Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

GRAZAX 75,000 SQ-T sublingual lyophilisate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

* [Standardised Quality units Tablet (SQ-T)]

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sublingual lyophilisate
White to off-white circular sublingual lyophilisate marked with a debossed image on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Disease modifying treatment of grass pollen induced rhinitis and conjunctivitis in adults and children (5 years or older), with clinically relevant symptoms and diagnosedwith a positive skin prick test and/or specific IgE test to grass pollen.

4.2 Posology and method of administration

Posology
The recommended dose for adults and children (5 years or older) is one sublingual lyophilisate (75,000 SQ-T) daily.
Grazax treatment should only be initiated by physicians with experience in treatment of allergic diseases and the capability to treat allergic reactions.

Elderly population
Clinical experience on immunotherapy with Grazax in elderly (65 years or older) is lacking.

Paediatric population
For treatment of children, physicians should be experienced in treating allergic diseases in children. Clinical experience on immunotherapy with Grazax in children younger than 5 years is lacking.

Method of administration
In order to enable patient and physician to discuss any side effects and possible actions it is recommended that the first sublingual lyophilisate is taken under medical supervision (20-30 minutes).
Clinical effect on grass pollen allergic rhinitis and conjunctivitis in the grass pollen season is expected when treatment is initiated at least 4 months prior to the expected start of the grass pollen season and continued throughout the season. If treatment is initiated 2-3 months before the season some efficacy may also be obtained. If no relevant improvement of symptoms is observed during the first pollen season, there is no indication for continuing the treatment. For long term efficacy and disease modifying effect, it is recommended to continue daily treatment for 3 consecutive years.

Grazax is a sublingual lyophilisate. The sublingual lyophilisate should be taken from the blister unit with dry fingers, and placed under the tongue, where it will disperse.

Swallowing should be avoided for about 1 minute. Food and beverage should not be taken for the following 5 minutes.

The sublingual lyophilisate should be taken immediately after opening the blister.

4.3 Contraindications

Hypersensitivity to any of the excipients(for a full list of excipients, see section 6.1). Malignancy or systemic diseases affecting the immune system e.g. autoimmune diseases, immune complex diseases or immune deficiency diseases.

Inflammatory conditions in the oral cavity with severe symptoms such as oral lichen planus with ulcerations or severe oral mycosis.

Patients with uncontrolled or severe asthma (in adults: FEV_1 < 70% of predicted value after adequate pharmacologic treatment, in children: FEV_1 < 80% of predicted value after adequate pharmacologic treatment) should not be treated with Grazax.

4.4 Special warnings and precautions for use

Severe systemic allergic reactions
In post marketing experience, cases of serious anaphylactic reactions have been reported and therefore the medical supervision at start of treatment is an important precaution. In some cases, the serious anaphylactic reaction has occurred at doses subsequent to the initial dose.

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 case of severe systemic reactions, angioedema, difficulty in swallowing, difficulty in breathing, changes in voice, hypotension or feeling of fullness in the throat a physician should be contacted immediately. In such cases treatment should be discontinued permanently or until otherwise advised by the physician.If patients with concomitant asthma experience symptoms and signs indicating asthma deterioration, treatment should be discontinued, and a physician consulted immediately in order to evaluate the continuation of treatment.

In patients who have previously had a systemic reaction to grass subcutaneous immunotherapy, the risk of experiencing a severe reaction with Grazax may be increased. Initiation of Grazax should be carefully considered and measures to treat reactions should be available.

Serious anaphylactic reactions may be treated with adrenaline. Consider whether your patient would be able to tolerate adrenaline (e.g. treatment with tricyclic antidrepressants, MAOIs, COMTIs and/or beta-blockers) in the rare case of a severe systemic allergic reaction.
Patients with cardiac disease may be at increased risk in case of severe systemic allergic reactions. Clinical experience with treatment with Grazax in patients with cardiac disease is limited.

Local allergic reactions
When treated with Grazax the patient is exposed to the allergen that causes the allergic symptoms. Therefore, primarily mild to moderate local allergic reactions are to be expected during the treatment period. If the patient experiences significant local adverse reactions from the treatment, anti-allergic medication (e.g. antihistamines) should be considered.

Oral conditions
In case of oral surgery, including dental extraction, and shedding of a deciduous tooth in children, treatment with Grazax should be stopped for 7 days to allow healing of oral cavity.

Asthma
Asthma is a known risk factor for severe systemic allergic reactions.
Grazax has not been studied in patients with severe and uncontrolled asthma.
Patients with asthma must be informed of the need to seek medical attention immediately if their asthma deteriorates suddenly.
In patients with asthma and experiencing an acute respiratory tract infection, initiation of Grazax treatment should be postponed until the infection has resolved.

Eosinophilic esophagitis
In post marketing experience, isolated cases of eosinophilic esophagitis have been reported in association with Grazax treatment. In patients with severe or persisting gastro-esophageal symptoms such as dysphagia or dyspepsia, discontinuation of Grazax treatment should be considered.

Simultaneous vaccination

Clinical experience in relation to simultaneous vaccination and treatment with Grazax is missing. Vaccination may be given without interrupting treatment with Grazax after medical evaluation of the general condition of the patient.

Food allergy
Grazax contains fish-derived gelatine. The available data have not indicated an increased risk of allergic reactions in severe fish allergic patients. However, awareness is suggested when initiating treatment with Grazax in these patients.

4.5 Interaction with other medicinal products and other forms of interaction

No studies investigating drug interactions have been conducted in humans.

Concomitant therapy with symptomatic anti-allergic agents (e.g. antihistamines, corticosteroids and/or mast cell stabilisers) may increase the tolerance level of the patient to immunotherapy.

There are limited data available on possible risks of simultaneous immunotherapy with other allergens during treatment with Grazax.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no data on the clinical experience for the use of Grazax in pregnant women. Animal studies do not indicate increased risk to the foetus. Treatment with Grazax should not be initiated during pregnancy. If pregnancy occurs during treatment, the treatment may continue afterevaluation of the general condition (including lung function) of the patient and reactions to previous administration of Grazax. In patients with pre-existing asthma close supervision during pregnancy is recommended.

Breastfeeding
No clinical data are available for the use of Grazax during lactation. No effects on the breastfed infants are anticipated.

Fertility
There is no clinical data with respect to fertility for the use of Grazax. In mice, there was no effect on mating or fertility with Grazax treatment (see section 5.3).

4.7 Effects on ability to drive and use machines

Treatment with Grazax has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile
Subjects taking Grazax should primarily expect mild to moderate local allergic reactions to occur early in therapy that tend to subside spontaneously within 1 to 7 days. The most commonly reported adverse reactions are oral pruritus, throat irritation and oedema mouth. For the majority of events, the reaction should be expected to start within 5 minutes after intake of Grazax on each day of occurrence and abate after minutes to hours. More severe local or systemic allergic reactions may occur (see section 4.4).

Tabulated list of adverse reactions
Table 1, which shows the adverse reactions, is based on data from placebo-controlled clinical trials investigating Grazax in adult and paediatric patients with seasonal grass-pollen induced rhinoconjunctivitis including patients with mild to moderate co-existing grass-pollen induced asthma and from spontaneous reporting.

Adverse reactions are divided into groups according to the MedDRA convention frequencies: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Table 1 Adverse reactions

System Organ Class	**Frequency**	**Adverse Drug Reaction**
Immune system disorders	***Uncommon***	Anaphylactic reaction, systemic allergic reaction
Nervous system disorders	***Uncommon***	Dysgeusia, paraesthesia
Eye disorders	***Common***	Eye pruritus, conjunctivitis, eye swelling
	Uncommon	Ocular hyperaemia, eye irritation, lacrimation increased

Ear and labyrinth disorders	***Very common***	Ear pruritus
	Uncommon	Ear discomfort, ear pain
	Rare	Ear swelling
Cardiac disorder	***Uncommon***	Palpitations
Respiratory, thoracic and mediastinal disorders	***Very common***	Throat irritation
	Common	Sneezing, cough, dry throat, dyspnoea, oropharyngeal pain, pharyngeal oedema, rhinorrhoea, throat tightness, nasal pruritus
	Uncommon	Pharyngeal hypoaesthesia, tonsillar hypertrophy, laryngeal oedema, dysphonia, pharyngeal erythema
	Rare	Bronchospasm
Gastrointestinal disorders	***Very common***	Oral pruritus, oedema mouth
	Common	Lip swelling, oral discomfort, paraesthesia oral, stomatitis, dysphagia, abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, oral mucosal erythema, mouth ulceration, oral pain, lip pruritus
	Uncommon	Dry mouth, lip blister, cheilitis, odynophagia, salivary gland enlargement**,** salivary hypersecretion, tongue disorder, glossitis, gastritis, gastroesophageal reflux disease, abdominal discomfort, lip ulceration, oral mucosal blistering
	Rare	Eosinophilic oesophagitis
Skin and subcutaneous tissue disorders	***Common***	Pruritus, urticaria, rash
	Uncommon	Angioedema, erythema
General disorders and administration site conditions	***Common***	Fatigue, chest discomfort
	Uncommon	Sensation of foreign body

Description of selected adverse reactions
If the patient experiences significant adverse events from the treatment, anti-allergic medication should be considered.

In post marketing experience, cases of serious anaphylactic reactions, including anaphylactic shock have been reported. Medical supervision at start of treatment is therefore an important precaution. In some cases the serious anaphylactic reaction has occurred at doses subsequent to the initial dose. Please refer to section 4.2 and 4.4.

In case of severe systemic reactions, angioedema, difficulty in swallowing, difficulty in breathing, changes in voice, hypotension or feeling of fullness in the throat a physician should be contacted immediately. In such cases treatment should be discontinued permanently or until otherwise advised by the physician.

Paediatric population
Overall, the adverse events profile in paediatric patients treated with Grazax was similar to that observed in adults. Most events were seen with a similar frequency category for paediatric patients compared to adults. In the paediatric population, eye irritation, ear pain, ear swelling, pharyngeal erythema and oral mucosal blistering are seen at a higher frequency than in table 1: eye irritation, ear pain, pharyngeal erythema and oral mucosal blistering were common and the ear swelling was uncommon. The events were primarily mild to moderate in severity.

Reportingofsuspectedadversereactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse via HPRA Pharmacovigilance;
Website : www.hpra.ie

4.9 Overdose

In phase I studies adult patients with grass pollen allergy were exposed to doses up to 1,000,000 SQ-T. No data is available in children regarding exposure to doses above the recommended daily dose of 75,000 SQ-T.

If doses higher than the recommended daily dose are taken, the risk of side effects may increase, including the risk of systemic allergic reactions or severe local allergic reactions. In case of severe reactions such as angioedema, difficulty in swallowing, difficulty in breathing, changes in voice, or feeling of fullness in the throat, immediate medical evaluation is needed. These reactions should be treated with relevant symptomatic medication.

In such cases treatment should be discontinued permanently or until otherwise advised by the physician.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Allergen extracts, Grass pollen.

ATC code: V01AA02.

Mechanism of action
Grazax is allergy immunotherapy. Allergy immunotherapy with allergen products is the repeated administration of allergens to allergic individuals with the purpose of modifying the immunological response to the allergen, providing sustained relief of symptoms, less need for medication, and improvement in quality of life during subsequent natural allergen exposure.
Grazax is disease-modifying treatment of grass pollen induced rhinitis and conjunctivitis for patients with clinically relevant symptoms. Disease modification in adults and children is demonstrated by sustained post-treatment effect on rhinoconjunctivitis observed 2 years after 3 years of treatment with Grazax.

The immune system is the target for the pharmacodynamic effect. The aim is to induce an immune response against the allergen with which the patient is treated. The complete and exact mechanism of action regarding clinical effect of specific immunotherapy is not fully understood and documented. Treatment with Grazax has shown to induce a systemic competitive antibody response towards grass, and it induces an increase in specific IgG4 over 3 years of treatment. 2 years after completed Grazax treatment the increase in specific IgG4 was still present. The clinical significance of these findings has not been established.

Clinical efficacy and safety in adults
The efficacy of Grazax once-daily on rhinoconjunctivitis was evaluated in a randomised, double-blind, placebo controlled multi-national trial (GT-08), including 634 adult patients with grass pollen induced rhinoconjunctivitis. 72% of the patients had positive skin prick tests to one or more allergens other than grass pollen. The efficacy was based on the average daily rhinoconjunctivitis symptom and medication score during one grass pollen season. Treatment was initiated at least 16 weeks before the anticipated start of the first grass pollen season and was continued all year round.

Daily treatment with Grazax in adult patients for 3 years resulted in disease modification as demonstrated by a sustained effect after the completion of treatment (effect demonstrated after 1 and 2 years of follow-up). The magnitude of effect varied over the 5 seasons with a peak in season 2 and a possible trend towards a gradual decrease from season 3 to season 5 (1 additional treatment season +2 treatment free follow-up seasons). The variation in treatment effect followed the variation in grass pollen exposure. However, it cannot presently be established if the decrease in grass pollen exposure is the sole explanation for the possible trend towards a gradual decrease in treatment effect seen in seasons 3-5.
The efficacy and safety of Grazax has not been established in patients with significant allergic symptoms in the grass pollen season caused by other allergens than grass pollen.

Results after 3 years of daily Grazax treatment (Year 1-3) and 2 years of follow-up (Year 4-5) in adults are available in table 2 and table 3.

Table 2 Primary efficacy endpoints years 1-5 in adults

	Treatment Year 1	**Treatment Year 2**	**Treatment Year 3**	**Follow up Year 4**	**Follow up Year 5**
Number of subjects in the analysis [A]					
Grazax	282	172	160	142	137
Placebo	286	144	127	115	104
Rhinoconjunctivitis Symptom Score [B]					
Grazax: mean (median)	2.85 (2.6)	2.40 (1.94)	**2.56 (2.04)**	**2.68 (2.27)**	**2.56 (2.18)**
Placebo: mean (median)	4.14 (3.8)	3.76 (3.45)	**3.59 (3.23)**	**3.63 (3.27)**	**3.40 (3.15)**

Difference in means					
Absolute	1.29	1.36	**1.04**	0.95	0.84
[CI 95%]	[0.90; 1.68]	[0.86; 1.86]	[0.52;1.56]	**[**0.40; 1.50**]**	**[0.28; 1.41]**
Relative to placebo (%)	31%	36%	**29**%	26%	25%
[CI 95%]	[22%; 41%]	[23%; 49%]	[14%; 43%]	[11%; 41%]	[9%; 37%]
p-value ANOVA	<0.0001	<0.0001	0.0001	0.0007	0.0037
Difference in medians					
Absolute	1.2	1.51	1.19	1.00	0.97
Relative to placebo (%)	32%	44%	37%	31%	31%
Rhinoconjunctivitis Medication Score[C]					
Grazax: mean (median)	1.65 (1.0)	1.74 (0.46)	1.82 (0.82)	2.32 (1.23)	2.42 (1.62)
Placebo: mean (median)	2.68 (2.2)	3.19 (1.71)	3.04 (2.07)	3.25 (2.58)	3.04 (2.06)
Difference in means					
Absolute	1.03	1.45	1.22	0.93	0.62
[CI 95%]	[0.63; 1.44]	[0.75; 2.16]	[0.52;1.92]	[0.14; 1.72]	[-0.15; 1.38]
Relative to placebo (%)	39%	46%	40%	29%	20%
[CI 95%]	[24%; 54%]	[24%; 68%]	[17%; 63%]	[4%; 53%]	[-8%; 40%]
p-value ANOVA	<0.0001	<0.0001	0.0007	0.0215	0.1136
Difference in medians					
Absolute	1.2	1.25	1.25	1.35	0.44
Relative to placebo (%)	55%	73%	60%	52%	21%

[A] The trial was initially planned as a 1-year trial. 546 of the original 634 subjects completed the first year. The trial was extended with 2 more years of treatment and 2 years of follow-up. At inclusion into the extension, 351 subjects chose to enrol (74 were not offered enrolment due to closure of sites), and these were a representative subgroup of the original 634 subjects. The numbers of subjects in the analyses are all subjects providing diary data during the grass pollen seasons.

[B] Symptom score: Mean daily rhinoconjunctivitis symptom score for each subject for the grass pollen season. Rhinoconjunctivitis symptoms included runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes and watery eyes. Rhinoconjunctivitis symptom score range was 0 – 18, the upper value indicates prolonged very severe symptoms in all mentioned categories. In the trial 95% of all recordings were 9 or less.

[C] Medication score: Mean daily rhinoconjunctivitis medication score for each subject for the grass pollen season. Medications that could be used were loratadine (6 points per tablet), olopatadine eye drops (1.5 point per drop) (years 2-5 only), budesonide nasal spray (1 point per puff) and prednisone 5 mg (1.6 point per tablet). Rhinoconjunctivitis

medication score range was 0 – 36, the upper value indicates prolonged need for high doses of all mentioned substances. In the trial 95% of all recordings were 11 or less.					

Table 3. Secondary efficacy endpoints years 1-5 in adults

	Grazax Mean (Median)	Placebo Mean (Median)	Absolute Diff. Mean [CI 95%]	Relative Diff.* [CI 95%]	p-value ANOVA
Treatment Year 1					
Number of subjects [A]	282	286			
Quality of life score [B]	1.03 (0.9)	1.40 (1.4)	0.37 [0.23; 0.50]	26% [16%; 36%]	<0.0001
Global evaluation [C]	82%	55%	27% [20%; 34%]	49% [36%; 63%]	<0.0001
Well days [D]	45% (40%)	33% (22%)	12% [8%; 17%]	38% [23%; 53%]	<0.0001
Percentage of patients with more than 50% well days [D]	40%	24%	16% [8%; 24%]	66% [34%; 98%]	<0.0001
Treatment Year 2					
Number of subjects [A]	172	144			
Quality of life score [B]	0.85 (0.63)	1.26 (1.05)	0.41 [0.23; 0.59]	33% [18%; 49%]	<0.0001
Well days [D]	49.6% (47.5%)	33.4% (26.5%)	16.2% [9.4% -22.9%]	48% [28%; 69%]	<0.0001
Percentage of patients with more than 50% well days [D]	47.1%	28.5%	18.6% [7.5; 29.7]	65% [26%; 104%]	0.0008
Symptom and medication free days [F]	45.8% (42.6%)	31.7% (24.1%)	14.2% [6.0%; 20.5%]	45% [19%; 65%]	<0.0001
Treatment Year 3					
Number of subjects [A]	160	127			
Quality of life score [B]	0.78 (0.60)	1.01 (0.92)	0.23 [0.07;0.40]	23% [7%; 40%]	0.0058
Well days [D]	43.0% (41.0%)	30.4% (22.0%)	12.6% [5.6%; 19.7 %]	41% [18%; 65%]	0.0004
Percentage of patients with more than 50% well days [DE]	43%	24%	19% (odds ratio¤ 2.4 [1.4; 4.0])	79%	0.0011#
Symptom and medication free days [F]	34.1% (26.6%)	24.1% (14.8%)	10.0% [3.3%;16.7%]	41.7% [14%; 69%]	0.0035
Follow-up, Year 4					
Number of subjects [A]	142	115			
Quality of life score [B]	0.82 (0.64)	1.07 (0.97)	0.25 [0.08;0.41]	23% [7%; 38%]	0.0041
Well days [D]	50.0% (51.9%)	38.1% (31.6%)	11.9% [4.4%;19.	31% [12%; 50%]	0.0020

			4%]		
Percentage of patients with more than 50% well days [DE]	53.1%	34.0%	19.1% (odds ratio¤ 2.2 [1.3; 3.7])	56%	0.0031#
Symptom and medication free days [F]	35.2% (25.7%)	27.6% (17.2%)	7.6% [0.41%; 14.8%]	27% [1%; 54%]	0.0384
Follow-up, Year 5					
Number of subjects [A]	137	104			
Quality of life score [B]	0.69 (0.56)	0.85 (0.85)	0.16 [-0.01; 0.33]	19% [-2%; 38%]	0.0587
Well days [D]	49.7% (51.1%)	40.0% (32.9%)	9.74% [1.5%; 17.9%]	24% [3%; 52%]	0.0203
Percentage of patients with more than 50% well days [DE]	49.5%	35.0%	14.5% (odds ratio¤ 1.8 [1.1; 3.1])	41%	0.0280#
Symptom and medication free days [F]	33.5% (25.9%)	28.0% (18.2%)	5.5% [-2.4%; 13.4%]	20% [-8%; 57%]	0.1737

* Relative difference = |Absolute difference|/Placebo; ¤ odds ratio for having excellent control; # p-value for the odds ratio.
[A] The trial was initially planned as a 1-year trial; 546 of the original 634 subjects completed the first year. The trial was extended with 2 more years of treatment and 2 years of follow-up. At inclusion into the extension, 351 subjects chose to enrol (74 were not offered enrolment due to closure of sites), and these were a representative subgroup of the original 634 subjects. The numbers of subjects are all subjects providing diary data during the grass pollen seasons.
[B] Quality of life was assessed by the Rhinoconjunctivitis Quality of Life Questionnaire including 28 items in the domains activity limitation, sleep problems, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems and emotional function. A higher score is reflecting a worse quality of life. Rhinoconjunctivitis Quality of Life Questionnaire score range was 0 – 6, the upper value indicates prolonged very severe impact on all items. In the trial 95% of all recordings were 4 or less.
[C] Global evaluation: percentage of subjects who noted an improvement in rhinoconjunctivitis symptoms in the treatment season as compared to their recollection of the previous seasons.
[D] Well days: percentage of days where the subjects did not use any rescue medication and had a symptom score not larger than 2.
[E] For year 3 and the 2 follow-up years, analysed by means of the odds ratio for having more than 50% well days during the corresponding grass pollen season.
[F] Symptom and medication free days: percentage of days where the subjects did not use any rescue medication and had no symptoms.

Statistically significant effect was demonstrated for each of the scored rhinoconjunctivitis symptoms (runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes and watery eyes).

In a trial with shorter pre-treatment, less reductions in symptom and medication scores were found; Grazax treatment approximately 2 months prior to and during the grass pollen season resulted in a symptom score reduction of 16% (p=0.071) and a medication score reduction of 28% (p=0.047) (full analysis set).

Paediatric population

The short term efficacy of Grazax on rhinoconjunctivitis has been investigated in a randomised, double-blind, placebo controlled trial (GT-12) including 238 children (5–16 years) with grass pollen induced rhinoconjunctivitis with/without asthma. Patients received treatment prior to the grass pollen season and continued throughout the entire season (table 4).

The long term efficacy of Grazax has been investigated in a randomised, double-blind, placebo-controlled, multinational trial (GT-21) including 812 children (5-12 years) with a clinically relevant history of grass pollen allergic rhinoconjunctivitis and no medical history of asthma. Daily treatment with Grazax for 3 years resulted in a sustained post-treatment effect on rhinoconjunctivitis symptoms. The effect on rhinoconjunctivitis symptoms was evident when assessed during the entire 5-year trial period, during the 2-year follow-up period after completion of treatment and at end of trial. Data on the clinical efficacy are shown in table 4.

Table 4. Efficacy of Grazax on rhinoconjunctivitis in children

	Grazax	**Placebo**	**Absolute Diff. [CI 95%]**	**Relative Diff.* (%) [CI 95%]**	**p-value**
GT-12					
Number of subjects included in the analysis	117	121			
Primary endpoints					
Rhinoconjunctivitis symptom score [A]	2.18	2.80	0.62 [0.10; 1.15]	22% [4%; 38%]	0.0215
Rhinoconjunctivitis medication score [B]	0.78	1.19	0.41	34%	0.0156
Key Secondary endpoints					
Rhinoconjunctivitis symptom score [A], peak grass pollen season	2.84	3.91	1.07 [0.32; 1.81]	27% [9%; 43%]	0.0059
Rhinoconjunctivitis medication score [B], peak grass pollen season	0.87	2.40	1.53	64%	0.0013
Well days [C]	52%	42%	9% [1%; 17%]	22% [3%; 45%]	0.0225
GT-21					
Number of subjects included in the full analysis set	398	414			
Secondary endpoint: Yearly rhinoconjunctivitis symptoms[D] during grass pollen season					
Treatment Year 1	19.4	25.5	6.1 [2.7; 9.4]	24%	<0.001
Treatment Year 2	20.3	28.8	8.4 [5.0; 11.9]	29%	<0.001
Treatment Year 3	21.9	31.1	9.23 [5.7; 12.8]	30%	<0.001
Follow-up, Year 4	23.5	30.3	6.7 [3.1; 10.3]	22%	<0.001
Follow-up, Year 5	19.6	25.5	5.8 [2.2; 9.4]	23%	0.002
Secondary endpoint: Daily rhinoconjunctivitis symptoms[E] during grass pollen season					
Follow-up, Year 5	15.2	19.5	4.4 [1.35; 7.40]	22%	0.005
Secondary endpoint: Daily rhinoconjunctivitis medication score[F] during grass pollen season					
Follow-up, Year 5	4.9	6.7	1.8 [0.9; 2.7]	27%	<0.001

*Relative difference = |Absolute difference|/Placebo. [A] Symptom score: Mean daily rhinoconjunctivitis symptom score for each subject for the grass pollen season. Rhinoconjunctivitis symptoms included runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes and watery eyes. Parametric analysis (square-root-transformed data), relative difference of back-transformed, adjusted means. [B] Medication score: Median daily rhinoconjunctivitis medication score for each subject for the grass pollen season. Medications used were loratadine tablets, levocabastine eye drops, budesonide nasal spray, prednisolone tablets. Non-parametric analysis, relative difference of medians. [C] Well days: percentage of days where the subjects did not use any rescue medication and had a symptom score not larger than 2. Parametric analysis (untransformed data), relative difference of adjusted means. [D] Symptoms measured by yearly VAS score: Visual analogue scale score describing 'how the subject's hay fever has been the last week', on a 100 mm scale from no symptoms to severe symptoms, assessed once. Parametric analysis, relative difference of adjusted means. [E] Symptoms measured by daily VAS score: Mean daily visual analogue scale score of 'how the subject's hay fever has been today?' on a 100 mm scale from no symptoms to severe symptoms, during a 14-day period. Parametric analysis (square-root-transformed data), relative difference of back-transformed, adjusted means. [F] Medication score: Mean daily rhinoconjunctivitis medication score during a 14-day period. Parametric analysis (square-root-transformed data), relative difference of back-transformed, adjusted means.					

5.2 Pharmacokinetic properties

The main part of the allergens in Grazax is polypeptides and proteins, which are expected to be broken down to amino acids and small polypeptides in the lumen of the gastrointestinal tract and in tissues. It is expected that allergens from Grazax are not absorbed into the vascular system to any significant extent. Thus, no pharmacokinetic studies in animals or clinical studies investigating the pharmacokinetic profile and metabolism of Grazax have been conducted.

5.3 Preclinical safety data

Conventional studies in general toxicity in mice revealed no special hazard for humans. In toxicological studies in dogs, daily dosing for 52 weeks was associated with vasculitis/perivasculitis in males, but not in females. It is not expected that there is a risk of developing vasculitis/perivasculitis in humans. In a combined fertility and embryo-foetal development study in mice, mating performance and fertility were unaffected, and there were no adverse foetal findings. In a pre-/postnatal development study, mouse development was normal.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin (fish source)
Mannitol
Sodium hydroxide (for pH adjustments)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medical product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium blister cards with removable aluminium foil in an outer carton box. Each blister card contains 10 sublingual lyophilisates.
Pack sizes: 30 (3 x 10) sublingual lyophilisates, 90 (9 x 10) sublingual lyophilisates and 100 (10 x 10) sublingual lyophilisates.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

ALK-Abello A/S
Boge Alle 6-8
DK-2970 Horsholm
Denmark

8 MARKETING AUTHORISATION NUMBER

PA1255/004/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th November 2006
Date of last renewal: 14th March 2011

10 DATE OF REVISION OF THE TEXT

September 2022