For the use only of a Registered Medical Practitioner

1. Generic Name and Brand Name

Bilastine Tablets 20 mg

Bilazest™

2. Qualitative and Quantitative Composition

Each uncoated tablet contains:

Bilastine ……20 mg

Excipients……. q.s.

3. Dosage Form & Strength

Refer section 1 & 2

4. Clinical Particulars

4.1 Therapeutic Indications

Bilastine Tablets is indicated for symptomatic treatment of allergic rhino-conjunctivitis (seasonal and perennial) and urticaria in adults.

4.2 Posology and method of administration

One tablet (20 mg) once daily for the relief of symptoms of allergic rhino-conjunctivitis (seasonal and perennial) and urticaria in adults. The tablet should be taken by oral route one hour before or two hours after intake of food or fruit juice.

Duration of treatment

For allergic rhinitis 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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Paediatric population

Efficacy and safety of bilastine in children under 2 years of age have not been established and there is little clinical experience in children aged 2 to 5 years, therefore bilastine should not be used in these age groups.

Moderate to severe renal impairment

In patients with moderate or severe renal impairment co-administration 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, co-administration of bilastine and P-glycoprotein inhibitors should be avoided in patients with moderate or severe renal impairment.

Geriatrics (> 65 years of age):

No dosage adjustments are necessary in patients over 65 years.

Cardiovascular:

Bilastine has been associated with QTc interval prolongation. Drugs that cause QT/QTc prolongation are suspected of increasing the risk of torsade de pointes. Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QT/QTc prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Bilastine should not be used in patients with a history of QTc prolongation and/or torsade de pointes, including congenital long QT syndromes.

Particular care should be exercised when administering antihistamines, including Bilastine to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging drug. This includes patients who have a history of cardiac arrhythmias; hypokalemia; hypomagnesaemia; significant bradycardia; family history of sudden cardiac death; concomitant use of other QT/QTc-prolonging drugs.

When drugs that prolong the QTc interval are prescribed, healthcare professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug.

Hepatic

Bilastine has not been studied in subjects with hepatic impairment. Since bilastine is not metabolized and renal clearance is the major route of elimination, hepatic impairment is not expected to increase systemic exposure above the safety margin.

4.5 Drug Interactions

Interaction with Ketoconazole or Erythromycin

Concomitant intake of Bilastine and ketoconazole or erythromycin 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 metabolized. 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 and Diltiazem 60 mg 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 Lorazepam

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

Interaction with Alcohol

The psychomotor performance after concomitant intake of alcohol and 20 mg Bilastine was similar to that observed after intake of alcohol and placebo.

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. The mechanism for this interaction is an inhibition of OATP1A2, an uptake transporter for which Bilastine is a substrate. Medicinal products that are substrates or inhibitors of OATP1A2, such as ritonavir or rifampicin, may likewise have the potential to decrease plasma concentrations of bilastine.

Interaction with food

Food significantly reduces the oral bioavailability of bilastine by 30%.

Paediatric population

Interaction studies have only been performed in adults. Extent of interaction with other medicinal products and other forms of interaction is expected to be similar in paediatric population from 12 to 17 years of age.

QTc-Prolonging Drugs:

The concurrent use of bilastine with other QTc prolonging drugs is not recommended.

Inhibitors of P-Glycoprotein:

Plasma levels of bilastine can be increased by inhibitors of P-glycoprotein; the concomitant use of these drugs with bilastine is not recommended. Drugs that inhibit P-glycoprotein include, but are not limited to certain azole antifungal, macrolide antibiotics, and HIV protease inhibitors.

Drugs that Cause Electrolyte Depletion:

The use of bilastine with drugs that can cause electrolyte imbalance is not recommended.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

There are no adequate and well controlled studies on pregnancy outcome with bilastine in pregnant women.

Studies in animals do not indicate direct or indirect harmful effects with respect to reproductive toxicity, parturition or postnatal development. As a precautionary measure, it is preferable to avoid the use of bilastine during pregnancy.

There are no or limited amount of clinical data on fertility. A study in rats did not indicate any negative effect on fertility.

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 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.

Children under 12 years

The safety and efficacy of bilastine in children under 12 years of age have not yet been established.

Geriatrics

No dosage adjustments are required in elderly patients.

Renal impairment

No dosage adjustment is required in patients with renal impairment.

Hepatic impairment

There is no clinical experience in patients with hepatic impairment. Since bilastine is not metabolized and renal clearance is its major elimination route, hepatic impairment is not expected to increase systemic exposure above the safety margin. Therefore, no dosage adjustment is required in patients with hepatic impairment.

Fertility

There are no or limited amount of clinical data. A study in rats did not indicate any negative effect on fertility

4.7 Effects on ability to drive and use machines

A study performed in adults to assess the effects of bilastine on the ability to drive demonstrated that treatment with 20 mg did not affect the driving performance. However, as the individual response to the medicinal product may vary, patients should be advised not to drive or use machines until they have established their own response to bilastine.

4.8 Undesirable Effects

The below adverse effects were determined based on data from the Bilastine clinical studies and frequencies are defined as: 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) and not known (cannot be estimated from the available data).

Infections and infestations

Uncommon: Oral herpes, pharyngitis.

Blood and lymphatic system disorders:

Not known: Anaemia

Metabolism and nutrition disorders

Uncommon: Increased appetite

Musculoskeletal and connective tissue disorders:

Back pain, muscular weakness and myalgia.

Psychiatric disorders

Uncommon: Anxiety, insomnia

Not known: Nightmare.

Reproductive system and breast disorders:

Not known: Menstruation delayed

Ear and labyrinth disorders

Uncommon: Tinnitus, vertigo, motion sickness.

Eye disorders:

Not known: Eye pain

Cardiac disorders

Uncommon: Right bundle branch block, sinus arrhythmia, bradycardia, ventricular extrasystoles other ECG abnormalities, electrocardiogram QT prolonged

Nervous system disorders

Common: Somnolence, headache

Uncommon: Dizziness

Not known: Disturbance in attention, hypersomnia

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnea, nasal discomfort, nasal dryness

Not known: Epistaxis, throat irritation.

Gastrointestinal disorders

Uncommon: Upper abdominal pain, constipation, dysgeusia, eructation, stomach discomfort, tongue dry, vomiting, nausea, stomach discomfort, diarrhea, dry mouth, dyspepsia and gastritis

Skin and subcutaneous tissue disorders

Uncommon: Pruritus

Not known: Dermatitis acneiform, rash popular, urticaria.

General disorders and administration site conditions

Uncommon: Fatigue, thirst, improved pre-existing condition, pyrexia, chest discomfort, discomfort, feeling jittery, pain and asthenia.

Investigations

Uncommon: Increased gamma-glutamyltranferase, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased, blood bilirubin increased, blood cholesterol increased, blood triglycerides increased, weight decreased, weight increased, blood triglycerides increased and increased weight.

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

Reporting of suspected adverse reactions

Health care professionals, patients/consumers are advised to closely monitor the possibility of the above ADRs associated with the use of the above drugs. If such reactions are encountered, please report to the Hetero either by filling of Suspect Adverse Drug Reactions. Reporting Form **(https://www.heteroworld.com)** or by **Hetero Helpline No.1800-120-8689** and for all India safety cases and complaints, please write to **drugsafetyindia@heterodrugs.com.**

4.9 Overdose

Information regarding acute overdose of bilastine is retrieved from the experience of clinical trials conducted during the development and the post-marketing surveillance. In clinical trials,

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 healthy volunteer's 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. The information collected in the post-marketing surveillance is consistent with that reported in clinical trials.

Critical evaluation of bilastine's multiple dose (100 mg x4 days) effect on ventricular repolarization by a "thorough QT/QTc cross-over study" involving 30 healthy volunteers 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.

5. Pharmacological Properties

5.1 Mechanism of action

Bilastine is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H1 receptors. The antihistaminic activity of bilastine has been documented in a variety of animal and human models. It shows moderate to high affinity for histamine H1-receptors and no affinity for muscarinic, serotonergic, dopaminergic and noradrenergic receptors. Bilastine has been demonstrated to have limited distribution to the brain following oral administration.

5.2 Pharmacodynamic properties

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

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

5.3 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 (Breast cancer resistance proteins) 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 $IC_{50} \geq 300$ 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.

Metabolism

Bilastine did not induce or inhibit activity of CYP_{450} isoenzymes in *in vitro* studies.

Elimination

In a mass balance study performed in healthy volunteers, after administration of a single dose of 20 mg ^{14}C-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.

Linearity

Bilastine presents linear pharmacokinetics in the dose range studied (5 to 220 mg), with a low interindividual variability.

6. Nonclinical Properties

6.1 Animal Toxicology or Pharmacology

Non-clinical data with bilastine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In reproduction toxicity studies effects of bilastine on the foetus (pre-and post-implantation loss in rats and incomplete ossification of cranial bones, sternebrae and limbs in rabbits) were only observed at maternal toxic doses. The exposure levels at the NOAELs are sufficiently in excess (> 30 fold) to the human exposure at the recommended therapeutic dose.

In a lactation study, bilastine was identified in the milk of nursing rats administered a single oral dose (20 mg/kg). Concentrations of bilastine in milk were about half of those in maternal plasma. The relevance of those results for humans is unknown.

In a fertility study in rats, bilastine administered orally up to 1000 mg/kg/day did not induce any effect on female and male reproductive organs. Mating, fertility and pregnancy indices were not affected.

As seen in a distribution study in rats with determination of drug concentrations by autoradiography, bilastine does not accumulate in the CNS.

7. Description

Bilazest is supplied for oral administration, as an uncoated tablet of Bilastine. Each uncoated tablet of Bilazest contains Bilastine 20 mg.

8. Pharmaceutical Particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Refer pack

8.3 Packing Information

Refer pack

8.4 Storage and handling instructions

9. Refer pack **Patient Counselling Information**

- Advise patients to stop taking the medicine, if they were allergic to bilastine or any of the other ingredients of bilastine.
- Advise patient to stop taking medicine if the patient had history of irregular heartbeat.
- Advise patient that bilastine is not suitable for use by children under 12 years of age.
- Advise patient about the major side effects of bilastine which may include headache, sleepiness, dizziness and stomach pain.

- Advise patient not to take bilastine along with drugs like ketoconazole, erythromycin, cyclosporine, ritonavir or diltiazem as they may increase plasmatic levels of bilastine and therefore increase the risk of adverse effects of bilastine.

10. Details of Manufacturer

Refer Pack for manufacturer details.

Marketed By:

Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. D-4, Gala No. 1 to 6 &
11 to 16 Ground Floor, 101 to 106 &
111 to 116 First Floor, 201 to 206 & 211 to 216
2nd Floor, Pimplas, Dist. Thane, Bhiwandi - 421 302, India.
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11. Details of permission or licence number with date

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12. Date of revision

Version 3.0, dated 13th February 2024