Pharmabilast

Bilastine 2.5mg/ml

Oral solution

1. NAME OF THE MEDICINAL PRODUCT

Pharmabilast 2.5 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral solution contains 2.5 mg of bilastine.

Excipients with known effect: methyl parahydroxybenzoate, propyl parahydroxybenzoate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral Solution.

Clear Colourless homogenous oral solution with characteristic odour

CLINICAL PARTICULARS

3.1. Therapeutic Indications

Symptomatic treatment of allergic rhino-conjunctivitis (seasonal and perennial) and urticaria.
Pharmabilast is indicated in children aged 6 to 11 years with a body weight of at least 20 kg.

3.2. Posology and method of administration

Posology

Paediatric population

- Children 6 to 11 years of age with a body weight of at least 20 kg
  10 mg bilastine (4 ml of oral solution) once daily for the relief of symptoms of allergic rhino-conjunctivitis (seasonal allergic rhinitis and perennial allergic rhinitis) and urticaria.
- The oral solution should be taken one hour before or two hours after intake of food or fruit juice (see section 4.5).

- Children under 6 years of age and under 20 kg
  bilastine should not be used in this age group.
- In adults and adolescents (over 12 years of age) the administration of bilastine 20 mg tablets is appropriate

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

Renal impairment
The safety and efficacy of bilastine in renally impaired children have not been established. 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
The safety and efficacy of bilastine in hepatically impaired children have not been established. There is no clinical experience in both adult and paediatric patients with hepatic impairment. However, since bilastine is not metabolized and is eliminated as unchanged in urine and feces, 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.

Method of administration
Oral use

3.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Children less than 6 years.

3.4. 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 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.

Pharmabilast contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

This medicine contains less than 1 mmol sodium (23 mg) per 4 ml, that is to say essentially 'sodium free'.

3.5. Interaction with other medicinal products and other forms of interactions

Interaction studies have only been performed in adults and are summarized below.

Interaction with food: Food significantly reduces the oral bioavailability of bilastine 20 mg tablets by 30% and that of bilastine 2.5 mg/ml oral solution by 20%.

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 (see section 5.2). 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 a substrate for P-gp and not metabolized (see section 5.2). 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 (see section 5.2), 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 o.d. bilastine 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

No interaction studies have been performed in children with bilastine oral solution. 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.

3.6. Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

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 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

Fertility

There are no or limited amount of clinical data.

3.7. 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 bilastine did not affect 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.

3.8. Undesirable effects

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 information collected in this population (adolescents) during post-marketing surveillance has confirmed clinical trial findings.

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 the percentage in the group receiving placebo (68.5% versus 67.5%).

The related AEs most commonly reported by 291 children (2-11 years) receiving bilastine 10 mg (orodispersible tablet formulation) during clinical trials 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 paedriatic population
AEs at least possibly related to bilastine and reported in more than 0.1% of children (2-11 years) receiving 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)
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		**Bilastine 10 mg (n=291)**
Infections and infestations		
Common	Rhinitis	1.0 %
Nervous system disorders		
Common	Headache	2.1 %
Uncommon	Dizziness	0.3 %
	Loss of consciousness	0.3 %
Eye disorders		
Common	Allergic conjunctivitis	1.4 %
Uncommon	Eye irritation	0.3 %
Gastrointestinal disorders		
Common	Abdominal pain / Upper	1.0 %
Uncommon	Diarrhoea	0.7 %
	Nausea	0.3 %
	Lip swelling	0.3 %
Skin and subcutaneous tissue disorders		
Uncommon	Eczema	0.3 %
	Urticaria	0.7 %
General disorders and administration site conditions		
Uncommon	Fatigue	0.7 %

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.

Summary of safety profile in adult 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

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.

System Organ Class Frequency Adverse reaction	
Infections and infestations	
Uncommon	Oral herpes
Metabolism and nutrition	
Uncommon	Increased
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
	Sinus
	Electrocardiogra
	Other ECG

Respiratory, thoracic and	
Uncommon	Dyspnoea
	Nasal
	Nasal dryness
Gastrointestinal disorders	
Uncommon	Upper
	Abdominal pain
	Nausea
	Stomach
	Diarrhoea
	Dry mouth
	Dyspepsia
	Gastritis
Skin and subcutaneous tissue	
Uncommon	Pruritus
General disorders and	
Uncommon	Fatigue
	Thirst
	Improved pre-
	Pyrexia
	Asthenia
Investigations	
Uncommon	Increased
	Alanine
	Aspartate
	Blood creatinine
	Blood
	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 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.

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 Pharma Cure Pharmaceutical Industries
Tel: 01145004525-002 / 0482657089-002 3223754-013-002 / 3236852-013-002 /
Fax: 002-013-3236711 / 002-0482657088
E.mail: Info@pharmacureonline.com
The Egyptian Pharmacovigilance Center (EPVC) E. mail: PV.followup.@edaegypt.gov.eg

3.9. Overdose

There are no data for overdose in children.

Information regarding acute overdose of bilastine is retrieved from the experience of clinical trials conducted during the development in adults 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 x4 days) effect on ventricular repolarization by a "thorough QT/QTc cross-over study" involving 30 healthy adult 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.

4. 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.

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 Pgp (see section 4.5 "Interaction with ketoconazole or erythromycin" and "Interaction with diltiazem") and OATP (see section 4.5 "Interaction with grapefruit juice").
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

The effects of bilastine in patients with renal impairment have been studied in adults.
In a study in subjects with renal impairment the mean (±SD) $AUC_{0-¥}$ 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.

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.

Paediatric population
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 orodispersible tablet. This formulation has been shown to be bioequivalent to bilastine 2.5 mg/ml oral solution. 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*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.

5. PHARMACEUTICAL PARTICULARS

5.1. List of excipients

Macrogols (6000), Methyl parahydroxybenzoate (Methylparaben), Propyl parahydroxybenzoate (Propylparaben), Glycerol (Glycerin), Sucralose, (Dilute hydrochloric acid 10%-Sodium hydroxide: for PH adjustment), Raspberry flavor, Purified water, (Raspberry flavor contains Monopropylene glycol).

5.2. Incompatibilities

Not applicable.

5.3. Shelf life

See outer pack.

5.4. Special precautions for storage

Store at temperature not exceeding 30 °C.

5.5. Nature and contents of container

Pharmabilast 2.5 mg/ml oral solution is packaged in an amber glass bottle (Type III glass) contain 120 ml oral solution sealed with plastic (HDPE) screw cap contain inner Teflon pulp covered with polyethylene on both sides.

5.6. Special precautions for disposal

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

6. MANFACTURER AND LICENSE HOLDER:

Pharma Cure Pharmaceutical Industries