AUSTRALIAN PRODUCT INFORMATION GRAZAX® (*Phleum pratense*) SUBLINGUAL TABLETS

AUST R 267955

1. NAME OF THE MEDICINE

Phleum pratense.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GRAZAX® sublingual tablets contain 75,000 SQ-T standardised allergen extract of Timothy grass pollen (*Phleum pratense*) which is a temperate grass.

SQ-T is the dose unit for GRAZAX®. SQ is a method for standardisation on biological potency, major allergen content and complexity of the allergen extract.

GRAZAX® sublingual tablets 75,000 SQ-T also contains gelatine (fish), mannitol and sodium hydroxide.

3. PHARMACEUTICAL FORM

GRAZAX® 75,000 SQ-T is supplied as white to off-white freeze-dried debossed tablets.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

GRAZAX® is indicated for disease modifying treatment of grass pollen (*Phleum pratense* or allergens cross reacting with *P. pratense)* induced allergic rhinitis with or without conjunctivitis in adults, adolescents and children above the age of 5 years.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment with GRAZAX® should be initiated by a clinician with experience in treatment of allergies. Patients should have a confirmed clinical history and diagnosis by a positive test of grass pollen sensitisation to *Phleum pratense* or cross reacting allergens (specific IgE and/or skin prick test) prior to treatment.

The recommended dose is one sublingual tablet (75,000 SQ-T) daily.

It is recommended that the first sublingual tablet is taken under medical supervision and that the patient is monitored for 30 minutes, to enable discussion and possible treatment of any immediate side effects. See also **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**. Management of specific allergy symptoms should be discussed prior to initiation of treatment.

The sublingual tablet should be taken with dry fingers from the blister unit immediately after opening the blister and placed under the tongue, where it will disperse. Swallowing should be avoided for approximately 1 minute.

Food and beverage should not be consumed for the following 5 minutes.

For clinical effect in the grass pollen season, treatment should be initiated at least 16 weeks before the grass pollen season and continued daily. If treatment is initiated 2-3 months before the grass pollen season some efficacy may also be obtained.

For long-term efficacy and disease modification treatment should be continued daily for 3 consecutive years. See also **5.1 PHARMACODYNAMIC PROPERTIES - Clinical Trials**.

Efficacy data is available for 3 years of treatment and 2 years of follow-up in adults. No data on treatment with GRAZAX® in children beyond 1 grass pollen season is available (see **5.1 PHARMACODYNAMIC PROPERTIES - Clinical Trials**). If no improvement is observed during the first year of treatment with GRAZAX® there is no indication for continuing treatment.

GRAZAX® is not recommended for use in patients below 5 years of age due to insufficient data on safety and efficacy in this population (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

4.3 CONTRAINDICATIONS

GRAZAX® is contraindicated:

- in patients with a known hypersensitivity to the any of the excipients
- in adult patients with uncontrolled asthma or FEV_1 <70% of predicted value (after adequate pharmacological treatment) at initiation of treatment
- in paediatric patients with uncontrolled asthma or FEV1 <80% of predicted value (after adequate pharmacological treatment) at initiation of treatment
- in patients with malignant or systemic disease affecting the immune system e.g. autoimmune diseases, immune complex diseases or immune deficiency diseases
- in patients with acute severe oral inflammation or oral wounds (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**)
- in patients who have experienced a severe asthma exacerbation within the last 3 months

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In patients with asthma and experiencing an acute respiratory tract infection, initiation of GRAZAX® treatment should be postponed until the infection has resolved.

If patients with concomitant asthma experience symptoms and signs indicating asthma deterioration, treatment should be discontinued and medical attention must be sought immediately in order to evaluate the continuation of treatment.

When treated with GRAZAX® the patient is exposed to the allergen that causes the allergic symptoms. Therefore, mild or moderate local allergic reactions are to be expected during the treatment period (see **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS**). The use of anti-allergic medication (e.g. antihistamines) could be considered at clinician's discretion for any potential significant local adverse reactions to GRAZAX®.

Treatment with GRAZAX® should be discontinued immediately and urgent medical attention sought in cases of serious anaphylactic reactions including anaphylactic shock, angioedema, difficulty in swallowing, difficulty in breathing, changes in voice, hypotension or feeling of fullness in the throat.

Initiation of GRAZAX® in patients who have previously had a systemic reaction to subcutaneous grass allergen immunotherapy should be carefully considered, and measures to treat any potential adverse reactions should be available.

Serious anaphylactic reactions may be treated with adrenaline. The effects of adrenaline may be potentiated in patients treated with tricyclic antidepressants, mono amino oxidase inhibitors (MAOIs) and/or COMT inhibitors with possible fatal consequences. This should be taken into consideration prior to initiating allergy immunotherapy. The effects of adrenaline may be reduced in patients treated with beta-blockers. Patient with cardiac disease may be at increased risk in case of severe systemic allergic reactions.

In patients with severe oral inflammation (e.g. oral lichen planus, mouth ulcers or thrush), oral wounds or following oral surgery, including dental extraction, or following tooth loss, initiation of GRAZAX® treatment should be postponed and any ongoing treatment should be temporarily interrupted to allow healing of the oral cavity.

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 treatment with GRAZAX® should be considered.

The efficacy and safety of GRAZAX® for the treatment of allergy induced by sub-tropical grasses has not been assessed in the submitted studies.

Use in the elderly
Special studies in the geriatric population have not been performed.

Paediatric use
The efficacy and safety of GRAZAX® has not been demonstrated in subjects aged less than 5 years.

Effect on laboratory tests
GRAZAX® has no effect on laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction trials have been conducted. Vaccination may be given without interrupting treatment with GRAZAX® after medical evaluation of the general condition of the patient.

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 no data available on possible risks of simultaneous immunotherapy with other marketed allergy immunotherapy products.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There is no human data available regarding fertility and use of GRAZAX®.

A fertility study in mice revealed no evidence of impaired fertility due to Timothy grass pollen allergen extract following oral dosing at up to approximately 1522 times the human clinical dose (based on body surface area comparisons).

Use in pregnancy (Category B2)

There is no data available regarding use of GRAZAX® during pregnancy. The effects of Timothy grass (*Phleum pratense*) pollen allergen extract, the active component of GRAZAX®, on embryo-fetal development was evaluated in mice. No adverse effects on embryo-fetal development were observed following oral dosing at up to approximately 1522 times the human clinical dose (based on body surface area comparisons) during the period of organogenesis.

Treatment with GRAZAX® should not be initiated during pregnancy. If pregnancy occurs during treatment, the treatment may continue after evaluation of the general condition (including lung function) of the patient and reactions to previous administration of GRAZAX®.

Because animal reproduction studies are not always predictive of human response, GRAZAX® should be used during pregnancy only if clearly needed.

Because systemic and local adverse reactions with immunotherapy may be poorly tolerated during pregnancy, GRAZAX® should be used during pregnancy only if clearly needed.

Close supervision during pregnancy is recommended for patients with pre-existing asthma.

Use in lactation

No clinical data are available for the use of GRAZAX® during lactation.

Studies in animals to investigate excretion of GRAZAX® into milk were not conducted.

Initiation of allergy immunotherapy while breast feeding is not recommended. However, if breast feeding is required during treatment, patients should be closely monitored.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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. 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 oropharyngeal allergic reactions may occur (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

In a pooled analysis of all subjects in the GRAZAX® clinical development program, 76% of subjects administered GRAZAX® reported a treatment emergent adverse event (TEAE). This was similar compared to those subjects administered placebo (73%).

The majority of subjects in the pooled GRAZAX® studies reported TEAEs that were mild to moderate in intensity.

The most frequently reported TEAEs (defined as those occurring in ≥ 5% of subjects in any active group) are summarised by system organ class (SOC) in Table 1.

Table 1. TEAEs in at least 5% of all subjects in the GRAZAX® clinical development program (safety population)[a]

System organ class/preferred term	Placebo (N=2756) n (%)	GRAZAX® 75,000 SQ-T (N=3990) n (%)
Ear and labyrinth disorders		
Ear pruritus	30 (1%)	426 (11%)
Gastrointestinal disorders		
Lip swelling	10 (<1%)	229 (6%)
Oedema mouth	24 (1%)	438 (11%)
Oral pruritus	107 (4%)	1296 (32%)
Paraesthesia oral	68 (2%)	296 (7%)
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	130 (5%)	197 (5%)
Throat irritation	88 (3%)	800 (20%)

N: number of subjects in pool
n: number of subjects with event
a: includes clinical studies GT-01, GT-02, GT-03, GT-04, GT-07, GT-08, GT-09, GT-10, GT-11, GT-12, GT-14, GT-16, GT-17, GT-18, GT-19, GT- 20, GT-21, GT-22, GT-23, GT-24, P05238 and P05239 , P08067, P006, GRAS 3001.

The most common TEAEs in subjects administered GRAZAX® included oral pruritus, throat irritation, and ear pruritus, reported by 32%, 20%, and 11% of subjects (Table 1).

Adverse reactions reported in clinical trials with frequencies <5% are listed below.

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).

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

Cardiac disorders
Uncommon: Palpitations

Ear and labyrinth disorders
Uncommon: Ear discomfort, ear pain
Rare: Ear swelling

Respiratory, thoracic and mediastinal disorders
Common: Sneezing, dry throat, dyspnoea, pharyngeal oedema, rhinorrhoea, cough, throat tightness, nasal pruritus,
Uncommon: Pharyngeal hypoaesthesia, tonsillar hypertrophy, laryngeal oedema, dysphonia, pharyngeal erythema
Rare: Bronchospasm

Gastrointestinal disorders
Common: oral discomfort, 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

Overall, the adverse event 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. However, the following adverse reactions were different to that reported above. Eye irritation, ear pain, pharyngeal erythema and oral mucosal blistering were common and ear swelling was uncommon in the paediatric population. The events were primarily mild to moderate in severity.

Post marketing experience
Cases of serious anaphylactic reactions including anaphylactic shock have been reported for GRAZAX® and are considered a class effect. Medical supervision at first sublingual tablet intake is therefore recommended (see **4.2 DOSE AND METHOD OF ADMINISTRATION**).

Isolated cases of eosinophilic esophagitis have been reported in association with GRAZAX® (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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 reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

If doses higher than the recommended daily dose are taken, the risk of undesirable effects, including systemic side effects or severe local adverse reactions, may increase. In case of severe reaction such as angioedema, difficulty in swallowing, difficulty in breathing, changes in voice, or feeling of fullness in the throat, immediate medical evaluation is needed.

In the event of an overdose, the adverse effects should be treated symptomatically.

Contact the Poisons Information Centre on 131 126 for advice on overdosage management.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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 to provide sustained relief of symptoms and less need for medications. The immune system is the target for the pharmacodynamic effect of allergy immunotherapy, but the complete and exact mechanism of action is not fully understood.

GRAZAX® is for the treatment of patients diagnosed with specific IgE-mediated allergy symptoms induced by grass pollen such as allergic rhinitis and/or allergic rhinoconjunctivitis. Daily treatment with GRAZAX® for 3 years has been demonstrated to induce an increase in specific IgG_4 and this effect was maintained after 2 years follow up. Treatment with GRAZAX® induces a systemic antibody response that can compete with IgE in the binding of grass allergens. This effect is observed after 8 weeks of treatment.

GRAZAX® works by modifying the immune response to grass pollen induced allergic disease. Daily treatment with GRAZAX® in adult patients for 3 years resulted in disease modification as demonstrated by a continued effect for 2 years after the completion of treatment (see **5.1 PHARMACODYNAMIC PROPERTIES - Clinical Trials**). The underlying protection provided by GRAZAX® leads to improvement in disease control and quality of life during subsequent natural allergen exposure.

Clinical trials

Adults

The efficacy and safety of GRAZAX® in adults with seasonal grass pollen induced rhinoconjunctivitis has been investigated in a pivotal Phase 3 randomised, double-blind, placebo-controlled, multicentre study (GT-08). The trial was initially planned as a 1-year trial (n=634). The trial was extended with 2 more years of treatment and 2 years of follow-up.

The trial commenced 4-8 months prior to the anticipated start of the (Northern hemisphere) grass pollen season 2005. The treatment period ended at the end

of the grass pollen season 2007, and subjects were followed up until end of the grass pollen season 2009. The trial remained blinded for the 5 years.

During the treatment phase of the trial (years 1-3), subjects were randomised to receive GRAZAX® 75,000 SQ-T or placebo once daily. Use of symptomatic medication in a step wise approach was permitted as needed during both the treatment period and the follow-up period. For symptoms of rhinoconjunctivitis, permitted medication included oral antihistamines (desloratadine tablets, 5 mg); antihistamine eye drops (olopatadine 1 mg/mL) nasal steroids (budesonide 64 mcg/dose) and oral steroids (prednisolone tablets up to 50 mg/day for 3 days). For symptoms of asthma, permitted medication included short acting beta agonists (SABA; salbutamol 200 mcg/dose), nasal steroids (fluticasone 250 mcg/inhalation), and oral steroids (prednisolone tablets up to 50 mg/day for 3 days).

The co-primary endpoints were average daily rhinoconjunctivitis symptom score as well as average daily rhinoconjunctivitis medication score for the entire grass pollen season each year.

The results for the primary endpoint are summarised in **Table 2**. Subjects administered GRAZAX® demonstrated statistically significant improvement in rhinoconjunctivitis symptom score at all time points through years 1 to 5, and statistically significant reduction in rhinoconjunctivitis medication score at years 1 to 4. The magnitude of effect varied over the 5 seasons. The results demonstrate long term efficacy and a disease modifying effect.

Table 2. Results for co-primary endpoints for Phase 3 trial GT-08

	Treatment year 1	Treatment year 2	Treatment year 3	Follow up year 4	Follow up year 5
Number of subjects in the analyses					
GRAZAX®	282	172	160	142	137
Placebo	286	144	127	115	104
Pollen exposure					
Average length of season (days) [range]	58 [16, 86]	59 [30,116]	77 [44, 117]	65 [21, 110]	68 [39, 116]
Median exposure (grains/m^3/day)[a]	34	33	22	30	21
Cumulative sum (grains/m3)[b] Day 20 Day 70	1047 3405	1593 3255	1291 2935	1147 3317	664 2619
Mean Rhinoconjunctivitis symptom score[c]					
GRAZAX®	2.85	2.40	2.56	2.68	2.56
Placebo	4.14	3.76	3.59	3.63	3.40
Absolute difference in means [CI 95%]	1.29 [0.90, 1.68]	1.36 [0.86, 1.86]	1.04 [0.52, 1.56]	0.95 [0.40, 1.50]	0.84 [0.28, 1.41]
Difference relative to placebo [CI 95%]	31% [22%, 41%]	36% [23%, 49%]	29% [16%, 40%]	26% [12%, 38%]	25% [9%, 37%]
p-value	<0.0001	<0.0001	0.0001	0.0007	0.0037
Mean Rhinoconjunctivitis medication score[d]					
GRAZAX®	1.65	1.74	1.82	2.32	2.42
Placebo	2.68	3.19	3.04	3.25	3.04

Absolute difference in means [CI 95%]	1.03 [0.63, 1.44]	1.45 [0.75, 2.16]	1.22 [0.52, 1.92]	0.93 [0.14, 1.72]	0.62 [-0.15, 1.38]
Difference relative to placebo [CI 95%]	39% [24%, 54%]	46% [24%, 68%]	40% [17%, 54%]	29% [2%, 44%]	20% [-8%, 40%]
p-value	<0.0001	p<0.0001	0.0007	0.0215	0.1136
Total Combined Score[e]					
GRAZAX®	4.46	4.10	4.39	4.96	4.96
Placebo	6.78	6.94	6.64	6.81	6.42
Absolute difference in means [CI 95%]	2.32 [1.67, 2.98]	2.84 [1.79, 3.88]	2.26 [1.25, 3.26]	1.85 [0.73, 2.97]	1.46 [0.31, 2.61]
Difference relative to placebo [CI 95%]	34.2% [26.3%, 42.0%]	40.9% [29.5%, 51.8%]	34.0% [21.4%, 45.5%]	27.2% [12.4%, 39.9%]	22.7% [6.3%, 37.1%]
p-value	<0.0010	<0.0001	<0.0001	0.0014	0.0128

a: From a post hoc analysis of the distribution of daily exposure for all subjects.
b: The cumulative sum of the daily pollen counts for all subjects until day 20 or day 70 from the defined start of the grass pollen season.
c: 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.
d: 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.
e: Total Combined Score = results of combined daily rhinoconjunctivitis symptom score and daily rhinoconjunctivitis medication score over the entire grass pollen season for years 1 to 5. Full analysis set (FAS).

Paediatrics

The efficacy and safety of GRAZAX® in children aged 5-16 years with grass pollen induced rhinoconjunctivitis with/without asthma has been investigated in a pivotal Phase 3 randomised, double-blind, placebo-controlled, multicentre study (GT-12) (n=253).

The trial commenced approximately 4 months prior to the anticipated start of the (Northern hemisphere) grass pollen season 2007 and ceased at the end of that grass pollen season.

Subjects were randomised to receive GRAZAX® 75,000 SQ-T or placebo once daily. Use of symptomatic medication in a step wise approach was permitted as needed. For symptoms of rhinoconjunctivitis, permitted medication included oral antihistamines (loratadine tablets, 5-10 mg); antihistamine eye drops (levocabastine 0.5 mg/mL), nasal steroids (budesonide 50 mcg/dose) and oral steroids (prednisolone tablets up to 25-50 mg/day for 7 days). For symptoms of asthma, permitted medication included short acting beta agonists (SABA; salbutamol 0.10%/dose), nasal steroids (fluticasone 125 or 250 mcg/inhalation), and oral steroids (prednisolone tablets up to 50 mg/day for 7 days).

The co-primary endpoints were average daily rhinoconjunctivitis symptom score as well as average daily rhinoconjunctivitis medication score for the entire grass pollen season.

The results for the primary endpoint are summarised in **Table 3**. GRAZAX® 75,000 SQ-T demonstrated statistical significance compared to placebo for rhinoconjunctivitis symptom score, and for rhinoconjunctivitis medication score. Subjects administered GRAZAX® demonstrated a 22% improvement in

rhinoconjunctivitis symptom score (p=0.0215) and a 34% reduction in rhinoconjunctivitis medication score (p=0.0156) compared to placebo.

Table3. Results for co-primary endpoints for Phase 3 trial GT-12

Number of subjects in the analyses	
GRAZAX®	117
Placebo	121
Rhinoconjunctivitis symptom score[a]	
GRAZAX®	2.18
Placebo	2.80
Absolute difference in means [CI 95%]	0.62 [0.10, 1.15]
Difference relative to placebo [CI 95%]	22% [4%, 38%]
p-value	0.0215
Rhinoconjunctivitis medication score[b]	
GRAZAX®	0.78
Placebo	1.19
Absolute difference in means [CI 95%]	0.41
Difference relative to placebo [CI 95%]	34%
p-value	0.0156
Total Combined Scores[c]	
GRAZAX®	3.70
Placebo	4.87
Absolute difference in means [CI 95%]	1.18 [0.19, 2.17]
Difference relative to placebo [CI 95%]	24.15% [4.10%, 40.55%]
p-value	0.0216

a: 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: 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:Total Combined Score = results of combined daily rhinoconjunctivitis symptom score and rhinoconjunctivitis medication score over the entire grass pollen season. Full analysis set (FAS).

5.2 PHARMACOKINETIC PROPERTIES

No clinical studies investigating the pharmacokinetic profile and metabolism of GRAZAX® have been conducted. The effect of allergy immunotherapy is mediated through immunological mechanisms, and there is limited information available on the pharmacokinetic properties.

The active molecules of an allergen extract are composed primarily of proteins. For sublingually administered allergy immunotherapy (SLIT) products, studies have shown that no passive absorption of the allergen through the oral mucosa occurs. Evidence points towards the allergen being taken up through the oral mucosa by dendritic cells, in particular Langerhans cells. Allergen which is not absorbed in this manner is expected to be hydrolysed to amino acids and small polypeptides in the lumen of the gastrointestinal tract.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Timothy grass allergen extract did not induce reversion mutations in bacteria or forward mutations in cultured mammalian cells *in vitro*. No *in vivo* studies of genotoxicity have been performed.

Carcinogenicity

Dedicated carcinogenicity studies with GRAZAX® have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to section **2. QUALITATIVE AND QUANTITATIVE COMPOSITION** for the complete list of excipients.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store GRAZAX® 75,000 SQ-T sublingual tablet below 25°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Packs contain 10, 30, 90 and 100 sublingual tablets supplied in aluminium blister foils.

Not all pack sizes may be available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by talking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure
No data available

CAS number
Not applicable

Pharmacotherapeutic group: Allergen extracts, grass pollen.

ATC Code: V01AA02

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine, S4

8. SPONSOR

Seqirus Pty Ltd ABN: 26 160 735 035
63 Poplar Road
Parkville VIC 3052
Telephone: 1800 642 865
www.seqirus.com.au

9. DATE OF FIRST APPROVAL

7 March 2017

10. DATE OF REVISION

3 November 2021

GRAZAX® is a registered trademark of ALK-Abelló A/S, used under licence.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	*Oral lyophilizate* replaced by *sublingual tablet* for clarity and consistency with registered dose form and route of administration
4.8	Update Adverse Events to align with new safety data
6.3	Section amended with standard TGA text
6.4	Addition of storage below 25°C.
8	Update to Sponsor contact number