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REVIEW ARTICLE

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Bilastine: a lifetime companion for the treatment of allergies

Martin K. Church[a], Marysia Tiongco-Recto[b], Erminia Ridolo[c] and Zoltán Novák[d]

[a]Dermatological Allergology, Allergie-Centrum-Charité, Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany; [b]Department of Paediatrics, Section of Allergy and Immunology, University of the Philippines-Philippine General Hospital, Manila, The Philippines; [c]Department of Medicine and Surgery, University of Parma, Parma, Italy; [d]Paediatric Department, University of Szeged, Szeged, Hungary

ABSTRACT

Objective: Bilastine is a potent and highly selective H_1-antihistamine approved for the treatment of allergic rhinoconjunctivitis and urticaria. This article summarizes available data on the use of bilastine in the treatment of allergic disorders in different age groups, including younger and older adults, and school-age children and adolescents.

Methods: A PubMed literature search ("bilastine") was conducted on 25 February 2019. Additional literature known to the authors and identified from the reference lists of cited publications was included.

Results: Bilastine is administered orally at a dose of 20 mg once daily in adults and adolescents aged ≥12 years and 10 mg once daily in children aged 6 to <12 years. Clinical trials have demonstrated its efficacy at improving nasal and ocular symptoms in patients with allergic rhinitis, and wheals and itching in patients with urticaria. It has a rapid onset of action and long duration of action. Bilastine does not undergo significant metabolism and does not interact with the CYP450 system, which limits its potential for drug-drug interactions. No dosage adjustments are required in patients with renal or hepatic impairment, or in the elderly. Bilastine is generally well tolerated, even when administered at above-standard doses. It does not exhibit anticholinergic effects or cardiotoxic effects, shows no central nervous system penetration and has minimal sedative properties. It has been shown to improve health-related quality of life.

Conclusions: Bilastine is a suitable option for the treatment of patients with allergic rhinoconjunctivitis or urticaria across age groups from school-age children to elderly patients.

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Introduction

Allergic diseases such as allergic rhinoconjunctivitis and urticaria are common worldwide, and the prevalence is increasing, particularly amongst children[1,2]. Allergies impose a substantial socioeconomic burden on patients, their families, and society[1]. These disorders have a negative impact on patients' physical, psychological, social, educational and work functioning, with financial implications for healthcare systems and also for society through lost work productivity[1,3,4].

Given the role of histamine in allergic responses, many allergic disorders, including allergic rhinoconjunctivitis and urticaria, are treated with H_1-antihistamines[5–7]. First-generation H_1-antihistamines have pronounced anticholinergic effects, sedative effects and interactions with alcohol and numerous drugs[5,7]. In contrast, modern second-generation H_1-antihistamines cause minimal or no sedation, are free of anticholinergic effects, and are recommended as first-line therapeutic options for patients with allergic rhinitis or urticaria[5–7].

Bilastine is a selective, second-generation H_1-antihistamine. It was first approved in the European Union in 2010 for the symptomatic treatment of allergic rhinoconjunctivitis (seasonal and perennial) and urticaria in patients aged 12 years or older, and is now available in approximately 100 countries worldwide[8]. More recently, it has been approved in Europe for use in children aged 6 to <12 years[8]. This narrative review summarizes available data on the use of bilastine in the treatment of allergic disorders in different age groups, including younger and older adults, and school-age children and adolescents.

Search methodology

A search of PubMed up to 25 February 2019 was undertaken using the search term "bilastine" to identify relevant publications about the drug. Preclinical and clinical publications were assessed for inclusion, with priority given to clinical papers, particularly randomized controlled trials when available.

CONTACT Martin K. Church mkc@southampton.ac.uk Dermatological Allergology, Allergie-Centrum-Charité, Berlin, Germany; Department of Dermatology and Allergy, Charité-Universitätsmedizin, Charitéplatz 1, 10117 Berlin, Germany

Bilastine: pharmacological profile

Bilastine is a second-generation H_1-antihistamine. Although the efficacy of second-generation H_1-antihistamines is generally similar, pharmacokinetic properties and the potential for drug-drug and food-drug interactions differ between individual drugs[9]. Bilastine has high specificity for H_1-receptors and negligible affinity for other receptors, and demonstrates antihistamine and antiallergic properties[10,11]. Bilastine has a rapid onset of action and a long duration of action[12–15]. It has been shown to have a long residence time at the H_1-receptor, resulting in prolonged receptor antagonism, with 60–70% antagonism evident 24 hours after dosing[8].

Bilastine is administered orally once daily. It is rapidly absorbed after oral administration, achieving maximum plasma concentrations after 1–1.5 hours[12,15,16]. Concurrent food intake reduces the bioavailability of bilastine. In a recent study, food intake reduced histamine-induced wheal significantly less at 0.5 and 1 hour after bilastine administration as compared to drug intake under fasting, but not thereafter. Once steady-state was reached at 4 days, food had no significant effect on the wheal response at any time[17]. Mean oral bioavailability is about 60% and it is 84–90% bound to plasma proteins[12,16,18]. It does not undergo significant hepatic metabolism and approximately 95% is excreted unchanged in either the faeces (67%) or urine (33%)[19]. Bilastine has a mean elimination half-life of approximately 12–14.5 hours[8,12,15,17]. No dosage adjustments are required in patients with renal or hepatic impairment or in elderly people[18,20]. Bilastine does not interact significantly with the cytochrome P450 (CYP) enzyme system[21]. This, and the lack of hepatic metabolism, limits the potential for drug–drug interactions. Bilastine is a substrate for P-glycoprotein[22], which restricts its passage across the blood–brain barrier, limiting the likelihood of central nervous system (CNS) effects such as sedation[23].

Adults with allergic rhinitis

Allergic rhinitis affects 10–40% of individuals worldwide[24], and it has a substantial negative effect on patients' quality of life (QoL), sleep and daily activities[1,24]. Patients with allergic rhinitis require a fast-acting, effective, and non-sedating treatment, and a modern second-generation oral H_1-antihistamine such as bilastine meets these criteria. Patients often do not take their antihistamine medication in accordance with allergic rhinitis guidelines; instead, they tend to treat themselves only when they have symptoms and to stop when they feel their symptoms are controlled[25,26]. Moreover, adherence tends to be worse in people taking a higher number of medications. Compliance may be better if patients only have to take one tablet daily. The practical message for physicians is to "keep it simple". Antihistamines that can be administered once daily and have a rapid onset of action, such as bilastine[12,13,15,18], are a practical option for patients with allergic rhinitis.

Patients with allergic rhinitis experience nasal symptoms including congestion, itching, rhinorrhoea, and sneezing. Those who also have allergic conjunctivitis experience redness, tears and itching of the eyes[27]. The goal of treatment in allergic rhinoconjunctivitis is symptom relief. The efficacy of bilastine 20 mg once daily has been demonstrated in several clinical trials in adults and adolescents with seasonal allergic rhinitis (SAR) or perennial allergic rhinitis (PAR). Studies conducted in Europe generally enrolled patients aged 12–70 years, whereas studies in Japan usually included adults aged 18–74 years.

Two randomized, controlled, crossover studies using environmental exposure chambers evaluated the effect of bilastine during 2–3 days of allergen exposure in subjects with allergic rhinitis[28,29]. Bilastine had a rapid onset and long duration of action. In European subjects exposed to grass pollen, the onset of action for bilastine 20 mg or cetirizine 10 mg was similar and both had a longer duration of action than fexofenadine 120 mg[28]; in Japanese subjects exposed to Japanese cedar pollen, bilastine 20 mg had a faster onset of action than fexofenadine 60 mg[29]. All active drugs were more effective than placebo.

Four randomized controlled clinical trials evaluated the efficacy of 2 or 4 weeks of treatment with once-daily bilastine 20 mg in adults/adolescents with SAR or PAR (Table 1). The primary efficacy endpoint was the area under the curve for the total symptom score (TSS; i.e. nasal and non-nasal symptoms) over the treatment period or the mean change from baseline in total nasal symptom score (TNSS). Overall, these studies indicated that bilastine 20 mg once daily was more effective than placebo at reducing symptoms in patients with SAR or PAR, and as effective as desloratadine 5 mg once daily, cetirizine 10 mg once daily or fexofenadine 60 mg twice daily[30–33]. Pooled analyses of seven clinical trials confirmed that bilastine was effective at controlling the nasal obstruction and ocular symptoms of allergic rhinoconjunctivitis[34,35].

Allergic rhinitis has a marked negative impact on QoL, causing limitations in many areas of daily activity, including concentration, productivity, sleep and sexual function[3,36]. Randomized controlled studies showed that bilastine 20 mg once daily was significantly more effective than placebo, and as effective as loratadine 10 mg or desloratadine 5 mg once daily, at improving health-related QoL in patients with allergic rhinitis, as assessed using the Rhinoconjunctivitis Quality of Life Questionnaire[30,37,38].

Long-term efficacy is important for antihistamine medications, particularly for patients with PAR. A single-arm study, in which 64 patients with PAR were treated for up to 52 weeks, confirmed that the efficacy of bilastine 20 mg once daily, including reductions in TSS, TNSS and total ocular symptoms score (TOSS), and an improvement in QoL, was maintained for up to 1 year[39].

The overall incidence of adverse events with bilastine in trials in allergic rhinitis was generally similar to that seen with placebo[30–33]. The most common treatment-emergent adverse events (TEAEs) included headache, somnolence and fatigue, with an incidence that was similar to that seen with placebo. Bilastine 20 mg once daily was found to be associated with significantly less somnolence (1.8 vs. 7.5%, $p < .001$) and fatigue (0.4 vs. 4.8%, $p = .02$) than cetirizine

Table 1. Bilastine in adults/adolescents with seasonal or perennial allergic rhinitis: double-blind randomized controlled trials of ≥2 weeks in duration.

Study	Indication/N	Treatment[a]/Duration	Results
Bachert et al. 2008[30]	SAR $N = 721$	Bilastine 20 mg Desloratadine 5 mg Placebo 2 weeks	Mean TSS-AUC significantly lower with bilastine vs. placebo (98.4 vs. 118.4, $p < .001$) but not vs. desloratadine (100.5). Significantly greater % change from baseline in NSS-AUC and NNSS-AUC with bilastine vs. placebo ($p < .001$ and $p = .003$) but not vs. desloratadine.
Kuna et al. 2009[31]	SAR $N = 683$	Bilastine 20 mg Cetirizine 10 mg Placebo 2 weeks	Mean TSS-AUC significantly lower with bilastine (76.5) and cetirizine (72.3) groups vs placebo (100.6, $p < .001$); no significant difference between the active groups. Bilastine and cetirizine similar and both significantly better vs. placebo for change from baseline in NSS-AUC and NNSS-AUC ($p < .001$).
Sastre et al. 2012[32]	PAR $N = 650$	Bilastine 20 mg Cetirizine 10 mg Placebo 4 weeks	Overall population: no significant difference in mean TSS-AUC between active and placebo groups. Region-specific difference found in *post hoc* analysis. Mean TSS-AUC similar with bilastine and cetirizine and both significantly better vs. placebo ($p < .05$) in Europe/Argentina. No significant difference vs. placebo in South Africa.
Okubo et al. 2017[33]	PAR $N = 765$	Bilastine 20 mg Fexofenadine 60 mg[b] Placebo 2 weeks	Mean change from baseline to week 2 in TNSS significantly greater with bilastine vs placebo (–0.98 vs. –0.63, $p = .023$) but not vs. fexofenadine (–0.96). Mean change in TNSS greater with bilastine vs. fexofenadine on Day 1 ($p = .032$).

[a]All treatments administered once daily unless indicated otherwise.
[b]Fexofenadine 60 mg twice daily.
Abbreviations. AUC, Area under the curve over the treatment period; N, Number of patients; NSS, Nasal symptom score (obstruction, rhinorrhoea, itching, sneezing); NNSS, Non-nasal symptom score (ocular itching, tearing, redness; itching of ears and/or palate); PAR, Perennial allergic rhinitis; SAR, Seasonal allergic rhinitis; TSS, Total symptom score.

10 mg once daily[31]. A lack of sedation and adverse cognitive effects is an important feature for an antihistamine, particularly since allergic rhinitis itself can have a sedative effect and impair psychomotor functions such as driving ability[40,41]. Antihistamine treatment has been shown to improve vigilance and partially counteract the negative effect of allergic rhinitis on driving ability[40,41]. Bilastine 20 mg once daily was shown to be safe and well tolerated over a 1-year treatment period in an open-label extension phase of a multicentre, randomized, placebo-controlled, double-blind, parallel-group study in 513 mainly Caucasian patients[32] and 55 Japanese patients diagnosed with PAR who received continuous bilastine 20 mg once daily for 52 weeks[39].

Adults with urticaria

Urticaria has a lifetime prevalence of more than 20%[1]. Chronic urticaria, with an estimated prevalence of 0.6–1.5%, has a substantial negative effect on patients' QoL and job performance, with work productivity impaired by 10–30%[1,7]. Urticaria is a mast-cell driven disease. The release of histamine from mast cells produces the characteristic symptoms and signs of urticaria – wheals, flare and itch. Antihistamines are inverse agonists of the histamine receptor and can counteract these histamine-driven features. The goal of treatment for urticaria is to achieve complete relief of symptoms[7]. Second-generation H_1-antihistamines are recommended as first-line therapy for urticaria. If control is inadequate after 2–4 weeks, the dose can be increased (by up to four-fold), with other treatments added only if antihistamine up-dosing still provides inadequate control[7].

The ideal antihistamine should be effective at relieving symptoms, have a rapid onset of action and long duration of action, preferably be administered once daily, and not cause unwanted effects such as drowsiness. Bilastine fits this profile for the treatment of patients with urticaria.

Studies in healthy adult volunteers showed that bilastine suppressed the wheal and flare response compared with placebo and that it had a rapid onset of action, with a high level of inhibition evident after 0.5–2 hours[14,15,42]. Bilastine had a faster onset of action than cetirizine, desloratadine and rupatadine[13,14]. At 1.5 hours, both wheals and flares were inhibited by >70% in 11 of 12 recipients of bilastine compared with 3 of 11 recipients of cetirizine ($p = .003$); differences were not significant at later timepoints[13]. In the study by Antonijoan et al., the onset of wheal inhibition was 1 hour for bilastine 20 mg and 4 hours for desloratadine 5 mg or rupatadine 10 mg whereas, for flare area inhibition, bilastine 20 mg had an onset of action at 30 minutes, while desloratadine and rupatadine needed 4 hours to show a significant difference compared with placebo. Bilastine also reduced itching significantly whereas this was not seen with desloratadine or rupatadine[14].

Bilastine has been evaluated in several randomized controlled clinical trials in adults with urticaria (Table 2). Studies conducted in Europe generally enrolled patients aged 12–70 years, whereas studies in Japan enrolled adults aged 18–74 years. Bilastine 20 mg once daily was significantly more effective than placebo at reducing the symptoms of chronic spontaneous urticaria (assessed using TSS)[43,44], with similar efficacy to levocetirizine 5 mg once daily[43]. Bilastine 20 mg once daily was also significantly more effective than placebo at controlling symptoms in patients with cold contact urticaria[45]. Bilastine had a rapid onset of action, with significant improvements in TSS seen after 1 day of treatment in patients with chronic spontaneous urticaria[43,44]. Bilastine 20 mg also provided significant improvements in individual symptoms, including wheal, flare and itching[43–45].

Chronic urticaria has a considerable adverse effect on patients' QoL[4,46]. Bilastine 20 mg once daily has been shown to improve QoL in patients with chronic spontaneous urticaria[38,43,44]. In the largest randomized trial, mean Dermatology Life Quality Index (DLQI) Global score

Table 2. Bilastine in adults with chronic spontaneous urticaria or cold contact urticaria: double-blind randomized controlled trials of ≥1 week in duration.

Study	Indication/N	Treatment[a]/Duration	Results
Zuberbier et al. 2010[43]	CSU[b] $N = 525$	Bilastine 20 mg Levocetirizine 5 mg Placebo 4 weeks	Mean reduction in TSS from baseline to week 4 significantly greater with bilastine 20 mg vs. placebo (–4.23 vs. –2.99, $p < .001$). No significant difference between bilastine and levocetirizine (–4.63). Difference vs. placebo evident from Day 2 onwards in both active treatment groups.
Hide et al. 2017[44]	CSU $N = 304$	Bilastine 10 mg Bilastine 20 mg Placebo 2 weeks	Mean reduction in TSS from baseline to 2 weeks significantly greater with bilastine 10 mg and 20 mg vs. placebo (–3.01 and –3.23 vs. –1.49, $p < .001$). TSS improved from day 1 in both bilastine groups.
Krause et al. 2013[45]	CCU $N = 20$[c]	Bilastine 20 mg Bilastine 40 mg Bilastine 80 mg Placebo 1 week	After 1 week, median CTT was significantly lower with bilastine 20 mg vs. placebo (6 °C vs. 18 °C, $p < .0001$). Median CTT was below 4 °C (the lowest provocation temperature tested) with bilastine 40 mg and 80 mg ($p < .0001$ vs. placebo). Median CTT with 80 mg was significantly lower vs. both 20 and 40 mg ($p = .003$ and $p = .04$). Whealing to a challenge of 4 °C was completely inhibited by bilastine 20 mg in 35% of patients, by bilastine 40 mg in 55% and by bilastine 80 mg in 60%.

[a]Administered once daily.
[b]Termed chronic idiopathic urticaria in this study.
[c]Study used a crossover design with 2-week washout periods between treatment periods.
Abbreviations. CCU, Cold contact urticaria; CSU, Chronic spontaneous urticaria; CTT, Critical temperature threshold (highest temperature producing a positive wheal response); N, Number of patients; TSS, Total symptom score (comprising wheals, flare, itch).

decreased significantly versus placebo after 4 weeks (–9.45 vs. –5.93, $p < .001$)[43].

Consistent with the results of studies in allergic rhinitis, bilastine 20 mg was well tolerated in adult patients with urticaria with an overall incidence of adverse events similar to that seen with placebo[43,44].

A 1-year noncomparative study involving 198 adults with chronic spontaneous urticaria ($n = 56$) or pruritus associated with other skin diseases (such as eczema/dermatitis, prurigo or cutaneous pruritus) showed that the efficacy of bilastine 20 mg once daily was maintained, and the drug remained well tolerated over the long term[47]. TSS, rash and itch scores, and DLQI score improved significantly ($p < .001$) compared with baseline from week 2 and remained the same thereafter. Bilastine-related adverse events (all mild to moderate in severity) occurred in 2.5% of patients during the 1-year study period; somnolence was reported for 1% of patients.

The EAACI/GA^{2}LEN/EDF/WAO guidelines recommend second-generation H_1-antihistamines at licensed doses as first-line therapy for patients with urticaria and suggest increasing the dose by two- to four-fold in patients who are unresponsive to the licensed dose[7]. The efficacy and safety of a bilastine updosing strategy has been demonstrated in two studies. In a randomized, crossover trial in patients with cold contact urticaria, the standard dose of 20 mg was effective at reducing the critical temperature threshold at which symptoms occurred, and efficacy was increased further when the dose was increased to 40 mg and 80 mg, such that 60% of patients were symptom-free when treated with the highest dose (Table 2)[45].

A small study in a real-world setting evaluated bilastine updosing in 29 patients with moderate-to-severe chronic spontaneous urticaria that had not responded adequately to other H_1-antihistamines at licensed doses[48]. All patients initially received bilastine 20 mg once daily for 2 weeks, after which any non-responders (defined as 7-day Urticaria Activity Score [UAS7] > 3) were updosed to bilastine 40 mg once daily for another 2 weeks, with any continuing non-responders subsequently updosed to bilastine 80 mg once daily for 2 weeks. After 2 weeks on bilastine 20 mg ($n = 29$), mean UAS7 decreased by 37% compared with baseline ($p < .001$). The pruritus and wheal components decreased by 44 and 29%, respectively. Updosing to bilastine 40 mg ($n = 23$) resulted in a further significant reduction (23%) in mean UAS7 ($p = .007$), with reductions in the pruritus and wheal components of 24 and 17%, respectively. Further updosing to bilastine 80 mg ($n = 21$) produced a modest reduction in UAS7 (7%) which was not statistically significant, with reductions in the pruritus and wheal components of 0 and 12%. The small difference seen between bilastine 40 mg and 80 mg is probably explained by the fact that bilastine is particularly effective against pruritus, with most of the inhibition of this symptom occurring at a dose of 20 mg (Figure 1)[45,48].

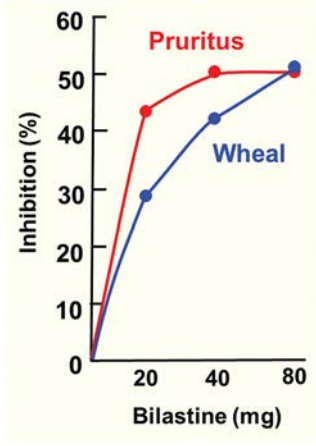

Figure 1. Differential effect of bilastine against the pruritus and wheal components of the 7-day urticaria activity score in patients with chronic spontaneous urticaria in a real-world study evaluating a bilastine updosing strategy in patients with an inadequate response to other H_1-antihistamines. Data from Weller et al. 2018[48].

In both updosing studies, bilastine was well tolerated at doses up to 80 mg once daily, with no evidence of increased sedation at higher doses[45,48].

Safety in adults

Bilastine is generally well tolerated[49]. In clinical trials involving adult/adolescent patients with allergic rhinoconjunctivitis or chronic idiopathic urticaria the incidence of adverse events was similar for bilastine (12.7%) and placebo (12.8%)[18]. The most common adverse drug reactions reported for bilastine 20 mg were headache, somnolence, dizziness and fatigue, which occurred at a similar frequency in placebo recipients[18]. Bilastine remained well tolerated in the long-term[32,33,47].

Bilastine is highly specific for the H_1-receptor, limiting the risk of adverse events caused by interactions with other receptors, such as anticholinergic effects[5,10]. Bilastine has minimal H_1-receptor occupancy (H_1RO) in the CNS, similar to placebo (in comparison, hydroxyzine 25 mg [positive control] was associated with significant brain H_1RO, resulting in sedation)[23]. Furthermore, an indirect comparison of published data showed that the cerebral H_1RO for bilastine 20 mg is one of the lowest among first- and second-generation H_1-antihistamines[50], resulting in the classification of bilastine as a non-brain-penetrating antihistamine[51]. Bilastine also has minimal adverse effects on psychomotor performance or subjective assessment of drowsiness[52] and does not augment the CNS effects of alcohol or lorazepam[18,53]. Bilastine remains non-sedating even at a dose of 80 mg once daily[45,48]. Driving ability was not altered by bilastine 20 mg, or even at a double dose (40 mg), in healthy volunteers[54] and bilastine 20 mg had no effect on driving performance in patients with allergic rhinitis and/or chronic urticaria using a Formula One-high speed simulator-driving test[55]. In the setting of simulated flight-associated hypobaric hypoxia, bilastine did not affect vigilance or cognitive performance[56,57]. In the most recent of these studies, a randomized, double-blind, comparative, placebo-controlled crossover study[56], bilastine 20 mg did not impair any of the tested abilities, either at ground level or under hypobaric hypoxia. In contrast, cetirizine 10 mg increased the number of errors at ground level and, at the simulated altitude (4000 m), additional impairment was observed in cetirizine 10 mg recipients in a distributive attention test[56]. Bilastine has no significant effect on QTc interval[58,59], and there is no evidence of cardiotoxicity even when updosed up to four times the standard licensed dose[60]. Based on the European Medicines Agency (EMA) periodic safety update report of post-marketing activity, a cumulative review of hypersensitivity reactions was performed for bilastine. Causality was assessed as possible in most of the cases, and as probable in a few cases. While acknowledging that the benefit-risk balance for bilastine remains unchanged, the EMA Pharmacovigilance Risk Assessment Committee concluded that hypersensitivity reactions (frequency not known) should be included in the bilastine product information[61].

Elderly patients

The number of people aged $\geq$65 years is increasing and by 2030 this age group will represent about 20% of the total world population[62]. The prevalence of allergic diseases is currently estimated to be approximately 5–10% in the elderly and is likely to rise due to the increasing number of people with allergies[62–64]. A decline in immune function and age-related changes in tissue structures have an impact on allergies in the elderly, while comorbidities, polypharmacy and adverse drug reactions can complicate the picture[65].

The most common allergic diseases in elderly people include allergic rhinitis (approximately 5–11%) and chronic urticaria (prevalence in elderly uncertain but general prevalence around 0.5–1%)[46]. In elderly individuals, allergic rhinitis often occurs in association with other types of chronic non-allergic rhinitis (e.g. atrophic rhinitis, vasomotor rhinitis, drug-related rhinitis)[66]. Chronic urticaria in the elderly is often associated with the general consequences of skin aging, such as atrophy of the epidermis and dermis, progressive deterioration of skin structural integrity and function, impaired skin barrier function and immune response, vascular impairment, and a build-up of reactive oxygen species[67]. Urticaria in the elderly may be induced by systemic diseases or may be drug-induced[68].

Comorbidities and the use of polypharmacy are common amongst the elderly[69,70]. Polypharmacy is associated with increased risks of drug–drug interactions and adverse drug reactions[70]. The aging process itself can also interfere with the pharmacokinetics and pharmacodynamics of medications. For example, reductions occur in liver blood flow, liver volume and renal glomerular filtration rate, which can result in impaired hepatic and/or renal drug clearance[71,72]. Older individuals may also have reduced cognitive performance, particularly executive function, and memory dysfunction[73]. They have an increased risk of developing drug-induced delirium, a condition which can, in part, be related to a reduction in cholinergic function[74]. Therefore, in elderly patients, it is important to avoid drugs which can cause confusion or sedation/drowsiness, as well as those which have effects on the cholinergic system, such as first-generation and some second-generation H_1-antihistamines. Although first-generation H_1-antihistamines are efficacious, they are associated with numerous important adverse effects, caused by interactions with CNS H_1-receptors, muscarinic receptors, serotonin receptors, α-adrenergic receptors and cardiac ion channels[5]. Consequently, although first-generation H_1-antihistamines are not recommended for use in any patients with allergic disease, they can be particularly hazardous in seniors (and children).

Non-sedating, second-generation H_1-antihistamines, such as bilastine, should be used in elderly patients with allergic disorders. As well as being efficacious, bilastine is safe and well tolerated even at supratherapeutic dosages and has additional features which make it suitable for use in this age group. As discussed elsewhere in this article, bilastine does not cause sedative effects or affect cognitive performance and does not potentiate the effects of alcohol or benzodiazepines[18,45,48,52,53]. It does not have anticholinergic effects[63] or exhibit cardiotoxic effects[58,59]. Since bilastine does not undergo significant metabolism, dose adjustments are not needed in elderly patients or those with renal or hepatic

Table 3. Tolerability of bilastine in elderly patients: treatment-emergent adverse events with an incidence ≥2% reported in elderly patients (≥65 years) with allergic rhinoconjunctivitis and/or urticaria treated with bilastine 20 mg once daily for a mean of 36 days.

Treatment-emergent adverse event	Number of events/Number of patients (% patients)
Nasopharyngitis	5/5 (3.4)
Urinary tract infection	5/5 (3.4)
Contusion	5/5 (3.3)
Back pain	4/4 (2.7)
Somnolence	4/4 (2.7)
Conjunctivitis	3/3 (2.1)
Dry mouth	3/3 (2.1)

Data from Sologuren et al. 2018[75].

impairment[18,20]. Finally, bilastine has limited propensity for drug–drug interactions[19,21].

Clinical trials with bilastine in adults allowed patients up to the age of 70 or 74 years to be enrolled. However, relatively few participants were aged ≥65 years. In clinical trials performed as part of the European development programme for bilastine, only 69 patients were aged ≥65 years, of whom 34 received bilastine[75]. Consequently, a prospective observational study in a real-world practice setting was undertaken to evaluate the safety profile in 146 patients aged ≥65 years with allergic rhinoconjunctivitis and/or urticaria who were prescribed bilastine 20 mg once daily and followed up for 3 months[75]. The mean ± SD age of participants was 74.8 ± 6.6 years; 74% had allergic rhinoconjunctivitis, 19% had urticaria and 7% had both disorders. At inclusion, 61 patients (41.8%) reported at least one previous medical condition and the most common comorbidities were hypertension (66.4%), osteoarthritis (43.8%), dyslipidaemia (29.5%), hypercholesterolaemia (24.0%) and depression (19.2%). The mean ± SD duration of treatment was 35.8 ± 29.7 days.

During the study period, 74 patients (50.7%) reported 129 non-serious TEAEs during the study period (Table 3) and, of these, only eight TEAEs (in seven patients, 4.8%) were judged to be at least possibly related to bilastine. Mild/moderate somnolence was the only bilastine-related TEAE reported by more than one patient (four patients, 2.7%). The monthly and quarterly incidence rates for TEAEs were 0.29 (95% confidence interval 0.229–0.367) and 0.88 (95% CI 0.688–1.100), respectively. No serious TEAEs considered to be related to bilastine occurred. Overall, this study showed that bilastine 20 mg once daily had a favourable safety profile, with a low incidence of TEAEs, in elderly patients with allergic rhinoconjunctivitis and/or urticaria. Moreover, the safety profile in elderly patients was not different from that in placebo-controlled clinical trials in which adverse event rates reported for bilastine were similar to those for placebo[75].

School-age children

Rhinoconjunctivitis is common in school-age children and adolescents, with an average global prevalence of 8.5% in children aged 6–7 years and 14.6% in those aged 13–14 years[76]. The prevalence of rhinoconjunctivitis appears to be increasing, particularly among older children[2]. The prevalence of acute urticaria in children is 1–14%, and that of persistent or chronic urticaria is 0.1–1.8%[77,78]. Allergic rhinitis and urticaria both have an adverse effect on QoL in children and adolescents, causing emotional and practical problems, limitations in daily activities and sleep problems[79–82]. Of importance in this age group, allergic rhinitis and urticaria can have a negative impact on school attendance and academic achievement[81,83,84].

Clinical trials in perennial and seasonal allergic rhinoconjunctivitis or urticaria performed as part of the main bilastine clinical development programme enrolled 198 patients aged 12 to 18 years, of whom 81 received bilastine 20 mg, including 68 who received it for 12 months[52]. Bilastine 20 mg once daily was determined to be effective and safe in this age group[52], and the original approval for bilastine covered adults and adolescents aged ≥12 years[18].

More recently, bilastine was approved widely for use in children aged 6–11 years (who weigh ≥20 kg)[85,86]. This approval was based on data from studies included in the bilastine Paediatric Investigation Plan, approved by the EMA Paediatric Committee, which included a paediatric pharmacokinetic study[87,88] and an international, double-blind, randomized, placebo-controlled study evaluating safety and tolerability[89], both performed in children aged >2 years to <12 years.

A model-informed development approach was used to select the paediatric dose and design the sampling schedule for the pharmacokinetic study[87,88]. The multicentre, adaptive, open-label, repeated-administration pharmacokinetic study enrolled children in two age groups, 6 to <12 years ($n = 24$) and 2 to <6 years ($n = 7$). Participants received bilastine 10 mg, as an orodispersible tablet, once daily for 6 days. Children in the older age group were enrolled first, and younger children only after an interim analysis had confirmed that pharmacokinetic profiles were as predicted, that there were no safety concerns, and that the dose was appropriate. Overall, the study established that in children aged 2 to <12 years a 10 mg dose of bilastine provided equivalent systemic exposure and similar pharmacodynamic outcomes to a 20 mg dose in adults[88].

To evaluate safety in children, 506 patients aged 2 to ≤12 years with symptomatic allergic rhinoconjunctivitis or chronic urticaria were randomized to treatment with either bilastine 10 mg orodispersible tablet or placebo for 12 weeks[89]. Patients were stratified into three age groups: 2 to <6 years (20% of patients), 6 to <9 years (40%) and 9 to <12 years (40%). The primary outcome was the proportion of children in each group *without* TEAEs during the study. After 12 weeks of treatment, there was no statistically significant difference between bilastine and placebo in the proportion of children *without* TEAEs (31.5 versus 32.5%; treatment difference 0.99%, 95% CI −9.10 to 7.10; Figure 2). The upper limit of the 95% CI for the difference was less than 10%, meeting the predefined criterion for non-inferiority. There were also no differences between bilastine and placebo for secondary endpoints, including the incidence of TEAEs (Figure 2) or related-TEAEs, either overall or within the different age groups. In addition, bilastine demonstrated similar outcomes to placebo in the four domains of the Paediatric Sleep Questionnaire (sleep-related breathing disorder,

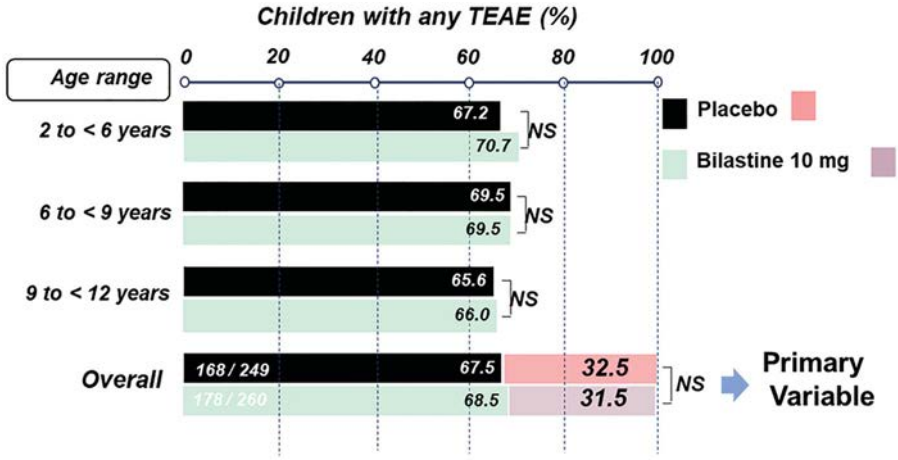

Figure 2. Tolerability of bilastine 10 mg once daily in children aged 2 to <12 years with allergic rhinitis or chronic urticaria: results of an international, double-blind, randomized, placebo-controlled clinical trial. Reproduced with permission from Novák et al.[89].

daytime sleepiness, snoring and inattention). Overall, this study showed that bilastine 10 mg had a tolerability profile similar to that of placebo in children aged 2 to ≤12 years[89].

Discussion

Oral second-generation H_1-antihistamines, such as bilastine, are recommended as first-line medication for the treatment of allergic rhinitis and chronic urticaria in adults and children[6,7,90,91]. The EAACI/ARIA guidelines group have defined the features that an ideal oral H_1-antihistamine should possess[92]. Bilastine has a high number of the specified attributes and meets the EAACI/ARIA criteria for medications for the treatment or allergic rhinitis[93].

Bilastine is a potent and highly selective oral H_1-antihistamine. It is efficacious in the treatment of allergic rhinoconjunctivitis and chronic urticaria in adults (at a dose of 20 mg once daily) and in children aged 2–11 years (at a dose of 10 mg once daily), is generally well tolerated, even at supratherapeutic doses, and improves patients' QoL. Bilastine displays only limited penetration across the blood-brain barrier, does not cause somnolence or affect cognitive performance or the ability to drive, and does not potentiate the effects of alcohol. It does not exhibit anticholinergic effects or cardiotoxic effects. No dosage adjustments are required in patients with renal or hepatic impairment, or in the elderly. In patients with moderate or severe renal impairment, coadministration of bilastine with P-glycoprotein inhibitors (e.g. ketoconazole, erythromycin, cyclosporine, ritonavir or diltiazem) may increase plasma levels of bilastine. Bilastine does not undergo significant metabolism and does not interact with the CYP system, which limits its potential for drug–drug interactions.

Allergic disorders affect people of all ages and can have a substantial adverse effect on an individual's QoL and their work or educational performance[3,4,36,46,79–82]. Bilastine is effective and well tolerated in different age groups, from school-age children through to elderly adults. The dose in elderly patients is the same as for younger adults (20 mg tablet once daily)[18]. The dose for adolescents aged ≥12 years is also 20 mg once daily[18]. In children aged 6–11 years with a bodyweight of ≥20 kg, the dose is 10 mg once daily[85,86]. In addition to the standard 20 mg tablet, two paediatric formulations are available – a 10 mg orodispersible tablet and a 2.5 mg/mL oral solution[85,86].

The EAACI/GA^{2}LEN/EDF/WAO guidelines for the treatment of chronic urticaria suggest that doses of second-generation H_1-antihistamines can be increased by up to four-fold above the licensed dose in patients who have failed to respond to a standard dose[7]. Bilastine has been shown to be safe and to provide additional efficacy at doses of up to 80 mg once daily (four times the standard adult dose) in patients with chronic urticaria. It has also been shown to be effective in patients who have failed to respond to other second-generation H_1-antihistamines.

Studies that compared bilastine with other oral second-generation H_1-antihistamines showed that bilastine was as effective as desloratadine, cetirizine and fexofenadine at reducing symptoms in patients with allergic rhinitis, and as effective as loratadine or desloratadine at improving health-related QoL. Bilastine was as effective as levocetirizine at improving symptoms in patients with chronic spontaneous urticaria. It was also shown that bilastine was associated with significantly less somnolence and fatigue than cetirizine.

In conclusion, bilastine displays good efficacy with a rapid onset of action and long duration of action and good tolerability with minimal sedative properties and a low propensity for drug-drug interactions. Bilastine is an attractive option for the treatment of patients with allergic rhinoconjunctivitis or urticaria across age groups from school-age children through to the elderly.

Transparency

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Declaration of financial/other relationships

Martin Church has been a speaker or consultant for Almirall, FAES FARMA, Menarini, Moxie, MSD, Novartis, UCB Pharma, Sanofi-Aventis and Uriach.

Marysia Recto has participated in advisory boards for A. Menarini and Abbott Nutrition. She has been a speaker for FAES FARMA, A. Menarini, Abbott Nutrition, Nestle Nutrition, Galderma, Leo Pharma, Mylan, Astra Zeneca, Novartis, Glenmark, Natrapharm and Kalbe Nutrition.

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