Histalis®
(Ebastine Tablet JP)

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COMPOSITION
Histalis 10mg Tablet
Each film-coated tablet contains:
Ebastine BP …… 10mg

Histalis 20mg Tablet
Each film-coated tablet contains:
Ebastine BP …… 20mg

(JP Specs.)

DESCRIPTION
Histalis contains Ebastine which is a second generation H1-receptor antagonist.

Ebastine belongs to the antihistamine class. The molecular formula is $C_{32}H_{39}NO_2$, which corresponds to a molecular weight of 470.

CLINICAL PHARMACOLOGY
Mechanism of Action
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.

Pharmacodynamics
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.

Pharmacokinetics
Absorption
Ebastine is rapidly absorbed and undergoes extensive first pass metabolism following oral administration.

Distribution & Metabolism
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.

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

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.

Elimination
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.

Pharmacokinetics in special populations
Renal & Hepatic impairment
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 linical significance.

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

INDICATIONS
Histalis is indicated for the symptomatic treatment of:

• Allergic rhinitis (seasonal and perennial) whether or not associated with allergic conjunctivitis.
• Idiopathic chronic urticaria.

DOSAGE AND ADMINISTRATION
Allergic rhinitis:
Histalis 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.

Histalis may be taken with or without food.

Pediatric dosage
The safety and efficacy of Histalis in children less than 12 years has not been established.

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.

CONTRAINDICATIONS
Patients with a known hypersensitivity to Histalis or any of its ingredients.
Patients with severe liver insufficiency.

WARNING AND PRECAUTIONS
Since there is a pharmacokinetic interaction with antimycotics of the imidazol type like ketoconazole or macrolid antibiotics like erythromycin, 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.

ADVERSE REACTIONS
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.

DRUG INTERACTIONS
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. 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.

USE IN SPECIAL POPULATIONS
Pregnancy
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.

Nursing mother
Ebastine is not recommended for nursing women, because it is not known whether ebastine is excreted in human milk.

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

Renal impairment
No dose adjustment is needed in patients with renal insufficiency.

Hepatic impairment
No dose adjustment is needed in patients with mild to moderate hepatic insufficiency. A dosage of 10 mg should not be exceeded in patients with severe hepatic insufficiency.

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

PRESENTATION
Histalis 10mg: Pack of 10 Tablets
Histalis 20mg: Pack of 10 Tablets

INSTRUCTIONS
Use as advised by the physician. Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture. Store below 30°C.
For suspected adverse drug reaction, email us at reports@pharmevo.biz

For more information on our products
Call pharmassist helpline 0800-82222
Monday to friday 9:00 am to 6:00 pm
Or email us at : pharmassist@pharmevo.biz

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