

Open-label safety assessment of bilastine in elderly patients with allergic rhinoconjunctivitis and/or urticaria

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ABSTRACT

Background: Bilastine is an H₁-antihistamine approved for symptomatic treatment of patients with allergic rhinoconjunctivitis or urticaria. The safety profile of bilastine in clinical trials of allergic rhinoconjunctivitis or urticaria, assessed by type and frequency of adverse events (AE), was similar to that of placebo.

Objective: As part of the risk management plan for bilastine, the safety profile of bilastine in the elderly was assessed.

Methods: A prospective, multicenter, observational, open-label, 3-month follow-up study was performed to assess the safety profile of bilastine 20 mg in patients aged ≥ 65 years with allergic rhinoconjunctivitis and/or urticaria.

Results: A total of 74 of 146 patients (50.7%) reported 129 treatment-emergent AEs (TEAE) during the study period. The incidence of TEAEs was low, with monthly and quarterly rates of 0.29 (95% confidence intervals [CI], 0.229–0.367) and 0.88 (95% CI, 0.688–1.100), respectively. Monthly and quarterly incidence rates were 0.04 (95% CI, 0.016–0.082) and 0.12 (95% CI, 0.048–0.246), respectively, for related TEAEs (eight TEAEs in seven patients) and were 0.02 (95% CI, 0.003–0.048) and 0.05 (95% CI, 0.010–0.143), respectively, for serious TEAEs (five TEAEs in three patients). All serious TEAEs were considered to be unrelated to bilastine.

Conclusion: Bilastine 20 mg showed a favorable safety profile with a low incidence of TEAEs in patients aged ≥ 65 years. The results were in accordance with the known safety profile of bilastine 20 mg and incidence of AEs reported in previous studies and described in the approved summary of product characteristics.

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Allergic rhinoconjunctivitis is a common disorder that affects 10 to 40% of the population and that occurs in people of all ages. Allergic rhinoconjunctivitis represents a significant burden because it impairs patients' quality of life, sleep, and work performance, and is a major risk factor for poor asthma control.^{1–3} The Allergic Rhinitis and its Impact on Asthma guidelines³ were developed to assist the treatment of patients with allergic rhinoconjunctivitis and were recently updated. In patients with (intermittent or persistent) allergic rhinoconjunctivitis, the Allergic Rhinitis and its Impact on Asthma guidelines recommend the use of modern second-generation oral H₁-antihistamines that do not cause sedation and do not interact with cytochrome

P450.³ These recommendations place a relatively high value on reducing the undesirable effects associated with the use of first-generation oral H₁-antihistamines.³

Urticaria, or hives, is a common disorder characterized by the appearance of edema and erythematous pruritic patches (wheals and flare), which are the consequence of mast cell degranulation. The lifetime prevalence of acute urticaria is $\sim 20\%$ and that of chronic urticaria is 1.8%. The underlying causes of persistent or chronic urticaria are known in only $\sim 30\%$ of cases; both immunologic and nonimmunologic precipitants have been described.^{4–7} In common with allergic rhinoconjunctivitis, chronic urticaria has a substantial negative influence on patients' quality of life and adversely affects objective functioning and subjective well-being.^{4,6,8–10} International guidelines recommend modern second-generation H₁-antihistamines over first-generation H₁-antihistamines as a first-line treatment of urticaria, especially in the elderly, because of their superior safety profile.⁶ The recommendation to increase, by up to fourfold, the standard dose of second-generation H₁-antihistamines as second-line treatment of urticaria⁶ further emphasizes the need for excellent safety.

Bilastine is a safe and effective nonsedating, second-generation H₁-antihistamine for symptomatic treatment of patients with allergic rhinoconjunctivitis and

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urticaria, and approved in 2010 as a 20-mg once daily dose in patients >12 years of age,¹¹ and, in 2017, as a 10-mg once daily dose in children aged 6 to 11 years with a body weight of at least 20 kg.¹² Bilastine is a potent and highly selective H₁-antihistamine.^{13,14} It does not interact with the cytochrome P450 system and does not undergo significant metabolism in humans, which thus limits its potential for drug-drug interactions.¹⁵ Because bilastine is eliminated largely unchanged (99.5%) in the urine and feces,¹⁶ no dosage adjustments are required in patients with renal or hepatic impairment or in the elderly.¹¹ Bilastine is generally well tolerated at therapeutic and suprathreshold doses, and has no demonstrable anticholinergic effects or cardiotoxicity.¹⁷ Due to limited penetration of the blood-brain barrier,^{18–20} bilastine does not potentiate the effects of alcohol or benzodiazepines, does not cause somnolence, and does not affect patients' performance or ability to drive.^{19–21} These attributes make bilastine an attractive therapeutic choice for the treatment of allergic rhinoconjunctivitis or urticaria.

In clinical trials of allergic rhinoconjunctivitis or urticaria, the safety profile of bilastine, assessed by the type and frequency of adverse events (AE), was similar to that of placebo, with insignificant AEs reported on the central nervous system.^{7,19,22} Bilastine thus far has been administered to >4700 patients in clinical trials conducted during its clinical development and postauthorization phases and to ~60 million patients (up to March 2017) since it received marketing authorization in September 2010. However, data from the clinical development phase on treatment of elderly patients (≥65 years) involved just 69 patients (34 treated with bilastine). As established in the Risk Management Plan (RMP Version 02.00 Release date: 19 July 2010; required and authorized by the German Agency, Bundesinstitut für Arzneimittel und Medizinprodukte), a postauthorization study of bilastine was planned to extend information on its safety profile in the elderly. The current study enrolled elderly patients, aged ≥65 years, with allergic rhinoconjunctivitis and/or urticaria. Safety was evaluated by assessing the incidence of AEs.

METHODS

This was a prospective, multicenter, open-label, observational, 3-month follow-up study of patients aged ≥65 years who started treatment with bilastine 20 mg according to usual clinical practice at primary health care centers in Spain, either as *de novo* treatment or after previous treatment with bilastine provided that it had not been taken for at least 3 weeks before study initiation. Because this was a postauthorization study, no exclusion criteria beyond those stated in the bilastine Summary of Product Characteristics (SmPC)¹¹ current at the time of the study (dated February 15, 2012)

were taken into account. The study was conducted according to ethical principles established in the Declaration of Helsinki and applicable international and local guidelines, laws, and regulations. Written informed consent was received from all the patients before participation in the study. The patients were followed up for 3 months from the first administration of bilastine, irrespective of treatment duration. Visits were scheduled according to the usual clinical practice of participating centers.

Because patients with any type of concomitant disease and treatments could be included provided that no contraindication was specified in the bilastine SmPC,¹¹ baseline signs and symptoms were recorded to differentiate between the safety profile of bilastine 20 mg and the baseline signs and symptoms profile of each patient. Information from additional tests, such as blood samples and electrocardiograms, performed when following usual clinical practice of participating centers could be included. The primary end point of the study was the safety profile of bilastine 20 mg, assessed by the incidence of treatment-emergent AEs (TEAE), in patients aged ≥65 years with allergic rhinoconjunctivitis and/or urticaria. Secondary end points were the incidence of TEAEs related to administration of bilastine, and the incidence of common (frequency, ≥1/100) and uncommon (<1/100) TEAEs as described in the bilastine SmPC¹¹.

Although the sample size was not based on a statistical rationale, it was calculated that a total of 150 patients would permit estimating an incidence rate of any AE < 5% with an estimate accuracy of 3.5% (two-sided alpha error of 0.05). AEs were coded by using the Medical Dictionary for Regulatory Activities dictionary (version 16.1, September 2013), which classifies AEs by system organ class and preferred term. Statistical analysis was performed by Linical (Madrid, Spain), using SAS version 9.2 (SAS Institute, Inc., Cary, NC). Descriptive statistics were used. Numerical data were described by the number of subjects, mean ± standard deviation (SD), range (minimum, maximum), and first and third quartile. Categorical data were described by absolute frequencies and percentages.

RESULTS

A total of 151 patients were enrolled in the study from April 30, 2013, to October 10, 2013, at 20 centers in Madrid and Cataluña, Spain. One patient did not take the study medication, and four patients were excluded for major protocol deviations (failed to meet inclusion and/or exclusion criteria). The demographic data and baseline characteristics of the modified safety population (*N* = 146) are summarized in Table 1. The mean ± SD age was 74.8 ± 6.6 years. The majority of the patients (74.0%) had allergic rhinoconjunctivitis, 19.2%

Table 1 Demographic data, baseline characteristics, and disease classification in the modified safety population (N = 146)

Variable	
Men, no. (%)	47 (32.2)
Age, mean $\pm$ SD, y	74.8 $\pm$ 6.6
Height, mean $\pm$ SD, cm	157.3 $\pm$ 9.0
Weight, mean $\pm$ SD, kg	69.9 $\pm$ 12.3
Body mass index, mean $\pm$ SD, kg/m ²	28.3 $\pm$ 4.9
Disease classification	
Allergic rhinoconjunctivitis, no. (%)	108 (74.0)
Urticaria, no. (%)	38 (19.2)
Allergic rhinoconjunctivitis and urticaria, no. (%)	10 (6.8)

SD = Standard deviation.

had urticaria, and 6.8% had both allergic rhinoconjunctivitis and urticaria. Sixty-one patients (41.8%) reported at least one previous medical condition at the time of inclusion, with the most frequent being basal cell carcinoma ($n = 5$ [3.4%]). The most frequently reported concomitant medical conditions were hypertension ($n = 97$ [66.4%]), osteoarthritis ($n = 64$ [43.8%]), dyslipidemia ($n = 43$ [29.5%]), hypercholesterolemia ($n = 35$ [24.0%]), and depression ($n = 28$ [19.2%]). Among the patients who received treatment with bilastine during the study, the mean $\pm$ SD treatment duration was 35.8 $\pm$ 29.7 days.

A total of 74 of 146 patients (50.7%) reported 129 TEAEs during the study period. The monthly and quarterly incidence rates of TEAEs were 0.29 (95% confidence interval [CI], 0.229–0.367) and 0.88 (95% CI, 0.688–1.100), respectively. Nonserious TEAEs with a reported incidence of $\geq 2\%$ in the modified bilastine safety population are summarized in Table 2. The most frequent nonserious TEAEs according to system organ class were infections and infestations (15.8%), muscle and connective tissue injuries (9.6%), and gastrointestinal disorders (8.2%). During the study period, a total of seven patients (4.8%) reported eight TEAEs that were considered to be at least possibly related to bilastine (Table 3). All bilastine-related TEAEs were mild to moderate in intensity. Somnolence was the only bilastine-related TEAE reported by more than one patient (moderate, $n = 2$; mild, $n = 2$). The monthly and quarterly incidence rates of bilastine-related TEAEs were 0.04 (95% CI, 0.016–0.082) and 0.12 (95% CI, 0.048–0.246), respectively.

During the study period, a total of three patients (2.1%) reported five serious TEAEs, which included empyema, pneumonia, recurrent lung carcinoma (non-specified cell type), pulmonary squamous cell carcinoma, and exacerbation of chronic obstructive pulmonary disease (Table 4). None of the serious TEAEs was

Table 2 Nonserious TEAEs, with an incidence $\geq 2\%$ in the modified bilastine safety population (N = 146)

System Organ Class: Preferred Term	No. Events/ No. Patients (% patients)
Any nonserious TEAE	124/74 (50.7)
Eye disorders	7/7 (4.8)
Conjunctivitis	3/3 (2.1)
Gastrointestinal disorder	13/12 (8.2)
Dry mouth	3/3 (2.1)
Infections and infestations	25/23 (15.8)
Nasopharyngitis	5/5 (3.4)
Urinary tract infection	5/5 (3.4)
Injury, poisoning, and procedural complications	7/7 (4.8)
Contusion	5/5 (3.3)
Musculoskeletal and connective tissue disorders	16/14 (9.6)
Back pain	4/4 (2.7)
Nervous system disorders	10/10 (6.8)
Somnolence	4/4 (2.7)

TEAE = Treatment-emergent adverse event.

considered to be related to bilastine in the opinion of the practising physicians. The monthly and quarterly incidence rates of serious TEAEs were 0.02 (95% CI, 0.003–0.048) and 0.05 (95% CI, 0.010–0.143), respectively. A total of six patients (4.1%) reported seven TEAEs, which led to discontinuation of bilastine during the study period. These included single events of dry mouth, dyspepsia, epigastric discomfort, lipedema, and insomnia reported in one patient each, and two events of somnolence reported in two patients.

DISCUSSION

Although clinical trials that investigated the efficacy and safety of bilastine for the treatment of allergic rhinitis and urticaria included populations that ranged in age from 12 to 70 years,^{23–26} the actual number of patients aged ≥ 65 years treated with bilastine was limited ($n = 34$). It is not uncommon for elderly patients to be underrepresented in randomized controlled trials because persons with coexisting diseases and/or those taking concomitant medications are generally excluded.²⁷ As established in the Risk Management Plan for bilastine, this postauthorization observational study was planned to expand the information available about the safety profile of bilastine in the elderly.

Irrespective of treatment duration, the study participants who started treatment with bilastine 20 mg un-

Table 3 Incidence of TEAEs at least possibly related to bilastine in the modified bilastine safety population (N = 146)

System Organ Class: Preferred Term	No. Events/No. Patients (% patients)		
	Moderate Intensity	Mild Intensity	Total
Any related TEAE	3/2 (1.4)	5/5 (3.4)	8/7 (4.8)
Gastrointestinal disorders	1/1 (0.7)	2/2 (1.4)	3/3 (2.1)
Dry mouth	1/1 (0.7)*		1/1 (0.7)
Dyspepsia		1/1 (0.7)#	1/1 (0.7)
Epigastric discomfort		1/1 (0.7)§	1/1 (0.7)
General disorders and administration site conditions		1/1 (0.7)	1/1 (0.7)
Fatigue		1/1 (0.7)¶	1/1 (0.7)
Nervous system disorders	2/2 (1.4)	2/2 (1.4)	4/4 (2.7)
Somnolence	2/2 (1.4)	2/2 (1.4)**	4/4 (2.7)

TEAE = Treatment-emergent adverse event.

*A 73-year-old woman.

#A 68-year-old man.

§A 70-year-old woman.

¶An 82-year-old woman.

||A 73-year-old woman and a 76-year-old woman.

**A 77-year-old man and an 80-year-old woman.

Table 4 Incidence of serious TEAEs in the bilastine safety population (N = 150), of which none were related to bilastine

System Organ Class: Preferred Term	No. Events/No. Patients (% patients)
Any serious TEAE	5/3 (2.1)
Infections and infestations	2/1 (0.7)
Empyema	1/1 (0.7)
Pneumonia	1/1 (0.7)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	2/2 (1.4)
Lung carcinoma cell type unspecified, recurrent	1/1 (0.7)
Squamous cell carcinoma of lung	1/1 (0.7)
Respiratory, thoracic, and mediastinal disorders	1/1 (0.7)
Chronic obstructive pulmonary disease	1/1 (0.7)

TEAE = Treatment-emergent adverse event.

der usual clinical practice conditions were followed up for 3 months. The incidence of TEAEs (primary end point) reported during this period was low, with monthly and quarterly rates of 0.29 and 0.88, respectively. The favorable safety profile of bilastine 20 mg was particularly evident in the low monthly and quar-

terly incidence rates of related TEAEs (0.04 and 0.12, respectively) and of serious TEAEs (0.02 and 0.05, respectively; all nonrelated). During the observation period, seven patients reported eight events with at least a possible causal relationship to bilastine. Of these, only somnolence was reported by more than one patient. These results align with those of placebo-controlled clinical trials of bilastine for the treatment of allergic rhinoconjunctivitis,^{23–25} and chronic idiopathic urticaria,²⁶ in which AE rates reported for bilastine were similar to those for placebo.

The safety profile of bilastine that we observed in our study of elderly patients correlated well with the results of two long-term, phase III studies.^{25,28} In a 1-year open-label extension phase of bilastine 20 mg for perennial allergic rhinitis (N = 513), six patients experienced serious AEs unrelated to treatment,²⁵ 68.8% of these patients reported at least one AE, and 31% of these patients reported at least one treatment-related AE. Of these, only headache (9.6%) and nasopharyngitis (2.5%) were reported with a frequency of ≥1.8%. An open-label study from Japan evaluated the safety and efficacy of bilastine 20 mg over 1 year for chronic spontaneous urticaria or pruritus associated with skin diseases.²⁸ Throughout the 52-week treatment period, AEs were reported in 127 patients (64.5%) and bilastine-related AEs in 5 patients (2.5%); all bilastine-related AEs were mild to moderate in severity and included a report each of somnolence in two patients.²⁸

In the present study, there were no reports of headache, and two reports each of mild (1.4%) and moderate (1.4%) treatment-related somnolence. This con-

trasted with higher reported frequencies of these events during the clinical development of bilastine, with incidences of 4.0% for headache and 3.1% for somnolence among patients treated with bilastine 20 mg ($N = 1697$) as per the current approved SmPC.¹¹ This may reflect differences in collecting and reporting AEs between randomized controlled trials and observational studies.

Although our study involved sites from only 2 of the 17 regions in Spain, these regions account for ~30% of the Spanish population aged ≥ 65 years,²⁹ and thus can be regarded as an optimized sampling approach. The final recruited population of 146 patients was in general agreement with the sample size assumptions made at the outset of the study. Due to the relatively short period of observation (3 months), it was not possible to identify incidences of AEs classified as rare, very rare, or unknown; this represented a potential study limitation. In agreement with the frequency of AEs described in the approved bilastine SmPC,¹¹ somnolence (common frequency, $\geq 1/100$) was reported by four patients, whereas dry mouth, dyspepsia, epigastric discomfort, and fatigue (uncommon frequency, $< 1/100$) were reported by one patient each. Thus, the safety profile of bilastine that we observed in patients aged ≥ 65 years was not different from that documented in younger populations.

The current study was open label in design, with no placebo- or active-comparator group, which represented a potential limitation. However, the study was designed to follow the usual clinical practice of participating centers, which left the decision to initiate treatment with bilastine 20 mg in the hands of the treating physician and involved a highly representative patient population (minimal inclusion and exclusion criteria). As such, the results were interpreted as satisfying the study objectives and could be generalized to the general population of patients aged ≥ 65 years who required symptomatic treatment of allergic rhinoconjunctivitis and/or urticaria.

CONCLUSION

Bilastine 20 mg showed a favorable safety profile, with a low incidence of TEAEs in elderly patients with allergic rhinoconjunctivitis and/or urticaria. These results were in accordance with the established safety profile of bilastine and incidence of AEs reported in previous studies and described in the approved SmPC.¹¹

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