Professional information for ILAXTEN ORAL SOLUTION

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

ILAXTEN ORAL SOLUTION 2,5 mg/mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of oral solution contains 2,5 mg of bilastine.

Excipients with known effect

Contains preservatives methyl parahydroxybenzoate (1,0 mg/mL) and propyl parahydroxybenzoate (0,2 mg/mL), ethanol (0,11 mg/mL).

Contains sweetener (0,5 mg/mL sucralose).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.

Clear, colourless, slightly viscous aqueous solution of pH 3,0 – 4,0 without precipitate, with a raspberry flavour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 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 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 the intake of food or fruit juice (see section 4.5).

Children under 6 years of age and under 20 kg

Currently available data are described in section 4.4, 4.8, 5.1 and 5.2 but no recommendation on a posology can be made. Therefore, ILAXTEN ORAL SOLUTION should not be used in this age group.

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 symptoms.

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 (see section 5.2).

Hepatic impairment

The safety and efficacy of bilastine in hepatically impaired children have not been established. There

is no clinical experience in adult or paediatric patients with hepatic impairment. However, since bilastine is not metabolised 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 (see section 5.2).

Paediatric population

The safety and efficacy of ILAXTEN OS in children under the age of 6 years have not yet been established (see section 4.4).

Method of administration

Oral use.

The bottle of oral solution is provided with a child-proof cap and must be opened as follows: press the plastic screwcap downwards and simultaneously turn anti-clockwise.

The oral solution is accompanied by a measuring cup for dosage with a mark of 4 mL (10 mg bilastine per dosing).

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, ciclosporin, ritonavir or diltiazem, may increase plasma 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.

ILAXTEN ORAL SOLUTION contains methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed).

ILAXTEN ORAL SOLUTION contains up to 0,44 mg of alcohol (ethanol) in each dose (4 mL) which is equivalent to 11 mg/100 mL (0,011 % *w/v*). The amount in 4 mL of ILAXTEN ORAL SOLUTION is equivalent to less than 0,02 mL beer or 0,005 mL wine.
The small amount of alcohol in ILAXTEN ORAL SOLUTION will not have any noticeable effects.

ILAXTEN ORAL SOLUTION contains less than 1 mmol sodium (23 mg) per 4 mL, that is to say essentially sodium free.

4.5 Interaction with other medicinal products and other forms of interaction

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

Food

Food significantly reduces the oral bioavailability of bilastine 20 mg tablets by 30 % and bilastine 2,5 mg/mL oral solution by 20 %.

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). Medicines that are substrates or inhibitors of OATP1A2, such as ritonavir or rifampicin, may likewise have the potential to decrease plasma concentrations of bilastine.

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 to 3-fold. These changes can be explained by interaction with intestinal efflux transporters, since bilastine is a substrate for P-gp and not metabolised (see section 5.2). These changes do not appear to affect the safety profile of bilastine and ketoconazole or erythromycin, respectively. Other medicines that are substrates or inhibitors of P-gp, such as ciclosporin, may likewise have the potential to increase plasma concentrations of bilastine.

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 (see section 5.2) and does not appear to affect the safety profile of bilastine.

Alcohol

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

Lorazepam

Concomitant intake of bilastine 20 mg o.d. and lorazepam 3 mg o.d. 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 medicines, 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 C_{max} due to interactions affect the safety profile of bilastine.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Animal studies did not indicate direct or indirect harmful effects with respect to reproductive toxicity, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of ILAXTEN ORAL SOLUTION during pregnancy.

Breastfeeding

The excretion of bilastine in milk has not been studied in humans. Available pharmacokinetic data in animals have shown excretion of bilastine in milk (see section 5.3).

Fertility

There are no or a limited amount of clinical data. A study in rats did not indicate any negative effect on fertility (see section 5.3).

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 bilastine did not affect driving performance. However, as the individual response to the medicines 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 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 patients 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 (#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 paedriatic population

Adverse events 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)

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

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 phase II and III clinical trials performed during the clinical development included 2 525 adult and adolescent patients treated with different doses of bilastine, of which 1697 received bilastine 20 mg. In these trials 1 362 patients received placebo. 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=1 697) 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 disorders	
Uncommon	Increased appetite
Psychiatric disorders	
Uncommon	Anxiety
	Insomnia
Nervous system disorders	
Common	Somnolence
	Headache
Uncommon	Dizziness
Ear and labyrinth disorders	
Uncommon	Tinnitus

System Organ Class **Frequency**	**Adverse reaction**
	Vertigo
Cardiac disorders	
Uncommon	Right bundle branch block
	Sinus dysrhythmia
	Electrocardiogram QT prolonged
	Other 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

System Organ Class **Frequency**	**Adverse reaction**
	Improved pre-existing condition
	Pyrexia
	Asthenia
Investigations	
Uncommon	Increased gamma-glutamyltransferase
	Increased alanine aminotransferase
	Increased aspartate aminotransferase
	Increased blood creatinine
	Increased blood triglicerides
	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.

The information collected during the post-marketing surveillance has confirmed the safety profile observed during the clinical development.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of ILAXTEN ORAL SOLUTION is important. It allows continued monitoring of the benefit/risk balance of ILAXTEN ORAL SOLUTION. Healthcare professionals are asked to report any suspected adverse reactions via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 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 x 4 days) effect on ventricular repolarisation by a 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 for bilastine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 5.7.1 Antihistaminics

Pharmacotherapeutic group: Antihistamines for systemic use; Other antihistamines for systemic use.

ATC code: R06AX29.

Mechanism of action

Bilastine is a non-sedating, second generation 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 doses.

Clinical efficacy

The efficacy of bilastine has been studied in adults and adolescents. According to guidelines, the proved efficacy in adults and adolescents can be extrapolated to children, having demonstrated that the systemic exposure with 10 mg bilastine in children from 6 to 11 years with a body weight of at least 20 kg is equivalent to the exposure in adults with 20 mg bilastine (see section 5.2). The extrapolation from adult and adolescent data is deemed appropriate for this product as the pathophysiology of allergic rhinoconjunctivitis and urticaria is the same for all age groups.

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.

Older patients (≥ 65 years) included in phase II and III studies showed no difference in efficacy or safety with respect to younger patients.

Clinical safety

In a 12-week controlled clinical trial with children aged 2 to 11 years (total 509 children, 260 treated with bilastine 10 mg: 58 at age 2 to < 6 years, 105 at age 6 to < 9 years and 97 at 9 to < 12 years and 249 treated with placebo: 58 at age 2 to < 6 years, 95 at age 6 to < 9 years and 96 at 9 to < 12 years), at the recommended paediatric dose of 10 mg once daily, the safety profile of bilastine (n=260) was similar to placebo (n=249), with adverse drug reactions seen in 5,8 % and 8,0 % of patients taking bilastine 10 mg and placebo, respectively. Both bilastine 10 mg and placebo showed a slight decrease in somnolence and sedation scores on the Paediatric Sleep Questionnaire during this study, with no statistically significant differences between treatment groups. In these children aged 2 to 11 years, no significant differences in QTc were observed following 10 mg bilastine daily compared with placebo. Quality of Life questionnaires specific for children with allergic rhinoconjunctivitis or chronic urticaria showed a general increase in scores over 12 weeks with no statistically significant difference between the bilastine and placebo arms. The total population of 509 children encompassed: 479 subjects with allergic rhinoconjunctivitis and 30 subjects diagnosed of chronic urticaria. 260 children received bilastine, 252 (96,9 %) for allergic rhinoconjunctivitis and 8 (3,1 %) for chronic urticaria. In analogy, 249 children received placebo, 227 (91,2 %) for allergic rhinoconjunctivitis and 22 (8,8 %) for chronic urticaria.

5.2 Pharmacokinetic properties

Absorption

Bilastine is rapidly absorbed after oral administration with a time to maximum plasma concentration of approximately 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 “Ketoconazole or erythromycin” and “Diltiazem”) and OATP (see section 4.5 “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 metabolised in humans. The mean elimination half-life calculated in healthy volunteers was 14,5 hours.

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) $AUC_{0-\infty}$ increased from 737,4 (± 260,8) (ng·hr/mL in subjects without impairment (GFR: > 80 mL/min/1,73 m^2) to 967,4 (± 140,2) ng·hr/mL in subjects with mild impairment (GFR: 50 – 80 mL/min/1,73 m^2), 1384,2 (± 263,23) ng·hr/mL in subjects with moderate impairment (GFR: 30 – < 50 mL/min/1,73 m^2), and 1708,5 (± 699,0) ng·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 metabolised 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 with 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.

5.3 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 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 1 000 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

Betadex (E459)

Hydroxyethylcellulose

Methyl parahydroxybenzoate (E218)

Propyl parahydroxybenzoate (E216)

Sucralose (E955)

Raspberry flavour (major components: ethanol, triacetin, water, ethyl butyrate, linalyl acetate)

Hydrochloric acid (for pH-adjustment)

Sodium hydroxide (for pH-adjustment)

Water, purified.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

The shelf life after first opening is 6 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Do not use ILAXTEN ORAL SOLUTION if you notice any visible signs of particles.

6.5 Nature and contents of container

ILAXTEN ORAL SOLUTION is packed in an amber glass bottle (Type III glass), sealed with an aluminium screw cap, with tamper-proof closure system and LDPE liner or sealed with a polypropylene cap, with child-proof closure and LDPE liner.

Packs include either a 15 mL or 25 mL polypropylene cup for dosage graduated at 4 mL.

Each bottle contains 120 mL oral solution.

7. HOLDER OF CERTIFICATE OF REGISTRATION

LeBasi Pharmaceuticals (Pty) Ltd

San Domenico Building, Unit 6, Ground Floor

10 Church Street

Durbanville

7551

8. REGISTRATION NUMBER

55/5.7.1/0006

9. DATE OF FIRST AUTHORISATION

04 June 2024

10. DATE OF REVISION OF THE TEXT

Not yet revised.