EXHIBIT B

EXPERT REVIEWS

Azelastine nasal spray for the treatment of allergic and nonallergic rhinitis

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Rhinitis affects millions of people around the world, places a huge burden on the economy and reduces patients' health-related quality of life. Azelastine nasal spray is a second-generation antihistamine, indicated for the treatment of allergic and nonallergic rhinitis in both adults and children. It offers a rapid onset of action (15 min) and flexibility of both dose (i.e., one or two sprays/nostril twice daily) as well as dosage (i.e., fixed or as needed). Compared with other agents used to treat allergic rhinitis, azelastine nasal spray exhibits superior efficacy to oral antihistamines (e.g., desloratadine and cetirizine), other intranasal antihistamines (e.g., levocabastine) and the intranasal corticosteroid mometasone furoate, and comparable efficacy to the potent intranasal corticosteroid fluticasone propionate (FP). Combination therapy with intranasal FP has the potential to enhance clinical benefit, as the combination of azelastine and FP nasal sprays reduce symptoms in allergic rhinitis patients more than either agent alone. Azelastine nasal spray has an excellent safety profile.

KEYWORDS: allergic rhinitis • azelastine nasal spray • intranasal corticosteroid • nonallergic rhinitis • oral antihistamine

Rhinitis is an inflammatory disease of the nasal mucosa affecting approximately 10–30% of adults and 40% of children, making it the sixth most common chronic illness in the USA. Over the past 30 years, the prevalence of this condition has risen dramatically in industrialized countries, with England, Sweden and Australia reporting a doubling in rates, a trend similar to that seen with other atopic conditions such as asthma. Rhinitis places a huge burden on the economy, being responsible for between US$2 and 5 billion annually in both direct and indirect costs [1], and approximately 3.5 million lost work days per year [2].

Traditionally, rhinitis has been classified as allergic, nonallergic and mixed. Definitions of these rhinitis classifications are discussed later. Patients with seasonal allergic rhinitis (SAR) present with a huge range of symptoms, including nasal congestion, runny nose, nasal and nasopharyngeal itching, ear symptoms, sneezing, and ocular symptoms in many patients, including itchy and watery eyes [3]. The symptoms of sneezing, itching and rhinorrhea are less common with perennial rhinitis (PR).

Rhinitis symptoms have a major negative impact on patients' health-related quality of life (HRQoL). They impair not only patients' daily activities, but furthermore disturb quality of sleep, which causes fatigue during the day and impairs cognitive function [4]. An inability to concentrate is a frequent complaint made by rhinitis sufferers, and in the case of SAR, patients often avoid outdoor activities to avoid allergen exposure. The Joint Task Force on Allergy Practice and Parameters mentions that improving the negative impact on daily life in rhinitis patients defines successful treatment as much as providing symptom relief.

A recent survey investigated symptom perception and the impact of allergic rhinitis (AR) in 447 patients and their doctors on HRQoL [5]. The results highlighted the high symptom burden and impaired HRQoL associated with AR. Interestingly, patients rated their disease as more severe than physicians did. At the time of the consultation, 44% of patients were suffering from nasal and ocular symptoms, 23.7% of patients reported that their current nasal and ocular symptoms were moderate or severe in nature, and approximately two-thirds of patients with intermittent disease reported some impairment of their professional or daily life as a result of AR [5]. HRQoL correlated negatively with the number of symptoms, with AR having a

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significantly greater impact on patients with more persistent disease compared with those with intermittent disease. Finally, more than 50% of patients surveyed were using two or more medications for their AR [5]. AR seems to be a disease that is poorly controlled and whose effects are underestimated.

Traditional classification of rhinitis

Traditionally, rhinitis has been classified as allergic, nonallergic or mixed (Figure 1) [6]. With AR, symptoms occur in association with a specific IgE-mediated response. With nonallergic rhinitis, symptoms are induced by irritant triggers but without an IgE-mediated response. AR is further classified as seasonal or perennial. SAR symptoms are induced by exposure to pollens, whilst PR is associated with environmental allergens that are generally present on a year-round basis.

As many as half of all patients diagnosed with rhinitis have nonallergic disease. Nonallergic rhinitis includes infectious rhinitis (also known as rhinosinusitis), occupational rhinitis, drug-induced rhinitis (e.g., rhinitis induced by aspirin and nonsteroidal anti-inflammatory drugs [NSAIDs]), hormonal rhinitis (e.g., during pregnancy), rhinitis in smokers, food-induced rhinitis (very rare), nonallergic rhinitis with eosinophilia and eosinophilic rhinitis, senilic rhinitis, atrophic rhinitis (often infected with *Klebsiella ozaenae*) and finally idiopathic rhinitis. Details of diagnosis and management of rhinitis are provided in the Allergic Rhinitis and its Impact on Asthma (ARIA) report [101], and the updated American Association of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology practice parameter [7].

New AR classification

The classification of AR into 'seasonal' and 'perennial' categories is not entirely satisfactory. The majority of AR patients are sensitized to many different allergens and are exposed throughout the year [8–10]. In many patients, perennial symptoms are often present, and patients experience seasonal exacerbations when exposed to pollens or molds. Therefore, the old classification of AR into seasonal and perennial categories is not indicative of the real-life situation. A major change in the subdivision of AR was proposed by ARIA (Figure 2). AR is subdivided into 'intermittent' and 'persistent' disease, and the severity classified as either 'mild' or 'moderate/severe'. However, it is important to remember that indications for treatment and clinical studies investigating the efficacy of azelastine still refer to the older rhinitis classification.

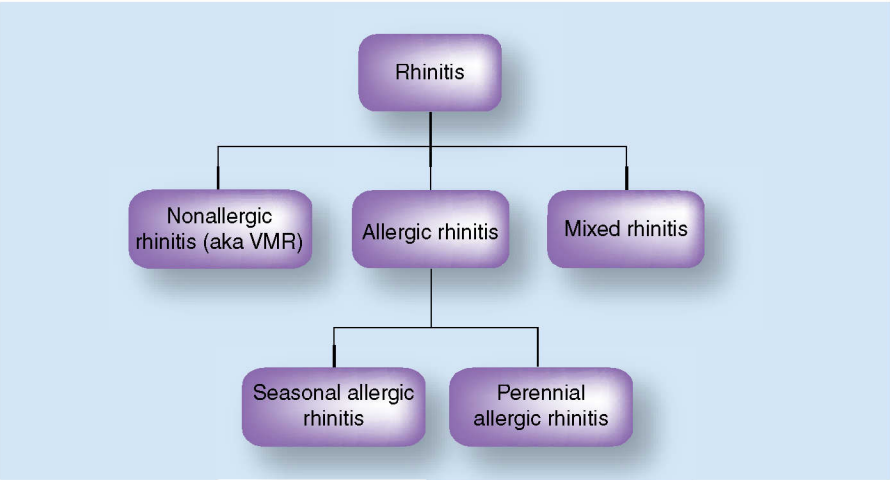

Figure 1. Traditional classification of rhinitis.
VMR: Vasomotor rhinitis.

Treatment guidelines

As many as 66% of adult allergy sufferers are dissatisfied with their current allergy medication due to a lack of effectiveness [11]. Clearly, effective and convenient therapies with a good safety profile are needed to treat patients with AR. The ARIA guidelines recommend a stepwise approach to therapy based upon the frequency and severity of symptoms (Table 1). Intranasal antihistamines are recommended for all severities of intermittent rhinitis symptoms and mild persistent symptoms. Treatment guidelines from the Joint Task Force and the WHO agree with ARIA, and recommend antihistamines (both topical and oral second-generation) be used as a first-line therapy for AR. Intranasal corticosteroids may also be considered as initial therapy for AR patients with more severe or persistent symptoms, particularly nasal congestion.

Azelastine

Azelastine hydrochloride nasal spray is a topically administered second-generation antihistamine, marketed as Allergodil® (Meda AB, Stockholm, Sweden) in Europe and Astelin® (Meda Pharmaceuticals Inc., NJ, USA) in the USA. It is indicated for the treatment of the symptoms of SAR (approved in 1996) such as rhinorrhea, sneezing, and nasal pruritus in adults and children 5 years of age and older. It is also indicated for the treatment of the symptoms of vasomotor rhinitis (VMR; approved in 1999) such as rhinorrhea, nasal congestion and postnasal drip in adults and children aged 12 years or older. The recommended dose of azelastine nasal spray depends on patient age. For those aged 12 years or older, two sprays per nostril twice daily is recommended, which reduces to one spray per nostril twice daily in children aged 5–11 years. A new formulation of azelastine nasal spray with sucralose as a taste-masking agent (Astepro®) was approved in the USA in October 2008 for the treatment of SAR in patients 12 years of age and older.

Applying azelastine topically to the nasal mucosa means that the drug is delivered directly to the site of inflammation, where it is needed most. Compared with systemic treatments, higher concentrations of azelastine can be applied topically, which should enhance its anti-allergic and anti-inflammatory effects. In addition, the risk of interaction with concomitant medication, and the potential for systemic adverse

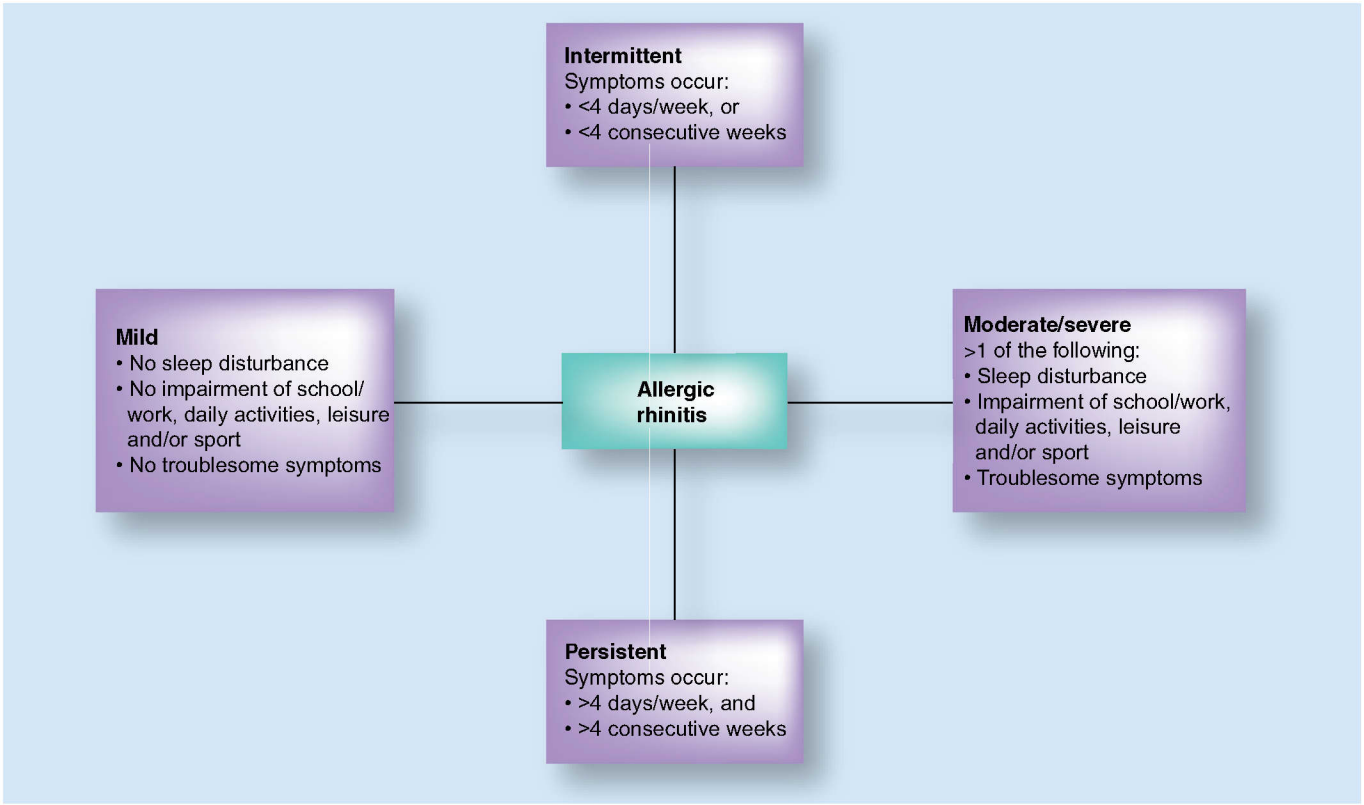

Figure 2. New Allergic Rhinitis and its Impact on Asthma classification of allergic rhinitis.

events is minimized. The efficacy and safety of azelastine nasal spray in treating AR and nonallergic rhintis have been determined in a number of US multicenter, randomized, double-blind, placebo-controlled trials. In all trials, azelastine was associated with a rapid onset of action, and a sustained improvement over time in rhinitis, congestion, and other symptoms [12]. The topical application of azelastine nasal spray has been shown to be effective in treating rhinitis patients who remained at least moderately symptomatic after therapy with either oral loratadine (Claritin®, Schering Plough, USA) or fexofenadine (Allegra®, Sanofi Aventis, USA) [13,14].

Dosage

A dosage of two sprays per nostril twicy daily improves not only all symptoms of allergic and nonallergic rhinitis, as shown in an open trial with 4000 patients [15], but also HRQoL [16] immediately.

Table 1. Summary of ARIA allergic rhinitis management guidelines.

Rhinitis severity	ARIA recommendation
Mild intermittent	Oral/intranasal antihistamines and/or decongestants
Moderate/severe intermittent	Oral antihistamines and/or decongestants, intranasal antihistamines, intranasal corticosteroids or cromones
Mild persistent	Oral antihistamines and/or decongestants, intranasal antihistamines, intranasal corticosteroids or cromones A step-wise approach is advised with reassessment after 2 weeks. If symptoms are controlled and the patient is receiving a intranasal corticosteroid, the dose should be reduced, but otherwise treatment continued. If symptoms persist and the patient is receiving antihistamines or cromones, a change should be made to an intranasal corticosteroid
Moderate/severe persistent	Intranasal corticosteroid (first-line treatment) If symptoms are uncontrolled after 2–4 weeks, medication should be added depending on the persistent symptom. For example, add an antihistamine if the major symptom is rhinorrhea, pruitis or sneezing, double the dose of intranasal steroid for persistent nasal blockage and add ipratropium for prominent complaint of rhinorrhea

ARIA: Allergic Rhinitis and its Impact on Asthma.

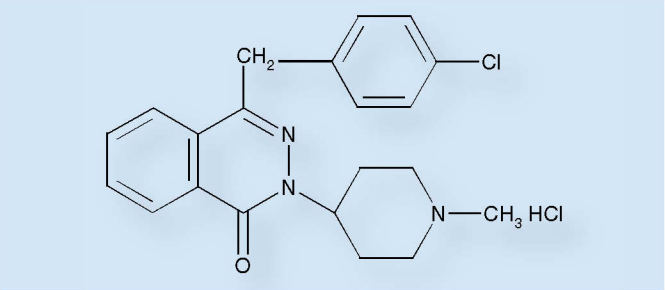

Figure 3. Azelastine hydrochloride.

Azelastine nasal spray at a dosage of one spray per nostril twice daily is also effective and has an improved tolerability profile compared with two sprays per nostril twice daily in patients (≥12 years; n = 554) with moderate-to-severe SAR [17].

In addition, one spray per nostril twice daily of azelastine was associated with significant improvements in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) daily activity and nasal symptoms domains and patient global evaluations compared with placebo. The incidence of a bitter aftertaste following azelastine application more than halved, and the incidence of somnolence was decreased almost 30-times in the one-spray group versus the labeled incidence with the two-spray regimen.

As needed

Azelastine nasal spray can also be used on an as-needed basis by virtue of its rapid onset of action, just 15 min after application [18]. Ciprandi and colleagues carried out a randomized, controlled study in 30 patients sensitized to *Parietaria* pollen and grass and treated them with azelastine (0.56 or 0.28 mg/day), or as needed [19]. Patients who received the 0.56- or 0.28-mg/day dose had a marked improvement in their rhinitis symptoms, and a concomitant reduction in markers of inflammation, most notably neutrophil and eosinophil counts and intracellular adhesion molecule (ICAM)-1 expression in nasal scrapings. Although this anti-inflammatory effect was absent in patients treated with azelastine nasal spray on an as-needed basis, these patients did show an improvement in their rhinitis symptoms [19]. Therefore, although patients derive maximum benefit from regular treatment with azelastine, as-needed therapy may be useful in the treatment of clinical symptoms and would be expected to improve drug tolerability and patient compliance.

Chemistry

The chemical name of azelastine hydrochloride is (±)-1-(2H)-phthalazinone,4-[(4-chlorophenyl) methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-monohydrochloride. Its empirical formula and molecular weight are $C_{22}H_{24}ClN_3O \cdot HCl$ and 418.37, respectively, and structurally it is arranged as a seven-membered ring (Figure 3).

Azelastine is a white, almost odorless crystal with a bitter taste. It is soluble in dichloromethane and chloroform, sparingly soluble in propylene glycol and methanol, slightly soluble in glycerin, octanol and ethanol, and almost insoluble in hexane.

Pharmacokinetics & metabolism

The systemic bioavailability of intranasally administered azelastine hydrochloride is approximately 40%, with maximum plasma concentrations (C_{max}) observed within 2–3 h. Based on intravenous and oral administration, the elimination half-life is 22 h, steady-state volume of distribution is 14.5 l/kg and plasma clearance is 0.5 l/h/kg, respectively. *In vitro* studies with human plasma indicate plasma protein binding of azelastine and desmethylazelastine of approximately 88 and 97%, respectively. Azelastine is oxidatively metabolized by the cytochrome P450 enzyme system into a principally active metabolite, desmethylazelastine and two inactive carboxylic acid metabolites. When azelastine is administered orally, desmethylazelastine has an elimination half-life ranging from 22 to 54 h. Approximately 75% of an oral dose of radiolabeled azelastine is excreted with feces, with less than 10% excreted unchanged.

Following oral administration, pharmacokinetic parameters of azelastine are not influenced by age, gender or hepatic impairment. However, oral, single-dose studies show that patients with renal insufficiency (i.e., creatinine clearance <50 ml/min) had a 70–75% higher C_{max} and AUC compared with normal subjects, but time to C_{max} remained the same.

Mode of action

Azelastine has a fast and long-lasting effect due to its complex anti-inflammatory mode of action [6,20]. It is a high-affinity histamine H_1-receptor antagonist, being ten-times more potent than chlorpheniramine, and also has some affinity for H_2 receptors. In a VCC trial, azelastine showed one of the fastest onsets of action (15 min with nasal spray) [18] among the currently available rhinitis medications, and its effect lasts at least 12 h, thus allowing for a once- or twice-daily dosing regimen.

Azelastine's anti-inflammatory activity is widespread. Azelastine inhibits TNF-α release, granulocyte macrophage colony-stimulating factor generation and reduces the number of a range of inflammatory cytokines, including IL-1β, IL-4, IL-6 and IL-8 [6,20]. These cytokines perpetuate the inflammatory response [21]. *In vitro* azelastine decreases free-radical production by human eosinophils and neutrophils, and calcium influx induced by platelet-activating factor. It reduces inflammatory cell migration in patients with rhinitis, most likely as a consequence of the downregulation of ICAM-1 expression [6,20], and inhibits kinin (e.g., bradykinin and substance P), platelet-activating factor and leukotriene release *in vitro* and *in vivo*. Leukotrienes are associated with dilation of vessels, increased vascular permeability and edema, which results in nasal congestion, mucus production and recruitment of inflammatory cells *in vitro* [22] and *in vivo* [21]. Clinically, substance P and bradykinin are associated with the AR symptoms of nasal itching and sneezing, but may also contribute to the onset of nonallergic rhinitis symptoms.

The widespread anti-inflammatory effects of azelastine ensure that it is a highly effective treatment, combating the broad range of clinical symptoms associated with rhinitis.

Clinical efficacy of azelastine

The clinical efficacy of azelastine nasal spray has been confirmed in a real-world setting for the treatment of allergic, mixed and