NOVARTIS

Zaditen® tablets

Zaditen® capsules

Zaditen® 0.2 mg/ml syrup (banana-flavoured)

Zaditen® 0.2 mg/ml syrup (strawberry-flavoured)

Zaditen® SRO film-coated tablets

Composition

Active substance: Ketotifen (as ketotifen hydrogen fumarate)

Excipients:
Zaditen capsules: silica (colloidal anhydrous); fumaric acid; magnesium stearate; maize starch; mannitol; titanium dioxide; gelatin.
Zaditen tablets: fumaric acid; magnesium stearate; maize starch; calcium hydrogen phosphate; lactose monohydrate*.
Zaditen SRO tablets: magnesium stearate; silica; ethyl cellulose; fumaric acid; polyvinylpyrrolidone; maize starch; glyceryl palmitostearate; lactose monohydrate*; polyethylene glycol 6000; talc; methylhydroxy-propylcellulose; iron oxide yellow; titanium dioxide.
Zaditen syrup***: fumaric acid; banana or strawberry flavoring agent; sodium propyl p hydroxybenzoate; sodium methyl p-hydroxybenzoate; citric acid (anhydrous); disodium hydrogen phosphate; maltitol liquid**; purified water, demineralized.
Zaditen oral solution: fumaric acid; propyl parahydroxybenzoate; methyl parahydroxybenzoate; citric acid; disodium hydrogen phosphate; maltitol liquid**; water, demineralized.
* Tablets contain lactose as an excipient .
** Syrup and oral solution contain maltitol liquid (hydrogenated glucose syrup) as an excipient .
*** Some country-specific formulations may contain ethanol.
Information might differ in some countries.

Pharmaceutical form and quantity of active substance per unit

Scored tablets containing 1 mg
Hard gelatin capsules containing 1 mg
SRO film-coated tablets containing 2 mg
Syrup containing 0.2 mg/ml

Indications/Potential uses

Prevention and treatment of multisystem allergic disorders:
- Chronic idiopathic urticaria (e.g. cold urticaria)
- Allergic rhinitis with or without concomitant asthma
- Allergic conjunctivitis
- Atopic dermatitis

It may take several weeks for Zaditen to achieve its full therapeutic effect.
Zaditen is not a substitute for corticosteroid treatment (inhaled or systemic) when corticosteroid is indicated in the treatment of asthma.

Dosage and Administration

Zaditen capsules and SRO tablets should be swallowed whole.

Adults
The usual daily dose is 2 mg: It should be taken with meals either as one tablet or capsule of 1 mg twice daily (mornings and evenings), or as one SRO tablet of 2 mg once daily (evenings). In patients susceptible to sedation, a progressive regimen is recommended during the first week of treatment. This should be started with half a standard tablet twice daily or one standard tablet or capsule in the evenings only, increasing to the full therapeutic dose over the next 5 days. If necessary, the daily dose may be increased to 4 mg, i.e. two standard tablets or capsules twice daily or two SRO tablets once daily in the evening. A more rapid onset of action can be expected with the higher dose.

Children
Children aged 6 months to 3 years: 0.05 mg (= 0.25 ml syrup) per kg body weight twice daily in the mornings and evenings with meals.
Example: A child weighing 10 kg can be given 2.5 ml syrup (i.e. the lowest amount on the measure) in the morning and evening.
Children ≥3 years of age: 5 ml syrup or one tablet or capsule of 1 mg twice daily (mornings and evenings) or one SRO tablet of 2 mg once daily (with the evening meal).
Clinical experience reflects pharmacokinetic findings and indicates that children may require a higher dose than adults (in mg/kg body weight) in order to achieve an optimal effect. Such doses are just as well tolerated as lower doses (see **Pharmacokinetics**).
Concomitant use of bronchodilators: In patients treated with bronchodilators concomitantly with Zaditen it is usually possible to reduce the frequency of bronchodilator usage.
The syrup is prepared using a sugar substitute (Lycasin) and can therefore also be given to diabetic children under appropriate supervision. 5 ml syrup is equivalent to 3 g carbohydrate.

Use in elderly patients
Experience with Zaditen in elderly patients has shown that no special measures are necessary.

Duration of treatment
It may take several weeks to achieve the full therapeutic effect. It is therefore recommended that in patients who show no satisfactory response after several weeks, treatment should be continued for a minimum of 2-3 months.
If withdrawal of Zaditen is necessary, this should be done progressively over 2-4 weeks. Symptoms of asthma may recur.

Contraindications

Hypersensitivity to ketotifen or to any of the excipients.
Epilepsy or a history of seizures (see **Warnings and Precautions**).
Additionally for the syrup only: Hypersensitivity to the preservatives E 216 and E 218 (para-group allergy).

Warnings and Precautions

Convulsions have been reported during Zaditen therapy. Zaditen may lower the seizure threshold, and is therefore contraindicated in patients with a history of epilepsy (see **Contraindications**).
There are insufficient data available on long-term treatment (>4 weeks) of patients with chronic idiopathic urticaria.
Any corticosteroid therapy that is already being given should not be withdrawn abruptly at the start of long-term Zaditen treatment. This applies particularly to systemic corticosteroids and ACTH, since there is a risk of adrenal insufficiency in steroid-dependent patients. In such cases recovery of a normal pituitary-adrenal response to stress may take as long as one year. Specific anti-infective agents should be given in addition to Zaditen to combat any intercurrent infections.
In diabetic patients, the carbohydrate content of the syrup (5 ml = 3 g carbohydrate) must be taken into account.
Zaditen tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take Zaditen tablets or Zaditen SRO tablets.
The syrup contains liquid maltitol. Patients with rare hereditary problems of fructose intolerance should not take Zaditen syrup.

Interactions

Zaditen may potentiate the effects of sedatives, hypnotics, antihistamines and alcohol.
A reversible fall in the platelet count has been reported in rare cases where Zaditen was given concomitantly with an oral antidiabetic agent. Platelet counts should therefore be performed in patients receiving Zaditen and antidiabetic medication concomitantly.

Pregnancy and Lactation

Pregnancy
Animal studies involving maternally tolerated dose levels have not shown any direct or indirect toxicity affecting pregnancy, embryonic development, fetal development and/or postnatal development.
No clinical data are available on use in pregnant women. Given these circumstances, Zaditen should not be administered during pregnancy unless absolutely necessary.

Lactation
Ketotifen is excreted in the milk of rats and is therefore assumed to be excreted in human milk also. Women being treated with Zaditen should therefore not breastfeed.

Fertility
No data are available on the effect of Zaditen on fertility (for relevant preclinical data see **Preclinical data**).

Effects on ability to drive and use machines

Zaditen may impair the patient's reactions. Caution is therefore necessary when carrying out activities such as driving or using machines.

Adverse effects

Sedation, dry mouth and dizziness may occur in the first few days of treatment but normally disappear quickly and spontaneously. In adults the incidence of sedation is 14.1% during the first three months of treatment and 2.2% after 12 months. In children, sedation is rare and is less severe than in adults.
In patients receiving the syrup, hypersensitivity reactions to the preservatives E216 and E218 may occur (para-group allergy).

Frequencies
Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10 000 to <1/1000), very rare (<1/10 000).

Infections
Uncommon: Cystitis.

Immune system disorders
Very rare: Erythema multiforme, Stevens-Johnson syndrome, severe skin reactions.

Metabolism and nutrition disorders
Rare: Weight gain.

Psychiatric disorders
Common: Agitation, irritability, insomnia, nervousness.

Nervous system disorders
Uncommon: Dizziness.
Rare: Fatigue.
*Not known**: Convulsions, drowsiness, headache.

Gastrointestinal disorders
Uncommon: Dry mouth.
*Not known**: Nausea, vomiting, diarrhoea.

Hepatobiliary disorders
Very rare: Hepatitis, increase in hepatic enzymes.

Skin disorders
*Not known**: Rash, urticaria.

* Post-marketing observations: The post-marketing observations are based on spontaneous reports. The adverse effects in question have been reported voluntarily from a population of uncertain size, so it is not possible to reliably estimate their frequency.

Overdose

Signs and symptoms
The main signs and symptoms of overdose are: drowsiness to severe sedation; confusion and disorientation; tachycardia and fall in blood pressure.
Particularly in children: Hyperexcitability or convulsions; reversible coma.

Management
Management should be symptomatic. Emptying of the stomach may be considered if only a very short time has elapsed since ingestion. Administration of activated charcoal may be helpful.
Symptomatic treatment and cardiovascular monitoring are recommended if necessary. Short-acting barbiturates or benzodiazepines may be given in cases of excitation or convulsions.

Properties and Actions

ATC code: R06AX17

Mechanism of action/Pharmacodynamics
Ketotifen is an anti-asthmatic agent that inhibits the effects of certain endogenous substances known to be inflammatory mediators, thereby exerting anti-allergic activity.
In vitro and *in vivo* laboratory experiments have shown ketotifen to have the following properties that may contribute to its activity:
- Inhibition of the release of allergic mediators such as histamine and leukotrienes
- Suppression of the priming of eosinophils by human recombinant cytokines, and thus inhibition of the influx of eosinophils into inflammatory loci
- Inhibition of platelet activation by PAF (platelet-activating factor) and of neural activation following exposure to an allergen

Ketotifen is an anti-allergic agent with non-competitive histamine (H_1)-blocking properties.

Pharmacokinetics

Absorption
Ketotifen is almost completely absorbed following oral administration. Bioavailability is approx. 50% due to a first-pass effect of about 50% in the liver. Peak plasma concentrations are attained within 2-4 hours.

Distribution
Protein binding is 75%.

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

Elimination
Elimination of ketotifen is biphasic, with a short half-life of 3-5 hours and a longer one of 21 hours. Within 48 hours about 1% of the active substance is excreted unchanged, and 60-70% as metabolites, in the urine.
The pattern of metabolism in children is the same as in adults, although clearance is higher in children. Children over 3 years of age thus require the same daily doses as adults.

Patients with hepatic impairment
No relevant pharmacokinetic studies have been performed with Zaditen in patients with hepatic impairment. Ketotifen is metabolized in the liver and its glucuronidation may be impaired by severe hepatic impairment. The clearance of ketotifen is likely to 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, it must be borne in mind that 60-70% of the dose is excreted in urine as metabolites, so that an increased risk of adverse effects due to accumulation of metabolites cannot be excluded.

Slow-release (SRO) formulation
The slow release of ketotifen from Zaditen SRO tablets results in a smoother pharmacokinetic profile, allowing once-daily administration. The peak plasma concentrations attained with a single dose of Zaditen SRO are lower (76%) than those found when the same daily amounts of ketotifen are given in two divided doses of any of the other dosage forms, while minimum plasma concentrations are the same. Daily fluctuations in plasma concentrations are thus lower with the SRO tablets than with the other forms. The relative bioavailability of Zaditen SRO tablets is 100% of that obtained with the other forms.
Bioavailability is not affected by food intake.

Preclinical data

Ketotifen revealed moderate acute oral toxicity in animals.

Mutagenic and carcinogenic potential
Ketotifen and/or its metabolites showed no genotoxic potential in *in vitro* tests for gene mutations in *Salmonella typhimurium*, for chromosomal aberrations in Chinese hamster V79 cells, or for primary DNA damage in rat liver cell cultures.
No clastogenic activity was observed *in vivo* (cytogenetic analysis of Chinese hamster bone marrow cells, mouse bone marrow micronucleus assay). Similarly, the dominant lethal test revealed no mutagenic effects on male mouse germ cells.
In rats given ketotifen continuously with their feed for 24 months, the highest tolerated ketotifen doses of 71 mg/kg/day showed no carcinogenic potential.
In mice that received doses of up to 88 mg/kg body weight with their feed for 74 weeks, there was likewise no evidence of carcinogenic effects.

Reproductive toxicity
Studies in rats and rabbits produced no evidence of embryotoxic or teratogenic effects. In male rats, fertility was unaffected at a tolerated dose of 10 mg/kg/day.
Treatment of male rats with a toxic dose of ketotifen (50 mg/kg/day) for 10 weeks prior to mating resulted in decreased fertility. Fertility was not impaired at doses relevant to human use.
The fertility of female rats, pregnancy, prenatal development and weaning of the offspring were not adversely affected by oral ketotifen doses of up to 50 mg/kg/day, although nonspecific toxicity was observed in the pregnant females given doses of 10 mg/kg/day and above. Treatment with ketotifen likewise produced no observable negative effect in the perinatal period.
Increased mortality and reduced weight gain were observed in the offspring during the first days of postnatal development due to the toxicity observed in the maternal animals given the high dosage of 50 mg/kg/day.
Ketotifen crosses the placental barrier in rats. Small amounts are found in particular in the fetal lung, liver and intestinal tract.

Other information

Shelf-life
Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage
Store Zaditen capsules, syrup and SRO film-coated tablets in a dry place at a temperature not above 25°C.
Store Zaditen tablets in a dry place at a temperature not above 30°C.
Keep out of the reach of children.

Pack sizes

Country specific pack sizes.

Manufacturer

See folding box.

Information last revised

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® = registered trademark
Novartis Pharma AG, Basle, Switzerland

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists