Summary of Product Characteristic

1. Name of the Medicinal Product

Bilastine Tablets 20 mg

Dosage Strength 20 mg

2. Quality and Quantitative Composition

Qualitative Declaration

Bilastine

Quantitative Declaration

Each tablet contains:

Bilastine	20 mg

For full list of excipients see section 6.1

3. Pharmaceutical Form

White to off white, scored oval shaped tablets debossed with '2' on one side of breakline and '0' on other side of breakline on one side, plain on other side.

4. Clinical Particulars

4.1 Therapeutic indications

Symptomatic treatment of allergic rhino-conjunctivitis (seasonal and perennial) and urticaria.

4.2 Posology and method of administration

Route of administration:

Oral Use

Adults and adolescents (12 years of age and over)

20 mg (1 tablet) once daily for the relief of symptoms of allergic rhinoconjunctivitis (SAR and PAR) and urticaria.

The tablet should be taken by oral route one hour before or two hours after intake of food or fruit juice. It is recommended to take the daily dose in one single intake.

Elderly

No dosage adjustments are required in elderly patients. There is little experience in patients above the age of 65.

Children under 12 years

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

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.

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.

4.3 Contraindications

Hypersensitivity to the active substance bilastine or to any of the excipients of this medicine.

4.4 Special warnings and precautions for use

Efficacy and safety of bilastine in children under 12 years of age have not been established.

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.

4.5 Interaction with other medicinal products and other forms of interaction 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. 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 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 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 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 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 lorazepam: Concomitant intake of bilastine 20 mg and lorazepam 3 mg for 8 days did not potentiate the depressant CNS effects of lorazepam.

4.6 Fertility, pregnancy and breast-feeding

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

Pregnancy: There are no or limited amount of data from the use of bilastine in pregnant women.

Animal studies 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 >invented name< during pregnancy.

Lactation: It is unknown whether bilastine is excreted in human breast milk. The excretion of bilastine in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with >invented name< should be made taking into account the benefit of breast-feeding to the child and the benefit of bilastine therapy to the mother.

4.7 Effects on ability to drive and use machines

A study performed to assess the effects of bilastine on the ability to drive demonstrated that treatment with 20 mg did not affect the driving performance. However, patients should be informed that very rarely some people experience drowsiness, which may affect their ability to drive or use machines.

4.8 Undesirable effects

The number of adverse events experienced by patients suffering from allergic rhinoconjunctivitis or chronic idiopathic urticaria treated with 20 mg bilastine in clinical trials was comparable with patients receiving placebo.

The ADRs most commonly reported by patients receiving 20 mg bilastine during phase II and III clinical trials were headache, somnolence, dizziness, and fatigue. These adverse events occurred with a comparable frequency in patients receiving placebo.

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 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)

Infections and infestations
Uncommon: Oral herpes
Metabolism and nutrition disorders Uncommon: Increased appetite *Psychiatric disorders*
Uncommon: Anxiety, Insomnia *Ear and labyrinth disorders* Uncommon: Tinnitus, Vertigo *Cardiac disorders*
Uncommon: Right bundle branch block, Sinus arrhythmia, Electrocardiogram QT prolonged, Other ECG abnormalities
Nervous system disorders

Common: Somnolence, Headache; Uncommon: Dizziness *Respiratory, thoracic and mediastinal disorders* Uncommon: Dyspnoea, Nasal discomfort, Nasal dryness *Gastrointestinal disorders*
Uncommon: Upper abdominal pain, Abdominal pain, Nausea, Stomach discomfort, Diarrhoea, Dry mouth, Dyspepsia, Gastritis
Skin and subcutaneous tissue disorders

Uncommon: Pruritus

General disorders and administration site conditions

Uncommon: Fatigue, Thirst, Improved pre-existing condition, Pyrexia, Asthenia

Investigations

Uncommon: Increased gamma-glutamyl transferase, Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood creatinine increased, Blood triglicerides increased, Increased weight

Reporting suspected adverse reactions after Authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national pharmacovigilance reporting system.

4.9 **Overdose**

Information regarding acute overdose is limited to experience from clinical trials conducted during the development of bilastine. After administration of bilastine at doses 10 to 11 times the therapeutic dose (220 mg (single dose); or 200 mg/day for 7 days) to 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 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 Pharmacodynamic properties

Pharmacotherapeutic group: Antihistamines for systemic use, other antihistamines for systemic use
ATC code: RO6AX29.

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.
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.
In two clinical trials performed in patients with chronic idiopathic urticaria, Bilastine 20 mg, administered once daily for 28 days was effective in relieving the itching intensity and the number and size of wheals, as well as the patients discomfort due to urticaria. Patients improved their sleep conditions and their quality of life.
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.
In controlled clinical trials at the recommended dose of 20 mg once daily, the CNS safety profile of bilastine was similar to placebo and the incidence of somnolence was not statistically different from placebo. Bilastine at doses of up to 40 mg q.d. did not affect psychomotor performance in clinical trials and did not affect driving performance in a standard driving test.
Elderly patients (≥ 65 years) included in phase II and III studies showed no difference in efficacy or safety with respect to younger patients.

5.2 Pharmacokinetic properties

Bilastine presents linear pharmacokinetics in the dose range studied (5 to 220 mg), with a low interindividual variability. Bilastine is rapidly absorbed after oral administration with a time to maximum plasma concentration of around 1.3 hours. No accumulation was observed. In vitro and in vivo studies have shown that bilastine is a substrate of Pgp and OATP. 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 Cmax 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.

Bilastine did not induce or inhibit activity of CYP450 isoenzymes in in vitro studies. In a mass balance study performed in healthy 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.
Patients with renal impairment:

In a study in subjects with renal impairment the mean (SD) AUC0-∞ increased from

737.4 (±260.8) ngxhr/ml in subjects without impairment (GFR: > 80 ml/min/1.73 m^2) to: 967.4 (±140.2) ngxhr/ml in subjects with mild impairment (GFR: 50-80 ml/min/1.73 m^2), 1384.2 (±263.23) ngxhr/ml in subjects with moderate impairment (GFR: 30 - <50 ml/min/1.73 m^2), and 1708.5 (±699.0) ngxhr/ml in subjects with severe impairment (GFR: < 30 ml/min/1.73 m^2). Mean (SD) half-life of bilastine was
9.3 h (± 2.8) in subjects without impairment, 15.1 h (± 7.7) in subjects with mild impairment, 10.5 h (± 2.3) in subjects with moderate impairment and 18.4 h (± 11.4) in subjects with severe impairment. Urinary excretion of bilastine was essentially complete after 48 -72 h in all subjects. These pharmacokinetic changes are not expected to have a clinically relevant influence on the safety of bilastine, since

bilastine plasma levels in patients with renal impairment are still within the safety range of bilastine.

Patients with hepatic impairment:

There are no pharmacokinetic data in subjects with hepatic impairment. Bilastine is not metabolized in human. Since the results of the renal impairment study indicate renal elimination to be a major contributor in the elimination, biliary excretion is expected to be only marginally involved in the elimination of bilastine. Changes in liver function are not expected to have a clinically relevant influence on bilastine pharmacokinetics.

Elderly patients:

Only limited data are available in subjects older than 65 years. No statistically significant differences have been observed with regard to PK of bilastine in elderly compared to young subjects.

5.3 Preclinical safety data

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 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.

6. Pharmaceutical Particulars:

6.1 List of excipients

Microcrystalline Cellulose
Sodium Starch Glycolate
Colloidal Anhydrous Silica
Magnesium Stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C, Protected from light and moisture.

6.5 Nature and contents of container

Alu-Alu blister pack of 10 tablets.

7. Marketing Authorization Holder

Unison Pharmaceuticals Pvt. Ltd.

"Unison House", Near Prernatirth Derasar, Near Ratnadeep-II, Satellite, Jodhpur, Ahmedabad-380 015, Gujarat, India.

8. Marketing Authorization number

CTD10612

9. Date of first authorization/renewal of the authorization

08/1/2024

10. Date of revision of the text

08/1/2024