



Grazax[▼] sublingual immunotherapy against grass pollen allergy



Summary

- Grazax[▼] offers an alternative to subcutaneous injection immunotherapy for grass pollen allergy.
- It should be taken daily for 16 weeks before, and continuously throughout, the grass pollen season (late May to August). Some efficacy may be obtained if taken 2–3 months before the season.
- It should be initiated only by physicians with experience in the treatment of allergic disease, and the first dose should be taken under medical supervision.
- Patients must have a positive skin prick test and/or specific IgE test to grass pollen before Grazax is initiated.
- In clinical trials, Grazax has been shown to produce a statistically significant reduction in symptoms and rescue medication vs. placebo. However, absolute benefits appear very modest, and the clinical significance is uncertain.
- Clinical and cost-effectiveness have yet to be established in comparison with subcutaneous immunotherapy.

Introduction

About 26% of the UK adult population have clinically confirmable allergic rhinitis; of these, about half are allergic to grass pollen.¹ Treatment with antihistamines and intranasal corticosteroids are the cornerstone of treatment, but are only of partial benefit, especially if symptoms are severe. For those who fail to respond to these treatments, allergen immunotherapy (desensitisation) by subcutaneous injection of allergen extracts is an option and may be effective for some patients.² When given for 3–4 years it can induce remission.³ However, because of the risk of anaphylactic shock, administration must be carried out where full facilities for cardio-respiratory resuscitation are immediately available.⁴

Sublingual immunotherapy for grass pollen allergy is now available in the UK as Grazax[▼] (ALK-Abelló) and may be provided as an alternative to injectable immunotherapy.⁵ Potentially, it offers a safer and more convenient means of administration, removing the need for repetitive visits to specialist centres for injections. In this article we consider the evidence for the safety and effectiveness of Grazax, and compare it with subcutaneous immunotherapy.

What is Grazax[▼]

Grazax is a once-daily sublingual tablet formulation containing 75,000 standardised quality units per tablet of Timothy grass (*Phleum pratense*) pollen allergen extract. It is only

licensed for use in adults with clinically relevant symptoms of pollen allergy who have been diagnosed with a positive skin prick test and/or specific IgE test to grass pollen.⁵ It needs to be taken four months before, and continuously throughout, the grass pollen season.⁵ In the UK, this season normally starts in late May and continues through to mid-August, with the main peak occurring usually in June and a second smaller peak typically occurring in early July.⁶ Grazax should only be initiated by physicians with experience in the treatment of allergic disease. Because of the possibility of side effects, it is recommended that the first dose is taken under medical supervision (20–30mins).⁵

What is the evidence of benefit?

The key evidence for the efficacy of Grazax in adults comes from two large, double-blind, placebo-controlled, randomised clinical studies of people with rhinoconjunctivitis.^{7,8} Statistically significant differences from placebo were identified with regard to symptom reduction and medication usage when given at least 16 weeks before the expected start of the grass pollen season.⁷ However, the differences were smaller and less certain when given approximately eight weeks prior to the expected grass pollen season.⁸ Both of these studies included adults with a history of grass pollen-induced allergic rhinoconjunctivitis and who had a positive skin prick test and elevated serum allergen-specific IgE to *Phleum pratense*. The results for the key endpoints of these studies follow.

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Study 1

A dose-finding study in 855 adults included a comparison of Grazax (75,000 standardised quality units per tablet, n=294) with placebo. Treatment was initiated about 8 weeks before the start of the grass pollen season, with 211 patients receiving Grazax for at least eight weeks before the season.⁸ Over the entire grass pollen season, there was no significant reduction in mean daily rhinoconjunctivitis symptom scores (Grazax 2.5, placebo 2.9, P=0.071), while the reduction in rescue medication usage scores just met the normally accepted criteria for statistical significance, i.e. P<0.05 (1.5 vs. 2.0, P=0.047).⁸ Subgroup analysis suggested that some efficacy may be obtained if treatment was initiated at least 8 weeks before the start of the grass pollen season.^{5,8}

Study 2

A subsequent study of 634 adults compared Grazax, initiated at least 16 weeks before the start of the grass pollen season, with placebo.⁷ Over the entire pollen season, mean daily rhinoconjunctivitis symptom scores (2.4 vs. 3.4) and medication scores (1.5 vs. 2.4) were both statistically significantly lower in the Grazax group compared with the placebo group (both P<0.0001). Other statistically significant differences (all P<0.0001) in favour of Grazax over placebo were identified for secondary outcomes, including the number of 'well-days' when rescue medication was not required (53% vs. 44%) and the mean daily patient-rated symptom scores (visual analogue scale, 12 vs. 18). Despite use of Grazax, the majority of patients in Study 2 used additional rescue medication at some point during the study (68% Grazax, 80% placebo).⁷ Although not mentioned in the published article,⁷ data presented in the Grazax Summary of Product Characteristics⁵ provide additional information on changes in disease-related quality of life. There was a statistically greater improvement in mean Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores with Grazax compared with placebo (1.08 vs. 0.84).⁵

What is the clinical significance?

Although the clinical trial results demonstrate a statistically significant difference between Grazax and placebo, the absolute changes in symptom and medication scores appear very modest in relation to the maximum scores achievable within the rating scales (0–18 and 0–30, respectively). However, identifying a large absolute and, thus, clearly clinically important difference was difficult, as the distribution of individual patient scores were heavily skewed towards the low end of the rating scales (i.e. fewer symptoms, less medication use) in the population studied [Personal communication, ALK-Abelló, February 2007] It is, therefore, uncertain whether or not the differences in

scores seen in this study represent a clinically significant benefit compared to symptomatic treatment alone.

Quality of life is an outcome of relevance and importance to patients, as it indicates the impact that the treatment has on their day-to-day physical and emotional well-being. The disease-related RQLQ is a validated instrument that considers six items (activities, emotions, sleep, non-nasal symptoms, practical problems, nasal symptoms), which are rated on a 7-point Likert scale. The overall rating score is the mean of the six item scores, which are rated equally.⁹ The 0.25 unit improvement seen in the mean overall score with Grazax relative to placebo in Study 2^{5,7} falls short of the 0.5 unit change that is considered a clinically important within-patient difference.⁹ In a recent Cochrane review, a meta-analysis of five placebo-controlled studies (four with grass pollen allergens) identified an improvement in the mean RQLQ score of 0.52 with subcutaneous immunotherapy for seasonal allergic rhinitis.¹⁰

An ongoing study is evaluating the efficacy of Grazax during three years of continuous treatment, with a 2-year follow up after cessation of treatment [Personal communication, ALK-Abelló, February 2007]. This will provide longer-term safety and efficacy data on its use beyond one season.

Although larger studies are required for confirmation, there is an indication from a small (n=114) double-blind, randomised study¹¹ that Grazax can be used safely in people with mild-to-moderate grass pollen-induced asthma and rhinoconjunctivitis. In this study, Grazax was initiated 10–14 weeks before the grass pollen season. Although asthma medication usage and symptom scores were similar in the Grazax and placebo groups, daily average rhinoconjunctivitis symptom scores (2.1 vs. 3.3, P=0.004) and medication scores (2.4 vs. 4.2, P=0.036) were statistically significantly lower in the Grazax group.

What about adverse effects?

According to the Summary of Product Characteristics, 70% of patients reported adverse events when treated with Grazax in clinical trials.⁵ However, these effects were mostly mild-to-moderate local reactions to the grass pollen allergen and of short duration. Oral pruritis was the most common; in Study 2, it was reported by 46% of patients who received Grazax, compared with 4% on placebo. There were five cases of Grazax-related adverse events (local angioedema/swelling/oedema) that led to patients being withdrawn from the trial. All of these events resolved satisfactorily after withdrawal of the drug, although treatment was required in some cases.⁷

How does Grazax compare with subcutaneous immunotherapy?

No comparative studies of Grazax with subcutaneous grass pollen allergen immunotherapy have been reported. Although the absolute reduction in mean symptom score of 1.0 (95%CI 0.7 to 1.3) for Grazax seen in Study 2⁵ does not appear dissimilar to that seen in the first year of subcutaneous therapy with 100,000 standardised quality units of Alutard grass pollen extract (1.3; 95%CI 0.6 to 1.9),¹² this provides only weak evidence for equivalence. Evidence from longer-term comparative studies is required before a judgement can be made of the relative risks and benefits compared with subcutaneous therapy, and whether or not Grazax offers a more cost-effective option.

The current cost of Grazax is £67.50 for 30 tablets. Assuming that it is taken for four months before, and three months during, the grass pollen season, this equates to an annual cost of

£472.50.¹² This is more expensive than the cost of one year of subcutaneous immunotherapy with Pollinex (£320).¹³

Conclusion

Published randomised clinical trial data suggest that Grazax is statistically significantly more effective than placebo in reducing rhinoconjunctivitis symptoms and the need for additional medication when given 16 weeks before, and continuously throughout, a single pollen season. Some benefit may be obtained if Grazax is initiated at least eight weeks before the season. However, in absolute terms the clinical benefits appear very modest in comparison with symptomatic treatment alone. Further information is required to establish the long-term safety and efficacy of Grazax when given over several seasons, and to identify whether or not there are significant benefits that justify its use ahead of subcutaneous immunotherapy.

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