

Ebastine in the Treatment of Allergic Rhinitis and Urticaria: 30 Years of Clinical Studies and Real-World Experience

Sastre J

Department of Allergy, Fundación Jimenez Diaz, Madrid. CIBERES, Instituto Carlos III Department of Medicine, Universidad Autónoma de Madrid, Madrid, Spain

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■ Abstract

Histamine, acting predominantly via the H₁-receptor, is an important mediator of the symptoms of allergy. H₁-antihistamines, which stabilize the receptor in its inactive form, are the treatment of choice for some chronic allergic conditions. Ebastine is a well-established second-generation oral H₁-antihistamine that is administered once daily at a dose of 10-20 mg and is available both as a standard tablet and as a fast-dissolving tablet that disintegrates in the mouth. Ebastine has been shown to relieve symptoms in patients with allergic rhinitis or urticaria in multiple clinical trials. In addition to its antihistamine effects, the drug has modulating effects on the allergic inflammatory process, thus potentially explaining its beneficial effect on nasal obstruction in some patients. Ebastine is generally well tolerated at recommended doses and is one of the lowest-risk antihistamines with respect to adverse cognitive/psychomotor effects, as confirmed by decades of pharmacovigilance. New long-term data confirm its efficacy and tolerability during up to 1 year of treatment in patients with chronic urticaria.

Key words: Allergic rhinitis. Urticaria. Ebastine. Antihistamines. H₁-receptor antagonists.

■ Resumen

La histamina, que actúa predominantemente a través del receptor H₁, es un mediador importante de los síntomas de alergia, y los antihistamínicos H₁, que estabilizan el receptor en su forma inactiva, son el tratamiento de elección para algunas afecciones alérgicas crónicas. La ebastina es un antihistamínico H₁ oral de segunda generación bien establecido. Se administra una vez al día en una dosis de 10 a 20 mg y está disponible como comprimido estándar y también como comprimido de disolución rápida que se desintegra en la boca. La ebastina ha demostrado en numerosos ensayos clínicos ser eficaz para aliviar los síntomas de pacientes con rinitis alérgica o urticaria. La ebastina tiene efectos moduladores del proceso inflamatorio alérgico además de sus efectos antihistamínicos, lo que pueden ayudar a explicar el efecto beneficioso que tiene sobre la obstrucción nasal en algunos pacientes. La ebastina es generalmente bien tolerada a las dosis recomendadas y es uno de los antihistamínicos de menor riesgo con respecto a los efectos adversos cognitivos / psicomotores, confirmado después de décadas de farmacovigilancia. Los nuevos datos a largo plazo confirman su eficacia y tolerabilidad hasta un año de tratamiento en pacientes con urticaria crónica.

Palabras clave: Rinitis alérgica. Urticaria. Ebastina. Antihistamínicos. Antagonistas del receptor H₁.

Introduction

Allergic disorders such as allergic rhinitis and urticaria are a common problem worldwide [1,2]. The estimated prevalence of confirmed allergic rhinitis in Europe ranges from 17% to 28.5% [1,3]. The prevalence of the disease is increasing in other countries with previously low-to-medium prevalence, such as China, and elsewhere [1,4-6]. The prevalence of urticaria is estimated to be 0.5%-5% [2,7-9]. In a cross-sectional population survey, lifetime prevalence for all types of urticaria was estimated to be approximately 9%, and this was considered to be a lower limit because of the conservative prevalence calculations employed [8].

Both allergic rhinitis and urticaria have an adverse impact on quality of life and daily functioning [7,10-14], and allergic rhinitis in particular is associated with a high

economic burden for society in terms of work absenteeism and presenteeism [15,16].

Histamine, acting predominantly via the H1-receptor, is an important mediator of the symptoms of allergy [17]. It is released as a preformed mediator from activated mast cells during the early phase of the immune response [18]. H1-antihistamines, which stabilize the receptor in its inactive form, are the treatment of choice for allergic conditions [17] and are included in international guidelines for the management of allergic rhinitis [1,19] and urticaria [20]. Ebastine is a well-established second-generation H1-antihistamine [21] that has been available across Europe and worldwide for almost 30 years. The most recent comprehensive review of ebastine was published 10 years ago [21]. The current review summarizes data on the use of ebastine to treat allergic rhinitis and urticaria and includes new information that has become available in the last decade.

Table 1. Pharmacodynamic Properties of Ebastine

Antihistamine Activity
Ebastine ≥ 10 mg reduced histamine-induced cutaneous wheal response vs placebo in healthy adults and adults with allergic rhinitis ($P < .05$) [22-29].
After single doses of ebastine 1-30 mg, peak inhibition of wheals occurred 2-12 h after intradermal histamine challenge (dose-dependent effect); after 24 h, wheals remained reduced by 50% with ebastine 10 mg vs placebo [27,28].
Inhibitory effect of ebastine on wheal/flare responses disappeared by 5 d after stopping administration [30].
Ebastine 10 mg as effective as cetirizine 10 mg, fexofenadine 120 mg, loratadine 10 mg, and mizolastine 10 mg at inhibiting histamine-induced wheal response [25,29]. Ebastine 20 mg more effective ($P < .05$) than cetirizine, loratadine, and fexofenadine at 24 h after dosing [22,25,26]. Results for flare response after cutaneous histamine challenge generally consistent with those for wheal response [22,26,31].
Ebastine fast-dissolving tablet 10 mg and 20 mg more effective than desloratadine 5 mg at inhibiting the histamine-induced wheal response at 24 h after dosing ($P < .001$) [23,24].
Ebastine 10 and 30 mg reduced histamine-induced bronchoconstriction vs placebo in patients with asthma; no dose-response relationship [32].
Antiallergy Effects
In patients with animal/plant allergies, wheal and flare responses to cutaneous allergen challenge reduced significantly ($P < .01$) by ebastine 20 mg versus placebo at 6, 24, and 48 h after completing 1 wk of treatment [30].
In patients with grass pollen allergy, ebastine 10 mg reduced pollen-induced wheal diameter significantly vs placebo ($P = .013$) and to a similar extent to cetirizine 10 mg, fexofenadine 120 mg, loratadine 10 mg, and mizolastine 10 mg [29]. All antihistamines reduced nasal blockage and sneezing (but not rhinorrhea) vs placebo at 4 h after nasal provocation with pollen ($P < .05$) [29].
In patients with grass pollen allergy, mean number of pollen grains needed to induce an allergic response after nasal provocation was higher in recipients of ebastine 10 or 20 mg vs placebo ($P < .05$) [33].
Effects on Other Mediators of Inflammation
In nasal polyp cells in vitro, ebastine inhibited anti-IgE-induced release of prostaglandin D_2 (PGD ₂) and leukotrienes C_4/D_4 (LTC ₄ /D ₄) ($P < .05$). It also inhibited granulocyte-macrophage colony-stimulating factor (GM-CSF), tumour necrosis factor- α and interleukin-8 release [33]. Carebastine had a smaller effect than ebastine.
In patients with grass pollen allergy, ebastine 10 and 20 mg reduced the release of GM-CSF (but not PGD ₂ , LTC ₄ /D ₄ or other cytokines) in nasal secretions in a dose-dependent manner [33].
In patients with grass pollen allergy, a smaller increase in nasal eosinophilia was seen after treatment with ebastine 10 mg vs placebo ($P = .004$); effect was similar to that seen with cetirizine, fexofenadine, loratadine, and mizolastine [29].
In patients with bronchial asthma, ebastine 10 mg reduced peripheral blood eosinophil count ($P < .0253$) and serum eosinophil cationic protein level ($P < .0014$) in atopic but not nonatopic patients [34].
In patients with persistent allergic rhinitis, ebastine increased interferon- γ production by peripheral blood mononuclear cells in response to stimulation by grasses ($P < .0001$) or house dust mite <i>Dermatophagoides farinae</i> ($P = .0015$) [35].
Ebastine demonstrated potent antiangiogenic activity in in vitro (human umbilical vein endothelial cell and human pulmonary artery cell) assays ($P \leq .03$) and in an in vivo (chick embryo chorioallantoic membrane) assay ($P < .001$) [36].

Pharmacological Properties

Ebastine is a second-generation H1-antihistamine. It has an oxypiperidine-based structure and is metabolized to carebastine, its active metabolite, after oral administration.

Pharmacodynamic Profile

Since ebastine was introduced 30 years ago, its pharmacodynamic activity has been extensively demonstrated using cutaneous histamine challenge tests, histamine-induced bronchoconstriction tests, cutaneous and nasal allergen challenge tests, and measurement of inflammatory mediators. The findings are summarized in Table 1 [22-36]. The key points are as follows: ebastine inhibited cutaneous reaction to histamine in a dose-dependent manner; and ebastine 20 mg reduced histamine-induced wheals to a greater extent than cetirizine 10 mg, fexofenadine 120 mg, and loratadine 10 mg. In addition, the quantity of pollen needed to induce a nasal allergic response was greater with ebastine, and the effects of the drug lasted for at least 48 hours (Table 1).

Ebastine also has effects on nonhistamine mediators of inflammation (Table 1). Two relevant studies have been published since the last review [21]. People with allergies

are often deficient in interferon γ , and it has been shown that ebastine increases production of interferon γ by peripheral blood mononuclear cells in response to stimulation by grasses ($P<.0001$) or the house-dust mite *Dermatophagoides farinae* ($P=.0015$) in patients with persistent allergic rhinitis [35]. This effect was significantly associated with an improvement in allergy symptoms, as measured by the total nasal symptom score ($P=.0038$) and patient-reported overall symptoms in a visual analog scale ($P=.004$). Angiogenesis, which is associated with increased expression of vascular endothelial growth factor (VEGF), is implicated in airway inflammation and remodelling in allergic rhinitis and asthma, and ebastine was found to have potent antiangiogenic activity in in vitro and in vivo assays [36]. Carebastine, the active metabolite of ebastine, inhibited the VEGF-induced angiogenic response in a chick embryo chorioallantoic membrane assay ($P<.001$), with the effect mediated predominantly by an H1-receptor-dependent mechanism and, albeit to a lesser extent, by an H1-receptor-independent mechanism [36].

Pharmacokinetic Profile

The pharmacokinetic profile of ebastine/carebastine is summarized in Table 2 [21,28,37-52]. Ebastine is administered

Table 2. Pharmacokinetic Properties of Carebastine [21,28,37-52]^a

Parameter	Finding
Maximum plasma concentration	Single dose: 10 mg, 80-115 ng/mL; 20 mg, 157-243 ng/mL Multiple doses: 10 mg, 130-162 ng/mL; 20 mg, 273-396 ng/mL
Time to maximum plasma concentration	Single dose: 10 mg, 2.6-5.7 h; 20 mg, 1-5 h Multiple doses: 10 mg, 5.1 h; 20 mg, 4.5-5 h
Area under the plasma-concentration time curve	Single dose: 10 mg, 1755-3189 ng/mL/h; 20 mg, 5721 ng/mL/h Multiple doses: 10 mg, 2742 ng/mL/h; 20 mg, 4200-5608 ng/mL/h
Time to steady-state concentration	Approximately 4 days
Effect of food	Ebastine can be administered with or without food
Plasma protein binding	>95%
Apparent volume of distribution	90-143 L (single 10 mg dose)
Metabolism	Via cytochrome P450 enzymes, including CYP3A4, CYP2J2, CYP4F
Urinary excretion	Accounts for 66% of administered dosage; mainly in form of conjugated metabolites
Clearance	4.8 L/h (single 10 mg dose)
Elimination half-life	Single dose: 10 mg, 10.3-19 h; 20 mg, 15 h Multiple doses: 10 mg, 19 h; 20 mg, 15-24.5 h
Effect of age and gender	Age has no clinically relevant effect on carebastine pharmacokinetics, and dose modifications are not needed in elderly patients
Hepatic and renal impairment	Hepatic and renal impairment have no clinically relevant effect on carebastine pharmacokinetics. No dose adjustment needed for renal impairment or for mild or moderate hepatic impairment. Maximum dose in severe hepatic impairment is 10 mg, as this was the highest dose evaluated in this subgroup
Drug interactions	Pharmacokinetic interaction with drugs metabolized by CYP3A4, eg, coadministration with ketoconazole, itraconazole or erythromycin leads to increased plasma concentrations of ebastine/carebastine Pharmacokinetic interaction with rifampin (rifampicin), leading to reduced plasma concentration of carebastine No significant interactions with cimetidine, diazepam, or alcohol

^aSpecific values are for adults taking the standard tablet formulation of ebastine.

Table 3. Randomized, Double-Blind, Controlled Trials Evaluating the Efficacy of Ebastine in Adults and Adolescents With Seasonal Allergic Rhinitis^a

Clinical Trial (Duration)	No.	Treatment	Results
[54] (4 wk)	40	Ebastine 10-40 mg (titrated) Placebo	Ebastine more efficacious than placebo for relief of nasal symptoms ($P<.05$) but not ocular symptoms. Global efficacy rated good/very good by more patients and physicians for ebastine than placebo (patients 84% vs 40%; physicians: 79% vs 35%; overall $P<.01$).
[55] (2 wk)	116	Ebastine 10 mg Placebo	Ebastine 10 mg more efficacious than placebo for relief of nasal symptoms such as rhinorrhoea ($P=.003$) and sneezing ($P=.008$) (but not nasal obstruction) and ocular symptoms such as tears and conjunctival irritation (p values not reported). Ebastine 10 mg more efficacious than placebo based on physician global efficacy rating of good/excellent (56% vs 46%, $P=.008$).
[56] (1 wk)	201	Ebastine 10 mg Ebastine 20 mg Placebo	Ebastine 10 and 20 mg more efficacious ($P<.05$) than placebo for relief of nasal symptoms (except obstruction) and ocular symptoms (except watering eyes with ebastine 20 mg). Ebastine 10 and 20 mg more efficacious than placebo based on patient ($P<.05$) and physician ($P<.01$) global efficacy rating. More patients and physicians rated ebastine 10 and 20 mg as "efficacious" (i.e. moderate/ good/excellent) than rated placebo as such (patients 61% vs 66% vs placebo 36%; physicians: 72% vs 64% vs placebo 33%). No significant differences between ebastine 10 and 20 mg.
[57] (3 wk)	396	Ebastine 10 mg (am) Ebastine 10 mg (pm) Ebastine 20 mg (am) Ebastine 20 mg (pm) Placebo	Ebastine 10 mg (am) and 20 mg (am or pm) [but not 10 mg (pm)] more efficacious than placebo at improving total symptom score and relieving individual nasal and ocular symptoms ($P<.05$). Mean change from baseline in total symptom score was -3.5 and -3.2 for ebastine 10 mg (am) and 10 mg (pm) vs -4.0 and -3.6 for ebastine 20 mg (am) and 20 mg (pm) vs -2.7 for placebo (estimated from graph). Ebastine 20 mg (am and pm) [but not ebastine 10 mg (am or pm)] better than placebo based on patient global efficacy rating ($P<.05$). Efficacy was maintained during a 4-month extension period.
[58] (2 wk)	343	Ebastine 10 mg Ebastine 20 mg Cetirizine 10 mg	No significant difference in change in total symptom score between groups at study end. Greater reduction in total symptom score with ebastine 20 mg vs ebastine 10 mg and cetirizine 10 mg after 1 week ($P<.05$). In a subgroup with more severe baseline symptoms ($n=158$), greater reduction in total symptom score at study end with ebastine 20 mg vs ebastine 10 mg ($P=.027$) but not vs cetirizine 10 mg. Physician (but not patient) global efficacy ratings better for ebastine 20 mg (but not 10 mg) vs cetirizine 10 mg (improvement in 85% vs 73%; $P=.048$).
[59] (4 wk)	749	Ebastine 10 mg Ebastine 20 mg Loratadine 10 mg Placebo	Ebastine 10 and 20 mg more efficacious than placebo for all composite scores ($P<.01$). Patient and physician global ratings not significantly different vs placebo for any active treatment. Reductions in reflective nasal index scores with/without congestion (but not in reflective total symptom score with/without congestion) and in all four snapshot composite scores were greater with ebastine 20 mg vs loratadine 10 mg ($P<.05$). No significant differences between ebastine 10 mg vs loratadine 10 mg for any composite scores. No significant difference for ebastine 10 or 20 mg vs loratadine for patient or physician global ratings.
[60] (4 wk)	565	Ebastine 10 mg Ebastine 20 mg Loratadine 10 mg Placebo	Ebastine 10 and 20 mg more efficacious than placebo for all composite scores ($P<.05$); loratadine better than placebo for all composite scores except snapshot total symptom score and nasal index. Patient and physician global ratings better with all active treatments vs placebo ($P<.05$). Greater reduction in all four mean daily reflective composite scores (total symptom score with/without congestion and nasal index with/without congestion), all four-morning snapshot composite scores and most individual scores with ebastine 20 mg vs loratadine 10 mg ($P<.05$). No significant difference between ebastine 10 mg vs loratadine 10 mg. Patient and physician global ratings did not differ significantly between active treatments.
[61] (2 wk)	703	Ebastine 20 mg Loratadine 10 mg Placebo	Greater reductions in all mean daily reflective and snapshot composite scores (total symptom score, nasal index) and individual nasal and ocular scores (except for snapshot nasal congestion) with ebastine 20 mg vs placebo ($P<.05$), but not for loratadine 10 mg vs placebo. Greater reduction in all mean daily reflective and snapshot composite and individual nasal and ocular scores with ebastine 20 mg vs loratadine 10 mg ($P<.05$). Change in mean daily reflective total symptom score -3.46 (-32.3%) with ebastine 20 mg vs -2.77 (-24.6%) with loratadine 10 mg ($P=.0018$). Patient and physician global ratings did not differ significantly between ebastine and loratadine.

^aEfficacy was generally based on evaluation of nasal symptoms (rhinorrhoea, sneezing, itching, obstruction) and ocular symptoms (itching, discharge, conjunctivitis). Symptoms were assessed individually and/or as composite scores, such as total symptom score, nasal index (composite of 4 nasal symptoms) or perennial index (nasal symptoms excluding obstruction). Symptoms were usually rated on a graded scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). In some trials, patients recorded symptom scores twice daily, based on their symptoms over the previous 12 hours (reflective score) and at the time of recording (snapshot score).

Table 4. Randomized, Double-Blind, Controlled Trials Evaluating the Efficacy of Ebastine in Adults and Adolescents With Perennial Allergic Rhinitis^a

Clinical Trial (Duration)	No.	Treatment	Results
5 [62] (1 wk)	151	Ebastine 10 mg Placebo	Ebastine 10 mg more efficacious than placebo for relief of all nasal symptoms (except obstruction) and ocular symptoms ($P < .05$). Efficacy rated as excellent/good/moderate by more patients and physicians for ebastine 10 mg than placebo (54%-55% vs 31%-32%; $P < .01$).
[63] (12 wk)	290	Ebastine 10 mg Ebastine 20 mg Placebo	Ebastine 20 mg more efficacious than placebo for reduction from baseline in mean daily perennial index (-1.9 [-39%] vs -1.2 [-26%], $P = .006$; estimated from graph), morning perennial index ($P = .007$) and mean daily nasal index ($P = .015$). Ebastine 10 mg more effective than placebo for reduction in morning perennial index ($P = .047$). More patients and physicians rated condition as somewhat/greatly improved with ebastine 10 mg (72%-80%) and 20 mg (84%) than with placebo (58%) ($P < .02$). No significant differences between ebastine 10 and 20 mg.
[64] (4 wk)	214	Ebastine 10 mg Cetirizine 10 mg	No significant difference between ebastine 10 mg and cetirizine 10 mg for mean percentage change in nasal index at study end. Greater mean percentage change in nasal index with cetirizine 10 mg after 1 week ($P < .04$). More cetirizine recipients had reduced nasal congestion ($P < .04$) and were symptom-free ($P = .02$) at study end.
[65] (4 wk)	317	Ebastine 10 mg Ebastine 20 mg Loratadine 10 mg	Ebastine 10 and 20 mg more efficacious than loratadine 10 mg at reducing perennial index, nasal index, nasal discharge and nasal congestion ($P < .05$). No significant differences between ebastine doses. Condition rated as improved by more patients and physicians for ebastine 10 and 20 mg (79%-85%) vs loratadine 10 mg (65%-66%) ($P < .05$).

^aEfficacy was generally based on evaluation of nasal symptoms (rhinorrhea, sneezing, itching, obstruction) and ocular symptoms (itching, discharge, conjunctivitis). Symptoms were assessed individually and/or as composite scores, such as total symptom score, nasal index (composite of four nasal symptoms) or perennial index (nasal symptoms excluding obstruction). Symptoms were usually rated on a graded scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). In some trials, patients recorded symptom scores twice daily, based on their symptoms over the previous 12 hours (reflective score) and at the time of recording (snapshot score).

once daily. After oral administration, ebastine undergoes rapid and extensive first-pass metabolism to carebastine, its active metabolite [28,48]. Carebastine exhibits dose-dependent pharmacokinetics [28,48]. Peak plasma concentrations of carebastine are reached at 4–6 hours after dosing, and steady-state levels are achieved within 4 days (Table 2). Pharmacokinetic bioequivalence between the fast-dissolving tablet formulation of ebastine (which disintegrates in the mouth) and the standard tablet formulation (which is swallowed) has been established [53].

Coadministration with drugs metabolized by CYP3A4, such as ketoconazole and erythromycin, leads to increased plasma concentrations of ebastine/carebastine [37]. Since the previous review, a pharmacokinetic interaction between rifampicin (rifampin) and ebastine has been reported: coadministration led to reduced oral bioavailability of ebastine, with a 15% decrease in the area under the plasma concentration time curve for carebastine ($P < .001$) [49].

Clinical Efficacy

Once-daily oral ebastine is indicated for the symptomatic treatment of allergic rhinitis/rhinoconjunctivitis (adults and adolescents aged ≥ 12 years) and urticaria (adults).

Allergic Rhinitis

Most clinical trials of ebastine in allergic rhinitis were conducted prior to the introduction of the ARIA classification

based on intermittent or persistent symptoms and therefore used the earlier terminology of seasonal and perennial allergic rhinitis. Studies generally enrolled adults and adolescents aged ≥ 12 years, and allergic rhinitis was usually diagnosed based on the clinical history and a positive skin prick test or IgE test result. The most common primary efficacy parameter was the change from baseline in total symptom score; however, some studies used a global evaluation of symptomatic improvement/efficacy by the physician or patient.

The results of controlled trials of ebastine in adults/adolescents with seasonal allergic rhinitis or perennial allergic rhinitis are summarized in Tables 3 [54–61] and 4 [62–65], respectively. Ebastine was significantly more effective than placebo at relieving the symptoms of seasonal and perennial allergic rhinitis [54–57,58–63].

The results of comparisons with other antihistamines indicate that ebastine 10 mg was at least as effective as cetirizine 10 mg and loratadine 10 mg at relieving the symptoms of allergic rhinitis and that ebastine 20 mg was generally more effective than loratadine 10 mg [58–61,64,65]. A meta-analysis of 4 studies in seasonal allergic rhinitis confirmed that ebastine 20 mg was superior to loratadine 10 mg, as indicated by the mean change from baseline in the overall mean daily reflective total symptom score during the first 2 weeks of treatment (-3.61 [-35.4%] vs -3.05 [-29.0%], $P < .001$) [66].

Whereas most nasal symptoms are due primarily to the effect of histamine, nasal obstruction is associated with multiple chemical mediators [67–69], and oral H1-antihistamines tend

to be less effective for nasal congestion than for other nasal symptoms [1]. Three studies that evaluated mean change from baseline in reflective and snapshot nasal congestion symptom scores (total of 6 scores across the 3 studies) found that ebastine 20 mg was more efficacious than placebo for 6 of 6 scores and ebastine 10 mg for 4 of 6 scores, whereas loratadine 10 mg was more efficacious than placebo for only 1 of 6 scores [70]. A small noncomparative study in patients with persistent allergic rhinitis (n=20) that specifically evaluated nasal symptoms found that ebastine 20 mg significantly improved rhinomanometry-assessed nasal airflow by 59% from baseline ($P=.0001$) and modified the response to the nasal decongestion test ($P=.0003$) [71].

Patient Acceptance and Satisfaction

It is important that therapies for allergic rhinitis are acceptable to patients to ensure that they adhere to long-term treatments in the real-world setting. Studies evaluating patients' perception of the fast-dissolving tablet formulation of ebastine and their willingness to use it have been reviewed in detail [21,72]. Patients generally preferred the taste and texture of the fast-dissolving tablet over the standard ebastine tablet [73]. Patients found that the fast-dissolving tablet was convenient and easy to use, perceived it to have a fast onset of action, and reported high levels of satisfaction with this formulation [73-76]. Most expressed a preference for it over their previous antihistamine treatment [74-76].

One of the patient preference studies, which was available only as a conference abstract for the last full review of ebastine, has since been published in full [76]. This international

observational study of patients who had been prescribed the ebastine fast-dissolving tablet 20 mg within the previous 2 months (n=461) used the Treatment Satisfaction Questionnaire for Medication (TSQM). The authors found that patients rated the ebastine tablet highly for effectiveness (TSQM score 74.2 out of a maximum 100), adverse effects (95.3), convenience (87.9), and global satisfaction (78.6) [76]. Compared with their previous antihistamine therapy, the ebastine fast-dissolving 20-mg tablet was rated better/much better by 81% of patients in terms of effectiveness, by 73% for tolerability, 79% for onset of action, and 94% for convenience. Overall, 94% of patients indicated they would like to continue using the ebastine fast-dissolving tablet [76].

Urticaria

The efficacy of ebastine in the treatment of chronic urticaria was evaluated in adult patients. Ebastine was assessed in patients with chronic idiopathic urticaria (which would now be designated chronic spontaneous urticaria) in 2 randomized, double-blind, placebo-controlled trials [77,78], 1 of which also included a comparison with terfenadine [78]. Ebastine 10 mg was significantly more efficacious than placebo at reducing the symptoms of urticaria and showed similar efficacy to terfenadine (Table 5) [9,77-84]. More recently, a randomized trial with the primary aim of evaluating a method for predicting response to treatment in patients with chronic spontaneous urticaria (n=213) reported that all antihistamines evaluated (ebastine, bilastine, cetirizine, desloratadine, fexofenadine) provided similar efficacy in terms of symptom relief (assessed using the Urticaria Activity Score) and quality

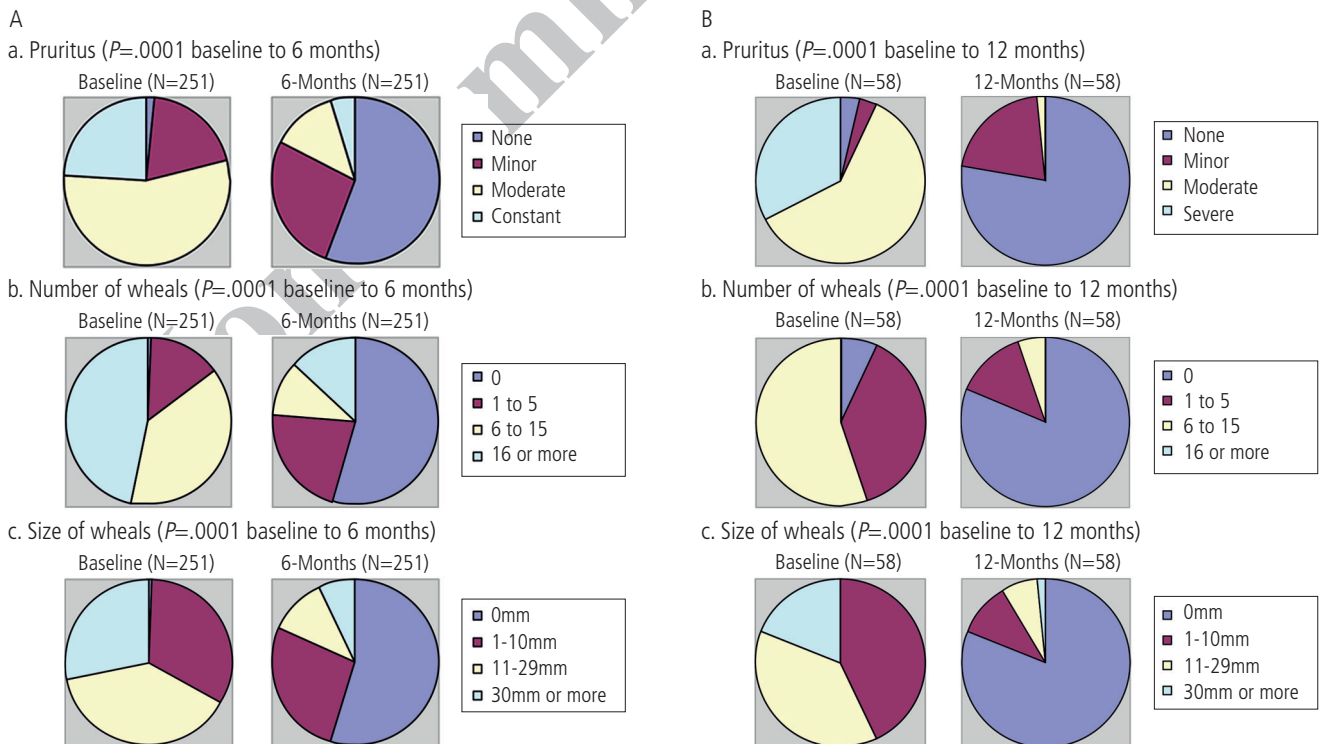


Figure. Long-term efficacy (1A 6 months; 1B 12 months) of ebastine in patients with chronic urticaria: a, pruritus; b, number of wheals; and c, size of wheals [80].

of life (Dermatology Life Quality Index) over 8 weeks of treatment (Table 5) [9].

In addition, efficacy data from 2 previously unpublished, long-term, open-label studies of the safety and efficacy of ebastine in patients with chronic urticaria have been reported [80,81]. The studies were both multicenter, open-label, noncomparative studies involving adults with chronic urticaria. Efficacy was evaluated through assessments of

symptoms, including pruritus and number and size of wheals, and patient and physician global evaluations. Both studies confirmed the long-term efficacy of ebastine 10 mg in this patient population.

In the first, 251 adults with chronic urticaria from 11 centers in Spain were enrolled in a 6-month, open-label study evaluating the long-term safety and tolerability of ebastine 10 mg, in which efficacy was assessed as a secondary

Table 5. Clinical Trials Evaluating the Efficacy of Ebastine in Adults With Urticaria

Clinical Trial (Duration)	No.	Treatment	Results
Randomized Controlled Clinical Trials in Chronic Spontaneous Urticaria			
[77] (2 wk)	204	Ebastine 10 mg Placebo	Ebastine 10 mg reduced itching and number and size of wheals vs placebo (all $P < .001$). Global efficacy rated by patients and physicians as moderate/good for more ebastine recipients than placebo recipients (80%-83% vs 51%-55%, $P < .001$).
[78] (12 wk)	211	Ebastine 10 mg Terfenadine 120 mg Placebo	Both ebastine 10 mg and terfenadine 120 mg were more efficacious ($P < .05$) than placebo at reducing severity of itch and number of wheals and lesions as assessed by patients (but not physicians). Ebastine was more efficacious than placebo based on patient/physician global ratings of improvement (73%-75% vs 51%-52%, $P \leq .004$). No significant differences were found between ebastine and terfenadine for relief of symptoms, or for global patient/physician ratings.
[9] (8 wk)	180	Ebastine 20 mg Bilastine 20 mg Cetirizine 20 mg Desloratadine 5 mg Fexofenadine 180 mg No treatment	24-h after administration of antihistamine, inhibition of the histamine wheal by $>75\%$ was significantly associated with better urticaria activity and dermatology life quality index (DLQI) scores. The safety and efficacy of the 5 antihistamines were similar. After up dosing, rates of disease control (DLQI score < 5) increased from 59% to 77% with no differences between treatments.
Open-Label Clinical Trials in Chronic Urticaria/Chronic Spontaneous Urticaria			
[79] (4 wk)	30	Ebastine 10-40 mg	Ebastine was safe and effective at higher doses in patients with chronic spontaneous urticaria, with 17, 8 and 2 patients becoming symptom-free when administered doses of 10, 20, and 40 mg, respectively.
[80] (6 mo + 6 mo follow-up in a subgroup of patients)	251/58	Ebastine 10 mg	The percentage of patients with constant pruritus decreased from 23.9% at baseline to 4.8% after 6 months, while the percentage who had ≥ 16 wheals decreased from 47% to 13.2% and the percentage who had wheals ≥ 30 mm in size decreased from 28.7% to 7.2% (all $P = .0001$). At 6 months, more than 70% of patients and physicians rated the overall efficacy of ebastine as optimum or good. Significant differences ($P = .0001$) were also seen in all symptoms in the subgroup of patients ($n = 58$) that followed 1 year of treatment.
[81] (12 mo)	192	Ebastine 10 mg	Over 12 months there was clear improvement in symptoms, including itching, time with symptoms, and wheal number/size. The percentage of patients with severe itching decreased from 22% at baseline to $< 1\%$ at 12 months, time with symptoms of urticaria decreased from 38 to 6 hours/week, the percentage of patients with wheals ≥ 30 mm decreased from 15% to 3%, and the percentage of patients with ≥ 16 wheals decreased from 27% to 6%. The overall evaluation of efficacy indicated that approximately 65% of patients and physicians considered there had been a major improvement in symptoms.
Longitudinal Study in Acute Urticaria			
[82] (4 wk)	150	Ebastine 20 mg Ebastine 10 mg Levocetirizine 5 mg	After 4 weeks the mean urticaria activity score was 1.08 for ebastine 20 mg, 1.98 for levocetirizine and 3.98 for ebastine 10 mg. In these 3 groups the percentage of patients with symptom relief were 80%, 70%, and 50%, respectively.
Double-Blind Crossover Study in Dermographic Urticaria: Pilot Study			
[83] (Single-dose)	7	Ebastine 20 mg Placebo	Ebastine prevented signs and symptoms of urticaria resulting from mechanical challenge. Of 7 patients with dermographic urticaria, all continued to experience wheals with placebo, but only 2 had wheals after ebastine.
Double-Blind Crossover Study in Acquired Cold Urticaria: Pilot Study			
[84] (Single-dose)	22	Ebastine 20 mg Placebo	Ebastine was significantly superior to placebo in terms of reducing the number of patients with wheals ($P < .001$), pruritus ($P < .001$), and experiencing a burning sensation ($P < .05$).

*Terfenadine administered as 60 mg twice daily. Terfenadine is no longer marketed.

Table 6. Long-Term Efficacy of Ebastine in Patients With Chronic Urticaria: Results From a 12-Month Noncomparative Evaluation of the Safety and Tolerability of Ebastine 10 mg in Europe [81]^a

Parameter	Percentage of Patients (Unless Otherwise Indicated)		
	Baseline	6 months	12 months
Pruritus ^b	N=192	N=134	N=104
None	2.6	50.8	59.6
Minor	27.6	41.8	34.6
Moderate	47.4	6.7	4.8
Severe	22.4	0.8	1.0
Mean no. of hours with symptoms/wkb	N=190 37.8 h	N=129 10.9 h	N=103 5.8 h
No. of whealsc	N=192	N=134	N=107
0	30.7	79.1	81.3
1-5	21.9	6.7	10.3
6-15	20.3	7.5	1.9
≥16	27.1	5.2	5.6
Not assessed	0.0	1.5	0.9
Size of whealsc	N=192	N=134	N=107
None	30.7	79.1	81.3
1-10 mm	26.6	7.5	11.2
11-29 mm	28.1	9.7	3.7
≥30 mm	14.6	2.2	2.8
Not assessed	0.0	1.5	0.9
Physician's global evaluation of efficacy			N=192
Major improvement	-	-	65.1
Minor improvement	-	-	20.1
No change or worse	-	-	11.6
Not done/not applicable	-	-	4.7
Patient's global evaluation of efficacy			N=192
Major improvement	-	-	65.6
Minor improvement	-	-	16.9
No change or worse	-	-	12.7
Not done/not applicable	-	-	6.4

^aMulticenter, open-label, non-comparative study at 36 centres across Europe.

^bPatient assessment.

^cPhysician assessment.

objective [80]. The primary evaluation was performed at 6 months. However, a subgroup of patients (n=58) continued into a second 6-month follow-up phase (ie, total of 12 months). All symptoms (pruritus, number and size of wheals) improved significantly ($P=.0001$) compared with baseline from month 1 (the first postbaseline visit) onwards and remained significantly improved at 6 months (Figure). The percentage of patients with constant pruritus decreased from 23.9% at baseline to 4.8% after 6 months (Figure, A, a), while the percentage who had ≥16 wheals decreased from 47.0% to 13.2% (Figure, A, b) and the percentage who had wheals ≥30 mm in size decreased from 28.7% to 7.2% (Figure, A, c) (all $P=.0001$). At 6 months, more than 70% of patients and physicians rated the overall efficacy of ebastine as optimum or good. Significant differences ($P=.0001$) from baseline in all symptoms were also seen at 12 months (Figure, B a, b, c) in the subgroup that continued into the extension period.

The other long-term study evaluated the safety and efficacy of ebastine 10 mg in 192 adults with chronic urticaria enrolled from 36 centers across Europe [81]. Some patients entered this open-label study after participating in the trial that compared ebastine with terfenadine and placebo [78], while others were enrolled de novo. Statistical comparisons with baseline were not performed, although there was a clear improvement in symptoms (including itching), the number of hours with symptoms, and wheal number and size during the 12-month treatment period (Tables 5 and 6). The percentage of patients with severe itching decreased from 22.4% at baseline to <1% at 12 months, the mean number of hours spent with symptoms of urticaria decreased from 38 to 6 hours per week, the percentage of patients with wheals of ≥30 mm in diameter decreased from 14.6% to 2.8%, and the percentage of patients with ≥16 wheals decreased from 27.1% to 5.6%. The overall evaluation of efficacy indicated that approximately 65% of both patients and physicians considered there had been a major improvement in symptoms during the study (Tables 5 and 6).

The EAACI/GA2LEN/EDF/WAO guidelines on urticaria suggest that in patients with an inadequate response to standard doses of second-generation H1-antihistamines, the dose can be increased by up to 4 times the standard recommended dose [20]. The approved dose for ebastine in patients with urticaria is 10 mg. A small noncomparative study found that ebastine was well tolerated and effective at higher doses in patients with chronic spontaneous urticaria (Table 5) [79]. Thirty patients were treated with ebastine for 4 weeks. The initial 10 mg dose could be increased after the first and second weeks in those patients with an inadequate response to 20 mg and then 40 mg (administered as 10 mg or 20 mg twice daily). At the end of the first week, the dose was increased in 10 of 27 patients (3 patients were lost to follow-up). At the end of the second week the dose was increased again in 2 of these 10 patients. The overall mean urticaria activity score decreased from 4.6 at baseline to 2.2 after 1 week, 1.1 after 2 weeks, and <1.0 at 4 weeks. In addition, 17, 8, and 2 patients became symptom-free on doses of 10, 20, and 40 mg, respectively. One patient reported mild sedation (at a dose of 40 mg) [79].

Studies of ebastine in types of urticaria other than chronic idiopathic/spontaneous urticaria have generally used a dose of 20 mg (Table 5). The results of 2 small, double-blind, crossover studies (n=22 and n=7) suggested that ebastine 20 mg might be effective at preventing the symptoms of acquired cold urticaria [84] and dermatographic urticaria [82], including wheals, burning, and itching. Recently, ebastine 20 mg was found to have similar efficacy to levocetirizine 5 mg and to be more effective than ebastine 10 mg in the treatment of acute urticaria in patients aged 10-70 years (n=150) [82]. By week 4 of the study, complete relief of symptoms was achieved in 80% of patients taking ebastine 20 mg, 70% of those taking levocetirizine, and 50% of those taking ebastine 10 mg. The mean Urticaria Activity Scores in these groups at week 4 were 1.08, 1.98, and 3.98, respectively (Table 5).

Safety and Tolerability

Ebastine 10-20 mg was generally well tolerated in clinical trials of 1-4 weeks' duration in patients with allergic rhinitis

or urticaria: the incidence of adverse events with ebastine was similar to that for placebo, and most events were mild or moderate in severity [54,55,57,59-62,77]. The incidence of adverse events with ebastine was similar to that for active comparators such as loratadine and cetirizine [58-60,64,65]. The most common adverse events with ebastine in placebo-controlled trials were headache (7.9%), drowsiness (3.0%), and dry mouth (2.1%) [21].

Ebastine was found to have a favorable risk-benefit ratio with respect to sedation and had no clinically relevant adverse effects on cognitive or psychomotor functioning [45,85-90]. A more recent analysis of the central nervous system effects associated with second-generation H1-antihistamines calculated proportional impairment ratios for each drug compared with all the others (with higher values indicating greater impairment) and ranked ebastine as one of the lowest for impairment of objective measures of cognitive and psychomotor function (ratio 0, 95%CI, 0-1.91) [91].

Ebastine had no clinically relevant adverse cardiac effects at recommended doses in clinical trials, although small increases in the QTc interval were seen when ebastine was coadministered with ketoconazole or erythromycin [37,92-94]. As a preventive measure, caution is recommended for some second-generation antihistamines such as ebastine or rupatadine in patients with known QTc interval prolongation or who use drugs that increase it. A recent case-control analysis of antihistamines using 7 population-based healthcare databases from 5 European countries (ARITMO project) found that ebastine was associated with an increased risk of ventricular tachyarrhythmia in 2 out of the 7 databases, one from Germany (GEPARD, 180 cases and 16 986 controls: adjusted odds ratio (aOR) 3.3, 95%CI, 1.1-10.8 vs no use of any antihistamine) and the other from The Netherlands (PHARMO, 538 cases and 52 890 controls: aOR 4.6, 95%CI, 1.3-16.2). However, no such increased risk was found in the other 5 databases or in the overall pooled analysis involving a much larger number of cases/controls (2507/239 523) [95]. Moreover, ebastine was not prescribed extensively in the countries covered by the study, and only 8 cases and 680 controls were included in total. Pharmacovigilance data collected since ebastine was first introduced in 1989 have not resulted in any relevant change in the tolerability and safety texts of the approved summary of product characteristics after an estimated 65.5 million patients have received the original product.

Studies of 3-4 months' duration indicated that ebastine 10-20 mg was well tolerated in the long term [57,63,78]. Data from 2 previously unpublished, open-label studies in which ebastine 10 mg was administered to patients with chronic urticaria for up to 1 year confirmed that ebastine was well tolerated during long-term treatment [80,81].

In the first of these studies, in which the main aim was to evaluate safety and tolerability over a 6-month period (n=251), the percentage of patients reporting adverse events decreased over time, from 17.9% at 1 month to 7.2% at 6 months [80]. The most common adverse events reported at 1 month were drowsiness (4.6%), headache (3.7%), and gastralgia (2.0%). The most common adverse events reported at 6 months were drowsiness (2.0%), gastralgia (1.7%), and increased appetite (1.2%). At 6 months, 87.2% of physicians and 84.5% of patients considered the overall tolerability of ebastine to be

“good” (options: good, average, poor, not done). Among 58 patients who continued for an additional 6 months (ie, total of 12 months), 8.6% reported adverse events beyond 6 months, and 100% of physicians and patients reported overall tolerability as “good” at 12 months.

The second long-term study in chronic urticaria evaluated the safety and tolerability of ebastine in 192 patients over a 12-month period [81]. Adverse events were reported for 59.4% of patients during the study period. Most were mild or moderate in severity. The most frequent treatment-related adverse events were weight gain (7.3%), increased appetite (5.2%), headache (4.7%), abdominal pain (4.7%), dry mouth (2.6%), and nervousness (2.6%). At the end of the study, physicians judged the overall tolerability of ebastine as “good” for 87.3% of patients (options: good, fair, poor, not done).

Conclusion

Antihistamines are recommended by allergic rhinitis and urticaria guidelines [1,19]. Because of their favorable efficacy-to-safety ratio, second-generation H1-antihistamines are recommended as first-line therapy for patients with allergic rhinitis/rhinoconjunctivitis or urticaria [1,20,94].

Ebastine is a once-daily, oral, second-generation H1-antihistamine. The standard starting dose of 10 mg can be increased to 20 mg in patients with more severe or difficult-to-control symptoms. The availability of 2 formulations in a number of countries (a standard tablet and a fast-dissolving tablet that disintegrates in the mouth) provides patients with different options to suit their daily lives and preferences. Ebastine has been demonstrated to be efficacious and well-tolerated in patients with allergic rhinitis or chronic urticaria in multiple clinical trials. The results of clinical trials published since the last in-depth review of ebastine support its efficacy and generally good tolerability when administered at recommended doses. In particular, new long-term data confirm its efficacy and tolerability for up to 1 year of treatment in patients with chronic urticaria. Recent findings also confirm that ebastine is one of the lowest-risk antihistamines in terms of cognitive and psychomotor effects. Ebastine was not associated with adverse cardiac effects in clinical trials. Finally, newer studies support previous evidence that in addition to its antihistamine effects, ebastine has modulating effects on the nonhistamine allergic inflammatory processes. This may help explain the beneficial effect of ebastine on nasal obstruction in some patients. No new tolerability or safety signals have emerged from worldwide use of the drug.

In conclusion, ebastine is an effective and well-tolerated second-generation H1-antihistamine for the treatment of symptoms in patients with allergic rhinitis or urticaria. Newer data support the findings of earlier clinical trials and further endorse the usefulness of ebastine in daily clinical practice.

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Conflicts of Interest

The author reports having served as a consultant to FAES Farma, GlaxoSmithKline, LETI, Mundipharma, Novartis, Sanofi, and ThermoFisher. He has also been paid lecture fees by FAES Farma, GlaxoSmithKline, LETI, Novartis, Sanofi, and Stallergenes and has received received grant support for research from ALK, Sanofi, and ThermoFisher.

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■ **Joaquín Sastre**

Allergy Service, Fundación Jiménez Díaz
Av Reyes Católicos 2, 28040 Madrid, Spain.
E-mail: jsastre@fjd.es

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