

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0968/002/004

Case No: 2042951

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Laboratorios Almirall S.A.

General Mitre, 151, 08022, Barcelona, Spain

an authorisation, subject to the provisions of the said Regulations, in respect of the product

KESTINE 20 mg Oral Lyophilisate

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **03/01/2008** until **19/01/2011**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Kestine 20 mg oral lyophilisate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each oral lyophilisate contains Ebastine 20 mg.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral lyophilisate

White, circular, freeze-dried units.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ebastine 20 mg oral lyophilisate is indicated for the symptomatic treatment of allergic rhinitis (seasonal and perennial) whether or not associated with allergic conjunctivitis.

4.2 Posology and method of administration

Ebastine at a dose of 20 mg once-a-day is efficacious in the relief of the symptoms of severe allergic rhinitis. In patients with less severe symptoms, a dose of 10 mg once-a-day is recommended.

Ebastine oral lyophilisate can be taken with or without food.

The safety and efficacy of ebastine in children less than 12 years of age has not been established.

Method of administration

The dose of ebastine oral lyophilisate is placed on the tongue, where it disperses instantly. Water or other liquid is not needed to swallow the dose.

Immediately before use, the blister must be carefully peeled open with dry hands and the dose of oral lyophilisate removed without crushing it. The dose must be taken as soon as the blister has been opened.

4.3 Contraindications

Patients with a known hypersensitivity to ebastine or any of the oral lyophilisate ingredients.

Patients with severe hepatic insufficiency.

4.4 Special warnings and precautions for use

As with other antihistamines, caution must be exercised when using ebastine in patients known to be at cardiac risk such as those with long QT syndrome, hypokalemia, treatment with any drug known to produce an increase in QT

interval or inhibit CYP3A4 enzyme systems such as azole antifungals and macrolide antibiotics (see section 4.5 Interaction with other medicaments and other forms of interaction).

Ebastine oral lyophilisate contains 2.0 mg aspartame per dose. Aspartame is a source of phenylalanine, which may be harmful for people with phenylketonuria.

Ebastine oral lyophilisate contains mannitol.

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 area under the plasma concentration curve (AUC) of the main active acid metabolite of ebastine. This increase does not alter the T_{max}. The administration of ebastine with food does not cause a modification in its clinical effect.

The interaction of ebastine in combination with either ketoconazole or erythromycin (both known to affect the corrected QT (QT_c) interval) has been evaluated. Interaction has been observed with these combinations, resulting in higher ebastine plasma levels but only in an about 10 msec increase in QT_c greater than the increase seen with ketoconazole or erythromycin alone.

4.6 Pregnancy and lactation

The safety of ebastine 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 ebastine did not induce any driving impairment even at 30 mg. Based on these results, ebastine at recommended therapeutic doses does not affect the ability to drive or operate machines.

4.8 Undesirable effects

In clinical trials, the most commonly reported side-effects with ebastine were headache, dry mouth and drowsiness, which were comparable to placebo.

Other less commonly reported adverse events include: pharyngitis, abdominal pain, dyspepsia, asthenia, epistaxis, rhinitis, sinusitis, nausea and insomnia.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antihistamines for systemic use.
ATC code: R06A X22.

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 or 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 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.

In a single dose trial, the oral lyophilisate formulation was well tolerated as documented by standard safety laboratory tests, physical examinations, vital signs and ECG. Ebastine oral lyophilisate was found to be bioequivalent to the film-coated tablet formulation of ebastine. Therefore, the efficacy of ebastine oral lyophilisate is expected to be the same as that of the film-coated tablet formulation.

Sedation was studied through pharmaco-EEG, cognitive performance, visual-motor coordination 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.

Cardiac effects of ebastine have been thoroughly investigated, following single doses from 2.5 to 50 mg and multiple doses from 10 to 80 mg/kg/day for 7 days, with no evidence of an effect on QT corrected interval.

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 and 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.

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.

The pharmacokinetics of ebastine, as well as that of its active metabolite carebastine were found to be linear in the

recommended therapeutic dose range of 10 to 20 mg.

In vitro studies with human liver microsomes show that ebastine is metabolised to carebastine predominantly via the CYP3A4 pathway. Concurrent administration of ebastine with ketoconazole 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 several degrees of renal insufficiency treated with daily doses of 20 mg ebastine, as well as in patients with mild to moderate hepatic insufficiency treated with 20 mg ebastine, or with severe hepatic insufficiency treated with 10 mg ebastine, plasma concentrations of ebastine and carebastine attained during the first and fifth day of treatment were similar to those attained in healthy volunteers. Thus, the pharmacokinetic profile of ebastine and its metabolites do not change significantly in patients with several degrees of hepatic or renal insufficiency.

In a single-dose crossover study of ebastine oral lyophilisate versus ebastine film-coated tablets, the formulations were found to be bioequivalent. Water intake after ebastine oral lyophilisate had no effect on the disposition of ebastine.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin
Mannitol
Aspartame (E951)
Mint flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Unit dose aluminium composed of a multilaminate blister film and a lidding foil.
The materials of the blister are polyvinyl chloride (PVC), orientated polyamide (OPA) and aluminium (Al); the lidding foil is composed of polyethylene terephthalate (PET), aluminium (Al) and bleached kraft paper.

Packs of 10, 20, 30, 50 or 100 doses of oral lyophilisate.

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 special requirements.

7 MARKETING AUTHORISATION HOLDER

Laboratorios Almirall S.A.
Rondo General Mire, 151
08022 Barcelona
Spain.

8 MARKETING AUTHORISATION NUMBER

PA 968/2/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 January 2006

10 DATE OF REVISION OF THE TEXT

July 2007