Scottish Medicines Consortium

Re-Submission

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

ALK-Abelló Ltd

7 December 2007

The Scottish Medicines Consortium 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 resubmission

standardised allergen extract of grass pollen 75,000 SQ-T 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.

Although modest clinical benefit has been shown, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

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.

Dosing information

Recommended dose for adults is one oral lyophilisate (75,000 standardised quality units per tablet (SQ-T)) daily.
Sublingual grass allergen extract treatment should only be initiated by physicians with experience in treatment of allergic diseases.

Date of licensing

26 October 2006

Product availability date

2 January 2007

Summary of evidence on comparative efficacy

Lyophilisate oral vaccine (containing standardised allergen extract of Timothy grass pollen) 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 is thought to involve a competitive antibody response towards grass with an increase in the production of IgG.

The pivotal, placebo-controlled, double blind study recruited 634 patients (18 to 65 years) with a clinical history of grass pollen-induced allergic rhinoconjunctivitis of ≥ 2 years with moderate (44%) to severe (56%) symptoms interfering with daily activities or sleep despite anti-allergic treatment. Patients were required to have a positive skin prick test response (wheal diameter ≥ 3mm) and specific IgE to *Phleum pratense,* cellulose acetate membrane precipitant (CAP) class ≥ 2. Patients were randomised equally to grass allergen extract oral lyophilisate 75,000 SQ-T or placebo taken once daily, starting 16 weeks before the expected start of the grass pollen season and planned to continue until the end of the third grass pollen season followed by 2 years of follow up. The primary outcomes were the average rhinoconjunctivitis symptoms score and the average rhinoconjunctivitis medication score. Symptoms which included runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes and watery eyes were scored daily by the patient on a scale of 0 (no symptoms) to 3 (severe symptoms) with a maximum daily symptom score of 18. All patients had access to stepwise rescue medication including desloratadine (6 points per dose), budesonide nasal spray (1 point per spray) and prednisone (1.6 points per 5mg). The results for the first grass pollen season have been published and unpublished results are available for the second grass pollen season. Treatment for the first grass pollen season was completed by 546 subjects. Grass allergen extract significantly reduced the mean daily rhinoconjunctivitis symptom scores by 30% (2.4 (SD, 1.6) versus 3.4 (SD, 2.2) and the mean rhinoconjunctivitis medication score by 38% (1.5 (SD, 1.9) versus 2.4 (SD, 2.5) compared to placebo. Secondary endpoints included well days, defined as days without intake of rescue medication and a symptom score of ≤ 2. The percentage of well days in the grass pollen season was significantly greater with grass allergen extract than with placebo.

At the end of the first pollen season, 351 patients consented to continue treatment for a further two years, with 195 patients withdrawing. At the end of the 2-year continuous treatment period grass allergen extract significantly reduced the mean daily rhinoconjunctivitis symptom scores by 36 % (2.4 versus 3.8) and the mean rhinoconjunctivitis medication score by 46% (1.7 versus 3.2) compared to placebo.

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

In the first year of the pivotal study, 84% (n=265/316) of patients receiving grass allergen extract and 64% (n=205/318) of patients receiving placebo reported at least one adverse event. The majority were mild to moderate in severity and application site-related. The most commonly reported adverse events were oral pruritus (50%), throat irritation (19%), mouth oedema (15%) and ear pruritus (13%). In many patients oral pruritus is transient (minutes to hours) lasting up to 7 days. The 4% (n=24/634) of patients who had adverse events resulting in withdrawal recovered without the use of adrenaline. Five cases of treatment-related withdrawal were initiated by the investigator and included: angioedema of the tongue; angioedema of the lips, pharyngeal hyperaemia, cough and mild dyspnoea; pharynx oedema; and swelling in throat and angioedema of the lips.

*Other data were also assessed but remain commercially confidential.**

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. Subcutaneous immunotherapy (SCIT) is an effective treatment for seasonal allergic rhinitis failing to respond to pharmacological measures. Following three years of SCIT therapy, benefits persist for at least a further three years. Sublingual immunotherapy may similarly lead to allergy remission.

Pollen allergen extract treatment is taken continuously for relief of symptoms that are only present 2-3 months of the year; therefore continued compliance may be an issue and would require considerable patient commitment. In the pivotal study, despite treatment, additional rescue medication was used by 68% of patients versus 80% in the placebo group.

After observation for 20-30 minutes following the first administration, grass allergen extract oral lyophilisate can be taken at home. Other grass allergen immunotherapies are given by subcutaneous injection on 6 occasions each year. In addition, patients must be observed for at least 60 minutes in an area where full cardiorespiratory resuscitation facilities are available.

The study drug contains only standardised allergen extract of grass pollen, therefore rhinoconjunctivitis caused by other allergens such tree pollen will not be covered. The proportion of patients affected by just one allergen and the proportion of patients who have cross-over allergy is unknown although SMC expert opinion suggests <10% of patients will be mono-sensitised to grass pollen.

Although the placebo tablet was similar in taste, smell and appearance to the grass allergen extract, the continued blinding of the study may have been compromised by 50% of patients experiencing oral pruritus with the grass allergen extract.

One of the primary endpoints was the mean rhinoconjunctivitis symptom score with a maximum theoretical value of 18. Considering that the patients recruited had moderate to severe rhinoconjunctivitis symptoms, the change in mean treatment effect scores appear modest. The applicant suggests that this can be attributed to daily variation in the level of airborne grass pollens and the variability of the individual patient's daily activities and exposure to pollen. However, with such a low mean value it is difficult to assess the clinically meaningful benefit of this treatment. The European Medicines Agency (EMEA), in their guidance on the clinical development of medicinal products for the treatment of allergic rhinoconjunctivitis, recommend as a primary endpoint for preventative medication 'days of freedom from symptoms or in the event of symptoms occurring the number of days of no or minimal symptoms as predefined.' In the pivotal study, the number of well days was investigated as a secondary endpoint.

Although long-term effects are yet to be established, the results of the second year do appear to suggest continued reduction in the mean daily rhinoconjunctivitis symptom scores and the mean daily rhinoconjunctivitis medication scores.

*Other data were also assessed but remain commercially confidential.**

Summary of comparative health economic evidence

The manufacturer presented three comparisons in the health economic analysis:

- Lyophilisate oral vaccine continuous treatment against symptomatic treatment;
- Lyophilisate oral vaccine seasonal treatment against symptomatic treatment;
- Lyophilisate oral vaccine continuous treatment against pre-seasonal SCIT.

The comparisons with symptomatic treatment were cost-utility analyses and drew efficacy data in terms of quality of life values and resource use data from the pivotal trial. Quality of life values were derived by modifying the results reported within a paper within the literature, rather than directly derived from trial data.

Seasonal use was assumed to require only 7 months of treatment with lyophilisate oral vaccine. Continuous treatment with lyophilisate oral vaccine was assumed to last for 3 years with no drop outs, the benefit from the first year of treatment being continued over the 3 years of treatment and an assumed 6 additional years when no treatment would be required.

The comparison with SCIT relied upon a literature survey, but no good trials were uncovered for SCIT. As a consequence, clinical equivalence was assumed. Lyophilisate oral vaccine was assumed to require one additional GP appointment, while SCIT required 6 hospital outpatient visits.

The resulting cost- effectiveness estimates were:

- £22,597 per QALY for seasonal use compared to symptomatic treatment;
- £13,693 per QALY for continuous use compared to symptomatic treatment;
- Dominance for continuous use compared to SCIT treatment, since the net drug cost of £501 was more than offset by drug administration savings of £772.

These results were sensitive to:

- The duration of the North European pollen season
- The assumed duration of treatment, with the WHO recommending 3 to 5 years for continuous treatment
- The assumed duration of continuation of benefit after treatment, and that the full benefit was maintained over this period

- The cost of hospital outpatient visits for the comparison with SCIT

There were also a number of weaknesses in the analysis:
- not considering the possible subgroups of severe and moderate grass pollen allergy
- treatment of dropouts and inclusion of adverse events only during the pollen season rather than across the entire treatment period
- questionable and non-transparent derivation of the annual QALY gain from a published study as there was no direct quality of life data available for the North European pollen season, as defined within the submission

As a consequence, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Summary of patient and public involvement

Patient Interest Group Submission: Joint application from Education for Health and Allergy UK

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: previous SMC advice

In April 2007 following a full submission, standardised allergen extract of grass pollen 75,000 per oral lyophilisate (Grazax®) was 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.

Additional information: comparators

Allergen avoidance, non-sedating antihistamines, corticosteroid nasal sprays, antihistamine nasal sprays, sodium cromoglicate and ipratropium nasal sprays, antileukotrienes, subcutaneous immunotherapy with grasses and rye extract.

Cost of relevant comparators

Drug	Dose regimen	Cost per treatment pre grass pollen season (£)	Cost per 60 day*[3] grass pollen season (£)	Cost per year (£)
Grass allergen extract	**One 75,000 SQ-T*[1] lyophilisate daily orally**	**252*[2]**	**135**	**819**
Grass and rye pollen extract	Four subcutaneous doses pre pollen season	320	N/A	N/A
Montelukast	10mg daily orally	N/A	58	N/A
Sodium cromoglicate	One spray into each nostril two to four times daily	N/A	25-50	N/A
Azelastine	One spray into each nostril twice daily	N/A	17	N/A
Ipratropium	Two sprays into each nostril two to three times daily	N/A	12-18	N/A
Mometasone	Two sprays into each nostril once daily	N/A	13	N/A
Budesonide	Two sprays into each nostril once daily	N/A	11	N/A
Beclometasone	Two sprays in each nostril twice daily	N/A	5	N/A
Loratadine	10mg daily orally	N/A	4	N/A
Cetirizine	10mg daily orally	N/A	3	N/A

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 4/10/2007. *[1]Standardised Quality units Tablet (SQ-T) *[2]Pre grass pollen treatment is for 16 weeks with grass allergen extract oral lyophilisate. *[3]Taken from the pivotal trial involving a number of pollen regions; the average grass pollen season lasted 57.8 days. N/A is not applicable.

Additional information: budget impact

The manufacturer estimated a gross drug cost of £175k in year 1, rising to £1.3M by year 5. This was based on 4,700 eligible patients of whom 1,200 currently receive treatments that would be displaced by lyophilisate oral vaccine. Market share was assumed to be 200 new patients in the first year (4%) rising to 1500 patients (32%) by the fifth year. The net drug cost was estimated at £142k in year 1, rising to £1.1M by year 5.

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 19 November 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.

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:* <http://www.scottishmedicines.org.uk/>

The undernoted references were supplied with the submission. The reference below, shaded grey, is additional to information supplied with the submission.

Dahl R, Kapp A, Colombo G, de Monchy J, Rak S. Emminger W, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablet for seasonal allergic rhinoconjunctivitis. Journal of Allergy and Clinical Immunology 2006 Aug;118(2):434-40.

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