Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ebastion 20 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ebastion 20 mg film-coated tablets:
1 film-coated tablet of Ebastion 20 mg contains: 20 mg ebastine

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Ebastion 20 mg film-coated tablets are white to off-white, round, bevelled film-coated tablets with a score line on one side and a diameter of 9.2 mm.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the symptomatic treatment of seasonal and perennial allergic rhinitis with or without allergic conjunctivitis.

4.2 Posology and method of administration

The experience in children under the age of 12 years is limited.

For children 12 years and above and adults the following dosage recommendations apply: 1 film-coated tablet (20 mg ebastine) once daily in cases of severe symptoms of allergic rhinitis. For patients with milder symptoms 1 film-coated tablet of 10 mg ebastine once daily is recommended. For this dose, Ebastion10 mg film-coated tablets are available.

Special subject groups:
In patients with renal insufficiency, no dose adjustment is necessary for treatment up to 5 days.
In patients with mild to moderate hepatic insufficiency, no dose adjustment is necessary for treatment up to 7 days.

Method of administration:
The film-coated tablets should be taken unchewed with liquid.
Ebastine can be taken at meal times or independently of meals.

Duration of use:
The physician decides on the duration of use.
For allergic rhinitis there is clinical experience of use for a duration of up to 1 year.

4.3 Contraindications

Hypersensivity to the active substance or to any of the excipients.
Patients with severe hepatic insufficiency.
Lactation.

4.4 Special warnings and precautions for use

As with other antihistamines, caution should be exercised when ebastine is administered to patients with known prolongation of the QTc interval on the ECG, hypokalaemia and in cases of concomitant use of medicinal products known to prolong the QTc interval or inhibit the hepatic CYP450 -2J2, -4F12 or -3A4 enzyme system, such as azole antifungal agents and macrolide antibiotics (see section 4.5). Caution should be exercised in patients with moderate hepatic insufficiency (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies of ebastine with ketoconazole or erythromycin (active substances known to prolong the QTc interval) showed interactions in the form of higher plasma ebastine levels and a prolongation of the QTc interval of only approx. 10 msec compared with the administration of ketoconazole or erythromycin alone. In corresponding clinical studies, no interactions of ebastine with theophylline, warfarin, cimetidine, diazepam or alcohol were observed. In cases of concomitant food intake there is a 1.5- to 2.0-fold rise in the plasma level of carebastine, the active principal metabolite of ebastine, and an increase in the AUC, while T_{max} remains unchanged. However, clinical efficacy is not affected.

4.6 Fertility, pregnancy and lactation

There are no data from the use of ebastine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy**,** embryonal/foetal development, parturition or postnatal development (see 5.3). Therefore, ebastine should be used in pregnancy only if clearly needed.

It is not known whether the active substance is excreted in human breast milk. In rat excretion of ebastin in milk has been shown. Ebastine should not be used during the lactation period.

4.7 Effects on ability to drive and use machines

Ebastine has negligible influence on the ability to drive and use machines.

Most patients treated with ebastine may drive or carry out other activities that require a good reaction capacity. However, in order to identify sensitive subjects who react unusually to ebastine, it is advisable to know the individual reactions before a patient drives or carries out complicated activities.

4.8 Undesirable effects

In the evaluation of undesirable effects the following frequency conventions are taken as the basis:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to 1/1,000)
Very rare (<1/10,000), not known (cannot be estimated from the available data)

Cardiac disorders:
Very rare: Tachycardia, Palpitations

Nervous system disorders:
Common: Somnolence, Headache
Very rare: Dysaesthesia

Respiratory, thoracic and mediastinal disorders:
Uncommon: Epistaxis, Pharyngitis, Rhinitis
Very rare: Sinusitits

Gastrointestinal disorders:
Common: Dry mouth
Uncommon: Nausea, Abdominal pain, Dyspepsia
Very rare: Vomiting

Skin and subcutaneous tissue disorders:
Very rare: Exanthema, Urticaria, Eczema, Rash, Dermatitis

General disorders:
Uncommon: Dizziness, Asthenia, Insomnia
Very rare: Oedema

Hepatobiliary disorders:
Very rare: Abnormal liver function test

Reproductive system and breast disorders:
Very rare: Dysmenorrhoea, Menstrual disorders

Psychiatric disorders:
Very rare: General nervousness

4.9 Overdose

In studies with a high dosage up to 100 mg once daily, no clinically significant symptoms or signs of overdose were seen. A specific antidote for ebastine is not known. In the event of overdose, monitoring of vital functions, including ECG monitoring with evaluation of the QT interval for at least 24 hours, symptomatic treatment and gastric lavage are indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other anti-histamines for systemic use
ATC code: R06AX22

Pre-clinical
In *in vitro* and *in vivo* studies ebastine demonstrates great affinity for H1 receptors, which are rapidly and selectively inhibited over a long period of time.
Impairment of central functions is only slight; the risk of occurrence of anticholinergic effects is low, but, on the basis of the studies available, cannot be completely ruled out.
After oral administration, neither ebastine nor its active metabolite cross the blood-brain barrier. This characteristic is consistent with the low level of sedation determined in experimental studies on the effects of ebastine on the central nervous system.
In vitro and *in vivo* data show that ebastine is a potent, highly selective antagonist of the histamine H1 receptors with prolonged effects, devoid of effects on the CNS and with no anticholinergic effects.

Clinical properties
Wheal tests revealed a statistically and clinically significant anti-histamine effect commencing 1 hour after administration and lasting more than 48 hours. When treatment with ebastine was halted after 5 days, its anti-histamine effect remained detectable for more than 72 hours. This effect is reflected in the plasma levels of the principal active metabolite, carebastine.
After repeated administration, inhibition of the peripheral receptors remained at a constant level, without tachyphylaxis. These results suggest that, at a dose of at least 10 mg, ebastine produces rapid, intense and prolonged inhibition of the peripheral H1 histamine receptors, which permits once-daily administration.

The sedative effect was studied by means of pharmacological EEG, cognitive tests, oculomotor coordination tests and on the basis of subjective evaluation. No significant increase in sedation was observed at the recommended therapeutic dose. These findings are consistent with those obtained in double-blind clinical studies: the incidence of sedative effects of ebastine is comparable to that of placebo.
Following administration at the recommended doses, no prolongation of the QT interval or other undesirable cardiac effects were observed in specific studies on the cardiac effects of ebastine.
While no effect of ebastine overdose on the QTc interval was observed with overdoses of up to 60 mg daily, overdoses of 100 mg daily produced a statistically significant, but clinically irrelevant increase of 10 ms (2.7%).

5.2 Pharmacokinetic properties

Ebastine is rapidly absorbed and undergoes extensive first-pass metabolism after oral administration. Ebastine is almost totally converted to its active metabolite, carebastine. After an oral dose of 10 mg ebastine, maximum plasma levels of 80 to 100 ng/ml carebastine were observed after 2.6 to 4 hours. The half-life of the metabolite is 15 - 19 hours, 66% of which is excreted in urine in the form of conjugated metabolites. After repeated administration of a daily dose of 10 mg, steady state with plasma levels of 130 - 160 ng/ml is reached after 3 to 5 days.
After a single 20 mg oral dose, peak plasma levels of ebastine occur at 1 to 3 hours and achieve a mean level of 2.8 ng/ml. Peak plasma levels of the metabolite, carebastine, achieve a mean value of 157 ng/ml.

More than 95% of both ebastine and carebastine is bound to plasma proteins.
In vitro studies on human hepatic microsomes show that ebastine is metabolised to carebastine predominantly via the CYP450 (-2J2, -4F12 and -3A4) enzyme systems. After concomitant administration of ketoconazole or erythromycin (both inhibitors of CYP450-3A4) significant increases in plasma ebastine and carebastine concentrations were observed (see 4.5).
In elderly patients, no changes in pharmacokinetics were observed compared with young adults.
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 ebastine, the plasma concentrations of ebastine and carebastine on the first and fifth day of treatment were similar to those obtained in healthy volunteers.
In patients with renal insufficiency, the elimination half-life of the metabolite, carebastine is prolonged to 23 - 26 hours. In patients with hepatic insufficiency, the half-life is 27 hours.

5.3 Preclinical safety data

Non-clinical data in rats and mice reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose, microcrystalline
Sodium starch glycolate (type A)
Silica, colloidal, anhydrous
Magnesium stearate

Tablet coat:
Hypromellose
Titanium dioxide (E171)
Macrogol 400

6.2 Incompatibilities

Not applicable

6.3 Shelf life

27 months

6.4 Special precautions for storage

Do not store above 25° C.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Alu-PVC/PVDC blister
Pack sizes: 10, 15, 20, 30, 50, 100 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Lindopharm GmbH
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40721 Hilden
Germany

8 MARKETING AUTHORISATION NUMBER

PA 1599/1/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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