

EXPERT OPINION

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Bilastine for the treatment of urticaria

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Introduction: Urticaria is a highly prevalent disease among people. First-choice treatment continues to be centred on the second-generation H1 antihistamines, including a wide group of drugs with a better therapeutic index (or risk:benefit ratio) than the classic ones, even in the high, off-label dosage occasionally required in chronic urticaria. Bilastine is a newly registered H1-antihistamine for treatment of allergic rhinoconjunctivitis and urticaria. With established antihistaminic and antiallergic properties, it is widely reviewed in the medical literature; however, to our knowledge, a specific review of bilastine's role in the treatment of urticaria was lacking.

Areas covered: This article reviews the medical literature on the effectiveness and safety of bilastine in urticarial syndromes, either spontaneous or inducible, by means of a Medline search from 1990 to present, completed with some nonpublished data provided by the manufacturer.

Expert opinion: Once-daily treatment with bilastine 20 mg is effective in managing symptoms and improving patient's quality of life in chronic urticaria, with at least comparable efficacy to levocetirizine. As far as studies in healthy volunteers, clinical assays, and recent clinical experience can establish, bilastine's safety profile is adequate, appearing to be entirely free from cardiovascular effects, and not impairing psychomotor performance or actual driving, even at twice the therapeutic dose.

Keywords: bilastine, chronic urticaria, H1-antihistamine, urticaria

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1. Introduction

Urticaria affects 15 – 30% of the people at any moment during their lifetime, and in 0.5 – 1%, it persists daily or almost daily for > 6 weeks and is therefore considered, as a convention, to be chronic. The symptoms are induced by the activation of mast cells and the secondary release of histamine and other inflammatory mediators. Histamine interacts with H1 and H2 receptors, increasing vasodilation and plasma extravasation, leading to stimulation of nerve endings and the release of neuropeptides responsible for pruritus [1].

Chronic urticaria (CU) is characterized by the spontaneous appearance of itchy wheals, angioedema, or both, recurring for > 6 weeks, being distressful and often challenging to treat. Elimination or treatment of eliciting stimulus should be the first step in the management of CU; however, in the majority of cases, the cause remains unknown. According to its possible etiology, CU is divided into two great groups: i) inducible urticarias, a heterogeneous group of conditions induced by exogenous physical triggers acting on the skin (cold, heat, solar radiation, friction, pressure, vibration etc.), as well as cholinergic, or exercise-induced, and contact urticarias [2]; ii) spontaneous urticarias, such as autoimmune, infection-related, diet-related and all cases of CU of unknown cause. As much as 45% of the latter might have an autoimmune origin, determined by the presence of IgG

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Box 1. Drug summary.

Drug name

Bilastine: 2-[4-(2-(4-(1-(2-ethoxyethyl)-1Hbenzimidazol-2-yl)piperidin-1-yl)ethyl)phenyl]-2-methyl propionic acid
Marketed

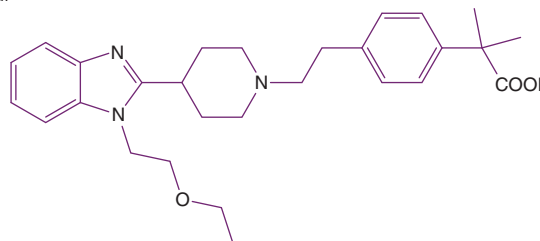
Phase

Indication

Pharmacology description

Route of administration

Chemical structure

Allergic rhinoconjunctivitis (seasonal and perennial) and urticaria
Highly Selective second-generation H1-antihistamine drug
Oral

Pivotal trial(s)

[9,36-38]

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autoantibodies against circulating IgE or against the IgE high-affinity receptor (FcεR-1), which upon binding to skin mast cells would trigger degranulation [3]. CU can also be associated to thyroid autoimmunity [4]. CU is not considered a severe disease, but none of the available treatments is fully satisfactory, and the condition can be overwhelming for some patients in terms of health-related quality of life [5].

The EAACI/GA2LEN guidelines for the management of urticaria recommend nonsedating H1-receptor antagonists as the first-line treatment in all cases [6], and even suggest to consider higher doses (up to fourfold) in nonresponding patients, before changing the therapeutic scheme, a matter only based on experts' opinions, however and actually under permanent discussion [7].

Bilastine (Box 1) is a new inhibitor of the histamine H1 receptor, now approved in many countries throughout the world for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria in adults and children older than 12 years. In crossover studies on healthy volunteers, bilastine 20 mg showed equivalent results and a probably faster onset of action than cetirizine 10 mg in the inhibition of histamine-induced cutaneous wheal and flare reaction [8]. In clinical Phase II studies in CU patients, bilastine was statistically different from placebo at 10, 20 or 30 mg doses in symptom control. In Phase III clinical trials, oral treatment with bilastine 20 mg/day was more effective than placebo and equivalent to levocetirizine 5 mg in CU, relieving symptoms, improving quality of life and controlling sleep disorder [9]. Bilastine shows a good safety profile, and does not affect cardiac conduction, vigilance, performance or driving ability, even at twice the therapeutic dose [10].

2. Overview of the market

Antihistamines are the most widely prescribed drugs for urticaria. For decades, first-generation antihistamines have been

preferred because of their lower cost, and their sedative effects appreciated by many doctors as a therapeutic advantage in the control of pruritus. However, they in fact reduce sleep quality, and a subsequent impairment of cognitive function that might persist throughout the following day, reducing learning and work efficiency [11]. All second-generation antihistamines are thought to be relatively free from significant anticholinergic effects, and to cause less sedation and somnolence-related problems than the classic ones. Within the group, they are considered not very different from each other from the standpoint of clinical efficacy, but they are actually a heterogeneous group of drugs showing different pharmacological properties and safety profiles. Some of them have been associated with drowsiness, weight gain, drug-drug interactions or cardiotoxicity [12] although cardiac effects are considered largely historical, as described later, since astemizole and terfenadine are no longer marketed.

Urticaria is a highly prevalent disease that can be upsetting for health-related quality of life, causing frequent sleep disruption, emotional concerns and reduced performance at work and daily activities [13]. A definitive treatment is still lacking and there is a constant search for effective, safe and harmless symptomatic therapies that can be taken for long periods of time and allow an active life for patients. Oral nonsedating H1 antihistamines are yet considered as the first-line therapy, but many patients still suffer from symptoms when receiving standard treatment; so up dosing might be considered before other therapies are taken into account, if and when safety considerations permit it.

2.1 Introduction to bilastine

Bilastine is a new H1 antihistamine, approved in many countries worldwide for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria in adults and children older than 12 years. Bilastine is an original benzimidazole-piperidinic drug highly selective for H1 receptors, with proper

pharmacokinetic characteristics, no hepatic metabolism, and a good safety profile: Studies in healthy volunteers and patients have shown that bilastine does not cause anticholinergic effects, or significant changes in laboratory tests, vital signs, or ECG patterns, and does not impair vigilance or driving ability. In clinical studies, oral treatment with bilastine 20 mg/day was as effective as levocetirizine in CU. This article reviews the pharmacology of bilastine and its efficacy and safety in treating urticaria.

2.2 Chemistry

Bilastine, or 2-[4-[2-[4-[1-(2-ethoxyethyl) benzimidazol-2-yl] piperidin-1-yl] ethyl] phenyl]-2-methylpropionic acid (Figure 1) has a chemical structure of benzimidazole-piperidinyl with a molecular weight of 463.6 daltons [14]. Bilastine is not structurally derived, nor is it a metabolite or enantiomer from any other antihistamine, but an original molecule designed with the intent of fulfilling all the requirements expected from a second-generation antihistamine [15].

2.3 Pharmacodynamics

Like all other antihistamines [12], bilastine is a histamine H1 receptor inverse agonist [10]. Bilastine binds to H1 receptors with an affinity equivalent to that of astemizole (no longer available) and diphenhydramine, and higher than that of cetirizine and fexofenadine [16]. In isolated organs of guinea pig (ileum and trachea) its *in vitro* antihistaminic potency is also greater than that of cetirizine and fexofenadine [16]. It is highly selective for H1 receptors, with little or no affinity for H2, H3 or H4, muscarinic, α 1- and β 2-adrenergic, bradykinin B1, leukotriene D4 or calcium receptors [16]. *In vivo* experiments in rats showed a dose-dependent, long-lasting antihistaminic activity and a higher activity than cetirizine in blocking histamine-induced bronchospasm in anesthetized guinea pigs [17]. Additionally, in an experimental study bilastine showed to inhibit histamine, IL-4 and TNF- α release from human mast cells and peripheral blood granulocytes [18]. However, it must be reminded that, albeit most second-generation antihistamines show some anti-inflammatory properties *in vitro*, the relevance of these in the final *in vivo* therapeutic effect is uncertain, at the blood and tissue concentrations that can be achieved by standard dosing.

A Phase I study in healthy male volunteers evaluated the effect of two different bilastine single doses (20 and 50 mg) on histamine-induced wheal and flare over a 24-h period, compared with cetirizine 10 mg [8]. Bilastine was at least as efficient as cetirizine, and at 1.5 h, 20 and 50 mg doses of bilastine reduced the wheal and flare reaction significantly more than cetirizine (Figure 2). When examining the relationship between kinetic and the antihistamine effects, measured as skin wheal-and-flare surface areas for 24 h, oral doses of 20 mg/day of bilastine achieved concentrations above the IC₅₀ – that is to say, capable of inhibiting 50% of the surface areas – throughout the whole administration interval [8].

2.4 Pharmacokinetics and metabolism

Pharmacokinetic parameters of bilastine are summarized in Table 1.

2.4.1 Absorption, bioavailability and distribution

Bilastine's oral absorption is quick in fasting conditions, attaining a mean peak plasma concentration (C_{max}) of 220 ng/ml approximately 1 h after single and multiple doses [19]. The estimated mean oral bioavailability is about 61% in healthy volunteers [19]; absorption is reduced by a fatty breakfast or fruit juice. Bilastine has linear pharmacokinetics in the 2.5 – 220 mg dose range in healthy adult subjects without evidence of accumulation after 14 days of treatment. Both the C_{max} and the area under the curve (or the proportion of administered bilastine that reaches systemic circulation) increased proportionally to the administered dose [19]. An apparent volume of distribution of 1.29 l/kg has been estimated for bilastine [19].

2.4.2 Metabolism

Bilastine is not substantially metabolized in humans, being essentially eliminated unchanged in urine and feces – 33 and 67% of the administered dose, respectively – according to a Phase I mass balance study with radiolabeled bilastine [20]. In liver cell cultures, bilastine is not metabolized and does not inhibit or induce the activity of cytochrome P450 isoenzymes. Bilastine has a slow elimination with a half-life around 10 – 14 h, and 96% of the administered dose is eliminated within 24 h [20].

2.4.3 Drug interactions and food effects

Preclinical data suggest interactions between bilastine and drugs or food which are inhibitors or inducers of P-glycoproteins (P-gps). Co-administration of bilastine and grapefruit juice (a known P-gp-mediated drug transport activator) significantly reduced bilastine systemic exposure [21]. This interaction is probably due to the effect of grapefruit flavonoids on intestinal transporter systems such as P-gp and organic anion transporting peptide [22]. When bilastine was administered together with ketoconazole (a known cytochrome P450-3A4 and P-gp inhibitor) for several days, systemic exposure in steady state was increased more than twofold [23]. Other studies with erythromycin and diltiazem show similar P-gp-mediated effects [24].

3. Clinical efficacy

3.1 Inhibition of histamine-induced wheal and flare

The relationship of two different doses of bilastine (20 and 50 mg), cetirizine 10 mg or placebo, to inhibition of skin wheal and flare after a prick test with histamine (100 mg/ml) was investigated in a randomized, double-blind, single-dose, four-period crossover study in 21 healthy male volunteers (Figure 2). Both doses of bilastine were equivalent or superior to cetirizine in diminishing histamine-induced wheal and flare

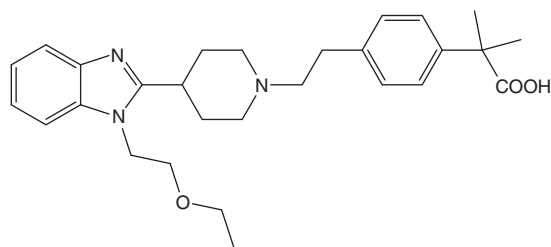


Figure 1. Chemical structure of bilastine.

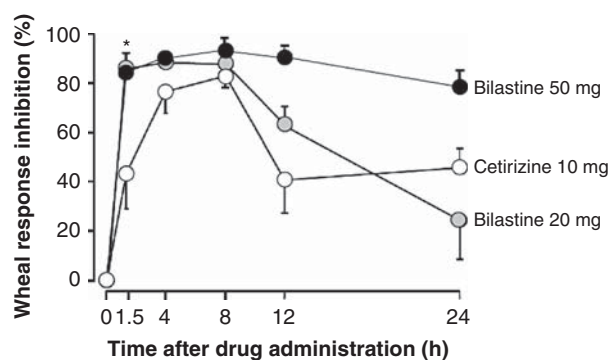


Figure 2. Inhibition of histamine-induced wheal area by cetirizine 10 mg oral dose versus different oral doses of bilastine (20 y 50 mg). Dose-effect and time-effect relationships.

Adapted from [8].

Table 1. Values of the main pharmacokinetic parameters obtained after oral administration of bilastine 20 mg in healthy volunteers

$t_{1/2}$ (h)	14.53
Vc (l)	59.2
Vp (l)	30.2
CL (l/h)	18.1
C _{max} (ng/mL)	220
T _{max} (h)	1.29
AUC (ng·h/ml)	1104.97
Oral F (%)	61

AUC: Area under the curve; CL: Clearance; C_{max}: Maximum plasma total concentration; F: Bioavailability; $t_{1/2}$: Elimination half-life; T_{max}: Time taken to reach C_{max}; Vc: Volume of distribution in central compartment; Vp: Volume of distribution in peripheral compartment.

(> 50% inhibition up to 12 h). At 1.5 h after administration of 20 mg of bilastine or 10 mg of cetirizine, the wheal and flare reaction were significantly inhibited versus placebo, but with bilastine, significantly greater percentages than that of cetirizine were obtained ($p < 0.02$). At 24 h, both bilastine doses successfully inhibited wheal by over 50%, but only the 50 mg dose was associated with a > 50% inhibition of flare.

In turn, cetirizine 10 mg inhibited both wheal and flare areas by over 50% [8].

3.2 Clinical efficacy in chronic spontaneous urticaria

A double-blind, randomized, dose-finding study was carried out in 218 CU patients, distributed in four parallel groups of 10, 20 and 30 mg bilastine versus placebo. All bilastine doses were superior to placebo ($p = 0.003$) in terms of reducing total symptom score, based on the variables of itching and the number and diameter of wheals, evaluated by the patients twice a day over a 28-day treatment period [25]. Also, a Phase III clinical trial in chronic idiopathic (spontaneous) urticaria was conducted, in which 516 adult patients were randomized to receive bilastine 20 mg ($n = 172$), levocetirizine 5 mg ($n = 163$) or placebo ($n = 181$) once daily over a 28-day treatment period. Evaluation was based on patients' reflective assessment of pruritus, the number of wheals and the wheal maximum size according to predefined scales [26]. The patient's reflective total symptom score had reduced progressively by all treatments from baseline, with significant differences noted between active drugs and placebo from day 2 onward over the entire treatment period (-4.23 and -4.63 respectively, vs -2.99 ; $p < 0.001$ for bilastine/levocetirizine vs placebo), while the active treatment groups were not significantly different from each other (Figure 3). The efficacy of bilastine was not dependent on ethnicity, age or gender of the patient [27]. Quality of life, assessed by means of the skin disease-specific Dermatology Life Quality Index, associated discomfort and sleep disruption were also improved to a greater extent in both bilastine and levocetirizine groups, with no significant differences between them, than in placebo-treated patients ($p < 0.001$). Adverse events were similar among the three groups and no serious adverse events were informed [9].

3.3 Clinical efficacy in inducible urticarias

A recent randomized, crossover, double-blind, placebo-controlled 12-week study on 20 patients suffering from cold-contact urticaria (CCU) assessed the effects of different doses (20, 40 and 80 mg) of bilastine in reducing the clinical symptoms of CCU following cold challenge by means of a cold stimulation device. Changes in critical temperature thresholds (CTTs), critical stimulation time thresholds and in levels of mast cell mediators (histamine, TNF- α , IL-6 and IL-8) collected by skin microdialysis, were assessed. All doses of bilastine were very effective ($p < 0.0001$) in reducing CTTs (median CTTs 6°C , $< 4^{\circ}\text{C}$ and $< 4^{\circ}\text{C}$) as compared with placebo (median CTTs 19°C), as well as in improving critical stimulation time thresholds ($p < 0.0001$). There was a significant difference in CTT values between bilastine 20 mg and 80 mg ($p = 0.003$), as well as bilastine 40 mg and 80 mg treatment ($p = 0.04$). Only the 80 mg dose showed to significantly decrease mast cell mediators (IL-6 and IL-8 but not TNF- α) 1–3 h after cold challenge as compared with baseline; this may suggest that the greater

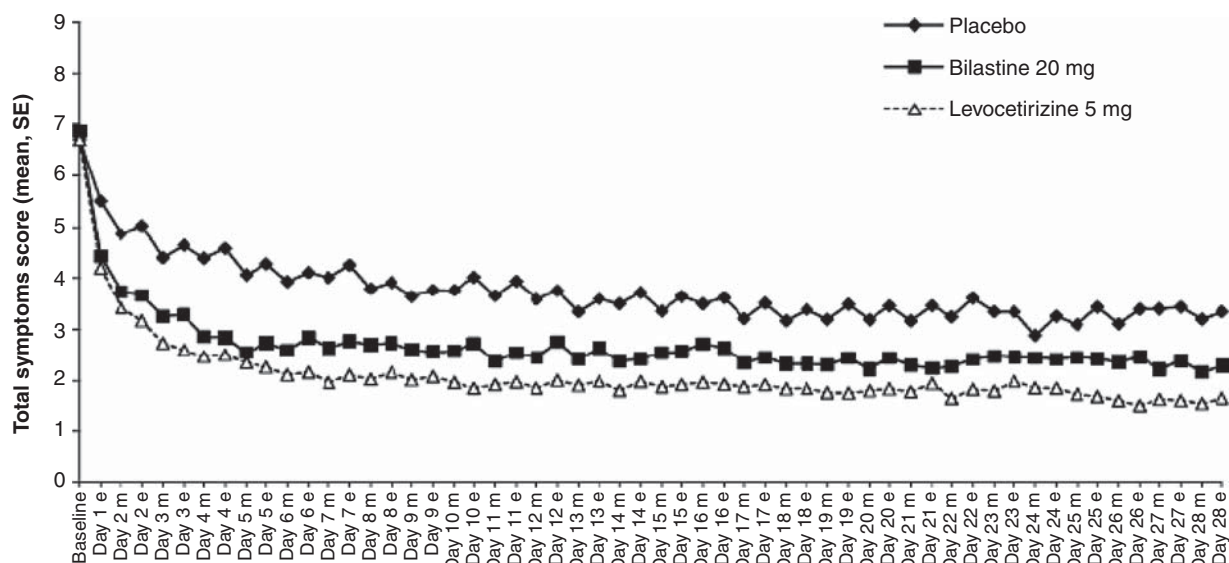


Figure 3. Comparison of the efficacy and safety of bilastine 20 mg versus levocetirizine 5 mg and placebo for the treatment of chronic idiopathic urticaria.

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effects of high doses of bilastine than standard doses could be related with anti-inflammatory effects. All bilastine doses were tolerated well, without evidence of increased sedation with dose escalation [28].

In summary, available results indicate that bilastine 20 mg/day is significantly superior to placebo and at least equivalent to levocetirizine 5 mg in improving the symptoms and health-related quality of life in chronic spontaneous urticaria. Considering inducible urticarias such as CCU, bilastine also has been shown to be effective in reducing CTTs following cold challenge, in a dose-dependent manner and with an observable additional benefit with updosing.

4. Safety and tolerability

Bilastine has proven to be well tolerated in clinical research, with an adverse events profile similar to that of placebo, in healthy volunteers and also in patients with allergic rhinoconjunctivitis and CU [28,29]. No serious adverse events were reported during the research and there were no clinically significant changes in vital signs, ECG or laboratory tests. Pharmacokinetic–pharmacodynamic profiles and studies in special populations indicate that bilastine dose adjustment is not necessary in elderly patients, or in hepatic or renal insufficiency [20,24]. Intentional updosing in CCU patients was well tolerated [28].

4.1 Central nervous system safety

Histamine as a neurotransmitter is concerned in waking–sleep cycle, attention, memory and learning, and hunger regulation. The adverse effects of antihistamines on the CNS depend on their ability to cross the blood–brain barrier (BBB) and bind

to the central H1 receptors. This in turn depends on the lipophilicity of the drug, its molecular weight, and overall its affinity for P-gp [29]. Second-generation antihistamines have shown to cause less somnolence than the classic ones, but many still go through the BBB to some extent, particularly when used in up dosing. According to preclinical data, bilastine is a good substrate for P-gp, which limits its route across the BBB. In fact, negligible penetration of bilastine into rat brain when given in massive doses has been demonstrated by autoradiography [30]. In addition to the lack of subjective drowsiness, bilastine has demonstrated irrelevant effects on objective psychomotor tests [31] or real driving ability [32] in doses of up to 40 mg, and a lack of relevant interaction with lorazepam and alcohol as well [30]. To confirm the negligible penetration of bilastine into human brain, a clinical trial using positron emission tomography methodology is ongoing (personal communication).

4.2 Cardiovascular safety

After five decades of antihistamines' use, it was with the introduction of astemizole and terfenadine in the 1980s when it was realized the H1-antihistamines' capability to elongate the cardiac QT interval in certain clinical situations, leading to the appearance of ventricular arrhythmias. The main mechanism underlying an acquired QT syndrome and *torsades de pointes* arrhythmia is the inhibition of the potassium channel encoded by hERG (the human 'ether-a-go-go'-related gene) [33,34].

Bilastine has no effect on ventricular repolarization, as was established in a trial conducted in 30 healthy subjects in a randomized, triple-dummy, double-blind, 5-way crossover, and placebo- and active comparator-controlled (moxifloxacin)

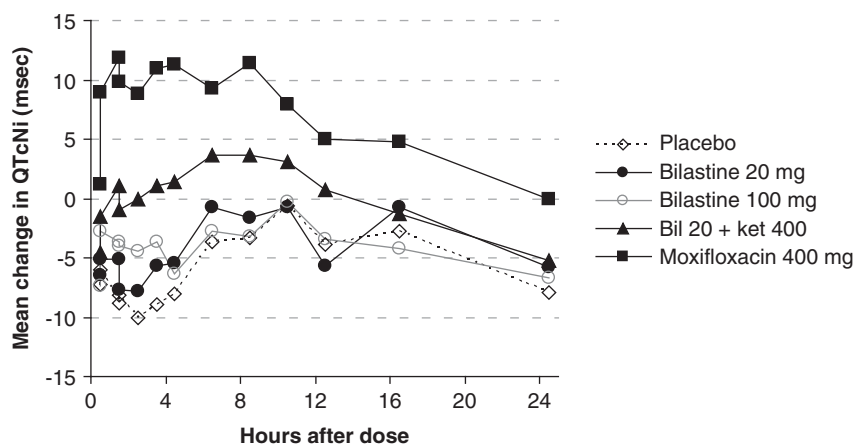


Figure 4. Electrocardiographic effects of different doses of bilastine, bilastine plus ketoconazole, moxifloxacin (positive control) and placebo in 30 healthy adults. Mean change in QTcNi* from time-matched baseline versus time by treatment.

Reprinted with permission from [35].

trial [35]; 20 and 100 mg doses of bilastine were investigated, and the 20 mg dose was administered together with ketoconazole 400 mg. Bilastine did not produce any significant effects on QT interval following either dose, up to 72 h. A significant ($p < 0.05$) increase was noted, however, for bilastine plus ketoconazole treatment at 4 h, but not different to the changes observed with the antifungal agent alone (Figure 4).

5. Regulatory affairs

Bilastine was registered by FAES Farma in the European Union for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria in adults and children over 12 years of age. Since 2007, Menarini Pharma holds the license for the compound in the majority of European countries and the Commonwealth of Independent States. Other license agreements include Yuhan Corp. for South Korea, Hikma Pharma in the Middle East and North Africa, Pfizer Inc., in Mexico, Nycomed Healthcare in Brasil, Merck Serono for India, Taiho Pharmaceutical in Japan and Invida (a Menarini company) in 17 markets in Asia Pacific.

6. Conclusion

Bilastine is a new H1-antihistamine useful for the symptomatic treatment of urticaria in adults and children older than 12 years at licensed doses, with an efficacy at least comparable to that of the most potent second-generation antihistamines, such as cetirizine and levocetirizine. This effectiveness is patent in all activity measures for urticaria, either symptom intensity or health-related quality of life as measured by skin disease-specific questionnaires. In addition, bilastine also has been shown to be effective in reducing CTTs following cold

challenge in CCU, in a dose-dependent manner and with a noticeable additional benefit with up dosing.

Bilastine's safety profile has shown to be excellent. From the background of clinical assays and studies in healthy volunteers, to the actual accumulated clinical experience, bilastine has a profile of adverse events similar to that of placebo, and does not appear to significantly influence cardiac conduction, alertness or driving ability, even in doses up to 40 mg.

7. Expert opinion

Current antihistamines have in general a good level of efficacy in most clinical situations, and therefore development of new antihistamines is primarily concerned with improving their tolerability or pharmacokinetic-pharmacodynamic profiles. After more than a decade without innovations in the antihistamine market, bilastine appears to be a useful therapeutic tool in acute and chronic urticaria, be it spontaneous or inducible, at least as effective as other second-generation antihistamines. Bilastine's tolerance profile is similar to that of placebo, and also very similar to that of levocetirizine, fexofenadine or desloratadine; and noticeably better than that of cetirizine, overall in the CNS setting.

On the other hand, bilastine's oral bioavailability seems to be somewhat lower than that of other second-generation antihistamines; even so, daily therapeutic doses of 20 mg achieve concentrations capable of inhibiting wheal and flare areas throughout the whole administration interval (24 h). Besides, bilastine's lack of metabolism and elimination profile (67% by feces, 33% by urine) makes a dose adjustment unnecessary in all situations.

Bilastine's initial good prospects appear to be confirmed after a 3-year period of the drug in the actual market. Current

studies concerning its future use in children under the age of 12 years are very advanced (personal communication). In the next few years, bilastine will share oral antihistamines' market with other second-generation molecules such as desloratadine, levocetirizine or fexofenadine in all the countries where it is marketed worldwide. The available experience indicates that it can be a competitive and safe alternative.

Declaration of interest

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