HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

16 February 2011

GRAZAX 75 000 SQ-T, oral lyophilisate
B/30 (CIP code: 378 011-6)
B/90 (CIP code: 381 472-0)
B/100 (CIP code: 378 012-2)

Applicant: ALK-ABELLO

Allergen extract of grass pollen from Timothy
ATC code: V01AA02

List I

Date of Marketing Authorisation: 8 February 2007 (mutual recognition)
Extension of indication to children aged five and over: 2 April 2010

Reason for request: Reassessment of the AB in adults 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

“Disease-modifying treatment of grass pollen induced rhinitis and conjunctivitis in adults and children (5 years or older), with clinically relevant symptoms and diagnosed with a positive skin prick test and/or specific IgE test to grass pollen.
Children should be carefully selected for treatment”

1.3. Dosage

The recommended dosage for adults and children (aged five and over) is one oral lyophilisate (75,000 SQ-T) daily. Clinical experience on immunotherapy with Grazax in children aged under five and the elderly (aged over 65) is lacking.
GRAZAX treatment should only be initiated by physicians with experience in treatment of allergic diseases and capable of treating allergic reactions.
Children should be treated by physicians with experience in the treatment of allergic diseases in children. Great care must be taken in selecting children who might benefit from this treatment, taking account of the expected level of efficacy in this population.
In order to enable the patient and the physician to assess the significance of any adverse effects and decide on what action to take, the first oral lyophilisate should be taken under medical supervision (20-30 minutes).
If no significant improvement of symptoms is observed during the first pollen season, there is no justification for continuing the treatment.
The recommended duration of treatment is three years. Efficacy data is available for adults covering a period of three years treatment and one year follow-up. No data relating to GRAZAX treatment for more than a single grass pollen season is available for children.
Clinical effect in the first grass pollen season is expected when treatment is initiated at least 4 months prior to the expected start of the grass pollen season. If treatment is initiated 2-3 months before the season some efficacy may also be obtained 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 (2010)

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

2.2. Medicines in the same therapeutic category

2.2.1 Strictly comparator medicines

ORALAIR (the application for inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services is currently under review).

2.2.2 Not-strictly-comparator medicines

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

2.3. Medicines with a similar therapeutic aim

Symptomatic treatments of allergic rhinitis and conjunctivitis: oral antihistamines, local or oral corticosteroids, cromones and decongestants.

3. REMINDER OF THE COMMITTEE'S PREVIOUS OPINIONS

Opinion of 07 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.

Opinion of 22 July 2009

(Request for reassessment of the IAB level following the submission of additional information).

The actual benefit of GRAZAX is low.

Improvement in actual benefit:
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 medicinal products. 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 and who do not respond adequately to treatments that address the symptoms, i.e. antihistamines and/or corticosteroids administered by any route.

Opinion of 21 July 2010

(Extension of indication to children aged five and over)

The actual benefit of this proprietary medicinal product is low.

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. The APSIs used in this treatment have not undergone assessment or received marketing authorisation as they are not proprietary medicinal products. There is therefore no comparative data or any assessment of the efficacy of the APSIs.

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 children aged five and over suffering from an allergy linked exclusively to grass pollen and who do not respond adequately to treatments that address the symptoms, i.e. antihistamines and/or corticosteroids administered by any route.

4. ANALYSIS OF AVAILABLE DATA

The pharmaceutical company has submitted data from the fifth year of study GT-08, covering the second year of treatment-free follow-up.
This randomised, double-blind, placebo-controlled study on adults included a treatment phase (three years: 2005, 2006 and 2007) and a treatment-free follow-up phase (2008 and 2009).
The results of the first two years of treatment (2005 and 2006) were submitted to the Transparency Committee in 2007 (opinion dated 7 November 2007).
The results for the final year of treatment (2007) and the first year of treatment-free follow-up (2008) were submitted to the Transparency Committee in 2009 (opinion dated 22 July 2009).

4.1. Efficacy

Methods:

- Placebo-controlled, randomised, double-blind study. Double-blinding was maintained throughout the five years of the study.
- Inclusion criteria: adults aged between 18 and 65 who had been suffering attacks of rhino-conjunctivitis 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 rhino-conjunctivitis 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 medication 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).
- Treatment:
  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 continued with treatment for two more years (2006 and 2007) and were monitored during 2008 and 2009 without receiving any treatment in those two years.

Results

Reminder: the results for the first four years of the study are given in *table 1*.
The study was originally to be conducted over one pollen season, but it was subsequently decided to amend the protocol and extend the study to a total of three years of treatment and two years of follow-up without treatment. Of the 546 patients who took part in the first year of the study, 68 had been recruited by centres which closed at the end of the first year and 127 did not agree to take part in the study extension.

Table 1: efficacy results for the first four years of the study

Year	2005 Placebo/GRAZAX	2006 Placebo/GRAZAX	2007 Placebo/GRAZAX	2008 (treatment-free) Placebo/GRAZAX
N included- *n analysed**	318-*286*/ 316-*282*	162-*144*/ 189-*172*	138-*127*/ 170-*160*	126-*115*/ 157-*142*
Mean symptom score	4.14 / 2.85†	3.76 / 2.40†	3.59 / 2.56‡	3.63 / 2.68§
Difference between the 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 medication score	2.68 / 1.65†	3.19 / 1.74†	3.04 / 1.82§	3.25 / 2.32 ||
Difference between the 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;

258 patients took part in the fifth year of the study. Their distribution and the results of this fifth year are given in *table 2*.

Table 2: efficacy results for the fifth year of the study

	Placebo	Grazax
N included- *n analysed**	113 / *104*	145/ *137*
Mean symptom score	3.4	2.56
Difference between the means (%) [95% CI]	0.84 (24.8%) [0.28 ; 1.4] †	
Mean medication score	3.04	2.42
Difference between the means (%) [95% CI]	0.62 (20.3%) [-0.15; 1.38] ‡	

* : with data during the pollen season; † : p=0.0037 ANOVA; ‡ : ANOVA not significant

4.2. Adverse effects

The most common adverse events occurring in the five years of the study that were regarded as attributable to treatment were local adverse effects such as oral pruritis and oedema of the tongue.
A total of 42 serious events were recorded during the five years of the study, 24 in the placebo group and 18 in the GRAZAX group. None was regarded as being attributable to treatment. No anaphylactic reaction occurred during the five years of the study.
No long-term adverse effects related to treatment occurred during the years of treatment-free follow-up.

In total, since GRAZAX was placed on the market, 31 cases of anaphylactic reaction (or systemic allergic reactions) were recorded. 17 of these were serious, six of which took place between two days and eight weeks after the start of treatment.

The SPC for GRAZAX specifies that the adverse effects reported very frequently (>1/10) were local allergic reactions of the mouth, which were generally mild 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 adverse effects noted during clinical trials on adults were:

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

Rare cases of severe systemic allergic reactions have been reported since the product was placed on the market. This underlines the importance of medical supervision at the start of treatment.
Systemic reactions may include: flushes, intense itching of the palms of the hands, soles of the feet and other parts of the body (similar to urticaria). A sensation of heat, general discomfort and agitation/anxiety may also occur. Patients must contact a doctor without delay if they experience severe systemic reactions, angioedema, difficulty in swallowing, difficulty in breathing, changes in voice, hypotension or laryngeal discomfort.

4.3. Conclusion

The efficacy and tolerance of GRAZAX have been tested in a randomised, double-blind, placebo-controlled study incorporating three years of treatment and two treatment-free follow-up years.

Only a third of the patients initially recruited took part in the second treatment-free year. In these patients, this proprietary medicinal product was statistically more effective than the placebo in respect of the mean daily rhinitis and conjunctivitis symptoms score, but the difference between the mean efficacy scores was only 0.84 for a score of 0 to 18. There was no difference between GRAZAX and the placebo in respect of the mean score.
The adverse effects observed very frequently (>1/10) in patients being treated with GRAZAX were oral allergic reactions, generally mild to moderate in intensity, which lasted from a few minutes to several hours and which generally disappeared spontaneously within the following one to seven days. Severe systemic reactions, angiooedema and pharyngeal oedema were reported in rare instances.

5. TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Actual benefit

Allergic rhinitis and allergic conjunctivitis are common conditions which can impair quality of life because of the inconvenience they cause.

This proprietary medicine provides preventive treatment.

The efficacy/adverse effects ratio is moderate.

> Public health benefit
> Allergic rhinitis represents a small public health burden. Improving its management is not a need which is part of an identified public health priority. The clinical data available for the proprietary medicinal product Grazax does not allow the anticipated impact of Grazax in terms of morbidity and quality of life to be estimated as compared with current therapeutic management of allergic rhinitis. Consequently, Grazax is not expected to benefit public health in this indication.

It is a second-line therapy.

There are treatment alternatives which have not been evaluated (APSIs).

The actual benefit of GRAZAX is low.

5.2. 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. It should be noted that the APSIs used in this treatment have not undergone assessment or received marketing authorisation as they are not proprietary medicinal products. 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 who are allergic solely to grass pollens and 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

Allergic rhinitis and allergic conjunctivitis are common conditions which can impair quality of life because of the inconvenience they cause.

5.3.1 Therapeutic strategy[1]

Treatment is based on three approaches: removing the allergen where possible, symptomatic treatment, and allergenic immunotherapy.

Symptomatic treatment features oral or local antihistamines, local or oral corticosteroids, sometimes cromones, and decongestants.

Allergenic immunotherapy requires that:

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

Allergenic immunotherapy has proven to be effective for mites, Alternaria mold and pollens (grass and pellitory pollens).

5.3.2 Therapeutic use of the proprietary medicinal product

GRAZAX can be offered as a second-line therapy when symptomatic treatment by antihistamines and/or corticosteroids has proven inadequate or is used too often. If no significant improvement in symptoms is seen after a year of treatment, there is no justification for continuing treatment the following year.

5.4. Target population

The adult target population for GRAZAX is made up of patients diagnosed with allergic rhinitis caused by grass pollen (confirmed by skin tests and/or the presence of specific IgEs) which is not sufficiently controlled by symptomatic treatments.

The prevalence of allergic rhinitis in France among the general adult population is estimated at 24.5%[1], which, according to projections of the French population in 2010 produced by the French National Institute for Statistics and Economic Studies (INSEE), amounts to approximately 9.8 million people aged between 18 and 65.

The study conducted by Bauchau et al.[2] found grass pollen allergy (presence of specific IgEs) in 52% of patients diagnosed with allergic rhinitis. Among patients diagnosed with allergic rhinitis during the study, 46% had already been diagnosed before the study and 85% of these patients were receiving drug treatment. 79% of these were receiving treatment. On this basis, the population receiving treatment for allergic rhinitis caused by grass pollen is estimated at approximately 1.5 million adults.

Almost 30% of the patients who were receiving treatment[3] report their treatment to be insufficiently effective: this is equivalent to 450,000 adults.

The target population for GRAZAX is estimated at approximately 450,000 adults.

5.5. Transparency Committee recommendations

The Transparency Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indication and at the dosage in the Marketing Authorisation.

The Transparency Committee recommends that the use of the proprietary medicinal product GRAZAX should be subject to the following conditions: that treatment should be initiated by doctors experienced in the treatment of allergic diseases, that patients should take their first

1 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

2 Bauchau V. & Durham S. R., Prevalence and rate of diagnosis of allergic rhinitis in Europe 2004, Eur. Respir. J., 24, 758-764

3 Didier A. et al. La rhinite allergique : le point de vue du patient 1999, [Allergic rhinitis: the patient's point of view] Rev. fr. Allergol., 39, 171-185

dose of oral lyophilisate under medical supervision for twenty to thirty minutes, so that the patient and the doctor can evaluate the significance of any adverse effects and decide on what action to take.

The Committee considers that a study should be set up to examine the following aspects under actual conditions of use:

- the characteristics of 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;
- the compliance rate for the treatment;
- the frequency of discontinuations and the reasons for them;
- the 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.

The Committee finds it regrettable that the reimbursement rate for other treatments which are not proprietary medicinal products and which have never been evaluated is 65%.

Packaging: Appropriate for the prescription conditions.

Reimbursement rate: 15%