Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zaditen 1 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1mg ketotifen (as the hydrogen fumarate).

Excipients with known effect: each tablet contains 96.88 mg of lactose as lactose monohydrate.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets
White, or yellow-tinged white, circular, flat, bevel-edged tablets with breakline, weighing 130mg, 7mm diameter. The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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. In patients susceptible to sedation, a 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 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: For younger children, who cannot swallow tablets or where the required dose cannot be administered using tablets, Zaditen Oral Solution 1mg/5ml is available. Dosage: 0.05 mg (=0.25 ml Zaditen Oral solution 1mg/5ml) per kilogram body weight twice daily (morning and evening).
Children over 3 years of age and adolescents: 1mg 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).

4.3 Contraindications

Hypersensitivity to the active substance or to 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

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 tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

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).

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.

Breast-feeding
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, 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 (≥ 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), 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 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
Uncommon: Dizziness*
Rare: Sedation*
Not known: Convulsions, somnolence, headache

Gastrointestinal disorders
Uncommon: Dry mouth*
Not known: Vomiting, nausea, diarrhea

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. There have been reports of nausea, vomiting, headache, convulsion, urticaria and rash.

**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, website: www.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.

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

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 ketotifen-N-glucuronide. This is practically inactive.

Elimination
Ketotifen is eliminated biphasically, with a short half-life of 3 of 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% is excreted as metabolites.

Effect of food
The bioavailability of Zaditen is not influenced by food. Therefore Zaditen can be taken with or without food. However, smooth plasma concentration profile may be observed when administered with meals.

Special populations

Pediatrics
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 the 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 severe hepatic impairment, the clearance of ketotifen will most likely 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, 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.

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 iv route. Adverse effects induced by overdose were dyspnoea 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

Magnesium stearate
Maize starch
Pregelatinised maize starch
Lactose monohydrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Do not store above 25ºC.

6.5 Nature and contents of container

PVC/PVDC blister pack, containing 7, 14 or 28 or 60 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Alfasigma S.p.A
Via Ragazzi del '99, n. 5
40133 Bologna (BO)
Italy

8 MARKETING AUTHORISATION NUMBER

PA2206/004/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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