BILAZINE 20 mg Tablets
Bilastine

NAME OF THE MEDICINAL PRODUCT
BILAZINE 20 mg Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 20 mg of bilastine.
For the full list of excipients, see section List of excipients

PHARMACEUTICAL FORM
Tablet.
It occurs as a white, oval biconvex scored tablet engraved with "20" on one side and "S" on the other side.
The score line is only to facilitate breaking for ease of swallowing and not to divided into equal doses.

CLINICAL PARTICULARS

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

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. (See section Interaction with other medicinal products and other forms of interaction)

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 (see section Pharmacodynamics and Pharmacokinetic properties).

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 (See section Pharmacokinetic properties).

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 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 Pharmacokinetic properties).

Paediatric population

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

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.

Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in (section List of excipients)

Special warnings and precautions for use

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.

Paediatric population
For summary of safety profile in children under 12 years of age, please refer to the package insert of Bilaxten 10mg Orodispersible tablets or Bilaxten 2.5mg/ml Oral Solution for more information.

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

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 (see section Pharmacokinetic properties). 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 400mg o.d. or erythromycin 500mg 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 (see section Pharmacokinetic properties). 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 Pharmacokinetic properties), 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 C_{max} due to interactions affect the safety profile of bilastine.

Fertility, pregnancy and lactation

Pregnancy: There are no or limited amount of data from the use of bilastine in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, parturition or postnatal development. As a precautionary measure, it is preferable to avoid the use of BILAZINE during pregnancy.

Breast-feeding: The excretion of bilastine in milk has not been studied in humans. Available pharmacokinetic data in animals have shown excretion of bilastine in milk. A decision on whether to continue/ discontinue breast-feeding or to discontinue/abstain from BILAZINE 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. A study in rats did not indicate any negative effect on fertility.

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.

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 phase II and III clinical trials performed during the clinical development included 2525 adult and adolescent patients treated with different doses of bilastine, of which 1697 received bilastine 20 mg. In these trials 1362 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 = 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		**Bilastine 20 mg**	**All Bilastine Doses**	**Placebo**
Frequency	**Adverse Reaction**	**N=1697**	**N=2525**	**N=1362**
Infections and infestations				
Uncommon	***Oral herpes***	2 (0.12%)	2 (0.08%)	0 (0.0%)
Metabolism and nutrition disorders				
Uncommon	***Increased appetite***	10 (0.59%)	11 (0.44%)	7 (0.51%)
Psychiatric disorders				
Uncommon	***Anxiety***	6 (0.35%)	8 (0.32%)	0 (0.0%)
	Insomnia	2 (0.12%)	4 (0.16%)	0 (0.0%)
Nervous system disorders				
Common	***Somnolence***	52 (3.06%)	82 (3.25%)	39 (2.86%)
	Headache	68 (4.01%)	90 (3.56%)	46 (3.38%)

System Organ Class		Bilastine 20 mg	All Bilastine Doses	Placebo
Frequency	**Adverse Reaction**	**N=1697**	**N=2525**	**N=1362**
Uncommon	***Dizziness***	14 (0.83%)	23 (0.91%)	8 (0.59%)
Ear and labyrinth disorders				
Uncommon	***Tinnitus***	2 (0.12%)	2 (0.08%)	0 (0.0%)
	Vertigo	3 (0.18%)	3 (0.12%)	0 (0.0%)
Cardiac disorders				
Uncommon	***Right bundle branch block***	4 (0.24%)	5 (0.20%)	3 (0.22%)
	Sinus arrhythmia	5 (0.30%)	5 (0.20%)	1 (0.07%)
	Electrocardiogram QT prolonged	9 (0.53%)	10 (0.40%)	5 (0.37%)
	Other ECG abnormalities	7 (0.41%)	11 (0.44%)	2 (0.15%)
Respiratory, thoracic and mediastinal disorders				
Uncommon	***Dyspnoea***	2 (0.12%)	2 (0.08%)	0 (0.0%)
	Nasal discomfort	2 (0.12%)	2 (0.08%)	0 (0.0%)
	Nasal dryness	3 (0.18%)	6 (0.24%)	4 (0.29%)
Gastrointestinal disorders				
Uncommon	***Upper abdominal pain***	11 (0.65%)	14 (0.55%)	6 (0.44%)
	Abdominal pain	5 (0.30%)	5 (0.20%)	4 (0.29%)
	Nausea	7 (0.41%)	10 (0.40%)	14 (1.03%)
	Stomach discomfort	3 (0.18%)	4 (0.16%)	0 (0.0%)
	Diarrhoea	4 (0.24%)	6 (0.24%)	3 (0.22%)
	Dry mouth	2 (0.12%)	6 (0.24%)	5 (0.37%)
	Dyspepsia	2 (0.12%)	4 (0.16%)	4 (0.29%)
	Gastritis	4 (0.24%)	4 (0.16%)	0 (0.0%)
Skin and subcutaneous tissue disorders				
Uncommon	***Pruritus***	2 (0.12%)	4 (0.16%)	2 (0.15%)
General disorders and administration site conditions				
Uncommon	***Fatigue***	14 (0.83%)	19 (0.75%)	18 (1.32%)
	Thirst	3 (0.18%)	4 (0.16%)	1 (0.07%)
	Improved pre-existing condition	2 (0.12%)	2 (0.08%)	1 (0.07%)
	Pyrexia	2 (0.12%)	3 (0.12%)	1 (0.07%)
	Asthenia	3 (0.18%)	4 (0.16%)	5 (0.37%)
Investigations				
Uncommon	***Increased gamma-glutamyltransferase***	7 (0.41%)	8 (0.32%)	2 (0.15%)
	Alanine aminotransferase increased	5 (0.30%)	5 (0.20%)	3 (0.22%)
	Aspartate aminotransferase increased	3 (0.18%)	3 (0.12%)	3 (0.22%)
	Blood creatinine increased	2 (0.12%)	2 (0.08%)	0 (0.0%)
	Blood triglicerides increased	2 (0.12%)	2 (0.08%)	3 (0.22%)
	Increased weight	8 (0.47%)	12 (0.48%)	2 (0.15%)

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

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 the post-marketing surveillance has confirmed clinical trial findings.

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.

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 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.

PHARMACOLOGICAL PROPERTIES

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.

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 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 adult 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) $AUC_{0-\infty}$ 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 - <50ml/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.

PHARMACEUTICAL PARTICULARS List of excipients
Silicified Microcrystalline Cellulose
Sodium Starch glycolate
Magnesium Stearate

Incompatibilities
Not applicable.

Shelf life
Please refer to the outer carton box for the expiry date.

Special precautions for storage
Store below 30°C.
Keep the tablets out of reach and sight of children.

Nature and contents of container
The medicinal product is packaged in a blister of 10 tablets. The blisters are packaged in cardboard boxes.

Pack sizes of 30 tablets.

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

NAME AND ADDRESS OF MANUFACTURER
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3.2.2026