Ebastine

Kestine® 10 mg Film-coated Tablet

Antihistamine

FORMULATION:
Each Ebastine (Kestine®) Film-coated tablet contains:
Ebastine.....10 mg

Excipients: microcrystalline cellulose, pregelatinised maize starch, lactose monohydrate, croscarmellose sodium, magnesium stearate, hypromellose, macrogol 6000 and titanium dioxide.

PHARMACEUTICAL FORM AND CONTENT OF PACKAGE:
Round, white film-coated tablets with one side marked E10. Boxes containing 10 (1x10), 20 (2x10) 30 (3x10), 50 (5x10) and 100 (10x10) tablets in PVC/Aluminium blisters.
Not all the presentations are available in all markets.

INDICATION:
Ebastine (Kestine®) is indicated in the treatment of allergic rhinitis (seasonal and perennial) with or without allergic conjunctivitis and chronic idiopathic urticaria.

MECHANISM OF ACTION:
Ebastine (Kestine®) produces rapid and prolonged inhibition of the effects induced by histamines, showing a strong affinity for binding to H1 receptors. After oral administration, neither ebastine (Kestine®) nor it's metabolites cross the blood-brain barrier. This characteristic is consistent with the low sedation observed in the results of experiments in which the effects of ebastine (Kestine®) on the central nervous system were studied. The in vitro and in vivo data demonstrate that ebastine (Kestine®) is a powerful antagonist with a prolonged effect and highly selective of the histamine H1 receptors, free of CNS side effects and anticholinergic effects.

PHARMACOKINETIC PROPERTIES:
Ebastine is rapidly absorbed after oral intake and undergoes a very significant intestinal and hepatic first-pass effect. It is almost completely transformed into its pharmacologically active acid metabolite, carebastine. After a single oral 10 mg dose, the peak plasma concentration is reached after 2 to 4 hours, with levels ranging from 80 to 100 ng/ml.
In vitro studies in human liver microsomes show that ebastine is metabolised primarily to carebastine via cytochrome CYP3A4.
The half-life of the acid metabolite is between 15 and 19 hours, with urinary excretion of 66%, mainly as a conjugated metabolite. After repeated administration of ebastine at a single 10 mg dose once daily, a steady state is reached in 3-5 days, with peak plasma concentrations ranging from 130 to 160 ng/ml.
Administration of ebastine with food increases the plasma levels of carebastine 1.5 to 2.0 fold.
Ebastine and carebastine are strongly bound to plasma proteins, with a binding rate greater than 97%.
Very little ebastine, or its active metabolite carebastine, crosses the blood-brain barrier.
Its excretion in human milk has not been studied.

Elderly patients
The pharmacokinetic parameters do not differ in a statistically significant manner from the values recorded in young adults.

Renal and hepatic failure
In patients with mild, moderate or severe renal failure treated with a daily dose of 20 mg of ebastine and in patients with mild to moderate hepatic failure treated with a daily dose of 20 mg of ebastine, or in patients with severe hepatic failure treated with a daily dose of 10 mg of ebastine, ebastine and carebastine concentrations between day 1 and day 5 were similar to those in healthy volunteers. Therefore, the pharmacokinetic profile of ebastine and its metabolite does not change significantly in patients with varying degrees of renal or hepatic failure.

DOSAGE AND ADMINISTRATION:
For oral use. Ebastine (Kestine®) 10 mg film-coated tablets may be taken with or without food. Tablets must be swallowed whole with a small amount of water.

Adults and children over 12 years of age
- Allergic Rhinitis: The usual dose is 10 mg of ebastine once daily. In the event of severe symptoms, the dose may be increased to 20 mg once daily.
- Chronic Idiopathic Urticaria: A dose of 10 mg once daily.

Children 12 years old and below
- The safety of Ebastine (Kestine®) 10 mg film-coated tablets has not been established for children under 12 years of age.

For elderly
- not necessary to adjust dose.

For patients with renal impairment
- not necessary to adjust dose.

For patients with hepatic impairment
- not necessary to adjust dose in patients with mild to moderate hepatic impairment. There is no experience with doses greater than 10 mg in patients with severe hepatic impairment. Therefore, the 10 mg dose should not be exceeded in patients with severe hepatic impairment.

SPECIAL PRECAUTIONS:
Prescription of ebastine should be prudent in patients with long QT syndrome, hypokalaemia, or receiving a drug known to prolong the QT interval or to inhibit CYP3A4, such as azole antifungals such as ketoconazole and itraconazole or macrolides such as erythromycin (see section Interaction with other medicinal products).

Given that ebastine achieves its therapeutic effect between 1 and 3 hours after administration, it should not be used to treat acute allergic emergencies.

Since there is a pharmacokinetic interaction with anti-TB drugs such as rifampicin (see section Interaction with other medicinal products), caution should be exercised when co-prescribing ebastine with molecules in this group.

Long-term treatment with ebastine may in certain patients increase the risk of dental caries because of dry mouth. The patients should therefore be instructed about the importance of oral hygiene.

Due to the presence of lactose, patients with rare hereditary problems such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Ebastine should be used with caution in patients with severe hepatic impairment (see section Dosage and administration).

FERTILITY, PREGNANCY AND LACTATION:
Fertility: There are no fertility data with ebastine in humans.
Pregnancy: There are limited data on the use of ebastine in pregnant women. Animal toxicity studies do not indicate direct or indirect harmful effects. As a precautionary measure, it is preferable to avoid the use of ebastine during pregnancy.
Lactation: It is not known whether ebastine is excreted in human milk. The high protein binding rate of ebastine (> 97%) and its main metabolite, carebastine, suggests that the medication is not excreted in human milk. As a precautionary measure it is preferable to avoid the use of ebastine during lactation.

UNDESIRABLE EFFECTS:
In a pooled analysis of placebo-controlled clinical trials with 5,708 patients on ebastine, the most commonly reported undesirable effects were dry mouth and drowsiness. Treatment-related adverse events in clinical trials in children (n=460) were similar to those seen in adults.
The following table lists undesirable effects reported in clinical trials and post-marketing studies by the following convention: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000) and very rare (<1/10,000).

medDRA SOC	Very common: ≥ 1/10	Common ≥ 1/100 to < 1/10	Rare ≥ 1/10,000 to < 1/1,000	Very rare < 1/10,000	Not Known
Immune system disorders			Hypersensitivity reactions (such as anaphylaxis and Quincke's oedema)	Severe allergic manifestations	
Metabolism and nutrition disorders					Increased appetite
Psychiatric disorders			Nervousness, insomnia		
Nervous system disorders	Headache	Somnolence	Dizziness, hypoesthesia, dysgeusia		
Cardiac disorders			Palpitations, tachycardia		
Gastrointestinal disorders		Dry mouth	Abdominal pain, vomiting, nausea, dyspepsia		
Hepatobiliary disorders			Hepatitis, cholestasis, abnormal liver function tests (increased transaminases, gamma GT, alkaline phosphatase and bilirubin)		
Skin disorders			Urticaria, rash, dermatitis		
Reproductive system disorders			Menstrual disorders		
General disorders			Oedema, asthenia		
Investigations					Weight Increased

ADHESIVE

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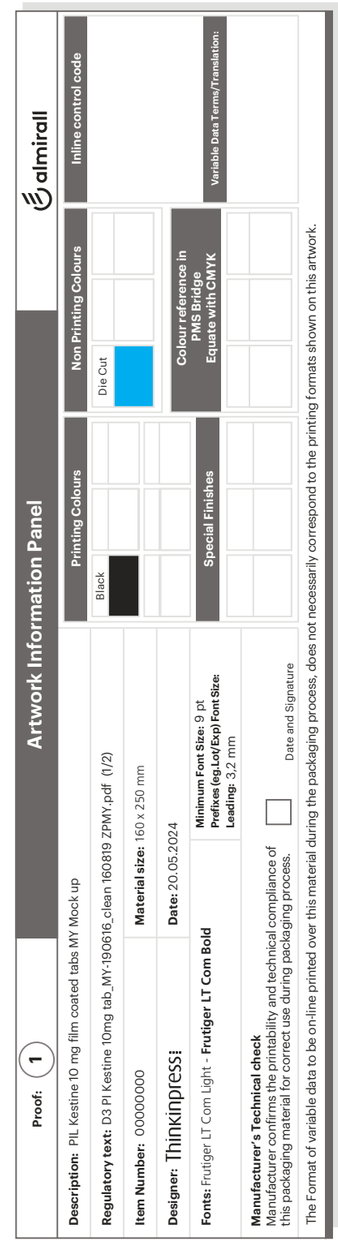

ADHESIVE

EFFECTS OF ABILITY TO DRIVE AND USE OF MACHINERY:
In humans, psychomotor function has been studied extensively and no effect has been found. Ebastine at recommended therapeutic doses has no influence on the ability to drive and use machines.

However, in sensitive subjects who react unusually to ebastine, it is advisable to know the individual reactions before a patient drives or carries out complex activities: drowsiness and dizziness may occur (see section Undesirable effects).

INTERACTION WITH OTHER MEDICINAL PRODUCTS:
Pharmacokinetic interactions were observed when ebastine was given with ketoconazole, or itraconazole and erythromycin. These interactions lead to an increase in plasma concentrations of ebastine and, to a lesser extent, carebastine, which were nonetheless not associated with a significant clinical consequence. However, as a precaution, combination with ketoconazole, itraconazole, erythromycin, clarithromycin or josamycin should be avoided: increased risk of developing ventricular arrhythmias in predisposed subjects (long QT syndrome, congenital).

Pharmacokinetic interactions were observed when ebastine was given with rifampicin. These interactions may lead to lower plasma concentrations of ebastine and reduce the antihistamine effect.
No interaction has been reported between ebastine and theophylline, warfarin, cimetidine, diazepam and alcohol.

The administration of ebastine with food does not alter its clinical effect.

OVERDOSAGE:
In high-dose studies, no significant clinical signs or symptoms were observed at doses of up to 100 mg daily.
Measures to take in case of massive overdose:
- No antidote is known at present,
- Gastric evacuation,
- Symptomatic treatment,
- Vital signs monitoring, including ECG monitoring

CONTRAINDICATION:
Children under 12 due to a lack of efficacy and safety data
History of hypersensitivity to the active substance or to any of the excipients.

STORAGE:
Store at temperatures not exceeding 30°C.

Reg. No.:
MAL19096029AZ

Manufactured by:
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Ctra. de Martorell, 41-61 - 08740 Sant Andreu de la Barca (Barcelona) SPAIN

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Artwork Information Panel

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Proof: 1

Description: PIL Kestine 10mg film coated tabs MY Mock up

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Minimum Font Size: 9 pt
Prefixes (eg.Lot/Exp) Font Size:
Leading: 3.2 mm

Manufacturer's Technical check
Manufacturer confirms the printability and technical compliance of this packaging material for correct use during packaging process.

Date and Signature

Inline control code

Variable Data Terms/Translation:

Non Printing Colours
Die Cut

Colour reference in PMS Bridge Equate with CMYK

Printing Colours
Black

Special Finishes

The Format of variable data to be on-line printed over this material during the packaging process, does not necessarily correspond to the printing formats shown on this artwork.