HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

22 July 2009

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

Applicant: ALK ABELLO

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

List I

ATC code: V01AA02

Date of Marketing Authorisation: 08 February 2007 (mutual recognition)

Reason for request: Reassessment of the IAB level following the submission of additional information.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

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

1.2. Indication

“Treatment of grass pollen induced rhinitis and allergic conjunctivitis in adults with clinical symptoms attributable to grass pollen allergy and diagnosed with a positive grass pollen skin test and/or the presence of IgEs specific to grass pollen.”

1.3. Dosage

“The recommended dose for adults is one oral lyophilisate (75,000 SQ-T) daily. Clinical experience on immunotherapy with Grazax in children or adolescents (< 18 years of age) and the elderly (> 65 years of age) is lacking.

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

In order to enable the patient and the physician to discuss any adverse effects and decide on what action to take, the first oral lyophilisate should be taken under medical supervision (20-30 minutes).

Efficacy data is available for a period of continuous treatment of two years. If no relevant improvement of symptoms is observed during the first pollen season, there is no justification for continuing the treatment.

In order to obtain the desired effect in the first grass pollen season, it is recommended that treatment be initiated at least four months before the date on which the grass pollen season is expected to start. A certain degree of efficacy may still be observed if treatment is not started until two to three months before the grass pollen season. Continuous daily administration of Grazax for at least two years gradually produces an immunomodulating effect. The recommended duration of treatment is three years.

Grazax is an oral lyophilisate. The oral lyophilisate should be taken from the blister unit with dry fingers and immediately placed under the tongue, where it instantly dissolves.

Swallowing should be avoided for at least one minute. Food and beverage should not be taken within five minutes after taking the medicine.

The oral lyophilisate must be taken immediately after opening the blister.”

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009):

V: Various
V01: Allergens
V01A : Allergens
V01AA: Allergen extracts
V01AA02: Grass pollen

2.2. Medicines in the same therapeutic category

Allergens prepared for a single individual (APSIs) governed by the decree of 23 February 2004 are not classed as proprietary medicines. APSIs can be administered subcutaneously or sublingually.

2.3. Medicines with a similar therapeutic aim

Symptomatic treatments of various forms of rhinoconjunctivitis: oral antihistamines, local corticosteroids, cromones and decongestants.

3. REMINDER OF THE COMMITTEE'S PREVIOUS OPINION

Opinion of 7 November 2007

The actual benefit of GRAZAX is moderate.

Improvement in actual benefit:
In view of the quantitative effect observed in the study presented, and given the lack of reliable comparative data, the Transparency Committee is of the opinion that GRAZAX offers no improvement in actual benefit (IAB V) within the current therapeutic management strategy.

4. ANALYSIS OF AVAILABLE DATA

The manufacturer has submitted the results of the extension study GT-08: 3rd year of treatment (2007) and of the first year of monitoring patients not receiving treatment (2008). The results for the first two years of treatment (2005 and 2006) had been presented to the Transparency Committee and were taken into consideration in its opinion published in 2007[1].

4.1. Efficacy: study GT-08

Method:

- Randomised, double-blind, placebo-controlled study.
- Inclusion criteria: adults aged between 18 and 65 who had been suffering attacks of rhinoconjunctivitis brought on by grass pollen for at least two years, a positive prick test result (wheal diameter > 3 mm), presence of IgEs specific to the *Phleum pratense* allergen.

- Primary efficacy endpoints:
  - mean daily rhinoconjunctivitis symptoms score (six symptoms, each scored on a scale of 0 to 3: nasal discharge, nasal obstruction, sneezing, irritation, eyes reddened and inflamed, and ocular discharge).
  - mean drug use score (the permitted treatments and dosages were defined according to the severity of the rhinoconjunctivitis and asthma symptoms, and a score was allocated to each treatment).
- Duration of the study:
  - For the first part of the study (2005 pollen season), treatment started at least 16 weeks before the projected start of the grass pollen season and continued throughout the 2005 season.
  - Subjects agreeing to take part in the extension to the study were required to continue with treatment for two more years (2006 and 2007) and to be monitored during 2008 but not to receive any treatment during that year.

Results

- The characteristics of patients in both groups were similar on inclusion. The efficacy results are shown in *table 1*:

Table 1: efficacy results

Year	2005 Placebo/GRAZAX	2006 Placebo/GRAZAX	2007 Placebo/GRAZAX	2008 (no treatment) Placebo/GRAZAX
N included- *n analysed**	318-*286*/ 316-*282*	162-*144*/ 189-*172*	138-*127*/ 170-*160*	126-*115*/ 157-*142*
Mean symptoms score	4.14 / 2.85†	3.76 / 2.40†	3.59 / 2.56‡	3.63 / 2.68§
Difference in means (%) [95% CI]	1.29 (31%) [0.90 ; 1.68]	1.36 (36%) [0.86 ; 1.86]	1.04 (29%) [0.52 ; 1.56]	0.95 (26%) [0.40 ; 1.50]
Mean drug use score	2.68 / 1.65†	3.19 / 1.74†	3.04 / 1.82§	3.25 / 2.32 ||
Difference in means (%) [95% CI]	1.03 (39%) [0.63 ; 1.44]	1.45 (46%) [0.75 ; 2.16]	1.22 (40%) [0.52 ; 1.92]	0.93 (29%) [0.14 ; 1.72]

*patients who completed their monitoring log; †: p<0.001 anova; ‡ : p=0.0001 anova; §: p=0.0007 anova; || : p=0.0215 anova;

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

The mean symptom scores and drug use scores in the GRAZAX group were significantly lower than those observed in the placebo group in each year of treatment and in the treatment-free year of monitoring.

4.2. Adverse effects

Adverse events occurred less often in the third year of the study than in the first two years.
During the 3rd year of treatment, 64% of patients in the GRAZAX group and 64% of patients in the placebo group reported at least one adverse event. Fifteen per cent of the adverse events reported by patients in the GRAZAX group were regarded as being attributable to the treatment, compared with 8% in the placebo group. They were mild to moderate in intensity. The most common adverse events regarded as being attributable to the treatment were: oral pruritus, ear pruritus, oedema of the mouth, irritation of the throat. One subject withdrew from the study following an adverse event of moderate intensity regarded as being attributable to the treatment (attack of asthma).

The SPC for GRAZAX specifies that the adverse effects reported very frequently (>1/10) were local allergic reactions of the mouth, which were generally slight to moderate in intensity. In most cases the reactions appeared at an early stage of treatment, lasted for a few minutes to several hours, and tended to disappear spontaneously within the following one to seven days.
The following adverse effects were mentioned during the first year of treatment:

- Very common (>1/10): ear pruritus, throat irritation, sneezing, oedema of the mouth, oral pruritus,
- Common (>1/100 <1/10): headache, oral paraesthesia, ocular pruritus, conjunctivitis, cough, asthma, pharyngitis, irritation of the nasal passages, constriction of the pharynx, oropharyngeal swelling, dyspepsia and nausea, oral discomfort, swelling of the tongue or glossodynia, skin pruritus.
- Uncommon (>1/1,000 <1/100): dizziness, palpebral oedema, bronchospasm, laryngeal discomfort, pharyngeal oedema, angiooedema with oedema of the face, oral cavity and pharynx, urticaria

The SPC also specifies that “The onset of systemic symptoms may include flushing, intensive itching in palms of hand and soles of the feet, and other areas of the body (like a nettle rash). Sense of heat, general discomfort and agitation/anxiety may also occur. In the event of severe systemic reactions, angioedema, difficulty in swallowing, difficulty in breathing, changes in voice or feeling of fullness in the throat a physician should be contacted immediately.”

4.3. Conclusion

The efficacy and safety of GRAZAX have been tested in a randomised, double-blind, placebo-controlled study incorporating three years of treatment and one treatment-free year of monitoring. Each year this proprietary drug was significantly more effective than the placebo in respect of a mean daily score of rhinoconjunctivitis symptoms, even in the treatment-free year of monitoring. It should be noted that the difference in the mean efficacy scores ranged from 0.9 to 1.5, on a scale of 0 to 18.
Patients on GRAZAX also made less frequent use of rescue treatments to address symptoms.
The adverse effects reported very frequently by patients being treated with GRAZAX were oral allergic reactions, generally slight to moderate in intensity, which disappeared spontaneously within the following one to seven days. Severe systemic reactions (urticaria, angiooedema, pharyngeal oedema) were reported in rare instances.

5. TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Reassessment of actual benefit

The actual benefit of GRAZAX is low.

5.2. Reassessment of the improvement in actual benefit (IAB)

The Transparency Committee took account of the small quantitative effect which GRAZAX has been shown to have on the treatment of rhinitis and conjunctivitis triggered by grass pollen. In addition, the APSIs used in this treatment have not undergone assessment or received marketing authorisation as they are not proprietary drugs. There is therefore no comparative data or any assessment of the efficacy of the APSIs. Finally, there is no alternative to GRAZAX which has been shown to be effective.

Consequently, the Committee is of the opinion that GRAZAX offers a minor improvement in actual benefit (IAB IV) in the management of allergic rhinitis and conjunctivitis triggered by grass pollen in patients not suffering from an allergy linked to multiple allergens who do not respond adequately to treatments that address the symptoms, i.e. antihistamines and/or corticosteroids administered by any route.

5.3. Therapeutic use

- Therapeutic strategy[2]

Treatment is based on three interventions: removing the allergen where possible, symptomatic treatment, and desensitisation.
Symptomatic treatment features oral or local antihistamines, local corticosteroids, sometimes cromones, and decongestants.
Several conditions must be met for desensitisation treatment to be given:

- The patient must be motivated, the discomfort experienced must be sufficiently severe, and the result of symptomatic treatment must be inadequate.
- The allergen must be identified by interviewing the patient and performing skin and/or blood tests.

Desensitisation can be carried out by injection or the sublingual route.

- Role of the product in treatment strategy

GRAZAX is a second-line treatment for patients who do not respond adequately to symptomatic treatment.

5.4. Target population

The target population for GRAZAX is comprised of adults with allergic rhinitis or conjunctivitis brought on by grass pollen (confirmed by a skin test or the presence of specific IgEs) who do not respond adequately to symptomatic treatments (antihistamines and/or corticosteroids administered by any route) and whose condition is sufficiently severe and disabling to require the use of desensitisation treatment.

It can be estimated based on the following data:

- The prevalence of allergic rhinitis in France among the general adult population is 24.5%[2], which, according to projections of the French population in 2008 produced by the French National Institute for Statistics and Economic Studies (INSEE), amounts to 9.7 million people aged between 18 and 65.
- The Thales database shows that, of the 4.0 million patients aged over 18 treated for allergic rhinitis, 1,200,000 patients were taking both antihistamines and local corticosteroids.

2 Bousquet J, Khaltaev N *et al.* Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Update (in collaboration with the World Health Organization, GA[2]LEN and AllerGen). Allergy 2008; 63:S8-160

- Around 50% of individuals with a clinical diagnosis of allergic rhinitis are thought to be allergic to grass pollen[3]. This means that there are probably 600,000 adults suffering from allergic rhinitis caused by grass pollen being treated with antihistamines and local corticosteroids.

A study performed in England in 1998 (White[4]) found that 54% of patients said that their symptoms were not adequately controlled despite the prescription of local antihistamines and corticosteroids. A French study conducted in 2008[5] indicated that 5% of patients taking antihistamines and 8% of patients using local corticosteroids were dissatisfied with their treatment.

In the light of this information, the target population for GRAZAX would be 80,000 to 320,000 individuals.

5.5. Transparency Committee recommendations

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

The Committee considers that a study should be set up to examine the following aspects under actual conditions of use:
- the characteristics or patients being treated with Grazax: sociodemographic data, antecedents, comorbidities, diagnosis and confirmation of diagnosis, history and severity of the disease, past treatments, etc.;
- the characteristics of prescribing physicians (discipline, practice type, etc.);
- the details of prescription (indication, dosage, concomitant treatments including antihistamines, local corticosteroids, cromones, decongestants, how long before the grass pollen season did treatment start, etc.) and the therapeutic strategy;
- level of treatment compliance;
- frequency of cessation of treatment and the reasons;
- frequency of adverse effects;

The duration of the study, to be decided by an independent scientific committee, must be justified and must be long enough to meet the Committee's request, and in particular must take account of the seasonal nature of allergic rhinoconjunctivitis triggered by grass pollen.

Packaging: Appropriate for the prescription conditions.

Reimbursement rate: 35%

3 Bachau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur. Respir.J 2004; 24: 758-764

4 White P, Smith H, Baker N et Al.Symptom control in patients with hay fever in UK general practice: how well are doing and is there a need for allergen immunotherapy? Clin Exp allergy 1998;28:266-70

5 Demoly P, Didier A *et al.* Physician and patient survey of allergic rhinitis in France: perceptions on prevalence, severity of symptoms, care management and specific immunotherapy. Allergy. 2008; 63: 1008-10014