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.

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.

Pharmacodynamics

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.

Pharmacokinetics

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.

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.

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.

Pharmaceutical formulations may vary between countries.

Incompatibilities

Not applicable.

Storage

See folding box.

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

Instructions for use and handling

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

Manufacturer:

See folding box.

International Package Leaflet

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