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MONOGRAPH

# BILASTINE

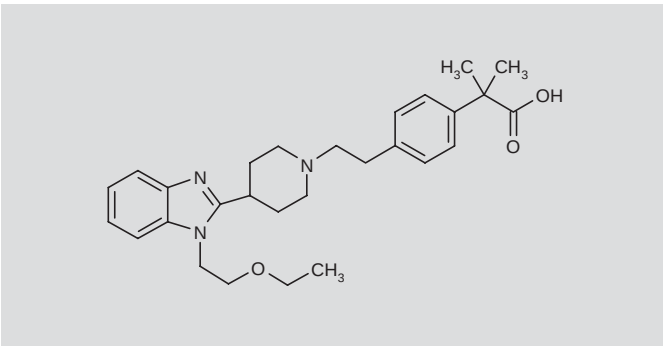
Rec INN

*Histamine $H_1$ Receptor Antagonist*
*Treatment of Allergic Rhinitis*
*Treatment of Urticaria*

F-96221-BM

2-[4-[2-[4-[1-(2-Ethoxyethyl)benzimidazol-2-yl]piperidin-1-yl]ethyl]phenyl]-2-methylpropionic acid

InChI: 1S/C28H37N3O3/c1-4-34-20-19-31-25-8-6-5-7-24(25)29-26(31)22-14-17-30(18-15-22)16-13-21-9-11-23(12-10-21)28(2,3)27(32)33/h5-12,22H,4,13-20H2,1-3H3,(H,32,33)




$C_{28}H_{37}N_3O_3$
Mol wt: 1463.6117
CAS: 202189-78-4
EN: 260868

**SUMMARY**

*Bilastine is a potent histamine $H_1$ receptor antagonist currently preregistered for the oral treatment of allergic rhinitis and chronic idiopathic urticaria, and undergoing clinical investigation for the treatment of seasonal allergic rhinoconjunctivitis. Data from preclinical studies confirmed bilastine's high selectivity for the histamine $H_1$ receptor over other receptors, and demonstrated antihistaminic and antiallergic properties in vivo. In clinical studies oral once-daily treatment with bilastine 20 mg effectively relieved the symptoms of allergic rhinitis, with significant superiority over placebo and comparable efficacy to standard treatments such as cetirizine and desloratadine. Bilastine 20 mg was also more effective than placebo and equivalent to levocetirizine in ameliorating chronic urticaria symptoms, improving quality of life and reducing the general discomfort and sleep disturbances associated with this condition. Studies in healthy volunteers and patients have demonstrated the favorable safety profile of bilastine, which lacks both sedative and cardiotoxic effects associated with some antihistaminic treatments.*

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**SYNTHESIS**

Bilastine can be synthesized following two alternative strategies:

In the first strategy, alkylation of 2-(4-piperidinyl)-1*H*-benzimidazole (I) with the tosylate ester (II) in the presence of $Na_2CO_3$ in DMF at 80 °C provides the *N*-substituted piperidine (III), which is subsequently alkylated with 2-chloroethyl ethyl ether (IV) by means of NaH in DMF, yielding the *N*-ethoxyethyl derivative (V) (1). Finally, oxazolidinone (V) is submitted to acidic hydrolysis (1, 2). Scheme 1.

In the other strategy, saponification of propanoate esters (VIa) or (VIb) with NaOH in EtOH at 50-55 °C is followed by acidification with aqueous AcOH (2). Scheme 1.

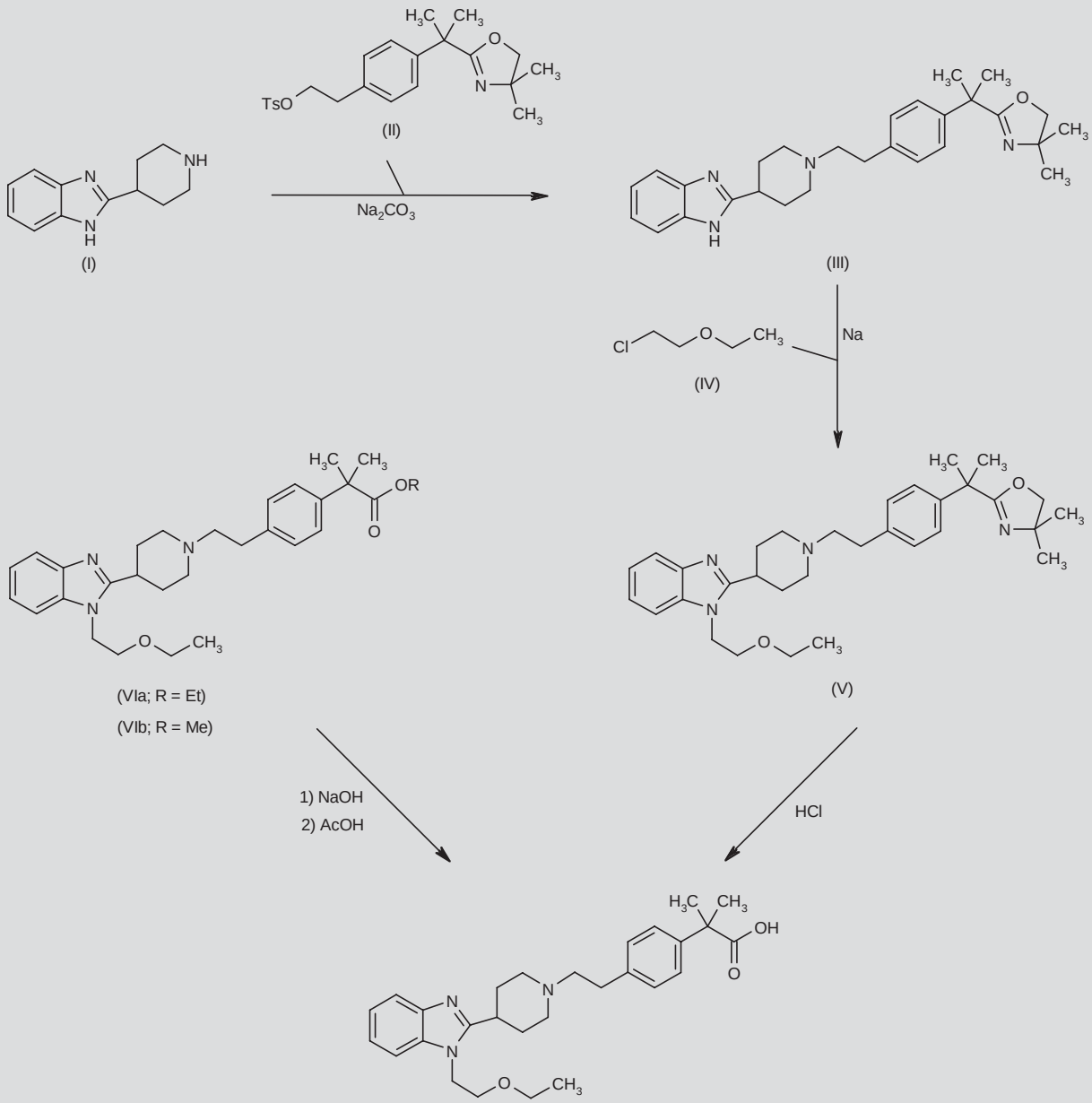
Oxazoline intermediate (V) can also be prepared by condensation of ethyl 2-[4-(2-hydroxyethyl)phenyl]-2-methylpropionate (VII) with 2-amino-2-methyl-1-propanol (VIII) by means of *t*-BuOK in $CH_2Cl_2$, followed by cyclization with $SOCl_2$ in acetonitrile to give the oxazoline (IX), which is then condensed with 1-(2-ethoxyethyl)-2-(4-piperidyl)benzimidazole (X) in the presence of $Na_2CO_3$ in refluxing MeOH (2). Scheme 2.

Synthetic precursors (VIa) and (VIb) are prepared as follows:

Protection of 2-(4-piperidinyl)benzimidazole (I) with $Boc_2O$ in MeOH yields the *N*-Boc derivative (XI), which is then alkylated with 2-ethoxyethyl mesylate (XII) by means of KOH in toluene to afford the 1-(2-ethoxyethyl)benzimidazole (XIII). After deprotection of intermediate (XIII) with HCl in $H_2O$, the resulting 1-(2-ethoxyethyl)-2-(4-piperidinyl)benzimidazole (X) is alkylated with mesylate (XIV) by means of $Na_2CO_3$ in refluxing MeOH, giving the ethyl ester (VIa). Scheme 3.

Condensation of mesylate (XV) with 2-(4-piperidinyl)benzimidazole (I) by means of $Na_2CO_3$ in refluxing MeOH yields adduct (XVI), which is further alkylated with 2-ethoxyethyl mesylate (XII) in the presence of *t*-BuOK in DMF at 50 °C to afford the methyl ester (VIb) (2). Scheme 3.

**Scheme 1.** Synthesis of Bilastine




Synthons (XIV) and (XV) are prepared by the following procedure:

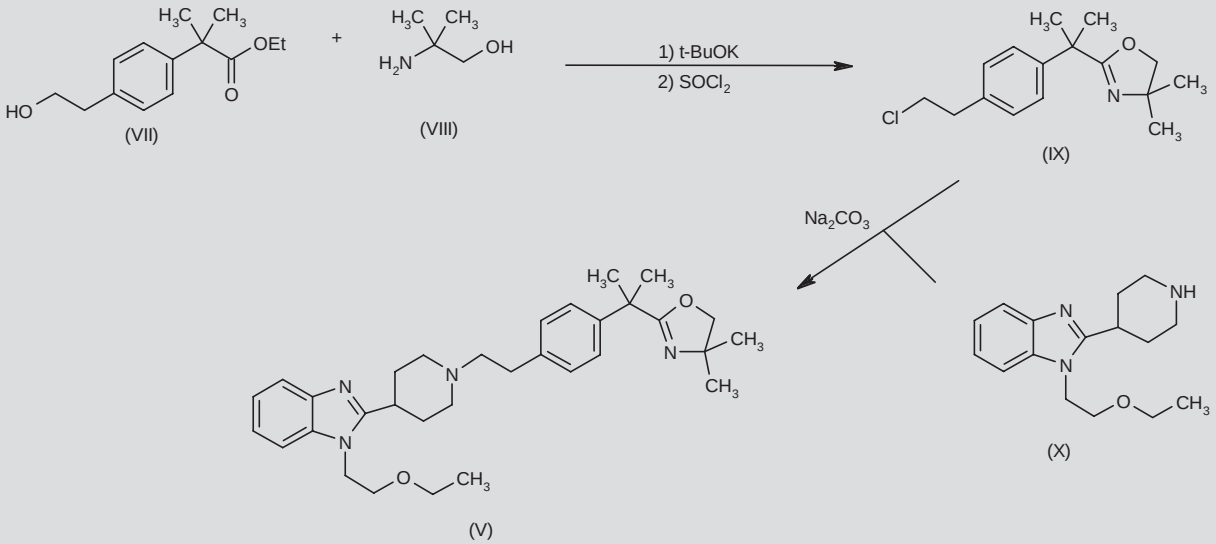
Coupling of 2-(4-bromophenyl)ethanol (XVII) with dimethylketene ethyl trimethylsilyl acetal (XVIIIa) in the presence of $Pd(dba)_2$, $(t\text{-Bu})_3P$ and $ZnF_2$ in DMF at 80 °C gives the 2-arylisobutyrate ester (XIXa). Subsequent hydroxyl group sulfonylation in (XIXa) with MsCl and $Et_3N$ in $CH_2Cl_2$ yields the mesylate ester (XIV). Scheme 4.

Similarly, 2-(4-bromophenyl)ethanol (XVII) (optionally pretreated with HMDS and $NH_4Cl$ in MeCN) is coupled with dimethylketene methyl trimethylsilyl acetal (XVIIIb) in the presence of $Pd(dba)_2$, $(t\text{-Bu})_3P$ and $ZnF_2$ in DMF at 80 °C, giving 2-arylisobutyrate ester (XIXb), which is then sulfonylated with MsCl in the presence of $Et_3N$ in $CH_2Cl_2$, affording synthon (XV) (2). Scheme 4.

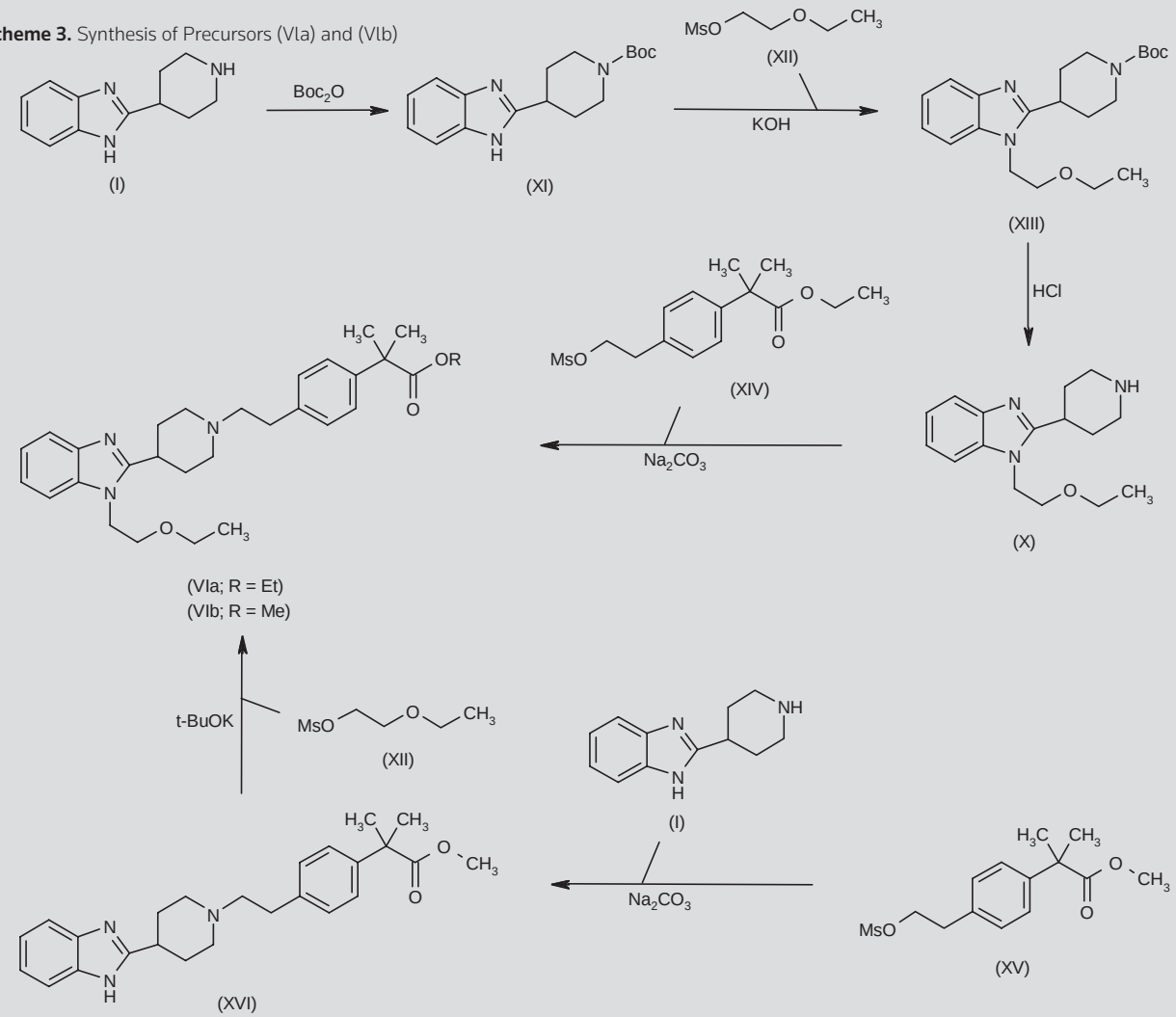
## BACKGROUND

Allergic rhinitis is a common disorder with an estimated prevalence of around 20%, although this could be even higher, as approximate-

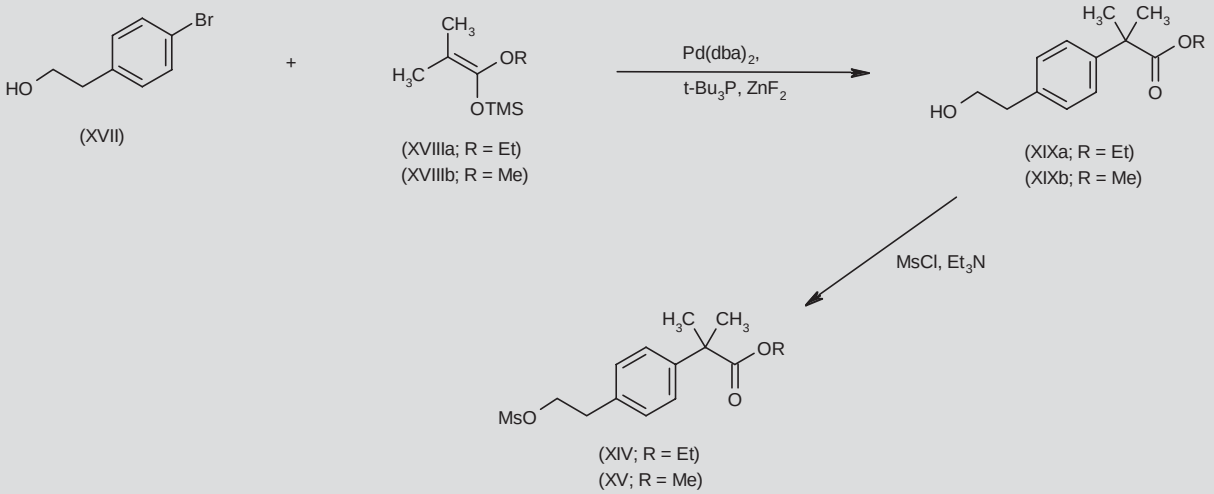
**Scheme 2.** Synthesis of Intermediate (V)




**Scheme 3.** Synthesis of Precursors (VIa) and (VIb)



**Scheme 4.** Synthesis of Synthons (XIV) and (XV)




ly 45% of patients remain undiagnosed (3). In fact, in patients suffering from allergic asthma, the prevalence reaches 100%. Although allergic rhinitis is not a life-threatening condition, symptoms can be quite bothersome and negatively affect the patient's quality of life, causing fatigue, sleep disorders and learning difficulties. Allergic rhinitis is also a major risk factor for the development of asthma (4). Patients with allergic rhinitis may exhibit a combination of nasal (sneezing, nasal congestion, nasal pruritus and rhinorrhea) and non-nasal symptoms (ocular itching and redness, tearing, headache, itching of ears, etc.), due to nose and ear inflammation, although sinuses and throat may also be affected. The inflammatory response in allergic rhinitis is triggered by an IgE-mediated reaction to different allergens that usually takes place in predisposed individuals (5).

Chronic urticaria is characterized by the recurrent appearance of wheals that last for more than 6 weeks, which can be accompanied or not by angioedema. Autoimmune etiology has been shown in 45% of cases of chronic urticaria, while in the remaining 55% the cause is unknown or idiopathic. However, growing evidence supports that chronic idiopathic urticaria may also have an autoimmune origin, with the potential association of thyroid autoimmunity (with or without clinical hypothyroidism). Patients may present with IgG autoantibodies against circulating IgE or, more often, against the α subunit of the IgE high-affinity receptor (FcεR-I), which upon binding to skin mast cells would trigger degranulation and the release of histamine, among other inflammatory mediators (6).

Given the role that histamine plays in the pathogenesis of these disorders via its action on $H_1$ receptors, antihistamines or $H_1$ receptor antagonists have been widely used to treat allergies and relieve pruritus. Second-generation histamine $H_1$ receptor antagonists are preferred to classic antihistaminic drugs due to their greater selectivity for peripheral $H_1$ receptors, hence improving their safety profile due to the lack of central nervous system (CNS) effects (somnolence, sedation) (7).

Bilastine is a second-generation histamine $H_1$ receptor antagonist currently preregistered in Europe by FAES for the oral treatment of allergic rhinitis, as well as for the oral treatment of chronic idiopathic urticaria. Phase II clinical studies are also under way in the U.S. for the symptomatic treatment of seasonal allergic rhinoconjunctivitis. In 2007, the product was licensed to Menarini, and in 2009 FAES licensed the product to Hikma in the Middle East and North Africa. Pfizer holds a license to the product in Mexico.

## PRECLINICAL PHARMACOLOGY

In vitro, bilastine displayed higher affinity for the histamine $H_1$ receptor ($K_i$ = 44.1 nM) in guinea pig cerebellum than other histamine $H_1$ receptor antagonists such as cetirizine ($K_i$ = 143.1 nM) and fexofenadine ($K_i$ = 248.1 nM). Concentration-dependent inhibition of the specific binding of tritiated pyrilamine to human recombinant $H_1$ receptors ($K_i$ = 64 nM) was also demonstrated. Binding studies showed high selectivity for the histamine $H_1$ receptor relative to more than 30 other receptors. In addition, bilastine suppressed $H_1$ stimulation-induced contractions in isolated guinea pig trachea and ileum preparations more potently than cetirizine and fexofenadine. Superior antianaphylactic activity compared to cetirizine and fexofenadine was also observed in ileum fragments from ovalbumin-sensitized animals ($IC_{50}$ = 95.5 nM vs. 759 and 282 nM, respectively; $E_{max}$ = 100%). At concentrations up to 100 μM bilastine did not interfere with $H_2$ agonist-induced atrial beat increase and $H_3$ agonist-induced twitch decrease in isolated guinea pig atria and jejunum preparations, respectively (8).

Further in vivo experiments demonstrated the potent, dose-dependent inhibitory activity of orally administered bilastine in the histamine-induced cutaneous capillary permeability reaction in rats ($ED_{50}$ = 2.45 mg/kg). Long-lasting antihistaminic activity (8 h) was evidenced following a single oral dose of 5 mg/kg. Substantially superior activity compared to cetirizine was shown in blocking hista-

mine-induced bronchospasm in guinea pigs ($ED_{50}$ = 4.57 µg/kg vs. 53.32 µg/kg i.v.). The potential efficacy of bilastine as an antiallergic drug was shown in monoclonal anti-DNP IgE-induced passive cutaneous anaphylaxis in rats ($ED_{50}$ = 5.96 mg/kg p.o.) and in the IgG- or IgE-dependent ear edema model of active anaphylaxis in mice ($ED_{50}$ = 3.82 and 4.15 mg/kg p.o., respectively) (9).

In addition to histamine $H_1$ receptor antagonism, bilastine has been shown to inhibit histamine and interleukin IL-4 release from human mast cells and peripheral blood granulocytes, in contrast to other $H_1$ antagonists such as cetirizine, which enhanced the release of these inflammatory mediators from human mast cells (10).

Bilastine's potential for the treatment of allergic conjunctivitis was tested in guinea pigs, where 30-min pretreatment inhibited histamine-induced vascular permeability ($ED_{50}$ = 0.034%) (11).

## PHARMACOKINETICS AND METABOLISM

Pharmacokinetic (PK) studies in rats have shown rapid absorption of bilastine, with time to peak plasma concentration ($t_{max}$) values of 1-2 h following oral administration of [$^{14}$C]-bilastine (275 mg/kg eq. to 100 mCi/kg), and mainly fecal excretion, with 81% of the dose recovered in feces within the first 24 h. Bilastine also underwent biliary elimination as an oxidized glucuronide and as the unchanged drug, while urinary excretion was less important. Whole-body autoradiography evidenced wide distribution of bilastine in the organs involved in absorption, metabolism and excretion, whereas no accumulation was seen in brain or other peripheral tissues (12).

Biphasic elimination from plasma was observed following single i.v. administration (10 mg/kg) to rats and dogs, which yielded $\alpha$ half-life values of 0.15 and 0.30 h and $\beta$ half-life values of 0.59 and 2.02 h, respectively. Terminal-phase volume of distribution (Vd) and total plasma clearance (Cl) were 2.8 and 1.7 L/kg and 3.42 and 0.58 L/h/kg, respectively, in rats and dogs. Plasma levels of bilastine were detected shortly after oral administration (< 10 min) at doses of 5-40 mg/kg in rats and 10-50 mg/kg in dogs. Bilastine showed linear pharmacokinetics, with dose-dependent increases in mean peak plasma concentrations ($C_{max}$) and AUC. Exposure of bilastine in dogs was 10 times greater than in rats at an equivalent dose and estimated bioavailability values ranged from 25% to 61% in rats and from 42% to 69% in dogs (13).

The absorption, metabolism and excretion profile of bilastine was investigated in a single-center, open-label, nonrandomized trial that recruited six male subjects who were administered a single oral dose of 20 mg of [$^{14}$C]-bilastine. Rapid absorption was evidenced, with maximal concentrations of total radioactivity in plasma and whole blood achieved within 1-3 h. Systemic exposure of bilastine was around 1.5-fold greater in plasma samples than whole blood, while $t_{max}$ and elimination half-life values were similar in both compartments, indicating limited association of the compound with the cellular component of whole blood. Bilastine was not significantly metabolized and its excretion was mostly fecal, with 67% of the administered dose recovered in feces, although urinary excretion was also detected (33.1%) (14) (ClinicalTrials.gov Identifier NCT00572611).

The PK, safety and tolerability of bilastine after once-daily oral administration were investigated in a 14-day, double-blind, placebo-controlled, multiple-ascending-dose clinical trial, enrolling 48 healthy male volunteers who were randomly assigned to bilastine 10, 20, 50 and 100 mg or placebo. Bilastine was rapidly absorbed, with $t_{max}$ values of approximately 1 h and linear PK within the studied dose range, as indicated by dose-proportional increases in $C_{max}$ and $AUC_{0\text{-}t}$. No evidence of drug accumulation was detected. The half-life on day 1 was significantly shorter than on day 14 (4.73 h vs. 9.63 h for the 20-mg dose), which was suggested to represent the functional half-life, while the highest value corresponded to drug elimination from peripheral sites (15).

The PK profile of bilastine was not modified by age and gender according to results from an open-label, parallel study in 32 healthy young (18-35 years of age) and elderly adults (> 65 years of age) who received a single 20-mg bilastine tablet. In general, no significant differences in drug exposure ($C_{max}$ and AUC) were seen between age groups (young male and female and elderly male and female subjects). With regard to gender, only younger female subjects exhibited significantly higher $C_{max}$ values, while AUC remained unaffected. Mean histamine-induced wheal size and flare were inhibited by more than 50% for up to 12 and 24 h, respectively, in all treatment groups (16).

Using available data from single- and multiple-dose bilastine studies comprising a total of 310 healthy volunteers, Jauregizar et al. generated a population pharmacokinetic/pharmacodynamic (PK/PD) model for bilastine. Results from the noncompartmental analysis indicated linear PK within the dose range of 2.5-220 mg/day. Peak plasma concentrations were observed at 1 h after oral administration (and maximal responses at 4 h or longer) and elimination half-life was approximately 14 h. In turn, compartmental analysis showed that the kinetics of bilastine after oral administration followed a two-compartment model with first-order absorption and elimination (first-order absorption rate constant $K_a$ = 1.5 $h^{-1}$). The population PK estimates for Cl, volume of distribution of the central ($V_c$) and peripheral ($V_p$) compartments and intercompartmental clearance (Q) were 18.1 L/h, 59.2 L, 30.2 L and 1.59 L/h, respectively, with interindividual variability ranging from 29% to 73.1%. Using these PK parameters, a PD type 1 indirect response model (also known as a model for inhibition of response production) was selected to describe bilastine PD, as it best fitted wheal and flare data. For the wheal effect, estimated parameters in this model were $K_{in}$ (zero-order rate constant for wheal/flare spontaneous appearance) of 0.44 ng/mL/h, $K_{out}$ (first-order rate constant for wheal/flare disappearance) of 1.09 $h^{-1}$ and $IC_{50}$ (plasma concentration that produced 50% inhibition) of 5.15 ng/mL, while for the flare effect $K_{in}$, $K_{out}$ and $IC_{50}$ values were 11.1 ng/mL/h, 1.03 $h^{-1}$ and 1.25 ng/mL, respectively. Interindividual variability in these parameters ranged from 14.04% to 55.95% for wheal and from 24.02% to 65.65% for flare effect. Considering the estimated $IC_{50}$ values for wheal and flare, computer simulations performed between 72 and 96 h (i.e., day 4 on a multiple-dose regimen), predicted that bilastine plasma concentrations at steady state after a daily dose of 20 mg remained over the flare $IC_{50}$ throughout the entire interdose period and decreased to less than the mean estimated wheal $IC_{50}$ value between 20 and 24 h. These results indicate that the antihistaminic activity of bilastine lasts for nearly the entire period between two once-daily dosing intervals and suggest an optimal dosing regimen of 20 mg every 24 h. In contrast, after doses of 5 and 10 mg plasma concentrations

were below the wheal $IC_{50}$ value for 10-16 h before administration of the next dose (17).

The recommended pediatric dose of bilastine was established through a predictive model, which used simulations of the evolution of plasma bilastine concentrations over time in 1,500 virtual children (2-12 years) at doses of 5, 10 and 20 mg. According to this model, after four consecutive oral doses or 10 mg plasma concentrations were always above the $IC_{50}$ value for wheal inhibition, while for flare the activity lasted for almost the entire dosing interval. Thus, 10 mg/day may be a safe and effective dose for children over 2 years of age. For younger children, a dose of 5 mg was considered adequate, as the antihistaminic activity was sustained throughout the entire treatment period (18).

## SAFETY

A lack of cardiotoxicity has been confirmed in a study addressing whether bilastine had an effect on ventricular repolarization, particularly on the prolongation of the Q-T/Q-$T_c$ interval. Thirty healthy subjects were enrolled in this randomized, triple-dummy, double-blind, 5-way crossover, placebo- and active comparator-controlled (moxifloxacin 400 mg) trial. Once daily administration at doses up to 100 mg (five times the therapeutic dose) was not associated with any significant increase in subject-specific heart rate-corrected Q-T (Q-$T_{cNi}$) or other Q-$T_c$ measures, suggesting that bilastine does not lead to any significant effect on vascular repolarization (19).

A good balance between desired peripheral and unwanted CNS antihistaminic effects was demonstrated in a randomized, crossover, placebo-controlled and positive standard-controlled study conducted in 20 healthy young subjects. The study evaluated peripheral and central effects of a single dose and repeated drug administration for 7 consecutive days of the following treatments: bilastine 20, 40 and 80 mg, the first-generation antihistamine hydroxyzine 25 mg as the positive control and placebo. Compared to placebo, all treatments showed significant peripheral $H_1$-blocking activity by attenuating histamine-induced wheal to a similar extent 1-8 h after single doses ($P < 0.001$). Unlike hydroxyzine, bilastine did not show a delay in the onset of peripheral action after the first dose. Following repeated dosing, a significant reduction of wheal area was shown with bilastine 40 and 80 mg and hydroxyzine in comparison to placebo and bilastine 20 mg ($P < 0.001$). Treatment effects on the CNS were assessed by means of psychomotor performance tests (evaluating motor activity, perception, attention and associative integration) and questionnaires for subjective reports on mood variables. Hydroxyzine was associated with the highest number of significant alterations in most psychomotor domains after single doses, while significant impairments decreased after repeated-dose administration, which may indicate the development of tolerance to sedation. While a single 80-mg bilastine dose resulted in significant impairment in associative skills, perception and attention domains, no difference compared with placebo was seen after bilastine 40 and 20 mg. On subjective measures, hydroxyzine was associated with the greatest drowsiness and least activity, in agreement with the sedative profile of classic antihistaminic drugs. Bilastine 20 mg was the only treatment not different from placebo, whereas drowsiness and activity decrease were reported for higher bilastine doses compared with placebo. These results corroborate bilastine's primary effect on peripheral $H_1$ receptors (only minimal CNS effects seen with the highest dose) and suggest that the 20-mg dose would be safe and effective for patients with peripheral $H_1$ symptoms (20).

## CLINICAL STUDIES

The relationship of bilastine dose to inhibition of skin reactivity (wheal and flare) in response to a histamine injection was investigated in a randomized, double-blind, single-dose, 4-period crossover study conducted in 21 healthy male volunteers who received bilastine (2.5, 5, 10, 20 and 50 mg), cetirizine 10 mg or placebo. All doses of bilastine were equivalent or superior to cetirizine in attenuating histamine-induced wheal and flare (> 50% inhibition up to 12 h). At 24 h, all 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%. For bilastine 20 mg and cetirizine 10 mg, PK analysis showed $C_{max}$ values of 285.7 and 319.5 ng/mL and $AUC_{(0\text{-}inf)}$ values of 1357 and 2986 ng/mL.h, respectively. Mean residence time (MRT) values for bilastine doses of 20 mg or lower were found to be < 50% compared to the MRT value for cetirizine 10 mg, indicating a faster elimination rate. Bilastine was safe and well tolerated, with mild adverse events and no clinically significant changes in electrocardiogram, vital signs or physical examination findings (21).

The safety and efficacy of bilastine for the relief of allergic rhinitis symptoms have been confirmed in two pivotal clinical trials evaluating over 1,400 patients (22, 23). Bilastine was found to be noninferior to the standard seasonal allergic rhinitis (SAR) treatment desloratadine in a multicenter, randomized, double-blind study in which 721 patients referring SAR symptoms were randomly assigned to a 2-week treatment with bilastine 20 mg, desloratadine 5 mg or matched placebo once daily. The severity of nasal (obstruction, rhinorrhea, itching, sneezing) and non-nasal (ocular itching, tearing, ocular redness, itching of ears and/or palate) symptoms was assessed on a predetermined scale to provide a total symptom score (TSS) combining both nasal (NSS) and non-nasal symptoms (NNSS). Once-daily treatment with bilastine 20 mg improved the symptoms of allergic rhinitis from baseline levels over a period of 2 weeks. It significantly reduced the AUC of TSS, the primary endpoint, compared to placebo (98.4 vs. 118.4; $P < 0.001$), but not compared to desloratadine (100.5). Bilastine was also similar to desloratadine in improving secondary outcomes, such as NSS, NNSS, rhinitis-associated discomfort scores and rhinoconjunctivitis quality of life questionnaire scores, both drugs being substantially superior to placebo. In terms of safety, bilastine, desloratadine and placebo showed a similar safety profile, with a comparable incidence of drug-related adverse events (20.6% vs. 19.8% vs. 18.8%) and no serious adverse events reported (22).

Similar results were obtained in a multicenter, double-blind trial in which 683 SAR patients were randomized to receive oral once-daily treatment with bilastine 20 mg, cetirizine 10 mg or placebo for 2 weeks (23). In this study, patients recorded reflective (over the past 12 h) and instantaneous NSS and NNSS, according to a predetermined severity scale to provide both reflective and instantaneous TSS. The primary efficacy parameter in this study was the AUC of the reflective TSS from day 0 to day 14 (TSS-$AUC_{0\text{-}14}$), based on the patient's evaluation of symptom severity over the past 12 h. Bilastine

was as effective as cetirizine and significantly superior to placebo in improving TSS-$AUC_{0-14}$ from baseline (76.5, 72.3 and 100.6, respectively; $P < 0.001$ for bilastine vs. placebo; $P = 0.63$ for bilastine vs. cetirizine). Bilastine also markedly improved instantaneous TSS-$AUC_{0-14}$, composite nasal and non-nasal scores and rhinitis-associated discomfort compared to placebo, with similar efficacy to cetirizine. With regard to safety, no serious adverse events were reported and bilastine treatment was associated with fewer adverse events than cetirizine (24.7% vs. 36%; $P = 0.03$) and placebo (29.6%). Drug-related adverse events were also significantly lower in the bilastine than in the cetirizine (14.5% vs. 24.6%; $P = 0.03$) and placebo group (19.5%). Significantly fewer reports of somnolence and fatigue were recorded after bilastine compared to cetirizine treatment (1.8% vs. 7.5% [$P < 0.001$] and 0.4% vs. 4.8% [$P = 0.02$]). These findings suggest a more favorable safety profile for bilastine compared with cetirizine (ClinicalTrials.gov Identifier NCT00504933).

Bilastine has also demonstrated therapeutic potential in the management of chronic idiopathic urticaria in a multicenter, double-blind clinical study in which 525 patients were randomized to receive bilastine 20 mg, levocetirizine 5 mg or placebo. The primary efficacy measure of the study was the change from baseline in the TSS over a 28-day treatment period based on patient's reflective assessment of pruritus, number of wheals and wheal maximum size according to predefined scales. Of 525 randomized patients, 516 were included in the intent-to-treat population, 457 of whom completed the study. The safety population comprised 522 patients. Both bilastine and levocetirizine groups reported a significantly greater mean change from baseline in patient's reflective TSS over 28 days than placebo (−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. This significant decrease in TSS was noted from the second day of treatment and was maximal from day 6-7 onwards. Bilastine and levocetirizine treatments were also associated with a greater mean change from baseline in patient's instantaneous TSS and in individual symptom scores (pruritus, wheal number and maximum size) compared with placebo. Quality of life, assessed using the Dermatology Life Quality Index, chronic urticaria-associated discomfort and sleep disruption were also improved to a significantly greater extent in both bilastine and levocetirizine groups, with no significant differences between them, than in placebo-treated patients. The lack of serious adverse events and the similarities in the incidence of overall and drug-related adverse events, which were comparable among the three groups, indicated that the recommended therapeutic dose of 20 mg bilastine was also well tolerated in the treatment of chronic urticaria symptoms (24).

## DRUG INTERACTIONS

An open-label, randomized, multiple-dose study in 24 healthy subjects evaluated the potential drug–drug interactions between bilastine and ketoconazole, a known cytochrome CYP3A4 and P-glycoprotein inhibitor. Coadministration of two 200-mg tablets of ketoconazole once daily for 6 consecutive days increased the systemic exposure of bilastine at steady state by more than twofold ($C_{max}$: 200 ng/mL vs. 518 ng/mL; $AUC_{(0-24)}$: 1023 ng/mL.h vs. 2061 ng/mL.h; bilastine vs. bilastine plus ketoconazole), while clearance remained unchanged. These results suggest that ketoconazole may increase bilastine absorption at the gut lumen, without affecting hepatic clearance. Concomitant administration of both drugs resulted in no clinically significant cardiotoxic effects (25).

The results of an open-label, randomized, two-way crossover study in 12 healthy adults showed that coadministration of grapefruit with bilastine markedly reduced systemic bilastine exposure, resulting in plasma $C_{max}$, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ values about 33%, 24% and 24% lower, respectively, compared to bilastine alone (26).

## SOURCE

FAES FARMA, SA (ES).

## DISCLOSURES

The authors state no conflicts of interest.

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