ZADITEN® Eye Drop

Ophthalmologicals, other antiallergics.

DESCRIPTION AND COMPOSITION

Pharmaceutical form(s)

Zaditen: Eye drops, solution in a 5 mL bottle. Clear, colorless to faintly yellow solution.

Active substance

Ketotifen hydrogen fumarate

Zaditen: One mL contains 0.345 mg of ketotifen hydrogen fumarate corresponding to 0.25 mg of ketotifen. Each drop contains 8.5 micrograms of ketotifen hydrogen fumarate corresponding to 6.15 micrograms of ketotifen.

Certain dosage strengths may not be available in all countries. Not all presentations may be available locally.

Active Moiety

Ketotifen.

Excipients

Zaditen: Benzalkonium chloride, Glycerol (E422), Sodium hydroxide (E524), Water for Injections.

Pharmaceutical formulations may vary between countries.

INDICATIONS

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

DOSAGE AND ADMINISTRATION

Dosage

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 pediatric 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.

Method of administration

Zaditen: 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.

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.

CONTRAINDICATIONS

Known hypersensitivity to ketotifen or to any of the excipients.

WARNINGS AND PRECAUTIONS

Zaditen: The multidose 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 discolor soft contact lenses.

Driving and using machines

Any patient who experiences blurred vision or somnolence (See section ADVERSE DRUG REACTIONS) should not drive or operate machines.

ADVERSE DRUG REACTIONS

Tabulated summary of adverse drug reactions from clinical trials

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.
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 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.

INTERACTIONS

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

WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY

Women of child-bearing potential

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

Pregnancy

There are no adequate data from the use of ketotifen eye drops in pregnant women.

Systemic levels after ocular administration are much lower than after oral use. When prescribing to pregnant women, the benefits to the mother should be weighed against the risk to the fetus.

Breast-feeding

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

Zaditen eye drops can be used during breast-feeding.

Fertility

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

OVERDOSAGE

Zaditen: 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.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA) and Pharmacodynamics (PD)

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 stabilizing effect of ketotifen.

Pharmacokinetics (PK)

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 (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.

CLINICAL STUDIES

Study: C-08-97-002

Title: 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, randomized 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 randomized 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. 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

Title: Double-masked, randomized, 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-randomized 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 randomized 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 randomized and would have been considered screening failures.

Efficacy was further analyzed 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 analyzed for efficacy.

The responder rates, the overall treatment response and the sign and symptom scores recorded at study visits and in patient diary booklets numerically favored ketotifen over the reference treatments. 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.

Table 0-1 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 Intent-to-Treat	Ketotifen	49.5		53.2	
	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

Title: Evaluation of the efficacy and safety of ketotifen fumarate 0.025% ophthalmic solution compared to vehicle placebo in a pediatric 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 pediatric 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, randomized, multicenter, fellow-eye, placebo-controlled, conjunctival allergen challenge trial conducted in 133 pediatric 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 postchallenge 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 postchallenge.

As with ocular itching, standardized 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.

NON-CLINICAL 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.

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.

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 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 WARNINGS AND PRECAUTIONS).

STORAGE

See folding box.

Zaditen should not be used after the date marked “EXP” on the pack.

Zaditen must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

Zaditen multiple dose containers (5 mL plastic bottle) must be discarded 4 weeks after opening.

INFORMATION FOR PATIENTS

How to use Zaditen eye drops

Zaditen eye drops - Multi Dose Unit

1. Wash your hands.
2. Tip your head back.
3. Pull down the lower eyelid with your finger and hold the drop-dispensing bottle upside down over the eye with the other hand.
4. Press the bottom of the bottle with your index finger so one drop falls into the eye. Always avoid touching the tip of the bottle.
5. Close your eye and press the tip of one finger against the inner corner of the eye for 1-2 minutes. This prevents the drop running through the tear duct into the throat. Most of the eye drop then remains in the eye to relieve the complaint.
6. Replace cap on bottle immediately after use. To avoid contamination do not touch any surface with the dropper tip.

Fig.1

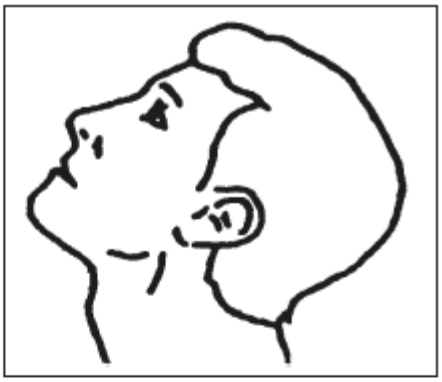

Fig.2

Fig.3

Manufacturer:

See folding box.

Package Leaflet:

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