HAUTE AUTORITÉ DE SANTÉ

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OPINION

7 November 2007

GRAZAX 75,000 SQ-T oral lyophilisate
B/30 (CIP 378 011-6)
B/100 (CIP 378 012-2)

Applicant: ALK ABELLO A/S Laboratories

Standardised allergen extract of pollen from Timothy grass (*phleum pratense*) 75,000 SQ-T per oral lyophilisate.

List I

Date of Marketing Authorisation: February 8, 2007

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for hospital use

Health Technology Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Standardised allergen extract of grass pollen from Timothy grass (*phleum pratense*) 75,000 SQ-T per oral lyophilisate

1.2. Indication

Treatment of grass pollen induced rhinitis and conjunctivitis in adults with clinically relevant symptoms and diagnosed with a positive skin prick test and/or specific IgE test to grass pollen.

1.3. Dosage

The recommended dose for adults is one oral lyophilisate (75,000 SQ-T) daily. Clinical data on immunotherapy with GRAZAX in children and adolescents (<18 years) and the elderly (>65 years) is not available.

GRAZAX treatment must only be initiated by physicians with experience in the treatment of allergic diseases.

In order to enable patient and physician to discuss any side effects and possible actions it is recommended that the first oral lyophilisate dose be taken under medical supervision for approximately 20 to 30 minutes.

At the present time no efficacy data on treatment with GRAZAX beyond one grass pollen season following treatment initiation is available. If no significant improvement of symptoms is observed during the first pollen season, there is no indication for continuing the treatment during the second year.

To observe the investigated clinical effect during the first pollen season, it is recommended that treatment be initiated at least 4 months prior to the expected start of the grass pollen season and continued throughout the whole grass pollen season. If treatment is initiated only 2-3 months before this season some efficacy may still be obtained.

GRAZAX is an oral lyophilisate. The oral lyophilisate tablet should be taken from the blister unit with dry fingers, and immediately placed under the tongue, where it will disperse instantaneously. Swallowing should be avoided for at least 1 minute.

Food and beverage should not be taken in the 5 minutes following administration of the medicine.

The oral lyophilisate must be taken immediately after opening the blister unit.
(See SPC)

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification 2006:

V: Various
01: Allergens
A: Allergens
A: Allergen extracts
02: Grass Pollen

2.2. Medicines in the same therapeutic category

Specially prepared allergens for individuals (APSI) are governed by the decree of 23 February 2004, not having the status of medicines. APSI are administered subcutaneously or sublingually.

2.3. Medicines with a similar therapeutic aim

The symptomatic treatment of rhinoconjunctivitis is undertaken through oral antihistamine products, topical corticosteroids, and sometimes through cromones and decongestants.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

Study GT-8[1]

Objective: To compare the efficacy and safety of GRAZAX (n=316) to placebo (n=318) in adults with grass pollen induced rhinoconjunctivitis.

Methodology:

- Randomised, double-blind, placebo-controlled study.
- Inclusion criteria: adults between 18 and 65 years with at least 2 years of grass pollen induced rhinoconjunctivitis episodes, a positive prick test result (skin papule diameter > 3mm), positive specific IgE test to *Phleum pratense* allergen.
- Primary efficacy endpoints:
  - Rhinoconjunctivitis symptoms score (6 symptoms, each rated from 0 to 3: nasal discharge, nasal obstruction, sneezing, irritation, itchy red eyes and tearing).
  - Medication score (number of days and dosage of rescue medication).
- Duration of the study: treatment was initiated at least 16 weeks before the anticipated start of the grass pollen season and was continued during the entire grass pollen season.

Results:

- The results presented are for the first year; the study protocol provided for a follow-up over 2 years.
- Baseline patient's characteristics were similar in both groups. 25% of these patients (161/634) were asthmatic.
- The number of study withdrawals was 46 in the placebo group (8 of which were due to adverse events) and 42 in the GRAZAX group (16 of which were due to adverse events). Analysis was therefore conducted on 286 patients in the placebo group and 282 patients in the GRAZAX group.

1 Dahl R et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis" J Allergy Clin Immunol 2006; 118: 434-40

- Mean daily symptom score was 2.4 in the treatment group and 3.4 in the placebo group, representing a 30% ($p<0.05$) difference
- Furthermore, 68% of patients of the treatment group used a rescue medication compared to 80% in the placebo group ($p<0.05$).

Table 1: Results

	Placebo (n=286)	GRAZAX (n=282)	Δ (CI 95%)
Symptoms Score	3.37	2.36	-1.01 [-1.33; -0.69]
Medication Score	2.23	1.38	-0.85 [-1.20; -0.50]

This randomised, double-blind study demonstrated GRAZAX's greater efficacy compared to placebo on symptom and medication score. The clinical significance of a single point difference on a scale of 18 is debatable.

Data on second pollen season year (provided by the laboratory):
- Among the patients of the first year, 351 (189 of the GRAZAX group and 162 of the placebo group) accepted to continue the study for a second year
- The study was conducted under the same conditions as for the first year,
- Results: symptom score was 3.76 in patients under placebo compared to 2.4 in GRAZAX patients ($p<0,05$); medication score was 3.19 under placebo and 1.74 under GRAZAX ($p<0,05$)

3.2. Adverse events

Very frequently reported undesirable effects (>1/10) in patients treated with GRAZAX were local oral allergic reactions, mostly mild to moderate, that spontaneously subsided within 1 to 7 days, even in cases of continued treatment.
Other very frequently reported undesirable effects (>1/10) were ear pruritus, throat irritation and sneezing, oedema and oral pruritus.
Possible systemic reactions included: flashes (vasomotor flushes), urticaria-type pruritus, hot flashes, or general discomfort. In case of severe systemic reactions, a physician should be contacted immediately.

3.3. Conclusion

In a randomised, double-blind study, using available data from two pollen seasons, GRAZAX was shown as having greater efficacy than placebo for symptom score (significant reduction by 30%). Patients under GRAZAX treatment also had less recourse to rescue medications for symptomatic relief.
The clinical relevance of a single point reduction on a scale of 18 for such generally benign disorders is debatable.
Very frequently reported adverse events in patients treated with GRAZAX were oral allergic reactions, generally of mild to moderate intensity that spontaneously subsided within 1 to 7 days, and a few systemic reactions such as flush or discomfort.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Allergic rhinitis and conjunctivitis represent frequent disorders that affect quality of life in light of the disturbances they entail.

The efficacy / undesirable effect ratio is average.

GRAZAX is intended as a preventive therapy.

This is a second-line therapy.

> Public health benefit:
> Allergic rhinoconjunctivitis represents a mild burden on public health. Improving its management does not constitute a necessity falling within the scope of an identified public health priority. Based on the available data, the expected impact of Grazax on quality of life, compared to the current therapeutic management of allergic rhinoconjunctivitis, cannot be determined. Therefore Grazax is not expected to have any public health benefit.

The actual benefit of GRAZAX in this indication is moderate.

4.2. Improvement in actual benefit:

Taking into account both the quantity of observed effect in the presented study and the absence of reliable comparative data, the Transparency Committee considers that GRAZAX does not provide any improvement in actual benefit (IAB V) under the current therapeutic use.

4.3. Therapeutic use

Allergic rhinitis and conjunctivitis represent frequent disorders that may affect quality of life as a result of the disturbances they entail .

Treatment is based on three processes: elimination of the allergen where possible, treatment of symptoms and desensitisation.

Treatment of symptoms is undertaken through oral antihistamines, local corticosteroids, and sometimes cromones and decongestants.

Desensitisation requires several conditions:

- The patient must be motivated, the discomfort experienced sufficiently significant and the treatment of symptoms unsatisfactory
- The allergen must be identified through questioning the patient, as well as skin and/or blood tests
- A good allergen must be available. Desensitisation has been proven effective for dust mites, Alternaria mould, and pollens (grass, parietary)

The parenteral route remains, to this day, the benchmark treatment. However, for a number of years now, the sublingual method is also available.

GRAZAX may be offered to patients with episodes of rhinoconjunctivitis for at least 2 years, when antihistamine or corticosteroid treatment of symptoms has proven ineffective. If significant improvement is not obtained, continuation of the treatment the following year is not justified.

4.4. Target population

The target population of GRAZAX comprises adults with grass pollen induced rhinitis or conjunctivitis (confirmed with a positive skin test and/or specific IgE) that is sufficiently significant and incapacitating to require recourse to a desensitisation treatment.

It may be estimated from the following data:

- Grass induced allergic rhinoconjunctivitis, clinically encountered between the months of May and August, affects approximately 12% of the French population.
- Approximately half of those affected are adults; clinical data on children and adolescents (< 18 years) and the elderly (> 65 years) are not available.
- Of this population, one quarter (expert opinion) could benefit from a GRAZAX type treatment

Based on this information, the GRAZAX target population comprises approximately 900,000 individuals.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for hospital use and various public services in the Marketing Authorisation.

Packaging: Appropriate for the prescription conditions.

Reimbursement rate: 35%