Pharmabilast
bilastine 20 mg
tablet

1. Name of the medicinal product :

Pharmabilast

2. Qualitative and quantitative composition

Each tablet contains 20 mg of bilastine.

3. pharmaceutical form :

tablet.

White round biconvex tablet .

4. Clinical particulars

4.1 Therapeutic indications

Symptomatic treatment of allergic rhino-conjunctivitis (seasonal and perennial) and urticaria.
Pharmabilast is indicated in adults and adolescents (12 years of age and over).

4.2 posology and method of administration :

- **Posology :**

Adults and adolescents (12 years of age and over)
20 mg bilastine (1 tablet) once daily for the relief of symptoms of allergic rhinoconjunctivitis (SAR and PAR) 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.

- **Special populations :**

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 feaces, 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 .

Paediatric population

- Children 6 to 11 years of age with a body weight of at least 20 kg

Bilastine 10 mg and bilastine 2.5 mg/mL oral solution are appropriate for administration to this population.

- Children under 6 years of age and under 20 kg

No recommendation on a posology can be made. Therefore bilastine should not be used in this age group
The safety and efficacy of bilastine in renally and hepatically impaired children have not been established.

- **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.

4.3.contraindications :

Hypersensitivity to the active substance or to any of the excipients listed *in section 6.1*.

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.

- 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 studies have only been performed in adults and are summarised below.
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 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.
Paediatric population:
Interaction studies have only been performed in adults. As there is no clinical experience regarding the interaction of bilastine with other medicinal products, food or fruit juices in children, the results obtained in adult interactions studies should be at present taken into consideration when prescribing bilastine to children. There are no clinical data in children to state whether changes to the AUC or Cmax due to interactions affect the safety profile of bilastine.

4.6 Fertility, pregnancy and lactation:

Pregnancy: There are no or limited amount of data from the use of bilastine in pregnant women.
Breast-feeding: The excretion of bilastine in milk has not been studied in humans. A decision on whether to continue/discontinue breast-feeding or to discontinue/abstain from Pharmabilast therapy must be made taking into account the benefit of breast-feeding for the child and the benefit of bilastine therapy for the mother.
Fertility: There are no or limited amount of clinical data.

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 :
Summary of safety profile in adults and adolescent patients
The incidence of adverse events in adult and adolescent patients suffering from allergic rhinoconjunctivitis or chronic idiopathic urticaria treated with 20 mg bilastine in clinical trials was comparable with the incidence in patients receiving placebo (12.7% versus 12.8%).
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.
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.

Tabulated summary of adverse reactions in adult and adolescent patients:

System Organ Class	
Frequency	**Adverse reaction**
Infections and infestations	
Uncommon	Oral herpes
Metabolism and nutrition disorders	
Uncommon	Increased appetite
Psychiatric disorders	
Uncommon	Anxiety
	Insomnia
Nervous system disorders	
Common	Somnolence
	Headache
Uncommon	Dizziness
Ear and labyrinth disorders	
Uncommon	Tinnitus
	Vertigo
Cardiac disorders	
Uncommon	Right bundle branch block
	Sinus arrhythmia
	Electrocardiogram QT prolonged
	ECG abnormalities
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-glutamyltransferase
	Alanine aminotransferase increased
	Aspartate aminotransferase increased
	Blood creatinine increased
	Blood triglicerides increased
	Increased weight

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 may be observed in patients treated with bilastine 20 mg.

Summary of safety profile in paediatric population

During the clinical development the frequency, type and severity of adverse reactions in adolescents (12 years to 17 years) were the same as observed in adults

The percentage of children (2-11 years) which reported adverse events (AEs) after treatment with bilastine 10 mg for allergic rhinoconjunctivitis or chronic idiopathic urticaria in a 12-week controlled clinical trial was comparable with patients receiving placebo (68.5% versus 67.5%). The related AEs most commonly reported by 291 children (2-11 years) receiving bilastine (orodispersible tablet formulation) during clinical trials (#260 children exposed in the clinical safety study, 31 children exposed in the pharmacokinetic study) were headache, allergic conjunctivitis, rhinitis and abdominal pain. These related adverse events occurred with a comparable frequency in 249 patients receiving placebo.

Tabulated summary of adverse reactions in paediatric population

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.

System Organ Class	
Frequency	**Adverse Reaction**
Infections and infestations	
Common	Rhinitis
Nervous system disorders	
Common	Headache
Uncommon	Dizziness
	Loss of consciousness
Eye disorders	
Common	Allergic conjunctivitis
Uncommon	Eye irritation
Gastrointestinal disorders	
Common	Abdominal pain / Upper abdominal pain
Uncommon	Diarrhoea
	Nausea
	Lip swelling
Skin and subcutaneous tissue disorders	
Uncommon	Eczema
	Urticaria
General disorders and administration site conditions	
Uncommon	Fatigue

Description of selected adverse reactions in paediatric population:

Headache, abdominal pain, allergic conjunctivitis and rhinitis were observed either in children treated with bilastine 10 mg or with placebo. The frequency reported was 2.1% vs. 1.2% for headache; 1.0% vs. 1.2% for abdominal pain; 1.4% vs. 2.0% for allergic conjunctivitis, and 1.0% vs. 1.2% for rhinitis.

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 Egyptian Pharmaceutical Vigilance Center (EPVC) **PV.followup@edaegypt.gov.eg** or via biomed company mail : Info@pharmacureonline.com

4.9 overdose :

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 healthy adult 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

Mechanism of action

Bilastine is a non-sedating, long-acting histamine antagonist with selective peripheral H_1 receptor antagonist affinity and no affinity for muscarinic receptors.

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

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 (see section "Interaction with ketoconazole, erythromycin and diltiazem") and OATP (see section "Interaction with grapefruit juice"). 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 $IC_{50} \geq 300$ 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.

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 ^{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.

Renal impairment
In a study in subjects with renal impairment the mean (SD) $AUC_{0-\infty}$ increased from 737.4 (± 260.8) ng x hr/mL in subjects without impairment (GFR: > 80 mL/min/1.73 m^2) to: 967.4 (± 140.2) ng x hr/mL in subjects with mild impairment (GFR: 50-80 mL/min/1.73 m^2), 1384.2 (± 263.23) ng x hr/mL in subjects with moderate impairment (GFR: 30 - <50 mL/min/1.73 m^2), and 1708.5 (± 699.0) ng x hr/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.

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

Pharmacokinetic data in children were obtained in a Phase II pharmacokinetic study including 31 children aged 4 to 11 years with allergic rhinoconjunctivitis or chronic urticaria, administered once daily with bilastine 10 mg Pharmacokinetic analysis of plasma concentration data showed that the pediatric dose of bilastine 10 mg once daily results in systemic exposure equivalent to that seen after a 20 mg dose in adults and adolescents, being the mean AUC value 1014 ng* x hr/mL for children 6 to 11 years. These results were largely below the safety threshold based on data from 80 mg once daily dose in adults in accordance to the drug safety profile. These results confirmed the choice of bilastine 10 mg p.o. once daily as the appropriate therapeutic dose for the paediatric population in the age range 6 to 11 years with a body weight of at least 20 kg.

6. Pharmaceutical particulars

6.1 List of excipients

Each tablet contains:

Inactive ingredients:

- Microcrystalline cellulose PH 102
- Sodium starch gylcolate
- Colloidal silicon dioxide (Aerosil 200)
- Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Store at temperature not exceeding 30°C in dry place.

6.5 Nature and contents of container
Carton box contains two (AL/transparent colorless PVC/transparent PVDC) blisters of 10 tablets with insert leaflet.

7. Manufacture and license holder:

Pharma Cure Pharmaceutical Industries