NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ZADITEN ® Eye Drops 0.25 mg/mL, multi-dose bottle.

ZADITEN ® Eye Drops 0.25 mg/mL, single dose unit.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zaditen contains the active ingredient ketotifen fumarate 0.345 mg in 1 mL equivalent to ketotifen 0.25 mg in 1 mL.

Excipient with known effect

Benzalkonium chloride 0.1 mg/mL as a preservative in the multi-dose bottle.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

Clear, colourless to faintly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.1 Dose and method of administration

Use in Adults

One drop of Zaditen Eye Drops into the conjunctival sac twice a day.

Use in children (aged 3 years and above)

One drop of Zaditen Eye Drops into the conjunctival sac twice a day. Safety and effectiveness in paediatric patients below the age of 3 years have not been established.

Geriatrics

No dosage adjustment is required in patients above 65 years of age.

Renal impairment

No dosage adjustment is required in patients with renal impairment.

Hepatic impairment

No dosage adjustment is required in patients with hepatic impairment.

Multi-dose bottles

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 dropper tip should also not come into contact with the eye as this may cause injury to the eye.

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. The tip of the container should also not come into contact with the eye as this may cause injury to the eye.

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

4.3 Contraindications

Known hypersensitivity to ketotifen or any of the excipients listed under Section 6.1.

4.4 Special warnings and precautions for use

FOR OCULAR USE ONLY.

Multi-dose Bottle

The formulation of Zaditen Eye Drops contains benzalkonium chloride as a preservative, which may cause eye irritation and 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.

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

Unpreserved Single Dose Units

No special warnings.

4.5 Interaction with other medicines and other forms of interaction

No interactions have been reported with ophthalmic use ketotifen at the recommended doses.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no special recommendations for women of child-bearing potential.

When prescribing to pregnant women, the benefits to the mother should be weighed against the risk to the fetus.

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.

Breast-feeding

Although animal data following oral administration show excretion into breast milk, topical administration to human is unlikely to produce detectable quantities in breast milk.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Tabulated summary of adverse drug reactions from clinical trials.

Adverse drug reactions from clinical trials (Table 7-1) 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 7-1 Adverse drug reactions from clinical trials

Immune system disorders	Uncommon: Hypersensitivity.
Nervous system disorders	Uncommon: Headache.
Eye disorders	Common: Punctate keratitis, corneal erosion, eye irritation, eye pain. Uncommon: Vision blurred (during instillation), dry eye, eye lid disorder, conjunctivitis, photophobia, conjunctival haemorrhage.
Gastrointestinal disorders	Uncommon: Dry mouth.
Skin and subcutaneous tissue disorders	Uncommon: Rash, eczema, urticarial.
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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting.

4.9 Overdose

Multi-dose bottle

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 container

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, other antiallergics, ATC code: S01GX08.

Mechanism of action

Ketotifen is a histamine H1-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.

Clinical efficacy and safety

Study: C-08-97-002: Safety and efficacy of ketotifen fumarate 0.025% ophthalmic solution compared with vehicle placebo control in the allergen challenge model of allergic conjunctivitis.

Study C-08-97-002 was a conjunctival allergen challenge (CAC) study in subjects having a history of allergy to pollen and/or animal dander, confirmed by a diagnostic test. The objective was to compare the efficacy and safety of ketotifen 0.025% with vehicle placebo for the prevention of ocular itching and hyperemia. It was a double-masked, randomised study including a fellow-eye vehicle placebo control.

Fifteen minutes after administration of ketotifen to one eye and vehicle placebo to the fellow- eye, both eyes were challenged with the appropriate allergen and the symptom ocular itching (primary efficacy criterion) was evaluated at 3, 7 and 10 minutes after challenge on an ordinal scale ranging from 0 (no itching) to 4 (incapacitating itch with an irresistible urge to rub). Signs of conjunctival, ciliary and episcleral injection (secondary efficacy criteria) were also evaluated 7, 10 and 15 minutes after challenge on an ordinal scale ranging from 0 (none) to 4 (unusually severe). This procedure was repeated at two subsequent visits (14 days apart) when ketotifen 0.025% and vehicle placebo eye drops were given 6 and 8 hours before allergen challenge, respectively.

Eighty nine subjects were randomised to masked trial medication. Ketotifen 0.025% eye drops prevented ocular itching induced by allergen challenge at 15 minutes, 6 hours and 8 hours after administration of one drop in a statistically significant manner as compared to vehicle placebo ($P<0.001$). The score difference exceeded 1.0 unit which is considered to be clinically significant. At the same time intervals, statistically significant superiority of ketotifen over vehicle placebo was also observed for the prevention of conjunctival, ciliary and episcleral injection ($P<0.05$). Ketotifen was also statistically superior to placebo in the percentage of subjects with no itching in their challenged eyes at all timepoints ($P<0.001$). Differences between ketotifen-treated eyes and placebo-treated eyes ranged from 51.7% to 61.1%. The local and systemic tolerability of ketotifen 0.025% eye drops was comparable to placebo.

Study: SH/DR 42000-97-2: Double-masked, randomised, parallel-group multicentre comparison of ophthalmic ketotifen with its vehicle and with levocabastine in patients suffering from seasonal allergic conjunctivitis (SAC).

Study SH/DR 42000-97 2 was an environmental study in SAC. The primary objective of the trial was to determine if ketotifen 0.025% eye drops administered twice a day to patients suffering from SAC is superior to its vehicle placebo in reducing allergy symptoms after 5 to 8 days of treatment. A secondary objective was to compare the efficacy and safety of ketotifen 0.025% with vehicle placebo and levocabastine 0.05% eye drops over a treatment period of 4 weeks.

The study was double-masked, parallel, balanced-randomised and comparative, using a vehicle placebo and an active control. Included were out-patients of both sexes, age 12 years or older. Diagnosis of SAC was based on history, a positive radio-allergosorbent test (RAST), and the presence of moderate to severe ocular itching with at least one of the following other signs or symptoms of SAC of moderate to severe intensity bilaterally: conjunctival hyperemia, conjunctival chemosis, eyelid swelling or tearing. Patients were allowed to be provisionally enrolled with the RAST result pending if they had the full-blown typical signs and symptoms of SAC, to avoid missing any eligible patients.

The primary criterion for evaluation of efficacy was the responder rate, defined as the proportion of patients with excellent or good global efficacy, i.e., distinct to complete relief of ocular allergy symptoms as assessed by the patient at the follow-up visit (day 5 to 8), when compared to the baseline condition immediately prior to starting treatment. Secondary efficacy variables included patient's and investigator's assessment of global efficacy, signs and symptoms of SAC, and the number of symptom-free days.

A total of 519 patients (ketotifen = 172, vehicle = 173, levocabastine = 174) were randomised to treatment. Efficacy was evaluated in the intent-to-treat (ITT) population including 497 patients. Analysis of the ITT subset of 322 patients with a positive RAST (RAST-positive ITT population) was considered the most valid assessment of test drug

efficacy as inclusion of RAST-negative patients was unavoidable because the test result took a few days to be known. Otherwise, RAST-negative patients would not have been randomised and would have been considered screening failures. Efficacy was further analysed in the per-protocol (PP) population of 238 patients.

Table 12-1 shows the responder rates at the follow-up visit (day 5 to 8) based on the patient's and the investigator's assessment of global efficacy, for the populations analysed for efficacy.

All results of the study were in favor of ketotifen 0.025% eye drop solution. The responder rates, the overall treatment response and the sign and symptom scores recorded at study visits and in patient diary booklets consistently favored ketotifen over the reference treatments. Many differences were statistically significant ($P<0.05$), for the comparison with vehicle placebo or with levocabastine or even with both. The beneficial effects of ketotifen were particularly noticeable during the first 4 to 5 days of treatment. After day 8, differences between treatments were less obvious but still consistently favored ketotifen for all variables.

Table 12-1 Study SH/DR 42000-97-2: Responder rates at follow-up visit (day 5 to 8).

		Patient Assessment		**Investigator Assessment**	
Population	**Treatment**	**Responder Rate (%)**	**P-Value***	**Responder Rate (%)**	**P-Value***
Intent-to-Treat	Ketotifen	47.9		50.3	
	Vehicle	39.4	0.125	38.2	**0.024**
	Levocabastine	38.6	0.089	41.0	0.088
RAST-Positive	Ketotifen	49.5		53.2	
Intent-to-Treat	Vehicle	33.0	**0.015**	32.1	**0.001**
	Levocabastine	41.1	0.197	45.8	0.235
Per-Protocol	Ketotifen	50.6		56.5	
	Vehicle	35.9	0.060	34.6	**0.005**
	Levocabastine	41.3	0.225	46.7	0.158

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

The mean treatment duration was 23.6, 23.3 and 23.2 days for ketotifen, vehicle placebo and levocabastine, respectively. During this treatment period patients receiving ketotifen eye drops had significantly more symptom free-days on average than patients on vehicle placebo ($p=0.024$).

Local and systemic tolerability of ketotifen fumarate 0.025% ophthalmic solution was *comparable to placebo.*

Study: C01-KETO-011: Evaluation of the efficacy and safety of ketotifen fumarate 0.025% ophthalmic solution compared to vehicle placebo in a paediatric population in the allergen challenge model of allergic conjunctivitis, following a single dose and four week treatment.

Study C01-KETO-011 evaluated the efficacy and safety of 0.025% ketotifen eye drops

versus vehicle placebo in paediatric subjects at 15 minutes (onset of action) and at 8 hours (duration of action) after the first instillation of trial medication. The secondary objective was to confirm the duration of action 8 hours after the last dose following a 4-week twice daily treatment period.

The study was a double-masked, randomised, multicentre, fellow-eye, placebo-controlled, conjunctival allergen challenge trial conducted in 133 paediatric subjects between the ages of 8 and 16 years. Qualified subjects had a documented history of allergy to cat dander, cat hair, or selected environmental allergens not currently in season at the investigative sites at the time of the trial.

The primary efficacy assessment was based on ocular itching scores, judged by the subject at 3, 7, and 10 minutes post-challenge using an ordinal scale ranging from 0 (no itching) to 4 (incapacitating itch with an irresistible urge to rub). Secondary efficacy assessments were subject evaluations of tearing and lid swelling and investigator evaluations of chemosis, mucous discharge, and composite hyperemia of 3 vessel beds (conjunctival, ciliary, and episcleral) at 7, 10, and 15 minutes post-challenge. As with ocular itching, standardised ordinal scales were used for each of these assessments. Ketotifen showed clinically (between-treatment difference of approximately 1 score unit) and statistically ($P<0.001$) significant efficacy in the inhibition of ocular itch at 15 minutes and 8 hours after a single dose and at 8 hours after a 4-week b.i.d. dosage regimen. Inhibition of ocular itch was similar in younger and older children (8-11 vs. 12-16 years, respectively). Composite hyperemia was statistically significantly decreased at 15 minutes after a single dose ($P\leq0.002$). This was retained for at least 8 hours after single- and multiple-dose regimens ($P<0.05$).

Superiority of ketotifen over placebo was also consistently observed for inhibition of chemosis, tearing, and lid swelling.

Local and systemic tolerability of ketotifen 0.025% eye drops was comparable to placebo.

Study: C-08-97-003: Six-week safety trial of ketotifen fumarate 0.025% ophthalmic solution in volunteers with normal ocular health.

Study C-08-97-003 was a double-masked, parallel-group, placebo-controlled multicentre study using a 2:1 randomisation. The main objective was to evaluate the ocular tolerability and safety of ketotifen 0.025% eye drops when instilled four times a day over a period of six weeks in healthy adults, adolescents and children (age 3 years and older). Further, ocular rebound vasodilatation and itching were assessed approximately 24 to 48 hours after the final treatment.

Safety was determined from comprehensive ophthalmological examinations including slit lamp biomicroscopy, distance visual acuity, pupil size and reactivity, intra-ocular pressure, dilated ophthalmoscopy, ocular signs and symptoms, blood pressure, heart rate, and adverse event reports.

Out of 495 subjects randomised and analysed for safety, 330 were assigned to ketotifen and 165 to vehicle placebo. These numbers include 61 children (3 to 11 years old), 42 receiving ketotifen and 19 vehicle placebo.

No deaths were reported during the study. Three ketotifen subjects and three placebo subjects experienced serious adverse events, which were considered not related to study medication. Serious adverse events reported for ketotifen subjects included abdominal pain secondary to gall stones, surgical removal of a breast tumor, and arthroscopic knee

surgery. Serious adverse events reported by placebo subjects included cholecystitis, myocardial infarction, and hospitalization for unknown reason.

The percentage of all patients reporting at least one adverse event considered causally related to study medication was similar for ketotifen (19.7%) and vehicle placebo (16.4%). The corresponding figures for the paediatric population were 4.8% and 5.3%, respectively. In either treatment group, burning/stinging, discharge, dry eyes, eyelid disorder, injection, itching, lacrimation disorder, and photophobia were the only adverse events considered to be related or possibly related to study medication. Paediatric subjects reported adverse events which were symptoms typically associated with common cold, flu syndrome, or ear infections.

Ocular rebound vasodilatation and itching were not observed after discontinuing treatment with ketotifen.

No clinically significant changes were observed at the ophthalmological examinations, including intra-ocular pressure. There were no clinically significant changes from baseline in blood pressure or heart rate in either treatment group. Differences between treatments were neither clinically nor statistically significant. The results for paediatric subjects were comparable to results for the overall study population.

Despite double the recommended daily dosage (four times instead of twice a day) ketotifen 0.025% eye drops administered for duration of six weeks to healthy subjects (including children as young as 3 years) with normal ocular health showed local and systemic tolerability was comparable to placebo.

5.2 Pharmacokinetic properties

Absorption

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).

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

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 reproductive toxicity to reproduction. Repeated ocular administration in animal studies showed no untoward effects.

Reproductive toxicity

Treatment of male rats with a toxic oral dose of ketotifen (50 mg/kg/day) for 10 weeks prior to mating resulted in decreased fertility. Effects on male fertility and postnatal development were observed only at doses considered sufficiently in excess of the therapeutic dose range in man, indicating little relevance to clinical use [61]. In the offspring of rats that received ketotifen orally from day 15 of pregnancy to day 21 post-

partum at 50 mg/kg/day a maternally toxic treatment protocol, the incidence of postnatal mortality was increased, and body weight gain during the first four days post-partum was slightly decreased.

Incompatibilities
The multi-dose formulation of Zaditen Eye Drops contains benzalkonium chloride as a preservative, which may cause eye irritation and may be deposited in soft contact lenses and may possibly discolor soft contact lenses (see section 4.4 Special warnings and precautions for use).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Zaditen multi-dose bottle

Benzalkonium chloride

Glycerol (E422)

Sodium hydroxide (E524)

Water for injections.

Zaditen single dose unit

Glycerol (E422)

Sodium hydroxide (E524)

Water for injections.

6.2 Incompatibilities

Unknown.

6.3 Shelf life

Multi-dose bottle

24 months: 5 mL dropper bottle.

18 months: 2.5 mL dropper bottle.

Single dose unit

Unopened blisters: 24 months.

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

Opened blister: 28 days.

6.4 Special precautions for storage

Multi-dose bottle

Store at temperatures below 25°C.

Contents should be discarded four weeks after opening.

Single-dose unit

Store at temperatures below 25°C.

Discard the single dose container immediately after opening.

6.5 Nature and contents of container

Multi-dose bottle

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.

Single dose unit

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.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Pharmacy Only Medicine

Except when sold in practice by a registered optometrist.

8. SPONSOR

Novartis New Zealand Limited

PO Box 99102

Newmarket

Auckland 1149

Free Phone: 0800 354 335

9. DATE OF FIRST APPROVAL

Multi-dose Bottles: 23 December 2004

Single Dose Units: 15 June 2006

10. DATE OF REVISION OF THE TEXT

11 August 2020

Summary Table of Changes

Section 8 - Sponsor	Removed Sponsor's old address and added the PO Box address.

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