

# Ebastine in the light of CONGA recommendations for the development of third-generation antihistamines

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**Abstract:** In 2003 a consensus group on new-generation antihistamines (CONGA) defined the characteristics required for a third-generation H<sub>1</sub> antihistamine as there had been much controversy about this issue since the early 1990s. One of the antihistamines that had been claimed to belong to such a group is the second-generation antihistamine, ebastine. The objective of this review is to analyze the pharmacology of ebastine, in light of the CONGA recommendations for the development of new-generation antihistamines: (1) anti-inflammatory properties, (2) potency, efficacy and effectiveness, (3) lack of cardiotoxicity, (4) lack of drug interactions, (5) lack of CNS effects, and (6) pharmacological approach. Ebastine seems to have anti-inflammatory properties that help to ameliorate nasal congestion, though this has not yet been conclusively demonstrated. Its pharmacological–therapeutic profile does not differ greatly from that of other second-generation antihistamines. Its cardiac safety has been widely assessed and no cardiac toxicity has been found at therapeutic doses despite initial concerns. The risk of potentially relevant drug interactions has been investigated and ruled out. Ebastine does not produce sedation at therapeutic doses and drug interaction studies with classical CNS depressants have not demonstrated a synergistic effect. Pharmacologically, ebastine is an H<sub>1</sub> inverse agonist. Perhaps the answer to the quest for new-generation antihistamines lies not only in H<sub>1</sub> but in a combined approach with other histamine receptors.

**Keywords:** ebastine, antihistamines, third-generation, CONGA, allergy

## Introduction

Allergic diseases are among the commonest causes of chronic ill health.<sup>1</sup> Discovered in the early 20th century, histamine is one of the major mediators of allergic reactions.<sup>2,3</sup> The work of the Swiss-Italian pharmacologist Daniel Bovet led to the discovery and production of H<sub>1</sub> receptor antihistamines for allergy relief and earned him the Nobel Prize for physiology or medicine in 1957.<sup>4</sup> The first antihistamine, 929 F (thymo-ethyl-diethylamine), was identified by Bovet and Staub in 1937,<sup>5,6</sup> and since then there have been great advances in the development of more efficacious and safer antihistamines. Throughout the last decades, these drugs have been clearly differentiated in first- and second-generation antihistamines.

First-generation antihistamines, such as chlorpheniramine, diphenhydramine, promethazine, and hydroxyzine, are characterized by their high H<sub>1</sub> receptor blocking power, and in spite of their side-effect profile they are still widely used.<sup>7</sup> One of their major downsides is their lack of selectivity for the H<sub>1</sub> receptor as they are able to bind to acetylcholine and serotonin receptors and calcium channels.<sup>8</sup> Furthermore, their lipophilic nature allows them to cross the blood–brain barrier, causing side-effects

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such as decreased alertness, impairment of reaction times, decreased vigilance, and sedation.<sup>9</sup>

Second-generation antihistamines, such as terfenadine, fexofenadine, loratadine, desloratadine, cetirizine, levocetirizine, ebastine, rupatadine, and bilastine, do not penetrate the blood–brain barrier and so provoke minimal central nervous system (CNS) effects. They have greater receptor specificity, with little or no affinity for muscarinic cholinergic receptors. In addition, some second-generation antihistamines exhibit properties, such as anti-inflammatory and analgesic activity, on systems other than H<sub>1</sub> receptors.<sup>7</sup> These properties and other pharmacological and pharmacokinetic differences among second-generation antihistamines are responsible for the emergence of the controversial term “third-generation” antihistamines for newer drugs.

Although second-generation antihistamines have been a clear step forward in the treatment of allergic diseases, they have not been devoid of problems. Cardiotoxicity has been a major issue, provoking the withdrawal of terfenadine and astemizole, for example, from the market<sup>10,11</sup> and introducing the requirement of formal cardiac safety assessment in the drug development paradigm.<sup>12,13</sup> Moreover, it has been demonstrated that some second generation antihistamines may cause somnolence,<sup>14</sup> especially when used at supra-therapeutic doses.<sup>9,15</sup>

In spite of the knowledge we have acquired over the past few decades, the search for the optimal antihistamine drug continues.<sup>16</sup> Coined in 1990, the terms third-generation<sup>17</sup> or “multifunctional” antihistamines have been used laxly and inappropriately. As a result, in 2003, a consensus group on new-generation antihistamines (CONGA), led by Dr Holgate, provided recommendations on the development of new antihistamines.<sup>7</sup>

To date, no antihistamine drug has fulfilled all the criteria proposed by Holgate et al.<sup>7</sup> However, some drugs, such as ebastine, appear to offer advantages that represent a step forward in the development of these so-called third generation antihistamines.

In this review we look critically at the information available on ebastine in the light of the CONGA criteria and present current information on the development of new generation antihistamines.

## CONGA recommendations

CONGA recommendations comprise 6 areas:

1. Anti-inflammatory properties: A third-generation antihistamine should possess anti-allergic properties demonstrable *in vivo*, in humans, at therapeutic doses

and under natural exposure to the offending allergens. It should be superior (in humans) to a comparator devoid of such properties. Nasal obstruction should be affected in a measurable way.

2. Potency, efficacy, and effectiveness: The drug should have a high therapeutic index and differ radically from existing compounds.
3. Lack of cardiotoxicity.
4. Drug interactions: A third-generation antihistamine should not affect cytochrome P450 (CYP) isoenzyme function or be affected by it. This new drug should not displace protein bound medication and it should not affect active transportation mechanisms important in drug absorption and excretion.
5. Lack of CNS effects: The minimum factors for classifying an antihistamine as “non-sedative” should include the study of incidence of subjective sleepiness, objective and psychomotor functions, and positron emission tomography (PET) measurement of H<sub>1</sub>-receptor occupancy.
6. Pharmacological approach: The drug could be either an H<sub>1</sub> blocker with an extra effect or a clean blocker of the H<sub>1</sub> effects, having a special feature (eg, neutral antagonist).

## Ebastine

Ebastine (4-diphenylmethoxy-1-[3-(4-terbutylbenzoyl)propyl] piperidine, Las-W-90, CAS 90729-43-4)<sup>18,19</sup> is a long-acting, second-generation, selective H<sub>1</sub>-receptor inverse agonist, discovered and developed by Almirall SA. After over 18 years of use in more than 80 countries around the globe, the efficacy and safety of ebastine has been extensively demonstrated. Its clinical indications include the treatment of seasonal<sup>20–24</sup> and perennial allergic rhinitis<sup>25,26</sup> and chronic idiopathic urticaria.<sup>27,28</sup> Small studies have found beneficial effects in patients suffering from allergic dermatitis, cold urticaria,<sup>29</sup> dermographic urticaria,<sup>30</sup> atopic asthma,<sup>30,31</sup> mosquito bites,<sup>32</sup> and the common cold (in combination with pseudoephedrine).<sup>33</sup> The pharmacology and the safety and efficacy profile of ebastine have been comprehensively reviewed.<sup>18,19,34,35</sup> When administered *in vivo*, at least one of its metabolites, carebastine, also possess anti-H<sub>1</sub> activity.<sup>36</sup>

## Ebastine according to the CONGA recommendations

### Anti-inflammatory properties

The efficacy of H<sub>1</sub> antihistamines in allergic disorders has traditionally been attributed to their effects on the

histamine receptor.<sup>8</sup> The involvement of histamine in the allergic process has long been known, but as Thurmond et al<sup>37</sup> recently suggested, its importance in modulating this reaction may have been underestimated. The allergic cascade is a complex response that is composed of three distinct immunological phases: sensitisation, early-phase allergic reaction and late-phase allergic reaction.<sup>38</sup> Histamine's role in this cascade comprises several cellular events involving the expression and/or release of cytokines, chemokines, adhesion molecules, and inflammatory mediators.<sup>39</sup> These inflammatory mediators are modulated by H<sub>1</sub> antihistamines, as has been demonstrated both *in vitro* and *in vivo*.<sup>40</sup> While some authors postulate that these effects are independent of the H<sub>1</sub> receptor,<sup>41–43</sup> others relate them to H<sub>1</sub> receptor blockade,<sup>44,45</sup> although recent evidence has shown that both statements could be true.<sup>40</sup>

H<sub>1</sub> receptor-dependent mechanisms involve stabilization of the histamine receptor in its inactive conformation. Consequently, this stabilization inhibits generation of, globin transcription factor 3 (GATA-3), activator protein-1 (AP-1) and nuclear factor  $\kappa$ B (NF- $\kappa$ B).<sup>8,40</sup> AP-1 and NF- $\kappa$ B are important transcription factors in inflammation. They regulate the expression of many pro-inflammatory mediators, such as CCL5/regulation upon transcription normal T cell expressed and secreted (RANTES), and play an important role in the pathogenesis of chronic inflammatory diseases such as asthma and allergy. Both are activated by the H<sub>1</sub> receptor in an agonist-dependent manner, and this activation is inhibited by various H<sub>1</sub>-receptor antihistamines.<sup>40,46</sup>

H<sub>1</sub> receptor-independent mechanisms, however, inhibit histamine release from mast cells and basophils. They also inhibit inflammatory cell activation, and possibly eicosanoid generation and oxygen free radical production.<sup>8</sup> The inhibition of inflammatory cell activation comprises the downregulation of adhesion molecule expression, mediator release, superoxide generation, chemotaxis and cytokine expression, and the upregulation of the number and function of  $\beta$ 2 adrenoceptors. The clinical relevance of this effect is still under discussion due to the fact that very high drug concentrations are needed and it is unlikely that these concentrations are achieved with therapeutic doses.

Modulation of adhesion molecule expression is important because molecules, such as inter-cellular adhesion molecule 1 (ICAM-1) influence the activity of eosinophils, mast cells, macrophages and lymphocytes, all of which play key roles in the allergic reaction.<sup>8,47</sup> This modulating mechanism has been demonstrated *in vitro* and *in vivo*. *In vitro*, it has been shown that antihistamines reduce ICAM-1 expression on nasal and

conjunctival epithelial cells, and it has also been observed that they reduce inflammatory infiltration after allergen challenge and during natural exposure. The mechanism underlying modulation of ICAM-1 is downregulation of the NF- $\kappa$ B transcription factor (that is necessary for adhesion molecule expression). Roumestan et al demonstrated that second generation H<sub>1</sub> receptor antihistamines, mizolastine and desloratadine, inhibit NF- $\kappa$ B activity via two distinct pathways. One of these involves the H<sub>1</sub> receptor (referred to earlier in this article), and the other is independent from this receptor. These authors also provided evidence that azelastine represses AP-1 activity via the same mechanisms.<sup>40</sup>

The inhibition of mediator release is another mechanism whereby antihistamines affect the allergic inflammatory reaction, independently of their anti-H<sub>1</sub> activity. *In vitro* studies have consistently established that H<sub>1</sub> antihistamines inhibit the release of mediators from both mast cells and basophils. Nevertheless, these results are difficult to replicate *in vivo* as 3- or 4-fold therapeutic concentrations of antihistamines would be needed.<sup>8</sup> As cytokines appear to contribute to the activation of basophils and eosinophils (chiefly interleukins [IL] 4 and 5) and the establishment and maintenance of allergic inflammation, the effect of H<sub>1</sub> antihistamines on cytokine secretion has also been studied with myriad compounds.

The inflammatory modulation of ebastine has been reported in various *in vitro*, and *in vivo* studies.<sup>31,36,48</sup> Campbell et al<sup>48</sup> performed an *in vitro* study using dispersed cells obtained from surgically resected nasal polyps. They examined the effects of ebastine and carebastine on the release of leukotrienes C4/D4 [LTC4/D4] and prostaglandin D2 [PGD2]) after stimulation by anti-IgE and the spontaneous release of granulocyte macrophage colony stimulating factor [GM-CSF], tumour necrosis factor- $\alpha$  [TNF- $\alpha$ ] and interleukin-8 [IL-8]. *In vitro*, ebastine and carebastine were shown to block the release of anti-IgE-induced eicosanoids LTC4/D4 and PGD2. Ebastine inhibited release of the two mediators by 30% at clinically relevant concentrations (IC<sub>30</sub> = 2.57–9.6  $\mu$ mol/L). Carebastine was less effective (IC<sub>30</sub> = 8.14  $\mu$ mol/L).

Campbell et al<sup>48</sup> also performed a double blind crossover study (n = 12) to compare the effect of ebastine 10 and 20 mg once daily with that of placebo on the release of inflammatory mediators. *In vivo*, ebastine 20 mg induced an increase in the mean threshold number of pollen grains required to induce a positive response compared with placebo ( $P < 0.003$ ) and ebastine 10 mg ( $P < 0.02$ ). Ebastine was found to decrease the release of GM-CSF in a dose-dependent manner. It did not significantly alter the release of LTC4/D4 and PGD2

observed in most patients during the nasal provocation test and it did not affect cytokine release.

Regarding the secretion of cytokines, Nori et al evaluated the effect of ebastine on the production of T helper 2 (T<sub>H</sub>2) type cytokines. Using T cells derived from healthy non-atopic volunteers, they showed that ebastine inhibited the secretion *in vitro* of IL-4 and IL-5, but not that of IL-2 and interferon  $\gamma$  (IFN $\gamma$ ).<sup>49</sup>

Ebastine's role in reducing airway inflammation has been suggested by Horiguchi et al<sup>51</sup> who performed an open label study in which 20 patients with bronchial asthma (11 with atopic disease and 9 with nonatopic disease) received ebastine 10 mg/day for 4 weeks. Serum eosinophil cationic protein (ECP) levels, peripheral blood eosinophil counts, morning peak expiratory flow rate (PEFR) and thresholds for airway hyper-responsiveness were determined before and after treatment. As a result, the atopic patients observed a decrease in serum ECP levels (from  $25 \pm 3$  mg/L to  $16.3 \pm 2.4$  mg/L;  $P < 0.0014$ ) and in peripheral blood eosinophil counts (from  $468.2 \pm 44.4/\text{mm}^3$  to  $417.3 \pm 47.8/\text{mm}^3$ ;  $P < 0.0253$ ). PEFR was significantly increased in the atopic patients ( $410.9 \pm 16.1$  L/min to  $440 \pm 19.1$  L/min;  $P < 0.0189$ ). No changes were found in the nonatopic patients and there was no change in the threshold for airway hyper-responsiveness.

The results of another *in vivo* study by Ciprandi et al have been published recently.<sup>50</sup> This group evaluated IFN $\gamma$  production by peripheral blood mononuclear cells (PBMNC) using different stimuli in un-treated and treated (ebastine 20 mg) patients with persistent allergic rhinitis. Clinical changes were assessed by subjective (total nasal symptom score and visual analogue scales [VAS]) and objective (rhinomanometry) evaluations. The main result from this study was that IFN $\gamma$  production stimulated by grasses and *Dermatophagoides farinae* was statistically increased ( $P < 0.0001$  and  $P < 0.0015$  respectively) in patients receiving ebastine.

Nasal obstruction is the leading symptom in patients with allergic rhinitis, with allergic inflammation, mucosal congestion and mucus hypersecretion playing key roles.<sup>51</sup> CONGA recommendations suggest that nasal obstruction should be affected in a measurable way by newer antihistamines. The decongestant activity of ebastine was first suggested by Ratner et al<sup>52</sup> after they performed 3 double-blind, randomized, placebo-controlled, parallel group studies that compared ebastine 20 mg, ebastine 10 mg, loratadine 10 mg and placebo in the control of symptoms of ragweed-induced rhinitis. Although the results showed that ebastine at both doses reduced nasal congestion as compared to placebo, nasal

congestion was measured subjectively (ie nasal congestion symptom scores). The effect of ebastine on nasal obstruction was further evaluated in a pilot study (n = 20) by Ciprandi et al.<sup>53</sup> These authors evaluated nasal symptoms (rhinorrhea, itching, sneezing and obstruction), nasal airflow (by means of rhinomanometry) and the response to a decongestion test with naphazoline 1 mg/mL in patients with persistent allergic rhinitis before and after 3 weeks of treatment with ebastine 20 mg/day. Results were positive and showed that ebastine induced symptom relief as assessed by comparing basal nasal symptom total scores with post-treatment scores ( $P = 0.0013$ ). Ebastine also increased nasal airflow ( $P = 0.0001$ ) and in the decongestion test the percentage of reversibility diminished significantly from baseline (111%) to post ebastine treatment (46%,  $P = 0.0003$ ). Although a double-blind, randomized controlled trial with active comparators and placebo would be the most suitable design to obtain conclusive evidence, this pilot study showed that nasal obstruction can be affected in a positive way by antihistamine treatment with ebastine.

Presently available evidence indicates that some second generation antihistamines possess properties that modulate the allergic inflammatory cascade by means of H<sub>1</sub> receptor dependent and independent mechanisms. All in all, *in vitro*, *in vivo* and clinical studies using subjective and objective measurements seem to indicate that ebastine possesses this characteristic and ameliorates nasal congestion to some degree. However, to clarify this effect a clinical trial including a comparator devoid of modulator effect should be carried out. Until this piece of the puzzle is put in place we can not conclusively claim that ebastine complies with the first requirement exposed in the CONGA. Including more than one comparator in future studies would be especially useful as it would provide further information that could help to elucidate the allergic/inflammation pathways that each antihistamine involves.

## Potency, efficacy, and effectiveness

Ebastine was initially conceptualized as the combination of the structural elements of the very potent, yet sedative antihistamine, diphenyl-pyraline and the less potent, but nonsedative, terfenadine.<sup>16</sup>

The receptor-binding affinity and receptor-dissociation rate for antihistamines on peripheral H<sub>1</sub> receptors help to better characterize novel anti-H<sub>1</sub> receptor drugs. They also allow an appraisal of the likely *in vitro* potency at the H<sub>1</sub> receptor in relationship to known standards, and provide potential information on duration of action.<sup>54</sup> The H<sub>1</sub> receptor affinities for ebastine and carebastine are  $48 \pm 6$  nM and



27 ± 4 nM, respectively, while two other minor metabolites also have good H<sub>1</sub> receptor affinity (HO-ebastine and diphenyl-norpyraline).<sup>55</sup>

The binding characteristics of an H<sub>1</sub> receptor antihistamine determine the extent to which histamine can be blocked from binding to the H<sub>1</sub> receptor. These binding characteristics are an integral component for the efficacy and safety of an antihistamine. However, specific characteristics of an H<sub>1</sub> receptor antihistamine may influence its potency, and high *in vitro* H<sub>1</sub> binding activity does not necessarily imply good clinical efficacy because many other factors (such as uptake, metabolism, and pharmacokinetics) are also relevant. Moreover, some H<sub>1</sub> receptor antihistamines may lack specificity and bind to other receptors, causing unwanted side effects.<sup>38</sup>

Ebastine has a potent and selective H<sub>1</sub> antihistamine activity, as assessed by *in vitro* and *in vivo* studies. Contrary to the properties of other antihistamines, the anticholinergic and anti-serotonergic properties of ebastine have proved to be negligible.<sup>56</sup> Ebastine and carebastine show a weak affinity for the 5-HT<sub>2</sub> receptor, and they do not bind to adrenergic α<sub>1</sub>, dopaminergic D<sub>2</sub>, benzodiazepine, muscarinic, cholecystokinin, N-methyl-D-aspartic acid (NMDA), calcitonin gene-related peptide (CGRP), neuropeptide Y, neurotensin, opiate, somatostatin, NK<sub>1</sub>, vasopressin V<sub>1</sub>, vasoactive intestinal peptide (VIP), bradykinin B<sub>2</sub>, or Ca<sup>++</sup> channels.<sup>55</sup>

*In vitro* potency has been demonstrated in a series of experiments performed by Almirall. Their results showed that ebastine inhibits histamine-induced contractions in an isolated ileum model. In a competitive antagonism assay, they found that the negative logarithm of the concentration (mol/L) of antagonist which would produce a 2-fold shift in the concentration-response curve for an H<sub>1</sub> agonist (pA<sub>2</sub>) was 7.9 for ebastine and 8.7 for carebastine.<sup>36</sup> When acetylcholine was used as the agonist, the ED<sub>50</sub> value of ebastine was greater than 30 mg, sustaining the almost null anticholinergic effect. In a noncompetitive antagonism assay the negative logarithm of the concentration (mL/L) required to reduce the maximum response to an H<sub>1</sub> agonist by half (pD<sub>2</sub>) was 5.8 for ebastine, showing ebastine was at least 100 times less potent as an "atropine-like" muscarinic antagonist than as an antihistamine.<sup>36</sup> In addition to this isolated ileum model, an *in vitro* study in tracheally perfused guinea pig lungs provided evidence that ebastine inhibits bronchoconstriction induced by leukotriene C<sub>4</sub>.<sup>56</sup>

Potency *in vivo* has mainly been studied in guinea pigs. It has been observed that ebastine causes a dose-related inhibition of histamine-induced bronchospasm with an

ED<sub>50</sub> value of 170 µg/kg po (80 µg/kg for carebastine) in comparison to terfenadine that required 780 µg/kg.<sup>36</sup> Llopia et al reported that ebastine had a ED<sub>50</sub> 115 µg/kg po against aerosol histamine-induced bronchospasm in guinea pigs. They also found that ebastine was a potent compound in inhibiting allergen-induced bronchospasm in conscious guinea pigs (ED<sub>50</sub> 334 µg/kg po). In another *in vivo* study, ebastine reversed the changes in pulmonary resistance induced by leukotriene C<sub>4</sub> in anesthetized guinea pigs, whereas cetirizine and loratadine were devoid of activity in this model.<sup>56</sup>

Potency in humans can be assessed by evaluating distinct biomarkers that may be related to histamine activity. Examples of biomarkers in this setting are the wheal and flare response after a skin-prick test, the measurement of inflammatory mediators after nasal challenge with histamine or allergens, and the inhibition of histamine-induced bronchospasm.<sup>54</sup>

The histamine wheal-and-flare response provides information on the preliminary efficacy of the H<sub>1</sub> receptor antihistamine following oral dosing and has been widely used. It is sometimes criticized, however, because it does not mimic the late phase response of the allergic process, mast cell degranulation, and inflammatory mediator release. It has also been stated that it does not correlate with results in patients.<sup>38</sup> Speed of onset of activity, magnitude of effect and duration of action can be assessed, as with skin-prick test studies, with nasal applications studies, using single-dose histamine challenges at repeated time points.

Ebastine at doses ≥10 mg significantly reduced the histamine-induced cutaneous wheal response in healthy adult volunteers and in adult patients with allergic rhinitis in comparison with placebo.<sup>19</sup> Studies have shown that the reduction in wheal size is significantly greater with ebastine 10 mg than with placebo after intradermal histamine challenge (*P* < 0.001). This reduction reaches its peak around 6 to 12 hours after drug administration. In children, ebastine 5 and 10 mg has shown to reduce histamine-induced wheal and flare compared with baseline values for up to 28 hours. Overall, ebastine 10 mg has shown to be as effective at inhibiting the histamine-induced wheal response as several other antihistamines, whilst ebastine 20 mg proved to be more effective than others (eg, loratadine, cetirizine, and fexofenadine).<sup>19,57–59</sup>

The effect of ebastine has been also assessed by cutaneous and nasal challenge with allergens, and through the measurement of inflammatory mediators. One study aimed to determine the time period required for the inhibitory effect of ebastine on allergen-induced skin reactivity to disappear

completely, and recruited patients ( $n = 23$ ) with an allergy to house dust mite, cat dander, a mixture of 5 grass pollens, or birch pollen. After 7 days' treatment with ebastine 20 mg, skin prick tests with allergens revealed a highly significant ( $P < 0.01$ ) inhibition of the wheal surface area at 6 hours, 24 hours, and 2 days after treatment compared with placebo. The inhibitory effect of ebastine on wheal disappeared by day 4 after discontinuing treatment, and the effect on flare by day 3. A marked inhibitory effect of ebastine was seen on the histamine-induced wheal surface area at 6 and 24 hours after treatment completion compared to placebo. There was no residual effect of ebastine compared to placebo 5 days after treatment discontinuation.<sup>19,60</sup> Additionally, in grass pollen allergic patients ( $n = 12$ ), van Steekelenburg et al compared 5 second generation antihistamines by assessing eosinophilia in nasal smears, histamine/grass pollen skin tests and grass pollen nasal provocation tests. In patients with grass pollen allergy, ebastine 10 mg reduced the diameter of grass pollen-induced wheals at 4 and 8 hours postdosing to a significantly greater extent than placebo ( $P = 0.013$ ) and to a similar extent to other antihistamines such as loratadine 10 mg, cetirizine 10 mg, fexofenadine 120 mg, and mizolastine 10 mg.<sup>19,61</sup>

The effect on inflammatory mediators has also been tested. As assessed by Campbell et al<sup>48</sup> (see section above), mean percent inhibition provoked by ebastine on mediator release from human dispersed nasal polyp cells was 50% for PGD<sub>2</sub>, 33% for LTC<sub>4</sub>/D<sub>4</sub>, 40% for tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), 35% for GM-CSF, and 52% for IL-8, compared to placebo (all  $P < 0.05$ ).

Antonijoan et al performed two double-blind, double-dummy, randomized, placebo-controlled, 3-period crossover clinical trials<sup>14,62</sup> to assess the pharmacodynamics of a fast-dissolving tablet (FDT) of ebastine. This relatively new formulation facilitates administration to patients who have problems swallowing tablets and hard gelatine capsules, such as geriatric patients and those who are ill in bed or those who may not have access to water to aid swallowing. In these studies ebastine (10 mg in the first and 20 mg in the second study) was compared with desloratadine 5 mg or placebo. Besides assessing the inhibition of wheal response to cutaneous histamine challenge using a histamine skin-prick test, both included subjective assessments of itching, flare and pain by means of VAS, tolerability assessments, as well as acceptability and convenience evaluation, measured by a questionnaire. The main outcome was inhibition of the response to the histamine challenge, defined as the percentage reduction from baseline in the wheal area of the

skin intradermal test conducted 24 hours after the fifth dose of study medication.

In the first trial<sup>62</sup> (FDT ebastine 10 mg), the mean percentage reduction from baseline in the wheal area 24 hours after completion of 5 days' treatment was significantly greater with ebastine than with desloratadine and placebo (44.6% vs 17.9% and -2.3%, respectively; both  $P < 0.0001$ ). Mean differences in reduction from baseline to 24 hours after 5 days of treatment in the wheal area were 26% for FDT ebastine 10 mg vs desloratadine 5 mg and 46.9% for ebastine vs placebo (both,  $P < 0.0001$ ). In the second trial<sup>14</sup> (FDT ebastine 20 mg), the mean percentage reduction from baseline in wheal area 24 hours after 5 days of treatment was significantly greater with ebastine compared with desloratadine, and placebo (55.8% vs 26.8% and 12.2%, respectively; both  $P < 0.001$ ). Mean differences in reduction from baseline in the wheal area were 29% for ebastine 20 mg vs desloratadine 5 mg, and 43.7% for ebastine vs placebo (both,  $P < 0.001$ ).

These studies showed that, after 5 days of administration, inhibition of the response to histamine injection was significantly greater with FDT ebastine 10 and 20 mg than with desloratadine 5 mg. As denoted by the authors, this test does not necessarily correlate with clinical responses. However, it is important to assess and compare the pharmacodynamic effects of antihistamines.<sup>14,62</sup>

Concerning the therapeutic index, evidence supports the notion that ebastine has a wide therapeutic index. In pharmacological safety models, ebastine showed no central nervous system effects and did not affect heart rate or blood pressure in conscious rats and dogs at doses up to 100 mg/kg (ie, 600 times the therapeutic dose).<sup>63</sup>

The toxicology profile also showed that ebastine is free of toxic effects in animals, even at doses representing extremely high multiples of the recommended therapeutic dose in humans (0.17 mg/kg).<sup>36</sup> In fact, since the lethal dose 50% (LD<sub>50</sub>) was impossible to calculate, the therapeutic safety ratio (LD<sub>50</sub>/ED<sub>50</sub>) of ebastine is more than 20000.<sup>36</sup>

As well as all of the pharmacodynamic characteristics described above, ebastine has shown to be effective for the relief of symptoms in adults and adolescents with allergic rhinitis or chronic idiopathic urticaria. The efficacy of ebastine for the treatment of seasonal and perennial allergic rhinitis has been evaluated in five pivotal trials<sup>20,25,26,64-66</sup> and several supporting trials.<sup>22,23,67-70</sup> Pivotal trials enrolled a total of 1394 patients (685 in the seasonal allergic rhinitis studies and 709 in the perennial allergic rhinitis). Four of the trials lasted 3 weeks and the other lasted 12 weeks. The goal was to show superiority of ebastine over placebo. Ebastine 10 and

20 mg were used. The primary goal of the comparative efficacy in supporting studies was to show the superiority of ebastine over other  $H_1$  receptor antihistamines.<sup>55</sup> In most trials, the evaluation of efficacy was based on the assessment of nasal symptoms (rhinorrhea, sneezing, itching and obstruction) and ocular symptoms (eg itch, discharge, conjunctivitis). Symptoms were assessed individually and/or as composite scores such as total symptom score, nasal index (a composite of 4 nasal symptoms) or perennial index (nasal symptoms excluding obstruction).<sup>19</sup>

Overall, ebastine has shown superiority over placebo in the treatment of seasonal and perennial allergic rhinitis and ebastine 10 mg has shown to be 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 the used dosages.<sup>19,55</sup> In contrast with the differences detected when using the skin wheal and flare test, few clinical differences were observed among the different antihistamines when the allergic rhinitis model was used.<sup>71</sup>

For chronic idiopathic urticaria, the efficacy of ebastine has been evaluated in 2 randomized, double-blind, controlled trials, one compared to placebo<sup>28,72</sup> and the other to terfenadine and placebo.<sup>28</sup> Efficacy evaluations included change from baseline in symptoms and global evaluation of efficacy by patients and physicians. Ebastine 10 mg was significantly more effective than placebo at reducing the symptoms of urticaria ( $P < 0.001$ )<sup>28,72</sup> and was similar to terfenadine 60 mg twice daily.<sup>28</sup>

Effectiveness, or  $H_1$  antihistamine activity in the real world, as expressed by patients' willingness to use a specific  $H_1$  antihistamine, has been extensively studied for the FDT formulation of ebastine.<sup>73–78</sup> Roger et al<sup>73</sup> performed a clinical study in which they assessed qualitative face-to-face interviews with physicians and allergy patients in order to understand the key attributes of the FDT formulation of ebastine (a placebo sample was used). The key attributes were convenience, ease of use, and perception of faster onset of action. Moreover, most patients (75%) expressed that the FDT formulation would improve compliance, and the likelihood of taking/prescribing this formulation was ranked high both by patients and physicians (6 to 8.8 for patients and 7.4 to 8.1 for physicians on a 1 to 10 scale). Ebastine FDT has also been rated better by patients for general assessment, texture, initial taste, after taste and sensation on dissolving.<sup>75</sup> This has been further proved by a quantitative, descriptive, cross-sectional opinion study in which pharmacists answered a structured questionnaire after evaluating the experience referred by

clients who had tried the ebastine FDT formulation. Ebastine FDT was conveniently rated for time to dissolving and sensation on dissolving (4.35 [SD 0.95] and 4.03 [SD 0.92] respectively).<sup>78</sup>

All the above-mentioned characteristics are examples of desirable properties in third-generation antihistamines. Notwithstanding, ebastine does not show a radically different profile from existing compounds that would allow its denomination as a third-generation antihistamine.

## Lack of cardiotoxicity

In the mid 1990s, some second generation  $H_1$  antihistamines were associated with prolongation of the QT interval and the development of fatal arrhythmias such as *torsade de pointes*.<sup>79,80</sup> Two second-generation antihistamines, terfenadine and astemizole (both now withdrawn from the market), block the rapid component of the delayed rectifier potassium current ( $IK_r$ ). As a result, these drugs potentially prolong the monophasic cardiac action potential and QT interval, induce the development of early after-depolarizations and dispersion of repolarization, and may thereby cause *torsade de pointes*.<sup>39</sup> It is noteworthy that these events are mostly associated with high plasma concentrations due to overdose or co-administration with other drugs that inhibit their metabolism via hepatic microsomal enzymes (such as CYP3A4). Moreover, cardiac toxic effects induced by  $H_1$  antihistamines are rare as they occur independently of the  $H_1$  receptor and are not a class effect.<sup>10,39,81</sup>

The withdrawal of terfenadine and astemizole, along with other drugs that have proven to be cardiotoxic, has brought cardiac safety in the drug development process to the forefront of regulatory medicine. Since 1997, regulatory guidelines have been available, emphasizing the strategy for assessing the propensity of new (nonantiarrhythmic) medicinal products to prolong the QT interval. The first of these was issued by the EU Committee for Proprietary Medicinal Products (CPMP). It included recommendations for the design of clinical and nonclinical testing in order to assess the cardiac safety profile of new chemical entities (NCEs).

In 2002, the US Food and Drug Administration (FDA) and Health Canada (HC) issued a joint preliminary concept paper on clinical strategies for evaluating the effects of NCEs on QT/QTc interval prolongation. This paper was later adopted by the International Conference on Harmonization (ICH) for global implementation as ICH topic E14 and published simultaneously with ICH topic S7B, which is primarily concerned with the nonclinical investigation of the

effects of new drugs on cardiac repolarization. Approved in 2005, ICH E14 is concerned mainly with the design, conduct, analysis, and interpretation of clinical studies to assess the potential of a drug to delay cardiac repolarization. The main tool proposed to meet this goal is the “thorough QT/QTc study”. Design is central to this study as it should be randomized and double-blind, and should involve the concurrent use of both a placebo control group and a positive control group (pharmacological or nonpharmacological) to establish assay sensitivity. Whenever possible this study should be crossover. To address intrinsic variability in the conduct of the thorough QT/QTc study, the collection of multiple electrocardiograms (ECGs) at baseline and during the study is strongly recommended. Moreover, the examination of concentrations that are higher than those achieved following the anticipated therapeutic doses is also deemed necessary. Reliability is further enhanced by digitally obtained ECG recordings, electronic transmission and central collection for measurement.<sup>13</sup>

Ebastine and its main active metabolite, carebastine, have been exhaustively evaluated for potential effects on cardiac repolarization.<sup>82</sup> Ebastine shares some structural features with terfenadine and it is able to interact with potassium channels. Some years ago this gave rise, to concerns about its possible cardiotoxic effects. Such concerns have now been addressed and discarded following results from experimental models both in animals and in the clinical setting. Ebastine either has no deleterious cardiac effects or shows only small and non-clinically significant effects at this level. One possible explanation for its increased  $H_1$  receptor activity and its almost null cardiotoxicity in comparison with terfenadine is that subtle modifications in structure not only make ebastine nonchiral but also determine the acquisition of a folded 3-dimensional conformation, as opposed to the extended conformation of terfenadine. The modifications in structure consist of the replacement of the alcoholic hydroxyl group by a ketone oxygen and the introduction of an ether link between the diphenyl-methyl moiety and the piperidine ring.<sup>16,83</sup>

*In vitro*, the electrophysiological effects of ebastine and carebastine have been studied in isolated rabbit Purkinje fibers. In normal and low potassium solutions (4 mM and 2.7 mM  $K^+$ ) ebastine (at a concentration of 1 nM to 1  $\mu$ M) and carebastine (at a concentration of 1 nM to 1  $\mu$ M) produced a concentration-dependent prolongation of action potential duration (APD) without impairment of the maximum rate of depolarization.<sup>55</sup>

Ko et al<sup>84</sup> performed a study on suppression of potassium channels by ebastine, utilizing the whole cell patch-clamp

technique. The  $I_{Kr}$  channel (delayed rectifying rapid) was examined in both the human Ether-à-go-go Related Gene (HERG)-expressing *X. laevis* oocytes and guinea pig ventricular myocytes; the  $I_{Ks}$  (delayed rectifying low) and the  $I_{K1}$  (inward rectifying) were studied in the guinea pig ventricular myocytes and the  $I_{to}$  (transient outward) and the  $I_{Kped}$  (rapidly activating delayed rectifier) were studied in the rat heart. This study showed that ebastine had significant suppressive effects on the  $I_{Kr}$ ,  $I_{Ks}$  and  $I_{Kped}$  channels, but it was less effective in blocking the  $I_{to}$  and  $I_{K1}$ . These results have been challenged in the past for quoting values for 50% inhibition of the maximum inhibition and not 50% of complete inhibition.<sup>55</sup>

Almirall performed studies transferring hERG channels to human embryonic kidney (HEK-293) cells. They compared ebastine to terfenadine and loratadine and calculated the  $IC_{50}$ . The results were 331 nM for ebastine, 208 nM for terfenadine and 200 nM for loratadine. With these data they concluded that ebastine is the least likely of the antihistamines tested to affect hERG channels.<sup>55</sup>

*In vivo* animal evidence concerning the effect of ebastine on cardiac conduction was controversial for many years. One of the *in vivo* models used to assess ebastine effects was the corrected QT (QTc) interval prolongation following drug administration to anesthetized guinea pigs.<sup>85</sup> Hey et al<sup>86–89</sup> (working for Schering-Plough Research Inc., US marketer of loratadine) showed that intravenously administered ebastine (3 to 50 mg/kg) caused dose-related prolongation of QTc in anesthetized guinea pigs in a manner comparable to that seen with terfenadine (1 to 10 mg/kg). This group also showed accentuation of QTc prolongation by ebastine (10 mg po, approximately 20 mg/kg) in conscious guinea pigs pretreated with ketoconazole (200 mg po, approximately 400 mg/kg). Gras et al<sup>90,91</sup> (employees at Almirall, marketer of ebastine) provided contradictory evidence of the dose-related prolongation of QTc. Ebastine showed no significant prolonging effect on the QTc interval, even when administered at a dose almost 120 times higher than the corresponding dose of terfenadine. In another study the same group found no interaction between ebastine (20 mg po) and ketoconazole (400 mg/kg) administered to conscious guinea pigs, although it should be pointed out that the positive control, terfenadine, was also negative.<sup>55</sup>

In anesthetized dogs intracoronary infusion of ebastine (30  $\mu$ g/min for 1 hour) was not associated with an increase in electrocardiographic QTc intervals that predisposed to ventricular arrhythmias.<sup>36,82</sup>

In another *in vivo* study in rats differences in accumulation of antihistamines into cardiac tissue were addressed.



Animals were administered antihistamines orally for 5 days at a dose calculated to achieve steady state concentrations substantially higher than in humans. The authors determined the ratio between the hERG  $IC_{50}$  and the plasma level of the free compound at steady state  $C_{max}$  ( $\mu M$ ) and the ratio between the hERG  $IC_{50}$  and the  $C_{max}$  in the rat heart at steady state. High ratios of ebastine and carebastine suggested that the putative arrhythmogenic potential of ebastine was lower than that of terfenadine.<sup>55</sup>

From the clinical point of view, the cardiac safety of ebastine has been evaluated in several studies. While some of them were specifically designed for this purpose, some others were pharmacokinetic–pharmacodynamic drug interaction studies. Additionally, placebo-controlled efficacy studies, comparative efficacy studies, and studies in special populations have been performed.

Several cardiac safety studies have been conducted. Firstly, Gillen et al<sup>92</sup> performed a 4-way crossover study to compare the effect of high doses of ebastine with terfenadine and placebo on QTc. Three and 5-fold the maximum recommended dose of ebastine (ie, 60 and 100 mg, once daily) and three-fold the maximum recommended dose of terfenadine (ie, 180 mg bid) or placebo were administered for 7 days. QT was corrected following both the Bazett and Friedericia corrections. According to the results of this trial, ebastine 60 mg did not significantly alter any QTc, vs placebo. Nevertheless, ebastine 100 mg produced a statistically significant prolongation of QTc according to Bazett's correction. In any case, the QTc increase after ebastine 100 mg was significantly less than with terfenadine (+10.3 ms vs +18.0 ms,  $P < 0.05$ ). Noteworthy is that the authors interpreted that they "overcorrected" the QT interval using Bazett's correction. Since then, Malik<sup>93</sup> has argued that measuring imprecision and natural variability can lead to mean QTc interval changes of 4 to 5 msec in the absence of drug treatment. He also stated that use of published heart rate correction formulas in the assessment of drug-induced QTc prolongation is inappropriate and that correction formulas optimized for pooled drug-free data are inferior to the formulas individualized for each subject.<sup>93</sup>

Later, a randomized, double-blind, placebo controlled parallel group study compared the electrocardiographic effect of ebastine 10, 20, 40 (in one randomization schedule) and 80 mg qd (in a second randomization schedule) with placebo for 9 days in healthy volunteers. The relationship between QTc prolongation and plasma ebastine/carebastine concentrations was also explored. Primary analysis comprised the change from baseline QTc measurements, according to Bazett's method. In this study, ebastine 10, 20, and 40 mg

caused a dose-dependent prolongation of QTc, corrected by Bazett's or Friedericia's formulae. As individual QT variation was very large, no post-hoc analyses of QTc by other methodology could be carried out.<sup>55</sup>

In another attempt to explore the relationship between QTc prolongation and ebastine administration, an open-label, placebo-controlled, single ascending dose study was performed with doses of 80, 150, 300, and 500 mg in 6 healthy male volunteers. Increases in heart rate and QTc, corrected by Bazett's or Friedericia's method, were dose-proportional, but no single QTc interval was greater than 500 msec, and no intra-individual postdose increase in the mean QTc interval was greater than 10%. The interpretation of these results was limited by the reduced sample size number.<sup>55,94</sup>

Various drug-interaction cardiac safety studies have been carried out. Chiefly, the risk of interaction between ebastine and erythromycin (2 studies) or ketoconazole (3 studies) has been evaluated.<sup>82,95</sup> Two additional studies were aimed at comparing the interaction of loratadine and ketoconazole with the interaction of ebastine and ketoconazole.<sup>55</sup>

One study ( $n = 15$ ) comprised multiple-dose administration of erythromycin stearate 500 mg every 6 hours on days 4 through 12 with single-dose ebastine 20 mg in the morning of days 1 and 9. Holter monitoring and telemetry showed no clinically relevant changes in QTc interval or cardiac parameters in spite of evident pharmacokinetic interaction between ebastine and erythromycin.<sup>55</sup> Nonetheless, in a separate crossover study ( $n = 30$ ), the co-administration of multiple-dose ebastine 20 mg qd with erythromycin ethylsuccinate 800 mg tid for 10 days produced a statistically significant prolongation of QTc interval (10 ms); no clinically significant changes occurred, however.<sup>82</sup> In comparison to the  $C_{max}$  and  $AUC_{0-24}$  achieved with ebastine plus placebo, when ebastine plus erythromycin was administered there was a 2-fold increase in the  $C_{max}$  and a 3-fold increase in the  $AUC_{0-24}$  of ebastine. Additionally there was a 2-fold increase in the  $C_{max}$  and 2.5-fold increase in the  $AUC_{0-24}$  of carebastine. After treatment, the difference for ebastine plus erythromycin over placebo plus erythromycin for QTc according to Bazett's correction (QTcB) was 10.7 msec. The uncorrected comparison was –2.8 msec. Post-hoc analyses did not change overall findings.<sup>55,82</sup>

Assessment of the interaction of a single dose of ebastine 20 mg combined with multiple doses of ketoconazole 400 mg qd on days 4 through 12 ( $n = 12$ ) produced no clinically relevant changes in cardiac parameters in healthy male volunteers.<sup>55,82</sup>

In a blinded, parallel group, placebo-controlled multiple dose study ( $n = 55$ ), ebastine 20 mg qd or placebo were administered for 5 days and ketoconazole 400 mg qd was added to that treatment for an additional 8 days. In the ebastine plus ketoconazole group the maximum plasma concentrations ( $C_{\max}$ ) of ebastine were 15-fold higher than placebo, the minimum plasma concentrations ( $C_{\min}$ ) were 70-fold higher and the area under the plasma concentration-time curve ( $AUC_{0-24}$ ) was 40-fold higher.<sup>55,82</sup> Initial analysis showed that the addition of 8 days of ketoconazole to ebastine at a steady state caused a  $18.1 \pm 2.5$  msec prolongation in the mean QTcB compared to an  $8.0 \pm 2.3$  msec prolongation for the placebo plus ketoconazole combination ( $P < 0.0023$ ). Post-hoc analyses with other QTc correction formulae (Friedericia, Malik and linear regression analysis) did not sizably modify results.<sup>55</sup> Data were later analyzed correcting QT for heart rate (QTc) using the parabolic log/log formula ( $QTc = QT/RR^\alpha$ ;  $\alpha = 0.25$  for Kawataki, 0.31 for Yoshinaga, 0.32 for Simonson, 0.33 for Fridericia, 0.38 for Hodges, 0.398 for Boudolas, 0.5 for Bazett and 0.603 for Mayeda), but individualized  $\alpha$  values derived from individual off-drug QT/RR relationships were used for each subject. Chaikin et al<sup>95</sup> argued that this avoids the problem of using formulae based on populations other than that under study, and allows for considerable interindividual variability in QT/RR relationships, but intraindividual variability over time is low. Using this approach, no changes in cardiac repolarization were evidenced by the absence of statistically significant changes in the increase of the mean QTc in the ketoconazole/placebo group ( $6.96$  [95% CI 3.31 to 10.62] ms) compared with ketoconazole/ebastine ( $12.21$  [95% CI 7.39 to 17.03] ms;  $P = 0.08$ ).<sup>95</sup>

A pivotal drug interaction cardiac safety study was designed with the input of the FDA and was the first of its kind to include women.<sup>55</sup> An individual QT correction factor was determined at baseline and used throughout the study. This methodology was deemed satisfactory considering the high inter and intra-individual variability of QT. This multiple dose ebastine and ketoconazole interaction study had a 2-period crossover design. Ebastine 20 mg q.d. was administered for 13 days and ketoconazole 400 mg qd or placebo was added on the last 8 days. The addition of ketoconazole caused a significant increase of 16-fold in  $C_{\max}$ , 44-fold in  $AUC_{0-23.5}$  and 52-fold  $AUC_{0-\infty}$  of ebastine. For carebastine, only the  $AUC_{0-\infty}$  was significantly increased. Ketoconazole increased the resting heart rate on day 13 by 4.6 msec over baseline compared to placebo and provoked a statistically significant ( $+11.9$  ms vs 0.38 msec mean QTc; difference 10.71 msec;  $P = 0.0000$ ) interval prolongation compared

to placebo (using Malik correction formula [QTcM]). This held true when using other correction formulae. Using pharmacokinetic/pharmacodynamic regression analysis, it was demonstrated that there was a plateau effect for prolongation of QTc at 10.71 msec. This suggests that if exposure increased above that observed in this study, the QTc would not be further prolonged. The FDA later challenged these results and considered that goodness of fit analysis did not support a single exposure-response QTc model due to the limitations inherent to inter- and intra-subject variability.

Results from studies comparing ebastine plus ketoconazole with loratadine plus ketoconazole pointed in the same direction. The mean QTcB change with the administration of ketoconazole was 16.5 for ebastine and 11.3 for loratadine in the first study. In the second study the mean QTcB change was 16.3 for ebastine and 9.6 for loratadine. Differences were of lesser magnitude using Marek Malik's correction.<sup>55</sup>

Pooled data from high-dose ebastine studies and drug interaction studies, particularly studies investigating the interaction between ebastine and ketoconazole, showed a positive relationship between increasing ebastine plasma concentrations and QTc interval changes. In contrast with findings using terfenadine, the QTc interval-plasma concentration curve reached a plateau at low level of QTc prolongation (10 msec) despite large, progressive increases in blood concentrations of ebastine and carebastine.<sup>82,96</sup>

During the placebo-controlled efficacy studies, ECGs were performed at baseline and weekly, at 3 to 5 hours after dosing (around the approximated  $T_{\max}$  for ebastine). Baseline and double-blind ECG evaluations were performed in a total of 1202 patients. Moreover, Holter monitoring was performed in a subset of patients in these studies ( $n = 226$ ). A dose-dependent increase of QTc outliers was seen, suggesting that ebastine prolonged QTc in some patients, although no clinically relevant changes were seen on Holter monitoring.<sup>55</sup> As opposed to placebo-controlled studies, comparative efficacy studies did not include Holter monitoring. With the exception of a few outliers, no definitive statements about cardiac safety could be made.<sup>55</sup>

The pharmacokinetics of ebastine have been investigated in several special situations. Evidence has emerged from a food interaction study, and from studies in patients with renal failure<sup>97</sup> and liver failure,<sup>98</sup> and in children<sup>82</sup> and elderly volunteers. In the food interaction study a single dose of ebastine 10 or 20 mg with and without food produced no clinically relevant electrocardiographic effects, despite the fact that exposure to carebastine was 50% higher with food than without.<sup>82</sup> No clinically relevant ECG findings have been observed

in patients with renal failure,<sup>97</sup> liver failure,<sup>98</sup> or children.<sup>82</sup> The electrocardiographic effect of ebastine in the clinical setting was studied by Huang et al.<sup>99</sup> These authors performed a randomized, double-blind, multiple-dose, placebo-controlled, parallel group study in healthy young and elderly volunteers. Twelve-lead electrocardiography was performed before dosing and repeated 4 hours after dosing on days 1, 5, and 10. Additionally, 24-hour Holter monitoring was performed after 10 days of treatment with ebastine 10 mg or placebo. The results showed no clinically significant abnormalities either in young or in elderly volunteers.

Undoubtedly, the most difficult and contentious issue facing ebastine has been proving its cardiac safety. Ebastine was first marketed in Spain in 1990 and in 1998 the first New Drug Application (NDA) submission was filed by Rhône-Poulenc Rorer, Almirall's strategic partner at that time. Because of cardiac safety concerns and significant pharmacokinetic interactions with drugs metabolized by CYP3A4 that resulted in increased plasma concentrations and potential QTc interval prolongation, the FDA decided not to approve ebastine for marketing in the US on March 23, 1999.<sup>55</sup> Three years later, in 2002, Almirall resubmitted an NDA for ebastine. They provided new clinical evidence of its safety and argued that Bazett's method for QT correction tended to overcorrect the QTc interval when heart rate is increased. Ebastine's cardiac safety has been assessed differently by different regulatory bodies around the globe. Ebastine is currently marketed in over 80 countries and there have been no reports of fatal arrhythmias linked to its use. Nevertheless, caution is warranted in patients with a long QT interval, in those who are on drugs that affect the P450 cytochrome system, and in patients with hypokalemia.

In retrospection, a thorough QT/QTc study with a concurrent positive control would have provided valuable information on the cardiac safety of ebastine and would possibly have eliminated the need for further studies. No such study was performed for ebastine as guidelines for QT/QTc studies were not published until 2005. A thorough QT/QTc study provides very reliable information, as the subjects serve as their own controls and hence reduce differences related to inter-subject variability. In addition, the thorough QT/QTc study design facilitates heart rate correction approaches based on individual subject data.<sup>13</sup>

## Drug interactions

The interactions described to date between H<sub>1</sub> antihistamines and other drugs or substances fundamentally take place via three different routes: the P450 cytochrome system

(CYP450), P glycoprotein (PgP), and the members of the organic anion transport polypeptide (OATP) family.<sup>100</sup> Other possibilities include displacement of a protein bound drug fraction. The most relevant and hence the most thoroughly studied of these have been those involving CYP450.

Given the previous background, studies to assess potential pharmacological drug interactions for new antihistamines comprise at least 2 general axes: interactions that could impair cardiac safety, mainly as a consequence of a pharmacokinetic interaction at the metabolic level, and interactions that could impair CNS safety, mainly as a consequence of a pharmacodynamic interaction with recognized CNS depressants.

The metabolism of ebastine to carebastine was demonstrated in rat small intestine and liver tissue.<sup>101</sup> Ebastine undergoes extensive metabolism to form desalkylebastine and hydroxyebastine.<sup>102–104</sup> Hydroxyebastine is subsequently metabolized to carebastine. Until recently, the specific hepatic CYP450 enzymes involved in these processes had eluded us. However, utilizing chemical inhibition and kinetic analysis studies in human liver microsomes, Liu et al<sup>104</sup> concluded that dealkylation of ebastine and its metabolites is mainly catalyzed by CYP3A4, and CYP3A5 to a lesser degree. Moreover, hydroxylation reactions are preferentially catalyzed by CYP2J2. Thus, when a therapeutic dose of ebastine is given together with therapeutic doses of other drugs metabolized by CYP3A4, a pharmacokinetic interaction can occur, usually producing increases in ebastine plasma concentrations. This interaction is associated with the possible prolongation of the QTc interval. Whether this prolongation occurs or not has been subject to debate, as discussed in the previous section. Nevertheless, even if it is present, it does not seem to be clinically relevant.

CYP3A4 inhibitors such as cimetidine, clarithromycin, clotrimazole, erythromycin, fluoxetine, gestodene and ketoconazole could increase the risk of toxic concentrations of substances such as ebastine that are metabolized via the CYP3A4 pathway.<sup>100</sup> To date ebastine has been investigated in drug interaction studies with ketoconazole, erythromycin and cimetidine. The first two of these studies were reviewed in a previous section of this manuscript.

Van Rooij et al<sup>105</sup> studied the influence of cimetidine in the metabolism of ebastine. They conducted a double-blind, placebo-controlled, randomized, crossover study in which 12 volunteers were administered a single dose of ebastine 20 mg on day 2 of a multiple administration of cimetidine (400 mg tid and 800 mg in the evening on the day preceding ebastine administration and 400 mg 4 times

daily on the following 2 days) or placebo. Blood samples for determination of ebastine and carebastine were taken over the course of the last 2 days. Ebastine concentrations were only detected in 1 subject and were negligible. The authors detected no significant effect of cimetidine on the conversion of ebastine to carebastine or on carebastine kinetics ( $AUC_{0-\infty} = 4049 \pm 985 \text{ ng}\cdot\text{h/mL}$  after cimetidine vs  $3795 \pm 959 \text{ ng}\cdot\text{h/mL}$  after placebo; 95% CI of the difference: -412 to 919). Furthermore, they did not find a significant effect on blood pressure or heart rate and sedation was not observed.

Based on the analysis of a series of patients receiving therapeutic anticoagulation, Garcia-Vallejo et al<sup>106</sup> suggested that ebastine, loratadine and cetirizine showed similar pharmacokinetic interactions when combined with acenocoumarol, perhaps due to hepatic enzymatic induction. Nevertheless, they also stated that this interaction did not result in a high rate of alterations in the international normalized ratio (INR) values or hemorrhagic events, and they concluded that ebastine can be safely administered in patients receiving oral anticoagulation. Besides acenocoumarol, drug interaction studies of ebastine 20 mg with theophylline or warfarin have also been performed and no interactions have been reported.<sup>55</sup>

Mattila et al did not detect any pharmacokinetic interactions between ebastine and ethanol or diazepam in healthy subjects.<sup>107,108</sup> They performed 2 double-blind, crossover studies in which ebastine 20 mg and placebo were each administered for 1 week. On day 6, drug effects were assessed and on day 7 of both periods, ethyl alcohol 0.8 g/kg or diazepam 15 mg were given. No pharmacokinetic interactions were observed, meaning that no change in ebastine, ethanol, or diazepam plasma levels was observed. Pharmacodynamic results (CNS effects) will be discussed in the following section (lack of CNS effects).

It is of note that some drugs (eg, azithromycin, cimetidine, digoxin, erythromycin, fluoxetine, or ketoconazole) that act as substrates or modulators of Pgp activity also act similarly in relation to CYP3A4 and OATP.<sup>100</sup> Certain  $H_1$  antihistamines are Pgp substrates (eg, fexofenadine, loratadine) and, as such, their bioavailability and clearance can be compromised, resulting in higher concentrations of antihistamine. However, drugs that are able to induce Pgp yield a lesser concentration of the antihistamine when co-administered and this interaction would therefore result in a decrease in antihistamine efficacy. For ebastine, its metabolite carebastine has been shown to be a substrate of Pgp-mediated efflux from the brain at the blood-brain barrier, and a second efflux system is also

possibly involved. The relatively low affinity of the uptake transport system for carebastine limits the brain distribution of ebastine/carebastine.<sup>109</sup>

Lastly, both ebastine and carebastine are highly protein-bound (98%) in the circulation, but the volume of distribution has been reported to be between 90 and 140 L.<sup>35</sup> Given this combination of factors, protein plasma binding displacement drug interactions are of little concern.

Drug interactions after co-administration of ebastine with a number of other drugs (CYP3A4 inhibitors or drugs with sedative effects) have been correctly investigated. According to the results of clinical trials performed to date, there seems to be no danger of clinically relevant drug interactions in terms of either cardiac or CNS safety. Nevertheless, to be classified as a third-generation compound, it is desirable that a new antihistamine has no drug interactions at all.

## Lack of CNS effects

One of the major disadvantages of first-generation antihistamines is the sedation they cause. This not only limits their use but can also cause accidents while driving and working, and contribute to a decline in productivity and learning efficiency.<sup>110-113</sup> However this unwanted CNS effect seems to develop tolerance, that is, to dissipate after 4 to 7 days of regular therapy. Sedation induced by these first-generation antihistamines is provoked by their penetration through the blood-brain barrier and consequent occupation of brain  $H_1$  receptors.<sup>114</sup> Thus, the main challenge facing second-generation antihistamines has been to block passage through the blood-brain barrier.<sup>115</sup>

Preclinical and clinical data indicate that ebastine has no sedative effect.<sup>116</sup> The potency and potential CNS effects of ebastine have been studied by means of competition binding and functional assays. *In vitro*, both ebastine and carebastine have shown a high affinity for the  $H_1$  receptor in the guinea pig cerebellum. Furthermore, they inhibit [ $^3\text{H}$ ]-mepyramine binding with a  $K_i$  of 7.1 nM and 7.9 nM, respectively. This effect is twice as potent as that shown by terfenadine ( $K_i = 14.3 \text{ nM}$ ), but less potent than that seen with astemizole ( $K_i = 1.7 \text{ nM}$ ). In experiments measuring inhibition of [ $^3\text{H}$ ]-mepyramine binding to rat cerebral cortex histamine  $H_1$  receptors *in vitro*, the concentration of drug required to inhibit binding by 50% ( $IC_{50}$ ) was 0.32  $\mu\text{mol/L}$  for ebastine and 0.17  $\mu\text{mol/L}$  for carebastine. These values, similar to those for other second-generation antihistamines, indicate 20 to 40 times less affinity for cerebral  $H_1$  receptors than the first-generation drug chlorpheniramine ( $IC_{50} 0.01 \mu\text{mol/L}$ ).<sup>36</sup>



*In vivo*, the oral dose required to cause 50% inhibition of [ $^3\text{H}$ ]-mepyramine binding to cerebral  $\text{H}_1$  receptors ( $\text{ID}_{50}$  value) was 10.3 mg/kg, indicating that ebastine is more than 500 times less active than chlorpheniramine (0.02 mg/kg). This emphasizes the fact that it does not easily cross the blood–brain barrier and supports its categorization as a non-sedating antihistamine.<sup>36</sup>

By comparing *in vivo* cerebral binding data and *in vivo* peripheral pharmacological data, it is possible to quantify the sedation potential of a given antihistamine. Different studies have shown that the  $\text{ID}_{50}$  value for *in vivo* inhibition of [ $^3\text{H}$ ]-mepyramine binding in mouse cortex is 25.6 mg/kg and the  $\text{ED}_{50}$  value for histamine-induced dermal lesions in mice  $\text{H}_1$  receptors is 0.09 mg/kg. These values indicate the calculated sedation potential is 0.0035, as opposed to 0.066 and 555 for terfenadine and d-chlorpheniramine respectively.<sup>36</sup>

CNS penetration has been extensively studied. As ebastine is rapidly metabolized to carebastine, we will focus on this metabolite. First, carebastine's polarity makes it more difficult to penetrate the CNS than ebastine.<sup>117</sup> Secondly, carebastine does not occupy brain  $\text{H}_1$  receptors in parallel with increasing plasma carebastine concentration, possibly because carebastine is a substrate of P-glycoprotein and other transporters expressed on the blood-brain barrier, which serve as efflux pumps from the brain to the blood.<sup>109</sup> Using the BUI (brain uptake index) method in rats, the efflux of [ $^{14}\text{C}$ ] carebastine by the transporters was not inhibited by a large amount of nonlabelled carebastine (150  $\mu\text{M}$ ) which was about 650 times the plasma concentration obtained from a phase I clinical trial.<sup>118</sup> This means that although it is theoretically a saturable system, in practice it is not saturated. Ebastine would therefore cause little sedation even when associated with a high plasma carebastine concentration as a result of overdosing or metabolic inhibition.<sup>119</sup>

In clinical trials the most common adverse effects experienced by patients after administration of ebastine have been headache and somnolence, though these effects have not been able to be differentiated from placebo.<sup>34</sup> Besides this field evidence, information from experimental studies in healthy volunteers specifically performed to assess possible CNS effects is available.

At least 4 studies have been performed to assess the CNS effects of ebastine in laboratory conditions. Psychomotor tests, VAS, and pharmaco-EEG have been used to test the drug against placebo and/or positive comparators (ie, vera). Additionally, a car driving performance study has been carried out in real traffic conditions, comparing ebastine with placebo and a positive comparator. Interactions with ethanol

and diazepam and the resulting effect on psychomotor performance have also been evaluated. Finally, central  $\text{H}_1$  receptor occupancy has been quantified by means of PET scans. Even if all these studies have been performed in healthy volunteers, their value as useful biomarkers of what happens in the clinical scenario is well known.

In a single blind, cross-over, placebo controlled study ( $n = 9$ ), Vincent et al<sup>116</sup> assessed the effects of 10 mg and 50 mg of ebastine on cardiovascular, autonomic and psychomotor function in healthy subjects. Evaluation was performed by means of psychomotor tests, both subjective (such as VAS for sedation and categorical questioning on mood) and objective (critical flicker fusion threshold, choice reaction time and recognition time). Autonomic tests measuring blood pressure, heart rate, salivary secretion and the standing to lying ratio have also been conducted. Besides no effect on blood pressure or heart rate, or any evidence of anticholinergic activity, ebastine did not impair psychomotor performance as assessed by the critical flicker fusion threshold. However, there was a marginal effect on the overall choice reaction time; this was most apparent at the higher dose and its clinical significance remains doubtful. Moreover, ebastine 10 mg had no effect on sedation, although ebastine 50 mg caused a modest increase in indices of sedation ( $P < 0.05$ ).

CNS effects in healthy male volunteers were also explored by Hopes et al<sup>120</sup> in a double blind, placebo-controlled trial with a latin square design ( $n = 16$ ). Single doses of ebastine 10 and 20 mg were compared to placebo and to clemastine, a  $\text{H}_1$  receptor antihistamine that is reported to affect visual-motor coordination and reaction time, and to cause subjective tiredness. The most relevant aspects of behaviour were evaluated: vigilance as measured by quantitative pharmaco-EEG, cognitive performance, visual motor coordination and subjective estimates of sedation. While clemastine produced impairment of psychomotor performance, drowsiness, a selective effect on cognitive processes and a general decrease in vigilance, ebastine did not differ at any time from placebo. Moreover, ebastine also differed positively from clemastine in the EEG features of vigilance (eg, a smaller increase in relative delta<sup>F</sup> power [ $P < 0.05$ ] and a smaller decrease in the relative power of the alpha<sub>1</sub> frequency band) and concerning its effect on pursuit tracking and subjective rating of drowsiness and general discomfort.

Hindmarch et al<sup>121</sup> performed a double-blind, randomized, 5-period, cross-over study to evaluate the cognitive and psychomotor effects of ebastine (10, 20, and 30 mg) compared with sustained-release triprolidine (10 mg) and placebo in healthy volunteers ( $n = 10$ ). Following each dose, the

subjects had to perform a battery of tests that comprised the critical flicker fusion threshold, choice reaction time, the simulated car tracking task, Sternberg memory scanning task, assessment of subjective sedation, and subjective evaluation of sleep by means of the Leeds Sleep Evaluation Questionnaire. Triprolidine produced an overall increase of the peripheral reaction time component of the simulated car tracking task, a clear decrement on the Sternberg memory scanning task in comparison to placebo ( $P < 0.05$ ), and significantly greater subjective reports of sedation when compared with placebo ( $P < 0.05$ ). Ebastine was found to be free of impairment on objective aspects of psychomotor and cognitive function.

Tagawa et al<sup>122</sup> performed another single-blind, randomized, cross-over study to evaluate the effect of ebastine 10 mg on cognitive performance compared to (+) chlorpheniramine 2 mg and 6 mg and placebo. Several attention demanding cognitive tasks (visual discrimination time task [VDT], choice reaction time task [CRT] and simple reaction time task [SRT]) were performed by healthy volunteers ( $n = 24$ ) at the moment when the plasma drug concentration was expected to be at its maximum value. Ebastine was found not to affect task performance or subjective sleepiness, while (+) chlorpheniramine 2 and 6 mg caused concentration-related impairment of task performance (eg, ratios of after/before dosing: placebo [ $0.998 \pm 0.113$ ] vs (+) chlorpheniramine 2 mg [ $1.103 \pm 0.083$ ;  $P < 0.05$ ] or (+) chlorpheniramine 6 mg [ $1.170 \pm 0.139$ ;  $P < 0.001$ ] in a 7 msec visual discrimination time task. Feelings of sleepiness in the chlorpheniramine groups also increased compared with the placebo group (placebo vs (+) chlorpheniramine 2 and 6 mg:  $P < 0.05$ ).

Brookhuis et al<sup>123</sup> performed a double-blind, placebo-controlled trial with triprolidine 10 mg as an active control. They tested ebastine 10, 20, and 30 mg on several parameters of driving performance in real traffic in healthy volunteers. Driving performance was tested on day 1 and after a 5-day treatment. As expected, triprolidine 10 mg significantly increased the amount of weaving and the delay in following speed manoeuvres of a leading car, compared to placebo, whereas ebastine did not produce any significant change at any dose.

Clinically significant drug interactions can occur when 2 or more drugs are taken in combination.<sup>124</sup> With antihistamines being among the most widely prescribed medications in the world, and as result of their widespread over-the-counter availability, a large number of ambulant patients using antihistamines could also concomitantly take other drugs. Consequently, understanding drug–drug

interaction issues associated with antihistamines is a pertinent topic.<sup>125</sup> A relevant pharmacodynamic drug interaction is one that consists of additive CNS depression effects. In terms of CNS safety, newer-generation agents have improved profiles over first-generation agents.<sup>126,127</sup> However, even the minimal potential of a drug to produce sedation could be important, since this sedative effect can be further worsened by other CNS depressant drugs, such as antidepressants, sedatives, narcotic pain relievers, and alcohol.<sup>128</sup>

In the clinical study for the evaluation of interactions between ebastine and ethanol, Mattila et al<sup>108</sup> evaluated the performance of volunteers by means of objective tests, such as digit symbol substitution, flicker fusion threshold, Maddox wing, nystagmus, simulated driving, and body balance. Subjective tests included VAS and questionnaires. Ebastine did not impair performance either objectively or subjectively. Ethanol impaired performance in most objective tests and produced clumsiness, muzziness, and mental slowness, while these effects were not increased or modified in any way by ebastine.

Using a very similar design to their ethanol-ebastine interaction study, Mattila et al<sup>107</sup> performed a double-blind, crossover study in which ebastine 20 mg or placebo were administered for 1 week each. On day 7 of both periods, volunteers were given diazepam 15 mg and the interaction between diazepam and ebastine was assessed. Performance was assessed by objective tests (digit symbol substitution, flicker fusion threshold, Maddox wing, simulated driving, and body balance). Subjective tests included VAS and questionnaires. Diazepam produced impaired performance in objective tests, and volunteers experienced drowsiness, weakness, clumsiness, mental slowness and poor performance according to the VAS. Ebastine, again, did not modify or increase the effects elicited by diazepam.

Interestingly, there is a study where the measurement of central  $H_1$  receptor occupancy in humans after ebastine intake has been assessed. In a single-blind, randomized, crossover study performed by Tagawa et al<sup>119</sup>  $H_1$  receptor occupancy by oral ebastine 10 mg, (+) chlorpheniramine 2 mg and 6 mg and placebo was studied using PET, in healthy volunteers. Thereafter, PET scans with [ $^{11}C$ ]-doxepin, a potent  $H_1$  receptor antihistamine, were conducted near the  $t_{max}$  reported for both drugs (90 minutes scanning). The binding potential of doxepin ( $BP = B_{max}/K_d$ ) for available brain  $H_1$  receptors was imaged on a voxel-by-voxel basis through graphical analysis and  $H_1$  receptor occupancy was calculated in several  $H_1$  receptor rich regions (mainly cortex, anterior cingulate cortex [ACC] and thalamus) using statistical

parametric mapping (SPM96).  $H_1$  receptor occupancies were approximately 9.9, 3.2 and 14.4% in the ebastine 10 mg group (cortex, ACC and thalamus, respectively), approximately 50.3 ( $P < 0.001$ , 95% CI for difference in the mean receptor occupancies: 26.6–54.3 vs ebastine) 49.2 ( $P < 0.001$ , 95% CI: 24.3–67.5 vs ebastine) and 49.7% ( $P < 0.01$ , 95% CI 14.8 to 55.9 vs ebastine) in (+) chlorpheniramine 2 mg. Comparisons against (+) chlorpheniramine 6 mg were in the same range and were also statistically different. Furthermore, receptor occupancies increased with increasing plasma concentrations of (+) chlorpheniramine (cortex:  $r = 0.9021$  [ $P < 0.001$ ]; ACC:  $r = 0.7483$  [ $P = 0.0051$ ]; thalamus:  $r = 0.5874$  [ $P = 0.0446$ ]), but not with concentrations of carebastine. Worth mentioning is the fact that other second generation antihistamines, such as epinastine, terfenadine, azelastine, mequitizine and astemizole, occupy 10% to 30% of brain  $H_1$  receptors.<sup>129</sup>

The lack of CNS effects is one of the characteristics that has been most thoroughly and satisfactorily assessed for ebastine. *In vitro*, *in vivo*, and clinical studies evaluating subjective and objective variables have made it clear that ebastine does not produce sedation at therapeutic doses. Drug interaction studies with classical CNS depressants have also discarded a synergistic effect. Furthermore, neuroimaging studies have now added to formerly available clinical evidence.

## Pharmacological approach

### Receptor antagonism or inverse agonism

The  $H_1$  receptors belong to the superfamily of G protein receptors (GPCRs) and are encoded on human chromosome 3. The cloning and expression of these elements by recombinant cells has allowed us to know that these receptors exhibit spontaneous activation of their intracellular messengers, requiring no binding by an agonist at surface level to be in an active state. This “constitutive activity” is attributable to an active and an inactive conformation coexisting in equilibrium.<sup>8</sup> As a result, the drugs that act upon these receptors have been reclassified. Accordingly, if the ligand stabilizes the active conformation, then the drug is an agonist, whereas if the inactive conformation is stabilized, the drug is said to be an inverse agonist.<sup>71</sup> In this sense, histamine is an agonist and  $H_1$  antihistamines are inverse agonists, rather than  $H_1$  receptor antagonists.<sup>39</sup> Until now, all existing  $H_1$  antihistamines evaluated have proved to be inverse agonists.<sup>39</sup> The advantages or disadvantages to develop a real  $H_1$  receptor antagonist instead of an inverse agonist are not yet clearly established.

### $H_3$ receptors

$H_3$  receptors, first described in 1983, have been reported to play a role as autoreceptors in the regulation of histamine synthesis and release from tissue nerve.<sup>130</sup> Localization studies in rodents have shown predominance in distinct regions of CNS, such as cerebral cortex, hippocampus, amygdala, nucleus accumbens, globus pallidus, striatum, and hypothalamus. Peripherally, these receptors have been identified in the gastrointestinal tract, airways, and cardiovascular system. The fact that  $H_3$  receptors are expressed in postganglionic cholinergic nerves in human bronchi has suggested that their stimulation may act as a protective mechanism against excessive bronchoconstriction.

Several centrally acting imidazole and nonimidazole based antagonists and inverse agonists have been studied in recent years for myriad conditions (eg, cognitive impairment, narcolepsy, obesity, diabetes mellitus, and neuropathic pain).<sup>131</sup> Peripherally acting hybrid structures are created by combining histamine  $H_1$  with  $H_3$  pharmacophores to treat nasal congestion in allergic rhinitis,<sup>131</sup> as it has been suggested that cutaneous itch and nasal congestion may be mediated both the  $H_1$  and  $H_3$  receptors.<sup>132–134</sup>

Combinations with  $H_1$  antihistamines have been reported in the field of imidazole and non-imidazole containing ligands.<sup>131</sup> A ketopiperazine compound, GW-784568X (GlaxoSmithKline), is now patented and has already passed a clinical phase I/II study aiming to assess the safety and efficacy of intranasal application in patients with allergic rhinitis.<sup>131</sup> Currently, GlaxoSmithKline’s pipeline lists 2 histamine  $H_1/H_3$  dual antagonists (GSK1004723 and GSK835726) in phase II of clinical development, targeted on allergic rhinitis.<sup>135</sup> GSK1004723 has already been administered intranasally in a phase I clinical trial, while GSK835726 is planned for a similar study.<sup>131</sup> The success of this approach will be known shortly.

### $H_4$ receptors

A fourth histamine receptor ( $H_4$ ) with very high affinity for histamine has recently been described.<sup>136,137</sup> Its presence on eosinophils had been suggested previously.<sup>138–140</sup> but it had not been identified as such.<sup>37</sup> Compared with the  $H_1$  and  $H_2$  receptors, the  $H_4$  receptor is chiefly found in dendritic cells, mast cells, eosinophils, monocytes, basophils, and T cells, suggesting perhaps an interesting target for drug development.

The antihistamines that are currently used in the clinic have little, if any, affinity for the  $H_4$  receptor. However, it has been observed that this receptor is involved in inflammatory and immunomodulatory responses *in vitro* and *in vivo*.<sup>37</sup>

It has been demonstrated, for instance, that histamine acting through  $H_4$  receptors can induce chemotaxis of murine mast cells *in vitro*.<sup>141</sup> Moreover, *in vivo* redistribution of mast cells to the tracheal epithelium has been successfully blocked by systemic administration of the  $H_4$  receptor antihistamine JNJ 7777120.<sup>142</sup> It has been hypothesized that this latter effect is probably linked to the epithelial lining of the nasal mucosa in rhinitic responses to allergens.<sup>143,144</sup> Additionally, activation of  $H_4$  receptors can induce chemotaxis of human eosinophils and dendritic cells,<sup>145,146</sup> and in human mast-cell precursors this activation can synergize with other chemoattractants,<sup>138,147,148</sup> such as CXCL12, a constitutive chemokine (ligand of CXCR4 and CXCR7) that is expressed in the skin and airway epithelium and plays a significant role in allergic airway diseases.<sup>149,150</sup>

All the above described properties, and the emerging role of the  $H_4$  receptor in inflammation, have spurred new interest in the functions of histamine in inflammation, allergy, and autoimmune diseases.<sup>37</sup> The apparent overlap in the functions of  $H_1$  and  $H_4$  receptors suggests that  $H_4$  receptor antihistamines could perhaps work in synergy with  $H_1$  receptor antihistamines for the relief of conditions such as asthma, a therapeutic area that has eluded  $H_1$  antihistamines to date.<sup>37</sup>

## Conclusions

Current evidence shows that like other second-generation  $H_1$  antihistamines, ebastine can modulate the allergic inflammatory process, and that this property might be directly linked to the amelioration of nasal congestion. To corroborate this putative effect, a clinical trial with one or more positive comparators and placebo is needed.

For potency, efficacy, and effectiveness, ebastine has shown interesting properties in relation to other antihistamines, although their therapeutic relevance has not been satisfactorily demonstrated. In other words, ebastine does not differ as much as would be needed to be considered a third-generation agent.

Despite initial concerns by the FDA, clinical trials and clinical evidence from the clinical development and postmarketing stages have provided sufficient evidence to eliminate any major cardiac toxicity problem when the drug is used at the recommended doses. In retrospect, a thorough QT/QTc study, as currently defined, might have provided valuable information on the cardiac safety of ebastine and possibly would have ruled out the need for further studies.

Drug interactions after co-administration of ebastine with a number of other drugs have been correctly explored, in particular, CYP3A4 inhibitors or drugs with sedative effects.

Results have demonstrated that there seems to be no danger of clinically relevant drug interactions.

A lack of CNS effects has been correctly and exhaustively studied. Ebastine does not produce sedation at therapeutic doses, and drug interaction studies with classical CNS depressants have also eliminated a synergistic effect. Neuroimaging studies have added to the available clinical evidence.

Recently, other research lines have been investigated to obtain novel agents. For instance, the potential overlap of functions between  $H_1$  and  $H_4$  receptors has spurred new hope for the development of a new generation of antihistamines. In this regard, hybrid agents are being tested.

In conclusion, ebastine is a  $H_1$  antihistamine with an interesting and widely proven therapeutic profile. It is one of the best documented second-generation antihistamines. However, taking CONGA recommendations into account, its classification as a third-generation antihistamine is far from applicable. It is still going to be some time before a novel agent, meriting the denomination of a third-generation agent, is developed.

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## Disclosures

The authors declare no conflicts of interest.

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