

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zaditen 1mg/5ml oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of oral solution contains 1 mg Ketotifen (as the hydrogen fumarate).

Excipients

Each 5 ml of oral solution contains 4,000 mg of maltitol liquid (hydrogenated glucose syrup), 1.655 mg of methyl parahydroxybenzoate (E218) 833 micrograms of propyl parahydroxybenzoate (E216) and 100 mg of ethanol (see section 4.4 special warnings and precautions for use).

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

3 PHARMACEUTICAL FORM

Oral Solution

Clear, colourless syrup with a strawberry odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Preventative treatment of bronchial asthma, especially when associated with atopic symptoms.

Symptomatic treatment of allergic conditions including rhinitis and conjunctivitis.

4.2 Posology and method of administration

Oral administration.

Adults

1 mg twice daily with food. If necessary the dose may be increased to 2 mg twice daily.

At the higher dose, an accelerated onset of efficacy may be expected.

Special populations

Pediatrics

Children aged 2 to 3 years:

0.05mg (=0.25 ml Zaditen Oral Solution 1mg/5ml) per kilogram body weight twice daily (morning and evening).

Pediatrics over 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.

Patients known to be easily sedated should begin treatment with 0.5 to 1 mg at night for the first few days.

Renal impairment

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

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.

4.3 Contraindications

Hypersensitivity to ketotifen or any of the excipients listed in section 6.1.

Epilepsy.

Patients being treated with oral antidiabetic agent.

Breastfeeding.

4.4 Special warnings and precautions for use

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

Symptomatic and prophylactic anti-asthmatic drugs already in use should never be withdrawn abruptly when long-term treatment with Zaditen is begun. Post-marketing surveillance has shown exacerbation of asthma in approximately 2 per 1,000 patients. Since some of these asthmatic attacks might have been related to stopping existing treatment, it is important to continue such treatment for a minimum of two weeks after starting Zaditen. This applies especially to systemic corticosteroids and ACTH 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 one year. If it is necessary to withdraw Zaditen this should be done progressively over a period of 2 to 4 weeks. Symptoms of asthma may recur.

If intercurrent infection occurs Zaditen treatment must be supplemented by specific antimicrobial therapy.

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.

Thrombocytopenia may occur in patients taking Zaditen at the same time as oral antidiabetic drugs (biguanides). 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 oral solution contains maltitol liquid (hydrogenated glucose syrup). Patients with rare hereditary problems of fructose intolerance should not take this medicine.

This medicinal product contains 2 vol% ethanol (alcohol), i.e. up to 100mg per dose, equivalent to 2ml beer and 0.83 ml wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.

This medicinal product contains parahydroxybenzoates. It may cause allergic reactions (possibly delayed). In diabetic patients, the carbohydrate content of the syrup (5 ml = 3 g carbohydrate) should be taken into consideration.

4.5 Interaction with other medicinal products and other forms of interaction

Zaditen may potentiate the effects of CNS depressants, antihistamines, anticoagulants and alcohol.

The simultaneous administration of oral antidiabetic drugs and Zaditen should be avoided (see section 4.3 and 4.4).

Ketotifen increases the effects of bronchodilators, whose frequency of use should be reduced when they are administered at the same time as Zaditen.

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

There are no or limited amount of data from the use of ketotifen in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Zaditen should not be used during pregnancy unless the clinical condition of the woman requires treatment with ketotifen..

Lactation

Available data in rats have shown excretion of ketotifen in milk, while there is no human data available. It is assumed that this drug is also excreted in human breast milk, and therefore mothers receiving Zaditen should not breast-feed (see section 4.3).

4.7 Effects on ability to drive and use machines

During the first 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 infestation

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*

Not known: Convulsions, somnolence, headache

Gastrointestinal disorders

Uncommon: Dry mouth*

Not known: Vomiting, nausea, diarrhoea

Hepatobiliary disorders

Very rare: Hepatitis, hepatic enzymes increased

Skin and subcutaneous tissue disorders

Not known: Rash, urticaria

* Somnolence and 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose**Signs and symptoms**

The main symptoms of acute overdose include: drowsiness to severe sedation; dizziness, confusion and disorientation; tachycardia and hypotension; especially in children, hyperexcitability or convulsions; reversible coma. Bradycardia and respiratory depression should be watched for.

Treatment

Treatment should be symptomatic. If the drug has been taken very recently, emptying of the stomach may be considered. Administration of activated charcoal may be beneficial. If necessary, symptomatic treatment and monitoring of the cardiovascular system are recommended; if excitation or convulsions are present, short-acting barbiturates or benzodiazepines may be given. Zaditen cannot be eliminated by dialysis.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

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

Pharmacodynamic effects

Zaditen is a non-bronchodilator, anti-asthmatic drug which inhibits the effect of certain endogenous substances known to be inflammatory mediators, and thereby exerts anti-allergic activity.

Laboratory experiments indicate that this anti-anaphylactic activity may be due to the inhibition of release of allergic mediators such as histamine and leukotrienes. The suppression of the priming of eosinophils by human recombinant cytokines and thereby suppression of the influx of eosinophils into inflammatory loci and the inhibition of the development of airway hyperactivity 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. In addition, Zaditen exerts a non-competitive blocking effect on histamine (H1) receptors. Therefore, it can also be used in place of classical histamine (H1) receptor antagonists.

Experimental investigations in asthmatic subjects have shown that Zaditen is as effective orally as a selective mast cell stabiliser administered by inhalation: antihistamines are ineffective in these tests.

The effectiveness of Zaditen in the prevention of bronchial asthma has been studied in long-term clinical trials. Asthma attacks were reduced in number, severity and duration and in some cases the patients were completely freed from attacks. Progressive reduction of corticosteroids and/or bronchodilators was also possible.

The prophylactic activity of Zaditen may take several weeks to become fully established. Zaditen will not abort established attacks of asthma.

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

5.2 Pharmacokinetic properties

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

Pharmacodynamic effects

Zaditen is a non-bronchodilator, anti-asthmatic drug which inhibits the effect of certain endogenous substances known to be inflammatory mediators, and thereby exerts anti-allergic activity.

Laboratory experiments indicate that this anti-anaphylactic activity may be due to the inhibition of release of allergic mediators such as histamine and leukotrienes. The suppression of the priming of eosinophils by human recombinant cytokines and thereby suppression of the influx of eosinophils into inflammatory loci and the inhibition of the development of airway hyperactivity 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. In addition, Zaditen exerts a non-competitive blocking effect on histamine (H1) receptors. Therefore, it can also be used in place of classical histamine (H1) receptor antagonists.

Experimental investigations in asthmatic subjects have shown that Zaditen is as effective orally as a selective mast cell stabiliser administered by inhalation: antihistamines are ineffective in these tests.

The effectiveness of Zaditen in the prevention of bronchial asthma has been studied in long-term clinical trials. Asthma attacks were reduced in number, severity and duration and in some cases the patients were completely freed from attacks. Progressive reduction of corticosteroids and/or bronchodilators was also possible.

The prophylactic activity of Zaditen may take several weeks to become fully established. Zaditen will not abort established attacks of asthma.

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

5.3 Preclinical safety data

Acute toxicity

Acute toxicity studies of ketotifen in mice, rats and rabbits revealed oral LD50 values above 300mg/kg bodyweight and between 5 and 20mg/kg by the i.v. route. Adverse effects induced by overdose were dyspnea and motor excitation followed by spasms and drowsiness. Toxic signs appeared rapidly and disappeared within hours; there was no evidence of cumulative or delayed effects. Other studies yielded an oral LD50 value of ketotifen in rats of 161mg/kg and demonstrated that the toxicity of Zaditen syrup (LD50 31.1mg/kg) was attributable to the sorbitol excipient alone.

A total daily dose of 10- ml administered to a child of 30kg would be equivalent to 0.33ml/kg Zaditen syrup and 0.07mg/kg ketotifen base, indicating a sufficiently wide safety margin.

No evidence of skin sensitizing potential of ketotifen was obtained in guinea pigs by intracutaneous injection.

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* (cytogenic 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 71mg/kg ketotifen per day revealed no carcinogenic potential. No evidence of tumorigenic effects was obtained in mice treated with up to 88mg/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 10mg/kg per day.

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 50mg/kg per day, although non-specific toxicity to the pregnant females was observed at and above 10mg/kg. Likewise, no adverse effect of treatment was found in the peri-natal 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 50mg/kg per day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propyl parahydroxybenzoate (E216)
Methyl parahydroxybenzoate (E218)
Strawberry flavour liquid
Citric acid anhydrous (E330)
Disodium hydrogen phosphate (E450)
Ethanol
Liquid maltitol (hydrogenated glucose syrup)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Brown glass bottles with a polyethylene closure (polyethylene wad faced with PP, PVDC or PET lining) containing 300 ml.

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, containing 300 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Alfasigma S.p.A
Viale Sarca
n.223
20126 Milan (MI)
Italy

8 MARKETING AUTHORISATION NUMBER

PA2206/004/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 November 1979

Date of last renewal: 31 May 2009

10 DATE OF REVISION OF THE TEXT

August 2017