PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**ZADITOR***

Ketotifen Fumarate Ophthalmic Solution

Solution, 0.025% as ketotifen, Ophthalmic use

Anti-allergy Agent

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Imported by:
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*ZADITOR is a registered trademark

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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

- treatment of allergic conjunctivitis.

1.1 Pediatrics

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

1.2 Geriatrics

- Geriatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use

2 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 6 DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Wearer of soft contact lenses should be instructed to remove lenses prior to instillation of drops and to wait at least 15 minutes after instilling ZADITOR* before inserting their contact lenses.
- To avoid contamination, do not touch any surface with the tip of the container.

4.2 Recommended Dose and Dosage Adjustment

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

4.4 Administration

Wash hands carefully prior to instillation.

To avoid contamination do not touch eye, eyelids or any surface with the dropper tip.

To administer close the effected eye and use nasolacrimal occlusion for 1-2 minutes after administration. This will help to reduce systemic absorption.

Close the bottle after every use.

4.5 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 apply double doses.

5 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Ophthalmic	Ophthalmic Solution 0.025% as ketotifen	Benzalkonium chloride, glycerol, hydrochloric acid/sodium hydroxide and water for injections

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

Each mL of ZADITOR* (ketotifen fumarate ophthalmic solution) contains:
Medicinal ingredient: 0.345 mg ketotifen fumarate equivalent to 0.25 mg ketotifen.
Preservative: benzalkonium chloride 0.01%
Non-medicinal ingredients: see Table 1 for complete list.

7 WARNINGS AND PRECAUTIONS

General

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

Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the contact lenses. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion.

Benzalkonium chloride may also cause eye irritation, especially in dry eyes or disorders of the cornea.

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.

Driving and using machines

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

7.1 Special Populations

7.1.1 Pregnant Women

There are no clinical trials on the use of ZADITOR* (ketotifen fumarate ophthalmic solution) in pregnant or nursing women. Animal studies using maternally toxic oral doses showed increased pre- and

postnatal mortality, but no teratogenicity. Therefore, ZADITOR* should not be used during pregnancy, except if the benefit justifies the potential risk to the foetus.

7.1.2 Breast-feeding:

Animal data following oral administration show excretion into breast milk. It is unknown whether topical ocular administration of ZADITOR is excreted in human breast milk. Caution should be exercised when ZADITOR is administered to a nursing mother.

7.1.3 Pediatrics

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In controlled clinical studies with ZADITOR* (ketotifen fumarate ophthalmic solution), conjunctival hyperemia 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.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most frequently reported ocular adverse reaction was conjunctival hyperemia and the most common non-ocular adverse reaction was headache (Table 2).

Table 2: Adverse Reactions Reported by ≥ 1% of Subjects Receiving ZADITOR

Adverse reaction	Number of subjects (Incidence (%))
Conjunctival hyperaemia	29 (7.0%)
Eye irritation / Eye pain	19 (4.6%)
Eye pruritus	12 (2.9%)
Dry eye	10 (2.4%)
Eye discharge	9 (2.2%)
Eyelid disorder	7 (1.7%)
Headache	6 (1.5%)

8.3 Less Common Clinical Trial Adverse Reactions

The less common adverse reactions (<1%) are presented below.

Cardiac disorders: tachycardia

Eye disorders: visual impairment, conjunctivitis, foreign body sensation in eye, keratitis, corneal lesion, photophobia, mydriasis

General disorders and administration site conditions: asthenia

Infection and infestations: rhinitis

Nervous system disorders: somnolence

Skin and subcutaneous tissue disorders: rash

8.5 Post-Market Adverse Reactions

The following post marketing events have also been observed (frequency not known):

Eye disorders: punctate keratitis, punctate corneal epithelial erosion, vision blurred (during installation) and conjunctival haemorrhage

Gastrointestinal disorders: dry mouth

Immune system disorders: hypersensitivity

Hypersensitivity reactions including local allergic reaction (mostly contact dermatitis, eye swelling, eyelid pruritis and oedema), systemic allergic reactions including facial swelling/oedema (in some cases associated with contact dermatitis) and exacerbation of pre-existing allergic conditions such as asthma and eczema.

Nervous system disorders: dizziness

Skin and subcutaneous tissue disorders: eczema, urticaria

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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. If an eye ointment is applied, it should be applied last.

The use of oral dosage forms of ketotifen may potentiate the effects of Central Nervous System depressants, antihistamines and alcohol. Although this has not been observed with ketotifen eye drops, the possibility of such effects cannot be excluded.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 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.

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.

10.3 Pharmacokinetics

Absorption

In a pharmacokinetic study conducted in 18 healthy human volunteers with ketotifen fumarate (0.025% w/v) eye drops, plasma levels of ketotifen after twice daily ocular administration for 14 days were, in most cases, below the limit of quantitation (20 pg/ml).

In animial studies, 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 Tmax was 15 minutes, and levels decreased rapidly thereafter.

Distribution

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.

After a single topical ocular administration of 50µL of 0.025% ketotifen solution in rabbit, 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.

11 STORAGE, STABILITY AND DISPOSAL

Store between 4°C and 25°C. After opening the bottle, the eye drops can only be stored for 4 weeks.

12 SPECIAL HANDLING INSTRUCTIONS

No special requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

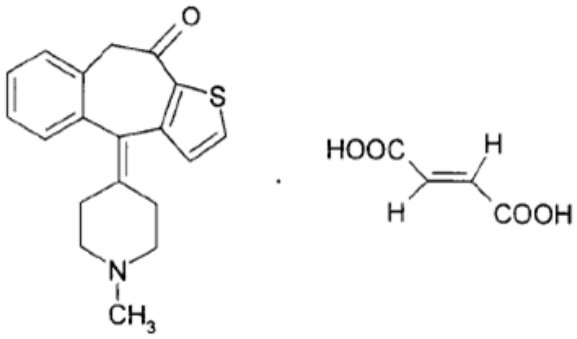
Drug Substance

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 and molecular mass: $C_{19}H_{19}NOS + C_4H_4O_4$, 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	Ka I = 8.43 ± 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 H_2O melts at approximately 130°C.

14 CLINICAL TRIALS

Detailed data on which indications were initially approved is not available in the product monograph.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: The acute toxicity of ketotifen fumarate has been investigated in mice, rats and rabbits. Oral LD_{50} 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 non-irritating, 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 non-irritating, 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.

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

Carcinogenicity: 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.

Reproductive and Developmental Toxicology: 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrZADITOR*

Ketotifen Fumarate Ophthalmic Solution

Read this carefully before you start taking **ZADITOR** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ZADITOR**.

What is ZADITOR used for?

ZADITOR is used in adults and children older than 3 years of age, to treat itchy, watery, red or swollen eyes and/or eyelids, caused by seasonal allergies.

How does ZADITOR work?

Seasonal allergies happen when allergens like pollen cause the cells of the eye to release a chemical called histamine. This can result in itching, redness and swelling on the surface of your eye. ZADITOR works by stopping the release of histamine and other chemicals that cause the allergic reaction, which reduces the eye symptoms.

What are the ingredients in ZADITOR?

Medicinal ingredients: Ketotifen fumarate

Non-medicinal ingredients: benzalkonium chloride, glycerol, hydrochloric acid/sodium hydroxide, water for injections.

ZADITOR comes in the following dosage forms:

Ophthalmic solution; 0.025% ketotifen (as ketotifen fumarate).

Do not use ZADITOR if:

- You are allergic to ketotifen or any of the nonmedicinal ingredients in ZADITOR.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ZADITOR. Talk about any health conditions or problems you may have, including if you:

- Wear soft contact lenses.
- Have dry eyes, or any problems with your cornea(s).
- Are pregnant, think you may be pregnant or are planning to have a baby.
- Are nursing or planning to nurse your baby.

Other warnings you should know about:

Use of ZADITOR and contact lenses: ZADITOR contains a preservative called benzalkonium chloride, which can be absorbed by soft contact lenses and change the colour of the lenses. Remove contact lenses before using ZADITOR and wait at least 15 minutes before putting them back in.

Benzalkonium chloride may cause eye irritation, especially if you have dry eyes, or problems with your cornea(s). If you feel abnormal eye sensation, stinging or pain in the eye after using ZADITOR, talk to your healthcare professional.

Use of ZADITOR with other eye medications: If you are using other eye medications, wait at least 5 minutes between the use of each eye medication. If you are using an eye ointment, apply this medication last.

Driving and using machines: ZADITOR may cause blurred vision and/or drowsiness. Avoid driving or using machinery until your vision is clear and you know how ZADITOR affects you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ZADITOR:

- Medicines used to treat depression, anxiety or sleep disorders.
- Antihistamines, used to treat allergies.
- Alcohol.
- **How to take ZADITOR:** ZADITOR is an eye drop, for use in your eye(s) only.
- To avoid contamination, do not touch your eye, eyelid, or any surface with the dropper tip.
- If you wear soft contact lenses, remove these before using ZADITOR and wait at least 15 minutes before putting them back in.

Steps for using ZADITOR:

1. Wash your hands carefully before use.
2. Remove the cap from the bottle, being careful not to touch the dropper tip.
3. Use your index finger to pull down the lower lid of the eye and add a drop of medicine.
4. After adding the drop, let go of the lower lid, close the eye and tilt your head back.
5. Using your middle finger, press down in the corner of your eye (closest to your nose) for 1 to 2 minutes. This helps the medicine get absorbed into your eye instead of your tear duct.
6. Close the bottle after each use.

Usual dose:

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

Overdose:

There is no danger if you accidentally swallow ZADITOR or if you use more than one drop in the eye. If you have any concerns, talk to your healthcare professional.

If you think you, or a person you are caring for, have taken too much ZADITOR, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

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 apply double doses.

What are possible side effects from using ZADITOR?

These are not all the possible side effects you may have when taking ZADITOR. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Dry, itchy, red, irritated or crusty eyes
- Eye or eyelid inflammation/swelling, or pain
- Feeling like you have something in your eye
- Blurred vision
- Dilated pupils
- Being sensitive to light
- Broken blood vessel in the eye
- Headache
- Nasal congestion, runny nose, sneezing
- Feeling weak or having a lack of energy
- Drowsiness
- Dizziness
- Dry mouth
- Rash, hives

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Keratitis (corneal ulcer): inflammation or irritation of the cornea, red eyes, excess tears or other discharge from your eye		✓	
Tachycardia (abnormally fast heartbeat): dizziness, light-headedness, shortness of breath, racing heart		✓	
UNKNOWN			
Allergic reaction: difficulty swallowing or breathing, wheezing, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 4°C and 25°C. After opening the bottle, the eye drops can only be stored for 4 weeks.

Keep out of reach and sight of children.

If you want more information about ZADITOR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website https://www.theapharma.ca, or by calling 1-888-805-8432.

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