Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Kestine 10 mg
Kestine 20 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Kestine 10 mg:
Each film-coated tablet contains 10 mg of ebastine.
Excipient with known effect: Each film-coated tablet contains 88.5 mg of lactose.

Kestine 20 mg:
Each film-coated tablet contains 20 mg of ebastine.
Excipient with known effect: Each film-coated tablet contains 177 mg of lactose.

See section 6.1 for the full list of excipients.

3. PHARMACEUTICAL FORM

Kestine 10 mg:
Film-coated tablet.
White to almost white round film-coated tablets engraved with E/10.

Kestine 20 mg:
Film-coated tablet.
White to almost white round film-coated tablets engraved with E/20.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kestine is indicated in the symptomatic treatment of:

- allergic rhinitis (seasonal and perennial) associated or not with allergic conjunctivitis
- idiopathic chronic urticaria

4.2 Posology and method of administration

Adults and children above 12 years
Allergic rhinitis (seasonal and perennial) associated or not with allergic conjunctivitis and idiopathic chronic urticaria
10 mg ebastine once daily. In cases of severe symptoms, the dose may be increased to 20 mg ebastine once daily.

Children under 12 years
Kestine 10 mg: The tablet form is not suitable for the administration of doses below 10 mg, or for those patients who have problems swallowing.
Kestine 20 mg: The safety of Kestine 20 mg has not been determined in children under 12 years.

Elderly patients
It is unnecessary to adjust the dose.

Renal impairment
It is unnecessary to adjust the dose in patients with slight, moderate or severe renal impairment.

Hepatic impairment
It is unnecessary to adjust the dose in patients with slight or moderate hepatic impairment. No studies have been carried out with doses above 10 mg in patients with severe hepatic impairment, so the maximum recommended dose should not be exceeded in these patients (10 mg of ebastine/day).
Treatment can continue until the symptoms disappear.

Method of administration
Oral route.
The tablets can be taken with or without food, with a glass of water.

4.3 Contraindications

Hypersensitivity to the active ingredient or to any of the excipients included in section 6.1.

4.4 Special warnings and precautions for use

Administer with caution in patients with known cardiac risk such as patients with prolonged QT interval, hypokalaemia, concomitant treatment with compounds increasing QT interval or inhibiting enzyme CYP3A4, such as azole antifungal agents like ketoconazole and itraconazole and macrolide antibiotics like erythromycin (see section 4.5).

Pharmacokinetic interactions could occur when administering ebastine with rifampicin (see section 4.5).

Ebastine should be used with caution in patients with severe hepatic impairment (see section 4.2).

Given that ebastine reaches its therapeutic effect between 1 and 3 hours after administration, it should not be used in emergency allergy situations.

Warnings about excipients

This medication contains lactose. Patients with hereditary galactose intolerance, Lapp lactase deficiency (deficiency observed in some populations in Lapland) or poor absorption of glucose or galactose should not take this medication.

4.5 Interaction with other medicinal products and other forms of interaction

The interaction of ebastine in combination with ketoconazole and erythromycin (both compounds cause an increase in the QTc interval) has been studied. A pharmacokinetic and pharmacodynamic interaction is observed with both combinations, giving rise to an increase in ebastine plasma levels and to a smaller extent, carebastine levels, without clinically significant pharmacodynamic consequences. The increase in QTc was only approximately 10 ms above that observed with ketoconazole or erythromycin alone. However, caution is recommended when administering Kestine to those patients undergoing concomitant treatment with azole antifungals such as ketoconazole or itraconazole and macrolid antibiotics such as erythromycin.

Pharmacokinetic interactions have been observed when administering ebastine with rifampicin. These interactions can give rise to a decrease in plasma concentrations and a reduction of the antihistamine effects.

There are no described interactions between ebastine and theophylline, warfarin, cimetidine, diazepam and alcohol.

When ebastine is administered with food, both plasma levels and AUC of the main metabolite of ebastine increase between 1.5 and 2 times. This increase does not modify Tmax. The administration of ebastine with food does not modify its clinical effect.

Ebastine can interfere with the results of skin allergy tests, so it is advised not to have them until 5-7 days after suspending treatment.

It can increase the effects of other antihistamines.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data regarding the use of ebastine in pregnant women. Animal studies do not suggest direct or indirect harmful effects in terms of reproduction toxicity. As a precautionary measure it is preferable to avoid the use of ebastine during pregnancy.

Breastfeeding

It is not known whether ebastine is excreted in mother’s milk. The high degree of binding to proteins (>97%) of ebastine and its main metabolite, carebastine, suggests that the medication is not excreted in mother’s milk. As a precautionary measure it is preferable to avoid the use of ebastine during lactation.

Fertility
There are no fertility data associated with ebastine in humans.

4.7 Effects on ability to drive and use machines

The psychomotor function has been widely studied in humans with no observed effects. At the recommended therapeutic doses ebastine does not affect the ability to drive or to use machinery.

However, in sensitive individuals who react unusually to ebastine, knowledge of their individual reactions is recommended before the patient drives or carries out complex activities: drowsiness or dizziness could appear (see section 4.8).

4.8 Undesirable effects

In a joint analysis of placebo-controlled clinical trials carried out in 5,708 patients treated with ebastine, the most frequently reported adverse reactions were headache, dry mouth and drowsiness.

The adverse reactions notified in clinical trials in children (n = 460) were similar to those observed in adults.

The table below includes the adverse reactions reported in clinical trials and during the post-marketing phase, using the following convention: very frequent (≥1/10), frequent (≥1/100 to <1/10), infrequent (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and frequency not known (cannot be estimated from the available data)

SOC	**Very frequent (≥1/10)**	**Frequent (≥1/100 to <1/10)**	**Rare (≥1/10,000 to <1/1,000)**	**Not Known**
Immune system disorders			Hypersensitivity reactions (such as anaphylaxis and angioedema)	
Metabolism and nutrition disorders				Increased appetite
Psychiatric disorders			Restlessness, insomnia	
Nervous system disorders	Headache	Drowsiness	Dizziness, hypoaesthesia, dysgeussia	
Cardiac disorders			Palpitations, tachycardia	
Gastrointestinal disorders		Dry mouth	Abdominal pain, vomiting, nausea,	

			dyspepsia	
Hepatobiliary disorders			Hepatitis, cholestasis, anomalies in hepatic function analytic tests (raised transaminases, gamma-GT, alkaline phosphatase and bilirubin)	
Skin and subcutaneous tissue disorders			Urticaria, rash, dermatitis	
Reproductive system and breast disorders			Menstrual irregularities	
General upsets and alterations at the administration site			Oedema, asthenia	
Investigations				Weight increased

4.9 Overdose

In studies carried out with high doses, no clinically significant signs or symptoms were observed at doses of up to 100 mg once daily. There is no specific antidote for ebastine. Gastric lavage should be considered, together with monitoring of vital constants, including ECG and symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihistamines for systematic use, Other antihistamines for systemic use, ATC code: R06AX22.

Mechanism of action
Ebastine causes rapid and prolonged inhibition of the effects induced by histamine, and presents a strong affinity for binding to H_1 receptors.

Neither ebastine nor its metabolites cross the blood-brain barrier after oral administration. This characteristic tallies with the low sedation profile observed 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 antagonist with a prolonged effect and highly selective to H_1 histamine receptors. It is free of adverse effects on the CNS and of anticholinergic effects.

Pharmacodynamic effects

Studies carried out on histamine-induced papulae have demonstrated a clinically and statistically significant antihistamine effect, initiating after 1 hour and lasting more than 48 hours. The antihistamine effect was apparent for more than 72 hours after suspending administration in a 5-day treatment with ebastine. This activity was parallel with plasma levels of the main active acid metabolite, carebastine.

The inhibition of the peripheral receptors remained at a constant level after repeated administration, with no tachyphylaxis. These results suggest that a dose of less than 10 mg of ebastine causes rapid, intense and lasting inhibition of the peripheral H_1 histamine receptors, consistent with a single daily administration.

Sedation was studied via the following tests: electroencephalogram, cognitive function, visual-motor coordination, as well as subjective estimations. No significant increase in sedation was observed at the recommended dose. These results tally with those obtained in double blind clinical trials: the incidence of sedation is comparable between placebo and ebastine.

The cardiac effects of ebastine have been investigated in clinical trials. No significant cardiac effects were observed in detailed analyses of doses of up to 100 mg daily (ten times the recommended daily dose).

5.2 Pharmacokinetic properties

Ebastine is rapidly absorbed after administration by the oral route. It undergoes notable first pass hepatic metabolism, giving rise to the appearance of its active acid metabolite, carebastine.

Maximum metabolite plasma levels after a single oral dose of 10 mg are obtained between 2.6 and 4 hours after administration. They reach values of 80 to 100 ng/ml. The half-life of the acid metabolite occurs between 15 and 19 hours, with 66% of the compound excreted in urine, mainly in the form of conjugated metabolites. After repeated administration of 10 mg once daily, steady state was reached after 3 to 5 days with maximum plasma levels between 130 and 160 ng/ml.

In vitro studies with human hepatic microsomes show that ebastine is metabolised to carebastine via enzyme CYP3A4. Concomitant administration of ebastine and ketoconazole or erythromycin (both are CYP3A4 inhibitors) in healthy volunteers was associated with significantly raised ebastine and carebastine plasma concentrations, particularly with ketoconazole (see section 4.5).

Both ebastine and carebastine present high protein binding: > 97%.

No statistically significant differences were observed in the pharmacokinetic profile of the elderly when compared to young adults.

Ebastine and carebastine plasma concentrations obtained on the first and fifth day of treatment in patients in studies of slight, moderate or severe renal impairment (daily doses of 20 mg), and in those of slight and moderate hepatic impairment (both with doses of 20 mg/day) or severe hepatic impairment (dose of 10 mg/day) were similar to those reached in healthy volunteers, indicating that the pharmacokinetic profile of ebastine and its metabolite do not undergo significant changes in patients with various degrees of hepatic or renal impairment.

5.3 Preclinical safety data

The preclinical data do not reveal significant toxic effects based on conventional pharmacological safety studies, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicology.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: microcrystalline cellulose, pregelatinized starch, lactose monohydrate, croscarmellose sodium and magnesium stearate.
Coating: hypromellose, macrogol 6000 and titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special conditions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

Package containing 10, 20, 30, 50 or 100 tablets in PVC/Aluminium blisters. Not all the presentations are available in all markets.

6.6 Special precautions for disposal

None.

7. MARKETING AUTHORISATION HOLDER

Zuellig Pharma Ltd.
Bangkok, Thailand

8. MARKETING AUTHORISATION NUMBER(S)

Kestine 10 mg Reg. No. XX/XX (NC)
Kestine 20 mg Reg. No. XX/XX (NC)

9. DATE OF FIRST AUTHORISATION

DDMMYY

10. DATE OF REVISION OF THE TEXT

None.