December 2023

SUMMARY OF PRODUCT CHARACTERISTIC (SMPC)

1. NAME OF THE MEDICINAL PRODUCT

ASMAFORT 1MG (Ketotifen 1 mg tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1.38 mg ketotifen fumerate equivalent to 1.0 mg ketotifen.
Excipient(s) with known effects:

Each tablet contains 61.12 mg of lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets
White to off-white, round, flat faced, bevelled edge tablets.
Marking: Face one: Embossed "Square Plain" & Embossed with "A"
Face two: Embossed "Square Plain".

4. CLINICAL PARTICULARS

4.1Therapeutic indications

Asmafort is indicated in the following:

- Preventative treatment of bronchial asthma especially when associated with atopic symptoms.
- Symptomatic treatment of allergic conditions including rhinitis and conjunctivitis.

4.2 Posology and method of administration

Oral administration

Adults:
1mg twice daily with food. If necessary the dose may be increased to 2mg twice daily. Patients known to be easily sedated should begin treatment with 0.5 to 1mg at night for the first few days.

Children:

- **2 to 3 years:** For younger children, who cannot swallow tablets or where the required dose cannot be administered using tablets, **Asmafort** syrup 1mg/5ml is available.
  Dosage: 0.05mg (=0.25ml **Asmafort** syrup) per kilogram body weight twice daily (morning and evening).
- **3 years and above:** 1mg twice daily with food.

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

4.3 Contraindications

- Known hypersensitivity to ketotifen or any of the excipients (see section 6.1 List of excipients).

4.4 Special warnings and precautions for use

Post-marketing surveillance has shown exacerbation of asthma in approximately 2 per 1,000 patients. Since some of these asthmatic attacks might have been related to stopping existing treatment, it is important to continue such treatment for a minimum of two weeks after starting ketotifen.
This applies especially to systemic corticosteroids and ACTH 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 one year.
If it is necessary to withdraw ketotifen this should be done progressively over a period of 2 to 4 weeks. Symptoms of asthma may recur.
If intercurrent infection occurs, ketotifen treatment must be supplemented by specific antimicrobial therapy.
As ketotifen may lower the seizure threshold it should be used with caution in patients with a history of epilepsy.
A reversible fall in the thrombocyte count in patients receiving ketotifen 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.
Asmafort contains lactose. This medicine is not recommended for patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or of glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

Ketotifen may potentiate the effects of sedatives, hypnotics, antihistamines and alcohol.

4.6 Pregnancy and lactation

Pregnancy:
Although there is no evidence of any teratogenic effect, recommendation for ketotifen in pregnancy cannot be given.

Lactation:
Ketotifen is excreted in breast milk; therefore mothers receiving **Asmafort** should not breast feed.

4.7 Effects on ability to drive and use machines

During the first few days of treatment with ketotifen, reactions may be impaired. Patients should be warned not to take charge of vehicles or machinery until the effect of ketotifen treatment on the individual is known. Patients should be advised to avoid alcoholic drinks.

4.8 Undesirable effects

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: 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), 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:	Excitation, irritability, insomnia, nervousness
Nervous system disorders	
Uncommon:	Dizziness
Rare:	Sedation
Gastrointestinal disorders	
Uncommon:	Dry mouth
Hepatobiliary disorders	
Very rare:	Hepatitis, increase in liver enzymes

Sedation, dry mouth and dizziness may occur at the beginning of treatment, but usually disappear spontaneously with continued medication. Symptoms of CNS stimulation have been observed.

4.9 Overdose

The reported features of overdose include confusion, drowsiness, nystagmus, headache, disorientation, tachycardia, hypotension, reversible coma; especially in children, hyperexcitability or convulsions. Bradycardia and respiratory depression should be watched for. Elimination of the drug with gastric lavage or emesis is recommended. Otherwise general supportive treatment is all that is required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Asmafort 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 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, ketotifen exerts a non-competitive blocking effect on histamine (H_1) receptors.

Experimental investigations in asthmatic subjects have shown that ketotifen is as effective orally as a selective mast cell stabiliser administered by inhalation: antihistamines are ineffective in these tests.
The effectiveness of ketotifen in the prevention of bronchial asthma has been studied in long-term clinical trials. Asthma attacks were reduced in number, severity and duration and in some cases the patients were completely freed from attacks. Progressive reduction of corticosteroids and/or bronchodilators was also possible.
The prophylactic activity of ketotifen may take several weeks to become fully established. Ketotifen will not abort established attacks of asthma.

5.2 Pharmacokinetic properties

Absorption
After oral administration, the absorption of ketotifen 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 ketotifen is not influenced by food.

5.3 Preclinical safety data

Acute toxicity
Acute toxicity studies of ketotifen in mice, rats and rabbits revealed oral LD_{50} values above 300mg/kg bodyweight and between 5 and 20mg/kg by the iv 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 161mg/kg and demonstrated that the toxicity of Ketotifen syrup (LD_{50} 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 Ketotifen 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 V_{79} 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 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 50mg/kg per day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Maize Starch
Polyvinyl Pyrrolidone (Povidone)
Magnesium Stearate
Microcrystalline Cellulose (Avice1 PH 102)
Ethanol 95% *
Purified Water *

6.2 Incompatibilities

Not stated.

6.3 Shelf life

36 months from the date of manufacturing.

6.4 Special precautions for storage

Store at a temperature of 15-25°C, in a dry place

6.5 Nature and contents of container

20 tablets in an Aluminium, PVC-PVDC film blister, 20 blisters packed in a printed cartoon along with a leaflet.

6.6 Special precautions for disposal and other handling

None.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

6460/NMR/2018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Aug 22, 2022

10. DATE OF REVISION OF THE TEXT

09. June. 2015