Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Kestine 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Ebastine 10 mg

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated Tablet
Film-coated, scored, round tablet engraved with E10

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Kestine is indicated for the symptomatic treatment of:
- Allergic rhinitis (seasonal and perennial) whether or not associated with allergic conjunctivitis.
- Idiopathic chronic urticaria.

4.2 Posology and method of administration

Allergic rhinitis:
Kestine at a dose of 10 mg once-a-day is efficacious in the relief of the symptoms of allergic rhinitis; in patients with more severe symptoms including perennial allergic rhinitis, 20 mg once-a-day provides additional benefit.

Idiopathic chronic urticaria:
The adult dose is one 10 mg tablet once daily.

Kestine may be taken with or without food.

Special populations:
No dose adjustment is needed in patients with renal insufficiency, nor in patients with mild to moderate hepatic insufficiency. A dosage of 10 mg should not be exceeded in patients with severe hepatic insufficiency.
The safety and efficacy of Kestine in children less than 12 years has not been established.

4.3 Contraindications

Patients with a known hypersensitivity to Kestine or any of its ingredients.

4.4 Special warnings and precautions for use

Since there is a pharmacokinetic interaction with antimycotics of the imidazol type like ketoconazole or macrolid antibiotics like erythromycin (see point 4.5, Interaction with other medicinal products and other forms of interaction), care should be taken when prescribing ebastine with medicines that contain such drugs.
Ebastine should be used with caution in patients with severe hepatic insufficiency.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

There is no interaction of ebastine with theophylline, warfarin, cimetidine, diazepam or alcohol.

When ebastine is administered with food, there is a 1.5 to 2.0 fold increase in the plasma levels and the AUC of the main active acid metabolite of ebastine. This increase does not alter the Tmax. The administration of ebastine with food causes no modification in its clinical effect.

Pharmacokinetic interactions have been observed when ebastine is given with either ketoconazole or erythromycin (see section 5.2, Pharmacokinetic properties). These interactions resulted in increased plasma concentrations of ebastine and to a lesser extent of carebastine which were, nevertheless, not associated with any clinically significant pharmacodynamic consequences in limited data from clinical studies.

4.6 Pregnancy and lactation

The safety of Kestine during human pregnancy has not been established. Studies in rats and rabbits do not indicate any direct or indirect harmful effects with respect to the development of the embryo or foetus, or the course of gestation and peri- and post-natal development. No teratogenic effects have been identified in animals. However, there are no well-controlled studies in pregnant women and reproductive studies are not always predictive of human response. Therefore, ebastine should be used during pregnancy only if clearly needed, category B1. Ebastine is not recommended for nursing women, because it is not known whether ebastine is excreted in human milk.

4.7 Effects on ability to drive and use machines

In man, psychomotor function has been investigated extensively and no effect was found at recommended therapeutic doses.

A study focused on car driving ability indicated that Kestine did not induce any driving impairment even at 30 mg. Based on these results, Kestine at recommended therapeutic doses does not affect the ability to drive or operate machines.

4.8 Undesirable effects

The adverse reactions reported in association with the use of ebastine presented according to system organ classes in a decreasing frequency, are listed below. According to frequency, reported adverse reactions have been classified in the category very rare (<1/10000).

Cardiac disorders: Palpitations, tachycardia.

Gastrointestinal disorders: Dry mouth, dyspepsia, abdominal pain, nausea, vomiting.

General disorders and administration site conditions: Asthenia, oedema.

Hepatobiliary disorders: Liver function test abnormal.

Infections and Infestations: Pharyngitis, rhinitis, sinusitis.

Nervous system disorder: Somnolence, headache, dizziness, dysaesthesia.

Psychiatric disorders: Insomnia, nervousness.

Reproductive system and breast disorders: Menstrual disorders.

Respiratory, thoracic and mediastinal disorders: Epistaxis.

Skin and subcutaneous tissue disorders: Rash, urticaria, dermatitis.

4.9 Overdose

In studies conducted at a high dosage, no particular signs or symptoms were observed up to 100 mg. There is no specific antidote for Kestine. Gastric lavage, monitoring of vital functions including ECG and symptomatic treatment should be carried out.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pre-Clinical:
Ebastine has been shown to produce a rapid and long-lasting inhibition of histamine-induced effect and to have a strong affinity towards H1-receptors.

Following oral administration neither ebastine nor its metabolites cross the blood brain barrier. This characteristic is consistent with the low sedative profile seen in the results of experiments studying the effects of ebastine on the central nervous system.
In vitro and *in vivo* data demonstrate that ebastine is a potent, long lasting and highly selective histamine H1-receptor antagonist devoid of untoward CNS actions and anticholinergic effects.

Clinical:
Histamine skin wheal studies have shown a statistically and clinically significant anti-histamine effect beginning at 1 hour and lasting in excess of 48 hours. After the discontinuation of the administration of a 5 day-course of treatment with ebastine, the anti-histamine activity remained apparent for more than 72 hours. This activity parallels the plasma levels of the main active acid metabolite, carebastine.

After repeated administration, inhibition of the peripheral receptors remained at a constant level, without tachyphylaxis. These results suggest that ebastine at a dose of at least 10 mg produces a rapid, intense and long-lasting inhibition of peripheral H1-histamine receptors, consistent with a once-a-day administration.

Sedation was studied through pharmaco-EEG, cognitive performance, visual-motor co-ordination tests and subjective estimates. There was no significant increase of sedation at the recommended dose. These results are consistent with those from double-blind clinical trials; the incidence of sedation is comparable between placebo and ebastine.

The actions of ebastine on the heart have been investigated in clinical trials. No influence on the heart, including prolongation of the QT interval, has been observed at the recommended doses. In two studies using repeated doses up to 100 mg per day or 500 mg as a single dose, with a limited number of subjects (n=24 and n=5) small increases in heart rate of a few beats per minute resulted in a shortening of the QT interval with no significant effect of the appropriately corrected QTc.

5.2 Pharmacokinetic properties

Ebastine is rapidly absorbed and undergoes extensive first pass metabolism following oral administration. Ebastine is almost totally converted to the pharmacologically active acid metabolite, carebastine. After a single 10 mg oral dose, peak plasma levels of the metabolite occur at 2.6 to 4 hours and achieve levels of 80 to 100 ng/ml.

The half-life of the acid metabolite is between 15 to 19 hours with 66% of the drug being excreted in the urine mainly as conjugated metabolites. Following the repeated administration of 10 mg once-daily, steady state was achieved in 3 to 5 days with peak plasma levels ranging from 130 to 160 ng/ml.

In vitro studies with human liver microsomes show that ebastine is metabolised to carebastine predominantly via the CYP3A4 pathway. Concurrent administration of ebastine with ketaconazole or erythromycin (both CYP3A4 inhibitors) to healthy volunteers was associated with significantly increased plasma concentrations of ebastine and carebastine (see Section 4.5, Interaction with other medicinal products and other forms of interaction).

Both ebastine and carebastine are highly protein bound, >95%.

In elderly subjects, no statistically significant changes were observed in the pharmacokinetics compared to those of young adult volunteers.

In patients with mild, moderate or severe renal insufficiency and in patients with mild to moderate hepatic insufficiency treated with daily doses of 20 mg of ebastine, as well as in patients with severe hepatic insufficiency treated with 10 mg of ebastine, the pharmacokinetic behaviour was not relevantly modified in comparison with healthy subjects. In patients with mild to moderate renal insufficiency, mean carebastine exposure was higher than that observed in healthy volunteers, whereas the plasma concentrations of this metabolite in patients with severe renal failure and in patients with mild, moderate or severe hepatic insufficiency were similar to those observed in healthy subjects. The elimination half-lives of ebastine and carebastine in all groups of patients were in the same range as those of healthy subjects.

Taking into account the high intraindividual variability of both parent drug and metabolite, as well as the wide therapeutic margin, the variations observed in the pharmacokinetic parameters are not likely to be of any clinical significance.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Lactose
Pregelatinised maize starch
Croscarmellose sodium
Magnesium stearate
Hypromellose
Macrogol 6000
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container.

6.5 Nature and contents of container

Boxes containing 1, 3 or 10 PVC aluminium blister cards.
Each blister card contains 10 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No specific instructions.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA0968/002/001

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