HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

21 July 2010

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

Applicant: ALK ABELLO

standardised allergen extract of grass pollen from Timothy (*Phleum pratense*) 75,000 SQ-T per oral lyophilisate
ATC code: V01AA02

List I

Date of Marketing Authorisation: 8 February 2007 (mutual recognition)
Extension of indication: 2 April 2010

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use in the extension of indication for children aged five and over.

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 dose 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 the 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 (see section 5.1).
In order to enable the patient and the physician to discuss any side effects and decide on what action to take, the first oral lyophilisate should be taken under medical supervision (20-30 minutes).
If no relevant 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 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 comparable medicines

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

2.2.2 Not strictly comparable medicines

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 rhinitis and conjunctivitis: oral antihistamines, local or oral corticosteroids, cromones and decongestants.

3. ANALYSIS OF AVAILABLE DATA

The pharmaceutical company submitted a phase III study.

3.1. Efficacy: study GT-12

Methods:

Randomised (1:1), double-blind, placebo-controlled study.

Main inclusion criteria:

- patients aged 5 to 16 years,
- with a history of grass pollen induced allergic rhinoconjunctivitis (with or without asthma) having received treatment during the previous grass pollen season,
- testing positive to a skin test performed with the allergen *Phleum pratense* (papula diameter ≥ 3 mm) and the presence of IgEs specific to the allergen *Phleum pratense* (IgE ≥ class 2).

Main exclusion criteria:

- history of seasonal allergy attributable to another allergen during, or partly overlapping, the grass pollen season,
- history of year-round allergy with or without asthma, caused by an allergen to which the patient is regularly exposed and for which symptomatic treatment is given,
- history of severe or uncontrolled asthma,
- history of severe atopical dermatitis, chronic urticaria or angio-oedema

Investigational treatment: GRAZAX or placebo taken once a day for at least 16 weeks before the 2007 pollen season and throughout that entire pollen season. The pollen season was defined as the period starting and finishing with three consecutive days on which the pollen count was equal to or greater than 10 grains/m^3.

Associated treatments permitted if the symptoms persisted, only with the investigator's agreement:

- first-line treatments: oral and ocular antihistamines to treat the symptoms of rhinoconjunctivitis, and short-acting beta-agonists to treat the symptoms of asthma,
- second-line treatments: nasal corticosteroids for the symptoms of rhinoconjunctivitis and inhalational corticosteroids for the symptoms of asthma,
- third-line treatment: oral corticosteroid.

Primary efficacy endpoints:

- rhinoconjunctivitis symptom score: the intensity[1] of each of the six symptoms (runny nose, blocked nose, sneezing, itchy nose, gritty feeling or red/itchy eyes, and watery
- eyes was graded on a scale of 0 to 3 and recorded each day by each patient for the entire pollen season;
  The score for a single patient was the mean of the scores given each day of the season. The symptom score for a group was the mean of the scores of each patient.
- rhinoconjunctivitis medication score: this was calculated in the same way as the symptom score, based on a predetermined medication use scoring scale. The maximum daily score was 34.

Main secondary endpoints

- rhinoconjunctivitis symptom score during the peak pollen period (a period of 15 days when the total average pollen count was highest),
- medication score during the peak pollen period,
- percentage of “good days”. A “good day” was a day on which no drugs were taken to treat symptoms, and the symptom score was ≤ 2,

Statistics:
ANOVA for values with normal distribution, non-parametric Wilcoxon test with Hodges-Lehmann estimate for other values.

Results:

Patients included:
A total of 253 patients took part: 126 in the GRAZAX group and 127 in the placebo group.
The characteristics of patients included are shown in *table 1*.

Table 1: patients included

	GRAZAX (n=126)	PLACEBO (n=127)
Gender % (n)		
Female	34% (43)	35% (44)
Male	66% (83)	65% (83)
Age (years)		
Mean ± standard deviation	10.1 ± 2.9	10.1 ± 3.1
Median (extended)	10 (5-16)	10 (5-16)
Intensity of grass pollen allergy		
Slight	7% (9)	7% (9)
Moderate	62% (78)	69% (88)
Severe	31% (36)	24% (30)
Length of time that patients had been suffering from grass pollen allergy (years)		
Mean ± standard deviation	3.5 ± 2.6	3.4 ± 2.4
Median (extended)	2.9 (0.5-12.6)	2.7 (1.6-4.6)
Asthma % (n)	42% (53)	39% (50)

The average length of the pollen season was 81.4 ± 23.9 days (42 to 126 days).
The average length of treatment before the start of the pollen season was 17.1 weeks (7.9 to 23.4).

Efficacy analyses were performed on patients whose symptom and medication scores were available for at least one day during the pollen season (117 patients in the active group and 121 in the placebo group).

1 0= no symptoms, 1= mild symptoms, 2= moderate symptoms, 3= severe symptoms.

Primary efficacy endpoints

- symptom score during the pollen season: the results are shown in *table 2*

Table 2: symptom score*

	GRAZAX (n=117)	PLACEBO (n=121)
Adjusted mean [95% CI]	2.18 [1.82-2.58]	2.80 [2.45-3.18]
Difference between placebo and GRAZAX [95% CI]	0.62 [0.10-1.15] p = 0.0215*	

* parametric analysis comparing the adjusted means; CI: confidence interval

- medication score (to treat rhinoconjunctivitis) during the pollen season: the results are shown in *table 3*

Table 3: rhinoconjunctivitis drug use score*

	GRAZAX (n=117)	PLACEBO (n=121)
Median [95% CI]	0.78 [0.43-1.30]	1.19 [0.74-2.64]
Hodges-Lehmann estimate (placebo-GRAZAX) [95% CI]	0.31 [0.01-0.68] p=0.016	

* non-parametric analysis; CI: confidence interval

Secondary endpoints

The results for these endpoints are presented in *table 4*

Table 4: main secondary endpoints

	Grazax n=117	Placebo n=121	Absolute difference, p
Rhinoconjunctivitis symptoms score, peak pollen period*	2.84	3.91	1.07 ; p=0.006†
medication score, peak pollen period*	0.87‡	2.40‡	0.80 ; p=0.0013 §
Percentage of "good days", entire season	51.57	42.33	9.24 ; p=0.0225†

*: period of 15 days with the highest total average pollen count; †: parametric analysis; ‡: median; §: non-parametric analysis - Hodges-Lehmann estimate (placebo-GRAZAX)

3.2. Adverse effects

Study GT-12

Tolerance was studied for the population receiving at least one GRAZAX or placebo tablet.

The most common adverse events regarded as being probably or possibly attributable to treatment are shown in *table 5*

Table 5: adverse effects

	Grazax n=117	Placebo n=121
All adverse effects (%, n patients)	53% (67)	29% (37)
Oral pruritus	32% (40)	2% (3)
Throat irritation	10% (12)	2% (2)
Swollen lips	7% (9)	0
Cough	5% (6)	2% (3)
Withdrawal from the trial because of adverse effects	2% (3)*	0

* One case of labial herpes + swollen tongue + dyspnoea + oral pruritus + tongue irritation, one case of facial swelling, one case of oral pruritus + throat irritation + migraine.

No serious adverse events regarded as attributable to treatment occurred.

SPC and PSUR
The SPC for Grazax refers to rare cases of severe systemic allergic reaction having been reported since the product was placed on the market.
The most recent PSUR, covering the period from 1 August 2009 to 31 January 2010, mentions three new cases of anaphylactic reaction in children, two of which were serious. Patient exposure to Grazax (all ages) during this period amounted to 9,439 treatment-years.

3.3. Conclusion
Study GT-12, which was a randomised, double-blind placebo-controlled study, investigated the efficacy of GRAZAX as disease-modifying treatment on the progress of allergic rhinitis and conjunctivitis triggered by grass pollen in children aged five to sixteen. It showed a significant difference in favour of Grazax compared to placebo in respect of:
- the score for allergic rhinoconjunctivitis symptoms triggered by grass pollen for the whole of the pollen season (2.18 vs. 2.80). It should be noted that the maximum possible symptom score was 18.
- the rhinoconjunctivitis medication score (0.78 vs. 1.19). The maximum possible score was 34.
The most common adverse effects were oral pruritus, throat irritation, swollen lips and cough. Three children withdrew from the trial because of adverse effects. No serious adverse effects regarded as attributable to treatment occurred.

The SPC and most recent PSUR for Grazax refer to rare cases of severe systemic allergic reactions and anaphylactic reactions.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

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

This proprietary medicinal product is intended to provide prophylactic treatment.

The efficacy/adverse effects ratio is low.

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 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 with respect to this indication.

There are treatment alternatives.

The actual benefit of this proprietary product is low.

4.2. 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. 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.

Consequently, the Committee is of the opinion that GRAZAX provides 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.

4.3. Therapeutic use

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

Therapeutic strategy[2] :

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

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

Specific Immunotherapy treatment 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.

Specific Immunotherapy has proven to be effective for mites, Alternaria fungus and pollens (grass and pellitory pollens).

The injection route is currently the standard treatment, but for a few years practitioners have been able to offer their patients medicines taken sublingually as well.

The proprietary product's therapeutic use
GRAZAX can be offered as a second-line treatment when symptomatic treatment by antihistamines and/or corticosteroids has proven inadequate. If no significant improvement in symptoms is seen, treatment should not be continued the following year.

4.4. Target population

The target population for GRAZAX is made up of children aged five and over with a confirmed diagnosis of allergic rhinitis caused by grass pollen which is not sufficiently controlled by symptomatic treatments.
The ISAAC study[3] carried out in Western European countries estimated the prevalence of allergic rhinitis at 8.5% among children aged six to seven and 14.4% among children aged thirteen to fourteen. Extrapolating this data to the French population of children aged between five and twelve and between thirteen and seventeen[4], gives a figure of around one million children and adolescents suffering from allergic rhinitis in France.

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
3 Aït-Khaled N. & al., Global map of the prevalence of symptoms of rhinoconjunctivitis in children : the international study of asthma and allergies childhood (ISAAC) phase three 2009, Allergy, 64, 123-148
4 Population of children aged five to twelve in France on 1 January 2010: 6,359,968; population of adolescents aged twelve to seventeen in France on 1 January 2010: 3,906,288 (Source: http://www.insee.fr)

The study conducted by Bauchau et al.[1] found grass pollen allergy (presence of specific IgEs) in 52% of patients diagnosed with allergic rhinitis. 54% of these patients had been diagnosed prior to the study and 79% were receiving treatment[5].
On the basis of this data, the number of children and adolescents being treated for allergic rhinitis caused by grass pollen is estimated at around 250,000.
Almost 30% of the patients who were receiving treatment[6] report their treatment to be insufficiently effective: a total of about 70,000 children and adolescents.
The paediatric target population for GRAZAX is estimated at around 70,000.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicinal products approved for hospital use and various public services in the marketing authorisation's extension of indication and dosage.

In accordance with article L. 5123-2 of the public health code, the Committee considers that GRAZAX should be first administered only by physicians experienced in the treatment of allergic diseases.

As with use in adults, 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;
- 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.

4.5.1 Packaging: Appropriate for the prescription conditions.

4.5.2 Reimbursement rate: 15%

5 Bauchau V. & Durham S. R., Prevalence and rate of diagnosis of allergic rhinitis in Europe 2004, Eur. Respir. J., 24, 758-764
6 Didier A. & al., La rhinite allergique : le point de vue du patient 1999, Rev. fr. Allergol., 39,171-185