

NEW DRUG EVALUATION

No.83

April 2007

GRAZAX[®]

Grazax[®] is a once-daily sublingual tablet licensed for adults with grass pollen-induced rhinoconjunctivitis. Although Grazax[®] significantly reduced the mean daily symptom scores and the use of rescue medication compared to placebo, 68% of patients still required rescue medication. There are currently insufficient data to support the use of Grazax[®] beyond one grass pollen season. The most commonly reported side effects were local allergic reactions in the mouth. Antihistamines and intranasal corticosteroids remain the first-line treatments for allergic rhinitis. Grazax[®] should only be considered after specialist review for severe grass pollen allergies (confirmed by positive skin-prick or specific IgE test) when other anti-allergy treatments have failed. It should not be used in patients with uncontrolled or severe asthma.

What is it?

Grazax[®] (*Phleum pratense*, ALK-Abelló) is a once-daily sublingual tablet containing standardised allergen extract of Timothy grass pollen (75,000 Standardised Quality units - Tablet (SQ-T)).¹ It is licensed for the treatment of grass pollen-induced rhinoconjunctivitis (hay fever) in adult patients with clinically relevant symptoms and a positive skin-prick test and/or specific IgE test to grass pollen. Treatment is initiated at least four months prior to the expected start of the grass pollen season and continued throughout the whole season. In the UK the season typically starts in late May and continues through to mid August, with the main peak usually occurring in June.² Some efficacy may be achieved if treatment is initiated two to three months before the season. If no improvement in symptoms is observed during the first pollen season there is no indication for continuing treatment during the second season.¹

How effective is it?

The efficacy of Grazax[®] in the treatment of seasonal allergic rhinoconjunctivitis has been assessed in two multicentre, double-blind, placebo-controlled trials. In the first study,³ 634 patients with a history of grass pollen-induced rhinoconjunctivitis for at least two years and confirmed IgE sensitivity (positive skin-prick test and serum-specific IgE) were randomised to receive sublingual Grazax[®] (75,000 SQ-T) or placebo once-daily. Patients with significant asthma outside the grass pollen season and those with rhinitis due to other allergens were excluded. Treatment was initiated at least 16 weeks before the anticipated start of the grass pollen season and continued throughout the season. The primary endpoints were the average self-rated rhinoconjunctivitis symptom and investigator-rated medication scores during the grass pollen season (rating scales 0-18, and 0-30, respectively). A total of 86% of patients completed the trial, with no major difference in the drop-out rate between the groups. Over the entire pollen

season, the mean daily 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 placebo (both $p < 0.0001$, respectively). Despite the use of Grazax[®] 68% of patients used additional rescue medication including antihistamines and intranasal corticosteroids compared with 80% of the placebo group.

In a second dose-ranging study with the same inclusion/exclusion criteria and primary outcome as above, 855 patients were randomised to once-daily Grazax[®] (2,500, 25,000 or 75,000 SQ-T) or placebo.^{4,5} Treatment was initiated approximately eight weeks before the grass pollen season and continued throughout. A total of 92% of patients completed the trial, with no major difference in the drop-out rate between the groups. In those taking the 75,000 SQ-T dose there was moderate but non-significant improvement in the mean daily symptom score (2.5 vs. 2.9, $p = 0.071$) and a marginally significant improvement in the medication score (1.5 vs. 2.0, $p = 0.047$). A *post-hoc* analysis in only those patients who started treatment at least eight weeks prior to the grass pollen season showed a significant reduction in the mean daily symptom and medication score in favour of Grazax[®] (2.5 vs. 3.2, $p = 0.002$ and 1.6 vs. 2.3, $p = 0.012$, respectively). However, the overall magnitude of improvement was similar to that in the whole trial population. The effect of Grazax[®] treatment on quality of life (QoL) was also examined in this study⁵ using the validated Juniper's Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).⁶ Overall, Grazax[®] treatment significantly improved QoL compared to placebo regardless of whether or not patients were using loratadine rescue medication ($p = 0.020$ and $p = 0.021$, respectively). Furthermore, Grazax[®] alone significantly improved QoL compared to loratadine alone ($p = 0.014$).

There are currently no published efficacy data beyond one grass pollen season although trials are ongoing.

How safe is it?

In studies using Grazax[®] 75,000 SQ-T daily 70% of patients reported adverse effects.^{1,7} Local allergic reactions in the mouth were common, as were throat irritation, sneezing and ear pruritis.^{1,3-5} In the majority of patients these reactions developed early in therapy, lasted from minutes to hours after each treatment and spontaneously resolved within one to seven days. More severe reactions reported in less than 1% of patients included angioedema, bronchospasm, and upper respiratory infection.¹ To date no anaphylactic reactions have been reported.

What other options are there?

Antihistamines and intranasal corticosteroids are the first-line treatments for allergic rhinitis.⁸ Current guidelines state that immunotherapy is an option for the treatment of seasonal allergic rhinoconjunctivitis only when other anti-allergy treatments have failed. Pollinex[®] (Allergy Therapeutics) is the only other grass pollen extract immunotherapy currently available and is administered via subcutaneous injection.

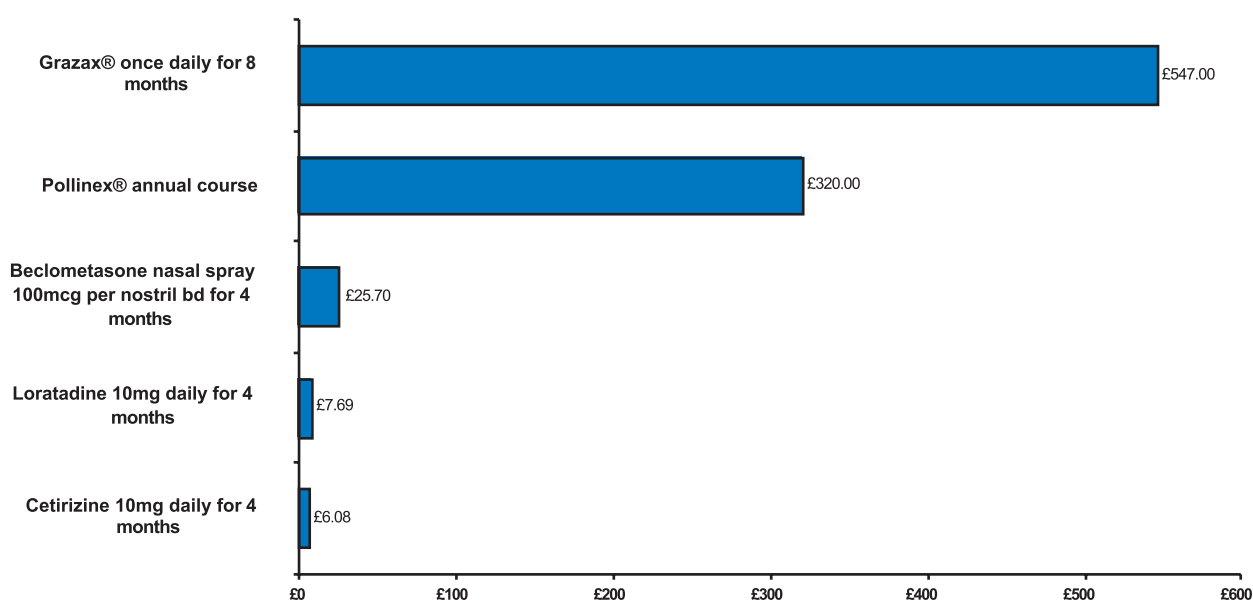
How much does it cost?

However, its use is limited to severe resistant cases due to the potential risk of anaphylaxis, and treatment should only be given where facilities for resuscitation are available.⁹

When should it be used?

Grazax[®] should only be considered for severe grass pollen allergies when other anti-allergy treatments have failed. It should not be used in patients with uncontrolled or severe asthma.¹ It should be initiated only by physicians with experience in the treatment of allergic diseases. Because patients require confirmation of IgE sensitivity it is anticipated that its use will initially be limited to specialist allergy clinics. There are insufficient data to support the use of Grazax[®] beyond one grass pollen season, and if no improvement in symptoms is observed during the first season there is no indication for continuing treatment during the second season.¹ Grazax[®] contains only standardised allergen extract of grass pollen; therefore rhinoconjunctivitis caused by other allergens such as tree pollen will not be covered.

Annual cost of treatment (Drug Tariff/ eMIMS, March 2007)



N.B. Doses shown for general comparison only and do not imply therapeutic equivalence.

REFERENCES

1. ALK-Abelló. Grazax 75,000 SQ-T oral lyophilisate. Summary of Product Characteristics. March 2007. <http://emc.medicines.org.uk> Accessed 13/03/07.
2. BBC. UK Pollen Index. <http://www.bbc.co.uk/weather/pollen/> Accessed 31/01/07.
3. Dahl R, Kapp A, Colombo G et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;118:434-40. (RCT)
4. Durham SR, Yang WH, Pedersen MR et al. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;117:802-9. (RCT)
5. Rak S, Yang WH, Pedersen MR et al. Once-daily sublingual allergen-specific immunotherapy improves quality of life in patients with grass pollen-induced allergic rhinoconjunctivitis: a double-blind, randomised study. *Qual Life Res* 2007;16:191-201. (RCT)
6. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy* 1991;21:77-83.
7. Medicinal Products Agency. Grazax - Public Assessment Report. http://www.lia.se/upload/43003/Sci_Discussion_Grazax.pdf Accessed 30/01/07.
8. PRODIGY guidance - Allergic rhinitis. http://cks.library.nhs.uk/allergic_rhinitis Accessed 31/01/07. (G)
9. MIMS. March 2007. Hyposensitisation agents. Ed Gowans J. Haymarket Publishing, London. p13-14.

KEY RCT - randomised controlled trial; G - guideline

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