Professional Information for ILAXTEN

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

ILAXTEN 20 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ILAXTEN tablet contains 20 mg bilastine.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Oval, biconvex, scored, white tablets.

No lines or cracks on tablet surface.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) and idiopathic chronic urticaria (ICU) in adults and adolescents (12 years and over).

4.2 Posology and method of administration

Posology:

Adults and adolescents (12 years and over):

One tablet (20 mg) ILAXTEN once daily and to be swallowed with water.

It is recommended to take the daily dose in one single intake.

ILAXTEN should be taken one hour before or two hours after intake of food or fruit juice (see section 4.5).

Special populations:

Elderly patients:

No dosage adjustments are required in elderly patients (see sections 5.1 and 5.2).

Renal impairment:

No dosage adjustment is required in patients with renal impairment because, despite the increase in AUC, the concentrations of bilastine were within the therapeutic range (see section 5.2).

Hepatic impairment:

There is no clinical experience in patients with hepatic impairment. Since ILAXTEN is not metabolised, hepatic impairment is not expected to increase systemic exposure above the safety margin. Therefore, no dosage adjustment is required in patients with hepatic impairment (see section 5.2).

Paediatric population:

The safety and efficacy in children below 12 years have not yet been established.

Duration of treatment:

Treatment should be discontinued after the symptoms have resolved. For seasonal allergic rhinitis treatment should not exceed 14 days, while for idiopathic chronic urticaria the duration of treatment should not exceed 28 days.

4.3 Contraindications

Hypersensitivity to bilastine or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Renal impairment:

In patients with moderate or severe renal impairment coadministration of ILAXTEN with P-glycoprotein inhibitors, such as e.g. ketoconazole, erythromycin, ciclosporin, ritonavir or diltiazem, may increase plasmatic levels of ILAXTEN and therefore increase the risk of adverse reactions of ILAXTEN (see section 4.5). Therefore, coadministration of ILAXTEN and P-glycoprotein inhibitors should be avoided in patients with moderate or severe renal impairment.

4.5 Interaction with other medicines and other forms of interaction

Interaction with food:

Food significantly reduces the oral bioavailability of ILAXTEN by 30 %.

Interaction with grapefruit juice:

Concomitant intake of ILAXTEN and grapefruit juice decreased ILAXTEN bioavailability by 30 %. The mechanism for this interaction is an inhibition of organic anion-transporting polypeptide 1A2 (OATP1A2), an uptake transporter for which ILAXTEN 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 ILAXTEN.

Interaction with ketoconazole or erythromycin:

Concomitant intake of ILAXTEN and ketoconazole or erythromycin increased ILAXTEN AUC 2-fold and C_{max} 2 – 3-fold. These changes can be explained by interaction with intestinal efflux transporters, since ILAXTEN is a substrate for P-gp and not metabolised by the hepatic enzymes (see section 5.2). These changes do not appear to affect the safety profile of ILAXTEN 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 ILAXTEN.

Interaction with diltiazem:

Concomitant intake of ILAXTEN and diltiazem 60 mg increased C_{max} of ILAXTEN 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 ILAXTEN.

4.6 Fertility, pregnancy and lactation

Pregnancy:

ILAXTEN should not be used during pregnancy. The safety of ILAXTEN in pregnancy has not been established.

There are no or limited amount of data from the use of ILAXTEN in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, parturition or postnatal development (see section 5.3).

Breastfeeding:

ILAXTEN should not be used during lactation or breastfeeding. The safety of ILAXTEN in lactation has not been established.

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

Fertility:

There are no or 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

ILAXTEN can cause drowsiness and dizziness. Patients experiencing drowsiness or dizziness should avoid driving and use of machines.

4.8 Undesirable effects

Summary of the safety profile:

The incidence of adverse events in clinical studies was comparable with the incidence in patients receiving placebo. The adverse drug reactions (ADRs) most commonly reported by patients receiving 20 mg ILAXTEN were headache, somnolence, dizziness and fatigue.

Tabulated summary of adverse reactions:

Adverse drug reactions (ADRs) reported in patients receiving ILAXTEN at recommended doses 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**	**Bilastine** **20 mg** **N=1 697**	**All Bilastine** **Doses** **N=2 525**
Infections and infestations			
Uncommon	***Oral herpes***	2 (0,12 %)	2 (0,08 %)
Metabolism and nutrition disorders			
Uncommon	***Increased appetite***	10 (0,59 %)	11 (0,44 %)
Psychiatric disorders			
Uncommon	***Anxiety***	6 (0,35 %)	8 (0,32 %)
	Insomnia	2 (0,12 %)	4 (0,16 %)

Nervous system disorders			
Common	***Somnolence***	52 (3,06 %)	82 (3,25 %)
	Headache	68 (4,01 %)	90 (3,56 %)
Uncommon	***Dizziness***	14 (0,83 %)	23 (0,91 %)
Ear and labyrinth disorders			
Uncommon	***Tinnitus***	2 (0,12 %)	2 (0,08 %)
	Vertigo	3 (0,18 %)	3 (0,12 %)
Cardiac disorders			
Uncommon	***Right bundle branch block***	4 (0,24 %)	5 (0,20 %)
	Sinus dysrhythmia	5 (0,30 %)	5 (0,20 %)
	Electrocardiogram QT prolonged	9 (0,53 %)	10 (0,40 %)
	Other ECG abnormalities	7 (0,41 %)	11 (0,44 %)
Respiratory, thoracic and mediastinal disorders			
Uncommon	***Dyspnoea***	2 (0,12 %)	2 (0,08 %)
	Nasal discomfort	2 (0,12 %)	2 (0,08 %)
	Nasal dryness	3 (0,18 %)	6 (0,24 %)
Gastrointestinal disorders			
Uncommon	***Upper abdominal pain***	11 (0,65 %)	14 (0,55 %)
	Abdominal pain	5 (0,30 %)	5 (0.20%)
	Nausea	7 (0,41 %)	10 (0.40%)
	Stomach discomfort	3 (0,18 %)	4 (0,16 %)
	Diarrhoea	4 (0,24 %)	6 (0,24 %)
	Dry mouth	2 (0,12 %)	6 (0,24 %)

	Dyspepsia	2 (0,12 %)	4 (0,16 %)
	Gastritis	4 (0,24 %)	4 (0,16 %)
Skin and subcutaneous tissue disorders			
Uncommon	**Pruritus**	2 (0,12 %)	4 (0,16 %)
General disorders and administration site conditions			
Uncommon	***Fatigue***	14 (0,83 %)	19 (0,75 %)
	Thirst	3 (0,18 %)	4 (0,16 %)
	Improved pre-existing condition	2 (0,12 %)	2 (0,08 %)
	Pyrexia	2 (0,12 %)	3 (0,12 %)
	Asthenia	3 (0,18 %)	4 (0,16 %)
Investigations			
Uncommon	***Increased gamma-glutamyl transferase***	7 (0,41 %)	8 (0,32 %)
	Increased alanine aminotransferase	5 (0,30 %)	5 (0,20 %)
	Increased aspartate aminotransferase	3 (0,18 %)	3 (0,12 %)
	Increased blood creatinine	2 (0,12 %)	2 (0,08 %)
	Increased blood triglycerides	2 (0,12 %)	2 (0,08 %)
	Increased weight	8 (0,47 %)	12 (0,48 %)

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) have been observed during the post-marketing period.

Paediatric population:

During the clinical development the frequency, type and severity of adverse reactions in adolescents (12 years to 17 years) were the same seen in adults. The information collected in this population (adolescents) during the post-marketing surveillance has confirmed clinical trial findings.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions of ILAXTEN is important. It allows continued monitoring of the benefit/risk balance of ILAXTEN. Health care providers are requested to report any suspected adverse drug reactions via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.8 Overdose

In clinical trials, after administration of ILAXTEN at doses 10 to 11 times the therapeutic dose (220 mg as single dose or 200 mg/day for 7 days) to healthy volunteers, the frequency of treatment emergent adverse events was two times higher than with placebo. The adverse reactions most frequently reported were dizziness, headache and nausea.

In the event of overdose, symptomatic and supportive treatment is recommended. There is no known specific antidote to ILAXTEN.

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: RO6AX29.

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 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 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 when co-administered with P-gp inhibitors, such as ketoconazole (24 subjects) and erythromycin (24 subjects). Additionally, a thorough QT study including 30 volunteers showed no significant increases in LS means for change in QTcNi from time-matched baseline for the therapeutic dose of bilastine (20 mg) and for the substantial multiple of the maximum therapeutic dose (up to 100 mg) at any time post-dose, neither for any placebo-corrected change in the same parameter. In conclusion, administration of bilastine, in oral doses of 20 and 100 mg, and 20 mg co-administered with ketoconazole, appeared to be safe and well tolerated by healthy male and female subjects in this study.

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. A total of 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.

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 4.5 “Interaction with ketoconazole, erythromycin and diltiazem”) and OATP (see section 4.5 “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} ≥ 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. A PK/PD (pharmacokinetic/pharmacodynamic) model based on data from 310 healthy volunteers (8 429 bilastine plasma concentrations) has been developed (report FF-0014). According to this model, the apparent central distribution volume (Vc/F) was 59,2 L and the apparent peripheral distribution volume (Vp/F) was 30,2 L.

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 ^{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 h.

Linearity:

Bilastine presents linear pharmacokinetic properties 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) 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), 1 384,2 (± 263,23) ngxhr/mL in subjects with moderate impairment (GFR: 30 < 50 mL/min/1,73 m^2), and 1 708,5 (± 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 metabolised in humans. 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 regards to the pharmacokinetics of bilastine in the elderly aged over 65 years compared to the 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

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 medicine concentrations by autoradiography, bilastine does not accumulate in the CNS.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica

Magnesium stearate

Microcrystalline cellulose

Sodium starch glycolate (type A).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

Aluminium/aluminium blister strips in a carton containing 10 or 20 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Menarini South Africa (Pty) Ltd

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8. REGISTRATION NUMBER

52/5.7.1/0120

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 April 2022

10. DATE OF REVISION OF THE TEXT

25 June 2025