

NILHIST®

Bilastine Tablets 20 mg

COMPOSITION

Each film coated tablet contains:
Bilastine.....20 mg
Excipients q.s.

Colours: Titanium Dioxide IP

PHARMACEUTICAL FORM

Film coated tablet.

THERAPEUTIC INDICATION

For Symptomatic treatment of allergic rhino-conjunctivitis (Seasonal and perennial) and urticaria in adults.

POSODOGY AND METHOD OF ADMINISTRATION

One tablet of Bilastine (20 mg) once daily for the relief of symptoms of allergic rhinoconjunctivitis (seasonal and perennial) and urticaria.

The tablet should be taken one hour before or two hours after intake of food or fruit juice.

Duration of Treatment

For allergic rhino-conjunctivitis the treatment should be limited to the period of exposure to allergens. For seasonal allergic rhinitis treatment could be discontinued after the symptoms have resolved and reinitiated upon their reappearance. In perennial allergic rhinitis continued treatment may be proposed to the patients during the allergen exposure periods. For urticaria the duration of treatment depends on the type, duration and course of the complaints.

Method of administration

Oral use.

The tablet is to be swallowed with water. It is recommended to take the daily dose in one single intake.

Special Population-

Elderly

No dosage adjustments are required in elderly patients.

Renal impairment

Studies conducted in adults in special risk groups (renally impaired patients) indicate that it is not necessary to adjust the dose of Bilastine in adults.

Hepatic impairment

There is no clinical experience in adult patients with hepatic impairment. However, since Bilastine is not metabolized and is eliminated as unchanged in urine and faeces, hepatic impairment is not expected to increase systemic exposure above the safety margin in adult patients. Therefore, no dosage adjustment is required in adult patients with hepatic impairment.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

SPECIAL WARNINGS & PRECAUTIONS FOR USE

In patients with moderate or severe renal impairment coadministration of Bilastine with P-glycoprotein inhibitors, such as e.g. ketoconazole, erythromycin, cyclosporine, ritonavir or diltiazem, may increase plasmatic levels of Bilastine and therefore increase the risk of adverse effects of Bilastine. Therefore, coadministration of Bilastine and P-glycoprotein inhibitors should be avoided in patients with moderate or severe renal impairment.

DRUG INTERACTIONS

Interaction with food: Food significantly reduces the oral bioavailability of Bilastine by 30%.

Interaction with grapefruit juice: concomitant intake of Bilastine 20 mg and grapefruit juice decreased Bilastine bioavailability by 30%. This effect may also apply to other fruit juices. The degree of bioavailability decrease may vary between producers and fruits.

Interaction with ketoconazole or erythromycin: Concomitant intake of Bilastine 20 mg o.d. and ketoconazole 400 mg o.d. or erythromycin 500 mg t.i.d. increased Bilastine AUC 2-fold and C_{max} 2-3 fold. These changes can be explained by interaction with intestinal efflux transporters, since Bilastine is substrate for P-gp and not metabolised. These changes do not appear to affect the safety profile of Bilastine and ketoconazole or erythromycin, respectively. Other medicinal products that are substrates or inhibitors of P-gp, such as cyclosporine, may likewise have the potential to increase plasma concentrations of Bilastine.

Interaction with diltiazem: Concomitant intake of Bilastine 20 mg o.d. and diltiazem 60 mg o.d. increased C_{max} of Bilastine by 50%. This effect can be explained by interaction with intestinal efflux transporters, and does not appear to affect the safety profile of Bilastine.

Interaction with alcohol: The psychomotor performance after concomitant intake of alcohol and 20 mg Bilastine o.d. was similar to that observed after intake of alcohol and placebo.

Interaction with lorazepam: Concomitant intake of Bilastine 20 mg o.d. and lorazepam 3 mg o.d. for 8 days did not potentiate the depressant CNS effects of lorazepam.

Pregnancy and Lactation

Pregnancy

There are no or limited amount of data from the use of Bilastine in pregnant women. As a precautionary measure, it is preferable to avoid the use of Bilastine during pregnancy.

Lactation

The excretion of Bilastine in milk has not been studied in humans. Available pharmacokinetic data in animals have shown excretion of Bilastine in milk. A decision on whether to continue/discontinue breast-feeding or to discontinue/abstain from Bilastine therapy must be made taking into account the benefit of breast-feeding for the child and the benefit of Bilastine therapy for the mother.

UNDESIRABLE EFFECTS

The ADRs most commonly reported by patients receiving 20 mg Bilastine for the indication of allergic rhinoconjunctivitis or chronic idiopathic urticaria were headache, somnolence, dizziness, and fatigue. These adverse events occurred with a comparable frequency in patients receiving placebo.

Tabulated summary of adverse reactions in adult and adolescent patients

ADRs at least possibly related to Bilastine and reported in more than 0.1% of the patients receiving 20 mg Bilastine during the clinical development (N = 1697) are tabulated below.

Frequencies are assigned as follows: 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)

Rare, very rare and reactions with unknown frequency have not been included in the table.

Frequency	System Organ Class Adverse reaction	Bilastine 20 mg N = 1697	All Bilastine Doses N = 2525	Placebo N = 1362
Infections and infestations				
Uncommon	Oral herpes	2 (0.12%)	2 (0.08%)	0 (0.0%)
Metabolism and nutrition disorders				
Uncommon	Increased appetite	10 (0.59%)	11 (0.44%)	7 (0.51%)
Psychiatric disorders				
Uncommon	Anxiety	6 (0.35%)	8 (0.32%)	0 (0.0%)
	Insomnia	2 (0.12%)	4 (0.16%)	0 (0.0%)
Nervous system disorders				
Common	Somnolence	52 (3.06%)	82 (3.25%)	39 (2.86%)
	Headache	68 (4.01%)	90 (3.56%)	46 (3.38%)
Uncommon	Dizziness	14 (0.83%)	23 (0.91%)	8 (0.59%)
Ear and labyrinth disorders				
Uncommon	Tinnitus	2 (0.12%)	2 (0.08%)	0 (0.0%)
	Vertigo	3 (0.18%)	3 (0.12%)	0 (0.0%)
Cardiac disorders				
Uncommon	Right bundle branch block	4 (0.24%)	5 (0.20%)	3 (0.22%)
	Sinus arrhythmia	5 (0.30%)	5 (0.20%)	1 (0.07%)
	Electrocardiogram QT prolonged	9 (0.53%)	10 (0.40%)	5 (0.37%)
	Other ECG abnormalities	7 (0.41%)	11 (0.44%)	2 (0.15%)
Respiratory, thoracic and mediastinal disorders				
Uncommon	Dyspnoea	2 (0.12%)	2 (0.08%)	0 (0.0%)
	Nasal discomfort	2 (0.12%)	2 (0.08%)	0 (0.0%)
	Nasal dryness	3 (0.18%)	6 (0.24%)	4 (0.29%)
Gastrointestinal disorders				
Uncommon	Upper abdominal pain	11 (0.65%)	14 (0.55%)	6 (0.44%)
	Abdominal pain	5 (0.30%)	5 (0.20%)	4 (0.29%)
	Nausea	7 (0.41%)	10 (0.40%)	14 (1.03%)
	Stomach discomfort	3 (0.18%)	4 (0.16%)	0 (0.0%)
	Diarrhoea	4 (0.24%)	6 (0.24%)	3 (0.22%)
	Dry mouth	2 (0.12%)	6 (0.24%)	5 (0.37%)
	Dyspepsia	2 (0.12%)	4 (0.16%)	4 (0.29%)
	Gastritis	4 (0.24%)	4 (0.16%)	0 (0.0%)
Skin and subcutaneous tissue disorders				
Uncommon	Pruritus	2 (0.12%)	4 (0.16%)	2 (0.15%)
General disorders and administration site conditions				
Uncommon	Fatigue	14 (0.83%)	19 (0.75%)	18 (1.32%)
	Thirst	3 (0.18%)	4 (0.16%)	1 (0.07%)
	Improved pre-existing condition	2 (0.12%)	2 (0.08%)	1 (0.07%)
	Pyrexia	2 (0.12%)	3 (0.12%)	1 (0.07%)
	Asthenia	3 (0.18%)	4 (0.16%)	5 (0.37%)
Investigations				
Uncommon	Increased gamma-glutamyltransferase	7 (0.41%)	8 (0.32%)	2 (0.15%)
	Alanine aminotransferase increased	5 (0.30%)	5 (0.20%)	3 (0.22%)
	Aspartate aminotransferase increased	3 (0.18%)	3 (0.12%)	3 (0.22%)
	Blood creatinine increased	2 (0.12%)	2 (0.08%)	0 (0.0%)
	Blood triglycerides increased	2 (0.12%)	2 (0.08%)	3 (0.22%)
	Increased weight	8 (0.47%)	12 (0.48%)	2 (0.15%)

Frequency not known (cannot be estimated from the available data): Palpitations, tachycardia, hypersensitivity reactions (such as anaphylaxis, angioedema, dyspnoea, rash, localised oedema/local swelling, and erythema), and vomiting have been observed during the post-marketing period.

Description of selected adverse reactions in adult and adolescent patients

Somnolence, headache, dizziness and fatigue were observed either in patients treated with Bilastine 20 mg or with placebo. The frequency reported was 3.06% vs. 2.86% for somnolence; 4.01% vs. 3.38% for headache; 0.83% vs. 0.59% for dizziness, and 0.83% vs. 1.32% for fatigue.

The information collected during the post-marketing surveillance has confirmed the safety profile observed during the clinical development.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Kindly report any suspected adverse reactions to pharmavigil@jbcpl.com

OVERDOSE

After administration of Bilastine at doses 10 to 11 times the therapeutic dose (220 mg as single dose; or 200 mg/day for 7 days) to 26 adult healthy volunteers frequency of treatment emergent adverse events was two times higher than with placebo. The adverse reactions most frequently reported were dizziness, headache and nausea. No serious adverse events and no significant prolongation in the QTc interval were reported. Critical evaluation of Bilastine's multiple dose (100 mg x 4 days) effect on ventricular repolarization did not show significant QTc prolongation. In the event of overdose symptomatic and supportive treatment is recommended. There is no known specific antidote to Bilastine.

PHARMACOLOGICAL PROPERTIES

Mechanism of Action

Bilastine inhibited histamine-induced wheal and flare skin reactions for 24 hours following single doses.

Pharmacodynamic properties

Pharmacotherapeutic group: Antihistamines for systemic use.

Bilastine is a non-sedating, long-acting histamine antagonist with selective peripheral H₁ receptor antagonist affinity and no affinity for muscarinic receptors.

In clinical trials performed in adult and adolescent patients with allergic rhinoconjunctivitis (seasonal and perennial), Bilastine 20 mg, administered once daily for 14-28 days, was effective in relieving symptoms such as sneezing, nasal discharge, nasal itching, nasal congestion, ocular itching, tearing and ocular redness. Bilastine effectively controlled symptoms for 24 hours.

No clinically relevant prolongation of QTc interval or any other cardiovascular effect has been observed in the clinical trials performed with bilastine, even at doses of 200 mg daily (10 times the clinical dose) for 7 days in 9 subjects, or even when coadministered with P-gp inhibitors, such as ketoconazole (24 subjects) and erythromycin (24 subjects). Additionally a thorough QT study including 30 volunteers has been performed.

Elderly patients (≥ 65 years) included in phase II and III studies showed no difference in efficacy or safety with respect to younger patients. A post-authorization study in 146 elderly patients showed no differences in the safety profile with respect to the adult population.

Pharmacokinetic properties

Absorption

Bilastine is rapidly absorbed after oral administration with a time to maximum plasma concentration of around 1.3 hours. No accumulation was observed. The mean value of Bilastine oral bioavailability is 61%.

Distribution

In vitro and *in vivo* studies have shown that Bilastine is a substrate of P-gp and OATP. Bilastine does not appear to be a substrate of the transporter BCRP or renal transporters OCT2, OAT1 and OAT3. Based on *in vitro* studies, Bilastine is not expected to inhibit the following transporters in the systemic circulation: P-gp, MRP2, BCRP, BSEP, OATP1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT1, OCT2, and NTCP, since only mild inhibition was detected for P-gp, OATP2B1 and OCT1, with an estimated IC₅₀ ≥ 300 μM, much higher than the calculated clinical plasma C_{max} and therefore these interactions will not be clinically relevant. However, based on these results inhibition by Bilastine of transporters present in the intestinal mucosa, e.g. P-gp, cannot be excluded.

At therapeutic doses Bilastine is 84-90% bound to plasma proteins.

Biotransformation

Bilastine did not induce or inhibit activity of CYP450 isoenzymes in *in vitro* studies.

Elimination

In a mass balance study performed in healthy adult volunteers, after administration of a single dose of 20 mg ¹⁴C-bilastine, almost 95% of the administered dose was recovered in urine (28.3%) and faeces (66.5%) as unchanged Bilastine, confirming that Bilastine is not significantly metabolized in humans. The mean elimination half-life calculated in healthy volunteers was 14.5 h.

INCOMPATIBILITIES

Not applicable.

PACKAGING INFORMATION

Blister of 2 tablets and 10 tablets

STORAGE AND HANDLING INSTRUCTIONS

Store at a temperature below 30°C.

Protect from light and moisture.



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Note: This prescribing information is applicable for India Market only.