SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gosall 20 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg of bilastine.
For the full list of excipients, see section 6.1.

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.
Gosall is indicated in adults and adolescents (12 years of age and over).

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).

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 sections 5.1 and 5.2).

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 5.2).

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 5.2).

Paediatric population

- Children 6 to 11 years of age with a body weight of at least 20 kg
  Bilastine 10 mg orodispersible tablets and bilastine 2.5 mg/mL oral solution are appropriate for administration to this population.

- 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 bilastine should not be used in this age group.

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

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.

4.3 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, 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.

Cases of Electrocardiogram QT prolonged have been reported in patients using bilastine (see sections 4.8, 4.9 and 5.1). Medicinal products that cause QT/QT_C prolongation are suspected to increase the risk of Torsade de pointes.
Therefore, caution should be exercised when administering bilastine to patients who are at increased risk of experiencing QT/QT_C-prolongation. This includes patients with a history of cardiac arrhythmias; patients with hypokalemia, hypomagnesaemia, hypocalcemia; patients with known prolongation of the QT interval or significant bradycardia; patients with concomitant use of other medicinal products associated with QT/QT_C-prolongation.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, 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.

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 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 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 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 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.

4.6 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 Gosall 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 continue / discontinue breast-feeding or to discontinue / abstain from Gosall 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).

4.7 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 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.

4.8 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 N = 1697**	**All Bilastine Doses N = 2525**	**Placebo N = 1362**
Frequency	**Adverse reaction**			
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%)
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%)

System Organ Class		Bilastine 20 mg N = 1697	All Bilastine Doses N = 2525	Placebo N = 1362
Frequency	**Adverse reaction**			
	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%)

*Electrocardiogram QT prolonged have also been reported post marketing.

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.

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 the 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 (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
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)
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 10 mg (n = 291)[#]	Placebo (n = 249)
Frequency	**Adverse Reaction**		
Infections and infestations			
Common	Rhinitis	3 (1.0%)	3 (1.2%)
Nervous system disorders			
Common	Headache	6 (2.1%)	3 (1.2%)
Uncommon	Dizziness	1 (0.3%)	0 (0.0%)
	Loss of consciousness	1 (0.3%)	0 (0.0%)
Eye disorders			
Common	Allergic conjunctivitis	4 (1.4%)	5 (2.0%)
Uncommon	Eye irritation	1 (0.3%)	0 (0.0%)
Gastrointestinal disorders			
Common	Abdominal pain / Upper abdominal pain	3 (1.0%)	3 (1.2%)
Uncommon	Diarrhoea	2 (0.7%)	0 (0.0%)
	Nausea	1 (0.3%)	0 (0.0%)
	Lip swelling	1 (0.3%)	0 (0.0%)
Skin and subcutaneous tissue disorders			
Uncommon	Eczema	1 (0.3%)	0 (0.0%)
	Urticaria	2 (0.7%)	2 (0.8%)
General disorders and administration site conditions			
Uncommon	Fatigue	2 (0.7%)	0 (0.0%)

[#]260 children exposed in the clinical safety study, 31 children exposed in the pharmacokinetic study.

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.

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 http://www.medicinesauthority.gov.mt/adrportal.

4.9 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 QT_C 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/QT_C cross-over study" involving 30 healthy adult volunteers did not show significant QT_C 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.

5. 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 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 and safety
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 QT_C 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.
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 a 12-week controlled clinical trial with children aged 2-11 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 QT_C 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.

The European Medicines Agency has waived the obligation to submit the results of studies with bilastine in all subsets of the paediatric population below 2 years of age (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 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 $IC_{50} \geq 300$ 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 ^{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
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 - <50 mL/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.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. 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 x 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.

5.3 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

This medicinal product does not require any special storage conditions.

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.
Each blister contains 10 tablets. The blisters are packaged in cardboard boxes.
Pack sizes: 20, 30, 40 or 50 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. MARKETING AUTHORISATION HOLDER

Menarini International Operations Luxembourg S.A.,
1, Avenue de la Gare, L-1611 Luxembourg

8. MARKETING AUTORISATION NUMBER(S)

MA204/00501

9. DATE OF FIRST AUTHORISATION /RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st February 2012
Date of latest renewal: 7th October 2015

10. DATE OF REVISION OF THE TEXT

15 April 2025