SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Profiten Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg Ketotifen (as fumarate).

For the full list of excipients and information on excipients with known effect, see section 4.4 and section 6.1.

3 PHARMACEUTICAL FORM

Clear to slightly yellow scored tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylactic treatment of bronchial asthma.
Symptomatic treatment of allergic conditions including bronchitis, rhinitis, hay fever and urticaria.

4.2 Posology and method of administration

Adults

1mg twice daily with food. If necessary the dose may be increased to 2mg twice daily.

Children
From 3 years of age: 1 mg twice daily with food.
For patients for whom a tablet form may no be suitable, an alternative dosage form should be considered.

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

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

4.3 Contraindications

- Hypersensitivity to ketotifen or 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, Profiten treatment must be supplemented by specific antimicrobial therapy.

Convulsions have been reported very rarely during Profiten therapy. As Profiten may lower the seizure threshold it should be used with caution in patients with a history of epilepsy.

Thrombocytopenia may occur in patients taking Profiten 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 Profiten, the dose should be reduced.

Excipients with known effect:
Profiten Tablets contains 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 interaction

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

The simultaneous administration of oral antidiabetic drugs and Profiten tablets should be avoided (see section 4.3).

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 Profiten 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). Profiten should not be used during pregnancy unless the clinical condition of the woman requires treatment with ketotifen.

Breast-feeding
Available data in rats 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, a n d therefore mothers receiving Profiten should not breast-feed (see section 4.3).

4.7 Effects on ability to drive and use machines

During the first few days of treatment with Profiten reactions may be impaired. Patients should be warned not to take charge of vehicles or machinery until the effect of Profiten 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, 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 skin 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, Somnolence, headache

Gastrointestinal disorders

Uncommon: Dry mouth*

Not known: Vomiting, nausea, diarrhoea

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

In addition, you can report online to Padagis Israel pharmaceuticals LTD at the following address: Padagis.co.il.

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. Profiten cannot be eliminated by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antihistamines for systemic use, ATC code: R06AX17

Pharmacodynamic effects

Profiten 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, Profiten exerts a non-competitive blocking effect on histamine (H1) receptors. Therefore, it can also be used in place of classical histamine (H1) receptor antagonists.

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

5.2 Pharmacokinetic properties

Absorption

After oral administration the absorption of Profiten 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 2-4 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 3-5 hours and a longer one of 21 hours. About 1% of the substance is excreted unchanged in the urine within 48 hours and 60-70% as metabolites.

Effect of food
The bioavailability of Profiten is not influenced by the intake of food. Therefore, Profiten 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 Profiten 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 Profiten 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 i.v. 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 Profiten 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 Profiten 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 postnatal development at the high dose level of 50mg/kg per day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, starch (maize), poly vinyl pyrrolidone (PVP), talc, colloidal silicone dioxide, Na-starch glycolate, magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a cool place below 25^{o}C.

6.5 Nature and contents of container

PVC/PVDC blister pack (30 tablets).

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

Padagis Israel Pharmaceuticals Ltd
1 Rakefet Street,
Shoham

8 MARKETING AUTHORISATION NUMBER(S)

12610.26758

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