AUSTRALIAN PRODUCT INFORMATION – ZADITEN (KETOTIFEN) EYE DROPS SOLUTION

1 NAME OF THE MEDICINE

ketotifen as ketotifen fumarate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Zaditen is a sterile ophthalmic solution containing ketotifen for topical administration to the eye. Each 1.0 mL contains 345 µg ketotifen fumarate corresponding to 250 µg ketotifen.

Excipients with known effect: Benzalkonium chloride (multidose bottle only).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Eye Drops - clear, colourless to faintly yellow, sterile ophthalmic solution for administration to the eye.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Symptomatic short term treatment of seasonal allergic conjunctivitis in adults and children 3 years or older.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults, elderly and children (age 3 and older): One drop of Zaditen into the conjunctival sac twice daily.

Instructions for Use and Handling

Multidose bottle:

The contents and dispenser remain sterile until the original closure is broken. To avoid contamination, do not touch any surface with the dropper tip. The tip of the container should also not come into contact with the eye as this may cause injury to the eye. The multidose formulation of Zaditen eye drops contains benzalkonium chloride as a preservative, which may be deposited in soft contact lenses and may possibly discolor soft contact lenses (see Section 4.4 Special Warnings and Precautions for Use).

After opening, Zaditen should not be used for more than 4 weeks and any remaining contents should be discarded.

After cap is removed, if tamper evident snap collar is loose, remove before using the product.

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. The tip of the container should also not come into contact with the eye as this may cause injury to the eye. After opening, single dose units must be used immediately. Contains no antimicrobial agent. Use once only and discard any residue. 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.

4.3 CONTRAINDICATIONS

Hypersensitivity to ketotifen or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

For ocular use only.

The multidose formulation of Zaditen eye drops includes benzalkonium chloride as a preservative which may cause eye irritation. Since benzalkonium chloride may be deposited in soft contact lenses and since it has not been shown that soft contact lenses do not absorb ketotifen, 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.

Use in the elderly

No data available.

Paediatric use (Use in children under 3 years of age)

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

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In a fertility study in which male rats were treated with oral doses of ≥2 mg/kg/day, there was a trend for a decrease in fertility. Ketotifen had no effect on fertility of female rats at oral doses up to 50 mg/kg/day. These doses would have resulted in systemic ketotifen levels several orders of magnitude higher than the MRHOD.

There is no data available on the effect of ketotifen hydrogen fumarate on fertility in humans.

Use in pregnancy – Pregnancy Category B1

Oral treatment of pregnant rats and rabbits during organogenesis with doses up to 100 and 45 mg/kg/day, respectively, did not result in any embryofoetal lethal effects or malformations. Animal studies using maternally toxic oral doses showed increased pre- and postnatal mortality, but no teratogenicity. In the offspring of rats that received ketotifen orally from day 15 of pregnancy to day 21 post partum at the maternally toxic dose of 50 mg/kg/day, postnatal mortality was increased, and body weight gain during the first four days post partum was slightly decreased. These doses would have resulted in systemic ketotifen levels several orders of magnitude higher than the MRHOD.

There are no adequate data from the use of ketotifen eye drops in pregnant women. Caution should be exercised when prescribing to pregnant women. When prescribing to pregnant woman, the benefits to the mother should be weighed against the risk to the fetus.

Use in lactation

Ketotifen has been identified in the milk of lactating rats following oral administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in human breast milk. Zaditen should be used with caution in breast-feeding women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Any patient who experiences blurred vision or somnolence (see Section 4.8 Adverse Effects (Undesirable Effects) should not drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Tabulated summary of adverse drug reactions from clinical trials [21,49]

Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

Table 1 Adverse drug reactions from clinical trials

Immune system disorders Uncommon: Hypersensitivity, allergic reactions
Nervous system disorders Uncommon: Headache.
Eye disorders Common: Punctate keratitis, corneal erosion, eye irritation, eye pain, Uncommon: Vision blurred (during instillation), dry eye, eyelid disorder, conjunctivitis, photophobia, conjunctival haemorrhage.
Gastrointestinal disorders

Immune system disorders Uncommon: Hypersensitivity, allergic reactions
Uncommon: Dry mouth
Skin and subcutaneous tissue disorders Uncommon: Rash, eczema, urticaria
General disorders and administration site conditions Uncommon: Somnolence

Adverse drug reactions from post marketing experience (Frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Zaditen eye drops. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.

Ocular adverse drug reactions

Post marketing cases have been reported of localized allergic/hypersensitivity reaction, including mostly contact dermatitis, eye swelling, and eyelid pruritis and oedema.

Systemic adverse drug reactions

In addition, post marketing systemic hypersensitivity reactions have been reported including but not limited to facial swelling/oedema (in some cases associated with contact dermatitis) and exacerbation of pre-existing allergic conditions such as asthma and eczema. Dizziness has also been reported.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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 and oral ingestion of the contents of a single dose unit would be equivalent to 0.1 mg of ketotifen. Clinical results have shown no serious signs or symptoms after oral ingestion of up to 20 mg of ketotifen.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Ketotifen has a non specific anti-inflammatory action and is a mast cell stabiliser. Ketotifen also decreases chemotaxis, activation and degranulation of eosinophils. Increased cAMP levels by phosphodiesterase inhibition may contribute to the cell stabilising effect of ketotifen.

Clinical trials

The efficacy of Zaditen was evaluated in 6 conjunctival allergen challenge studies in a total of 634 sensitised subjects (573 receiving Zaditen, including 133 paediatric subjects aged 8-16 years) and 2 four-week environmental studies in a total of 1023 patients with seasonal allergic conjunctivitis (346 receiving Zaditen).

In conjunctival allergen challenge studies, Zaditen was significantly more effective than placebo in preventing ocular itching associated with allergic conjunctivitis. The action of ketotifen occurred rapidly with an effect seen within minutes after administration. The duration of action of a single dose was found to be 8 to 12 hours. In children the efficacy of Zaditen was superior to placebo and similar to that in adults.

The 2 environmental studies were identical in design, both double-masked, parallel group, comparative studies. Results are summarised in Table 2.

Table 2: Responder Rate (proportion of patients with excellent or good global efficacy at day 5 to 8)

Treatment (n*)	Patient Assessment		Investigator Assessment	
	Responder Rate (%)	P-Value**	Responder Rate (%)	P-Value**
Study 1				
Ketotifen (109)	49.5		53.2	
Vehicle (106)	33.0	0.015	32.1	0.001
Levocabastine (107)	41.1	0.197	45.8	0.235
Study 2				
Ketotifen (149)	45.6		45.6	
Vehicle (150)	44.0	0.775	48.0	0.679
Levocabastine (134)	49.3	0.543	52.2	0.268

* RAST-positive intention-to-treat.

** Ketotifen response compared with that of either vehicle or levocabastine.

In view of the high placebo response observed in Study 2, an exploratory subgroup analysis was performed which included only those patients recruited during the peak pollen season. At day 5 to 8 the responder rates based on the patient assessment of global efficacy were 52.3% (ketotifen), 38.5% (vehicle) and 52.7% (levocabastine). Both levocabastine and ketotifen were significantly superior to vehicle (p=0.048 and 0.045, respectively).. This exploratory subgroup analysis cannot be used to support efficacy but might be useful in the design of another study.

The safety of Zaditen was evaluated in a total of 12 studies including 947 patients with an ocular pollen allergy who participated in efficacy studies and an additional 442 healthy volunteers (including 42 paediatric subjects aged 3-11 and 133 aged 8-16 years) who were enrolled in pharmacokinetic, local tolerance, safety and special studies. There were no significant findings noted on visual acuity, pupil size and reactivity or slit lamp examination. Dilated ophthalmoscopy and measurements of intraocular pressure revealed no abnormalities.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

In a pharmacokinetic study conducted in 18 healthy volunteers with Zaditen eye drops, plasma levels of ketotifen after ocular administration for 14 days were in most cases below the limit of quantitation (20 picograms/mL).

Biotransformation and elimination

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Please refer to Section 4.6 Fertility, Pregnancy and Lactation.

Carcinogenicity

Long-term studies in mice and rats revealed no evidence for carcinogenicity of ketotifen at dietary doses up to 93 and 71 mg/kg/day, respectively. These doses would have resulted in systemic ketotifen levels several orders of magnitude higher than those after administration of the maximum recommended human ocular dose (MRHOD). Ketotifen was not genotoxic in a battery of *in vitro* and *in vivo* assays including the Ames test, chromosomal aberration test with V79 Chinese hamster cells, micronucleus test in mice and mouse dominant lethal test.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Multidose bottle:

Benzalkonium chloride 0.1 mg/mL as preservative, glycerol, sodium hydroxide and water for injections.

Single dose units:

Glycerol, sodium hydroxide and water for injections.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. (See Instructions for Use and Handling.)

6.5 NATURE AND CONTENTS OF CONTAINER

Multidose bottle:

2.5 mL and 5 mL.

Single dose units:

Blocks of 5 x 0.4 mL single dose units each packed in a blister and supplied in cartons containing 20 x 0.4mL.

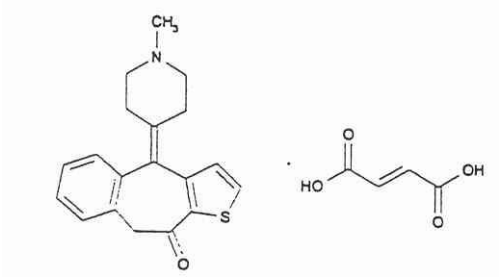
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Ketotifen fumarate is a white to brownish-yellow, fine crystalline powder. It is sparingly soluble in water, slightly soluble in methanol and very slightly soluble in acetonitrile.

Chemical structure



Chemical name: 4-(1-methylpiperidin-4-ylidene)-4,9-dihydro-10H-benzo[4,5]cyclohepta[1,2-b]thiophen-10-one hydrogen (E)-butenedioate

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

Molecular weight: 425.5

CAS number

34580-14-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 2 (Pharmacy Medicine)

8 SPONSOR

Novartis Pharmaceutical Australia Pty Limited

ABN 18 004 244 160

54 Waterloo Road

Macquarie Park NSW 2113

9 DATE OF FIRST APPROVAL

17 April 2007

10 DATE OF REVISION

28 January 2021

® = Registered Trademark

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	PI reformat

Internal document code

zad280121i.doc