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SUMMARY OF PRODUCT CHARACTERISTICS FOR PHARMACEUTICAL PRODUCTS

1 NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

BILAXTEN 20 mg tablets

1.1 Strength

Each tablet contains 20 mg of Bilastine

1.2 Pharmaceutical form

Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 *Qualitative declaration*

Bilastine
Cellulose, microcrystalline
Sodium Starch glycolate type A (derived from potato)
Silica, colloidal anhydrous
Magnesium Stearate

2.2 *Quantitative declaration*

Bilastine	20.0 mg
Cellulose, microcrystalline	103.0 mg
Sodium Starch glycolate type A (derived from potato)	1.0 mg
Silica, colloidal anhydrous	0.5 mg
Magnesium Stearate	0.5 mg

3 PHARMACEUTICAL FORM

Tablet.
Oval biconvex scored white tablets (length 10 mm, width 5 mm).
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1.*Therapeutic indications*

Symptomatic treatment of allergic rhino-conjunctivitis (seasonal and perennial) and urticaria.
BILAXTEN 20 mg<Invented name> is indicated in adults and adolescents (12 years of age and over).

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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 (see section 4.5).

Special populations

Elderly

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 (see section 5.2).

Hepatic impairment

There is no clinical experience in patients with hepatic impairment. Since bilastine is not metabolized and renal clearance is its major elimination route, 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

There is no relevant use of bilastine in children aged 0 to 2 years for the indications of allergic rhino-conjunctivitis and urticaria. The safety and efficacy in children below 12 years have not yet been established.

Duration of treatment:

For allergic rhinitis 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.

4.3.*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.

4.4.*Contraindications*

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

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4.5. *Special warnings and precautions for use*

Paediatric population

Efficacy and safety of bilastine in children under 12 years of age have not been established.

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 reactions of bilastine. Therefore, coadministration of bilastine and P-glycoprotein inhibitors should be avoided in patients with moderate or severe renal impairment.

4.6. *Interaction with other medicinal products and others forms of interaction*

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 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 and ketoconazole or erythromycin increased bilastine AUC 2-fold and Cmax 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 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 and diltiazem 60 mg increased Cmax 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 bilastine was similar to that observed after intake of alcohol and placebo.

Interaction with lorazepam: Concomitant intake of bilastine 20 mg and lorazepam 3 mg for 8 days did not potentiate the depressant CNS effects of lorazepam.

4.7. *Additional information on special populations*

Paediatric population

Interaction studies have only been performed in adults. Extent of interaction with other medicinal products and other forms of interaction is expected to be similar in paediatric population from 12 to 17 years of age.

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4.8. *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 (see section 5.3). As a precautionary measure, it is preferable to avoid the use of <Invented name> 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 (see section 5.3). A decision on whether to discontinue/abstain from <Invented name> 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 (see section 5.3).

4.9.*Effects on ability to drive and use machines*

A study performed to assess the effects of bilastine on the ability to drive demonstrated that treatment with 20 mg did not affect the driving performance. However, patients should be informed that very rarely some people experience drowsiness, which may affect their ability to drive or use machines.

4.10. *Undesirable effects*

a) Summary of the safety profile

The incidence of adverse events in 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 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.

b) Tabulated list of adverse reactions

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)

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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=1697	All Bilastine Doses N=2525
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 arrhythmia	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%)

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System Organ Class Frequency	Adverse reaction	Bilastine 20 mg N=1697	All Bilastine Doses N=2525
	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-glutamyltransferase*	7 (0.41%)	8 (0.32%)
	Alanine aminotransferase increased	5 (0.30%)	5 (0.20%)
	Aspartate aminotransferase increased	3 (0.18%)	3 (0.12%)
	Blood creatinine increased	2 (0.12%)	2 (0.08%)
	Blood triglicerides increased	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.

c) Description of selected adverse reactions

The most frequently reported adverse reactions were two common (somnolence and headache) and two uncommon (dizziness and fatigue). Their frequencies in bilastine vs. placebo were 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.

Almost all the adverse reactions, included in the above table, were observed either in patients treated with bilastine 20 mg or with placebo with a similar incidence.

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

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d) 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.

e) 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.

4.11. 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 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 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.

5 PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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 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.

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

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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.

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. 128 adolescents received bilastine during the clinical studies (81 in double blind studies in allergic rhino-conjunctivitis). A further 116 adolescent subjects were randomised to active comparators or placebo. No differences in efficacy and safety between adults and adolescents were seen.

The European Medicines Agency has deferred the obligation to submit the results of studies with <Invented name> in one subset of the paediatric population in the treatment of allergic rhino-conjunctivitis and the treatment of urticaria (see section 4.2 for information on paediatric use).

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, 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 IC50 ≥ 300 µM, much higher than the calculated clinical plasma Cmax 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.

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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 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) AUC0-∞ increased from 737.4 (±260.8) ngxhr/ml in subjects without impairment (GFR: > 80 ml/min/1.73 m2) to: 967.4 (±140.2) ngxhr/ml in subjects with mild impairment (GFR: 50-80 ml/min/1.73 m2), 1384.2 (±263.23) ngxhr/ml in subjects with moderate impairment (GFR: 30 - <50 ml/min/1.73 m2), and 1708.5 (±699.0) ngxhr/ml in subjects with severe impairment (GFR: < 30 ml/min/1.73 m2). 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.

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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 1000 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

Cellulose, microcrystalline
Sodium Starch glycolate type A (derived from potato)
Silica, colloidal anhydrous
Magnesium Stearate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

5 years.

6.4. Special precautions for storage

Store below 30ºC

6.5. Nature and contents of container

The medicinal product is packaged in a blister, consisting of two parts:
laminate, consisting of oriented polyamide (outer side of laminate), aluminium and PVC (inner side of laminate)
Aluminium foil
The aluminium foil is thermosealed with a heat-seal lacquer (PVC-PVAC copolymer and resins of butylmethacrylate) to the laminate after molding and filling of the tablets.

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Each blister contains 10 tablets. The blisters are packaged in cardboard boxes.
Pack sizes: 10, 20, 30, 40 or 50 tablets.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

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SPAIN

8 MARKETING AUTHORISATION NUMBER

73.027

9 DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

Date of first registration: November 2010

10 DATE OF REVISION OF THE TEXT

Oct 2015

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