GOSALL

BILASTINE

"EPITOMIZES THE EVOLUTION OF RESEARCH ON ANTIHISTAMINES CONCERNING BOTH EFFICACY AND SAFETY[1]"

MCI 2951906MT
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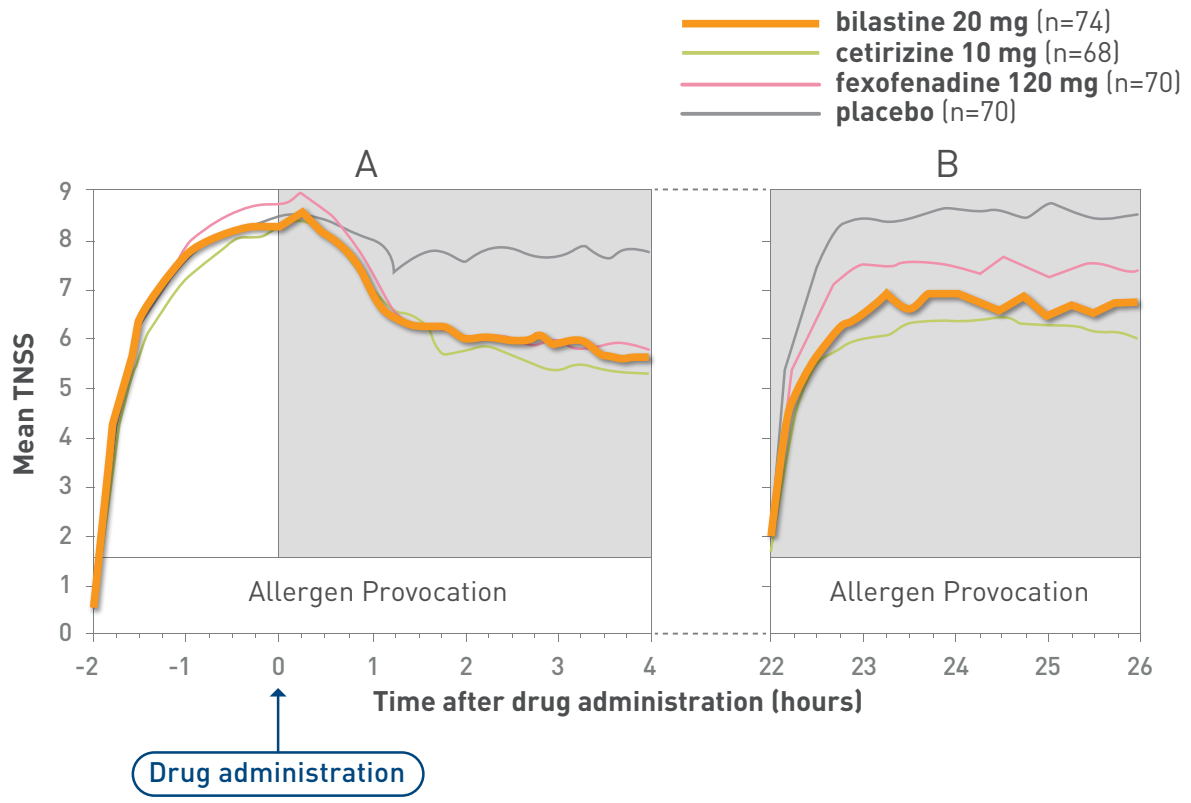
MENARINI group

GOSALL:

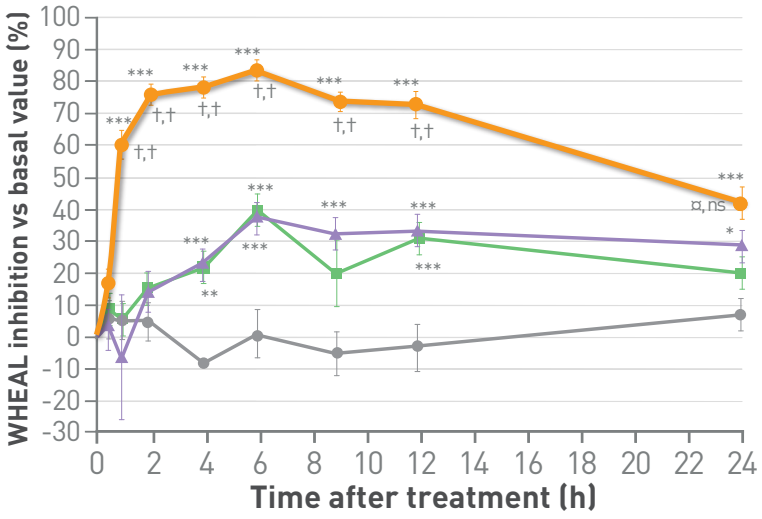
Bilastine had a rapid onset of action, within 1 hour, and a long duration of action, greater than 26 hours[2]



Adapted from Figure 1 in (2). Single centre, double-blind, randomised, placebo-controlled, balanced four-treatment, four-period crossover phase II study in 75 individuals with asymptomatic seasonal allergic rhinitis. The primary objective of this study was to compare the effects of a single dose of bilastine 20 mg with those of cetirizine 10 mg, fexofenadine 120 mg, and placebo on the TNSS in subjects with SAR exposed to an allergen for 6 h in the VCC. The time course of the effects of bilastine 20 mg, cetirizine 10 mg, fexofenadine 120 mg, and placebo against the allergen-induced increase in total nasal symptom score (TNSS) assessed every 15 min in the Vienna Challenge Chamber. Subjects were exposed to 6 h of allergen provocation on day 1 (A) followed by a further 4 h of provocation with the same concentration of allergen on day 2 (B). The speed of onset of action was 1 h for all three drugs (P<0.05 vs. placebo). There were no statistically significant differences between the effects of the three antihistamines. Comparisons of the effects of the three antihistamines revealed that, although there was no statistical difference between the activities of bilastine and cetirizine, both bilastine (P = 0.0012) and cetirizine(P<0.001) were significantly more active than fexofenadine between 22 and 26 h after dosing suggesting that they have a longer duration of action.

ONSET OF ACTION

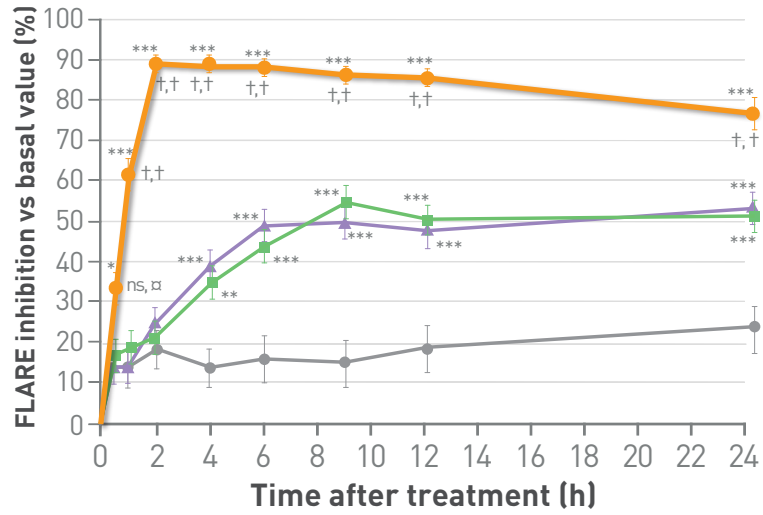
Compared with desloratadine 5 mg and rupatadine 10 mg, Bilastine had the fastest onset of action[3] Bilastine produced the greatest inhibition of wheal and flare response[3]



WHEAL

Treatment *vs.* Placebo: *: p<0.05; **: p<0.01; ***: p<0.001

Bilastine *vs.* Desloratadine, Bilastine *vs.* Rupatadine: ¤ : p<0.01; † : p<0.001



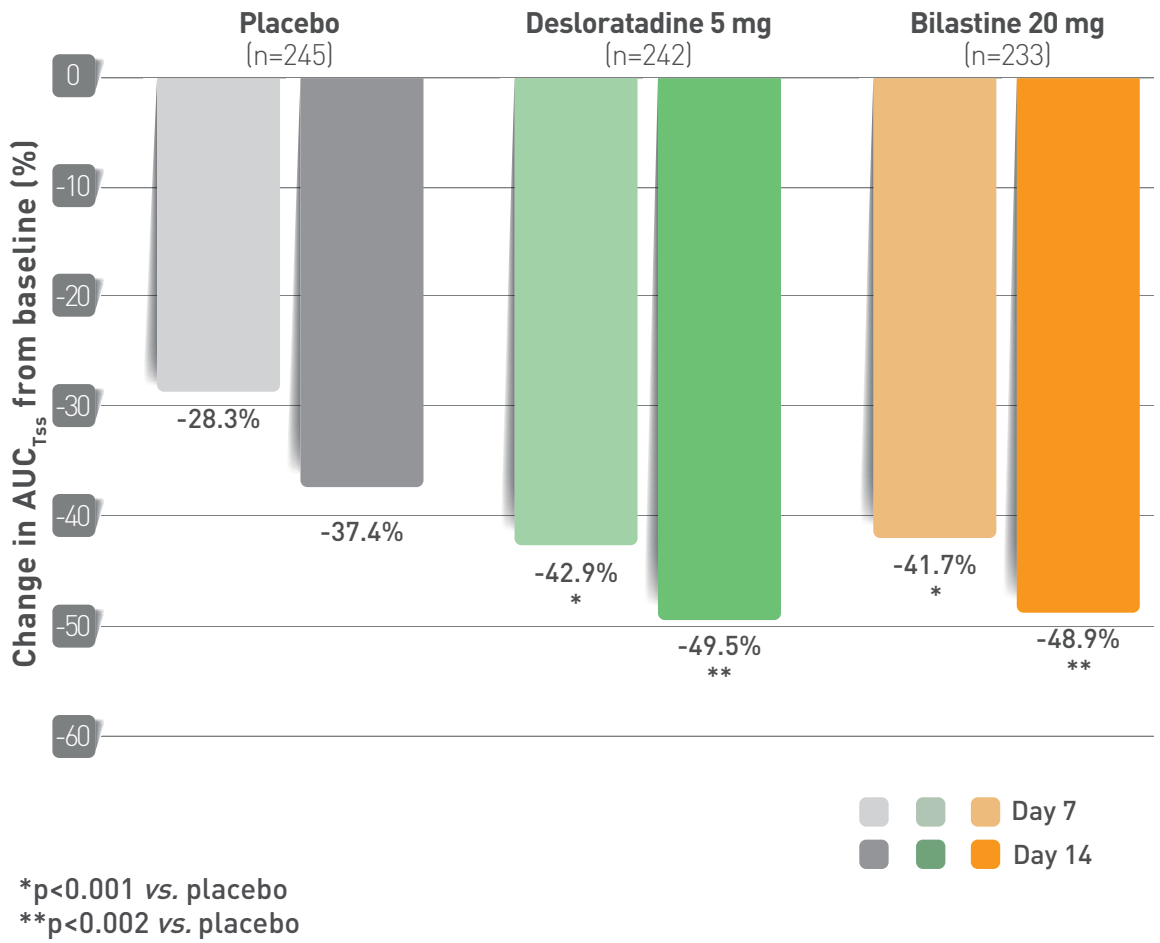
FLARE

Treatment *vs.* Placebo: *: p<0.05; **: p<0.01; ***: p<0.001

Bilastine *vs.* Desloratadine, Bilastine *vs.* Rupatadine: ¤ : p<0.01; † : p<0.001

*Adapted from Figures 1 and 2 in (3). Percentage inhibition of wheal area (mean ± SEM, up) and percentage inhibition of flare area (mean ± SEM, down) after crossover treatment with single oral doses of bilastine 20 mg, desloratadine 5 mg, rupatadine 10 mg and placebo. Treatment vs. placebo = *: p<0.05; **: p<0.01; ***: p<0.001; Bilastine vs. desloratadine, Bilastine vs. rupatadine = ¤ : p<0.01; † : p<0.001. Crossover, randomized, double-blind, placebo-controlled clinical study in 24 healthy volunteers aged 18-40 years who received single doses of bilastine 20 mg, desloratadine 5 mg, rupatadine 10 mg and placebo. Primary outcome measure was the percentage reduction in wheal and flare areas after each active treatment compared with corresponding basal values. Wheal and flare responses induced by intradermal injection of histamine 5 µg were evaluated before treatment (basal value) and at 0.5, 1, 2, 4, 6, 9, 12 and 24 hours after treatment. Significant differences in percentage reduction of the wheal response versus placebo were observed from 1 to 24 hours (all p < 0.001) with bilastine; from 4 to 12 hours (p < 0.001) and at 24 hours (p = 0.022) with rupatadine; and at 4 hours (p = 0.002), 6 hours (p < 0.001) and 12 hours (p = 0.001) with desloratadine. Desloratadine did not show a significant difference relative to placebo at 24 hours (p > 0.05), indicating a duration of activity less than 24 hours. Significant differences in percentage reduction of the flare response versus placebo were observed at 0.5 hours (p = 0.023) and all time points to 24 hours (p < 0.001) with bilastine; at 4 hours and all time points to 24 hours with rupatadine (p < 0.001); and at 4 hours (p = 0.002) and all time points to 24 hours (p < 0.001) with desloratadine.*

GOSALL:
Bilastine effectively relieved the including nasal and

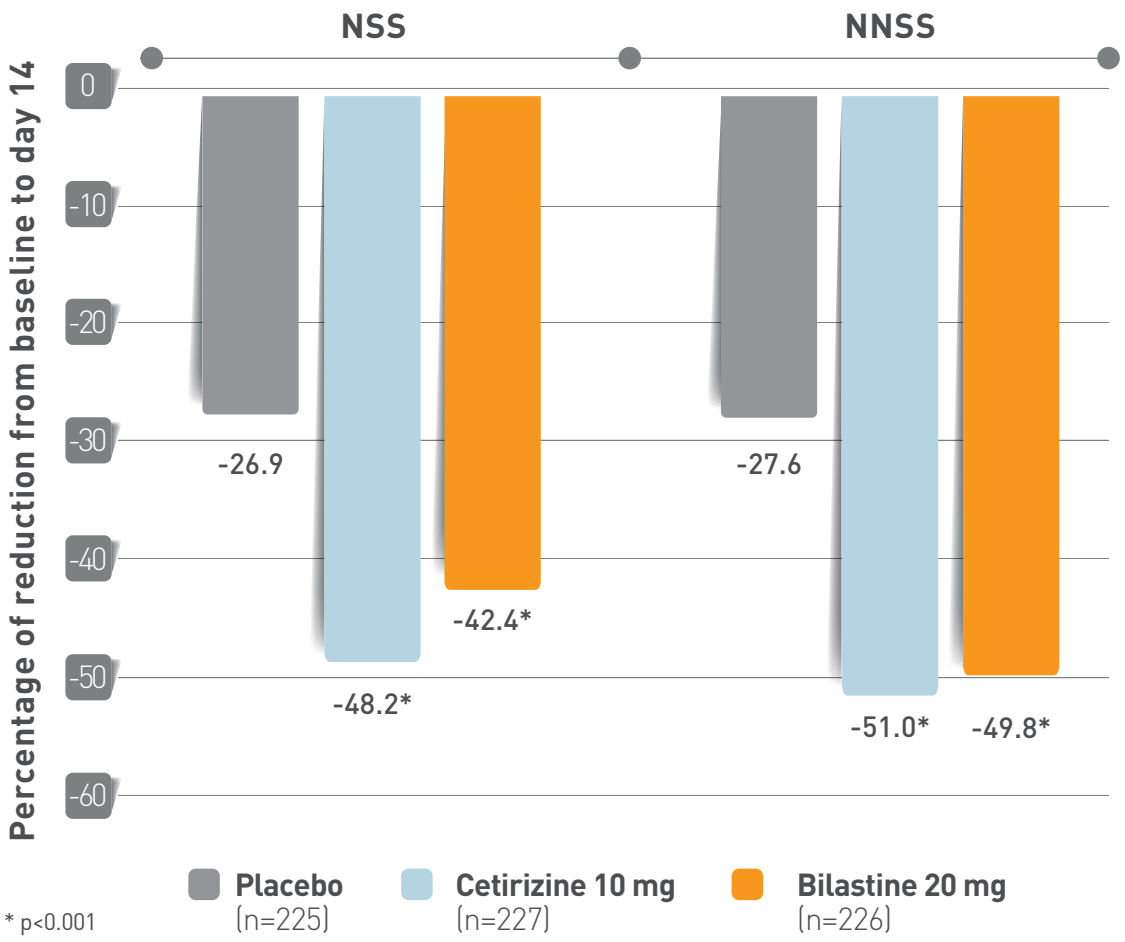


*p<0.001 *vs.* placebo
**p<0.002 *vs.* placebo

Data from Table 2 in (4). ***Effect of treatment on rhinitis total symptom score (TSS)****. This randomized, double blind, placebo-controlled, parallel-group multicentre study evaluated the effect of 2 weeks' treatment with bilastine 20 mg, desloratadine 5 mg or matched placebo once daily, in 12–70 years old symptomatic patients with seasonal allergic rhinitis. The AUC of TSS, the primary outcome measure, was decreased to a significantly greater extent in the bilastine 20 mg treated group compared with placebo-treated group (P < 0.001). Assessment of change from baseline in TSS at days 7 and 14 also indicated significantly greater improvements in the symptoms of rhinitis after 7 and 14 days of treatment with bilastine 20 mg compared with placebo (P < 0.001 and <0.002, respectively). Desloratadine 5 mg-induced decreases in AUC of TSS and change from baseline in TSS at days 7 and 14 were also significantly greater compared with placebo (P<0.001 to <0.002), but these were not significantly different compared with bilastine 20 mg. AUC, area under the curve.*

EFFICACY IN AR

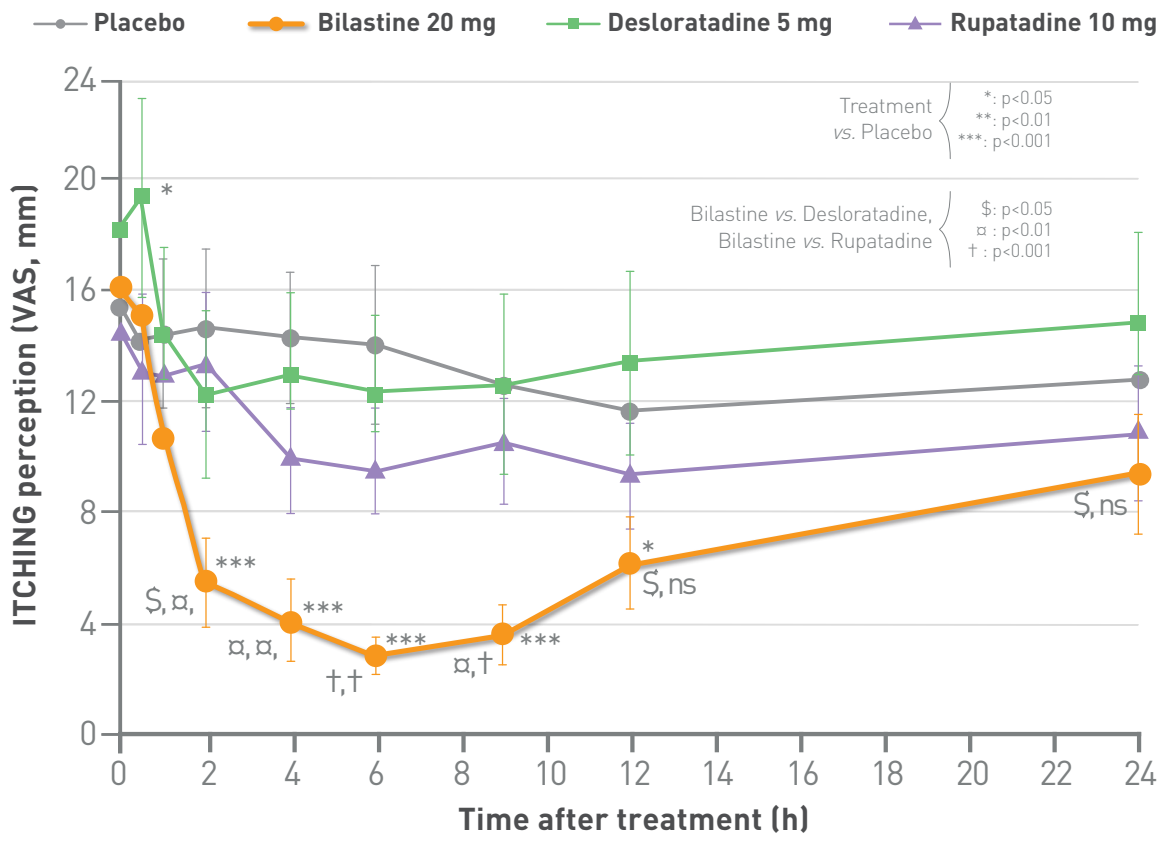
symptoms of allergic rhinoconjunctivitis, non-nasal symptoms[4]



*Adapted from data in (5). Percentage decrease from baseline in nasal symptom score (NSS) and nonnasal symptom score (NNSS) in a double-blind, placebo-controlled study of bilastine versus cetirizine in patients with seasonal allergic rhinitis (n=683) randomized to bilastine 20 mg, cetirizine 10mg or placebo, once daily for 14 days[6]. The primary efficacy parameter was the area under the curve (AUC) of the reflective total symptoms score (TSS) from day 0 (D0) to day 14 (D14) based on the patient's evaluation of symptom severity over the past 12 h. The TSS was calculated daily as the sum of four nasal (rhinorrhoea, congestion, itching and sneezing) and three non-nasal (ocular symptoms: tearing, redness and itching) symptom scores. Bilastine and cetirizine displayed similar efficacy: both compounds significantly reduced total symptom score + non nasal symptom score, relative to placebo. The percentage decrease from baseline in NSS was significantly greater (P<0.001) with bilastine and cetirizine. *P=0.001 versus placebo. The primary efficacy measure was the area under curve (AUC) of reflective TSS over 14 days of treatment (TSS-AUC0-14 days).*

GOSALL:

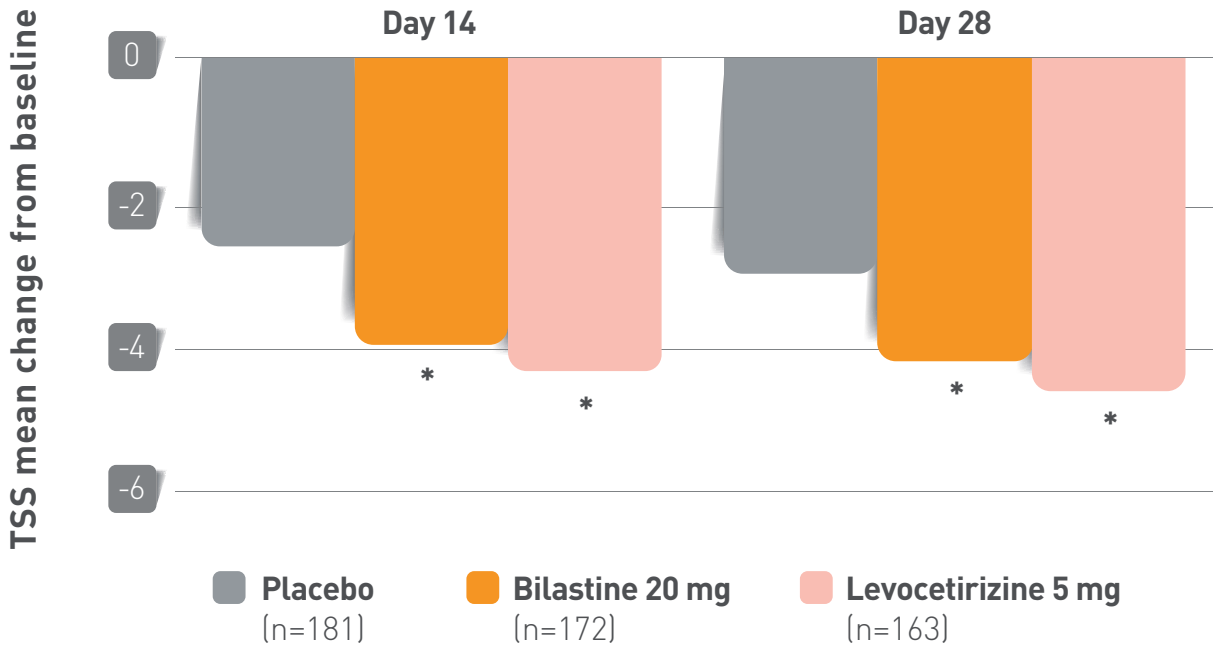
Bilastine, but not desloratadine or rupatadine, significantly reduced itching sensation compared with placebo between 2-12 hours[3]



*Adapted from Figure 3 in (3). Itching perception scores recorded on a 0-100 mm visual analog scale (VAS) (mean ± SEM) after crossover treatment with single oral doses of bilastine 20 mg, desloratadine 5 mg, rupatadine 10 mg and placebo. Treatment vs. placebo = *: p<0.05; **: p<0.01; ***: p<0.001; Bilastine vs. desloratadine, Bilastine vs. rupatadine = $: p<0.05; ¤ : p<0.01; † : p<0.001. Crossover, randomized, double-blind, placebo-controlled clinical study in 24 healthy volunteers aged 18-40 years who received single doses of bilastine 20 mg, desloratadine 5 mg, rupatadine 10 mg and placebo. Primary outcome measure was the percentage reduction in wheal and flare areas after each active treatment compared with corresponding basal values. Wheal and flare responses induced by intradermal injection of histamine 5 µg were evaluated before treatment (basal value) and at 0.5, 1, 2, 4, 6, 9, 12 and 24 hours after treatment. The maximum reduction in itching scores was obtained with bilastine. Compared with baseline, VAS scores were significantly lower with bilastine at all time points from 1 to 24 hours (1 hour: p=0.007; 2 to 9 hours: p < 0.001; 12 hours: p=0.001; 24 hours: p=0.008). Desloratadine significantly reduced itching scores versus baseline from 1 to 12 hours (1 hour: p=0.041; 2 hours: p=0.002; 4 hours: p=0.003; 6 hours: p=0.012; 9 hours: p=0.040; 12 hours: p = 0.045). Rupatadine significantly decreased itching perception with respect to baseline at 4 hours (p=0.032), 6 hours (p=0.038) and 12 hours (p=0.030). Compared with placebo, significant differences in VAS scores were observed from 2 to 12 hours with bilastine (2 hours: p=0.001; 4 and 6 hours: p < 0.001; 9 hours: p=0.001; 12 hours: p=0.018), whereas scores with desloratadine and rupatadine did not differ significantly from placebo at any evaluation time point.*

EFFICACY IN CU

Bilastine 20 mg/day was more effective than placebo and equivalent to levocetirizine 5 mg in CU[6, 7]

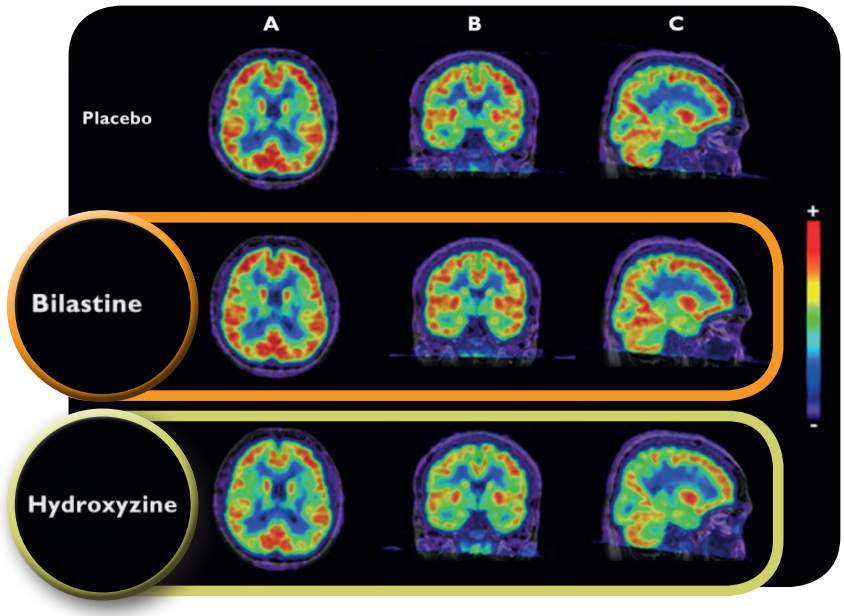


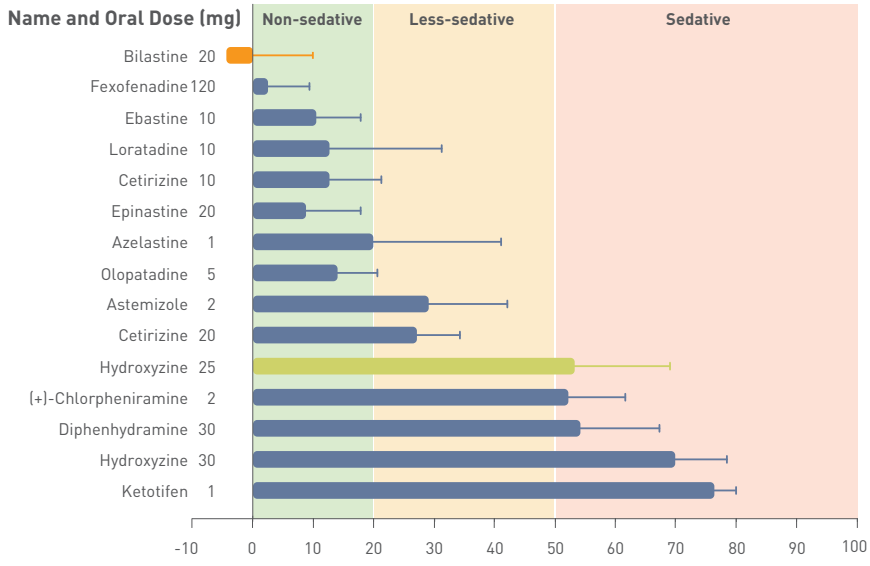
* p<0.001 vs. placebo

Figure based on Table 2 in (7). The mean change from baseline (defined as the mean of the 3 days with maximum symptoms before randomization) in the patients' reflective daily TSS (Total Symptoms Score) over the 28-day treatment period, the primary efficacy measure, was significantly greater for bilastine 20 mg and levocetirizine 5 mg treated groups compared with placebo treated group (P < 0.001 for bilastine and levocetirizine vs placebo), but not significantly different between the active treatment groups. Multi-centre, double-blind, randomised, placebo-controlled study in 525 chronic urticaria patients with moderate-to-severe symptoms who were treated with bilastine 20 mg, levocetirizine 5 mg, or placebo for 28 days.[7]

GOSALL 20 MG

has the lowest cerebral histamine H_1 receptor occupancy compared with the other second-generation anti-H_1[8]





*Crossover trial (phase I, double-blind) designed **to determine H_1 receptor occupancy (H_1RO) in the brain** in 12 healthy male volunteers.*

***Upper panel: Adapted from Figure 3 in (9).** Co-registered Magnetic resonance image and [^{11}C]-doxepin* positron emission tomography images after single dose administration of placebo, bilastine (20 mg) and hydroxyzine (25 mg) (9). Scale + to –: from maximum to minimum binding potential values. Horizontal (A), coronal (B) and sagittal (C) plane.*

***Lower panel: Adapted from Figure 3 in (8).** Positron emission tomography (PET) data (mean ± SD). Percentage brain histamine H_1-receptor occupancy of orally administered antihistamines. Data shown in orange and light green were obtained from (9). * [^{11}C] **doxepin** is radiotracer of choice because of its **high affinity to H_1 receptors**[11].*

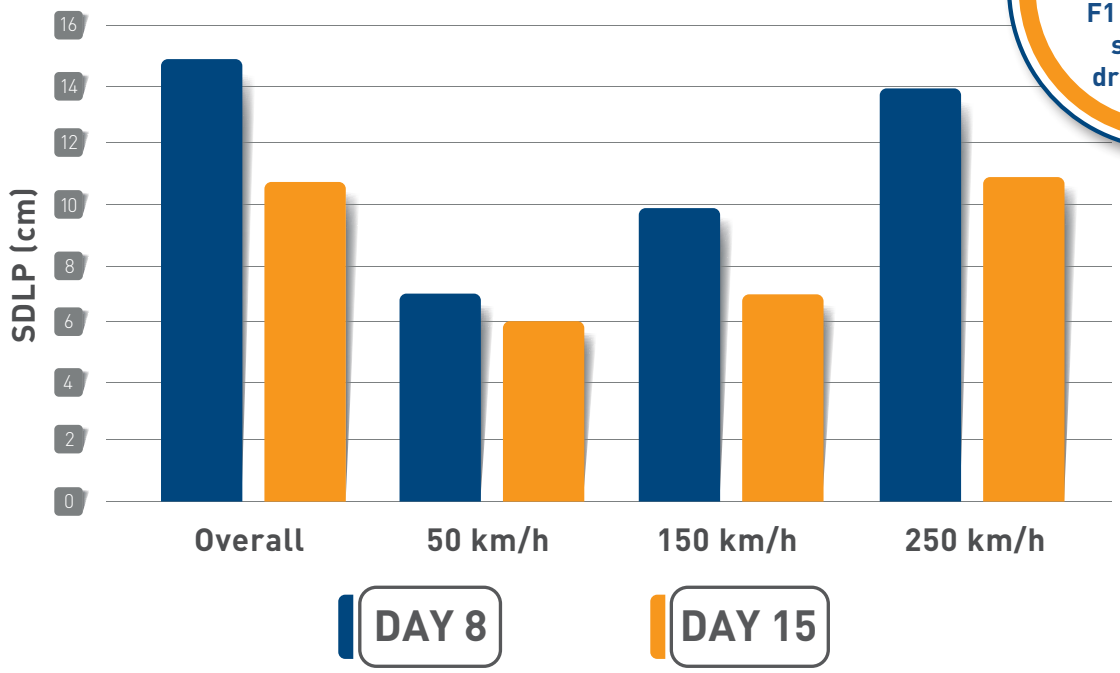
> Among the non-sedating antihistamines, **Bilastine** has been classified as **non-brain penetrating antihistamine**[10#]

#Together with fexofenadine

GOSALL SAFETY PROFILE

No negative effects of bilastine on driving performance even at high speed[12#]

First study in allergic outpatients performing a F1 high speed simulator driving test[12]



Data from Table 2 in (12). ***Standard Deviation of Lateral Position (SDLP, Primary Endpoint****, mainly assessing attention capacities). Phase IV, interventional, prospective, mono-centric, single arm, open-label trial. Eighteen outpatients affected by allergic rhinitis and/or chronic urticaria, able to perform a preliminary driving test on F1 simulator were considered (V-1). First, the patients had a screening visit to assess their eligibility (V0). Visit 1 (V1), at the end of placebo before bilastine treatment and Visit 2 (V2), at the end of bilastine treatment. The primary variable parameter was* ***the ability to maintain the vehicle in a central position at different speeds*** *(50, 150, and 250 km/h).*

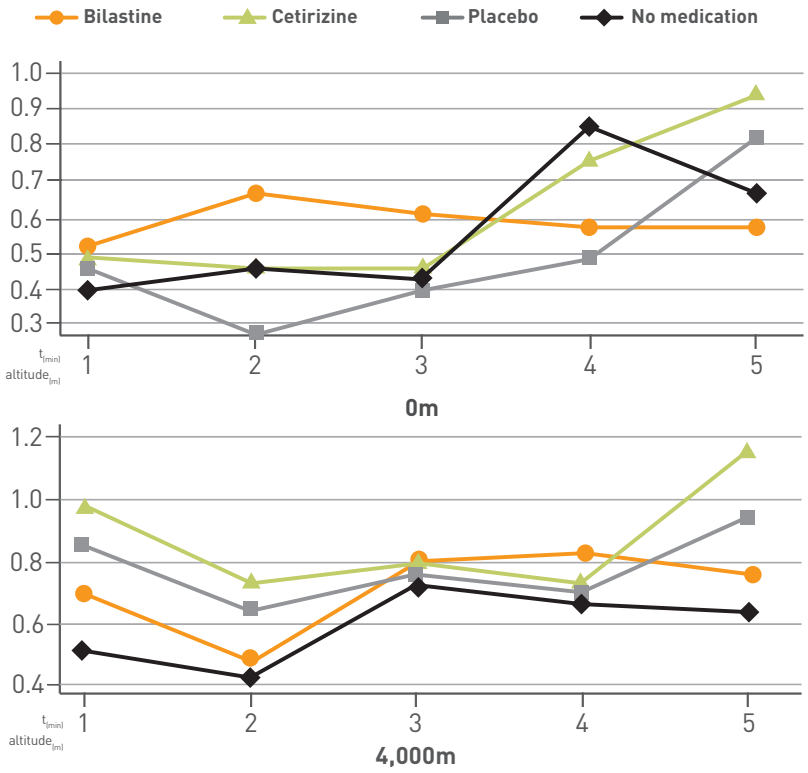
> **Bilastine did not have any negative effect on the ability to maintain the requested path, a constant speed as well as on attention and reactivity levels, even in extreme driving conditions[12]**

#However, patients should be informed that very rarely some people experience drowsiness, which may affect their ability to drive or use machines[13]

GOSALL SAFETY PROFILE

No impairment of tested abilities in comparison with the control groups either at ground level or at 4,000 m altitude[14]

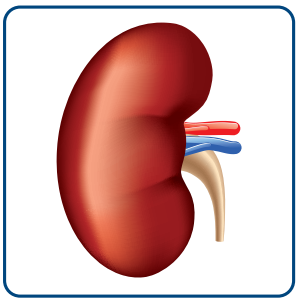
Exposure to hypobaric hypoxia[14]



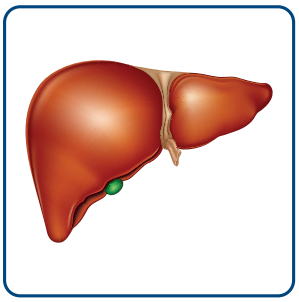
*Adapted from Figure 5 in (14).Displaying mean values of error counts of distributive attention test at different altitudes (ground level, upper panel; 4,000 m, lower panel) in a minutal timeframe. Randomised, placebo-controlled, double-blind, single-center, four-period, crossover study comparing the effect of bilastine 20 mg to cetirizine 10 mg and placebo (20 mg pyridoxine) in **33 healthy volunteers at ground level and at 4,000 m altitude simulated hypobaric chamber**. Levels of vigilance, ultrashort memory, combined distributive attention, monotony tolerance and peripheral blood oxygen saturation were assessed.*

> Bilastine does not significantly affect the performance at any of the test altitudes in healthy adult volunteers, in comparison with placebo and drug-free controls, in functions necessary for piloting an aircraft, such as ultra-short visual memory, combined distributive attention and monotony tolerance[14]

SPECIAL POPULATION



No dosage adjustment is required in patients with renal impairment[13, †]



No dosage adjustment is required in patients with hepatic impairment[13]

No dosage adjustments are required in elderly patients[13]

Bilastine 20 mg once daily did not enhance the effects of alcohol or CNS sedatives (lorazepam)[1, 13]

†Co-administration of bilastine and p-glycoprotein inhibitors should be avoided in patients with moderate or severe renal impairment[13]

REFERENCES

1. *Ridolo E, et al. Bilastine: New insight into antihistamine treatment. Clin Mol Allergy. 2015;13:1.*
2. *Horak F, et al. The effects of bilastine compared with cetirizine, fexofenadine, and placebo on allergen-induced nasal and ocular symptoms in patients exposed to aeroallergen in the vienna challenge chamber. Inflamm Res. 2010;59:391-398.*
3. *Antonijoan R, et al. Comparative efficacy of bilastine, desloratadine and rupatadine in the suppression of wheal and flare response induced by intradermal histamine in healthy volunteers. Curr Med Res Opin. 2016:1-23.*
4. *Bachert C, et al. Comparison of the efficacy and safety of bilastine 20 mg vs desloratadine 5 mg in seasonal allergic rhinitis patients. Allergy. 2009;64:158-165.*
5. *Kuna P, et al. Efficacy and safety of bilastine 20 mg compared with cetirizine 10 mg and placebo for the symptomatic treatment of seasonal allergic rhinitis: a randomized, double-blind, parallel-group study. Clin Exp Allergy, 2009 Sep;39(9):1338-47.*
6. *Jauregui I, et al. Bilastine for the treatment of urticaria. Expert Opin Pharmacother. 2013;14:1537-1544.*
7. *Zuberbier T, et al. Comparison of the efficacy and safety of bilastine 20 mg vs levocetirizine 5 mg for the treatment of chronic idiopathic urticaria: A multi-centre, double-blind, randomized, placebo-controlled study. Allergy. 2010;65:516-528.*
8. *Jauregui I, et al. Bilastine: A new antihistamine with an optimal benefit-to-risk ratio for safety during driving. Expert Opin Drug Saf. 2016;15:89-98.*
9. *Farrè M, et al. Bilastine vs. Hydroxyzine: Occupation of brain histamine h1 -receptors evaluated by positron emission tomography in healthy volunteers. Br J Clin Pharmacol. 2014;78:970-980.*
10. *Kawauchi H et al. Antihistamines for Allergic Rhinitis Treatment from the Viewpoint of Nonsedative Properties. Int J Mol Sciences 2019; 20: 213.*
11. *Suzuki A, et al.Use of reference tissue models for quantification of histamine H 1 receptors in human brain by using positron emission tomography and [11C]doxepin. Annals Nucl Med 2005; 19: 425-433.*
12. *Demonte A, et al. Bilastine safety in drivers who need antihistamines: new evidence from high-speed simulator driving test on allergic patients. Eur Rev Med Pharmacol Sci 2018; 22: 820-828*
13. *Gosall. Summary of product characteristics. Last revision of the text: 01/2017.*
14. *Reményi A', et al. Comparative study of the effect of bilastine and cetirizine on cognitive functions at ground level and at an altitude of 4,000 m simulated in hypobaric chamber: a randomized, double-blind, placebo-controlled, cross-over study. Exp Opin Drug Saf 2018; 7:859-868.*
15. *Scaglione F. Safety profile of bilastine: 2nd generation h1-antihistamines. Eur Rev Med Pharmacol Sci. 2012;16:1999-2005.*
16. *Jauregui I, et al. Bilastine and quality of life. J Investig Allergol Clin Immunol. 2011; 21 Suppl 3: 16-23.*
17. *Conen S, et al. Acute and subchronic effects of bilastine (20 and 40 mg) and hydroxyzine (50 mg) on actual driving performance in healthy volunteers. J Psychopharmacol. 2011;25:1517-1523*
18. *Valk PJ, et al. Cognitive Performance Effects of Bilastine 20 mg During 6 Hours at 8000 ft Cabin Altitude. Aerosp Med Hum Perform. 2016;87:622-7.*
19. *Wang XY, et al. Treatment of allergic rhinitis and urticaria: A review of the newest antihistamine drug bilastine. Ther Clin Risk Manag. 2016;12:585-597.*

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bilastine 20 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg of bilastine.

For a 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).

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 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.

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 special 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.

4.5 Interaction with other medicinal products and other 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 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 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.

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.

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.

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 animals. Available pharmacokinetic data in animals have shown excretion of bilastine in milk (see section 5.3). A decision on whether to discontinue/abstain from Gosall therapy must be made taking into account the benefit of breast-feeding to the child and the benefit of bilastine therapy to 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 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.

4.8 Undesirable effects

Summary of 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.

Tabulated summary 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)

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%)
	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 and tachycardia* have been observed during the post-marketing period.

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.

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 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 ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal.

4.9 Overdose

Information regarding acute overdose 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 (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 R06AX29.

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 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 Gosall 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 "4.5 Interaction with ketoconazole, erythromycin and diltiazem") and OATP (see "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 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 14.5h.

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) 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), 1384.2 (±263.23) ngxhr/ml in subjects with moderate impairment (GFR: 30 - <50 ml/min/1.73 m^2), and 1708.5 (±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 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 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.

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 the container

This 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: 10, 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

MA204/00501

9. DATE OF FIRST AUTHORISATION /RENEWAL OF AUTHORISATION

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

10. DATE OF REVISION OF THE TEXT

01/2017

GOSALL

Effective for the symptomatic treatment of **allergic rhinoconjunctivitis and urticaria**[13,15]

Rapid onset of action and a **long duration** of effect[2]

One of the lowest rates of brain H_1 receptor occupancy *vs.* other 2nd generation H_1-antihistamines[8]

Contributes to **improve the health-related quality of life** in patients with both allergic rhinitis and CU[16]

Does not enhance the effects of alcohol or lorazepam[8,13]

Interferes neither with driving ability nor with tasks related to flying[12,14,17,18#]

Does not interact with the cytochrome P450 system[19*]

No dosage adjustments are required in patients with hepatic or renal impairment[13, †]

Therapeutic indications[13]
Symptomatic treatment of allergic rhinoconjunctivitis (seasonal and perennial) and urticaria.

Posology and method of administration[13]

Adults and adolescents (12 years of age and over): 20 mg (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.

Please be informed that the contents of this material may be used only if compliant with local laws and regulations TO WHOM IT MAY CONCERN - Please insert local updated SmPC if required by local laws and regulations or local competent regulatory authorities. INFORMATION FOR PHYSICIANS - Please do not hesitate to request a copy of the SmPC to our local representative.

**in vitro* studies[13]

† *Co-administration of bilastine and p-glycoprotein inhibitors should be avoided in patients with moderate or severe renal impairment*[13]

 # However, patients should be informed that very rarely some people experience drowsiness, which may affect their ability to drive or use machines[13]

MENARINI group

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