SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

ZADITEN Tablets 1mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ketotifen hydrogen fumarate 1.38 mg (equivalent to 1 mg ketotifen base).

Excipients with known effect: each tablet contains lactose (102 mg).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White tablets, 7 mm diameter, with break-line on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of allergic conditions including rhinitis and conjunctivitis.

4.2 Posology and method of administration

Adults
1 mg twice daily with food. If necessary the dose may be increased to 2mg twice daily. At the higher dose, an accelerated onset of efficacy may be expected.

Special populations

Pediatrics (from 3 years of age and adolescents)

1 mg twice daily with food. For patients for whom a tablet form may not be suitable, an alternative dosage form should be considered.

Geriatrics (aged 65 years and above)

No evidence exists that elderly patients require different dosages or show different side-effects from younger patients.

Renal impairment

No studies have been performed in renal 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 hepatic impaired patients and hence no dosing recommendations can be provided for these patients (see section 5.2).

Patients known to be easily sedated should be given 0.5 -1 mg at night for the first few days.

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 a 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 2 to 4 weeks. Symptoms of asthma may recur.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Epilepsy.

A reversible fall in the thrombocyte count in patients receiving ZADITEN concomitantly with oral anti-diabetic agents has been observed in a few cases.

This combination of drugs should therefore be avoided until this phenomenon has been satisfactorily explained.

Breastfeeding.

4.4 Special warnings and precautions for use

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

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.

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 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 (biguanides) has been observed in rare cases. 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 is not effective in preventing or treating acute asthma attacks.

4.5 Interaction with other medicinal products and other forms of interaction

ZADITEN may potentiate the effects of sedatives, hypnotics, antihistamines and alcohol. Patients should be warned not to take charge of vehicles or machinery until the effect of ZADITEN treatment on the individual is known.

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
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 therefore be given to pregnant women only in compelling circumstances.

Lactation

Although there is no evidence of any teratogenic effect, recommendation for ZADITEN in pregnancy cannot be given. Ketotifen is excreted in breast milk, 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 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.

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 (Table 1) are ranked under heading of Preferred Term (PT) frequency, with 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*
Very rare:	Convulsions
Not known:	Somnolence, headache
Gastrointestinal disorders	
Uncommon:	Dry mouth*
Not known:	Vomiting, nausea, diarrhoea
Hepatobiliary disorders	
Very rare:	Hepatitis, increase in liver enzymes
Skin and subcutaneous tissue disorders	
Not known:	Rash, urticaria

*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 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 the internet at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Signs and symptoms

The reported features of overdose include confusion, drowsiness, dizziness, nystagmus, headache, disorientation, tachycardia, hypotension, reversible coma; especially in children, hyperexcitability or convulsions. Bradycardia and respiratory depression should be watched for.

Treatment

Treatment should be symptomatic. Treatment with activated charcoal should be considered if the overdose has been taken within approximately one hour. If necessary, symptomatic treatment and monitoring of the cardiovascular system are recommended; if excitation or convultions are present, short acting barbiturates or benzodiazepines may be given.

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Treatment

Treatment should be symptomatic. Treatment with activated charcoal should be considered if the overdose has been taken within approximately one hour. If necessary, symptomatic treatment and monitoring of the cardiovascular system are recommended; if excitation or convultions are present, short acting barbiturates or benzodiazepines may be given.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

Protein binding is 75%.

Elimination

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

Biotransformation

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

Effect of food

The bioavailability of Zaditen 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 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

Ketotifen revealed a moderate acute oral toxicity in animals.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate, pre-gel cornstarch, maize starch and lactose.

6.2 Incompatibilities

None known.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Sore below 25^{o}C.

6.5 Nature and contents of container

PVDC opaque blister pack (60 tablets)

6.6 Special precautions for disposal

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(S)

PL 48053/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 April 1980

Date of latest renewal: 30 March 2007

10 DATE OF REVISION OF THE TEXT

13/03/2024