Critical appraisal of bilastine for the treatment of allergic rhinoconjunctivitis and urticaria

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Abstract: Bilastine is a second generation antihistamine indicated for the treatment of seasonal or perennial allergic rhinoconjunctivitis and chronic urticaria with a daily dose of 20 mg, in adults and children over 12 years of age. The efficacy of bilastine has been shown to be similar to that of the comparator drugs for the control of the nasal and nonnasal symptoms of allergic rhinoconjunctivitis, while also showing a subjective improvement in the quality of life and in overall clinical impression. For chronic urticaria the symptoms (itching and the development of papules) lessens from the second day of treatment onwards, in a similar way to other antihistamines used as comparators. Bilastine should not be administered at meal times to avoid interference with the absorption process. It is not distributed to the central nervous system, is scarcely metabolized, and elimination is through the kidneys and feces, with a 14-hour elimination half-life. It has no effect on cytochrome P450. During clinical development, bilastine was shown to be a drug that is adequately tolerated, with a similar effect to placebo with regard to drowsiness and changes in heart rate. In relation to its use, headaches were the most frequent adverse effect to be reported. No cardiotoxic effects have been observed, and the therapeutic dose does not alter the state of alertness.

Keywords: bilastine, allergic rhinoconjunctivitis, chronic urticaria, second generation antihistamine, drowsiness, CYP450

Bilastine

Bilastine is a recently marketed, orally administered antihistamine for the treatment of allergic rhinoconjunctivitis and chronic urticaria in adults and adolescents. The treatment of both disorders with antihistamines has been clearly established. Second generation antihistamines have surpassed first generation ones due to their improved tolerance, primarily based on their lack of anticholinergic effects and lower risk of cardiotoxicity. However, second generation antihistamines are able to cross the blood-brain barrier and, therefore, can induce drowsiness. Likewise, many of these antihistamines are metabolized by cytochrome P450 enzymes, and thus can possibly interact with other drugs. As discussed below, these characteristics have been addressed and modified with bilastine. The aim of this paper is to assess the present situation of the aforementioned antihistamine for the treatment of chronic urticaria and allergic rhinoconjunctivitis, through an evaluation of the results published regarding the efficacy and safety of this new drug.

Pharmacodynamics

Bilastine, or 2-[4-[2-[4-(1-(2-ethoxyethyl) benzimidazol-2-yl] piperidin-1-yl] ethyl] phenyl]-2-methylpropionic acid (Figure 1), is a molecule with a molecular weight of 463.6 Daltons. Based on bilastine’s structure, it is classified within the group...
of new antihistamines, as a second generation original molecule.

Bilastine is highly selective for histamine receptor (H1) binding, without inhibiting other receptors (muscarinic, adrenergic, serotonergic, other histamine receptors, bradykinin, leukotriene d4, or calcium). It shows great affinity for the H1, comparable to other antihistamines, such as astemizole or diphenhydramine, and a three and five fold greater affinity than fexofenadine and cetirizine, respectively. The inhibition of this receptor blocking is dose dependent. The antimuscarinic effect was specifically studied in preclinical trials and in healthy volunteers alike; this effect was not observed in the cellular models. In humans, no change was observed in pupillary reactivity following treatment with different dose levels of bilastine (20, 40, and 80 mg/day) over a 7-day period. It can therefore be concluded that bilastine does not present undesirable anticholinergic effects associated with first generation antihistamines.

In different murine models, bilastine antagonizes the effect of histamine in a concentration-dependent manner (inhibiting increased capillary permeability, decreased microvascular extravasation, and decreased bronchospasm), with a similar potency to fexofenadine and cetirizine, respectively. The inhibition of this receptor blocking is dose dependent. The antimuscarinic effect was specifically studied in preclinical trials and in healthy volunteers alike; this effect was not observed in the cellular models. In humans, no change was observed in pupillary reactivity following treatment with different dose levels of bilastine (20, 40, and 80 mg/day) over a 7-day period. It can therefore be concluded that bilastine does not present undesirable anticholinergic effects associated with first generation antihistamines.

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In studies on animals with radiolabeled bilastine, the drug was distributed in the gastrointestinal tract and liver, without reaching the brain.12

Bilastine is scarcely metabolized, and is excreted unchanged through the kidneys and feces. A mass balance study showed that 33% of bilastine was excreted in the urine and 67% in the feces.13 A study with hepatocyte cultures and liver microsomes demonstrated the non-existence of cytochrome P450 mediated metabolization, nor was any inhibiting or inducing effect observed with regard to this same enzyme.7 This lack of inhibition is one of the characteristics that makes bilastine a compound of interest, according to the recommendations published by a group of experts on the treatment of allergic rhinitis;1 96% of the dose administered was eliminated in 24 hours and at 72 hours it was completely eliminated from urine, with an elimination half-life of around 14 hours. Renal function impairment did not significantly alter the pharmacokinetics of bilastine10 although an increase in the plasma concentrations of the antihistamine was observed. In general, this suggests that there is no need to modify the dose in the event of renal impairment, although this precaution should be taken into account in situations in which the concentrations of bilastine may be increased in the blood as a result of the concomitant administration of P glycoprotein inhibitors, as was observed with ketoconazole.14

No evaluation of bilastine administration to patients with liver damage has been made, although given the fact that bilastine does not metabolize, no pharmacokinetic modification or the need for dosage adjustment whatsoever is to be expected for these patients.

No differences in bilastine pharmacokinetics have been observed with regard to sex or age, except for the highest maximum plasma concentration (Cmax) values in young women (18–35 years). In a population pharmacokinetics analysis, no influence of various covariables was observed (age, weight, height, sex, heart rate, serum albumin, creatinine, bilirubin, liver transaminases, alkaline phosphates, or urea).7

Based on data from adults, it was estimated that the dose for children aged 2 to 12 years should be 10 mg per day and 5 mg per day for children under the age of two,15 although studies are currently being conducted to confirm this dose.

The possibility of bilastine interacting with food and other drugs was previously evaluated. As mentioned, grapefruit juice reduces the bioavailability of bilastine.10,11 The mechanism responsible for this interaction could be the inhibition of the organic anion-transporting polypeptide membrane transporter, which facilitates the absorption of some drugs.9 This effect on the transporter could be avoided by taking bilastine either one hour before or two hours after the intake of juices or food. Some substrate drugs or inhibitors of this transporter, such as ritonavir or rifampicin, could reduce bilastine plasma concentrations,16 although this point has not been specifically evaluated.

No effect of bilastine has been observed on the pharmacokinetics of ketoconazole in healthy volunteers.14 On the other hand, exposure to bilastine increased as a result of coadministration with ketoconazole, which doubled the exposure of the antihistamine, probably due to the inhibitor effect on the membrane transporters, such as P glycoprotein, in the intestinal lumen without modifying the hepatic clearance.17

No interaction was observed with the central nervous system depressors, such as lorazepam18 or alcohol.19

Pharmacokinetics/pharmacodynamics

When jointly evaluating the pharmacokinetic and pharmacodynamic data, it was concluded that bilastine is characterized by two compartment kinetics, with a rapid absorption phase and a maximum response 4 hours after administration. The pharmacodynamics of the disappearance of the wheal or flare was fitted to an indirect response model to define a concentration that produces a 50% inhibition (IC50) of 5.15 ng/ml and 1.25 ng/ml, respectively. With a daily administration of 20 mg of bilastine to adults, the plasma concentrations remain above these values for 20 and 24 hours, respectively, indicating that a once a day administration is adequate.7 In a simulation performed for children aged from 2 to 12, the 10 mg dose was sufficient to maintain the plasma concentrations above this value for the entire administration interval.15

Efficacy

Efficacy evaluation of bilastine from clinical investigation is shown in Table 2.

The onset of action and the duration of the antihistaminic effect are both decisive factors in selecting an antihistamine. Along these lines, an evaluation was made of the effects of bilastine on allergen-induced nasal and eye symptoms in 75 patients allergic to pollen. The patients were exposed to controlled concentrations of pollen using a standard allergy provocation method (Vienna Challenge Chamber).20 The subjects underwent two provocation tests with pollen on two consecutive days, for 6 hours on the first day and for 4 hours on the second day. The nasal symptoms were assessed every
### Table 2 Bilastine efficacy determined during clinical investigation

<table>
<thead>
<tr>
<th>Author</th>
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<tr>
<td>Bachert et al</td>
<td>Seasonal allergic rhinitis (n = 721). Randomized, double blind, placebo-controlled, parallel group, 14 days, bilastine 20 mg, desloratadine 5 mg, and placebo</td>
<td>Mean AUC of the reflective TSS from day 0 to day 14, composed of NSS (congestion, rhinorrhea, sneezing, and itch) and NNSS (ocular itching, burning, redness, sensation of foreign body in eye, tearing, and itching of ears and/or palate)</td>
<td>NSD between active treatments but significantly more effective than placebo in reducing AUC-TSS over the entire treatment period, improving the NSS, NNSS, rhinitis-associated discomfort, rhinoconjunctivitis, and quality of life</td>
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<tr>
<td>Kuna et al</td>
<td>Seasonal allergic rhinitis (n = 681). Randomized, double blind, placebo-controlled, parallel group, 14 days, bilastine 20 mg, cetirizine 10 mg, and placebo</td>
<td>Mean AUC of the reflective TSS from day 0 to day 14, calculated daily as the sum of four nasal (rhinorrhea, congestion, itching and sneezing) and three nonnasal, ocular symptoms (tearing, redness and itching)</td>
<td>NSD between active treatments but significantly more effective than placebo in reducing AUC-TSS over the entire treatment period</td>
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<td>Zuberbier et al</td>
<td>Chronic idiopathic urticaria (n = 525). Double-blind, randomized, placebo-controlled, 28 days, bilastine 20 mg, levocetirizine 5 mg, and placebo</td>
<td>TSS was calculated as the sum of scores for pruritus, number of wheals, and the maximum wheal size recorded in the patients’ diaries each day, from day 0 to day 28</td>
<td>NSD between active treatments more effective than placebo to improve Dermatology Life Quality Index, general discomfort, and sleep disruption. Treatment with bilastine and levocetirizine reduced instantaneous and reflective TSS in a similar manner</td>
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<tr>
<td>Sastre et al</td>
<td>Perennial allergic rhinitis (n = 650). Randomized, placebo-controlled, double-blind, parallel-group, 4 weeks, bilastine 20 mg, cetirizine 10 mg, and placebo</td>
<td>Mean AUC of the reflective TSS from day 0 to day 28: total of 6 reflective or instantaneous symptom scores (T6SS) as well as T4NSS (rhinorrhea, nasal itching, sneezing, nasal congestion) and T2OSS (ocular redness, tearing)</td>
<td>Statistically significant differences existed between active treatments and placebo in the mean AUC of T6SS and T4NSS (not in South Africa patients). Bilastine 20 mg, but not cetirizine 10 mg, reached maximum response in a statistically significant shorter time than placebo</td>
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<td>Horak et al</td>
<td>Asymptomatic patients (n = 75). Double-blind cross-over, allergen-induced symptoms in the Vienna Challenge, single dose, bilastine 20 mg, cetirizine 10 mg, fexofenadine 120 mg</td>
<td>Reflective NSS in patients challenged with allergen for 6 hours</td>
<td>Bilastine and cetirizine had a rapid onset of action, within 1 hour, duration of action greater than 26 hours. Fexofenadine was less effective on day two</td>
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</table>

**Abbreviations:** AUC-TSS, the area under curve of total symptom scores; NNSS, nonnasal symptom scores; NSD, no significant differences; NSS, nasal symptom scores; T2OSS, total 2-ocular symptom scores; T4NSS, reflective and instantaneous total 4-nasal symptom scores; T6SS, total 6-symptom scores.

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15 minutes. Four of these symptoms (rhinorrhea, nasal congestion, sneezing, and nasal itching) were considered to be the principal study variables. The treatments studied were 20 mg of bilastine, 10 mg of cetirizine, 120 mg of fexofenadine, or a placebo, administered 2 hours after the first provocation. In this study, onset of action was observed at around 1 hour for bilastine and cetirizine, with duration of action of at least 26 hours. The duration of action of fexofenadine was considered shorter, given the fact that it was less effective on the second day of the study. A similar study compared the effect of 20 and 50 mg of bilastine to 10 mg of cetirizine with respect to the inhibition of cutaneous wheal and flare following a skin prick test at different times in relation to the drug administration. The response was similar for 20 mg of bilastine and 10 mg of cetirizine at the different measurement points, with the exception of the analysis obtained 1.5 hours following administration, which indicated that bilastine had a faster onset of action. The administration of 50 mg of bilastine prolonged the duration of the antihistaminic effect. In a study on healthy volunteers, the results observed showed the existence of a certain dose dependency in regards to the inhibition of wheals following subcutaneously administered histamine.

### Clinical studies

**Allergic rhinoconjunctivitis (seasonal and perennial)**

H1 antihistamines are first line drugs for the treatment of allergic rhinoconjunctivitis. Allergic rhinitis is one of the most common chronic diseases in the world, with an estimated prevalence of 10%–25%. The most frequent
symptoms of allergic rhinitis are nasal itching, sneezing fits, rhinorrhea, and nasal obstruction. Patients with allergic rhinitis show a reduced quality of life due to the inherent symptoms of rhinitis and the physiopathology, which can result in sleep disorders.

The nasal response to allergen stimulation provokes all the symptoms characteristic of allergic rhinitis. This response comprises two phases: the immediate response is observed 20 minutes after contact with the allergen and can continue for up to hours afterwards. This is primarily the result of mast cell degranulation. This phase is characterized by itching, sneezing, and rhinorrhea. Mast cells release chemotactic substances and cytokines that are able to attract other cells to the inflammatory focus, including eosinophils. This gives rise to the late phase of the allergic response (48 hours later), which comprises the cellular response. The principal response in this phase is nasal obstruction.

Histamine is one of the substances released by the mast cells and basophils. This amine is released in a few seconds in E immunoglobulin (IgE) mediated hypersensitivity reactions. A minute after the nasal allergic stimulation, the histamine released reaches its maximum concentration. Ten minutes after this peak, there is an abrupt drop in concentration. Histamine induces increased chemotaxis of eosinophils, increased cytokine (IL-1β, IL-6, IL-4, and IL-5) release, increased vascular cell adhesion molecule (VCAM)-1 expression and activation of nuclear factor (NF)-κβ. Histamine is responsible for the characteristic symptomatology of allergic rhinitis, including nasal obstruction.

H1 antihistamines can act through different routes of action; they counteract the effects of histamine on the H1 receptors and they are also able to inhibit the release from mast cells and basophils, which contribute to the late phase of the allergic response. Bilastine is a highly selective antihistamine, with moderate to high H1 receptor affinity. Furthermore, in vitro studies have shown anti-inflammatory activity by inhibiting the release of histamine, IL-4, and tumor necrosis factor (TNF)-α, and also by inducing the release of different stimulants.

The efficacy of bilastine in allergic rhinoconjunctivitis has been confirmed in several studies comparing it to either a placebo or to other antihistamines. Bachert et al conducted a multicenter study to assess clinical efficacy through the rating of nasal and nonnasal symptoms at the start and after 14 days of treatment, and the safety of 20 mg of bilastine compared to 5 mg of desloratadine and placebo in patients with seasonal allergic rhinitis (n = 721). A significant decrease was observed in the nasal and nonnasal symptoms of patients treated with both drugs in relation to the placebo. Along these same lines, a reduction in the patient-rated discomfort score and an improvement in the investigator’s overall clinical impression were observed. However, no differences were found between bilastine and desloratadine.

A further study compared the administration of 20 mg of bilastine to 10 mg of cetirizine or placebo in patients with seasonal rhinitis, finding statistically significant differences in the improvement of the nasal symptoms in the group administered with bilastine (−43.8% after 7 days and −48.5% after 14 days) and cetirizine (−40.2% after 7 days, and −50.6% after 14 days) in relation to the placebo group (P < 0.001), yet without any differences between treatment groups.

Daily treatment with 2 mg of bilastine was effective for the treatment of perennial allergic rhinitis, a disease which affects a high percentage of the population (10%–15%). An assessment was made of the nasal symptoms (rhinorrhea, sneezing, congestion, itching) and eye symptoms (redness, tears) compared to the placebo; the results showed bilastine and cetirizine were similar in Europe and superior in Argentina, achieving an approximate 34% reduction in nasal symptoms after 28 days of treatment.

Bartra et al reviewed clinical trials conducted with bilastine in order to assess its effect on eye symptoms of allergic rhinoconjunctivitis (itching, redness, and tearing). The clinical test results showed bilastine to be as effective as the comparator drugs for controlling the eye symptoms in seasonal allergic rhinitis.

Likewise, an evaluation of the effects of bilastine on nasal obstruction in allergic rhinitis was performed. The efficacy of 20 mg of bilastine for controlling this symptom was tested and was determined to be along the same lines as that observed with active comparators (desloratadine 5 mg and cetirizine 10 mg).

The quality of life variable was also recently analyzed separately, given the fact that it has been studied as a secondary objective in three clinical studies on allergic rhinitis, by means of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) questionnaire on a total number of 2335 patients and in chronic urticaria through the Dermatology Life Quality Index (DLQI) questionnaire on a total of 525 patients, compared to levocetirizine and placebo. The results are parallel to the efficacy results observed in the clinical trials.

**Chronic urticaria**

Chronic urticaria significantly affects patients’ quality of life. It is characterized by the appearance of pruritic
erythematous papules. The papules have a duration of less than 24 hours in which they may appear daily or more than once a week for 6 weeks. In 50% of cases, this is associated with the appearance of angioedema.\textsuperscript{34}

The clinical guidelines for the treatment of chronic urticaria suggest increasing the normal dosage of the antihistamine by up to 4-fold, if the normal therapeutic dosing is not effective.\textsuperscript{35} However, in the literature, there are no randomized, double blind trials that study whether there is any difference in efficacy between the therapeutic doses and higher doses for controlling chronic urticaria. In this respect, preliminary data with bilastine are available, such as the data obtained in a phase I double blind single dose clinical trial with four crossover periods on 21 volunteers administered with either placebo, 10 mg of cetirizine, or 2.5, 5, 10, or 50 mg of bilastine. An evaluation of the relationship between the dose of bilastine and the inhibition of the cutaneous response to histamine (measured by wheal and flare) was made. All bilastine doses inhibited the histamine-induced wheal between 1.5 and 12 hours and the flare between 4 and 24 hours following administration, showing a response that is similar or better than cetirizine. No clear dose dependent effect was observed, although it was seen that the 20 and 50 mg dose levels had a longer lasting effect.\textsuperscript{11}

Audicana et al conducted a phase II study on 222 patients with chronic urticaria. The effect of bilastine (10, 20, and 30 mg) was evaluated against a placebo in the control group for the appearance of papules and itching. Statistically significant differences were observed in the three treatment groups administered bilastine compared to the placebo group, although no dose dependent effect was observed, as reported by Ferrer et al.\textsuperscript{36}

Bilastine was also assessed in a double blind controlled clinical trial with placebo and levocetirizine both administered for 28 days. A compound variable was evaluated by calculating the data for itching, number of wheals, and the maximum size of the wheals, based on patients’ diaries. The symptoms were reduced from the second day of treatment with 20 mg of bilastine, which was also the case for levocetirizine, showing better results than placebo.\textsuperscript{37}

**Tolerance and safety**

In the various studies conducted during the preclinical development of bilastine, no significant toxicity was demonstrated. The acute toxicity of bilastine was investigated through the oral and intravenous administration in mice and rats. Following the oral administration of 5000 and 2000 mg/kg in mice and rats respectively, no mortality was observed in either of the two species. However, following intravenous administration, the lethal dose for 50% of the animals was 33 mg/kg for mice and 45–75 mg/kg for rats.\textsuperscript{38}

In chronic toxicity studies of bilastine administered both orally and intravenously, no signs of toxicity were observed in any organ.\textsuperscript{38} No effects on fertility, either on embryo-fetal toxicity or on teratogenicity, were observed in the studies conducted on mice and rabbits.\textsuperscript{39}

When studies were conducted on humans during the assessment of the efficacy of bilastine in the treatment of chronic urticaria and allergic rhinitis, tolerability was studied in relation to a placebo and other antihistamines (levocetirizine, desloratadine, and cetirizine), and most of the data correspond to the therapeutic dose of 10 mg a day; Table 3 shows results of these clinical trials. Specific studies were also conducted to evaluate the incidence of problems commonly associated with the use of antihistamines, such as drowsiness and heart rate changes.

In general, bilastine was well tolerated and the majority of the adverse events described were either mild or moderate. The incidence of drug related adverse effects was 15%–30%, similar to observed with the placebo. There were no serious drug related adverse effects in any of the clinical trials. No significant changes were detected in vital signs (heart rate or blood pressure), in the electrocardiogram (ECG) parameters or in laboratory values (hematology and liver and kidney function).\textsuperscript{29,30,37}

The adverse events most commonly described by patients treated with bilastine and to some extent related to the drug, are: headache, drowsiness, dizziness, and fatigue.\textsuperscript{29,30,37} In a study in which the treatment was administered for 1-year, the most commonly described adverse effects were headache (9.6%) followed by nasopharyngitis (2.5%), while other less common bilastine related adverse effects included some changes in the ECG trace, which were not consistent over time.\textsuperscript{31}

No differences were observed in the tolerance of bilastine compared to cetirizine and desloratadine.\textsuperscript{29,37} One study described a statistically significant minor incidence in the appearance of drowsiness, (bilastine and cetirizine, 1.8% versus 7.5%) and fatigue, (bilastine and cetirizine, 0.4% versus 4.8%) with 20 mg a day of bilastine compared to cetirizine at normal dose levels.\textsuperscript{30}

Some second generation antihistamines have been associated with adverse cardiac effects, such as the prolongation of the QT interval and the development of torsades de pointes. These effects have been attributed to the direct blocking of the potassium channels. For this reason, and following the guidelines of International Conference on Harmonisation (ICH) E14, a study was conducted to evaluate the effect of...
The evaluation of neurological tolerance was conducted with specific studies to evaluate the appearance of drowsiness/sedation and the effect on attention when driving a vehicle following bilastine treatment. The sedating effect of first generation antihistamines is widely known, which in some cases has led these drugs to be used as sleeping pills. This effect is related to the affinity for the P glycoprotein, which is responsible for the efflux of drugs and other substances from the central nervous system, and to drug lipophilicity; the greater the affinity and the lower the lipophilicity, the lower the blood-brain barrier crossing.

In a repeat dose crossover trial with healthy volunteers, three doses of bilastine (20, 40, and 80 mg) were compared to 25 mg of hydroxyzine and placebo following 7 days of treatment and with a washout period of 15 days between each scheduled administration. An evaluation was made of the effects on psychomotor function (motor activity, perception, attention, associative integration) and state of mind. Hydroxyzine caused an increase in the time to react, a decrease in the blinking rate, and a worsening of attention or motor activity. With the 20 and 40 mg doses of bilastine, no changes were observed in the parameters evaluated, although changes were observed with the highest dose (80 mg) when evaluating objective parameters. Subjectively, only the 20 mg dose was distinguishable from the placebo.

A clinical trial was conducted with 22 healthy volunteers, who were administered daily doses of bilastine (20 mg and 40 mg) for an 8-day period, and compared to a placebo and 50 mg a day of hydroxyzine (positive control) to evaluate the effect of the drug on driving. This was a crossover study with a 7-day interval between treatment periods. The position of the car was evaluated at a constant speed, recording the deviation of the car in relation to the standard deviation of lateral position. No changes were observed with the 20 and
40 mg doses of bilastine, providing results similar to the placebo, with evaluations made on the first and eighth day of treatment. With hydroxyzine, a significant increase was observed in the deviations for all measurements, although it was reduced in relation to the first administration, in a situation of pharmacokinetic balance, following the final dose. In the overall analysis of the data on the development of sleepiness observed in the different studies conducted with bilastine, it was concluded that its appearance is similar to that observed with a placebo, and significantly less than that observed with cetirizine.

Further studies have been conducted to evaluate the effects of bilastine on the central nervous system in combination with other drugs such as lorazepam or substances such as alcohol, whose sedative effect is well known. None of these studies with 20 mg of bilastine produced such an effect, neither did they increase the effect produced by these known central nervous system depressants.

**Conclusion**

Bilastine is a second generation antihistamine developed for the treatment of allergic rhinoconjunctivitis and chronic urticaria. It is a product that does not undergo hepatic metabolism nor does it modify the activity of the cytochrome P450 isoenzymes. It should not be administered at meal times, which may increase its bioavailability. Treatment with 20 mg, administered orally, is effective in controlling the symptoms and improving the quality of life of these patients. The studies conducted to date indicate that bilastine has an acceptable tolerability profile, given the fact that no cardiotoxic effects have been observed, and the therapeutic dose does not change a patient’s state of alertness.

**Disclosure**

The authors report no conflicts of interest in this work.

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