

Standardised allergen extract of grass pollen from Timothy (*Phleum pratense*) 75,000 SQ-T per oral lyophilisate (Grazax[®]) No. (367/07)

ALK-Abelló Ltd

6 April 2007

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

Standardised allergen extract of grass pollen 75,000 per oral lyophilisate (Grazax[®]) is not recommended for use within NHS Scotland for the treatment of grass pollen induced rhinitis and conjunctivitis in adult patients with clinically relevant symptoms and diagnosed with a positive skin prick test and/or specific IgE test to grass pollen.

The place in the treatment of seasonal allergic rhinitis, the patient population and the long-term benefits of Grazax[®] still have to be fully established as evidence from only the first year of a three-year treatment programme has been published. The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

The licence holder has indicated their decision to resubmit.

Overleaf is the detailed advice on this product.

**Chairman
Scottish Medicines Consortium**

Indication

Treatment of grass pollen induced rhinitis and conjunctivitis in adult patients with clinically relevant symptoms and diagnosed with a positive skin prick test and/or specific IgE test to grass pollen. Lyophilisate should be initiated by a physician with experience in treatment of allergic disease.

Dosing information

Recommended dose for adults is one oral lyophilisate (75,000 SQ-T) daily. To enable patient and physician to discuss any side effects and possible actions it is recommended that the first oral lyophilisate is taken under medical supervision. No efficacy data on treatment beyond one grass pollen season is available yet. If no relevant improvement of symptoms is observed during the first pollen season, there is no indication for continuing the treatment during the second year.

Product availability date

02 January 2007.

Summary of evidence on comparative efficacy

Lyophilisate oral vaccine is a biological grass allergen immunotherapy administered sublingually. The aim of immunotherapy is to desensitise the immune system so that it does not respond when challenged with environmental allergens. The mechanism of action of this oral vaccine is not fully understood but is thought to involve three overall mechanisms. A suppression of the allergic response through an increase in the production of IgG antibodies, primarily the IgG4 subtype over IgE; possibly an induction of regulatory T cells (T cell tolerance); and due to the mucosa being rich in oral Langerhans dendritic cells the immune response elicited following oral immunisation is biased towards tolerance induction.

There have been two randomised, double-blind; placebo-controlled studies of oral lyophilisate 75000 SQ-T, in a total of 748 adult patients with at least a two year clinical history of significant grass pollen-induced allergic rhinoconjunctivitis, and confirmation of IgE sensitivity. The primary outcomes were the average rhinoconjunctivitis symptom and medication scores during the grass pollen season. Symptoms included runny nose, blocked nose, sneezing, itchy nose, gritty feeling/ red/itchy eyes and watery eyes, each symptom scored daily by the patient on a scale of 0-3 (0=no symptoms and 3=severe symptoms, giving a maximum possible score of 18). Patients had free access to relief medication that they used in a stepwise fashion depending on the persistence and severity of their symptoms. Use of this relief medication was then scored using predetermined criteria.

The pivotal study randomised 634 patients with moderate (44%) to severe (56%) allergy to either lyophilisate or placebo once daily, starting 16 weeks prior to the onset of the grass pollen season. Treatment continued all year round, and is planned to continue until after the end of the third grass pollen season. Permitted rescue medication included desloratadine (6 points/dose), budesonide nasal spray (1 point/per spray) and prednisone (1.6 points per 5mg). Results for the first grass pollen season have been published.

Over the entire grass pollen season, on average 58 days, lyophilisate significantly reduced the mean daily rhinoconjunctivitis symptom score by 30% compared with placebo (2.4(SD, 1.6) versus 3.4(SD, 2.2), $p<0.0001$) and the mean daily rhinoconjunctivitis medication score by 38% compared with placebo (1.5 (SD, 1.9) versus 2.4 (SD 2.5), $p<0.0001$).

The primary aim of the second trial was to confirm the safety of lyophilisate however efficacy endpoints were also reported. In this study, 114 patients with concomitant mild to moderate grass pollen-induced asthma and rhinoconjunctivitis were randomised (2:1) to lyophilisate or placebo once daily, for 10–14 weeks prior to, and throughout, the grass pollen season. Efficacy outcomes were the average daily rhinoconjunctivitis symptom and medication scores during the grass pollen season in the per protocol population. Permitted rescue medication included loratadine (6 points/dose), levocabastine eye drops (2 points/dose), budesonide nasal spray (1 point/puff), prednisone (1.6 points/5mg). For patients in the lyophilisate group, mean daily symptom scores over the whole grass pollen season were reduced by 37% ($p=0.004$) compared with placebo. Mean rescue medication scores were also significantly reduced in the lyophilisate group by 41%, $p=0.0036$. About 33% of patients in each group did not use rescue medication.

Summary of evidence on comparative safety

In the safety study of 114 patients, the primary safety endpoints were the average daily asthma medication and symptom scores during the pollen season in the randomised population. Asthma symptoms included cough, wheeze, chest tightness (dyspnoea) and exercise-induced symptoms. Permitted rescue medication for asthma included salbutamol (2 points/200 μ g dose), fluticasone inhaler (2 points/250 μ g dose), prednisone (1.6 points/5mg). Prior to the grass pollen season asthma medication and symptom scores were low and similar between treatment groups. During the grass pollen season asthma medication and symptom scores were slightly higher but still similar between groups. The mean difference in asthma medication score was less than 0.1 and mean asthma symptom score 0.3. There is no comparative safety information, but in placebo-controlled studies the most commonly reported adverse events in the oral lyophilisate group were oral pruritus in 50% of patients, throat irritation in 19%, mouth oedema in 15% and ear pruritus in 13%. In many patients oral pruritus is transient (minutes to hours) and after 1-7 days tends to spontaneously subside.

Only one drug-related adverse event was reported as serious in the clinical trial programme. The event (oral swelling at the uvula) was not systemic or life-threatening, did not require treatment, and the subject continued on the study medication.

Summary of clinical effectiveness issues

While there are many symptomatic treatments for seasonal allergy, immunotherapy is the only therapy that potentially can affect the disease process. Clinical experts highlighted that for certain groups of patients there is an unmet need in the management of severe seasonal allergic rhinitis. Subcutaneous immunotherapy is an effective treatment for seasonal allergic rhinitis failing to respond to pharmacological measures. Following three years with this therapy benefits persist for at least a further three years after discontinuation of treatment. However, due to the risk of severe systemic reactions this treatment is only available through specialist referral centres with facilities for resuscitation available. Subcutaneous immunotherapy has a systemic effect on the immune system, and although the mechanism of action is not fully understood it is suggested that sublingual immunotherapy will similarly lead to allergy remission, and long-term efficacy.

However there is no direct comparison of sublingual and subcutaneous immunotherapy for grass pollen allergy. A Cochrane review of sublingual immunotherapy concluded that it can significantly reduce both rhinitis symptoms and the requirement for anti-allergic medication, although due to the difficulty in assessing the magnitude of effect it was not possible to make direct comparison with injected immunotherapy.

The key studies were both of double-blind, placebo design but as around half of the patients on active therapy reported pruritus of the mouth with a high incidence of throat irritation, mouth oedema and ear pruritus, it is possible that these adverse events may have confounded the blinding. How patients with other allergens along with grass pollen will benefit from this treatment is not known as patients with allergic rhinitis requiring medication caused by allergens other than grass were excluded from the studies. There have been no reported severe systemic reactions in the clinical trial programme but the safety population of 1423 patients is still relatively small for capturing a rare reaction. Advantages for this treatment are the potential for home treatment, the lack to date of any severe systemic adverse events and the potential to alter disease course. Therefore sublingual immunotherapy is expected to be more widely available than subcutaneous therapy. However the requirement to take medication daily for three years to achieve maximum benefit, against symptomatic treatment only during the grass pollen season raises issues of compliance and it is difficult to anticipate the patient population who will comply and who will be eligible for treatment.

Although the pivotal study was designed to determine the primary efficacy end points for a period of one year some patients opted to continue treatment during years two and three. In a press release the company have announced positive results from the second treatment season in the pivotal study, with outcomes in 350 patients showing a mean reduction in symptom scores of 36% and a mean reduction in the use of rescue medication of 46%; an improvement of 6% and 8% respectively, on the first season results. At this stage it is unclear what proportion of the reduction in patients completing year two compared to year one is for opting out and what proportion is for drop out due to side effects or lack of efficacy.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis based on the protocol of the pivotal randomised controlled trial (RCT), comparing oral lyophilisate with the types of rescue medication commonly available to primary care prescribers. Assuming results from the first year of the RCT also applied to the second and third year of treatment and that this treatment conferred six further years of benefit after treatment ended, the estimated cost per QALY gained was £9,129.

The economic evaluation reflected the RCT protocol i.e. patients with a history of the disease used oral lyophilisate after anti-histamines. Scottish secondary care clinicians consulted said the product would be used in patients with severe symptoms uncontrolled by current treatments. However, the economic evaluation does not consider oral lyophilisate as an alternative to subcutaneous immunotherapy, at a late stage of the treatment process. The manufacturer's budget impact suggested the medicine would be used in secondary care in the first year but would be prescribed by GPs with experience of allergy medicines thereafter. No further explanation was offered of which GPs would qualify.

The symptom scores in the clinical trial suggest the patients may have had relatively mild disease: this is of concern in the economic model because the results are interpreted as providing support for moderate to severe disease.

The main issues with the clinical evidence used were that the first year results were extrapolated to the second and third year of the RCT with no evidence to support this assumption; no drop-out rate was assumed despite patients having to take the medicine every day irrespective of their level of symptoms. A strength was that EQ5D data were collected directly as part of the RCT. However, it appears that two-thirds of the QALY gain

arises outside the grass pollen season and the manufacturer has not provided a robust explanation for why this would be the case.

Resource use and costing were generally presented in a transparent way. There were some small criticisms but sensitivity analysis showed that these would make little difference to the results. The results were analysed and presented in a clear way, but the sensitivity analysis could have considered the use of results from the first year of the RCT as a basis for treatment in years 2 and 3.

In summary, concerns about where in treatment the medicine would be used, the generalisability of the clinical trial data to more severe cases, the lack of results from the second and third years of the trial, the extent of extrapolation, and the finding that two-thirds of the QALY gain occurs at a time when patients would not be expected to be experiencing symptoms anyway suggest that the uncertainty around the cost-effectiveness estimate is very substantial.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

There are no published guidelines although there are a number of consensus documents and recommendations of good practice published.

Additional information: comparators

Allergen avoidance, non-sedating antihistamines, corticosteroid nasal sprays, antihistamine nasal sprays, sodium cromoglycate and ipratropium nasal sprays, antileukotrienes, subcutaneous immunotherapy with grass or tree pollen extract.

Additional information: costs

Drug	Dose	Cost for 90 days (£)	Cost per annum (£)
Grass pollen lyophilisate, oral	One 75,000 SQ-T* daily	202.50	821.29
Grass or tree pollen extract injection (Pollinex®)	Four subcutaneous doses	na	320
Loratadine	10mg daily	6.18	na
Certirizine	10mg daily	4.89	na
Azelastine nasal spray	One spray into each nostril twice daily	24.18	na
Mometasone nasal spray	One - two sprays in each nostril once daily	23.49 – 39.15	na
Beclometasone nasal spray	Two sprays into each nostril twice daily	20.56	na
Budesonide nasal spray	Two sprays into each nostril once daily	17.96	na
Sodium cromoglycate nasal	One application into each	9.10-13.65	na

spray	nostril 2-4 times daily		
Ipratropium nasal spray	Two sprays into each nostril 2-3 times daily	18.20-27.30	na
Montelukast	10mg daily	86.69	

* Standardised Quality units Tablet (SQ-T); na – not applicable

The prices quoted are from eVadis accessed on the 31st January 2007. Doses are for general comparison and do not imply therapeutic equivalence.

Additional information: budget impact

The manufacturer estimates the gross cost of oral lyophilisate will be £164k in year 1 rising to £821k in year 5, based on its use in patients with severe and unresponsive symptoms treated in specialist centres.

The number of patients was assumed to be 200 in year 1 rising to 1,000 in year 5. This was based on an assumption that the medicine would be used in secondary care in the first year but with primary care use commencing in year two. One secondary care expert supported these figures but other experts stated that a significant minority of patients with rhinitis in the community have poor control (about 10%) or are dissatisfied with current treatment (about 40%). If oral lyophilisate were widely available from primary care prescribers the numbers of patients who might be eligible could be very significant (several tens of thousands). However, not all patients who seek treatment will want to take it once they became aware of the long-term nature of the treatment. Others may drop-out from treatment.

Overall, the budget impact was highly uncertain, with the risk it might be considerably greater than predicted if there were substantial primary care use.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 22 March 2007.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

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(a)

Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. Allergy 2006; 61: 185–190

ALK-Abello Press Release: ALK-Abello announces positive second year results form clinical study with Grazax® www.alk-abello.com

Wilson DR Torres Lima M and Durham SR. Sublingual immunotherapy for allergic rhinitis: a systematic review and meta-analysis Allergy 2005;60;4-12