

Allergy immunotherapy tablet: Grazax® for the treatment of grass pollen allergy

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Immunotherapy is the only treatment for allergy that alters the natural course of this disease. Sublingual immunotherapy has been developed to make immunotherapy more suitable for allergic patients. In the largest clinical program ever conducted with grass allergen-specific immunotherapy, over 2000 adults and more than 500 children have been exposed to Grazax® (ALK-Abellø A/S, Høersholm, Denmark). Grazax is an oral lyophilisate tablet (allergy immunotherapy tablet [AIT]) for sublingual administration, containing 75,000 standardized quality tablet units of allergen extract of grass pollen (*Phleum pratense*). Grazax is indicated for treatment of grass pollen-induced rhinitis and conjunctivitis in adult and pediatric patients. Results from the GT-08 trial (first, second and third treatment years) showed a reduction of 31, 36 and 29%, respectively, in symptom scores and a reduction of 38, 45 and 40% of medication scores, respectively, compared with placebo. Subjects treated with Grazax also had an increased number of well days and a relevant improvement in quality of life. More subjects experienced excellent and complete rhinoconjunctivitis control in comparison with patients treated with symptomatic medications only. Grazax treatment is also associated with a sustained and relevant increase of specific IgG4. This increase is also observed after stopping AIT treatment. The most common adverse events related to Grazax treatment are local reactions, such as oral itch, edema of the mouth, ear pruritus, throat irritation and sneezing. Clinical efficacy of Grazax is observed also after 1 and 2 years of follow-up after stopping the AIT treatment. Grazax is efficacious and safe for treatment of grass-pollen rhinoconjunctivitis in both adults and children. Grazax is the first AIT showing a disease-modifying effect on grass pollen-induced allergic rhinoconjunctivitis.

KEYWORDS: grass pollen allergy • immunotherapy • rhinoconjunctivitis • sublingual immunotherapy • tablet

Allergic rhinitis & immunotherapy

Of the European population, 25% suffers from respiratory allergies such as allergic rhinitis and asthma [1]. Epidemiological data also show that the prevalence of these diseases is increasing. Grass pollen is the most common cause of respiratory allergies and is associated with more than 50% of allergic rhinitis cases [2]. Allergic rhinitis should not be considered a trivial disease: symptoms of allergic rhinitis have a considerable impact on the quality of life of the sufferer [3]. Sneezing, runny nose, blocked nose and headache are some of the most common symptoms of allergic rhinitis, which affects the work, home and social lives of many patients [4]. Allergic rhinitis can leave a significant burden of residual symptoms even among those receiving optimal symptomatic treatment [5]. People of all ages may be affected but the peak age of onset is adolescence. Risk factors include a personal or family history of atopy, male

sex and birth order (first born). In children, poorly controlled symptoms may contribute to learning problems and sleep disturbance [6]. Other allergic problems such as asthma and eczema frequently coexist [7], adding further impact to this clinical condition. A person with hayfever may be allergic to one, several or many types of different pollen, but approximately 52–90% of people with hayfever are allergic to airborne grass pollens [8]. People with moderate-to-severe hayfever (according to the international Allergic Rhinitis and its Impact on Asthma guidelines [9]) are defined as having one or more of the following: abnormal sleep; impairment of daily activities, sport or leisure; and problems at work or school. Estimates of people that are affected by moderate-to-severe symptoms range from 30 to 62% [10]. Rhinitis is traditionally classified as allergic, nonallergic or mixed. In the allergic form, rhinitis symptoms are associated with a specific IgE-mediated response. In more

detail, allergic rhinitis is an inflammation of the nasal mucosa caused by hypersensitivity reactions to specific inhaled allergens. The condition may occur seasonally, usually in response to pollens from trees, grasses and weeds. It may also be perennial, a response to constant exposure to animal dander, dust mites, molds or chemicals in the workplace. The onset of allergic rhinitis is common in children and adolescents, and symptoms often continue into adulthood. However, in 10–20% of children, the condition resolves within 10 years. There is very often a genetic predisposition to developing allergic rhinitis. Allergic rhinitis and allergic asthma are both atopic (an inherited tendency to develop IgE immune responses). Asthma is often triggered by the same allergens such as dust mites, cats, dogs, as well as pollens (parietaria and ragweed among others), which are involved in allergic rhinitis. Cross-sectional epidemiologic studies have shown that asthma and allergic rhinitis frequently coexist. Rhinitis is diagnosed in up to 78% of patients with asthma, and asthma is diagnosed in up to 58% of patients with rhinitis. In the general population of patients with both diseases, rhinitis precedes asthma in up to 64% of cases. This suggests that allergic rhinitis may be a significant risk factor for asthma. In a 23-year follow-up study, allergic rhinitis patients had a threefold increase in the incidence of asthma compared with those without rhinitis [11]. Patients suffering from seasonal and perennial allergic rhinitis who have no asthma symptoms frequently have hyperactive airways. This change in lung function reinforces the concept that rhinitis is a risk factor for asthma. The therapeutic approach of allergic rhinitis is commonly initiated with symptomatic drugs. However, symptomatic treatment has relevant limitations. In a recent meta-analysis of treatments for allergic rhinitis, the effect sizes for antihistamines (7%), leukotriene receptor antagonists (5%) and intranasal corticosteroids (12%) were modest compared with placebo [12]. In addition, the symptomatic treatment approach is not able to cure the allergic condition. On the other hand, specific immunotherapy (SIT) is the only treatment modality for allergic rhinoconjunctivitis with the potential to modify the course of the disease and provide efficacy in post-treatment years. Both subcutaneous and sublingual SIT have shown to induce a protective immune response and provide sustained symptom prevention for allergic patients [13]. Sublingual immunotherapy has the advantage of being more convenient and easy to use [14]. However, several characteristics of the sublingual formulations (i.e., excipients, volume, standardization and allergen content) could modulate and influence the pharmacokinetic and pharmacodynamic properties of the compound.

Grazax®: a new approach to specific immunotherapy

Specific immunotherapy has been shown to induce a specific immune response, providing sustained symptom prevention for allergic patients [15]. It is not clear how many patients are currently receiving immunotherapy, although expert opinion puts this figure at approximately 1% of the general population. However, only allergen SIT targets the underlying allergic disease, having the potential to produce long-term remission and to prevent the development of new sensitizations and asthma [16]. Therefore, SIT is considered the only treatment that could alter the history and the course of allergic diseases. SIT increases the tolerability to a specific allergen, thereby

reducing the allergic symptoms and the consumption of symptomatic treatment [17]. Grazax® (ALK-Abello A/S, Hoersholm, Denmark) is the first registered and marketed allergy tablet (oral lyophilisate) to treat the underlying cause of grass pollen-induced rhinoconjunctivitis in adult and pediatric subjects [18]. Grazax tablet uses a peculiar pharmaceutical formulation (Zydis®). This formulation provides an enhanced delivery of therapeutic agents, increasing both the bioavailability and absorption profile. The Zydis fast-dissolving dosage form is a unique freeze-dried medicinal tablet [19], made from well known and acceptable materials. When Zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. At the moment, the Zydis formulation is utilized for several active compounds such as antihistamine, anti-emetic and anti-Parkinson drugs [20]. To date, Grazax is the only sublingual allergen product with this pharmaceutical formulation. After sublingual application, Zydis-formulated products melt instantly on contact with moisture, offering a convenient way to administer medication orally, especially in children, and provides an important differentiation for pharmaceutical products. This oral formulation is so far the fastest dissolving oral dosage form on the market.

Grazax: the allergen immunotherapy tablet

The recommended daily dose for adults is one tablet of oral lyophilisate (75,000 standardized quality tablet [SQ-T]), containing approximately 15 µg of the major allergen *Phleum pratense* [21]. The dose of 75,000 SQ-T was chosen after a specific dose-finding trial [22]. In this study, 75,000 SQ-T has demonstrated the best efficacy/tolerability ratio. Subjects should start treatment at least 2 months prior to the grass pollen season without any up dosing period [23]. Grazax contains the same active pharmaceutical ingredient as Alutard SQ® (ALK-Abello A/S, Hoersholm, Denmark) grass pollen, which has been used for more than 20 years as a subcutaneous SIT. The active pharmaceutical ingredient is a standardized allergen extract from *P. pratense* grass pollen. It has been shown to have extensive cross-reactivity of allergenic components of grass pollens from different species [24]. As the active molecules of the allergens in Grazax are polypeptides and proteins, it is expected that these are hydrolyzed to amino acids and small polypeptides in the lumen of the GI tract and in the local tissues. There is no evidence to suggest that the allergens present in Grazax are absorbed into the vascular system to any significant extent. As stated by EMA guidelines [25], pharmacokinetic studies are not possible for SIT products. Owing to the nature of the product, plasma levels are not measurable. Consequently, no pharmacokinetics trials have been conducted with Grazax. The site of action of Grazax is therefore the oral mucosa.

Efficacy in grass pollen-induced rhinoconjunctivitis data in adult patients

In a multicenter, randomized, double-blind, placebo-controlled, Phase III trial (the GT08 study) [26], the safety and efficacy of Grazax was assessed in 634 patients with seasonal grass pollen-induced rhinoconjunctivitis. Primary outcomes included the recording of rhinoconjunctivitis symptoms and use of rescue medication. Secondary

outcomes included quality of life. The results at the first year of treatment demonstrated that Grazax reduced hayfever symptoms by 30% and reduced the need for symptom-relieving medication by 38% compared with placebo. The efficacy data after 2 and 3 years of treatment with grass allergy immunotherapy tablet (AIT) are also available [27,28]. Grazax demonstrated a mean reduction of 36 and 29%, respectively, in daily rhinoconjunctivitis symptom scores and a mean reduction of 45 and 40% in daily rhinoconjunctivitis medication scores compared with placebo after the second and the third treatment years, respectively. Subjects treated with Grazax also had an increased number of well days and improved quality of life, and more subjects experienced excellent rhinoconjunctivitis control. It is important to note that the Phase III GT08 study, evaluating the efficacy of SIT in seasonal allergy, is one of the most relevant studies in terms of large sample size. As pointed out by Malling *et al.*, most studies performed in the past evaluating the clinical efficacy of sublingual immunotherapy have included too few patients to ensure a high power of detecting significant changes in disease severity [29]. On the contrary, the GT08 study has sufficient statistical power in terms of allowing a valid conclusion to be made regarding the amplitude of clinical efficacy of the grass tablets. In addition, GT08 was conducted using electronic diaries for the collection of symptom and medication scores assuring an accurate daily 'online' data collection. This is a relevant methodological advantage in comparison with studies in which only paper diaries were used. It is also important to underline that the extent of the clinical efficacy of Grazax observed in the GT08 trial was comparable to the efficacy observed with subcutaneous immunotherapy in a similar clinical setting (grass-allergic rhinoconjunctivitis patients) [30]. In fact, in comparison with the placebo group, the GT08 trial (first treatment season) showed a mean reduction of 30 and 38% for symptom and medication scores, respectively. In the Subcutaneous Immunotherapy Trial [27], conducted with a study design similar to the GT08 trial, the mean reduction in symptom and medication score with active therapy in comparison with the placebo group was -29 and -38%, respectively.

Efficacy in grass pollen-induced rhinoconjunctivitis

Data in pediatric patients have been obtained from two double-blind randomized trials, evaluating the efficacy and safety of one-season treatment in 599 pediatric patients with grass pollen-induced rhinoconjunctivitis. Bufe *et al.*, evaluating a total of 254 pediatric patients, have shown that treatment with Grazax is associated with a significant symptom reduction score (the GT12 trial) [31]. In this trial, the rhinoconjunctivitis, medication and the asthma symptom scores were all statistically significantly different between the two treatment groups in favor of AIT-treated children. The differences in medians relative to placebo

were 24, 34 and 64% in favor of AIT active treatment (FIGURE 1). The immunologic response, evaluated measuring specific serum IgG4, was similar to that observed in adults. The most common adverse reaction was oral itch, reported by 40 subjects (32%) in the active group and three (2%) in the placebo group. Six subjects withdrew because of adverse events. No serious adverse events were assessed as treatment related. The rhinoconjunctivitis symptom and medication scores and the asthma symptom score were all statistically and clinically significantly different between the two treatment groups. Blaiss *et al.* have evaluated the efficacy of Grazax in a double-blind, placebo-controlled trial in 345 grass pollen-allergic children [32]. In this trial, Grazax treatment was again associated with a significant reduction of symptom and rescue medication use, evaluated through a combined score. The reduction of the combined score was 18% ($p = 0.028$), a reduction that could also be considered clinically significant [33]. Immunotherapy with the AIT grass tablet reduced grass pollen-induced rhinoconjunctivitis and asthma symptoms in a pediatric population and introduced an immunomodulatory response, consistent with treatment of the underlying allergic disease. In addition, treatment with Grazax was well tolerated in the Blaiss trial.

Long-term efficacy & the disease-modifying effect

The GT08 trial was performed evaluating the clinical efficacy of 3-year treatment with Grazax in comparison with placebo [34]. The study design also evaluated the carry-over effect of this AIT after 1 and 2 years after stopping the treatment (4 and 5 years after starting the trial). In comparison with the placebo group, patients who were treated with Grazax for 3 years showed a statistical and clinically significant reduction in the symptom and medication score both after 1 and 2 years of follow-up. In particular, the mean symptom score was reduced by 26% in comparison with the placebo group

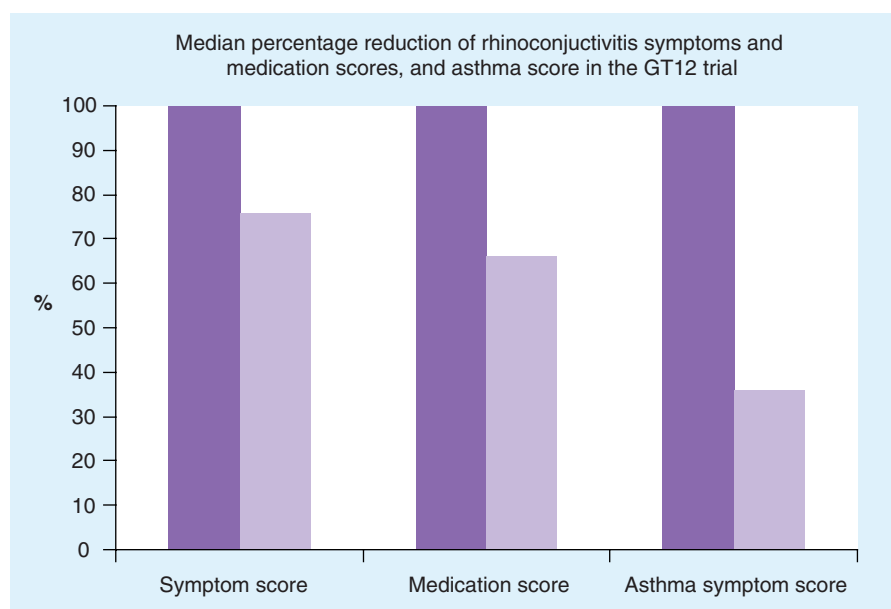


Figure 1. Clinical efficacy of allergy immunotherapy tablet with Grazax® in pediatric patients. Dark purple bar: control group; light purple bar: Grazax group. Modified with permission from [31].

after the first follow-up year after the conclusion of the 3-year AIT. The efficacy of AIT treatment was also observed in the second year of follow-up. In particular, the reduction of the median of symptom and medication score was of -31 (FIGURE 2) and -21%, respectively (% reduction in the median values in comparison with the control group). During the 3-year treatment period of GT08, a progressive immunologic effect in IgG4- and IgE-blocking factor of active treatment was also observed, with significant differences from values seen in the placebo group from the first assessment (at 2 months of treatment) and onwards. After 1 year following treatment, the differences in change from baseline values between the groups were still significantly different for both *P. pratense*-specific IgG4 ($p < 0.0001$) and IgE-blocking factor ($p < 0.0001$). The GT08 trial, with its treatment phase (3 years) and follow-up phase (2 years), is currently the largest randomized placebo-controlled trial ever to be conducted to evaluate the efficacy of SIT in grass respiratory allergy. Grazax treatment is therefore associated with a specific and relevant increase of specific anti-IgG4 *P. pratense*. The results of GT08 thereby confirm the disease modification and effective symptomatic treatment of allergic rhinoconjunctivitis obtained with AIT treatment.

The AIT Grazax & compliance to the treatment

Compliance to drug treatment is defined as 'the extent to which a person's behaviour (e.g., in terms of taking medication) coincides with medical or health advice' [35]. Complete medication

compliance occurs when a patient follows the instructions completely. Noncompliance falls into the following categories: accidental, where the patient forgets to take the dose or takes the medication incorrectly because the instructions were not well understood or could not be followed; triggered, where the patients starts to feel better and stops taking the medicine, or conversely, the patients feels worse, and therefore believes that the medication is doing no good; or intentional, where the patient makes a conscious decision not to take the medicine as recommended. Compliance problems are observed in all situations where self-administration of treatment is required, regardless of type of disease, disease severity and accessibility to health resources. Data from patients with asthma showed that patients took the recommended doses of medication on 20–73% of days. Education of the patient regarding management of their disease can be one strategy to increase compliance. In order to obtain its full clinical potential, SIT should be used for at least 3–5 years consecutively. High compliance during a full vaccination program optimizes the likelihood that the patient will benefit from the treatment. In a randomized 48-week trial conducted in 237 patients with grass allergy, the overall compliance with Grazax treatment was high (>90%), demonstrating that this formulation allowed a good adherence to this type of treatment [36].

Grazax safety & tolerability

As for other sublingual immunotherapy products, Grazax treatment is generally well tolerated [37]. Grazax treatment side effects are primarily characterized by local reactions, located in the mouth and throat, which were mostly mild to moderate [38]. In the majority of subjects, these reactions started early in therapy, lasted from minutes to hours after each intake of Grazax, and tended to subside spontaneously within 1–7 days [39]. The most common reported adverse events were oral pruritus, edema of the mouth (in general mild), ear pruritus, throat irritation and sneezing. Less commonly reported adverse events were oral paresthesia, eye pruritus, conjunctivitis, cough, asthma, pharyngitis, rhinorrhea, nasal congestion, rhinitis throat tightness (in general mild), pruritus and fatigue. The first tablet administration should be performed in the clinic under medical supervision. Grazax is contraindicated in the case of hypersensitivity to any of the excipients in the tablet. AIT treatment is not indicated in the case of tumor or systemic diseases affecting the immune system. SIT is also not indicated in the case of chronic inflammatory conditions in the oral cavity with severe symptoms such as oral lichen planus with ulcerations or severe oral mycosis, and in patients with uncontrolled or severe asthma (forced expiratory volume in 1 s $\leq 70\%$ of

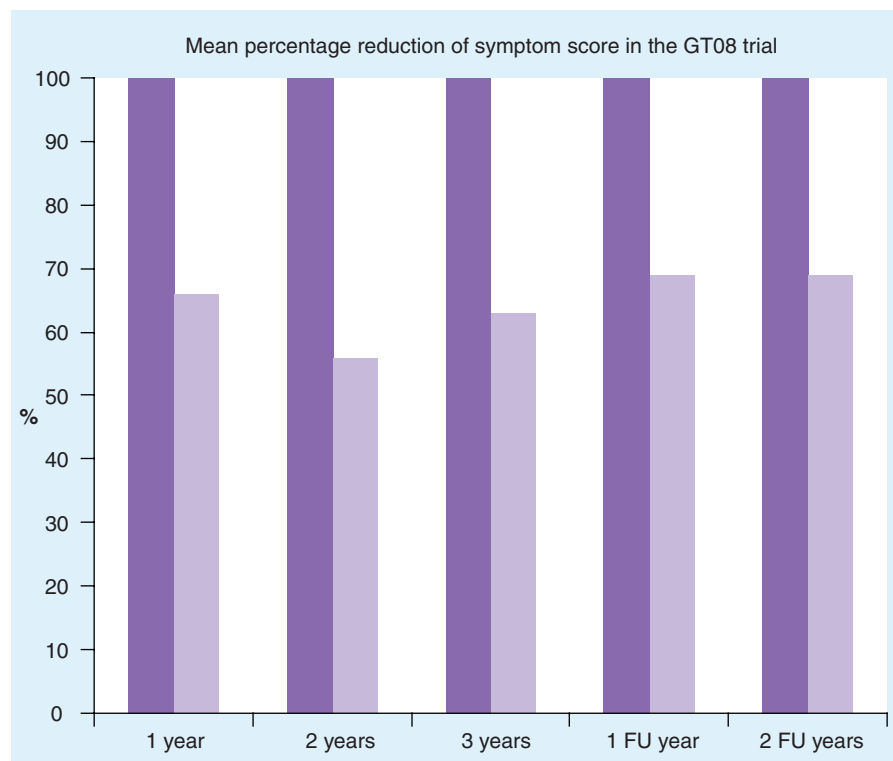


Figure 2. Clinical efficacy of allergy immunotherapy tablet with Grazax® in adult patients. Dark purple bar: control group; light purple bar: Grazax group. FU: Follow-up. Modified with permission from [31].

predicted value after adequate pharmacologic treatment). Safety and tolerability were also assessed in three trials in the pediatric population [40], including more than 500 children. Grazax was well tolerated in children, and further clinical investigations [29] of the efficacy and safety in children have shown corresponding effects to the results from the trials in adults [23]. In pediatric trials with Grazax, there was no difference in side effects between children below or above 10 years of age. The safety and tolerability profile of Grazax, both in adults [23] and children [28] with allergic rhinoconjunctivitis, was comparable in patients with or without concomitant mild or moderate asthma.

Expert commentary

Allergic respiratory diseases such as rhinitis and asthma are a common and relevant health problem. Although trivial for some, the symptoms of allergic rhinitis may have a considerable impact on the quality of life of the sufferer. In a survey involving 260 allergic patients, sneezing, runny nose, blocked nose, headache, itchy and watery eyes, and itchy nose were the most common symptoms of allergic rhinitis. The symptoms were reported to affect work (29%), home (34%) and social life (30%), and symptoms were well controlled only in 34% of patients with seasonal allergic rhinitis [41]. Symptomatic treatment, even if clinically effective, is not a causative approach of respiratory allergies. Immunotherapy, on the other hand, is effective in the management of allergic asthma, allergic rhinitis and conjunctivitis. Specific allergen immunotherapy is recognized to be a biological response modifier, capable of influencing allergen-driven immunological responses and restoring, to a certain degree, the Th1/Th2 imbalance in allergic subjects. B cells, T cells, blocking antibodies, IL-10 and other cytokines are involved in the mechanisms of action of SIT [42]. Allergen immunotherapy might prevent the development of asthma in individuals with allergic rhinitis. On the basis of efficacy, safety and tolerability data coming from well-designed large-scale Phase III trials in both adult and pediatric patients suffering from grass-induced rhinoconjunctivitis, the fast-dissolving grass AIT should be considered as a first-line treatment option in those patients with grass pollen-induced rhinoconjunctivitis whose symptoms remain uncontrolled

with symptomatic medications. Grazax efficacy was observed during the 3 years of treatment but a sustained long-term and carry-over effect was observed in the 2 years of follow-up. Grazax treatment was also associated with a disease-modifying effect with a sustained and strong increase in specific IgG4. The results of the clinical trials conducted in adults and in children thereby confirm the efficacy both after the first pollen season treatment as far as after 3 years of treatment. Immunotherapy with Grazax is also associated with a carry-over effect, maintaining a clinical benefit at least 2 years after stopping the therapy. Grazax AIT has shown to be an effective symptomatic treatment of allergic rhinoconjunctivitis with a disease modification.

Five-year view

Respiratory allergies affect 25% of the European population (one subject out of four). In addition, epidemiological data show that the prevalence of these diseases is increasing. Therefore, allergic rhinitis and asthma will become even more relevant health problems in the coming years. Asthma and allergic rhinitis frequently coexist and it is now well established that allergic rhinitis may be a significant risk factor for asthma. The only causative treatment of respiratory allergies is immunotherapy. SIT also has the potential advantage to interfere with the so-called 'allergic march'. Even if we currently have some data regarding the capability of SIT to reduce the risk of asthma developing in patients with seasonal allergic rhinitis [43,44], well-designed double-blind trials with an appropriate sample size are currently lacking. In the coming year, such trials (Grazax Asthma Prevention trial) will be available, giving the possibility to assess the real therapeutic role of SIT in the approach to treating respiratory allergic conditions.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Key issues

- Immunotherapy is the only treatment for allergy that has the potential to alter the natural course of this disease.
- Grazax® (ALK-Abello A/S, Hoersholm, Denmark), a standardized grass allergen extract, is formulated as an oral lyophilisate (tablet) for sublingual administration, containing 75,000 standardized quality tablet units.
- Several large sample size clinical trials, involving more than 1400 patients and conducted both in adults and in children, have evaluated the clinical efficacy of Grazax after one pollen season.
- Clinical data regarding the long-term effects of Grazax are also available.
- Grazax induces a mean reduction of 31, 36 and 29%, respectively, in daily rhinoconjunctivitis symptom scores and a mean reduction of 38, 45 and 40%, respectively, in daily rhinoconjunctivitis medication scores compared with placebo over the entire grass pollen seasons after 1, 2 and 3 years of treatment.
- Subjects treated with Grazax also had an increased number of well days and a relevant improvement in quality of life, and more subjects experienced excellent and complete rhinoconjunctivitis control in comparison with patients treated with symptomatic medications only.
- Treatment with Grazax is associated with a sustained and relevant increase in specific IgG4.
- Grazax is also associated with a carry-over effect, maintaining a clinical benefit at least 2 years after stopping the therapy.
- Grazax allergy immunotherapy tablet has shown to be an effective symptomatic treatment of allergic rhinoconjunctivitis with a disease modification.

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