

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

ZADITEN ELIXIR 1mg/5ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ketotifen hydrogen fumarate 1.38mg/5ml

Excipients with known effect: each ml of solution contains propyl hydroxybenzoate (0.167 mg), methyl hydroxybenzoate (0.333 mg) ethanol (20 mg), maltitol liquid (800 mg).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Clear, colourless, strawberry flavoured elixir.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of allergic conditions including rhinitis and conjunctivitis.

4.2 Posology and method of administration

Adults

1mg twice daily with food. In patients susceptible to sedation, a slow increase in dosage is recommended during the first week of treatment. If necessary the dose may be increased to 2mg twice daily. At the higher dose, an accelerated onset of efficacy may be expected.

Special populations

Pediatrics (from 3 years of age and adolescents)

1 mg twice daily with food.

Geriatrics (aged 65 years and above)

No evidence exists that elderly patients require different dosages or show different side-effects from younger patients.

Renal impairment

No studies have been performed in hepatic impaired patients and hence no dosing recommendations can be provided for these patients (see section 5.2).

Hepatic impairment

No studies have been performed in hepatic impaired patients and hence no dosing recommendations can be provided for these patients (see section 5.2).

Patients known to be easily sedated should be given 0.5 - 1 mg at night for the first few days.

Efficacy guidance

In the prevention of bronchial asthma it may take several weeks of treatment to achieve the full therapeutic effect. It is therefore recommended that treatment with Zaditen should be maintained for a minimum of two to three months, even in patients not adequately responding within a few weeks.

Concomitant bronchodilator therapy: if bronchodilators are used concomitantly with Zaditen, the frequency of bronchodilator use can be reduced.

If it is necessary to stop treatment with Zaditen, this should be done gradually over a period of 2 to 4 weeks. Symptoms of asthma may recur.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Epilepsy.

A reversible fall in the thrombocyte count in patients receiving ZADITEN concomitantly with oral anti-diabetic agents has been observed in a few cases. This combination of drugs should therefore be avoided until this phenomenon has been satisfactorily explained.

Breastfeeding.

4.4 Special warnings and precautions for use

Convulsions have been reported very rarely during Zaditen therapy. As ZADITEN may lower the seizure threshold it should be used with caution in patients with a history of epilepsy.

Zaditen Elixir contains maltitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Zaditen Elixir contains methyl and propyl hydroxybenzoate. They may cause allergic reactions (possibly delayed).

This medicine contains 100 mg of alcohol (ethanol) per 5 ml of solution. The amount in 1 ml of this medicine is equivalent to less than 0,5 ml beer or 0,2 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

This medicine contains less than 1 mmol sodium (23 mg) per 5 ml dose, that is to say essentially “sodium-free”.

Symptomatic and prophylactic anti-asthmatic drugs already in use should never be stopped abruptly when long-term treatment with Zaditen is started. This applies especially to systemic corticosteroids, because of the possible existence of adrenocortical insufficiency in steroid-dependent patients; in such cases, recovery of a normal pituitary-adrenal response to stress may take up to 1 year.

A reversible fall in the thrombocyte count in patients receiving Zaditen concomitantly with oral antidiabetic agents (biguanides) has been observed in rare cases. The simultaneous administration of these drugs should therefore be avoided (see section 4.3).

In case of reduced attention, possibly due to the sedating effect of Zaditen, the dose should be reduced.

Zaditen is not effective in preventing or treating acute asthma attacks.

4.5 Interaction with other medicinal products and other forms of interaction

ZADITEN® may potentiate the effects of sedatives, hypnotics, antihistamines, anticoagulants and alcohol. Patients should be warned not to take charge of vehicles or machinery until the effect of ZADITEN treatment on the individual is known.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

There is no data to support any special recommendations in women of child-bearing potential.

Fertility

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, but was not impaired at doses relevant for human use. The fertility of female rats as well as prenatal development, pregnancy and weaning of the offspring were not adversely affected by ketotifen treatment at oral dose levels of up to 50 mg/kg per day. There is no data available on the effect of Zaditen / Zaditen SRO on fertility in humans.

Pregnancy

Although ketotifen was without effect on pregnancy and on peri- and post-natal development in animals at dose levels which were tolerated by the mother animals, its safety in human pregnancy has not been established. Zaditen should therefore be given to pregnant women only in compelling circumstances.

Lactation

Although there is no evidence of any teratogenic effect, recommendation for ZADITEN in pregnancy cannot be given. Ketotifen is excreted in breast milk, therefore mothers receiving ZADITEN should not breast feed.

4.7 Effects on ability to drive and use machines

During the first few days of treatment with ZADITEN reactions may be impaired. Patients should be warned not to take charge of vehicles or machinery until the effect of ZADITEN treatment on the individual is known. Patients should be advised to avoid alcoholic drinks.

4.8 Undesirable effects

Adverse drug reactions from clinical trials, spontaneous reports and literature cases are listed by MedDRA system organ class. Adverse drug reactions are ranked under heading of Preferred Term (PT) frequency, with the most frequent first. Since reactions from spontaneous reports and literature cases 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. The following convention is used: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$) very rare ($< 1/10,000$), not known (cannot be estimated from the available data), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Infections and infestations

Uncommon: Cystitis

Immune system disorders

Very rare: Erythema multiforme, Stevens-Johnson syndrome, severe cutaneous adverse reaction

Metabolism and nutrition disorders

Rare: Weight increased

Psychiatric disorders**

Common: Agitation, irritability, insomnia, nervousness

Nervous system disorders

Uncommon: Dizziness*

Rare: Sedation*

Very rare: Convulsions

Not known: Somnolence, headache

Gastrointestinal disorders

Uncommon: Dry mouth*

Not known:	Vomiting, nausea, diarrhoea
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Hepatobiliary disorders

Very rare:	Hepatitis, hepatic enzymes increased
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Skin and subcutaneous tissue disorders

Not known:	Rash, urticaria
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*Sedation, dry mouth and dizziness may occur at the beginning of treatment, but usually disappear spontaneously with continued medication.

**Symptoms of CNS stimulation, such as agitation, irritability, insomnia, and nervousness, have been observed particularly in children.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Signs and symptoms

The reported features of overdose include confusion, drowsiness, dizziness, nystagmus, headache, disorientation, tachycardia, hypotension, reversible coma; especially in children, hyperexcitability or convulsions. Bradycardia and respiratory depression should be watched for.

Treatment

Treatment should be symptomatic. Treatment with activated charcoal should be considered if the overdose has been taken within approximately one hour. If necessary, symptomatic treatment and monitoring of the cardiovascular system are recommended; if excitation is present, short acting barbiturates or benzodiazepines may be given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antihistamines for systemic use, ATC code: R06AX17

ZADITEN is a potent antiallergic drug which inhibits the effects of certain endogenous substances known to be inflammatory mediators. ZADITEN exerts a non-competitive blocking effect on histamine (H₁) receptors.

Laboratory experiments have revealed a number of properties of ketotifen, which may contribute to its anti-asthmatic activity:

- Inhibition of the release of allergic mediators such as histamine and leukotrienes

- Suppression of the priming of eosinophils by human recombinant cytokines and thereby suppression of the influx of eosinophils into inflammatory loci
- Inhibition of the development of airway hyper-reactivity associated with activation of platelets by PAF (platelet-activating factor) or caused by neural activation following the use of sympathomimetic drugs or the exposure to allergen.

Zaditen is an established product. There are no new clinical studies.

5.2 Pharmacokinetic properties

Absorption

After oral administration the absorption of ZADITEN® is nearly complete. Bioavailability amounts to approximately 50% due to a first pass effect of about 50% in the liver. Maximal plasma concentrations are reached within 2-4 hours.

Distribution

Protein binding is 75%.

Elimination

Ketotifen is eliminated biphasically with a short half-life of 3-5 hours and a longer one of 21 hours. In urine about 1% of the substance is excreted unchanged within 48 hours and 60-70% as metabolites.

Biotransformation

The main metabolite in the urine is the practically inactive ketotifen-N-glucuronide.

Effect of food

The bioavailability of Zaditen is not influenced by the intake of food. Therefore Zaditen can be taken with or without food. However, smooth plasma concentration profile may be observed when administered with meals.

Special populations

Pediatrics

The pattern of metabolism in children is the same as in adults, but the clearance is higher in children below 3 years. Therefore, the ketotifen dose per kilogram is higher for children compared to the adults.

Children over the age of 3 years therefore require the same daily dose regimen as adults.

Hepatic impairment

No relevant pharmacokinetic studies have been performed with Zaditen in patients with hepatic impairment. Since ketotifen is metabolized in the liver and its glucuronidation may be impaired in severe hepatic impairment, the clearance of ketotifen will most likely be reduced in patients with severe hepatic impairment and the possibility of accumulation of unchanged drug cannot be excluded.

Renal impairment

No relevant pharmacokinetic studies have been performed with Zaditen in patients with renal impairment. However, considering that 60-70% of the dose is excreted in urine as metabolites, an increased risk of adverse reactions due to accumulation of metabolites cannot be excluded.

5.3 Preclinical safety data

Acute toxicity

Ketotifen revealed a moderate acute oral toxicity in animals.

Mutagenicity

Ketotifen and/or its metabolites were devoid of genotoxic potential, when investigated *in vitro* for induction of gene mutation in *Salmonella typhimurium*, for chromosome aberrations in V79 Chinese hamster cells, or for primary DNA-damage in rat hepatocyte cultures. No clastogenic activity was observed *in vivo* (cytogenetic analysis of bone marrow cells in the Chinese hamster, bone marrow micronucleus assay in mice). Likewise, no mutagenic effects were evident on the germ cells of male mice in the dominant lethal test.

Carcinogenicity

In rats treated continuously in the diet for 24 months, maximum tolerated doses of 71 mg/kg ketotifen per day revealed no carcinogenic potential. No evidence of tumorigenic effects was obtained in mice treated with up to 88 mg/kg body weight in the diet for 74 weeks.

Reproductive toxicity

No embryotoxic or teratogenic potential of ketotifen was revealed in rats or rabbits. In male rats treated for 10 weeks (i.e. more than a complete spermatogenic cycle) before mating, fertility was unaffected at a tolerated dose of 10 mg/kg per day.

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. Fertility was not impaired at doses relevant for human use.

The fertility of female rats as well as prenatal development, pregnancy and weaning of the offspring were not adversely affected by ketotifen treatment at oral dose levels of up to 50 mg/kg per day, although non-specific toxicity to the pregnant females was observed at and above 10 mg/kg. Likewise, no adverse effect of treatment was found in the perinatal phase. Due to the maternal toxicity, some decrease in pup survival and weight gain was recorded during the first days of post-natal development at the high dose level of 50 mg/kg per day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Strawberry flavour, propyl hydroxybenzoate, methyl hydroxybenzoate, citric acid anhydrous, disodium phosphate anhydrous, ethanol 96% v/v, maltitol liquid (grade 80/55) and purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Amber glass bottle with a child resistant, tamper evident closure, composed of a polypropylene or polyethylene outer, a polypropylene or polyethylene inner, with a wad faced with PP, PVDC or PET lining. Bottle sizes of 150ml and 300ml.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Alfasigma S.p.A.,
Via Ragazzi del '99, n.5,
40133 Bologna (BO),
ITALY

8 MARKETING AUTHORISATION NUMBER(S)

PL 48053/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 April 1997

Date of the latest renewal: 18 April 2002

10 DATE OF REVISION OF THE TEXT

13/03/2024