

Review article

Ebastine in allergic rhinitis and chronic idiopathic urticaria

Histamine is a key mediator in the development of allergy symptoms, and oral H₁-antihistamines are among the most widely used treatments for symptomatic relief in conditions such as allergic rhinitis and chronic urticaria. Ebastine is a second-generation antihistamine which has been shown to be an effective treatment for both seasonal and perennial allergic rhinitis. In controlled clinical trials in adult and adolescent patients with allergic rhinitis, ebastine 10 mg once-daily improved symptoms to a significantly greater extent than placebo and to a similar extent as loratadine 10 mg and cetirizine 10 mg (both once-daily), while ebastine 20 mg proved to be more effective than these two comparator antihistamines. In addition, ebastine was significantly more effective than placebo at relieving the symptoms of chronic idiopathic urticaria. Ebastine provides efficacy throughout the 24-h dosing interval with once-daily administration and clinical benefit is seen from the first day of treatment. Small studies have found beneficial effects for ebastine in patients with other disorders, including cold urticaria, dermographic urticaria, atopic asthma, mosquito bites and (in combination with pseudoephedrine) the common cold. In addition to the regular ebastine tablet, a fast-dissolving tablet (FDT) formulation, which disintegrates in the mouth without the aid of a drink, is also available. It has been shown to be bioequivalent to the regular tablet, and to be significantly more effective than desloratadine at reducing histamine-induced cutaneous wheals. A number of patient surveys demonstrated that the majority of individuals who tried the fast-dissolving formulation reported it to be convenient for use, fast-acting and preferred it to their previous antihistamine medication. Perhaps most importantly, a large proportion of patients indicated that they would prefer to use this new formulation in the future. Ebastine has a rapid onset of action and it can be administered once-daily, with or without food. Dose modifications are not needed in elderly patients, or in those with renal or mild to moderate hepatic impairment. Ebastine is generally well-tolerated, and clinical studies showed that at usual therapeutic doses of 10 and 20 mg once-daily, it had no clinically relevant adverse effects on cognitive function and psychomotor performance or on cardiovascular function. In conclusion, ebastine is an effective and generally well-tolerated treatment for allergic rhinitis and chronic idiopathic urticaria. In addition to the regular tablet formulation, ebastine is available as a FDT, providing a treatment option that is particularly convenient for patients.

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Allergic disorders represent a worldwide health problem, and the prevalence of conditions such as allergic rhinitis is increasing (1, 2). In addition to having a negative effect on patients' daily activities and quality of life, allergic disorders are associated with a considerable economic burden (2, 3). Histamine is a key mediator in the development of allergy symptoms, acting predominantly via H₁-receptors (4). Consequently, oral H₁-antihistamines are among the most widely used treatments in the management of these conditions (4, 5).

This review summarizes the pharmacological and clinical profile of ebastine, a second-generation H₁-receptor antagonist. Two formulations of ebastine are available – a regular tablet and a fast-dissolving tablet (FDT). Much of the data concerning the use of the regular formulation of ebastine in patients with allergic rhinitis have been reviewed previously (6, 7). In addition to providing an overview of these findings, this article also expands on the use of ebastine in chronic idiopathic urticaria, considers its potential role in other indications, and review data on the FDT formulation.

Background

Allergic rhinitis

Allergic rhinitis is a chronic disorder mediated by IgE that involves inflammation of the nasal membrane after exposure to an allergen. The principal symptoms of rhinitis include rhinorrhoea, nasal itching, sneezing and nasal obstruction, which commence soon after exposure and continue while the allergen remains present (8).

Allergic rhinitis is a common condition, with a prevalence as high as 40%, depending on age and geographical location (1). In the US alone, as many as 40 million people are affected by the disease (9). In Western Europe, the prevalence of clinically confirmed allergic rhinitis was 23% on the basis of an analysis of six countries, with a range of 17% (Italy) to 29% (Belgium) for individual countries (10).

The prevalence of the condition appears to be increasing (1, 2), and a number of possible contributory factors have been suggested. These include higher levels of air pollution, increased numbers of dust mites in modern houses with central heating and reduced ventilation, and changes in the pattern of childhood infection (2, 11). The 'hygiene hypothesis' proposes that reduced exposure to allergens and micro-organisms during childhood leads to an underdeveloped immune system and an increased risk of allergic disease (2).

Allergic rhinitis is associated with various other conditions, including asthma, sinusitis, conjunctivitis and nasal polyps (1, 3). Asthma and allergic rhinitis are linked epidemiologically and pathophysiologically (8, 12). The two conditions frequently coexist, and allergic rhinitis has been identified as a risk factor for asthma (8, 12). Inflammation of the nasal and bronchial airways is evident in both disorders, and it is hypothesized that they share a common inflammatory process that affects both the upper and lower airways (12).

Although it is not usually a serious condition, allergic rhinitis has a marked negative effect on patients' quality of life, and can be associated with impaired sleep and reduced performance and productivity (2, 3). Very few studies have assessed the costs of managing allergic rhinitis in Europe (13). However, in one study, the direct medical cost of treating the disease in France was estimated to be Euro 510 million in 1997 (14), which is significantly higher than the costs for treating diseases such as epilepsy and colorectal cancer (13). Interestingly, in the US alone, it accounts for 3.5 million lost work-days and 2 million lost school-days each year (3). Consequently, it is also associated with a high economic burden (2, 3), and ranks fifth amongst chronic diseases in the US for overall costs (including direct costs associated with medical care and indirect costs such as those associated with absenteeism or reduced productivity) (3). Despite the significant effect it has on people's lives, allergic rhinitis often goes undiagnosed; one study

estimated that 45% of those affected were not formally diagnosed (10).

Traditionally, allergic rhinitis was classified into seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR), on the basis of the time of exposure (8). SAR is caused by allergens found outdoors, such as pollen and moulds. PAR is most commonly caused by allergens found indoors, such as house dust mites, moulds, animal dander and cockroaches. However, this division is not exact; for example, some pollens are present throughout the entire year, while symptoms associated with perennial allergies can vary over time. In addition, many patients are sensitive to several different allergens, further blurring the division (8).

In 2001, the Allergic Rhinitis and its Impact on Asthma (ARIA) group and the WHO jointly introduced a new classification system on the basis of the duration and severity of symptoms (8). The main division are the following:

- Intermittent allergic rhinitis: symptoms <4 days/week or <4 weeks.
- Persistent allergic rhinitis: symptoms >4 days/week and >4 weeks.

Severity is classified as:

- Mild: normal sleep + no impairment of daily activities, sport or leisure + no impairment of work and school + no troublesome symptoms.
- Moderate-severe: greater or equal to one of the following: – abnormal sleep; impairment of daily activities, sport, leisure; impaired work and school; troublesome symptoms (8).

On the basis of a population survey in Europe, approximately half of the patients had PAR according to the traditional SAR/PAR classification, while approximately one-third had persistent allergic rhinitis using the ARIA classification (10).

Chronic idiopathic urticaria

Urticaria is characterized by the development of wheals and/or angio-oedema. Recently, attempts have been made to rationalize the classification of urticaria. For example the European Academy of Allergology and Clinical Immunology (EAACI) guideline (5) divides the disorder into three main groups: spontaneous urticaria (i.e. no external physical cause), physical urticaria and other urticaria disorders. The spontaneous urticaria heading includes the subgroups of acute and chronic urticaria.

Chronic urticaria is characterized by recurrent wheals that arise spontaneously several days per week for at least 6 weeks. The wheals are accompanied by erythema and itching, and sometimes also angio-oedema (15). Historically, the term chronic idiopathic urticaria was frequently used, because the aetiology was often not clear. However,

various causes of chronic urticaria have now been identified, including autoimmune disease, food or chemical allergies and chronic bacterial infections (16). According to the EAACI classification, chronic idiopathic urticaria would fall within the chronic urticaria subgroup under the heading of spontaneous urticaria.

The prevalence of chronic urticaria is estimated to be around 1% (16). The itching can be debilitating and the visible nature of the skin changes can affect social activities. As a result, chronic urticaria can have adverse effects on work and social life and severely affect patients' quality of life (17, 18).

Relevance of allergic/inflammatory cascade

Allergic rhinitis is an immunological disorder involving IgE-mediated inflammation (12). Like other allergic disorders, allergic rhinitis involves initial sensitization, during which allergen-specific IgE binds to receptors on mast cells and basophils, followed by an allergic/inflammatory response on subsequent re-exposure to the allergen (19). The allergic response can be divided into early and late phases and involves a wide range of cells and mediators (Fig. 1) (20).

Early phase response. Within 5 min of re-exposure to the allergen, mast cell degranulation leads to the release of preformed mediators (e.g. histamine and proteases), and within 15 min to the synthesis of newly generated mediators (e.g. leukotrienes, prostaglandins, platelet-activating factor and various cytokines [interleukins, bradykinin, tumour necrosis factor, granulocyte-macrophage stimulating factor]). These mediators cause vasodilatation, increased glandular secretions and sensory nerve stimulation, leading to the immediate symptoms in allergic rhinitis, such as sneezing, rhinorrhoea, itching and some congestion (19).

Late phase response. The late phase response occurs around 3–12 h after allergen exposure. The early mediators recruit circulating inflammatory cells, includ-

ing eosinophils, basophils, monocytes and lymphocytes, leading to further mediator release, and promoting inflammation and tissue damage. This results in an increase in symptoms, particularly congestion (19).

The pathogenesis of urticaria is complex and a range of underlying mechanisms may be involved in the different types of chronic urticaria. These include IgE receptor autoantibodies, chronic infections and nonallergic food intolerance (15, 16). However, ultimately, symptoms result from the release of mast cell mediators. In particular, histamine causes increased capillary permeability and vasodilatation, leading to the wheal and flare reaction characteristic of urticaria (5).

Role of antihistamines

As discussed, histamine is a key mediator involved in the pathophysiology of both allergic rhinitis and urticaria. In the context of allergies, histamine acts principally through H_1 -receptors in relevant tissues. Consequently, H_1 -receptor antagonists play an important role in the treatment of allergic disorders. It is possible that these drugs actually act as inverse agonists, stabilizing the receptor in an inactive conformation (4).

In patients with allergic rhinitis, antihistamines relieve symptoms such as rhinorrhoea, sneezing and itching but are generally less effective against nasal congestion (21). They are also effective at reducing the symptoms of urticaria, such as wheals and itching (5).

First-generation antihistamines, such as diphenhydramine and chlorphenamine (chlorpheniramine), provide effective relief of symptoms; however, they can be associated with sedation and anticholinergic effects (21). Second-generation antihistamines, including ebastine, do not cross the blood–brain barrier as easily as first-generation drugs and are less likely to cause sedation, while still providing effective symptomatic relief (21).

Ebastine

Ebastine is a second-generation H_1 -receptor antagonist with an oxypiperidine-based structure, whose active form is the metabolite carebastine (Fig. 2). Ebastine is administered orally once-daily and is indicated for the treatment of the symptoms of allergic rhinitis and chronic idiopathic urticaria, and in some countries for relief from mosquito bites or atopic dermatitis.

Pharmacological profile

Pharmacokinetic properties

Ebastine is absorbed rapidly after oral administration, but undergoes extensive first-pass metabolism to its active metabolite, carebastine (22, 23). Consequently, plasma

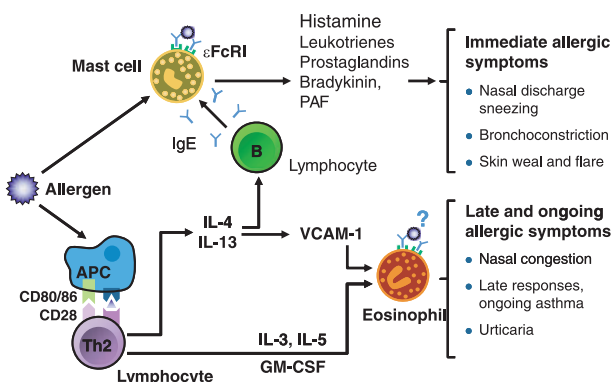


Figure 1. The allergic inflammatory cascade (with permission from Blackwell-Munksgaard) (20).

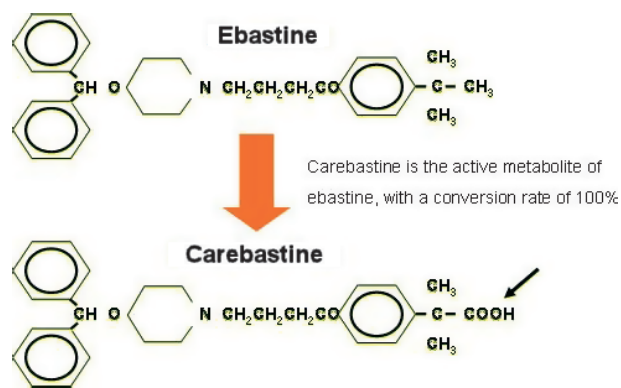


Figure 2. Structure of ebastine and its active metabolite carebastine.

concentrations of ebastine are extremely low (23, 24), and carebastine concentrations were measured in pharmacokinetic studies. Key pharmacokinetic parameters for carebastine are summarized in Table 1.

The pharmacokinetics of carebastine are linear, with values for both peak plasma concentration ($C_{\max}$) and area under the plasma concentration-time curve (AUC) being dose-dependent (22, 24). $C_{\max}$ for carebastine was achieved 4–6 h after single oral doses of ebastine 5–40 mg (24). Steady-state concentrations were achieved after 4 days of administration (24). $C_{\max}$ at steady-state was up to twofold higher than that after a single dose of ebastine 20 mg (23, 24).

Food intake was shown not to affect the pharmacokinetics and gastrointestinal absorption of the parent compound ebastine following administration of single oral doses of 5, 10, 20 and 40 mg, and multiple doses of 20 mg once-daily for 7 days (24). On the basis of another study in 652 patients treated with ebastine 20 mg once-daily for 2 weeks, steady-state concentrations of carebastine were 15% higher when ebastine was administered with food than without food ($P < 0.05$) (25). However, there was no significant difference in the percentage improvement in rhinitis symptoms between those taking ebastine with food and without food in this study (25). Consequently, ebastine can be administered with or

without food and similar levels of antiallergic activity are achieved.

Carebastine is highly bound to plasma proteins ($> 95\%$) (24). After a single dose of ebastine 10 mg, the apparent volume of distribution of carebastine was reported to range from 90 to 143 l, which is indicative of extensive distribution throughout the body (26, 27). Metabolism of ebastine is principally via cytochrome P450 (CYP) enzymes (28). CYP3A4 is responsible for *N*-dealkylation to a desbutyrphenone metabolite whereas hydroxylation, which leads to the production of carebastine, is mediated by other CYP enzymes (28). It has been shown that CYP2J and CYP4F, are involved in the hydroxylation of ebastine (29) with a major role being played by CYP2J2 in this metabolic pathway (30).

The clearance of ebastine was 4.8 l/h after a single dose of 10 mg (26). Urinary excretion accounts for 66% of the elimination of the administered dosage, principally in the form of conjugated metabolites (31), and the terminal elimination half-life ($t_{1/2}$) of carebastine is generally 16–25 h (23, 32).

Effects of age and gender. The pharmacokinetics of ebastine are not affected by gender (23). Generally, there are no clinically relevant differences in the pharmacokinetics of ebastine/carebastine between young adults and elderly patients. In one study, carebastine $t_{\max}$ was statistically significantly shorter in elderly patients than in younger ones after a single dose of ebastine 10 mg (4.8 vs 5.7 h; $P < 0.004$), but did not differ between the age groups after multiple dosing (4.5 vs 5.1 h) (26). In another study, carebastine AUC_{last} was increased (10 088 vs 7457 ng/ml/h) and $t_{1/2}$ prolonged (26 vs 19 h) in elderly patients compared with younger ones after 5 days administration of ebastine 20 mg (both $P < 0.05$); however, AUC_{0-24} and $C_{\max}$ values did not differ significantly, and the differences were not considered clinically significant (23). Dose modifications are not necessary in elderly patients.

In children aged 6–12 years who were administered a single dose of ebastine syrup 5 or 10 mg, the pharmacokinetics of carebastine were linear (33). After a dose of 10 mg, a $C_{\max}$ of 209 ng/ml was reached after 3.4 h; AUC was 3602–3316 ng/ml/h and $t_{1/2}$ was 10–14 h (33).

Hepatic and renal impairment. The presence of mild to severe renal or hepatic impairment does not alter the pharmacokinetics of carebastine to a clinically significant extent, despite changes in $t_{1/2}$ occurring in some studies. Renal impairment had no significant effect on the pharmacokinetics of carebastine (6, 31, 34) except for a prolongation of $t_{1/2}$ in patients with moderate or severe renal impairment in one study (23–26 h vs 17–19 h in healthy volunteers; statistics not reported) (6). Hepatic impairment had no clinically relevant effect on the pharmacokinetic parameters of carebastine (32). Dose modifications are not necessary in patients with renal or

Table 1. Key pharmacokinetic properties of carebastine following administration of single or multiple doses of ebastine 10 or 20 mg once-daily to healthy young volunteers (22–24, 26, 27, 30, 32)

	Single dose		Multiple dose	
	10 mg	20 mg	10 mg	20 mg
$C_{\max}$ (ng/ml)	80–115	157–243	130–162	273–396
$t_{\max}$ (h)	2.6–5.7	1–5	5.1	4.5–5
AUC (ng/ml/h)	1755–3189	5721	2742	4200–5608
$t_{1/2}$ (h)	10.3–19	15	19	15–24.5

$C_{\max}$, maximum plasma concentration; $t_{\max}$, time to $C_{\max}$; AUC, area under the plasma concentration-time curve; $t_{1/2}$, elimination half-life.

mild–moderate hepatic impairment. The maximum dose evaluated in patients with severe hepatic impairment was 10 mg once-daily and therefore this is the maximum recommended dose for this particular subgroup of patients.

Drug interactions. As ebastine is partly metabolized by CYP3A4, there is the possibility of interactions between ebastine and drugs that are metabolized via the same enzyme system, such as ketoconazole and erythromycin. Co-administration of ketoconazole with ebastine led to significant alterations in the pharmacokinetics of both ebastine and carebastine (35). In healthy volunteers receiving ebastine 20 mg once-daily, the addition of ketoconazole 400 mg once-daily for 8 days increased AUC, C_{max} and t_{max} of carebastine by 1.4-, 1.1- and 3.4-fold, respectively (all $P < 0.05$), while these parameters increased 43-, 16- and twofold for ebastine (all $P < 0.05$). Carebastine $t_{1/2}$ increased from 25 to 81 h. Importantly, the greater exposure to ebastine and its main metabolite resulting from co-administration with ketoconazole was not accompanied by a significant increase in cardiac repolarization as measured by QTc interval (35).

Co-administration of erythromycin with ebastine also altered the pharmacokinetics of ebastine and carebastine. For example, ebastine 20 mg co-administered with erythromycin 2400 mg daily for 10 days led to increases in AUC and C_{max} for both carebastine and ebastine of two- to threefold compared with ebastine administered alone (6). In volunteers receiving ebastine 10 mg, the addition of erythromycin 4800 mg daily increased carebastine $t_{1/2}$ from 17 to 22 h (6).

In contrast, there was no significant interaction between cimetidine, another CYP inhibitor and ebastine (36). Other studies showed that there were no significant interactions between ebastine and diazepam (37) or alcohol (38).

Pharmacodynamic properties

Antihistamine activity. The antihistamine activity of ebastine has primarily been assessed using cutaneous histamine challenge tests. In most studies, histamine solution was injected intradermally and the surface area of the resulting wheal (and in some studies also the flare) was measured 15 min after challenge.

Ebastine at doses ≥ 10 mg significantly ($P < 0.05$) reduced histamine-induced cutaneous wheal response compared with placebo in healthy adult volunteers (22, 39–41) and adult patients with allergic rhinitis (42, 43). Reduction in wheal size with ebastine 10 mg compared with placebo over a 24-h period after intradermal histamine challenge is shown in Fig. 3 (42). In a study performed in children (aged 6–12 years) with allergic rhinitis, a single dose of ebastine syrup 5 or 10 mg significantly reduced histamine-induced wheal and flare compared with baseline for up to 28 h (33).

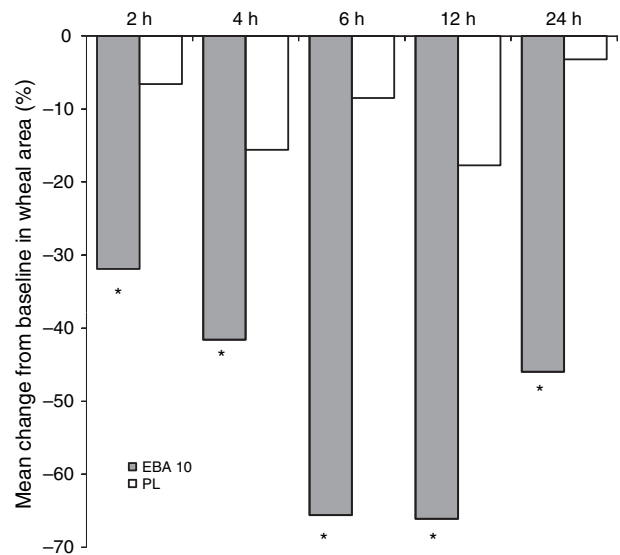


Figure 3. Antihistamine effect of ebastine 10 mg. Percentage reduction in wheal area compared with baseline, following intradermal histamine challenge. Data from a double-blind, placebo-controlled study in 40 patients with allergic rhinitis who received a single dose of ebastine 1, 3, 10 or 30 mg (42). Data for the approved dosage of ebastine 10 mg are shown in comparison with placebo. * $P < 0.05$ vs placebo.

Following single doses of ebastine 1–30 mg, peak inhibition of wheals after intradermal histamine testing occurred between 2 and 12 h (22, 42). The effect was dose-dependent and lasted for at least 24 h, at which time wheals were still reduced by approximately 50% with ebastine 10 mg compared with placebo (22, 42). The inhibitory effect of ebastine on the cutaneous histamine reaction (wheal and flare) had disappeared by 5 days after stopping treatment (44).

Overall, ebastine 10 mg has been shown to be as effective at inhibiting the histamine-induced wheal response as several other antihistamines, including loratadine, cetirizine, fexofenadine and mizolastine, whilst ebastine 20 mg proved to be more effective than the antihistamines with which it was compared. For example:

- A single dose of ebastine 10 mg reduced histamine/grass pollen skin reactivity after 4 and 8 h to a similar extent to that seen with cetirizine 10 mg, loratadine 10 mg, fexofenadine 120 mg and mizolastine 10 mg in patients with allergic rhinitis (43). Ebastine 20 mg once-daily reduced histamine-induced wheal significantly ($P < 0.05$) more than seen with loratadine 10 mg or fexofenadine 120 mg at 24 h after a single dose and also 24 h after the last dose following 5–7 days' treatment in healthy volunteers (40, 41). The comparison with loratadine also included assessments at 4 and 8 h after administration; ebastine was significantly more effective at these timepoints ($P < 0.05$) (40).

- The reduction in histamine-induced wheal with ebastine 10 mg was similar to that produced by cetirizine 10 mg at 24 h after the end of a multiple dose regimen (39). Ebastine 20 mg reduced wheals significantly ($P < 0.05$) more than cetirizine 10 mg and loratadine 10 mg at 24 h after a single dose and 24 h after the last dose following 6–7 days' treatment (39, 40). The authors noted that the results of these trials confirm the longer-term effectiveness of ebastine 20 mg, which was superior to that of cetirizine 10 mg and loratadine 10 mg, and this may result from a more sustained effect of its metabolite carebastine, or from a more prolonged capacity to bind to the histamine-receptor. Importantly, the durability of ebastine's effectiveness over a 24-h period during continued therapy confirms its suitability as a true once-daily treatment in allergic disorders.
- Flare response after cutaneous histamine challenge was assessed in several studies comparing ebastine with loratadine, cetirizine or fexofenadine, and the results were generally consistent with those for the wheal area (39–41, 45).

Ebastine 10 and 30 mg both significantly protected against histamine-induced bronchoconstriction compared with placebo in asthmatic patients, although there was no apparent dose-response relationship (46). As histamine is only one of many mediators contributing to airways obstruction in chronic persistent asthma, it is unlikely that H_1 -receptor antagonists such as ebastine will provide major benefit in such patients. Nevertheless, its use in allergic rhinitis may give some added benefit in terms of protecting the lower airways in patients with co-existent asthma.

Antiallergy effects. The antiallergy effects of ebastine have been assessed by cutaneous and nasal challenge with allergens, and through the measurement of inflammatory mediators.

In patients with an allergy to house dust mite, cat dander, grass pollen or birch pollen, both wheal and flare responses to allergen were reduced significantly ($P < 0.01$) by ebastine 20 mg in relation to placebo at 6, 24 and 48 h after completing 7 days' treatment (44). In this skin prick test study, the inhibitory effect of ebastine on wheal had disappeared by day 4 after discontinuing treatment, and the effect on flare by day 3.

In patients with grass pollen allergy, a single dose of ebastine 10 mg reduced the diameter of grass pollen-induced wheals at 4 and 8 h postdosing to a significantly greater extent than placebo ($P = 0.013$) and by a similar amount to other antihistamines, including loratadine 10 mg, cetirizine 10 mg, fexofenadine 120 mg and mizolastine 10 mg (43). In the same study, all antihistamines, including ebastine 10 mg, led to a significant ($P < 0.05$) reduction in nasal blockage

and sneezing, although not rhinorrhoea compared with placebo at 4 h after nasal provocation with grass pollen (43). In another nasal provocation study in patients with grass pollen allergy, the mean number of pollen grains needed to achieve an allergic reaction was significantly higher in patients treated with ebastine 10 and 20 mg compared with recipients of placebo (both $P < 0.05$) (47).

In addition to blocking the H_1 -receptor, antihistamines often have other effects that contribute to their antiallergy effects. Consequently, the effect of ebastine on various mediators of inflammation has been investigated:

- In nasal polyp cells *in vitro*, ebastine 0.1–10 $\mu\text{mol/l}$ significantly ($P < 0.05$) inhibited the anti-IgE-induced release of prostaglandin D_2 (PGD_2) and leukotrienes C_4/D_4 (LTC_4/D_4), with IC_{30} values of 2.57 and 9.6 $\mu\text{mol/l}$. Ebastine also inhibited the release of cytokines, including granulocyte-macrophage colony-stimulating factor (GM-CSF), tumour necrosis factor- α and interleukin-8. Carebastine inhibited the release of PGD_2 , but was markedly less active than ebastine (IC_{30} of 8.14 $\mu\text{mol/l}$) and, furthermore, it had little effect on cytokine release (47).
- In patients with grass pollen allergy, ebastine 10 and 20 mg reduced the release of GM-CSF in nasal secretions in a dose-dependent manner ($P < 0.05$ for ebastine 20 mg vs placebo), but did not have a significant effect on the release of other cytokines, or on LTC_4/D_4 or PGD_2 (47).
- In patients with grass pollen allergy, a significantly smaller increase in nasal eosinophilia (assessed using nasal smears) occurred following treatment with ebastine 10 mg in relation to placebo ($P = 0.004$) (43). The effect of ebastine was similar to that seen with loratadine, cetirizine, fexofenadine and mizolastine.
- In patients with bronchial asthma, 4 weeks' treatment with ebastine 10 mg once-daily led to significant reductions from baseline in serum eosinophil cationic protein (ECP) level ($P < 0.0014$) and peripheral blood eosinophil count ($P < 0.0253$) in atopic patients, but not in nonatopic patients (48). Eosinophil cationic protein is a marker of eosinophil activation and airways inflammation.

Conclusions

- The pharmacokinetics of ebastine/carebastine is linear in the therapeutic dose range; maximum plasma concentrations of carebastine are achieved 4–6 h after dosing; and steady-state is reached after 4 days.
- Ebastine can be administered once-daily, with or without food.

- Dose modifications are not needed in elderly patients, or in those with renal or mild–moderate hepatic impairment. The maximum dose in patients with severe hepatic impairment is 10 mg once-daily.
- Co-administration of ebastine with ketoconazole or erythromycin increases systemic exposure to ebastine and carebastine, but these changes do not appear to have clinical consequence.
- Ebastine produces a dose-dependent inhibition of the cutaneous reaction to histamine.
- Ebastine 20 mg reduces histamine-induced wheals to a greater extent than loratadine, cetirizine and fexofenadine at 24 h after dosing.
- Ebastine increases the threshold quantity of pollen required to induce an allergic response in nasal provocation tests.
- The antihistamine/antiallergy effect of ebastine lasts for more than 48 h.

Clinical profile

The efficacy of once-daily oral ebastine in the management of allergic rhinitis and chronic idiopathic urticaria has been evaluated in a number of well-designed clinical trials in adults and adolescents. Most trials were randomized, double-blind and placebo- or active-controlled.

Almost all major clinical trials with the regular formulation of ebastine in allergic rhinitis were performed before the current ARIA classification of ‘intermittent’ and ‘persistent’ symptoms was introduced in 2001. Patients in these studies were classified using the earlier ‘seasonal’ and ‘perennial’ terminology, and the latter terms will be used when discussing these trials in the current review. In one noncomparative study specifically evaluating nasal obstruction, patients were classified as having persistent allergic rhinitis (49). In addition, patient preference studies with the FDT formulation also used the ARIA classification (see Ebastine fast-dissolving tablets).

Historically, the term ‘chronic idiopathic urticaria’ has been widely used to encompass all forms of chronic urticaria arising without a known aetiology, although it is now known that in fact there are a number of different causes of spontaneous chronic urticaria. According to EAACI guidelines, chronic idiopathic urticaria would fall within the subgroup ‘chronic urticaria’ under the main classification of ‘spontaneous urticaria’ (15). Clinical trials with ebastine enrolled patients with chronic idiopathic urticaria.

Allergic rhinitis

A number of controlled trials have evaluated the use of ebastine in patients with SAR and PAR. As mentioned above, almost all trials were performed prior to the

introduction of the ARIA classification of intermittent and persistent disease. The diagnosis of allergic rhinitis was generally on the basis of medical history and a positive response to skin prick test or IgE test. Patients were aged ≥ 18 years or ≥ 12 years depending on the study, although in one trial in PAR children aged 6–17 years were evaluated. Key exclusion criteria included a history of desensitization therapy or hypersensitivity to antihistamines, the need for additional rhinitis medicines, and the presence of significant concurrent illness that could affect evaluation. Patients generally underwent a washout period of 24 h to 3 months for common rhinitis medications.

In most trials, the evaluation of efficacy was on the basis of an assessment of nasal symptoms (rhinorrhoea, sneezing, itching and obstruction) and ocular symptoms (e.g. itch, discharge, conjunctivitis). Symptoms were assessed individually and/or as composite scores such as total symptom score, nasal index (a composite of the four nasal symptoms) or perennial index (nasal symptoms excluding obstruction). Symptoms were usually rated by patients and/or investigators using a graded scale, where 0 = absent; 1 = mild; 2 = moderate; 3 = severe. In some studies, the patients recorded symptom scores twice daily, taking into account their symptoms over the previous 12 h (reflective score) and their symptoms at the time of recording (snapshot score). For PAR, the perennial index (which excludes obstruction) was also assessed. In most studies, the primary efficacy parameter was the change from baseline in the total symptom score, although in some trials it was a global evaluation of symptomatic improvement/efficacy by the patient or investigator.

Seasonal allergic rhinitis. A number of trials showed that ebastine was significantly more effective than placebo at relieving symptoms of SAR (Table 2) (50–57). Overall, most trials found that doses of 10 and 20 mg once-daily were more effective than placebo (Table 2). One trial demonstrated that ebastine 20 mg administered either in the morning or afternoon and ebastine 10 mg administered in the morning (but not when administered in the afternoon) were more effective than placebo at reducing the total symptom score. In terms of the patient’s global evaluation of efficacy ebastine 20 mg (but not 10 mg), whether taken in the morning or afternoon, was rated significantly ($P < 0.05$) better than placebo (53).

In terms of dose response, few trials included statistical comparisons of different ebastine doses. One study ($n = 101$) reported no significant difference in efficacy between ebastine 10 and 20 mg once-daily (51); whereas, in another trial ($n = 343$) the mean change from baseline in total symptom score was significantly greater with ebastine 20 mg than with 10 mg (54). A study in 459 patients with ragweed allergy evaluating ebastine 1, 3, 10, 20 and 30 mg, found that efficacy plateaued at 20 mg once-daily as estimated by changes

Table 2. Clinical trials of ebastine in adults and adolescents (≥ 12 years) with seasonal allergic rhinitis (SAR)

Study	Treatment (dose: mg od)	n	Duration (weeks)	Results
Comparisons with placebo				
Ankier & Warrington (50)	Eba 10–40 (titrated on the basis of response)	19	4	Eba significantly more effective than placebo for relief of nasal symptoms ($P < 0.05$) but not for ocular symptoms. Global efficacy rated as very good/good by significantly more patients and physicians for Eba than placebo (overall 79–84% for Eba vs 35–40% for placebo; $P < 0.01$).
	Placebo	20		
de Molina et al. (51)	Eba 10	32	1	Eba 10 and 20 significantly more effective ($P < 0.05$) than placebo for relief of nasal symptoms (except obstruction) and ocular symptoms (except watering eyes with Eba 20) and for both patient and physician global efficacy rating ($P < 0.05$ and $P < 0.01$). Treatment considered moderate/good/excellent by significantly more patients and physicians for Eba 10 and 20 than for placebo (overall, 61–72% for Eba vs 33–36% for placebo. No significant differences between Eba 10 and 20.
	Eba 20	36		
	Placebo	33		
Peláez (52)	Eba 10	116	2	Eba 10 significantly more effective ($P < 0.01$ where stated) than placebo for relief of nasal symptoms (except obstruction) and ocular symptoms, and for physician global efficacy rating (good/excellent response for 56% vs 46% of pts; $P = 0.008$).
	Placebo	85		
Storms (53)	Eba 10 am	78	3	Eba 10 am, Eba 20 am, Eba 20 pm (but not Eba 10 pm) were significantly more effective ($P < 0.05$) than placebo for improvement in TSS (primary variable) and relief of individual nasal and ocular symptoms. Mean change from baseline in TSS was -3.5 vs -3.2 for Eba 10 am and pm vs -4.0 vs -3.6 for Eba 20 am and pm vs 2.7 for placebo, respectively.* Eba 20 am and pm (but not Eba 10) were significantly better than placebo for patient global efficacy rating ($P < 0.05$). Efficacy maintained during a 4-month noncomparative extension.
	Eba 10 pm	79		
	Eba 20 am	81		
	Eba 20 pm	80		
	Placebo	78		
Comparisons with other antihistamines				
Gehanno et al. (54)	Eba 10	116	2	No significant difference between groups for change in TSS (primary variable) at study end. Significantly greater reduction in TSS with Eba 20 than Eba 10 or Cet 10 after 1 week ($P < 0.05$). In a subgroup with more severe symptoms ($n = 159$), greater reduction in TSS at study end with Eba 20 than Eba 10 ($P = 0.027$) but not vs Cet 10. Physician (but not patient) global efficacy ratings significantly favoured Eba 20 (but not 10) over Cet 10 (improvement in 85% vs 73%; $P = 0.048$).
	Eba 20	111		
	Cet 10	116		
Hampel et al. (55)	Eba 10	188	4	Patients had ragweed SAR. Significantly ($P < 0.05$) greater reductions in reflective NI score with or without congestion (but not in rTSS with [primary variable; see Fig. 4] or without congestion) and in all four snapshot composite scores with Eba 20 compared with Lor 10. No significant difference between Eba 10 and Lor 10 for any composite scores. Eba 10 and 20 more effective than placebo for all composite scores ($P \leq 0.01$). Patient and physician global ratings did not differ significantly from placebo for any active treatment group.
	Eba 20	186		
	Lor 10	189		
	Placebo	186		
Ratner et al. (56)	Eba 20	282	2	Patients had autumn SAR (e.g. ragweed). Significantly greater reduction in mean daily rTSS (primary endpoint) with Eba 20 [-3.46 (-32.3%)] than with Lor 10 [-2.77 (-24.6%); $P = 0.0018$] or placebo [-2.64 (-23.4%); $P = 0.0024$]. Reductions in all mean daily reflective nasal and ocular scores (composite and individual) were significantly greater with Eba 20 than Lor 10 or placebo ($P < 0.04$). Patient and physician global ratings did not differ significantly between active treatments.
	Lor 10	279		
	Placebo	142		
Ratner et al. (57)	Eba 10	140	4	Patients had ragweed SAR. Significantly greater reduction in mean daily rTSS (primary variable; see Fig. 4), other daily reflective and morning snapshot composite scores and most individual scores, with Eba 20 than with Lor 10 ($P < 0.05$). No significant difference between Eba 10 and Lor 10. All treatments more effective than placebo ($P < 0.05$). Patient and physician global ratings did not differ significantly between active therapies.
	Eba 20	143		
	Lor 10	141		
	Placebo	141		

All trials used a randomized, double-blind, parallel group design.

am, morning; Cet, cetirizine; Eba, ebastine; Lor, loratadine; n, number of patients; NI, nasal index; od, once-daily; pm, afternoon; pts, patients; rTSS, reflective total symptom score; TSS, total symptom score.

*Estimated from graph.

from baseline in mean total rhinitis symptom scores over a 24-h period (58).

In comparisons with other second-generation antihistamines, ebastine was as effective as cetirizine and at least as effective as loratadine in the treatment of symptoms of SAR (Table 2). Ebastine 10 and 20 mg once-daily was as effective as cetirizine 10 mg once-daily at improving total symptom score after 2 weeks in patients with SAR (Table 2) (54). Maximum symptom relief was achieved earlier (within 1 week) with ebastine 20 mg than with ebastine 10 mg or cetirizine. Ebastine 20 mg was significantly more effective than ebastine 10 mg in a subgroup of patients with more severe symptoms at baseline ($P = 0.027$) (54).

In patients with SAR, ebastine 10 mg and loratadine 10 mg were similarly effective in producing symptomatic relief, whereas ebastine 20 mg was significantly more effective than loratadine 10 mg for some parameters (Table 2). For example, in two of these trials ebastine 20 mg reduced the primary endpoint, mean daily reflective total symptom score, significantly more than that seen with loratadine 10 mg (56, 57). In the third trial, although there was no significant difference in the mean daily reflective total symptom score, nasal index scores were significantly lower with ebastine 20 mg than loratadine 10 mg ($P < 0.05$) (55). Results for the primary efficacy variable from the two trials that included both ebastine 10 and 20 mg are shown in Fig. 4. Data from

several other studies reported only as abstracts also provide evidence for ebastine being as effective as loratadine (59, 60).

In addition, a meta-analysis of four of the studies discussed above (55–57, 59) found a significant difference in favour of ebastine when comparing mean change from baseline in overall mean daily reflective total symptom score over the first 2 weeks of treatment [-3.61 (-35.4%) for ebastine 20 mg vs -3.05 (-29.0%) for loratadine 10 mg; $P < 0.001$] (61). Another pooled analysis of three trials in ragweed-induced allergic rhinitis looked specifically at nasal congestion symptom scores (morning and evening reflective and snapshot scores; total of 6 scores) (62). In this analysis, ebastine 20 mg was more effective than placebo in six out of 6 scores, ebastine 10 mg in four out of 6 scores and loratadine 10 mg in one out of 6 scores (62).

Perennial allergic rhinitis. Ebastine was significantly more effective than placebo at relieving most symptoms of PAR (Table 3) (63–66). In one study, both ebastine 10 and 20 mg produced significant reductions in nasal index score compared with placebo after 1 week, but by 12 weeks only ebastine 20 mg was associated with a significant benefit; the higher dose was also associated with a significant improvement in perennial index score compared with placebo (Table 3) (63).

Ebastine 10 and 20 mg were significantly more effective than loratadine 10 mg at reducing perennial index, nasal index and some individual symptom scores (nasal discharge and congestion) after 4 weeks in patients with PAR (Fig. 5) (65). In another study, both ebastine 10 mg and cetirizine 10 mg significantly improved patient symptom scores after 4 weeks' treatment (66).

In a noncomparative, study ebastine 10 mg daily was used to treat 30 children (aged 6–17 years) with perennial rhinitis (67). After 30 days, there was a disappearance/reduction in histamine wheals and specific antigen wheals in 93% and 68% of patients respectively, and the response to nasal or conjunctival provocation disappeared/decreased in 69–80% of patients. Clinical efficacy was evaluated as good/very good in 22 (73%) of the patients (67).

Persistent allergic rhinitis. One small noncomparative study specifically evaluated the effects of ebastine on nasal obstruction in patients meeting the ARIA definition of persistent allergic rhinitis using objective criteria (49). In this pilot study, in which all 20 patients received ebastine 20 mg once-daily for 3 weeks, ebastine improved nasal airflow and exhibited a decongestant effect. Rhinomanometry-assessed nasal airflow increased significantly by 59% compared with baseline ($P = 0.0001$) and the percentage of airflow reversibility in decongestion tests decreased significantly (from 111% at baseline to 46% after ebastine; $P = 0.0003$). Treatment with ebastine also significantly relieved nasal symptoms compared

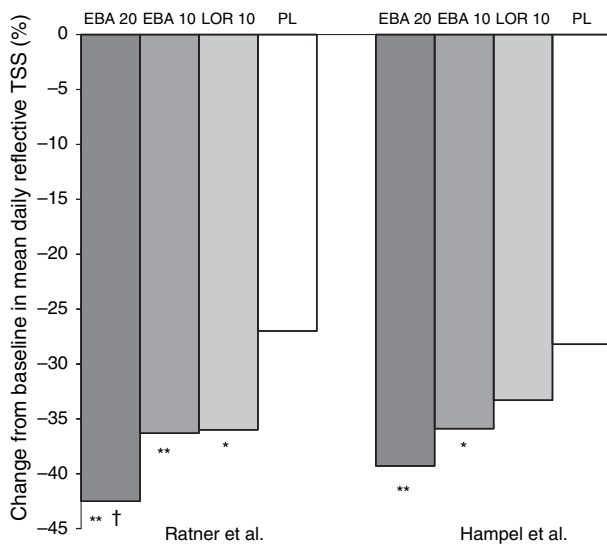


Figure 4. Efficacy of ebastine in patients with seasonal allergic rhinitis. Comparisons of ebastine 10 and 20 mg once-daily (EBA 10; EBA 20) with loratadine 10 mg once-daily (LOR 10) and placebo (PL) for reduction in mean daily reflective total symptoms score during 4 weeks' treatment. Data from randomized, double-blind trials in 565 patients (57) and 749 patients (55). * $P < 0.01$; ** $P < 0.001$ vs placebo; † $P < 0.05$ vs loratadine.

Table 3. Clinical trials of ebastine in adults and adolescents (≥ 12 years) with perennial allergic rhinitis (PAR)

Study	Treatment (dose: mg od)	<i>n</i>	Duration (weeks)	Results
Comparisons with placebo				
Bousquet et al. (63)	Eba 10	88	12	Compared with placebo, significantly greater reduction from baseline in mean daily PIN score (primary variable) with Eba 20 [−1.9 (−39%) vs −1.2 (−26%); <i>P</i> = 0.006], in morning PIN score with Eba 20 (<i>P</i> = 0.007) and Eba 10 (<i>P</i> = 0.047) and in mean daily NI score with Eba 20 (<i>P</i> = 0.015). No significant difference between Eba 10 and 20. Condition rated as somewhat/greatly improved by significantly more patients and physicians for Eba 10 and 20 than for placebo (overall 72–84% for Eba vs 58% for placebo; <i>P</i> < 0.02).
	Eba 20	102		
	Placebo	100		
Picado Vallés et al. (64)	Eba 10	76	1	Eba 10 significantly more effective than placebo for relief of most rhinitis symptoms, including all nasal symptoms (except obstruction) and ocular symptoms (<i>P</i> < 0.05). Efficacy rated as excellent/good/moderate by significantly more patients and physicians for Eba 10 (54–55%) than placebo (31–32%; <i>P</i> < 0.01).
	Placebo	75		
Comparisons with other antihistamines				
Davies et al. (65)	Eba 10	103	4	Eba 10 and 20 significantly (<i>P</i> < 0.05) more effective than Lor 10 at reducing PIN (primary variable; see Fig. 5), NI, nasal discharge and nasal congestion. No significant difference between Eba doses. Condition rated as improved by significantly (<i>P</i> < 0.05) more patients and physicians for Eba 10 and 20 (79–85%) than for Lor 10 (65–66%).
	Eba 20	111		
	Lor 10	103		
Murrís-Espin et al. (66)	Eba 10	108	4	No significant difference between Eba 10 and Cet 10 for mean % change in NI at study end. However, Cet 10 led to a greater mean % change in NI after 1 week (<i>P</i> < 0.04), reduced nasal congestion in a larger proportion of patients at study end (<i>P</i> < 0.04) and more Cet recipients were symptom-free at study end (<i>P</i> = 0.02).
	Cet 10	106		

All trials used a randomized, double-blind, parallel group design.

Cet, cetirizine; Eba, ebastine; Lor, loratadine; n, number of patients; NI, nasal index; od, once-daily; PIN, perennial index; pts, patients; TSS, total symptom score.

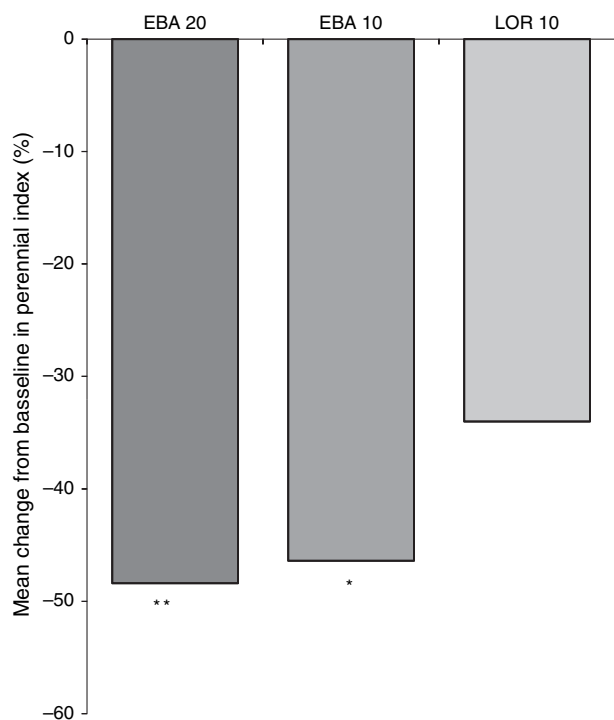


Figure 5. Efficacy of ebastine in patients with perennial allergic rhinitis. Comparison of ebastine 10 and 20 mg once-daily (EBA 10; EBA 20) with loratadine 10 mg once-daily (LOR 10) in the reduction of mean daily perennial index after 4 weeks' treatment. Data from a randomized, double-blind trial involving 317 patients (65). * $P = 0.015$; ** $P = 0.003$ vs loratadine.

with baseline values, including symptoms associated with irritation (rhinorrhoea, itch, sneezing; $P = 0.0001$) and nasal obstruction ($P = 0.0025$) (49).

Urticaria

Chronic idiopathic urticaria. The efficacy of ebastine in patients with chronic idiopathic urticaria was evaluated in two randomized, double-blind, controlled trials (Table 4) (68, 69). In an active comparator trial, ebastine was compared with terfenadine. Although terfenadine has since been withdrawn from the market for safety reasons, the results are discussed briefly. Chronic idiopathic urticaria would now come under the classification of spontaneous urticaria according to EAACI guidelines (15).

In one study, the patients were enrolled if they had a 3-month history of chronic urticaria with only cutaneous eruptions; patients with other types of urticaria (e.g. physical) were excluded (68). In the other, patients were required to have cutaneous urticarial lesions present on ≥ 2 days per week for 6 consecutive weeks if not receiving treatment, 3 weeks if receiving steroids, or 7 days if receiving other urticaria treatment (e.g. H₁-receptor antagonists) (69). While a majority of the patients in this trial had idiopathic urticaria, some had physical or cholinergic urticaria (69). Other treatments were discontinued 1 day to 2 weeks before the start of the study. Efficacy evaluations included change from baseline in symptoms (including itch and number and size of wheals), and a global evaluation of efficacy by patients

Table 4. Clinical trials with ebastine in patients with chronic idiopathic urticaria

Study	Treatment (mg)	n	Duration (weeks)	Results
Peyri et al. (68)	Eba 10 od Placebo	100 104	2	Eba 10 significantly reduced itching and the number and size of wheals compared with placebo (all $P < 0.001$). Global efficacy rated by patients and physicians as good/moderate in significantly more Eba than placebo recipients (80–83% vs 51–55%; $P < 0.001$).
Kalis (69)	Eba 10 od* Ter 60 bid Placebo	69 78 64	12	Efficacy of Eba 10 od was similar to Ter 60 bid for relief of individual symptoms and for global patient and physician ratings. Both active treatments significantly ($P < 0.05$) more effective than placebo at reducing severity of itch and number of wheals and lesions, as assessed by patients. Eba (but not Ter) significantly more effective than placebo according to patient and physician global ratings (improvement in 73–75% Eba recipients vs 51–52% placebo recipients; $P \leq 0.004$).

Trials used a randomized, double-blind, parallel group design.

Eba, ebastine; n, number of patients; bid, twice daily; od, once-daily; pts, patients; Ter, terfenadine.

*Active drug administered in the morning and placebo in the evening.

and physicians. Symptoms were graded on a 4-point scale, where 0 = none and 4 = severe.

Ebastine 10 mg once-daily was significantly more effective than placebo at reducing the symptoms of urticaria, including itching and the number and size of wheals (Table 4) (68, 69). Ebastine was also significantly more effective than placebo according to patient and physician global ratings; overall, treatment was rated as effective, or condition as improved, in 80–83% of ebastine recipients vs 51–55% placebo recipients (Table 4). The efficacy of ebastine was apparent from 1 week after starting the treatment, as indicated by significantly greater reductions in itch severity, number and size of wheals with ebastine than with placebo at this timepoint ($P < 0.001$) (68).

The efficacy of ebastine 10 mg once-daily was significantly superior to placebo ($P < 0.004$) and similar to that of terfenadine 60 mg twice daily with regards relieving the symptoms of urticaria in a study involving 211 patients with chronic urticaria (most of whom had idiopathic urticaria) (Table 4) (69). Histamine challenge testing found similar reductions in the size of histamine-induced wheals with ebastine and terfenadine.

Cold and dermatographic urticaria. Several second-generation antihistamines have been shown to be effective in the treatment of acquired cold urticaria, which is a chronic physical urticaria rather than a spontaneous urticaria (5, 15). A small double-blind, placebo-controlled, crossover study investigated the effects of ebastine in 22 patients with a minimum 6 week history of cold urticaria (70). Treatment with a single dose of ebastine 20 mg led to a significant reduction in the number of patients who developed wheals (4 vs 17 patients; $P < 0.001$), moderate/severe pruritis (5 vs 18; $P < 0.001$) or moderate/severe burning (4 vs 12; $P < 0.05$) during cold challenge testing (70). Overall, this small trial suggests ebastine could have a role in preventing symptoms of acquired cold urticaria. Similarly, in a double-blind crossover preliminary study, ebastine 20 mg reduced pruritis, burning and the number

of wheals in seven adult patients with dermatographic urticaria who underwent a challenge involving shearing forces (71). Furthermore, ebastine had no negative effect on cognitive performance or mood in this study.

Combination therapy

In a randomized, double-blind, factorial-design study involving 403 patients with SAR, the global efficacy rating for the combination of ebastine 10 mg plus pseudoephedrine retard 120 mg once-daily for 2 weeks was higher than that for either agent administered alone (72). Compared with baseline, a significant improvement in nasal obstruction was seen after 1 week in the combination therapy group (76%; $P = 0.03$) and the pseudoephedrine group (67%; $P = 0.05$).

Other indications

Asthma. On the basis of two small studies, ebastine appears to have some beneficial effects in patients with atopic asthma. A noncomparative study in 20 patients with either atopic ($n = 11$) or nonatopic ($n = 9$) asthma assessed the effects of ebastine on serum ECP, peripheral blood eosinophil count, peak expiratory flow rate (PEFR) and thresholds for airway hypersensitivity ($D_{\min}$) (48). After 4 weeks' treatment with ebastine 10 mg once-daily, there were significant decreases in serum ECP ($P < 0.014$) and eosinophil count ($P < 0.0105$), and an increase in PEFR ($P < 0.026$), compared with baseline. When analysed according to either the presence or the absence of atopy, significant changes were apparent in atopic patients only; mean ECP decreased from 25 to 16 mg/l ($P < 0.0014$), eosinophil count decreased from 468 to 417 mm^3 ($P < 0.0253$) and PEFR increased from 411 to 440 l/min ($P < 0.0189$). Ebastine had no significant effect on $D_{\min}$ in either atopic or nonatopic patients. Overall, these data suggest that ebastine may inhibit airway inflammation in patients with atopic asthma.

A small double-blind, randomized study in 12 atopic asthmatics found that ebastine 10 or 30 mg daily for 3 days provided significant protection against histamine-induced bronchoconstriction in an inhalation challenge ($P = 0.008$ for 10 mg and $P = 0.001$ for 30 mg) compared with placebo (46). Ebastine 10 mg also provided significant protection against methacholine-induced bronchoconstriction, but it was not associated with bronchodilation as measured by forced expiratory volume in 1 s (46).

Mosquito bites. Mosquito bites are associated with itching, wheals and delayed bite papules. A double-blind, placebo-controlled cross-over trial evaluated the effects of 4 days' treatment with ebastine 20 mg in 28 bite-sensitive adults exposed to *Aedes communis* bites (73). Itching intensity and bite lesion size were measured 15 min and 2, 6 and 24 h after the bite. Ebastine significantly decreased itching and median bite size compared with placebo at 15 min ($P < 0.001$). It also significantly reduced itching at 2- and 24 h ($P < 0.01$). At the 2-, 6- and 24-h timepoints the median bite size in ebastine-treated subjects was always less than that in placebo-treated subjects, but the differences did not achieve statistical significance at these timepoints. These results indicate ebastine was effective at reducing the immediate symptoms after a mosquito bite, and it also decreased itching associated with the delayed bite lesion, although it did not affect the size of the delayed lesion (73).

Common cold. In a double-blind, controlled trial, the efficacy of ebastine 10 mg in combination with pseudoephedrine 120 mg once-daily was compared with placebo in 204 patients with the common cold (74). Patients had to have had symptoms of the common cold in the 36 h prior to enrolment, including runny nose and blocked nose, and were excluded if they had a history of rhinitis. The primary variable was a global assessment of efficacy by the physician. After 3 days' treatment, the proportion of patients in whom efficacy was rated as excellent or good was significantly higher in the active treatment group than among recipients of placebo (76% vs 58%; $P < 0.001$). Although there was no difference between the groups for change in nasal peak flow, the sum of scores for nasal and ocular symptoms and the total symptom score decreased significantly in the ebastine-pseudoephedrine group compared with placebo ($P < 0.006$ and $P < 0.0016$ respectively).

Overall, this trial indicated that the combination of ebastine plus pseudoephedrine helped relieve the symptoms of the common cold.

Conclusions

- Ebastine is an effective treatment for the relief of symptoms in adults and adolescents with allergic rhinitis or chronic idiopathic urticaria.

- Ebastine is effective when administered once-daily.
- Ebastine was superior to placebo in clinical trials in allergic rhinitis and chronic idiopathic urticaria.
- Ebastine 10 mg was at least as effective as loratadine 10 mg and cetirizine 10 mg at reducing symptoms in patients with allergic rhinitis, whereas ebastine 20 mg was generally more effective than the comparator antihistamines at these dosages.

Safety profile

General tolerability

In clinical trials in patients with allergic rhinitis or chronic urticaria, ebastine was generally well-tolerated, with an incidence of adverse events similar to that for placebo (50, 52, 53, 55–57, 63, 64, 68). In active comparator trials, the incidence of adverse events with ebastine was similar to that with loratadine (55, 57, 65) or cetirizine (54, 66) in patients with allergic rhinitis. Most adverse events were of mild or moderate severity.

On the basis of data from more than 3000 patients treated with ebastine 10 or 20 mg, the most common adverse events in adults and adolescents aged > 12 years included headache (7.9%), drowsiness (3%) and dryness of the mouth (2.1%). Adverse events occurring at a frequency of $< 1\%$ included abdominal pain, dyspepsia, epistaxis, rhinitis, sinusitis, nausea and insomnia (31). In children < 12 years old, the most frequent adverse events were headache (11.7%), dryness of the mouth (2.6%) and drowsiness (1.25%) (31). Ebastine continued to be well-tolerated in the longer term, on the basis of a 4-month noncomparative study in allergic rhinitis and a 3-month study in urticaria, with the most common adverse event reported being headache (53, 69).

Cardiac safety

Some H_1 -receptor antagonists, such as terfenadine and astemizole, have been associated with prolongation of the QTc interval and the development of arrhythmias such as *torsade de pointes* (8). This effect is thought to relate to blockade of potassium channels involved in the repolarization phase of the cardiac action potential by certain drugs, and not to blockade of the H_1 -receptor. It is therefore not a class effect for H_1 -receptor antihistamines (8). Nonetheless, evaluation of any potential for cardiac toxicity is an important requirement for drugs of this type.

Data on the cardiac safety of ebastine are available from studies in healthy volunteers and clinical trials in patients, and show that at therapeutic doses of 10 and 20 mg daily, ebastine has no clinically relevant effect on the QTc interval (75), including in elderly patients (26).

The effects of supratherapeutic doses of ebastine on the ECG were assessed in a randomized, investigator-blinded, four-way cross-over study in 32 healthy male

volunteers (76). Volunteers received ebastine 60 and 100 mg once-daily (three and five times the maximum recommended dose), terfenadine 180 mg twice daily (three times the recommended dose) and placebo, for 7 days each, with treatment periods separated by a 13-day washout period. ECGs were performed for up to 24 h at baseline and after each treatment.

Compared with placebo, mean heart rate increased significantly with ebastine (increase of 8–10 beats/min; $P \leq 0.002$), but not with terfenadine (76). Ebastine was associated with a decrease in uncorrected QT interval, which was consistent with the increased heart rate seen in these groups. When analysed using Bazett's correction, ebastine 60 mg did not cause a significant change in QTc interval compared with placebo (+3.7 vs +1.4 ms). The change in QTc with ebastine 100 mg (+10.3 ms) was statistically significantly greater than that seen with placebo ($P = 0.0034$); however, it was significantly less than that seen with terfenadine (+18.0 ms; $P < 0.05$). In addition, when QTc was corrected using the Friderica formula, there was no significant difference between either dose of ebastine and placebo, whereas terfenadine caused a significantly greater change in QTc interval than ebastine or placebo ($P < 0.0001$) (76). No recipients of ebastine experienced an increase in QTc interval of $> 10\%$ (75).

It has been reported that Bazett's formula may be inaccurate at describing the relationship between QTc and RR intervals, and it is possible that this formula overcorrected for heart rate in this study, leading to the significant difference in Bazett-corrected QTc interval seen in the ebastine 100 mg group (76). Additional analysis of the data from this study confirmed that the outcome for ebastine depended on the particular correction used, whereas results for terfenadine were largely independent of the formula (77). Using an optimized correction for QTc interval, regression analysis comparing off- and on-drug data for each treatment group demonstrated no significant effect with either dose of ebastine, whereas terfenadine significantly prolonged QTc ($P < 0.00025$). The outcome was similar when off- and on-drug data for individual volunteers was analysed (77).

Additional evidence regarding the effects of supratherapeutic doses of ebastine come from an open-label, placebo-controlled, single increasing-dose study in six healthy male volunteers (78). Doses of 80, 150, 300 and 500 mg were evaluated. There were neither intra-individual changes in QTc interval of $> 10\%$ (assessed using the formulas of Bazett, Fridericia and Malik), nor did any QTc value > 500 ms occur at any dose including 500 mg (which is 25 times the maximum recommended dose) (78).

The ECG effects of ebastine at therapeutic doses (10 and/or 20 mg once-daily) were evaluated in pharmacokinetic studies in elderly volunteers (multiple doses) and in those with renal or hepatic insufficiency (single doses) (75). Ebastine was not associated with any clinically relevant changes in ECG parameters in these patients,

although there was high inter- and intra-subject variability in QTc interval in patients with severe renal impairment (75). In children aged 6–11 years, ebastine syrup 15 mg/day for 6 days was not associated with any adverse ECG effects (75).

Data are also available from patients with allergic rhinitis. On the basis of pooled data from five double-blind, placebo-controlled clinical trials in adult patients with allergic rhinitis (842 treated with ebastine 1–30 mg/day; 360 treated with placebo), there were no statistically significant differences in mean QTc interval between ebastine and placebo as assessed by serial ECGs (74). No clinically significant findings were noted over periods of 24 h in 226 patients who underwent Holter monitoring (75). In an open-label study in adult patients treated with ebastine 10 or 20 mg once-daily for 4 months, no patient had a QTc interval prolonged to ≥ 500 ms or by $\geq 20\%$ (75).

No clinically significant ECG effects were noted in a pooled analysis of QTc data from three clinical trials in children aged 6–12 years with allergic rhinitis who received ebastine 1–10 mg/day. One patient who underwent Holter monitoring experienced second-degree AV block while receiving ebastine 5 mg; 6 days after withdrawal from the study, there were no abnormal findings (75).

Ketoconazole and erythromycin can be associated with QTc prolongation. In addition, co-administration of either of these agents with ebastine increases the plasma concentration of ebastine (see Pharmacokinetic properties). In a study in healthy volunteers, co-administration of ebastine 20 mg/day with ketoconazole 400 mg/day for 8 days led to a statistically significant increase in QTc interval of 12 ms compared with baseline ($P < 0.00001$); however, this increase was not significantly different from that seen with ketoconazole alone (7 ms) (35). No participant experienced a QTc interval > 500 ms. The addition of a single dose of ebastine 20 mg to patients receiving multiple doses of erythromycin stearate 2000 mg/day did not cause any clinically relevant changes in QTc interval (75). However, co-administration of ebastine 20 mg/day with erythromycin ethylsuccinate 2400 mg/day for 10 days led to a statistically significant increase in QTc interval of 10 ms above that seen with erythromycin alone ($P < 0.05$) (75). Two recipients of the combination had an increase in QTc of $> 10\%$. The authors considered these effects to be clinically insignificant and concluded that the cardiac safety profile of ebastine was very favourable.

CNS tolerability

Second-generation antihistamines are generally less sedating than the first-generation antihistamines (79). Based on a review of the literature which assessed the sedative potential of a range of antihistamines the authors calculated a risk : benefit ratio using the number of

cognitive and psychomotor tests in which significant impairment was reported. Ebastine was one of the few antihistamines to produce no impairment in any test and thus had a risk : benefit ratio for sedation of 0 (79).

The lack of sedative effect may be at least partly explained by ebastine displaying low brain H_1 -receptor occupancy (80). In a neuroimaging study in healthy volunteers, it was calculated that ebastine 10 mg occupied 10% of brain H_1 receptors, which was significantly lower than the $\geq 50\%$ occupancy seen with chlorphenamine ($P < 0.01$) (79).

In trials in healthy volunteers, ebastine 10 or 20 mg caused no clinically significant psychomotor or cognitive impairment. The effects of ebastine were generally similar to those of placebo in tests of vigilance, cognitive performance, visual motor coordination, subjective estimates of drowsiness and driving performance (37, 81–84). In one study, ebastine 10 mg caused a marginally significant increase in choice reaction time compared with placebo at 8 h after a single dose (95% CI for the difference 0.01–0.23), and a dose of 50 mg (2.5 times the maximum recommended dose) caused an increase in this parameter at 4 and 8 h (95% CI for the difference at both timepoints 0.01–0.25) as well as modest increases in indices of sedation ($P < 0.05$ vs placebo) (81). Neither dose affected critical flicker fusion.

In trials including a positive control as well as a placebo group, the effects of ebastine 10 and 20 mg were similar to those of placebo, whereas, as expected, the positive controls (clemastine 2 mg and sustained-release triprolidine 10 mg) were associated with significant impairment of cognitive and psychomotor function (82–84). Clemastine impaired visual-motor coordination, decreased vigilance and increased subjective drowsiness in healthy volunteers (82). Compared with clemastine, ebastine 20 mg caused significantly less drowsiness and less general discomfort, and both ebastine 10 and 20 mg caused significantly less impairment in pursuit tracking at 2.5 and 4.5 h after dosing. Ebastine 10 mg caused significantly less impairment of vigilance than clemastine at 2.5 and 4.5 h, as assessed by EEG (82).

Triprolidine was associated with significant impairment of cognitive and psychomotor function compared with placebo, as measured by the simulated car tracking test, Sternberg memory scanning task, line analogue rating scale and Leeds sleep evaluation questionnaire (84). The only significant change seen with ebastine in this study was with a dose of 30 mg (above the maximum recommended dose), which impaired the ability to fall asleep on the first night of treatment ($P < 0.05$) and increased subjective sedation scores at 4 h on day 5 ($P < 0.05$) compared with placebo. Statistical comparisons between ebastine and triprolidine were not reported (84).

Second-generation antihistamines, including ebastine, cause less impairment of driving performance than the first-generation antihistamines (85). In a study evaluating

parameters of driving performance in actual traffic, ebastine 10–30 mg daily did not cause any significant changes in driving performance after 1 and 5 days of treatment, whereas sustained-release triprolidine 10 mg daily significantly reduced the ability to control weaving of the car compared with ebastine 10 mg ($P < 0.012$) and the ability to follow speed manoeuvres of a leading car compared with placebo ($P < 0.003$) (83).

Treatment with ebastine 20 mg daily generally did not enhance the psychomotor impairing effects of a single dose of diazepam 15 mg (37). Compared with diazepam alone, the only significant difference seen with the combination of ebastine plus diazepam was an increase in body sway with eyes open (but not with eyes closed) at 3 h after dosing ($P = 0.022$).

Conclusions

- Ebastine is generally well-tolerated. The most frequently reported adverse events in clinical trials were headache, somnolence and dry mouth.
- At the recommended doses of 10 and 20 mg daily, ebastine has no clinically relevant effect on the QTc interval.
- Co-administration of ebastine with ketoconazole or erythromycin led to small increases in QTc interval of up to around 10 ms above that seen with ketoconazole or erythromycin alone, but these changes were not considered to be clinically significant.
- At therapeutic doses, ebastine is not sedative and has no clinically relevant effect on cognitive or psychomotor performance, including driving ability.

Ebastine fast-dissolving tablets

The regular formulation of ebastine is usually swallowed with the help of a drink such as water. A new fast-dissolving formulation that is bioequivalent with the regular tablet form has been developed for ebastine. This is a unique freeze-dried medicinal tablet that disintegrates instantaneously in the mouth. This new formulation can be taken without a drink and a number of studies have compared the pharmacological properties of the FDT with the regular formulation, and evaluated its acceptability to patients.

Pharmacological profile

Bioequivalence. Pharmacokinetic bioequivalence between ebastine FDT and the regular ebastine tablet was demonstrated in healthy male volunteers (86). Two randomized, open-label, crossover trials in 30 volunteers compared single doses of both formulations; one study evaluated 10 mg and the other 20 mg. As ebastine is rapidly metabolized to its active metabolite carebastine,

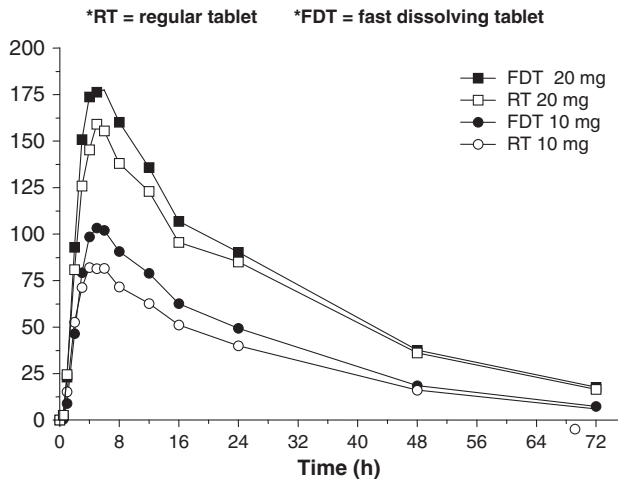


Figure 6. Mean plasma carebastine concentrations after single doses of regular formulation and fast-dissolving ebastine tablets (86).

assessments were on the basis of plasma concentrations of the metabolite. Although C_{max} and AUC for carebastine were slightly higher with ebastine FDT compared with the regular tablet (Fig. 6), ANOVA showed that the point estimates and 90% confidence intervals for these parameters were within the range for equivalence of 0.8–1.25. The FDT disintegrated 12–18 times faster than the regular tablets (5 s vs 60–90 s) (86).

Pharmacodynamic properties. Two studies in healthy adults ($n = 42$ and $n = 36$) compared the effects of ebastine FDT 10 and 20 mg (evaluated in separate studies) with desloratadine 5 mg and placebo with respect to the inhibition of the cutaneous histamine reaction (87, 88). In both of these double-blind, double-dummy, placebo-controlled cross-over studies, volunteers received study medication once-daily for 5 days, with a 7–10 day washout between treatment periods. In each period, skin prick tests were performed at baseline, every 20 min for the first 2 h, at 24 h after the first dose, and at 24 h after the final dose. The primary efficacy variable was the percentage reduction in wheal area from baseline to 24 h after the final dose.

At 24 h after the final dose of treatment, ebastine FDT 10 and 20 mg inhibited the wheal response to histamine challenge significantly more than that seen with desloratadine 5 mg or placebo (87, 88). In the study involving ebastine FDT 10 mg, mean percentage reduction from baseline in wheal area after 5 days was 44.6% with ebastine compared with 17.9% with desloratadine ($P < 0.0001$). Wheal area increased by 2.3% with placebo ($P < 0.0001$ for ebastine and $P = 0.0001$ for desloratadine) (86). In the second study, mean percentage reduction in wheal area after 5 days was 55.8% with ebastine FDT 20 mg vs 26.8% with desloratadine ($P < 0.001$) vs 12.2% with placebo ($P < 0.001$ for

ebastine; $P < 0.002$ for desloratadine) (88). In addition, both ebastine FDT 10 and 20 mg caused significantly greater reductions in wheal area at 24 h after the first dose than desloratadine or placebo ($P < 0.0001$ and $P < 0.001$ respectively).

Patient preference studies

Several qualitative and quantitative studies have evaluated the acceptability of the FDT to patients (89–94). One study used a validated treatment satisfaction questionnaire (93); all other studies surveyed patients using structured interviews.

Surveys of patients with allergies found that the majority would prefer a fast-dissolving formulation to a regular tablet, and that key attributes associated with such tablets included convenience and ease of use (89). In a randomized study in patients with allergic rhinitis given placebo versions of both the FDT and regular ebastine tablet, the FDT was rated significantly better than the regular tablet for general assessment, texture, initial taste, aftertaste and sensation on dissolving. Overall, 83% of patients preferred the FDT (94).

In surveys of patients who had received treatment with active ebastine FDT, the majority of patients expressed satisfaction with the FDT tablet. Most perceived its onset of action to be fast, and considered it to be convenient to use (Table 5). A retrospective, observational study of 461 patients with intermittent or persistent allergic rhinitis, evaluated patient satisfaction with ebastine FDT during the previous 2 months using the validated Treatment Satisfaction Questionnaire for Medication (TSQM) scale (93). Satisfaction with ebastine FDT was high, as indicated by high mean scores for all four dimensions of the TSQM (effectiveness, side-effects, convenience and global satisfaction; see Table 5). Compared with baseline, significant improvements in sneezing, nasal discharge, nasal itching, nasal obstruction and ocular itching were reported ($P < 0.001$) (93).

Conclusions

- Ebastine FDT dissolves rapidly in the mouth and can be taken without the aid of a drink.
- Ebastine FDT is bioequivalent to the regular ebastine tablet.
- Ebastine FDT 10 and 20 mg inhibits the wheal response to histamine challenge significantly more than desloratadine 5 mg or placebo.
- Patients find ebastine FDT convenient and easy to use, perceive it to have a rapid onset of action and report high levels of satisfaction with treatment.
- Ebastine FDT may be of particular help for patients who have difficulty swallowing, gastrointestinal problems, or an active lifestyle without easy access to drinks.

Table 5. Patient preference studies with ebastine fast-dissolving tablet (FDT)

Study	Treatment (mg)	<i>n</i>	Study design* (country)	Results
Roger et al. (89)	FDT 10 or 20	100	Quantitative survey (Spain)	41% of pts had IAR and 57% had PAR. Onset of action of FDT perceived as fast or very fast by 85% of pts, and 77% said it acted faster than their usual antihistamine. Pts also scored it highly for aspects related to convenience and ease of use compared with other oral antihistamines. Overall 96% were satisfied with treatment.
Roger et al. (90)	PL-FDT	60 patients 82 physicians	Qualitative (France, Germany, Belgium, Italy and Finland)	78% of patients and 66% of physicians would be likely to take/prescribe ebastine in the new FDT formulation. FDT formulation of ebastine was preferred both by physicians and patients because it is easier to comply with, more convenient and is associated with a perception of faster onset of action.
Roger et al. (91)	FDT 10 or 20	7686	Market research (Spain)	The majority of pts were satisfied with the physical properties and the rate of dissolution of the tablet, and 93% said they would choose the FDT formulation if given the choice. 88% of the patients want to change their current antihistamine for a new medicinal product with the fast-dissolving tablets formulation.
Roger et al. (92)	FDT 10 or 20 or PL-FDT	2834 pharmacists	Quantitative survey (Spain)	Pharmacists reported that their pts scored the FDT well for time to disintegration, sensation on dissolving, convenience, ease of use and perceived speed of action. 80% said their pts were satisfied/very satisfied with FDT. 38% said their pts preferred FDT, 33% the regular tablet and 25% expressed indifference.
Roger et al. (94)	PL-FDT 10 or 20 vs PL-EBA 10 or 20	420	Market research* (Germany, Italy, Mexico)	70% of pts had IAR and 24% had PAR. Using a rating from 0 (don't like it at all) to 10 (like it very much), PL-FDT was rated better than PL-EBA for general assessment, texture, initial taste, aftertaste and sensation on dissolving (mean scores 7.85–8.30 for the PL-FDT vs 6.6–7.2 for PL-EBA). PL-EBA scored better than PL-FDT for appearance, size and shape. Overall, 83% of patients preferred the PL-FDT.
Roger et al. (93)	FDT 10 or 20	461	Observational study using TSQM† (Belgium, Mexico, Spain)	54% of pts had IAR and 46% had PAR. Pt satisfaction with FDT during the previous 2 months was high, with high mean TSQM scores for all four dimensions: 74.2 (95% CI 72.4–75.9) for effectiveness; 95.3 (95% CI 93.9–96.6) for side-effects; 87.9 (95% CI 86.7–89.1) for convenience and 78.6 (95% CI 76.7–80.4) for global satisfaction. No significant differences between pts with IAR and PAR. Significant improvements in sneezing, nasal discharge, nasal itching, nasal obstruction and ocular itching vs baseline ($P < 0.001$). Onset of action perceived to be fast/very fast by 79% of pts, and 94% said they would like to use FDT again.

EBA, regular ebastine tablet; PAR, persistent allergic rhinitis; PL-EBA, placebo version of regular ebastine; PL-FDT, placebo version of FDT; pts, patients; R, randomized; IAR, intermittent allergic rhinitis; TSQM, Treatment Satisfaction Questionnaire for Medication.

*All studies were noncomparative, retrospective studies except for one that used a randomized crossover design to compare the perceived attributes of placebo versions of EBA and FDT (94).

† TSQM comprises 14 items covering 4 dimensions (effectiveness, side-effects, convenience and global satisfaction), rated on a scale of 0 to 100, with a higher score indicating greater satisfaction.

Second-generation antihistamine: ebastine in clinical practice

The role of histamine in the pathophysiology of both allergic rhinitis and chronic urticaria is well established, and antihistamines are a key element of the management of symptoms in patients with these conditions (5, 21, 95).

The first generation of antihistamines, such as chlorphenamine, were effective at relieving symptoms, but were associated with significant adverse effects, including sedation and anticholinergic effects, and had to be

administered up to four times daily (4). Subsequently, newer antihistamines were developed that were effective with once or twice-daily administration and had minimal sedative effects. These 'second-generation' antihistamines include ebastine as well as cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, mizolastine and rupatadine (95).

In controlled clinical trials in adult and adolescent patients with allergic rhinitis, ebastine 10 and 20 mg once-daily improved symptoms to a significantly greater extent than placebo, and ebastine 20 mg proved to be

more effective than loratadine 10 mg and cetirizine 10 mg. Almost all trials were performed prior to the introduction of the ARIA classification and its recent update (1, 8, 96) and so patient populations in these studies were defined in terms of SAR and PAR; ebastine was effective in patients with both types of allergic rhinitis. Improvement was seen from the first day of treatment and continued throughout the trials (up to 12 weeks). Ebastine was also significantly more effective than placebo at relieving the symptoms of chronic idiopathic urticaria.

It is recognized that H₁-receptor antagonists may have other antiallergy effects in addition to blocking the H₁ receptor (4, 97, 98). Research on this aspect has shown that ebastine increased the threshold quantity of pollen needed to achieve an allergic reaction in patients with grass pollen allergy. Ebastine also decreased nasal eosinophilia and the release of GM-CSF in patients, although effects on other inflammatory mediators were limited.

Although larger trials would be needed to confirm the potential role of ebastine in cold urticaria, dermographic urticaria and atopic asthma, small studies have demonstrated promising results with ebastine administered once-daily in patients with these disorders.

Ebastine was well-tolerated in clinical trials and, at usual therapeutic doses of 10 and 20 mg once-daily, it had no clinically relevant adverse effects on cognitive functioning and psychomotor performance, including having no effect on driving ability.

Some second-generation antihistamines, notably astemizole and terfenadine, were found to prolong the QTc interval and so increase the risk of arrhythmias. However, this was the result of an effect on potassium channels in cardiac myocytes by certain drugs and it was not a class effect of the H₁-receptor antagonists. Studies with ebastine showed that it had no clinically relevant effect on QTc interval either at therapeutic or supratherapeutic doses. Co-administration of ebastine with ketoconazole or erythromycin (both of which inhibit CYP3A4 and can increase the systemic exposure of drugs metabolized via the same enzyme system and thus increase the risk of adverse effects) led to a prolongation of the QTc interval. However, this was only by about 10 ms more than that seen with either ketoconazole or erythromycin alone, and

was considered to be clinically insignificant by the authors.

Ideally, antihistamines should be suitable for administration once-daily (4). This is the case for ebastine, and its long duration of action ensures efficacy throughout the full 24-h dosing interval. Furthermore, whilst a dosage of 10 mg once-daily produces symptomatic relief comparable to that of other second-generation antihistamines, ebastine has the advantage of flexible dosing as a dosage of 20 mg once-daily can be administered for control of more severe/chronic disease (63). Surveys of patients with allergic rhinitis, as well as physicians and pharmacists, have reported a clear preference for FDTs since they were considered to be convenient and easy to use (89–92). The newer, fast-dissolving, formulation of ebastine helps meet these requirements more fully. Ebastine FDT disintegrates in the mouth without the aid of a drink, which potentially makes it easy to take at any time or location. Indeed, evaluation of patient preferences showed that patients generally found the new formulation convenient and preferred it to other oral antihistamines they had taken in the past. This formulation could also be of use in patients with swallowing difficulties or gastrointestinal disorders that might affect absorption.

In conclusion, ebastine is an effective and generally well-tolerated treatment for allergic rhinitis and chronic urticaria. In addition to the regular tablet formulation, ebastine is available as a FDT that disintegrates in the mouth without the aid of a drink, providing a treatment option that is particularly convenient for patients.

Conflicts of interest

The author has received honoraria for consultation services from GSK, Novartis, Phadia, Almirall, Schering-Plough, Stallergenes, ALK-Abello, and Uriach and study grants from GSK, Novartis, Phadia, Schering-Plough, Stallergenes, ALK-Abello, Astra-Zeneca and Uriach.

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