NOVARTIS

Zaditen® / Zaditen® SRO

Antihistamines for systemic use.

DESCRIPTION AND COMPOSITION

Pharmaceutical form(s)

Tablets (scored);

SRO (slow release oral) film coated tablets;

Syrup

Active substance

Zaditen tablets (scored) containing the equivalent of 1 mg ketotifen (as hydrogen fumarate).

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

Zaditen syrup containing the equivalent of 1 mg ketotifen (as hydrogen fumarate) per 5 mL.

Active moiety

Ketotifen

Excipients

Zaditen tablets: magnesium stearate; maize starch; maize starch preswollen; lactose monohydrate*.

Zaditen SRO tablets: magnesium stearate; silica (colloidal anhydrous); ethyl cellulose; polyvinylpyrrolidone; maize starch; glyceryl palmitostearate; lactose monohydrate*; polyethylene glycol 6000; talc; methylhydroxy-propylcellulose; iron oxide yellow; titanium dioxide.

Zaditen syrup: strawberry flavoring agent; sodium propyl p-hydroxybenzoate; sodium methyl p-hydroxybenzoate; citric acid (anhydrous); disodium hydrogen phosphate; maltitol liquid**; purified water, demineralized.

* Tablets contain lactose as an excipient (see section WARNINGS AND PRECAUTIONS).

** Syrup contains maltitol liquid (hydrogenated glucose syrup) as an excipient (see section WARNINGS AND PRECAUTIONS).

INDICATIONS

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

Zaditen is not effective in aborting established attacks of asthma. Zaditen is not a substitute for corticosteroid treatment (inhaled or systemic) when corticosteroid is indicated in the treatment of asthma.

Prevention and treatment of multisystem allergic disorders:

- chronic urticaria
- atopic dermatitis
- allergic rhinitis and conjunctivitis

DOSAGE AND ADMINISTRATION

Dosage

General target population

One Zaditen SRO tablet (2 mg) in the evening, or one Zaditen tablet (1 mg) twice daily (with morning and evening meals). In patients susceptible to sedation, slow increase in dosage is recommended during the first week of treatment, starting with ½ tablet twice daily and increasing to the full therapeutic dose. If necessary, the daily dose may be increased up to 4 mg, i.e. two Zaditen SRO tablets once a day in the evening, or two Zaditen tablets twice daily.

Special populations

Renal impairment

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

Hepatic impairment

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

Pediatric patients (aged 6 months to 3 years)

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 in the evening.

Children over 3 years of age and adolescents

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

Geriatric patients (aged 65 years and above)

There is no evidence to suggest that the dosage needs to be adjusted in elderly patients.

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 the first 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 two to four weeks. Symptoms of asthma may recur.

Instructions for use

Zaditen SRO tablets should be swallowed whole.

CONTRAINDICATIONS

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

Epilepsy or history of seizures (see section WARNINGS AND PRECAUTIONS).

WARNINGS AND PRECAUTIONS

Convulsions have been reported during Zaditen therapy. As Zaditen may lower the seizure threshold it is contraindicated in patients with a history of epilepsy (see section CONTRAINDICATIONS).

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 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 measured in patients concomitantly taking antidiabetics.

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

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 therefore patients should exercise care when driving a vehicle or operating machinery.

INTERACTIONS

Observed interaction resulting in a concomitant use not recommended

Oral antidiabetic agents

A reversible fall in the thrombocyte count in patients receiving ketotifen concomitantly with oral antidiabetic agents has been observed in rare cases. Thrombocyte counts should therefore be measured in patients taking ketotifen concomitantly with antidiabetics (see section WARNINGS AND PRECAUTIONS).

Anticipated interactions to be considered

Medicinal products causing CNS depression

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

PREGNANCY, BREAST-FEEDING AND FERTILITY

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 not be given to pregnant women except if clearly needed and the benefits outweigh the potential risks.

Breast-feeding

Ketotifen is excreted in rat milk. While there is no human data available, it is likely that this drug is also excreted in human breast milk, and therefore mothers receiving Zaditen should not breast-feed.

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 fertility was not impaired at doses relevant for human use. 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 (see section NON-CLINICAL SAFETY DATA). There is no data available on the effect of Zaditen / Zaditen SRO on fertility in humans.

ADVERSE DRUG REACTIONS

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 first. Within each frequency grouping, adverse reactions are ranked 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, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000).

Table 1 Adverse drug reactions in clinical trials

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		
	Common:	Sedation*
	Uncommon:	Dizziness*
Gastrointestinal disorders		
	Uncommon:	Dry mouth*
Hepatobiliary disorders		
	Very rare:	Hepatitis, hepatic enzymes increased

* Sedation, dry mouth and dizziness may occur at the beginning of treatment, but usually disappear spontaneously with continued medication. In adults the incidence of sedation is 14.1% during the first three months of treatment and 2.2% after 12 months.

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

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Zaditen / Zaditen SRO via spontaneous case reports and literature cases. 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. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness:

Table 2 Adverse Drug Reactions from spontaneous reports and literature (Frequency not known)

Nervous system disorders

Convulsions, somnolence, headache
Gastrointestinal disorders
Vomiting, nausea, Diarrhoea
Skin and subcutaneous tissue disorders
Rash, Urticaria

OVERDOSAGE

Signs and symptoms

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

Treatment should be symptomatic. If excitation or convulsions are present, short-acting barbiturates or benzodiazepines may be given. Monitoring of the cardiovascular system is recommended. If the drug has been taken very recently, emptying of the stomach may be considered. Administration of activated charcoal may be beneficial.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS (PD)

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 an antiallergic substance possessing non-competitive histamine (H_1) blocking properties.

PHARMACOKINETICS (PK)

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%.

Metabolism

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

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 other dosage 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 (i.e. immediate or modified release formulations) 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 for the modified-release tablet when administered with meals.

Special populations

Pediatric patients

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 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 hepatic impairment, the clearance of ketotifen will most likely be reduced in patients with 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. Thus caution is required in administering Zaditen in patients with mild to moderate renal impairment and, Zaditen should not be administered with severe renal impairment.

NON-CLINICAL SAFETY DATA

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.

INCOMPATIBILITIES

Not applicable.

STORAGE

Zaditen tablets: Do not store above 30°C

Zaditen SRO tablets: Store below 25°C

Zaditen syrup: Store below 30°C

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

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

INSTRUCTIONS FOR USE AND HANDLING

None.

Manufacturer:

See folding box.

Pack Size

Zaditen tablets: 30 and 100 tablets

Zaditen SRO tablets: 30 tablets

Zaditen syrup: 100 ml bottle

International Package Leaflet

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Novartis Pharma AG, Basel, Switzerland