctival injection was the most common ocular adverse reaction related to therapy, with a reported incidence of 7.0%. Headache was the most common non-ocular adverse reaction related to therapy, with a reported incidence of 1.5%. The occurrence of these side effects were generally mild and did not result in discontinuation or interruption of trial medication.

The following ocular adverse reactions related to therapy were reported at an incidence of less than 3%.

Itching, dry eyes, burning or stinging, eyelid disorder and discharge.

DRUG INTERACTIONS

If ZADITOR* (ketotifen fumarate ophthalmic solution) is used concomitantly with other eye medications, patients should be advised to wait at least 5 minutes between the medications.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop in the affected eye(s) every 8 to 12 hours.

OVERDOSAGE

Oral ingestion of the contents of a 5 mL bottle would be equivalent to 1.25 mg of ketotifen fumarate. Clinical results have shown no serious signs or symptoms after the ingestion of up to 20 mg of ketotifen fumarate.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Ketotifen is a fast acting non-competitive histamine antagonist (H1-receptor). In addition, ketotifen inhibits the release of mediators from mast cells involved in hypersensitivity reactions. Decreased chemotaxis and activation of eosinophils has also been demonstrated. Additionally, ketotifen attenuates the effects of PAF and inhibits cAMP phosphodiesterase.

In human conjunctival allergen challenge studies, ZADITOR* (ketotifen fumarate ophthalmic solution) was significantly more effective than placebo in preventing ocular itching and redness associated with allergic conjunctivitis. The effect was seen within minutes after administration and lasted up to 12 hours.

Pharmacodynamics

In human conjunctival allergen challenge studies, ZADITOR* was significantly more effective than placebo in preventing ocular itching and redness associated with allergic conjunctivitis. The effect was seen within minutes after administration and lasted up to 12 hours.

In a placebo-controlled clinical study designed to evaluate safety, ZADITOR*, administered four times a day for 6 weeks, was shown to be safe and well-tolerated in subjects aged 3 years and older.

STORAGE AND STABILITY

Store between 4°C and 25°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each mL of ZADITOR* (ketotifen fumarate ophthalmic solution) contains:

Active: 0.345 mg ketotifen fumarate equivalent to 0.25 mg ketotifen.

Preservative: benzalkonium chloride 0.01%

Inactives: glycerol, hydrochloric acid/sodium hydroxide and purified water.

Packaging :

ZADITOR* is available in multi dose in white plastic bottles with controlled dropper tips containing 5 mL of clear solution.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

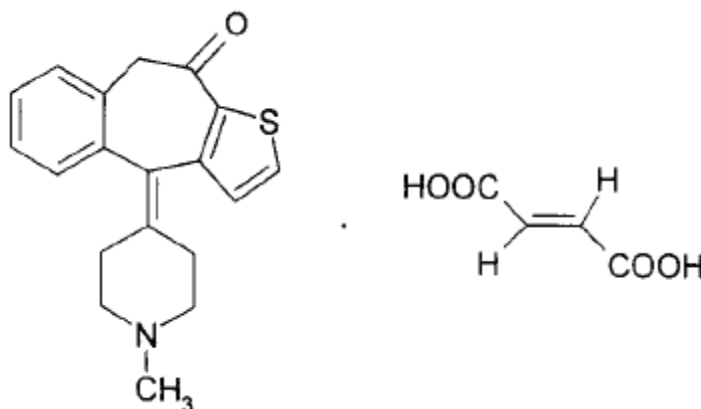
Proper name: Ketotifen fumarate

Chemical name: 4,9-Dihydro-4-(1-methyl-4-piperidylidene)-10Hbenzo[4,5]cyclohepta[1,2-b] thiophen-10-one fumarate

Molecular formula: $C_{19}H_{19}NOS + C_4H_4O_4$

Molecular Weight: 425.50

Structural formula:



Physicochemical properties:

Description: Fine crystalline, white to yellowish or brown-tinged yellowish powder

Solubility: In the form of the hydrogen fumarate, it is soluble in water.

pH: The pH of a 1.2% solution in water is 3.6

pKa Value $K_a I = 8.43 \pm 0.11$

Estimated with ketotifen base by linear extrapolation with values from 5 different mixtures in ethanol/water.

Melting Point: Ketotifen hydrogen fumarate melts with decomposition at about 190°C. Ketotifen hydrogen fumarate with 2.5 H₂O melts at approximately 130°C.

DETAILED PHARMACOLOGY

Pharmacodynamics

Ketotifen is a benzocycloheptathiophene derivative. Based upon animal pharmacology studies, it exerts anti-anaphylactic and antihistaminic activities, mainly through inhibition of the release of chemical mediators such as histamine and leukotrienes from sensitized mast cells. It also inhibits platelet activating factor (PAF)-induced acute bronchoconstrictor response, airway hyperresponsiveness and accumulation of eosinophils in the airways as well as antigen-induced degranulation of eosinophils in allergic subjects. In addition, ketotifen exhibits a powerful and sustained non-competitive H₁-receptor blocking activity distinctly dissociated from its antianaphylactic properties.

The efficacy of ophthalmic solutions of ketotifen fumarate was evaluated by a method utilizing dye leakage in the conjunctiva and/or eyeball following intravenous Evans blue dye. The procedure was originally described as an indicator of accelerated permeability in IgE-mediated conjunctivitis in rats. Ketotifen suppressed dye leakage dose dependently in a model system in which allergic-like effects were induced in the eyes of rats by the single instillation of compound 48/80, which induces the release of histamine and other inflammatory/allergy mediators from mast cells leading to ocular edema. Topical ketotifen ophthalmic solution also resulted in dose-dependent inhibition of vascular permeability in passive anaphylactic IgE-mediated conjunctivitis in rats and guinea pigs. These positive effects on IgE-mediated conjunctivitis in rats were also supported by an improved histopathological picture.

Pharmacokinetics

After topical single or repeated administrations of 50 mL drops of approximately 10 mg/mL in albino rabbits, the highest levels of radioactivity were found in the cornea, the conjunctiva, the sclera and the iris, soon after drug administration. In these structures, the experimental T_{max} was 15 minutes, and levels decreased rapidly thereafter. In a whole body autoradiography study in male albino rats, it was shown that the instilled test substance migrated from around the eyes to the nasal and oral cavities via the lacrimal ducts, then to the digestive tract. Tissue migration, other than to the ocular tissues, following ocular instillation, does not differ fundamentally from the distribution following oral administration. .

The urinary excretion rate was 9.8% after ocular instillation. This rate was found quite similar to urinary excretion rates after oral (10.5%) or intravenous (13.0%) administrations. In addition, the fecal excretion rate after ocular instillation (83.3%) was not significantly different than the rate after oral (94.0%) or intravenous (82.9%) administration.

After a single topical administration, the highest AUCs were found in the cornea, then the conjunctiva, the iris and the anterior sclera. Levels of ketotifen were 5-14 fold higher in most tissues 6 hours after multiple topical administrations as compared to the levels after a single administration (except from the plasma and aqueous humor, where a 2-fold rise was observed). The kinetics in blood and plasma after ocular instillation were similar. The half-life was

approximately 1.5 hours, while the AUC was 0.3-0.4 mg-hr/mL, and the mean residence time in the body was approximately 3 hours. The mean level was found as low as 0.1-0.2 mg/mL during the steady state with administration at 24-hour intervals.

Clinical Pharmacology

In human conjunctival allergen challenge studies, ZADITOR* (ketotifen fumarate ophthalmic solution) was significantly more effective than placebo in preventing ocular itching and redness associated with allergic conjunctivitis. The effect was seen within minutes after administration and lasted up to 12 hours.

In a placebo-controlled clinical study designed to evaluate safety, ZADITOR*, administered four times a day for 6 weeks, was shown to be safe and well-tolerated in subjects aged 3 years and older.

TOXICOLOGY

The acute toxicity of ketotifen fumarate has been investigated in mice, rats and rabbits. Oral LD₅₀ values were 165, mg/kg, 360 mg/kg and 790 mg/kg in mice, rats and rabbits, respectively. Subchronic and chronic oral toxicity studies in rats and dogs demonstrated that the liver was a target organ for ketotifen fumarate toxicity. In general, toxicity was observed only after long-term administration of ketotifen fumarate at doses up to 700 times those required to obtain antiallergic and anti-histaminic effects.

In a 4-week ocular toxicity study in rabbits, ketotifen fumarate concentrations of up to 0.267% were classified as practically nonirritating, while 1.104% was considered minimally irritating. In a 13-week ocular study in rabbits, ketotifen fumarate at a concentration of 0.069% was classified as practically nonirritating, while concentrations of 0.276% to 1.104% were classified as minimally irritating. In both studies, histopathological and ultrastructural evaluations revealed no abnormalities in ocular tissue.

A chronic toxicity study was conducted with ketotifen fumarate in albino and pigmented rabbits. Administration of ketotifen fumarate ophthalmic solution 0.025% BID or QID had no effects on mortality, clinical signs, body weight, food consumption, ophthalmoscopic examinations, hematology, clinical chemistry, and urinalysis. No treatment-related findings were observed in gross and histopathological examinations of the tissues and organs particularly on the eye and adnexa.

Carcinogenesis: Ketotifen fumarate demonstrated no carcinogenic effects in lifetime studies in mice and rats at dietary doses more than 70,000 times and 59,000 times the maximum recommended ocular human use level of 0.0012 mg/kg/day for a 50 kg adult respectively.

Mutagenesis: No mutagenic potential was observed when ketotifen fumarate was tested in a battery of *in vitro* tests including: a bacterial mutation (Ames) test, a bacterial reverse mutation

(Ames) test, a mammalian chromosome aberration test and a mutagenicity test in V79 Chinese hamster cells or in the following *in vivo* tests: a mouse dominant lethal test, a mouse micronucleus test and a Chinese hamster chromosome aberration test on bone marrow cells.

Reproduction and Teratology: There was no evidence of impaired fertility or reproductive capability in studies with ketotifen fumarate in male rats at 8,330 times and in female rats at 41,000 times the maximum recommended ocular human use level. Teratology and peri- and post-natal studies have been conducted with ketotifen fumarate in rats and rabbits. At 80,000 times and 37,000 times the maximum recommended ocular human use level, ketotifen fumarate was shown not to be teratogenic in rats and rabbits respectively and no effects on peri/post-natal development were observed in rats at 37,000 times the maximum recommended ocular human use level.

REFERENCES

1. Abelson MB, Chambers WA and Smith LM. Conjunctival Allergen Challenge – A Clinical approach to Studying Allergic Conjunctivitis. Arch Ophthamol 1990; 108:84-88.
2. Abelson MB, McGarr PJ and Richard KP. Antiallergic Therapies in Textbook of Ocular Pharmacology. Ed. TJ Zimmerman et al. Lippincott-Raven Publishers, Philadelphia; 1997:609-633.
3. Ishizaki M et al. Long-Term Use of Ketotifen Ophthalmic Solution in the Treatment of Allergic Conjunctivitis and Vernal Conjunctivitis. Progress in Medicine 1989; 9(5):1625-1634.
4. Mikuni I et al. Evaluation of Ketotifen Ophthalmic Solution in Efficacy and Safety on Allergic Conjunctivitis and Vernal Conjunctivitis - Result on Multiclinic Open Trial. Rinsho Iyaku (J Clin Ther Med) 1988; 4(12):2371-2383.
5. Mikuni I et al. Clinical Effect of Ketotifen Ophthalmic Solution on Allergic Conjunctivitis and Vernal Conjunctivitis - Multicenter Double Blind Study in Comparison with Sodium Cromoglycate Ophthalmic Solution. Clin Eval 1989; 17(2):275-297.

PART III: CONSUMER INFORMATION

ZADITOR*
Ketotifen Fumarate Ophthalmic Solution
Multi dose container

This leaflet is part III of a three-part "Product Monograph" published when ZADITOR* was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ZADITOR*. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

Treatment of seasonal allergic conjunctivitis (itchy, watery, red or swollen eyes and/or eyelids).

What it does:

ZADITOR* is an anti-allergy agent.

When it should not be used:

Do not use ZADITOR* if you are allergic to ketotifen or any of the nonmedicinal ingredients or any component of the container.

What the medicinal ingredient is:

Ketotifen fumarate

What the important nonmedicinal ingredients are:

Benzalkonium chloride, glycerol, hydrochloric acid/sodium hydroxide, purified water.

What dosage forms it comes in:

White plastic bottles with controlled dropper tips, containing 5 mL of clear 0.025% ketotifen solution.

INTERACTIONS WITH THIS MEDICATION

If you are using ZADITOR* with any other eye medications, you must wait at least 5 minutes between the use of each medication

PROPER USE OF THIS MEDICATION**Usual dose:**

The usual dose is one drop of ZADITOR* in the affected eye every 8 to 12 hours.

- If you wear contact lenses, you should remove your lenses before using ZADITOR*. Before you put your contact lenses back in, you should wait at least 10 minutes after using ZADITOR*.
- To avoid contamination, do not touch any surface with the tip of the container.

Missed Dose:

If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose,

skip the missed dose and go back to the regular schedule. Do not double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects are red eyes and headache.

Other side effects are itching, dry eyes, burning or stinging in the eyes, sore eyelids and discharge from the eyes.

This is not a complete list of side effects. For any unexpected effects while taking ZADITOR, contact your doctor or pharmacist.*

HOW TO STORE IT

Store between 4°C and 25°C.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345

toll-free fax 866-678-6789

By email: cadmp@hc-sc.gc.ca

By regular mail:

National AR Centre

Marketed Health Products Safety and Effectiveness

Information Division

Marketed Health Products Directorate

Tunney's Pasture, AL 0701C

Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Laboratoires Thea – 12, Rue Louis Blériot – 63017 Clermont-Ferrand Cedex 2 – France

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