

	<i>Thirst</i>
	<i>Improved pre-existing condition</i>
	<i>Pyrexia</i>
	<i>Asthenia</i>
Investigations	
<i>Uncommon</i>	<i>Increased gamma-glutamyltransferase</i>
	<i>Alanine aminotransferase increased</i>
	<i>Aspartate aminotransferase increased</i>
	<i>Blood creatinine increased</i>
	<i>Blood triglycerides increased</i>
	<i>Increased weight</i>

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 reporting system listed. You may report any side effects or adverse drug reactions directly to the National Centre for Adverse Drug Reaction Monitoring by visiting the website www.npra.gov.my (Consumers→Reporting).

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 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. 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 x 4 days) effect on ventricular repolarization by a “thorough QT/QTc cross-over study” involving 30 adult healthy volunteers did not show significant QTc prolongation.

There are no data for overdose in children.

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: R06AX29

Mechanism of action

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.

Clinical efficacy and safety

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. A post-authorization study in 146 elderly patients showed no differences in the safety profile with respect to the adult population.

Paediatric population

Adolescents (12 years to 17 years) were included in the clinical development. 128 adolescents received bilastine during the clinical studies (81 in double blind studies in allergic rhinoconjunctivitis). A further 116 adolescent subjects were randomised to active comparators or placebo. No differences in efficacy and safety between adults and adolescents were seen.

For safety profile in children under 12 years of age, please refer to the package insert of other products intended for paediatric use for more information.

5.2 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 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.

Linearity

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

Renal impairment

In a study in subjects with renal impairment the mean (SD) AUC_{0-∞} increased from 737.4 (± 260.8) ng x hr/mL in subjects without impairment (GFR: > 80 mL/min/1.73 m²) to: 967.4 (± 140.2) ng x hr/mL in subjects with mild impairment (GFR: 50-80 mL/min/1.73 m²), 1384.2 (± 263.23) ng x hr/mL in subjects with moderate impairment (GFR: 30 - <50 mL/min/1.73 m²), and 1708.5 (± 699.0) ng x hr/mL in subjects with severe impairment (GFR: <30 mL/min/1.73 m²).

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.

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

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 older people aged over 65 years compared to adult population aged between 18 and 35 years.

Paediatric population

No pharmacokinetic data are available in adolescents (12 years to 17 years) as the extrapolation from adult data was deemed appropriate for this product.

5.3 Preclinical safety data

Not Applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose, Sodium Starch Glycolate, Silica Colloidal Anhydrous, Magnesium Stearate

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

30 Months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

A carton containing a leaflet and alu-alu blister pack of 1×10's tablets.

A carton containing a leaflet and alu-alu blister pack of 3×10's tablets.

A carton containing a leaflet and alu-alu blister pack of 5×10's tablets

Note: Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Product Registration Holder

Glenmark Pharmaceuticals (Malaysia) Sdn Bhd
D-31-02, Menara Suezcap 1,
No. 2, Jalan Kerinchi,
59200 Kuala Lumpur, Malaysia

8. Manufacturer

Glenmark Pharmaceuticals Limited.
Plot No. S-7, Colvale Industrial
Estate, Colvale, Bardez,
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9. Product Registration No.

MAL24106024AZ

10. Date of Revision

04/10/2024

PE00000 MY

ICONGRAPHICS CODE:

PANTONE SHADE
PANTONE BLACK PROCESS C
Supersedes Artwork Code

PHARMACODE:

Note: Dimensions may change during commercialization of the product depending on the machine feasibility.