LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Grazax / Grazura

allergen extract from *Phleum pratense*

SE/H/612/MR / SE/H/613/MR

This module reflects the scientific discussion for the approval of Grazax and Grazura. The procedure was finalised at 2006-09-25. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

ALK-Abelló A/S has applied for a marketing authorisation for Grazax, an oral lyophilisate tablet, 75000 SQ-T. The active substance is an allergen extract of pollen from Timothy Grass, *Phleum pratense*. The mechanism of action most probably involves an immunomodulatory action. The product is indicated for "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".

Grazura is a duplicate application to Grazax.

II. QUALITY ASPECTS

II.1 Introduction

Grazax is presented in the form of oral lyophilisate tablets containing extract of Timothy Grass pollen. The excipients are fish gelatine and mannitol. The tablets are packed in aluminium blister cards with removable aluminium foil in an outer carton box.

II.2 Drug Substance

The drug substance is a frozen allergen extract derived from extraction of the source material, grass pollen *Phleum pratense* (Timothy Grass), followed by purification, clarification and freezing.

Each batch of drug substance is tested relative to the current In-House Reference with regard to qualitative (antigen profile; allergen profile; protein profile) and quantitative (major allergen activity; total allergenic activity) parameters. The specification is in agreement with the Ph Eur monograph "Allergen products". The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the shelf-life.

II.3 Medicinal Product

Grazax/Grazura, 75 000 SQ-T, oral lyophilisate, is formulated using excipients described in the current Ph Eur. The only material of animal origin in the product is fish gelatine. The supplier of the fish gelatine does not produce any bovine or porcine gelatine, and there is thus no possibility of cross contamination from these sources. There is thus *no TSE/BSE issue.* The applicant states that the manufacturing process of fish gelatine contains several steps where a virus would be eliminated in the unlikely event that it could be present in the raw materials. Extensive testing of the raw material, heat extraction, ultrafiltration and heat sterilisation are also stated to ensure the safety of the fish gelatine. There are thus *no viral safety issues.*

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC (30 months), with no special storage conditions.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

The grass pollen extract contains a number of allergens, composed primarily of polypeptides and proteins of which some bear carbohydrate structures. In the present preclinical file, studies on primary pharmacodynamics in mice revealed dose-dependent increased titres of systemic circulating allergen-specific antibodies (total IgG (4x) > IgE (2-3x)) and no allergen-specific activation of T cells in the spleen from the sublingual prophylaxis per se (5000-25000-125000 SQ U/animal: 0.07-0.3-1.7x clinical dose). The average multiple of increased total IgG was similar in HD mice as reported in man (about 5x). Following sensitisation (3x IP-injected alum adsorbed allergen), the prophylactic mice had significantly lower titres of circulating IgE, higher levels of serum IgG and mucosal-secreted antibody titres (IgA in the bronchoalveolar fluid), and lower allergen-specific T cell activation in the spleen as compared with animals without prophylaxis. These changes of immune suppression (IgE and splenic T cell) / activation (serum IgG and mucosal IgA) to the specific allergen following sensitisation were considered by the applicant to support the concept of prophylactic treatment. The induction of allergen specific non-IgE antibodies (IgG and IgA) during prophylaxis is suggested to contribute to the efficacy by competitively inhibiting the interaction between allergen and IgE (blocking antibodies). Further effects suggested reduction in release of pro-allergic mediators, reduction in active eosinophils in affected mucosa and favourable shift in Th1/Th2 balance. In the present file, no supportive primary efficacy data were reported in available animal disease models of pollen-induced allergic rhinitis/rhinoconjunctivitis/airway hyperreactivity. (Data was provided during the MRP.)

III.2 Toxicology

The toxicology programme consisted of studies on acute toxicity (mice), repeat dose toxicity (4-15-26 weeks in mice, 4-52 weeks in dogs), and on reproduction toxicity (a pilot study on embryo-foetal toxicity, a combined fertility/embryo-foetal study and a peri-post natal study). The same dose levels were used in all studies with repeated administrations (0-25000-75000-500000 SQ unit/animal/day) corresponding to 0.3-1-7x clinical dose per patient. The highest dose was limited by applicable dose volume and grass pollen protein solubility (mice) or by applicable number of tablets (dogs). The average multiple of increased total IgG was similar in high dosed mice as reported in man.

Increased incidence of systemic arteritis/periarteritis was reported in male dogs (but not female dogs) treated daily for 52 weeks. The vascular inflammation arose somewhere between 4 (negative study) and 52 weeks of treatment. The historical findings were fully compatible with that of Idiopatic Beagle Pain Syndrome, a condition known to occur in laboratory Beagle dogs. The potential for reversibility was not investigated. The observation of arteritis/periarteritis is mentioned in the SPC section 5.3.

In the reproductive toxicity studies some slight alterations were noted, such as a slight increase in total major fetal abnormalities in the low and medium dose in the combined fertility and teratology study. However, the incidences were low and there was no dose dependency or no specific pattern of defects. These findings are therefore assessed as of minor toxicological importance.

III.3 Discussion on the non-clinical aspects

For products such as Grazax and Grazura, the safety evaluation mainly has to be evaluated in humans since animal species are considered less relevant.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Not applicable.

IV.2 Pharmacodynamics

The applicant has conducted five clinical trials with Grazax which incorporated an immunological analysis of blood samples: the efficacy and safety study *GT-02* and the safety trials *GT-01, GT-03* and *GT-04.* Immunological parameters are measured in the ongoing *GT-08* trial (Danish sites only) and results from the first 10 months have been submitted. Comparative immunological data from a trial using the subcutaneous formulation (Alutard SQ *Phleum pratense*; *UK22*) is also submitted.

It is a reasonable assumption that sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT) work via the same basal mechanisms. The immunological measurements from the Grazax studies show a clear serum antibody response which was dose-dependent in *GT-01* and *GT-02*. Immunological data from two different studies, the Grazax 75000 SQ-T cohort in study *GT-02* and the 10000 SQ-U cohort in study *UK-22* (subcutaneous immunotherapy with Alutard SQ *Phleum pratense*) show similar serum antibody response. A direct comparison of data from two different studies must be performed with caution, however the results support the hypothesis of the same basal mechanisms in SLIT and SCIT. There is also a possibility of slightly different mechanisms, SLIT could be more effective in inducing immunological effects at mucosal surfaces and less effective in producing a serum antibody response than SCIT (in analogy with vaccinations against pathogens).

The exact mechanism of action for specific immunotherapy is not yet fully understood.

IV.3 Clinical efficacy

At the time for the national application, two studies were submitted as proof of efficacy, the *GT-02* and the supportive study *GT-07*.

The *GT-02* trial, which first was claimed to be pivotal, has a somewhat complicated design. The most important results are the comparisons between group 1-4, which were the placebo group, the 2500 SQ-T group, the 25000 SQ-T group and the 75000 SQ-T group with approximately 140 patients in each group. All groups took the same rescue medication. The goal was to start the treatment at least 8 weeks before the pollen season, however, this goal was not achieved in every case. The primary efficacy endpoints were both the average rhinoconjunctivitis symptom score and the average medication score over the entire pollen season. The study failed to show statistically significant effect for the 75000 SQ-T treatment

compared to the placebo group. The rhinoconjunctivitis symptom score improved 16 % (p=0.071) compared to placebo and the medication score decreased 28 % (p=0.047) compared to placebo. A tendency for dose-effect relation was seen.

A *post hoc* analysis in only those patients who started the treatment at least 8 weeks before the pollen season showed more convincing results with statistical difference compared to the placebo group for both the rhinoconjunctivitis symptom and medication score. The MPA considered these results as important, however, they had to be confirmed by another study.

The smaller *GT-07* study in mild to moderate grass allergic asthmatics was not primary aimed as an efficacy study. The statistical analyses made *post-hoc* supported the hypothesis that a longer pre-seasonal treatment period was important for a relevant treatment effect on the rhinoconjunctivitis symptom. The reduction in symptom score and medication score in Grazax treated subjects compared to placebo is of clinical relevance.

The two studies, *GT-02 and GT-07* were not assessed as sufficient for the efficacy evaluation of Grazax. As the GT-08 study was ongoing, the analysis was awaited and the national application was complemented in October 05.

The *GT-08* is a phase III study comparing the treatment with Grazax 75000 SQ-T (316 patients) with placebo (318 patients) after one pollen season (2005) and where all patients started treatment 4-6 months prior to the grass pollen season. The result from this study was much more convincing and strongly supported the hypothesis that a long pre-seasonal treatment is important in order to achieve effect during the first pollen season. The primary endpoints were the same as in *GT-02* as well as the same rescue medication. The rhino-conjunctivitis symptom score improved 30 % (p<0.0001) compared to placebo and the medication score decreased 38 % (p<0.0001) compared to placebo. The results from secondary and other endpoints showed similar and consistent results.

The two-year double-blind extension followed by two years follow up is important and very relevant. In analogy with SCIT, further improvement could be expected. For many patients treated at least three years with SCIT, a long-standing effect is achieved. If the same is possible to achieve with sublingual treatment with grass pollen extract is of high scientific interest to investigate.

The *GT-02* study recruited a number of patients with mild allergic symptoms. Approximately 5 % had not used any medication in previous years. During the study, 30-40 % of the placebo treated patients did not use any rescue medication. This fact, together with the short average pre-seasonal treatment period could be plausible explanations for the weak efficacy results. The opposite could be said about *GT-08*, the study recruited patients with more severe allergic symptoms, 20 % of placebo patients did not use rescue medication and the pre-seasonal treatment period was longer. These facts might explain the improved efficacy results.

To conclude, the *post hoc* analyses in *GT-02* and *GT-07* give proof of efficacy for patients who started treatment at least 8 weeks prior pollen-season. The *GT-08* study in which patients started treatment 4-6 months prior pollen season shows clinically relevant effect.

IV.4 Clinical safety

Overall, 722 adult patients have been exposed to Grazax 75000 SQ-T for a reasonable period.

There was a high frequency of adverse events, 70 % of active treated patients reported any adverse event. Most adverse events were local effects from the oropharynx and mild to moderate in intensity. The onset was often almost immediate after taking the tablet, and lasted from minutes to hour after intake. These events tended to resolve within 1 – 7 days.

It is not surprising that a purified, potent allergen extract given sublingually causes allergic symptoms from the oral mucosa. This could be a problem for the compliance to the treatment rather than a safety concern itself, particularly since the treatment must start long time before the pollen season and the symptom relief will appear later. The importance of treatment duration is mentioned in the SPC.

The side effects presented as oropharyngeal swelling, swollen tongue and swelling of lips have been considered as part of the local reaction since they were not accompanied by urticaria and/or other symptoms indicating that these should be interpreted as angiooedema or Quincke oedema. Some adverse events classified as angioneurotic oedema have been reported.

No anaphylactic reactions are reported which is reassuring. However, some patients have experienced adverse events with severe intensity. These have not been life threatening, however certainly troublesome and unpleasant for the patients. If a patient will react with a severe allergic reaction, this will most probably occur after the first tablet. A statement in the SPC section 4.2 about taking the first tablet under medical supervision is a precautionary action. A patient with severe asthma, who was included in the ongoing GT-10 trial, experienced a severe asthma attack a few minutes after the first tablet. The SPC also specifies that patients with severe asthma should not initiate this treatment.

To summarise, the Grazax studies confirm the reports from literature about SLIT that no anaphylactic or other life-threatening events have occurred in the population specified in the SPC. The high frequency of local allergic reactions from the oral mucosa could be troublesome for some patients and might affect compliance to the treatment, however they are mostly mild to moderate and will resolve over time. The studies also show that grass allergic patients with concomitant mild to moderate asthma symptoms can use Grazax safely.

As a precaution, the first tablet should be taken under medical supervision. This also enables the patient and physician to discuss any side effects and possible actions. The clinical programme has shown that the further tablets could, with an acceptable safety, be taken at home.

A Risk Management Plan is included in the MR submission. It follows the guidelines and, the MPA considers the contents as relevant.

IV.5 Discussion on the clinical aspects

From the recent literature, sublingual immunotherapy (SLIT) appears to be a promising concept for treatment of allergic rhinoconjunctivitis. Many different allergen extracts have been used. A Cochrane Review (Wilson 2003) evaluated 22 randomised, controlled trials with a total of 979 subjects with allergic rhinoconjunctivitis. The authors concluded: “SLIT is a safe treatment which significantly reduces symptoms and medication requirements in allergic rhinitis. The size of this benefit compared to that of other available therapies, particularly

injection immunotherapy, is not clear, having been assessed directly in very few studies. Further research is required concentrating on optimising allergen dosage and patient selection." The American Technology Evaluation Center emphasizes a negative opinion to the SLIT-concept after a meta-analysis of 21 placebo controlled trials (n=1,075). Most of the studies were deemed as small; only 2 trials enrolled more than 100 patients. Only very few of the studies were judged to be of good quality, the others were judged to be of poor or fair quality. In most of the trials, when SLIT was compared to placebo, the decline in allergy symptom score was statistically significant". However, it was uncertain whether the score changes were clinically meaningful, a pervasive problem in this literature". Other more enthusiastic authors have expressed the need of large scale, properly randomised and controlled studies to define the role of SLIT. Many uncertainties remain as to the magnitude of the effect, SLIT in comparison to subcutaneous immunotherapy (SCIT), the optimal treatment regimen, optimal dose and length of treatment. If long-term SLIT studies could show a long standing and preventive effect comparable with SCIT, the concept will have a wider acceptance.

At present, it is difficult to compare SLIT with SCIT. There are very few studies with direct comparisons. SCIT is a well-established method in many countries and is probably still the treatment of choice for patients with moderate to severe hay fever symptoms with or without mild to moderate asthma symptoms. However, this treatment is complicated, with a potential risk for severe side effects and requires access to highly specialised allergy clinics.

There is a need for alternative methods of specific immunotherapy and the sublingual administration method could be a self-administered option.

IV.6 MRP/CMD discussions

Potential serious risk to public health concerns were raised by one CMS which questioned the immunomodulatory effect of the product since efficacy was shown only over one season. At the CMD(h) meeting the RMS presented their view and the company was invited for an oral hearing. The general opinion of CMD(h) was that the outstanding issue could be solved by appropriate changes to the SPC and a post-approval commitment to provide yearly results from the already ongoing GT-08 extension study which will be concluded after the pollen season 2009. Consensus was reached based on the revised SPC and the commitment given by the applicant.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The size of effect of Grazax on rhinoconjunctivitis symptom demonstrated in study *GT-08* is judged as clinically relevant. The efficacy results (*post-hoc* analyses) from the *GT-02* and *GT-07* studies are considered as supportive. The treatments should start at least 4 months before the pollen season. Efficacy data is only available for one pollen season.

The safety profile demonstrated in the submitted studies is considered acceptable, also for grass allergic patients with mild to moderate asthma symptoms

The clinical trials concerning Grazax comply with GCP guidelines.

To ensure a proper use of Grazax, only physicians with experience in treatment of allergic diseases should initiate the treatment (from SPC section 4.2)

The risk/benefit ratio is considered positive for the intended target population and Grazax 75000 SQ-T, oral lyophilisate is approved.

The indication for Grazax is
"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"

During the Mutual Recognition Procedure, potential serious risk to public health concerns were raised by one CMS which questioned the immunomodulatory effect of the product since efficacy was shown only over one season. At the CMD(h) meeting the RMS presented their view and the company was invited for an oral hearing. The general opinion of CMD(h) was that the outstanding issue could be solved by appropriate changes to the SPC and a post-approval commitment to provide yearly results from the already ongoing GT-08 extension study which will be concluded after the pollen season 2009. Consensus was reached based on the revised SPC and the commitment given by the applicant.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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