NOVARTIS

Drug Regulatory Affairs

ZADITEN® / ZADITEN® SRO

(ketotifen)

1 mg capsule, hard

1 mg tablet

2 mg film coated tablet

1 mg/5 mL syrup

1 mg/mL oral solution

Basic Prescribing Information

NOTICE

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to the characterisation of risks and benefits.

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1 Name of the medicinal product

ZADITEN® 1 mg capsule, hard/ZADITEN® 1 mg tablet/ZADITEN® SRO (slow release oral) 2 mg film coated tablet/ ZADITEN® 1 mg/5 mL syrup/ ZADITEN® 1 mg/mL oral solution

2 Qualitative and quantitative composition

Zaditen hard capsules contain 1 mg ketotifen (as the hydrogen fumarate).

Zaditen tablets (scored) contain 1 mg ketotifen (as the hydrogen fumarate).

Zaditen SRO (slow release oral) tablets (film-coated) contains 2 mg ketotifen (as the hydrogen fumarate).

Zaditen syrup contains 1 mg ketotifen (as the hydrogen fumarate) per 5 mL.

Zaditen oral solution contains 1 mg ketotifen (as the hydrogen fumarate) per 1 mL (= 20 drops).

Tablets contain lactose as an excipient (see section 4.4 Special warnings and precautions for use).

Syrup and oral solution contain maltitol liquid (hydrogenated glucose syrup) as an excipient (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

Capsules, hard; tablets (scored); SRO (slow release oral) film coated tablets; oral solution and syrup.

Information might differ in some countries.

4 Clinical particulars

4.1 Therapeutic indications

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

Zaditen is not effective in aborting established attacks of asthma.

- Prevention and treatment of multisystem allergic disorders:
  - chronic urticaria
  - atopic dermatitis
  - allergic rhinitis and conjunctivitis

4.2 Posology and method of administration

Adults

1 Zaditen SRO tablet (2 mg) in the evening, or 1 Zaditen capsule (1 mg), or 1 Zaditen tablet (1 mg) twice daily (with morning and evening meals). In patients susceptible to sedation, a slow increase in dose is recommended during the first week of treatment, starting with ½ tablet twice daily or 1 capsule in the evening only, and increasing to the full therapeutic

dose. If necessary, the daily dose may be increased up to 4 mg, i.e. 2 Zaditen SRO tablets once a day in the evening, or 2 Zaditen capsules or 2 Zaditen tablets twice daily. At the higher dose, an accelerated onset of efficacy may be expected.

Children

Children aged 6 months to 3 years

Oral solution

0.05 mg (= 1 drop of Zaditen oral solution) per kilogram body weight twice daily (morning and evening).

Example: an infant weighing 10 kg may receive 10 drops in the morning and 10 drops in the evening.

Syrup

0.05 mg (= 0.25 mL syrup) per kilogram body weight twice daily (morning and evening).

Example: an infant weighing 10 kg may receive 2.5 mL (= ½ teaspoonful) of Zaditen syrup in the morning and evening.

Children over 3 years of age

5 mL (1 teaspoonful) syrup, or 1 capsule, or 1 tablet twice daily with morning and evening meal, or 1 tablet SRO (2 mg) in the evening.

Note

In the prevention of bronchial asthma it may take several weeks of treatment to achieve the full therapeutic effect. It is therefore recommended that for patients not adequately responding within a few weeks, treatment with Zaditen should be maintained for a minimum of 2 to 3 months.

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

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.

Zaditen SRO tablets should be swallowed whole.

Use in children

Clinical observations reflect pharmacokinetic findings and indicate that children may require a higher dose in mg/kg body weight than adults in order to obtain optimal results. This higher dose is as well tolerated as lower doses (see also under section 5.2 Pharmacokinetic properties).

Use in the elderly

Experience with Zaditen has shown that there are no special requirements in elderly patients.

4.3 Contraindications

Known hypersensitivity to ketotifen or any of the excipients (see section 6.1 List of excipients).

4.4 Special warnings and special precautions for use

Symptomatic and prophylactic anti-asthmatic drugs already in use should never be withdrawn abruptly when long-term treatment with Zaditen is begun. 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 has been observed in rare cases. Thrombocyte counts should therefore be carried out in patients taking antidiabetics concomitantly.

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.

In diabetic patients, the carbohydrate content of the syrup (5 mL = 3 g carbohydrate) should be taken into consideration.

The tablets and SRO film coated tablets contain lactose. This medicine is not recommended for patients with rare hereditary problems of galactose intolerance, of severe lactase deficiency or of glucose-galactose malabsorption.

The syrup and oral solution contain maltitol liquid. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Pregnancy and lactation

Pregnancy

Although ketotifen was without effect on pregnancy and on peri- and post-natal development 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

Ketotifen is excreted in rat milk. It is assumed that this drug is also excreted in human breast milk, and 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 the patient’s reactions may be impaired and he/she should therefore exercise care when driving a vehicle or operating machinery.

4.8 Undesirable effects

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000) very rare (< 1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1

Infections and infestations		
	Uncommon:	Cystitis
Immune system disorders		
	Very rare:	Erythema multiform, Stevens-Johnson syndrome, severe skin reaction
Metabolism and nutrition disorders		
	Rare:	Weight increased
Psychiatric disorders		
	Common:	Excitation, irritability, insomnia, nervousness
Nervous system disorders		
	Uncommon:	Dizziness
	Rare:	Sedation
Gastrointestinal disorders		
	Uncommon:	Dry mouth
Hepatobiliary disorders		
	Very rare:	Hepatitis, increase in liver enzymes

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 excitation, irritability, insomnia, and nervousness, have been observed particularly in children.

4.9 Overdose

The main symptoms of acute overdose include: drowsiness to severe sedation; confusion and disorientation; tachycardia and hypotension; especially in children, hyperexcitability or convulsions; reversible coma.

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.

5 Pharmacological properties

5.1 Pharmacodynamic properties

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

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

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

Ketotifen is a potent antiallergic substance possessing non-competitive histamine (H_1) blocking properties. Therefore, it can also be used in place of classical histamine (H_1) receptor antagonists.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

Protein binding is 75%.

Biotransformation

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

The pattern of metabolism in children is the same as in adults, but the clearance is higher in children. Children over the age of 3 years therefore require the same daily dose regimen as adults.

Elimination

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

Slow release (SRO) formulation

The slow release of ketotifen from Zaditen SRO tablets results in a smoother pharmacokinetic profile with reduced daily variations in the plasma concentrations, which improves tolerability and allows once-a-day administration. The peak plasma levels attained with a single daily dose of Zaditen SRO are lower (76%) than those found when the same daily amounts of ketotifen are given in 2 divided doses of any of the other galenical forms. However, minimum plasma concentrations (trough levels) and relative bioavailability (AUC) are the same for both dose regimens.

Effect of food

The bioavailability of either form of Zaditen is not influenced by the intake of food.

5.3 Preclinical safety data

Acute toxicity

Acute toxicity studies of ketotifen in mice, rats, and rabbits revealed oral LD_{50} values above 300 mg/kg body weight and between 5 and 20 mg/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 LD_{50} value of ketotifen in rats of 161 mg/kg and demonstrated that the toxicity of Zaditen syrup (LD_{50} 31.1 mL/kg) was attributable to the sorbitol excipient alone. A total daily dose of 10 mL administered to a child of 30 kg would be equivalent to 0.33 mL/kg Zaditen syrup and 0.07 mg/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* (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.

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

Zaditen capsules: silicic acid; fumaric acid; magnesium stearate; maize starch; mannitol; titanium dioxide; gelatin.

Zaditen tablets: fumaric acid; magnesium stearate; maize starch; calcium hydrogen phosphate; lactose.

Zaditen SRO tablets: magnesium stearate; silica; ethyl cellulose; fumaric acid; polyvinylpyrrolidone; maize starch; glyceryl palmitostearate; lactose; polyethylene glycol 6000; talc; methylhydroxy-propylcellulose; iron oxide yellow; titanium dioxide.

Zaditen syrup: fumaric acid; banana or strawberry flavoring agent; propyl p-hydroxybenzoate; methyl p-hydroxybenzoate; citric acid; disodium hydrogen phosphate; maltitol liquid; water, demineralized. Some formulations may contain ethanol.

Zaditen oral solution: fumaric acid; propyl parahydroxybenzoate; methyl parahydroxybenzoate; citric acid; disodium hydrogen phosphate; maltitol liquid; water, demineralized.

Information might differ in some countries.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

1½ to 5 years, depending on climate, container, and formulation.

Information might differ in some countries.

6.4 Special precautions for storage

Zaditen tablets: depending on climate and container, store below 30 °C.

Zaditen SRO tablets: store below 25 °C.

Zaditen syrup: store below 25 °C in both hot and tropical climates.

Zaditen oral solution: store below 25 °C in both hot and tropical climates.

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

Information might differ in some countries.

6.5 Nature and contents of container

Zaditen hard capsules are packed in glass containers or PVC blister packs.

Zaditen tablets are packed in glass containers, PVC blister packs or multilayer blister foils.

Zaditen SRO film coated tablets are packed in PVC blister packs, multilayer blister foils or glass containers.

Zaditen syrup is available in glass or plastic bottles.

Zaditen oral solution is available in glass bottles.

Information might differ in some countries.

6.6 Instructions for use and handling

None.