



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Allergen Pollen Extract of 5 Grasses

Proprietary Product Name: Oralair Sublingual
Tablets

Sponsor: Helex-A Pty Ltd

June 2011

TGA Health Safety
Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to Product Submission

Submission Details

| | |
|------------------------------------|--|
| <i>Type of Submission</i> | New Route of Administration and New Dosage Form |
| <i>Decision:</i> | Approved |
| <i>Date of Decision:</i> | 19 April 2011 |
| <i>Active ingredient(s):</i> | Allergen pollen extract of 5 grasses |
| <i>Product Name(s):</i> | Oralair Sublingual Tablet |
| <i>Sponsor's Name and Address:</i> | Helex-A Pty Ltd Unit 9, 7 Anella Avenue Castle Hill NSW 2154 |
| <i>Dose form(s):</i> | Sublingual tablet |
| <i>Strength(s):</i> | 100 IR and 300 IR ¹ |
| <i>Container(s):</i> | Blister pack |
| <i>Pack size(s):</i> | Initial treatment: 1 x 3 tablets of 100 IR in small blister + 1 x 28 tablets of 300 IR in blister. One per pack. Continuation treatment: 1 x 30 tablets of 300 IR in blister. Packs of 1 or 3. |
| <i>Approved Therapeutic use:</i> | Treatment of grass pollen allergic rhinitis with or without conjunctivitis in adults, adolescents and children (above the age of 5) with clinically relevant symptoms, confirmed by a positive cutaneous test and/or a positive titre of the specific IgE to the grass pollen. |
| <i>Route(s) of administration:</i> | Oral |
| <i>Dosage:</i> | The therapy is composed of an initiation treatment (including a 3-day dose escalation) and a continuation treatment (see Dosage and Administration section of the Product Information for full details). |
| <i>ARTG Number (s):</i> | 167565, 167566 |

Product Background

Allergies have emerged as a major public health problem in developed countries during the twentieth century; Australia and New Zealand have among the highest prevalence of allergic disorders in the developed world. In 2007, ACCESS Economics estimated:

- 4.1 million Australians (19.6% of the population) have at least one allergy, of which
- 2.2 million (55%) are female and 1.9 million (45%) are male;

¹ The Index of Reactivity (IR) is a biological unit used by the manufacturer to define biological activity. An allergen extract is said to have a titre of 100 IR/mL if, in a prick-test performed in 30 subjects sensitised to the allergen in question, it produces a wheal measuring 7 mm in diameter. Skin reactivity in these subjects is simultaneously demonstrated by a positive response to a prick test with 9% codeine phosphate or 10 mg/mL histamine dihydrochloride. There is no general consensus on an international unit for biological activity of allergen extracts. Hence units are not comparable between manufacturers.

- the prevalence of allergies is highest in the age range of the working population; 78% of people with allergies are between the age 15 to 64 years.

For affected adults, allergic disorders can lead to impaired quality of life, absenteeism from work and other reduced productivity.

Most patients with allergic disorders have associated co-morbid conditions.

Literature evidence indicates increases in the prevalence of many types of allergies in recent decades.

Various sources from around the world (Wilson et al, 2006, Asher et al, 2006; Wjst et al, 2005; Hopper et al, 1995) estimate allergies to affect around one in six children aged 6-7 years, one in ten children aged 13-14 years, 18% of those aged 15-34 years and 10% of older adults aged 35-54 years.^{2,3,4,5} Symptoms generally persist for at least ten years, often longer (Greisner et al, 1998).⁶ Typical complaints are those of a blocked and runny nose with clear mucus, itchy nose, sneezing and cough from post nasal drip, a symptom that can be mistaken for asthma cough. Allergic rhinitis may masquerade as continuous or recurrent respiratory infection, frequent sore throats and may be complicated by sinusitis or otitis media. Those with allergic rhinitis suffer more frequent and prolonged sinus infections and with treatment of the allergic component this risk of infection may be reduced (Cirillo et al, 2007).⁷ Allergic conjunctivitis usually accompanies rhinitis with red and itchy eyes, sometimes complicated by infective conjunctivitis due to frequent rubbing. Seasonal symptoms are most commonly triggered by pollen exposure, while perennial rhinoconjunctivitis is aggravated by exposure to house dust mite, mould spores or indoor pets (Plaut and Valentine, 2005; Van Hoecke and Van Cauwenberge, 2007).^{8,9} Allergic rhinitis (AR) predispose people to obstructive sleep apnoea, which results from collapse of the upper airways during sleep.

Lethargy, poor concentration and behavioural changes may arise as a result of persistent symptoms and poor quality sleep which can impact on learning in young children (Simons, 1996; Marshall and Colon, 1993; Gauci et al, 1993).^{10,11,12} These factors may be aggravated by use of sedating (as opposed to the more expensive non-sedating) antihistamines as a cost saving measure (Nolen, 1997; Storms, 1997; Vuurman et al, 1993).^{13,14,15} Since

- ² Wilson DH, Adams RJ, Tucker G, Appleton S, Taylor AW, Ruffin RE . Trends in asthma prevalence and population changes in South Australia 1990-2003. *Med J Aust* 2006; 184: 226-9.
- ³ Asher MI, Montefort S, Bjorksten B et al. ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; 368: 733-43.
- ⁴ Wjst M, Dharmage S, André E et al. Latitude, birth date, and allergy. *PLoS Med* 2005; 2: e294.
- ⁵ Hopper JL, Jenkins MA, Carlin JB, Giles GG. Increase in the self-reported prevalence of asthma and hay fever in adults over the last generation: a matched parent-offspring study. *Aust J Public Health* 1995; 19: 120-4.
- ⁶ Greisner WA 3rd, Settupane RJ, Settupane GA .Natural history of hay fever: a 23-year follow-up of college students. *Allergy Asthma Proc* 1998; 19: 271-5.
- ⁷ Cirillo I, Marseglia G, Klersy C et al. Allergic patients have more numerous and prolonged respiratory infections than non allergic subjects. *Allergy* 2007; 62: 1087-1090.
- ⁸ Plaut M, Valentine MD. Clinical practice. Allergic rhinitis. *N Engl J Med* 2005; 353: 1934-44.
- ⁹ Van Hoecke H, Van Cauwenberge P. Critical look at the clinical practice guidelines for allergic rhinitis. *Respir Med* 2007; 101: 706-14.
- ¹⁰ Simons FE. Learning impairment and allergic rhinitis. *Allergy Asthma Proc* 1996; 17: 185-9.
- ¹¹ Marshall PS, Colon EA . Effects of allergy season on mood and cognitive function. *Ann Allergy* 1993; 71: 251-8.
- ¹² Gauci M et al .A Minnesota Multiphasic Personality Inventory Profile of women with allergic rhinitis. *Psychosom Med* 1993; 55: 533-40.
- ¹³ Nolen TM. Sedative effects of antihistamines: safety, performance, learning, and quality of life. *Clin Ther* 1997; 19: 39-55.
- ¹⁴ Storms WW. Treatment of allergic rhinitis: effects of allergic rhinitis and antihistamines on performance. *Allergy and Asthma Proc* 1997; 18: 59-61.

avoidance of exposure to the allergen is often not possible, the cornerstones of management revolve around the use of medication (one or more of topical nasal corticosteroids, oral or topical antihistamines.(Plaut and Valentine, 2005; Van Hoescke and Van Cauwenberge, 2007).^{8,9}

Allergen immunotherapy (IT) is a treatment that can address the immune problem that causes allergies altering the natural history of disease. This treatment involves administration of increasingly larger amounts of commercial allergen extracts with the aim of inducing tolerance to allergen following subsequent natural exposure. This form of treatment has been found to be effective at reducing the severity of allergic rhinitis and conjunctivitis and to have a beneficial impact in some patients with asthma. There is also preliminary evidence that early use of IT may reduce disease progression from allergic rhinitis to asthma and reduce the development of new sensitisations. Injection of allergen (subcutaneous immunotherapy, SCIT) has been the traditional method of choice for several decades but recent research has demonstrated the efficacy of high dose sublingual/oral immunotherapy (SLIT), opening up this form of treatment to young children who might otherwise not have been able to tolerate treatment by traditional methods (Pajno, 2007; Canonica and Passalacqua, 2006; Saltoun, 2002, Calderon 2010).^{16,17,18,19} IT has been shown to be cost effective compared to medication alone (Keiding and Jorgensen, 2007; Petersen et al, 2005; Ariano et al, 2006).^{20,21,22}

Immunotherapy with conventional SCIT is disease modifying but has the disadvantage of producing occasional systemic, severe and rarely, fatal anaphylaxis. These reactions are more severe in patients with bronchial asthma. An important advantage of SLIT is that it is generally perceived to be safer, positioning SLIT to be an effective and safe method of immunotherapy, especially for patients with asthma who are at greater risk for systemic and more severe reactions to IT.

Many studies using SLIT have been published, however, most randomised controlled trials (RCTs) carried out before 2005 were underpowered and can only be considered as exploratory studies. Furthermore, there are major differences in allergen formulation, dose of allergen and vehicle used making it impossible to compare these studies. Nevertheless wide experience with SLIT in both children and adult populations suffering from immediate hypersensitivity reactions to pollen and dust mite resulting in allergic reactions with or without asthma has resulted in recommendations for its use in several documents:

¹⁵ Vuurman EF et al. Seasonal allergic rhinitis and antihistamine effects on children's learning. *Ann Allergy* 1993; 71: 121-6.

¹⁶ Pajno GB .Sublingual immunotherapy: the optimism and the issues. *J Allergy Clin Immunol* 2007; 119: 796-801.

¹⁷ Canonica GW, Passalacqua G. Sublingual immunotherapy in the treatment of adult allergic rhinitis patients. *Allergy* 2006; 61(Suppl 81): 20-3.

¹⁸ Saltoun CA .Update on efficacy of allergen immunotherapy for allergic rhinitis and Asthma. *Allergy Asthma Proc* 2002; 23: 377-80.

¹⁹ Calderon M, Mosges R, Hellmich M, Demoly P. Towards evidence-based medicine in specific grass pollen immunotherapy. *Allergy* 2010; 65: 420-434.

²⁰ Keiding H, Jorgensen KP. A cost-effectiveness analysis of immunotherapy with SQ allergen extract for patients with seasonal allergic rhinoconjunctivitis in selected European countries. *Curr Med Res Opin.* 2007; 23: 1113-20.

²¹ Petersen KD, Gyrd-Hansen D, Dahl R. Health-economic analyses of subcutaneous specific immunotherapy for grass pollen and mite allergy. *Allergol Immunopathol(Madr)* 2005; 33: 296-302.

²² Ariano R, Berto P, Tracci D, Incorvaia C, Frati F. Pharmacoeconomics of allergen immunotherapy compared with symptomatic drug treatment in patients with allergic rhinitis and asthma. *Allergy Asthma Proc* 2006; 27: 159-63.

1. The WHO position on allergen immunotherapy (1998;Bousquet et al).²³
2. The allergic rhinitis and its impact on asthma (ARIA) workshop group paper in collaboration with WHO (2001; Bousquet et al).²⁴
3. The Cochrane review of SLIT for AR/C in 22 studies involving 979 patients (children and adults) (2003; Wilson et al).²⁵
4. ARIA 2008 update (Bousquet et al).²⁶

In his 2002 review “Is sublingual immunotherapy clinically effective?” Malling analysed 23 papers published in peer reviewed journals covering double blind placebo controlled studies on SLIT. His conclusions were that it was a promising treatment for allergic rhinoconjunctivitis (AR/C) but that further large scale properly randomised controlled studies were necessary to better define parameters. A follow up publication by Malling in 2006 provided a summary of 39 double-blind, placebo-controlled studies on SLIT published between 1990 and 2006.²⁷ In this document he highlighted deficiencies in the quality of many of the reviewed papers. Most papers reviewed were underpowered to detect statistical significance and only 40% of the published studies in his review showed statistically significant differences between active and placebo treatment arms.

Following the highlighting of such deficiencies, several groups published guidelines for the performance of immunotherapy studies. One of these entitled “Guidelines in sublingual immunotherapy” was written by an expert panel convened by the World Allergy Organisation.

Many of the recommendations have been adopted by the European Medicines Agency (EMA). In a recent publication, (Calderon et al) examined the utility of specific grass pollen immunotherapy using the principles of evidence based medicine.²⁸ In this publication they identified 33 randomised, double- blind, placebo-controlled (including 7 paediatric studies) with a total of 440 specific immunotherapy treated subjects in 7 trials for SCIT with natural pollen extracts, 168 in 3 trials for SCIT with allergoids, 906 in 16 trials (5 paediatric) for natural extract SLIT drops and 1,605 in 5 trials (2 paediatric) for natural extract SLIT tablets. They comment that “the multinational rigorous trials of natural extract SLIT tablets correspond to a high level of evidence in adult and paediatric populations for the efficacy of this form of immunotherapy”.

This AusPAR describes the evaluation by the TGA of a submission from Regulatory Concepts Pty Ltd on behalf of the sponsor, Helex-A Pty Ltd, to register Oralair (allergen pollen extract of five grasses) 100 IR and 300 IR sublingual tablets as:

1. Oralair sublingual tablets initiation composite pack of 100 IR and 300 IR allergen pollen extract of five grasses

²³ Bousquet J, Lockey R, Malling HJ et al. Allergen immunotherapy: therapeutic vaccines for allergic diseases. World Health Organization. American academy of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol* 1998; 81: 401-5.

²⁴ Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108: S147-334.

²⁵ Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and metaanalysis. *Allergy* 2005; 60: 4-12.

²⁶ Bousquet J, Khaltaev N, Cruz AA 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 Suppl 86: 8-160.

²⁷ Malling HJ, Abreu-Nogueira J, Alvarez-Cuesta E, Bjorksten B, Cox LS, Linnemann DL, Nolte H, Weldon D, Finegold I, Nelson HS. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol* 2006; 117: 1021-35.

²⁸ Calderon M, Mosges R, Hellmich M, Demoly P. Towards evidence-based medicine in specific grass pollen immunotherapy. *Allergy* 2010; 65: 420-434.

2. Oralair sublingual tablets continuation treatment, 300 IR allergen pollen extract of five grasses

Oralair (Five Grasses) 100 IR and 300 IR sublingual tablets are a new dosage form of the following currently registered products:

- Alustal Extract of Five Grasses 10 IR/mL injection suspension vial (AUST R 132847)
- Alustal Extract of Five Grasses Composite Pack injection suspension vial composite pack (AUST R 132848)

The registered indication for these products is:

Treatment of patients with Type 1 allergy (Gell and Coombs classification), particularly presenting as seasonal or perennial rhinitis, conjunctivitis, rhinoconjunctivitis, with or without associated asthma.

The route of administration is subcutaneous injection.

The above Alustal products contain allergen extracts of a mixture of pollens from the following five grasses: Cocksfoot (*Dactylis glomerata* L.), Sweet Vernal grass (*Anthoxanthum odoratum* L.), Rye grass (*Lolium perenne* L.), Meadow grass (*Poa pratensis* L.) and Timothy (*Phleum pratense* L.).

The same allergen extract of this mixture of five grasses is used for Oralair sublingual tablets. Each sublingual tablet contains 100 IR or 300 IR of the five grass pollen allergen extracts.

The proposed indication is as follows:

Treatment of grass pollen allergic rhinitis with or without conjunctivitis in adults, adolescents and children (above the age of 5) with clinically relevant symptoms, confirmed by a positive cutaneous test and/or a positive titre of the specific IgE to the grass pollen.

In adults, adolescents and children above the age of 5 years, therapy with Oralair is composed of an initiation treatment, including a three day dose escalation, and a continuation treatment. The initiation treatment corresponds to the first month of treatment with Oralair and the dosage regimen is as follows:

| | | | |
|---------------|---|--------|--------------------|
| Small blister | } | Day 1 | 1 x 100 IR tablet |
| | | Day 2 | 2 x 100 IR tablets |
| Large blister | } | Day 3 | 1 x 300 IR tablet |
| | | Day 4 | 1 x 300 IR tablet |
| | | Day 5 | 1 x 300 IR tablet |
| | | . | . |
| | | Day 30 | 1 x 300 IR tablet |

The continuation treatment is given from the second month onwards and is one Oralair 300 IR sublingual tablet per day until the end of the pollen season.

The proposed route of administration is sublingual. It is recommended that the tablet is taken in the morning, on an empty stomach. The tablet is placed under the tongue until complete dissolution (for at least one minute) and then swallowed. The two 100 IR tablets to be taken on the second day of treatment must be placed under the tongue simultaneously and then swallowed.

It is stated in the proposed product information (PI) that that treatment should be initiated approximately four months before the expected onset of the pollen season and that treatment must be maintained throughout the pollen season.

Regulatory Status

These products for subcutaneous injection (Alustal) were entered on the Australian Register of Therapeutic Goods (ARTG) on 3 October 2006. A similar application to the current submission for sublingual tablets was submitted in Germany and in 22 European Union (EU) countries under the Mutual Recognition Procedure with Germany as the Reference Member State. The application was approved in Germany on 23 June 2008 and has now been approved in most other EU countries during 2010. The application is also under evaluation in New Zealand.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Structure/Composition

The drug substance is an extract of five grasses as shown in Table 1.

Table 1: Allergen composition of grass pollens

| Species name | Allergen Name | Mol. Wt. (kDa) |
|--|----------------------|-----------------------|
| <i>Dactylis glomerata</i> (Cocksfoot) | Dac g 1 | 32 |
| | Dac g 2 | 11 |
| | Dac g 3 | 14 |
| | Dac g 4 | 60 |
| | Dac g 5 | 25/28 |
| <i>Lolium perenne</i> (Rye-grass) | Lol p 1 | 27 |
| | Lol p 2 | 11 |
| | Lol p 3 | 11 |
| | Lol p 4 | 57 |
| | Lol p 5 | 31 |
| | Lol p 11 | 16 |
| <i>Phleum pratense</i> (Timothy) | Phl p 1 | 27 |
| | Phl p 2 | 10-12 |
| | Phl p 4 | 55 |
| | Phl p 5 | 32 |
| | Phl p 6 | 11 |
| | Phl p 7 | 6-9 |
| | Phl p 11 | 20 |
| | Phl p 12 | 14 |
| | Phl p 13 | 55 |
| <i>Poa pratensis</i> (Meadow grass) | Poa p 1 | 33 |
| | Poa p 5 | 34 |
| <i>Anthoxanthum odoratum</i> (Sweet vernal grass) | Ant o 1 | 27 |

Manufacture

The manufacture consisted of a 12 step process which was satisfactorily described.

Physical and Chemical Properties

The main physicochemical characteristics of this drug substance, which corresponds to the physical form of the extract used for the tablets manufacturing are:

- solid state form
- freely soluble in water (freeze dried extract)
- particle size distribution.

Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product were evaluated and considered satisfactory. Appropriate validation data were submitted in support of the test procedures.

Stability

The results for the stability indicating parameters show that the grass pollen allergen extract (as sieved freeze dried) packaged in a polyethylene bag, within a watertight aluminium drum, is stable for 36 months when stored at $+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$. The sieved grass pollen allergen extract is stable for at least 6 months when stored at $+25^{\circ}\text{C} \pm 2^{\circ}\text{C} / 60\% \text{RH} \pm 5\%$.

The sponsor proposed a 36-month shelf-life at $+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ for the grass pollen allergen extract (as sieved freeze dried) packaged in polyethylene bag, within a watertight aluminium drum, with the expectation that this shelf-life will be extended as more data become available from scheduled stability time-points.

Drug Product

Formulation

The composition of the drug product included the sieved freeze-dried grass pollen allergen extract with excipients microcrystalline cellulose, croscarmellose sodium, magnesium stearate and lactose monohydrate.

Manufacture

The chronology of the Oralair manufacturing process was satisfactorily described.

Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product were evaluated and considered satisfactory. Appropriate validation data were submitted in support of the test procedures.

Stability

Based on the acceptable 36 months normal condition stability data ($+25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{RH} \pm 5\%$), 24 months intermediate conditions stability data ($+30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{RH} \pm 5\%$) and 6 month accelerated stability data ($+40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{RH} \pm 5\%$), a shelf life of 24 months was proposed for Oralair 100 IR and 300 IR packaged in aluminium blisters.

Advisory Committee Considerations

This submission was considered by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee of Prescription Medicines (ACPM) and the committee recommended that there should be no objection on quality and pharmaceutical grounds to approval of the application provided all outstanding issues were addressed to the satisfaction of the TGA. All issues were addressed to the satisfaction of the TGA.

Quality Summary and Conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological and biopharmaceutical data submitted in support of this application were evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

III. Nonclinical Findings

Introduction

The proposed treatment regimen includes a three dose escalation; the maximum recommended dose is one 300 IR tablet daily. The maximum recommended dose of Alustal is 8 IR/week. Nonclinical data were not submitted to the TGA for evaluation in the previous submission, in light of overseas marketing experience. For simplicity, the proposed tablet formulation will be referred to in this report as Oralair and the registered product for injection will be referred to as Alustal.

Immunological basis of allergy

Type I hypersensitivity, or allergy, is defined mechanistically as the production of allergen-specific immunoglobulin E (IgE) and activation of IgE-binding cells upon challenge, leading to an excessive inflammatory response. An estimated 40% of people in Western populations show an exaggerated tendency to mount such IgE responses to innocuous environmental allergens (WAO Position Paper, 2009), which is known as atopy.²⁹ Under normal conditions, IgE is important for host defence against multicellular parasites. Thus, it is predominantly distributed at sites of entry of such parasites, including under the skin, under the epithelial surfaces of the airways and in the submucosa of the gastrointestinal (GI) tract. IgE is produced by plasma cells in draining lymph nodes, and is predominantly localised within tissues, bound with high affinity to the IgE receptor (FcεR) on mast cells, and to some extent eosinophils and basophils. IgE production is predominantly driven by type 2 helper T lymphocytes (T_H2 cells), which differentiate from undifferentiated T₀ cells following exposure to cytokine mediators such as interleukin 4 (IL-4), IL-5, IL-9, IL-10 and IL-13. In contrast, IgE production can be inhibited by T_H1 cells, which develop in response to IL-12 and interferon (IFN)-γ (Janeway *et al.*, 2005).³⁰

The activation of IgE-binding cells by specific antigen is characterised initially by the release of pro-inflammatory molecules (for example histamine and prostaglandins), which is known as the 'immediate response'. This results in effects such as increased local blood flow and vascular permeability, increased fluid accumulation and/or secretion and increased muscular contractility. This leads to the accumulation of fluid and other immune cells and factors at the target site, for enhancement of the immune response, while increased muscular contractility may facilitate actions such as sneezing or coughing for expulsion of pathogens or other foreign antigens. In the continuous presence of antigen, the immediate response is followed by a more sustained 'late-phase response', which involves the synthesis and release of cytokines (for example, tumour necrosis factor [TNF]-α, interleukin [IL]-4, IL-13), prostaglandins and leukotrienes and recruitment of other effector cells (T_H2 cells, eosinophils and basophils; Janeway *et al.*, 2005).³⁰

Allergens are also taken up by Langerhan's-like dendritic cells (LLDCs) by phagocytosis, macropinocytosis or receptor-mediated endocytosis. Distinct from true Langerhans cells of the skin, LLDCs are characterised by expression of the FcεRI (IgE) receptor. LLDCs are unique to the oral mucosa, and migrate to proximal draining lymph nodes upon activation, which represent specialised microenvironments favouring the induction of mucosal tolerance. There they differentiate into professional antigen-presenting cells with co-stimulatory activity. This favours the maintenance of a T_H2-favoured cytokine environment for the continuation and amplification of the immune response, which results in the continued secretion of high levels of IL-4, IL-5 and IL-13 cytokines. Together,

²⁹ Bousquet PJ *et al.* Sub-lingual immunotherapy: World Allergy Organization position paper 2009. *Allergy* 2009; 64: Supp91: 1-59.

³⁰ Janeway CA *et al.* Immunobiology, 6th Edition. Garland Science Publishing, USA, 2005.

these effects account for the typical symptoms observed in allergy (Janeway *et al.*, 2005; Moingeon *et al.*, 2006).^{30,31}

The aetiology behind the development of an allergic response in susceptible individuals is not entirely clear, but atopic individuals commonly have higher levels of circulating IgE and eosinophils, the cause of which may have a genetic component (for example genetic variation in the IL-4 gene promoter, variation of expression of a protein subunit of IL-2 or inheritance of predisposing major histocompatibility complex (MHC) class II haplotypes). Increased levels of IgE often result in increased FcεRI expression on mast cells, enhanced sensitivity of such cells to activation by low antigen concentrations and increased release of chemical mediators and cytokines. Immune deficits, such as impaired production of IL-10 by dendritic cells, and reduced activity of CD4⁺CD25⁺ regulatory T cells (T_{reg} cells; discussed further below) have also been associated with allergic rhinitis.³² Moreover, a common feature of most allergens is that they are relatively small, highly soluble proteins present in small quantities, which are readily diffusible into the mucosa upon inhalation. The presentation of low doses of antigen, as seen with allergens, appears to favour the activation of T_H2 cells over T_H1 cells. (Janeway *et al.*, 2005).³⁰

Allergen-specific immunotherapy

Allergen-specific immunotherapy is the only therapy currently clinically available with the potential to treat the underlying causes of allergy. The aim of allergen-specific immunotherapy is to shift the antibody response away from one dominated by IgE, and towards an immunoglobulin G (IgG)-mediated response (Janeway *et al.*, 2005).³⁰ An IgG-mediated response is considered more desirable, as pro-inflammatory cells are not activated, which are the source of most adverse symptoms of allergy. Allergen-specific immunotherapy has a long clinical history, although the immunological mechanisms behind it are not well understood (Bousquet *et al.*, 2009).²⁹ Historically, protocols employing subcutaneous injection of allergen (SC immunotherapy; SCIT) predominated, but immunotherapy by sublingual administration (SLIT) has emerged in response to safety concerns associated with SCIT. As a locally-applied therapy, SLIT is believed to confer a much lower clinical risk of anaphylaxis than that observed with the systemic administration of antigen via SCIT (Janeway *et al.*, 2005).³⁰ Several products for SCIT are registered in Australia (primarily against Hymenoptera venom) and also include Alustal. The rationale behind SLIT is that the natural mechanisms underlying the induction of oral tolerance at mucosal surfaces may represent an effective approach for modulating the adverse immune responses associated with allergy (Akdis *et al.*, 2006).³³

Different SLIT protocols have been investigated clinically, particularly regarding whether or not the allergens are swallowed by patients following sublingual contact. There is evidence that the combination of holding the allergen under the tongue for 1–2 minutes prior to swallowing (referred to as sublingual-swallow; this protocol is proposed for Oralair treatment) appears to be better than either route alone, as both the oral mucosa and the GI tract immune systems probably contribute to the induction of tolerance (Akdis *et al.*, 2006).³³ A role for intestinal absorption of allergen is considered unlikely (Fрати *et al.*, 2007).³⁴ Contact with the oral mucosa appears to be necessary for efficacy of SLIT; no

³¹ Moingeon P *et al.* Immune mechanisms of allergen-specific sublingual immunotherapy. *Allergy* 2006; 61: 151–165.

³² CD25= α-chain of IL-2 receptor

³³ Akdis CA *et al.* Immunological mechanisms of sublingual immunotherapy. *Allergy* 2006; 61 Supp81:11–14.

³⁴ Frати F *et al.* Mucosal immunization application to allergic disease: sublingual immunotherapy. *Allergy Asthma Proc* 2007; 28: 35–39.

effect on IgE levels was observed in a nonclinical study following gastric intubation of ovalbumin in rats compared with sublingual administration (Holt *et al.*, 1988).³⁵

Early clinical studies of SLIT showed limited efficacy compared with SCIT protocols (Bousquet *et al.*, 2009).²⁹ SLIT was consequently slow to gain acceptance outside Europe, particularly in the USA, and still remains controversial (Bousquet *et al.*, 2008).²⁶ However, more recent studies demonstrated similar levels of clinical efficacy of SLIT but at allergen dose levels at least 50–100 times higher than for SCIT. This may be in part due to the frequent inclusion of adjuvants in SCIT but not SLIT protocols. A recent position paper from the World Allergy Organization (Bousquet *et al.*, 2009) was generally supportive of the clinical safety and efficacy of SLIT; nonclinical findings were not discussed in this report. The FDA has not approved any SLIT therapy.

Mechanisms of oral tolerance

Oral tolerance is the specific and active unresponsiveness to foreign antigens within the GI tract, usually directed towards food antigens and commensal bacteria. Oral tolerance is believed to occur subsequent to antigen presentation to LLDCs in the absence of inflammatory stimuli (for example with food intake; Janeway *et al.*, 2005).³⁰ The nature of the downstream response following activation of LLDCs appears to be critical in determining whether an active response (allergy) or tolerance occurs (Fрати *et al.*, 2007).³⁴ The mechanisms behind this are not clearly understood but oral tolerance induction is believed to involve shifting the usual allergy-associated T cell responses from those dominated by T_H2 cell activity to T_H1-mediated responses and the induction of specific active tolerance pathways, namely (i) anergy, in which T cells presented with peptide in the absence of co-stimulatory signals become refractory to further stimulation with antigen, (ii) deletion of antigen-specific T cells by apoptosis (this has been observed in animals in response to the oral intake of very large doses of antigen, as would occur with food intake) and (iii) the development of T_{reg} cells, which actively suppress antigen-specific responses after re-challenge (Moingeon *et al.*, 2006; Allam *et al.*, 2009).^{31,36} The magnitude of the T cell responses appears to be directly proportional to the number of LLDCs that migrate to lymph nodes (Incorvaia *et al.*, 2008).³⁷ Other factors which may contribute to oral tolerance include the properties of local antigen-presenting cells (APCs) and contributions from epithelial/structural cells, secreted IgA and commensal bacteria (Scadding and Durham, 2009).³⁸ Evidence is emerging that T_{reg} cells make a key contribution to efficacy in SLIT, as discussed below.

Regulatory T cells

T_{reg} cells act directly and indirectly on several immune pathways associated with tolerance, and therefore also allergy. These effects include (i) suppression of mast cell, basophil and eosinophil activity, (ii) suppression of the inflammatory properties of dendritic cells and induction of tolerogenic dendritic cells, (iii) mediation of class switching from IgE to IgG₄ and immunoglobulin A (IgA) production by B cells, (iv) suppression of effector T_H1 and T_H2 cells and (v) suppression of T cell migration to target tissue. These functions are mediated by several cytokines, primarily by IL-10 and

³⁵ Holt PG *et al.* Sublingual allergen administration. I. Selective suppression of IgE production in rats by high allergen doses. *Clin Allergy* 1988; 229–234.

³⁶ Allam JP *et al.* Dendritic cells as potential targets for mucosal immunotherapy. *Curr Opin Allergy Clin Immunol* 2009; 9: 554–557.

³⁷ Incorvaia C *et al.* Effects of sublingual immunotherapy on allergic inflammation. *Inflamm Allergy Drug Targets* 2008; 7: 167–172.

³⁸ Scadding G and Durham S. Mechanisms of sublingual immunotherapy. *J Asthma* 2009; 46: 322–334.

transforming growth factor (TGF)- β (Palomares *et al.*, 2010).³⁹ IL-10 and TGF- β are both anti-inflammatory cytokines with T cell-suppressive activity (Scadding and Durham, 2009); their functions in terms of T_{reg} cell function and SLIT are discussed below.³⁸

Three major classes of T_{reg} cells have been identified in humans. The best-characterised of these are CD4⁺CD25⁺ T cells, which are also referred to as 'natural' T_{reg} cells. These cells mature from CD4⁺ T cells and are generally identified based on expression of the transcription factor FoxP3, which may in turn drive expression of CD25, IL-10 and TGF- β . Adoptive transfer experiments in mouse models of allergy and asthma have demonstrated the essential role of CD4⁺CD25⁺ T_{reg} cells for the induction and maintenance of tolerance to allergens. When activated, CD4⁺CD25⁺ cells suppress antigen-specific T cell proliferation *in vitro* and *in vivo*, possibly via direct contact with target cells and/or by secretion of inhibitors of T cell proliferation (IL-10 and TGF- β). T_{reg} cells also demonstrate anergic activity *in vitro*. There is no clear evidence that CD4⁺CD25⁺ cells act directly on dendritic cells and other APCs although IL-10 secretion may inhibit the differentiation of dendritic cells, and therefore impair their ability to activate T cells. (Janeway *et al.*, 2005; Scadding and Durham, 2009; Palomares *et al.*, 2010; Nicolson and Wraith, 2006).^{30,38,39,40} Allergic disease may be at least in part due to a relative imbalance between the effects of T_{reg} cells and T_H2 cells (Scadding and Durham, 2009). Indeed, *in vitro* inhibition of T cell proliferation mediated by CD4⁺CD25⁺ cells from patients with allergy was reduced compared with non-atopic patients, particularly in patients during pollen season (Ling *et al.*, 2004).⁴¹

Other types of (CD25⁻) T_{reg} cells include T_H3 and T_R1 cells, which appear to be particularly important in the mucosal immune system and are sometimes referred to as 'induced' T_{reg} cells. T_H3 cells produce IL-4 and IL-10, and are distinguished from T_H2 cells by the production of TGF- β . T_R1 cells secrete high levels of IL-10, and also TGF- β , IFN- γ , IL-5, IL-2, but not IL-4. Induction of oral tolerance results in expansion of T_H3 and/or T_R1 populations (Janeway *et al.*, 2005; Nicolson and Wraith, 2006). Both demonstrate antigen-dependent suppression of T cells *in vitro* and *in vivo*; T_H3 cells also inhibit IgG production by B cells (Nicolson and Wraith, 2006). T_R1 cells represent the dominant subset present in non-allergic individuals if an immune response to a common environmental allergen is detectable (Palomares *et al.*, 2010).

Duration of treatment

Based on the proposed treatment duration of four months prior to onset of the pollen season and continuing throughout the pollen season, a patient, depending on their specific allergies, may theoretically require continuous treatment with Oralair. The assessment of the nonclinical safety of Oralair was therefore conducted taking this potential chronic treatment duration into account.

Choice of allergen extracts

The product comprises extracts of a mixture of pollens from five grasses (the same allergen extract as for Alustal is proposed for Oralair): Cocksfoot/Orchard grass (*Dactylis glomerata* L.), Sweet vernal grass (*Anthoxanthum odoratum* L.), Rye grass (*Lolium perenne* L.), Meadow/Kentucky Blue/June grass (*Poa pratensis* L.) and Timothy grass (*Phleum pratense* L.). Four of these grasses (all but sweet vernal grass) are described as common

³⁹ Palomares O *et al.* Role of Treg in immune regulation of allergic diseases. *Eur J Immunol* 2010; 40: 1232–1240.

⁴⁰ Nicolson KS and Wraith DC. Natural and induced regulatory T cells: Targets for immunotherapy of autoimmune disease and allergy. *Inflamm Allergy Drug Targets* 2006; 5: 141–148.

⁴¹ Ling EM *et al.* Relation of CD4⁺CD25⁺ regulatory T-cell suppression of allergen-driven T-cell activation to atopic status and expression of allergic disease. *Lancet* 2004; 363: 608–615.

pollen allergens by the Australasian Society of Clinical Immunology and Allergy.⁴² All five are widely distributed in Australia, and most have long flowering seasons, as summarised in Table 2 below.

Table 2: Distribution and flowering of grasses in Australia

| Grass | Distribution | Flowering ^a | Source |
|--------------------|--------------------------|------------------------|---------------------|
| Cocksfoot | All states except NT | Sep–Feb | www.allergy.org.au |
| Sweet vernal grass | All states except NT | Oct–Jan | www.flora.sa.gov.au |
| Rye grass | All states except NT | Aug–Feb/Mar | www.allergy.org.au |
| Meadow grass | All states except NT, WA | Sep–Dec | www.allergy.org.au |
| Timothy grass | ACT, QLD, VIC, TAS | Sep–Dec, Jan (QLD) | www.allergy.org.au |

^aFlowering times generally vary between states; the longest range is listed.

Thus, all chosen grasses are expected to be suitable for use as a specific immunotherapy in the Australian population.

Overall quality of the nonclinical dossier

The submitted nonclinical data comprised single and repeat dose toxicity studies, genotoxicity studies, reproductive toxicity studies and local tolerance studies in rodents. No pharmacology, pharmacokinetic or carcinogenicity studies were submitted. As justification for this, the sponsor stated that the nonclinical testing strategy was limited to those aspects that were deemed to require new dedicated evaluation, taking into account the clinical experience already gained with these allergen extracts. However, as the nonclinical safety of grass pollen allergen extracts has not been previously evaluated by the TGA, such studies are warranted. Apart from some acute toxicity studies, most studies were Good Laboratory Practice (GLP) compliant and were generally adequate. Further discussion of data adequacy is provided in the relevant subsections below.

Administration of test substances by the intended clinical route, when feasible, is recommended for toxicity studies, however in patients, Oralair tablets are placed sublingually until completely dissolved, then swallowed. The sponsor's *Nonclinical Overview* stated that "Therefore, no animal models are available that closely mimic the actual conditions of human administration." Oralair was administered by oral gavage in a number of toxicity studies, which bypasses the oral cavity. In order to address this limitation, several studies investigated local tolerance in the cheek pouch model in hamsters.

Nonclinical studies with Oralair were conducted from 1989 onwards, and included developmental batches, and batches at different stages of the manufacturing process. Some of these studies were considered commercially confidential by the sponsor and are not included in this AusPAR. Studies initiated after March 2006 used test material manufactured with the final optimised process.

Pharmacology

Primary pharmacodynamics

No nonclinical studies investigating the pharmacodynamics of Oralair were submitted. As justification, the sponsor stated that no standardised and validated animal models are available to demonstrate the potential efficacy of any allergen extract for use as a specific

⁴² www.allergy.org.au

immunotherapy via the sublingual route. However, several published studies (including some cited by the sponsor) are available in which the immunomodulatory mechanisms of SLIT have been successfully investigated in animal models of allergy (for example, Holt *et al.*, 1998; Winkler *et al.* 2006; Kildsgaard *et al.*, 2007; Rask *et al.*, 2000; Sato *et al.*, 2002).^{35,43,44,45,46} The oral mucosal immune system is relatively well-characterised in mice; therefore any findings in this species could be extrapolated to humans. It is also possible to obtain *in vivo* data in these models considered unattainable in humans, such as from dissection of regional lymph nodes. Although any available nonclinical models are not standardised and validated, the use of such models in studies with Oralair may have contributed greatly to the limited understanding of its mechanism of action and efficacy.

In the absence of nonclinical pharmacodynamic studies with Oralair, the sponsor submitted a relatively limited review of the published literature discussing aspects of the mechanism of action and efficacy of allergen-specific immunotherapy. Thus, a more detailed discussion is provided under *Immunological effects of sublingual immunotherapy* below. Most of the available scientific literature regarding the pharmacodynamics of SLIT pertains to *in vitro* data obtained using samples from patients during clinical trials. As any such data obtained from human immune tissues is likely to be more clinically relevant than studies in animals, the nonclinical assessment of the primary pharmacodynamics of Oralair therefore relied primarily on these data.

Immunological effects of sublingual immunotherapy

The immunological mechanisms underlying clinical efficacy in SLIT are not well understood; some nonclinical data are available but explanatory models have developed primarily from findings of differences in immune system components in treated patients. As with normal oral tolerance pathways, SLIT involves local (within the oral mucosa) capture of allergen by LLDCs, most likely through FcεRI binding (Allam *et al.*, 2009).³⁶ This appears to result in changes to three different immunological pathways, including (i) modulation of specific antibody responses, (ii) reduction in the recruitment and activation of pro-inflammatory cells and (iii) changes in the pattern of T cell responses (Moingeon *et al.*, 2006; Akdis *et al.*, 2006).^{31,33} Each of these is discussed in subsequent subsections.

Modulation of the immune response to allergens during SLIT appears to be largely dependent on IL-10. IL-10 is produced by T_R1, T_H1 and T_H2 cells, mononuclear macrophages and NK cells, and may be produced by LLDCs (Scadding and Durham, 2009).³⁸ Increased IL-10 levels are associated with prolonged inhibition of the allergen-specific T cell response, reduced numbers of resident mast cells and increased eosinophils, reduced activation of specific T_H2 cells, reduced production of pro-inflammatory cytokines, a shift in IgE/IgG ratios, reduction of co-stimulatory signals between T_H and APC cells, and inhibition of APC-mediated production of T_H-activating signals. IL-10 may also be required for anergy (Incorvaia *et al.*, 2008).³⁷ Successful SCIT has been associated with increased IL-10 production in allergen stimulated T cell cultures *in vitro*, and increased IL-10 levels *in vivo* (Scadding and Durham, 2009; Ciprandi *et al.*, 2005).^{38,47}

⁴³ Winkler B *et al.* The role of Foxp3+ T cells in long-term efficacy of prophylactic and therapeutic mucosal tolerance induction in mice. *Allergy* 2006; 61: 173–180.

⁴⁴ Kildsgaard J *et al.* Sublingual immunotherapy in sensitized mice. *Ann Allergy Asthma Immunol* 2007; 98: 366–372.

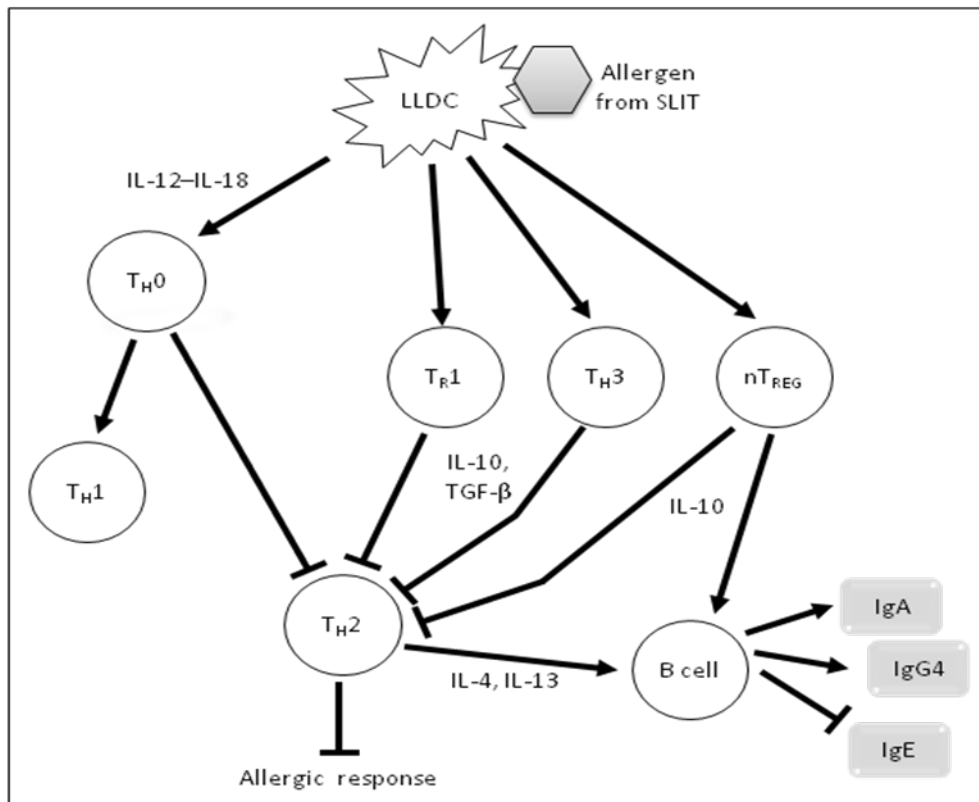
⁴⁵ Rask C *et al.* Prolonged oral treatment with low doses of allergen conjugated to cholera toxin B subunit suppresses immunoglobulin E antibody responses in sensitized mice. *Clin Exp Allergy* 2000; 30: 1024–1032.

⁴⁶ Sato MN *et al.* Oral tolerance induction to *Dermatophagoides pteronyssinus* and *Blomia tropicalis* in sensitized mice: occurrence of natural autoantibodies to immunoglobulin E. *Clin Exp Allergy* 2002; 32: 1667–1674.

⁴⁷ Ciprandi G *et al.* Sublingual immunotherapy affects specific antibody and TGF-β serum levels in patients with allergic rhinitis. *Int J Immunopathol Pharmacol* 2009; 22: 1089–1096.

A putative model of the immunological effects of SLIT is shown in Figure 1 below.

Figure 1: Putative immunological effects of SLIT (adapted from Incorvaia *et al.*, 2008)



Models of SLIT function indicate a relatively rapid down-regulation of pro-inflammatory cells and up-regulation of blocking antibodies (within days to weeks), whereas a detectable impact of T cells responses and adaptive immunity generally occurs after months of treatment. One SLIT study in children with house dust mite-induced asthma/rhinitis demonstrated some persistence of effects 4–5 years following discontinuation of treatment (treatment was of similar duration; Di Rienzo *et al.*, 2003).⁴⁸ The potential duration of the immunomodulatory effect of SLIT with Oralair is currently unknown.

Modulation of antibody responses

Consistent with its stated aims, allergen-specific immunotherapy is usually associated with changes to allergen-specific Ig levels, although considerable variability in the nature of the response has been reported in different studies. There also appear to be differences in the antibody responses seen with SCIT and SLIT. Typically, SLIT protocols (for example, for grass pollen or house dust mite allergy) are associated with increases in serum IgE and IgG4 levels. This was shown to be dose-related in three studies, and was usually associated with some degree of clinical efficacy (Scadding and Durham, 2009).³⁸ Increases in specific IgA levels were also reported in some studies (Moingeon *et al.*, 2006).³¹ In contrast, SCIT generally induces an initial increase in IgE levels, followed by a subsequent decrease. This is usually associated with increases in specific IgG1 and IgG4 levels and often increases in

⁴⁸ Di Rienzo V *et al.* Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. *Clin Exp Allergy* 2003; 33: 206–10.

IgA responses (Moingeon *et al.*, 2006). In one study, the magnitude of IgG induction was about 4 times lower than with SCIT.

In nonclinical studies, reductions in IgE levels were frequently observed following oral administration of allergen in mouse models of house dust mite allergy (Sato *et al.*, 2002) and models of milk protein-associated allergy or allergic asthma (Pecquet *et al.*, 1999; Chung *et al.*, 2002), but similar results were not seen in some SLIT protocols for grass pollen allergy (Kildsgaard *et al.*, 2007) and ovalbumin-associated allergic asthma (Razafindrasita *et al.*, 2007).^{44,46,49,50,51} Changes to other Ig levels in these models were less consistent (when measured), with reductions in levels of IgG1, IgG2a and IgG2b observed in response to oral immunotherapy with one of two house dust mite allergens in mice (Sato *et al.*, 2002) but no effects on IgG1 or IgG2 levels with grass pollen SLIT in mice (Kildsgaard *et al.*, 2007).

Functionally, it is thought that IgGs and IgA compete with IgE for allergen binding and act as 'blocking' antibodies, thereby preventing the IgE-associated inflammation cascade. The class switching of B cells to produce IgG and IgA rather than IgE is mediated by LLDCs (Scadding and Durham, 2009).³⁸ The significance of the difference in responses between SCIT and SLIT is unknown.

Role of T lymphocytes

Changes to different T cell populations have been observed in SLIT clinical trials. The *in vitro* proliferative ability of T cell populations in response to specific allergen was reduced following birch pollen and grass pollen SLIT in clinical trials; the former was shown to be modulated by CD25⁺ T_{reg} cells and IL-10. Reduced allergen-specific proliferation of splenic lymphocytes was also observed following oral immunotherapy to β -lactoglobulin in mice (Pecquet *et al.*, 1999).⁴⁹ However, a non-specific or lack of a similar response was observed in a clinical study with house dust mite SLIT. Doses were comparable in the different studies; thus, the reason for the discrepancy is unclear (Scadding and Durham, 2009).³⁸ Additionally, long-term efficacy of intranasal immunotherapy in a mouse model of birch pollen allergy was associated with the presence of FoxP3⁺ T cells (Winkler *et al.*, 2006).⁴³ Thus, although T_{reg} cells appear to be necessary for the efficacy of SLIT, particularly in the long term, the exact nature of their role remains to be elucidated.

Other studies demonstrated evidence for changes to TH1- and TH2-mediated pathways. Reduced levels of TH2-related cytokine mRNA (IL-4 and IL-5) and increased levels of TH1-related cytokine mRNA (IL-18) were observed in peripheral blood mononuclear cells during SLIT for tree pollen. In contrast, no difference in the relative numbers of TH1, TH2 or TH0 clones were observed following other grass pollen SLIT studies (Scadding and Durham, 2009). Similarly, no significant effect on the number of T cells was observed in the oral mucosal epithelia or lamina propria of rhinoconjunctivitis patients following olive pollen SLIT in one clinical trial (Moingeon *et al.*, 2006). This lack of a response was generally attributed to the lower allergen dose used. Circulation of allergen-specific activated T cells and the persistence of memory cells ultimately results in both systemic and local (mucosal) protective immune responses; thus activation of T_{reg} cells is postulated to underlie the long-lasting effects of immunotherapy.

⁴⁹ Pecquet S *et al.* Immunoglobulin E suppression and cytokine modulation in mice orally tolerized to β -lactoglobulin. *Immunology* 1999; 96: 278–285.

⁵⁰ Chung Y *et al.* Preventive and therapeutic effects of oral tolerance in a murine model of asthma. *Immunobiology* 2002; 206: 408–423.

⁵¹ Razafindrasita A *et al.* Improvement of sublingual immunotherapy efficacy with a mucoadhesive allergen formulation. *J Allergy Clin Immunol* 2007; 120: 278–285.

Effect on pro-inflammatory cells

SLIT is associated with changes to pro-inflammatory cell activity at target sites, consistent with effects on circulating allergen-specific antibodies.

SLIT against a flowering plant species (*Parietaria* sp.) has been shown to prevent the recruitment of neutrophils and eosinophils in the eye and nose after allergen challenge. (Moingeon *et al.*, 2006). Similar results were observed in clinical trials with house dust mite SLIT; however a similar study reported no change in nasal smear eosinophil numbers (Scadding and Durham, 2009). Modulation of local and systemic levels of pro-inflammatory mediators (eosinophil cationic protein, tryptase) was also observed with SLIT against grass pollens (Moingeon *et al.*, 2006).

Collectively, the available data have identified some evidence for the induction of oral tolerance pathways with SLIT, although considerable inconsistencies remain. Although the studies discussed above were generally conducted using other immunotherapy products, similar mechanisms of action are likely to apply for Oralair. However, they are considered to be generally supportive, but not directly applicable to Oralair. Therefore, the assessment of the efficacy of Oralair will rely on the clinical data.

Secondary pharmacodynamics and safety pharmacology

No secondary pharmacodynamics or safety pharmacology studies were conducted with Oralair. Typical safety pharmacology endpoints were also not investigated in repeat dose toxicity studies. The sponsor considered secondary pharmacology studies to be unnecessary, given that the use of allergen extracts for specific immunotherapy was generally considered to be a therapy of well-known clinical use, with well defined adverse effects. This was considered acceptable.

Safety pharmacology studies were not considered necessary by the sponsor, based on the range of adverse effects observed clinically. Although the available nonclinical data do not generally indicate any specific cause for concern, such studies are generally expected to support the nonclinical safety of a medicinal product. Such studies may have further elucidated the mechanisms responsible for clinical adverse effects of Oralair. Thus, the absence of safety pharmacology studies was considered a limitation.

Pharmacokinetics

No data investigating the nonclinical pharmacokinetics of Oralair were submitted. The sponsor provided a relatively detailed justification for the lack of nonclinical pharmacokinetic studies (shown in italics); each point is discussed separately below:

- (i) *The allergen extract is comprised primarily of polypeptides and peptides, which are expected to be broken down into amino acids and small polypeptides in the GI tract and tissues, thus resulting in no significant systemic exposure.*

While proteolytic digestion in the GI tract is expected to be the predominant fate of Oralair *in vivo*, systemic exposure to radioactivity has been demonstrated clinically following swallowing of radiolabelled allergen extracts (primarily due to free radiolabel and small peptides; Bagnasco *et al.*, 1997 and 2001).^{52,53} The extent of systemic absorption of the allergen extracts included in Oralair tablets, clinically or nonclinically, is unknown but is expected to be very low or negligible.

⁵² Bagnasco M *et al.* Absorption and distribution kinetics of the major *Parietaria judaica* allergen (Par j 1) administered by noninjectable routes in healthy human beings. *J Allergy Clin Immunol* 1997; 100: 122–129.

⁵³ Bagnasco M *et al.* Pharmacokinetics of an allergen and a monomeric allergoid for oromucosal immunotherapy in allergic volunteers. *Clin Exp Allergy* 2001; 31: 54–60.

(ii) *No standardised and validated animal model of allergen-specific immunotherapy by the sublingual-swallow route is available.*

As discussed under *Primary pharmacology* above, SLIT protocols have been successfully investigated in several rodent models of allergy, and the relevance of these findings to humans is relatively well understood. Similar models could be utilised for pharmacokinetic studies with Oralair.

(iii) *The radioactivity measured following the sublingual or oral administration of a labelled allergen extract cannot be reliably demonstrated to reflect the actual disposition of the whole extract in the body.*

The two studies discussed under point (i) above indeed demonstrated the limitations of disposition studies; however, the considered use of appropriate analytical techniques, could enable determination of the fate of whole allergen *in vivo*, to a greater extent in animals than is possible in humans. The use of immunological detection methods, rather than direct measurement of protein levels, may represent a more appropriate approach.

(iv) *No relationship has so far been shown to exist between the measured levels of an allergen extract in body fluids or tissues, and the magnitude or nature of the elicited immune response.*

As discussed in the previous point, immunological measurements of Oralair exposure would address this point.

Together, these points indicate that appropriate methodologies are available for investigating the systemic absorption profile of Oralair. However, systemic exposure to Oralair is expected to be very low or negligible. This is reflected in statements in the Product Information.

Relative exposure

Relative exposure calculations based on the area under the plasma concentration time curve (AUC) or maximal plasma concentration (C_{max}) were not possible in the absence of pharmacokinetic/toxicokinetic data for Oralair. Thus, comparison of relative exposure in the major nonclinical studies was made based on dose per body surface area, as summarised in Table 3. The maximum recommended clinical dose of Oralair is 300 IR/day, which is equivalent to 6 IR/kg or 198 IR/m² for a 50 kg adult. Doses highlighted in bold in both tables represent the No Observable Adverse Effect Levels (NOAELs) for respective studies; relative exposure at NOAELs in repeat dose studies was consistently high. However, the relative immunological potency of Oralair in animals compared with humans was not characterised. Thus, the accuracy of the calculated exposure margins relative to the safety profile seen in nonclinical studies is unknown.

Table 3: Extract of 5 grasses exposure (IR/m²) calculations in PO toxicity studies

| Study no. | Species | Duration | Dose (IR/kg/day) | Dose (IR/m ²) ^a | Exposure multiple (IR/m ²) |
|-----------------------------------|---------|-----------------------|---------------------------|--|--|
| Single dose toxicity | | | | | |
| 1105 | Mouse | NA | 1000 | 3000 | 15 |
| Repeat dose toxicity | | | | | |
| 1140 | Rat | 12 days | 100 | 600 | 3.0 |
| 30925 | | 26 weeks | 155, 525, 910 | 930, 3150, 5460 | 4.6, 16, 28 |
| 33650 | | 10 weeks ^b | 375, 750, 1500 | 2250, 4500, 9000 | 11, 23, 45 |
| Reproductive toxicity | | | | | |
| 33084 | Rat | GD6-17 | 100, 300, 1000 | 600, 1800, 6000 | 3.0, 9, 30 |
| 33085 | Rabbit | GD6-18 | 50, 100, 300, 1000 | 750, 1500, 4500, 15000 | 3.8, 8, 23, 76 |
| 33086 | | GD6-18 | 100, 300, 1000 | 1500, 4500, 15000 | 8, 23, 76 |
| Local tolerance | | | | | |
| 20050063 | Hamster | 13 weeks ^c | 800, 2400, 4000 | 3200, 9600, 16000 | 16, 48, 81 |
| Pharmacokinetics in humans | | | | | |
| NA | Human | NA | 300 IR (6 IR/kg) | 198 | NA |

^aBased on conversion factors of 6 (rat), 4 (hamster), 15 (rabbit) and 33 (human; based on a 50 kg adult)

^bStudy in juvenile rats

^cAnother study of 14 days duration with the same dosage levels was also conducted

Toxicology

General toxicity

The toxicity of Oralair was investigated following a single dose to mice, rats and guinea pigs (intraperitoneal [IP], SC and oral [PO] dosing) and after daily dosing by the PO (gavage) route for up to 26 weeks to rats (including a 10-week study in juveniles). Some toxicity data were also obtained following administration of Oralair to the cheek pouch of hamsters in studies of up to 13 weeks duration; adequacy of these studies is discussed under *Local tolerance* below. Most studies were GLP compliant. Documentation (including details of study numbers, laboratories, dates, dosage levels) was limited in most of the single dose studies, such that the data were considered uninformative. There was no dose-ranging in the only informative single dose study (an IP/PO study in mice). The repeat dose toxicity studies were generally adequate although toxicokinetic data were not obtained. Dosage levels in a four-week study in rats were not expressed in terms of IR/kg or mg/kg. The highest dosage levels tested generally represented NOAELs.

No studies in a non-rodent species were conducted. Such studies are generally expected for medicinal products, particularly for a product which may be administered chronically. Chronic repeat dose toxicity studies in dogs have been conducted to support the nonclinical safety of other allergen extracts⁵⁴, and should have been considered for

⁵⁴ Public Assessment Report for Grazax/Grazura allergen extract from *Phleum pratense* (SE/H/612/MR, SE/H/613/MR), Swedish Medical Products Agency www.mpa.se

Oralair. Additionally, no studies were conducted in sensitised animals, which may provide data more predictive of effects in the indicated population.

Oralair was generally well tolerated with repeated dosing in rats, with no overt toxic effects at doses up to 28 times greater than the maximum recommended clinical dose, based on mg/m². An increased incidence of enlarged submaxillary lymph nodes was reported, without histopathological correlation, in treated rats following 4 weeks Oralair administration. Although this finding may be consistent with the primary pharmacology of Oralair, it was not considered to be toxicologically significant, given the absence of similar findings in the 26-week study. Administration of Oralair to juvenile rats (between post natal days [PND]10–80) was also generally well-tolerated (mg/m²-based exposure 11- to 45- times the maximum recommended daily clinical dose); possible fertility effects following mating are discussed in *Reproductive toxicity* below. A slight, generally dose-related reduction in activated partial thromboplastin time (APTT) levels was observed in treated juvenile rats (significant at the high dose [HD] in males). This finding was considered to be of minor toxicological concern, as there were no associated clinical or pathology findings and all values were generally higher than historical control ranges. There was no evidence for systemic toxic effects following administration of Oralair in the cheek pouch to hamsters for 13 weeks, at doses ≤81 -fold the maximum recommended daily clinical dose.

Genotoxicity

The genotoxicity of different Oralair extracts (representing different stages in the manufacturing process) was investigated *in vitro* with two bacterial reverse mutation assays and several mammalian gene mutation assays, and *in vivo* with one chromosomal aberration assay and an unscheduled DNA synthesis assay in rats. The studies were GLP compliant, the concentrations used were adequate, and the assays were validated with appropriate positive and negative controls.

Oralair produced negative results in both *in vivo* assays in rats, following one SC or two IP doses of ≤4.7x10⁵ IR/kg. Exposure in these studies relative to the maximum recommended clinical exposure could not be determined due to the different routes of administration, but is expected to be markedly greater. In *in vitro* studies, the results were negative with the 5 grasses pollen extract issued from the final manufacturing process selected for Oralair.

The battery of genetic toxicology assays used to investigate Oralair was consistent with the relevant TGA-adopted EU guidelines and the weight of evidence from these assays suggested that Oralair presented no significant genotoxic potential at the proposed clinical dose range, but there are limitations with such assays for the analysis of protein products.

Carcinogenicity

No carcinogenicity studies were conducted for Oralair. The sponsor stated that this was due to the low expected systemic exposure to a protein-based product, the absence of any histological lesions after repeated administration for up to 26 weeks in rats, the lack of genotoxicity *in vitro* and *in vivo*, and the extensive clinical experience gained with these and similar extracts of the same taxonomy family.

The TGA-adopted EU guideline states that “Carcinogenicity studies should be performed for any pharmaceutical whose expected clinical use is continuous for at least 6 months.⁵⁵ The guideline further states “For pharmaceuticals used frequently in an intermittent

⁵⁵ EMEA, Committee for Proprietary Medicinal Products (CPMP), 25 July 2002. Note for Guidance on Carcinogenic Potential, CPMP/SWP/2877/00.

manner in the treatment of chronic or recurrent conditions, carcinogenicity studies are generally needed. Examples of such conditions include allergic rhinitis,

Many compounds naturally present in plants are known to be genotoxic and/or carcinogenic, for example ptaquiloside in bracken fern (Potter and Baird, 2000), aristolochic acid in *Aristolochia* spp. (Schmeiser *et al.*, 2009) and several compounds in piper betel leaves and areca nuts.^{56,57,58} Botanical products such as Oralair are regulated by the FDA as per any other medicinal product, including the need for carcinogenicity studies⁵⁹. Therefore, despite the justifications provided by the sponsor, the lack of carcinogenicity studies is considered a limitation.

Reproductive toxicity

The submitted studies included adequate GLP compliant embryofetal development studies by the PO route in rats and rabbits. No fertility and early embryonic development study nor a peri/postnatal development study was conducted. However, histopathological examination of the male and female reproductive organs in repeat-dose toxicity studies revealed no adverse findings. Some fertility data were also obtained in a juvenile animal study although Oralair treatment had ceased prior to mating. The potential transfer of Oralair to offspring across the placenta or during lactation was not investigated but is considered unlikely.

Oralair was well tolerated in both species at exposures ≤ 76 times greater than the maximum recommended daily clinical exposure, with no overt toxicity to treated females or effects on the embryofetal development of offspring. A low incidence of fetal malformations (cleft lip and palate, malrotated paw and malpositioned digit, omphalocele and short tail, gastroschisis and absent gonads) was observed in treated rabbits. These findings were within historical control ranges and were not considered treatment related. The sponsor highlighted a possible increase in the incidence of short or absent innominate artery in fetuses from treated rabbits; however, the findings were not dose-related and appeared to reflect a strain- and supplier-specific effect.

In a repeat dose toxicity study in juvenile rats (rats were treated PO daily with Oralair between PND10–80), treated males and females were paired on PND81 for an assessment of fertility. An increased incidence of pre-implantation loss (not statistically significant) was reported following mating in this study at all doses, accompanied by slightly increased early resorptions at the two highest doses. This finding was unlikely to be toxicologically significant, as rats were no longer exposed to Oralair, there was no clear dose-response, and no mechanistic basis for the finding. Historical control data, which may have clarified the significance of the findings, were not provided.

Pregnancy classification

Antigen preparations for desensitisation are exempted from pregnancy classification⁶⁰. Accordingly, similar registered products, including Alustal, are not assigned Pregnancy Categories. Nevertheless, the sponsor proposed a Pregnancy Category C for Oralair, although a justification for this category was not provided. This would imply pharmacological effects of Oralair that have caused or may be suspected of causing

⁵⁶ Potter DM and Baird MS. Carcinogenic effects of ptaquiloside in bracken fern and related compounds. *Br J Cancer* 2000; 83: 914–920.

⁵⁷ IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 85: Betel-quid and areca-nut chewing and some areca-nut-derived nitrosamines.

⁵⁸ Schmeiser HH *et al.* Chemical and molecular basis of the carcinogenicity of *Aristolochia* plants. *Curr Opin Drug Discov Devel* 2009; 12: 141–8.

⁵⁹ FDA Guidance for Industry: Botanical drug products.

(www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070491.pdf)

⁶⁰ Appendix A, Prescribing medicines in pregnancy, 4th Edition (1999).

harmful effects on the fetus or neonate without causing malformations. The available nonclinical data and statements in the proposed Product Information are not consistent with such effects. Pregnancy Category B2 appears to be most consistent with the available nonclinical data, as studies in animals are limited but available data show no evidence of increased fetal damage. This Pregnancy Category was therefore recommended by the nonclinical evaluator. However, there may insufficient data available to support clinical aspects of this statement.

Use in children

As discussed under *General toxicity* and *Reproductive toxicity* above, administration of Oralair to juvenile rats (PND10–80) was generally well tolerated, at PO doses providing mg/m²-based exposure ≤45 times the maximum recommended clinical exposure. There were no effects on physical development pre- and post-weaning. Thus, as there do not appear to be significant differences in the post-natal development of the rat and human immune systems (Holsapple *et al.*, 2003), there are no additional safety concerns expected with administration of Oralair to children ≥5 years of age.⁶¹

Local tolerance

The local tolerance of Oralair via the sublingual route was investigated in three studies of up to 13 weeks duration in hamsters by administration in the cheek pouch. The sponsor considered the hamster cheek pouch model to be the closest available model to mimic sublingual-swallow administration. This was considered acceptable. The studies were GLP compliant, and generally adequate, although analysis was limited to in-life findings and gross pathology analysis in two 4 week studies, and the dosage strength administered in one of these studies was not specified. There was no evidence of local irritation or histological changes to the buccal mucosa following prolonged administration of Oralair in the cheek pouch (hamsters were fitted with collars to prevent evacuation of the test substance), at mg/m²-based exposures ≤81 times greater than the maximum recommended clinical exposure. Quantifiable serum levels of specific IgG were not detected after 13 weeks. According to the proposed PI, local irritation (that is, pruritis) is a very common adverse effect of Oralair.

Nonclinical Summary and Conclusions

No nonclinical data were available regarding the pharmacology (including safety pharmacology), pharmacokinetics or carcinogenicity of Oralair. The submitted nonclinical data (single and repeat dose toxicity, genotoxicity, reproductive toxicity and local tolerance) were generally adequate, apart from the limitations discussed below. Oralair was administered by gavage in most nonclinical studies (except for local tolerance studies), rather than the clinical route of sublingual swallow.

The rationale behind sublingual immunotherapy (SLIT) is that the natural mechanisms underlying oral tolerance at mucosal surfaces may represent an effective approach for modulating the adverse immune responses associated with allergy. Published literature for other products demonstrated some evidence for the induction of oral tolerance pathways with SLIT, although inconsistencies exist. These studies were considered to be generally supportive of, but not directly applicable to the efficacy of Oralair. Assessment of the efficacy of Oralair will therefore rely on clinical data.

Toxicity studies of up to 26 weeks duration by the PO route were conducted in rats, including one 2-month study in juvenile rats. Some toxicity data were also obtained

⁶¹ Holsapple et al. Species comparison of anatomical and functional immune system development. *Birth Def Res* 2003; 68: 321–334.

following a single IP or PO dose to mice, and following administration in the cheek pouch of hamsters for up to 13 weeks. No studies in non-rodents or in sensitised animals were conducted. Oralair was well-tolerated in all species, with no overt toxic effects at exposures up to 28–81 times greater than the maximum clinical exposure (however, the potency of Oralair in nonclinical species was not investigated).

An adequate battery of genotoxicity studies was conducted with Oralair. It was not genotoxic in *in vivo* assays in rats, at exposures expected to be markedly greater than the maximum recommended clinical exposure. Batches manufactured with the final process were not genotoxic *in vitro*.

No carcinogenicity studies were submitted for Oralair.

There were no significant toxicological effects to dams or fetuses in oral embryofetal development studies in rats and rabbits at exposures up to 76 times greater than the maximum recommended daily clinical exposure. No fertility and early embryonic development study, nor a peri/postnatal study was conducted with Oralair. However, histological examination of the reproductive organs in repeat-dose toxicity studies showed no adverse findings.

Administration of Oralair in the cheek pouch of hamsters for up to 13 weeks was not associated with local irritation or histological changes to the buccal mucosa.

The submitted studies did not identify particular risks relating to general toxicity, local tolerance or reproductive toxicity, including teratogenicity. The weight of evidence indicated that Oralair presents no significant genotoxic potential at the maximum recommended clinical dose.

Although the nonclinical data were limited, this should be considered in light of the international clinical experience with the drug, including experience in Australia with Alustal. There were no nonclinical objections to the registration of Oralair, provided the clinical data adequately address the efficacy of the product.

IV. Clinical Findings

Introduction

This submission was a mixed data application for a known active substance comprising published literature justifying the use of immunotherapy (IT), as well as the original data contained in two pivotal trials (one paediatric) and two supporting trials with the product submitted for approval.

A summary of the submitted studies is provided in the tables below.

Table 4: Summary of pivotal clinical efficacy studies in patients with SAR/C with clinically relevant sensitivity to Northern grass pollen as demonstrated by positive SPT +/-specific IgE

| Study ID | No. of centres | Design | Subjects by arm: entered (completed) | Dosing Oralair | Duration | Results 1° efficacy | Results 2° efficacy |
|----------|-----------------------------------|--|--|---|---|---|---|
| VO34.04 | 42 10 European countries | Randomised double blind (DB) placebo controlled (PC) multicentre Phase IIb/III | Entry criteria = RRTSS ≥ 12 18-45 yrs 628 entered ITT: 569 PP: 524 Safety: 628 Discontinued: 69 | 1:1:1:1 100 IR 300IR 500IR Placebo (P) maintenance | First entered 30 Nov 2004, last completed 5 Sep 2005 Dosing 4 months before and during pollen season | Mean RTSS in pollen season 300IR: 3.58 P: 4.93 p=0.0001 | Individual scores Global evaluation of efficacy PSFD 300IR: 10.9 P: 0 p<0.0006 RQLQ 300IR: 0.9 P: 1.27 p<0.0001 RMS 300IR: 0.16 P: 0.31 P=0.0047 Medication score 300IR: 10.6% P: 19.7% |
| VO52.06 | 29 5 European countries | Randomised DB PC multicentre Phase III | RRTSS ≥ 12 5-17 yrs 278 entered 95.7% completed ITT: 266 PP: 227 Safety: 278 | 1:1 300IR Placebo (P) | Start Dec 2006, completed Sep 2007 Dosing 4 months before and during pollen season Mean duration 171.1 days | Mean RTSS during pollen season 300IR: 3.25 P: 4.51 p=0.0001 | Individual scores RMS 300IR: 0.39 P: 0.76 P=0.0064 PSFD 300IR: 5.2 P: 0 P=0.0037 |

Notes: For VO34.04 results for 300IR vs placebo given only as this was found to be optimal dose
 DBPC: double blind, placebo controlled, RRTSS: Retrospective rhinoconjunctivitis total symptom score,
 RTSS: Rhinoconjunctivitis total symptom score, S/s: symptom score, RMS: rescue medication score, PSFD:
 proportion of symptom free and medication free days

Table 5: Summary of 3 supportive studies in patients with seasonal allergic rhinoconjunctivitis (SAR/C).

| Study No. | Design | Subjects | Treatment/Dosing | Duration |
|-----------|--|--|---|--|
| VOX01.96F | Phase IIb Randomised DB PC multicentre France OPD setting | 7-58 yrs Screened subjects: 126 | SLIT (drops + tablets) 100IR dose Placebo (P) Build up phase with drops Maintenance phase tablets | First enrolled: 7 Feb 1996 Last completed: 2 Aug 1996 |
| GR02.97UK | Phase IIb Randomised DB PC multicentre General practice setting | 19-59 yrs 181 subjects randomised 180 subjects treated 159 analysed P: 54 Active 1 yr: 53 Active 2 yr: 52 | 5 grasses mix SLIT solution 11R, 10IR, 100IR updosing schedule 100IR tablets Maintenance dose 100IR tablets 3 times/wk | First enrolled: April 1998 Last completed: 2000 24-28 weeks/yr 2 consecutive yrs |

The two pivotal studies will be discussed in detail in the sections below while the supporting studies will be included in the safety evaluation but as they were conducted with an allergen dose below the one found to be efficacious, they do not contribute anything to the information on clinical efficacy as the primary outcomes were not met.

Pharmacokinetics and Pharmacodynamics

No pharmacokinetic or pharmacodynamic data were provided.

Efficacy

Dose response studies

Study V034.04 was both a dose finding and pivotal study. V052.06 was submitted as a pivotal study and also served as a study in a “special population” that is, the paediatric age group. One dose formulation was used in this study, informed by the findings from Study V034.04. These will be considered together under “Main studies”.

Main (pivotal) studies

STUDY V034.04-Pivotal Phase IIb/III Study

This was a randomised, double blind, placebo controlled, multinational, multicentre Phase IIb/III study of the efficacy and safety of three doses of sublingual immunotherapy (SLIT) administered as tablets once daily to patients suffering from grass pollen rhinoconjunctivitis. It was conducted in 10 European countries (Austria, Bulgaria, Czech Republic, Denmark, France, Germany, Hungary, Italy, Slovakia and Spain). A total of 47 centres were initiated, at 44 centres patients were screened and at 42 centres patients were randomised. The first patient was screened on 30 November 2004 and the last patient completed on 5 September 2005.

STUDY V052.06 – Pivotal paediatric study

This was a randomised, double blind placebo controlled multinational multicentre Phase III paediatric study of the efficacy and safety of 300IR sublingual immunotherapy (SLIT) administered as allergen based tablets once daily to children suffering from grass pollen rhinoconjunctivitis. It was conducted in 5 European countries (Denmark, France,

Germany, Poland, Spain) with 29 investigators participating 29 study centres. The first patient was randomised on 3 January 2007 and the last patient completed on 12 September 2007.

The 2 main studies comprising the submission used similar patient selection criteria, inclusion and exclusion criteria, outcomes for primary and secondary efficacy assessments and product for treatment.

Methods - Studies VO34.04 and VO52.06

Primary Objectives

The aim of the studies was to evaluate the efficacy and safety of SLIT for grass pollen allergens compared with placebo for reduction of symptoms and rescue medication usage. This was assessed by comparing the effect of treatment vs placebo on the rhinoconjunctivitis total symptom score (RTSS).

For VO34.04 evaluation of safety and efficacy of three doses of SLIT tablets (100IR, 300IR, 500IR) was compared with placebo.

Secondary Objectives

To assess the efficacy of SLIT for grass pollen allergens on:

- Rescue medication score (RMS) in VO52.06, Rescue Medication usage in VO34.04
- Combined score (CS) taking into account the RTSS and RMS. In Study VO52.06, this was calculated as $CS = (RTSS/6 + RMS)/2$ with CS ranging from 0-3.
- Each of the six individual RSS
- Proportion of symptom free days (a score of 0 for all six individual symptoms)
- Global evaluation of efficacy by patient
- To document the safety of the treatment

Exploratory objectives

A number of exploratory objectives were included; these were designed to show some immunological effect of treatment.

- changes in IgE levels
- changes in IgG4 levels
- changes in SPT diameter

Study Participants

Participants consisted of people suffering from seasonal grass pollen-related AR/C for at least two years with sensitisation confirmed by specific IgE tests and skin prick tests. Age criteria were for

- VO34.04-Male or female outpatients, 18-45 years inclusive.
- VO52.06- Male or female outpatients, 5-17 years inclusive.

Other inclusion criteria included positive skin prick test (SPT) for grass pollen (greater than 3 mm diameter), positive specific IgE (greater than or equal to Class 2) for grass pollen and a score of greater than or equal to 12 on the retrospective rhinoconjunctivitis total symptom score (RRTSS) which is an evaluation of the most severe symptoms during the previous pollen season.

All withdrawn or discontinued patients who received at least one dose of the investigational product were considered for the intention to treat (ITT) population analysis.

Treatments

In all studies the active treatment (Oralair) was a tablet formulation containing freeze dried allergen extracts of five grasses (cocksfoot, meadow grass, perennial rye grass, sweet vernal grass and timothy grass) supplied in strengths of 100IR, 300IR (and for VO34.04, 500 IR) with cellulose (microcrystalline), croscarmellose sodium, silica (colloidal and hydrous anhydrous), magnesium stearate, lactose monohydrate QS,) manufactured by Stallergenes SA. For all medication in the studies lyophilised extracts of the relevant allergens were reconstituted with a diluent to obtain a parent compound with an immunologic activity equal to 100 IR p/ml (defined as a concentration eliciting by skin prick test a geometric mean wheal size of 7mm in 30 patients sensitive to the corresponding allergen).

The placebo consisted of tablets matching the active treatment in size, shape and colour and containing caramel, quinoline yellow, cellulose (microcrystalline), croscarmellose sodium, silica (colloidal and hydrous), magnesium stearate, lactose monohydrate QS.

For VO34.04 the treatment was commenced using a short up dosing phase over 5 days then the same dose was continued until the end of the study. The same number of placebo tablets was administered to match the active treatment.

For VO52.06 male or female patients aged 5-17 years with seasonal grass pollen related AR/C were randomised to one of two treatment groups. They received either active immunotherapy tablets or placebo tablets sublingually once a day. The first dose was administered under supervision and the patient was observed for 30 minutes for any local or systemic reactions. The dose was escalated in increments of 100IR from a starting dose of 100IR to the randomised dose of 300IR. From Day 3 of treatment patients took one tablet of the randomised dose 300IR sublingually daily until Visit 6.

Treatment compliance

Compliance was required to be between 80% and 120%. Non-compliance was defined as less than 80% or more than 120% of the predicted number of tablets taken during the treatment phase.

At each visit patients returned all unused investigational products and rescue medications as well as any empty containers and blister packs. A drug reconciliation was done in the patients presence in order to obtain required explanations in respect to possible discrepancies in compliance with dosing regimen. The number of tablets returned and the date was recorded on the drug accountability form. Explanations of non compliance were recorded. Use of rescue medication was recorded in a daily record card and compared to the unused medication returned.

Evaluator comment

This is a crude and relatively weak assessment of compliance but is the one that is generally used for similar studies. By this method patient compliance is more likely to be overestimated.

Outcomes/endpoints

Primary Efficacy Assessment- Rhinoconjunctivitis total symptom score (RTSS)

The RTSS is used as the primary efficacy variable in all studies. This is calculated as the sum of the 6 rhinoconjunctivitis symptoms – sneezing, rhinorrhoea, nasal pruritus, nasal congestion, ocular pruritus, watery eyes.

These are assessed on a 4-point scale for the previous 24 hours as follows:

0 = absent symptoms

1 = mild symptoms (present but minimal awareness and easily tolerated)

2 = moderate symptoms (definite awareness that is bothersome but tolerable)

3 = severe symptoms (hard to tolerate, causes interference with activities of daily living and/or sleeping)

The RTSS ranges from 0-18.

The average RTSS is a calculation of the daily average score during the pollen season on treatment.

Secondary Efficacy Variables

Both studies employed rhinoconjunctivitis individual symptom scores. These were scored daily before administration of the product under investigation and each score was scored on a scale of 0-3 as described above.

Global efficacy was assessed by the patient. At the end of the study the patient made a global evaluation relative to the previous pollen period using the following scale –

0 – worsening

1 – no change

2 – slight to moderate improvement

3 – good to excellent improvement

In V 052.6 (paediatric study) a 5 point Likert scale was used for this parameter.

Safety assessments included adverse events (AEs), physical examination and clinical laboratory assessments

Rescue medication was assessed as follows:

For V034.04, in all studies patients were permitted to access rescue medication if symptoms required it. There were three steps:

Step 1 – Antihistamine (oral or eye drop) and if symptoms were not alleviated;

Step 2 – Intranasal corticosteroid, if symptoms were severe and if after contact with the investigator patients could use

Step 3 – Oral corticosteroids

Rescue medication was noted on daily record cards recording the start and stop dates and number of doses required.

For V052.06, the contribution of rescue medication analysis was refined based on the experience from V 034.04.

Rescue medication score (RMS) and usage RMS was scored 0-3; if a patient took more than one medication on the same day, the medication with the highest score was used.

The Combined score (CS) took into account the RTSS and RMS. This was calculated as $CS = (RTSS/6 + RMS)/2$ with CS ranging from 0-3.

The proportion of symptom free days was scored with a score of 0 for all 6 individual symptoms.

For VO34.04 only, a Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was administered. This is a validated questionnaire developed for adults with rhinoconjunctivitis and has been shown to have excellent evaluative and discriminative properties. It consists of 28 questions in seven domains:- activity limitations, sleep problems, non nose and eye symptoms, practical problem, nose symptoms, eye symptoms and emotional function.

The questionnaire is self-administered and patients recall their experiences over the preceding week giving responses on a 7 point Likert scale. All items within a domain are weighted equally and domain score is the mean of all items within each domain. The overall score is calculated as the mean across all items.

Exploratory Objectives

A number of other measures were conducted during the studies.

- Skin prick test diameter-SPT were performed on Visits 1 and 6. Diameter of the grass pollen SPT was recorded and the result from the last visit compared to the first.
- Immunological markers – IgE and IgG4 values Specific IgE, expressed as kU p/L and divided into Class 0 to Class 6. IgG4 results were expressed in g p/L. These were done on Visit 1 and Visit 6. Sensitisation (mono- and poly-sensitivity) was derived from SPT results (asthma presence or absence)
- For VO34.04- a Combined Score was assessed. This combined the RTSS adjusted for rescue medication usage. The combined score was patient specific.

Sample size

VO34.04

This was calculated with the knowledge gained from previous studies where it was found that a sample size of 137 patients per treatment group (assuming an overall α of 0.05 and a common standard deviation [SD] of 2.1) would have a power of 90% to detect a mean difference of 0.81 in mean TSS per 24 hrs between placebo and 300 IR. Using 150 patients per group would allow for a 10% drop out rate and would result in a total of 600 patients. Patients were randomised in a ratio of 1:1:1:1 to 100:300:500IR and placebo groups respectively.

VO52.06

Given an $\alpha = 0.05$ and a common SD= 3.261 the results of study VO34.04 suggested that a sample size of 117 patients per treatment group would have a power of 80% to detect a mean difference of 1.2, that is, an average difference of 0.2 per symptom between placebo and 300IR in the average RTSS during the peak pollen period while on treatment. Assuming a 20% screening failure rate and 15% drop out rate, it was decided to screen 350 patients to have 140 randomised patients in each treatment group at the start of the study. Patients were randomly assigned in a 1:1 ratio 300IR or placebo.

The safety population included all patients who received at least one dose of the product. The ITT population included all patients that received at least one dose of the investigational product and had an RRTSS and at least one RTSS during the pollen period while on treatment. The ITT population was regarded as primary for the efficacy analyses.

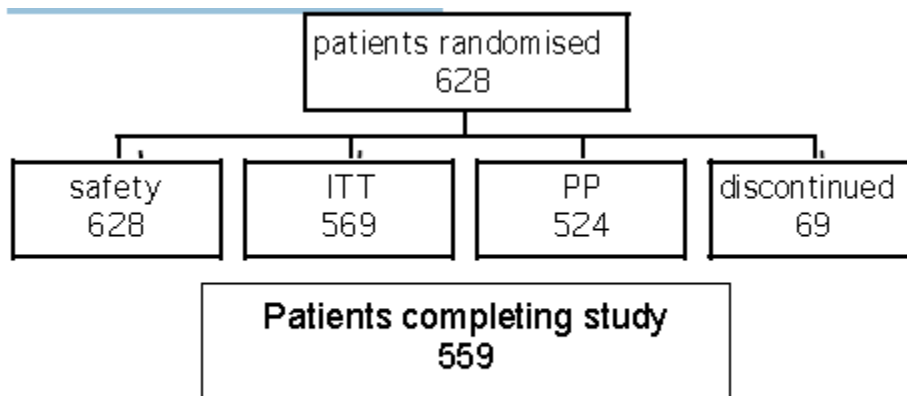
The “per protocol” (PP) population included all patients who completed the study according to the protocol and had no major protocol violations. Patients withdrawn from the study due to lack of efficacy or an AE related to the investigational product were included in the PP population if they were otherwise valid.

Results - V034.04

Participant flow

A total of 749 patients were screened over 44 centres with 628 being randomised at 42 centres. The overall figures for each group and each aspect of the study is summarised in Figure 2.

Figure 2: Patient disposition in Study V034.04



Baseline data

Baseline demographic data showed males were more predominant in all groups compared to females but otherwise the groups were suitably similar. The age distribution certainly reflects the patient population of seasonal allergic conjunctivitis. The proportion of patients entered into the study with asthma range from 8.8% (n = 13) to 11% (n= 15) and was similar for all groups averaging 10% (57). Patients who were poly sensitised as opposed to mono-sensitised to grass pollen alone was overall 54.7% (311 patients) and this was similar for all treatment and placebo groups. There were no significant differences between groups for other characteristics such as results for physical examination, prior concomitant medication use or other diagnoses.

There were no significant differences between groups as regards treatment compliance defined in this study by the number of tablets of investigational product they took (number dispensed minus number returned) as being between 80% and 120% of the number of tablets they should have taken.

The number of patients for each group is shown in Table 6.

Table 6: Number of patients in each group

| Population | Dose Group | | | | | | | | | |
|------------|------------|---------|--------|---------|--------|---------|---------|---------|-----|---------|
| | 100 IR | | 300 IR | | 500 IR | | Placebo | | All | |
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| Safety | 157 | (100.0) | 155 | (100.0) | 160 | (100.0) | 156 | (100.0) | 628 | (100.0) |
| ITT | 142 | (90.4) | 136 | (87.7) | 143 | (89.4) | 148 | (94.9) | 569 | (90.6) |
| PP | 132 | (84.1) | 123 | (79.4) | 133 | (83.1) | 136 | (87.2) | 524 | (83.4) |

n = number of patients, % = percentage of patients, ITT = intent-to-treat, PP = per protocol

Outcomes

For the primary efficacy variable of average RTSS during the pollen period while on treatment in the ITT population, patients receiving 300IR had the lowest average RTSS and those in the placebo group had the highest average RTSS (3.58 (SD 2.976) and 4.93 (SD 3.229) respectively). In the PP population patients in the 300IR group had the lowest average RTSS while patients in the 100IR group had the highest average RTSS just above those in the placebo group (Table 7).

Table 7: Average RTSS scores during the pollen period

| Variable | ITT Population | | PP Population | |
|-------------|----------------|------------|---------------|------------|
| | Mean (SD) | Range | Mean (SD) | Range |
| RTSS | | | | |
| 100 IR | 4.72 (3.141) | 0.0 – 13.4 | 4.89 (3.129) | 0.0 – 13.4 |
| 300 IR | 3.58 (2.976) | 0.0 – 15.1 | 3.49 (2.897) | 0.0 – 12.9 |
| 500 IR | 3.74 (3.142) | 0.0 – 14.2 | 3.69 (3.143) | 0.0 – 14.2 |
| Placebo | 4.93 (3.229) | 0.0 – 14.2 | 4.78 (3.217) | 0.0 – 14.2 |

ITT = intent-to-treat, PP = per protocol, SD = Standard deviation, Range = minimum value – maximum value, RTSS = Rhinoconjunctivitis Total Symptom Score

The retrospective RTSS, presence of asthma and sensitisation status were used as co-variants with treatment and pooled sites as factors. This showed a highly statistically significant difference between the 300IR and 500IR groups versus placebo groups (p = 0.0001 and 0.0006 respectively) per population of analysis in the worst pollen period showed similar results (Table 8).

Table 8: Average RTSS – analysis of co-variants

| Source | Degrees of Freedom | F-value | P-value |
|---|--------------------|-----------------|----------|
| Treatment | 3 | 7.48 | 0.0001 |
| Pooled sites | 16 | 4.03 | < 0.0001 |
| RRTSS | 1 | 5.10 | 0.0243 |
| Asthma | 1 | 1.24 | 0.2652 |
| Sensitised | 1 | 1.21 | 0.2720 |
| Difference in Adjusted Means (Treatment – Placebo) | | | |
| Treatment versus Placebo | Point Estimate | 95% CI | P-value |
| 500 IR | -1.22 | (-1.91 ; -0.53) | 0.0006 |
| 300 IR | -1.39 | (-2.09 ; -0.69) | 0.0001 |
| 100 IR | -0.26 | (-0.95 ; 0.43) | 0.4606 |

RRTSS = Retrospective rhinoconjunctivitis total symptom score, CI = confidence interval

Secondary Outcome Variables

Use of rescue medication was examined in a number of ways. The comparison of proportion of days in which a patient used at least one rescue medication was compared between treatment groups and placebo using non-parametric Wilcoxon-Par one way test. The following is a summary of findings:

The proportion of patients using at least one type of rescue medication during pollen period while on treatment was:

- 73% for placebo
- 64.7% for 300IR group.

There were no significant differences between active treatment groups versus placebo for rescue medication use during pollen period.

There were no statistically significant differences between active treatment groups and placebo for rescue medication use in worst pollen period.

In decreasing order the rescue medication used most frequently were oral antihistamines, followed by nasal steroids followed by eye drops with very few patients using systemic corticosteroids (0.7% of the 300 IR group compared to 2.7% of placebo group).

No patients in 300 IR group used oral corticosteroids during the worst pollen period.

Examination of proportion of days on any rescue medication in the pollen period showed that the 300 IR group versus placebo group ($p = 0.0194$) was significant.

For the worst pollen period proportion of days on any rescue medication showed:

- 300 IR group vs placebo ($p = 0.420$)
- 500 IR group vs placebo ($p = 0.0146$).

An analysis of the proportion of days with any medication used showed:

- 19.7% (300 IR) vs 27.8% (placebo).

An analysis of the proportion of days with any medication used during worst pollen period showed:

- 20.4% (300IR) vs 29.66% (placebo).

The mean improvement in the individual symptoms in the 300 IR group were:

- Sneezing 18%
- Runny nose 23%
- Itchy nose 28%
- Nasal congestion 36%
- Watery eyes 34%
- Itchy eyes 30%

The analysis of covariance (ANCOVA) of any of the symptom scores all showed statistically significant differences in the 300 IR and 500 IR groups vs placebo (all p values < 0.309). The 300 IR group had a mean improvement of 27.4% over placebo group with a median improvement of 37%.

Evaluator Comment

In the immunotherapy literature it has been accepted that an improvement of 30% or greater is considered efficacious although the rationale behind this is not clear. In the antihistamine studies literature, an improvement of 20% is taken as clinically significant improvement.

Proportion of symptom free days

A symptom free day was defined as a day in which there was a score equal to 0 for all six symptoms. In the ITT population during the pollen period on treatment, the 300IR group had 26.22% symptom free days compared to 16.71% in patients in the placebo group.

Trends for mean proportion of symptom free days in the worst pollen periods were similar.

Overall Rhinoconjunctivitis Quality of Life Questionnaire score

Using the RQLQ, scores approaching six indicate extremely troubled while low scores approximating 0 indicate not troubled. At randomisation (Visit 2), the mean overall RQLQ scores were similar across the four groups (the ANCOVA of overall quality of life score (treatment and pooled sites as factors, and RRTSS, Visit 2 overall RQLQ, asthma and sensitisation status as covariates) showed a statistically significant difference with the 100 IR group versus placebo at Visit 4 (p = 0.0090). Visit 4 was before the pollen season hence this result is not clinically significant. At Visit 5 there was a highly statistically significant difference between 300IR and 500 IR groups vs placebo (p = /< 0.0001).

Visit 5 is the peak of pollen season. At Visit 7 there was also a statistically significant difference between 300 IR and 500 IR vs placebo (p = /< 1 0.0031).

Trends were similar for each of the seven domains of the RQLQ. Overall the majority of patients across all treatment groups had no overall change in quality of life scores from Visit 2 to Visits 4 and 7.

Global Evaluation by Patient

The overall difference in global evaluation by patients between 300IR and 500IR groups versus placebo was statistically significant (p = /< 0.0001). The majority of patients indicated a slight to moderate improvement across all 4 treatment groups. The comparison treatment success rates between 300IR and 500IR groups vs placebo was statistically significant (p = 0.0017 and 0.0001 respectively).

Exploratory Analyses

The combined score compensates for rescue medication usage and is thus a clinically relevant indicator. This score showed a highly statistically significant difference between the 300 IR and 500 IR groups vs placebo group ($p = /< 0.001$ and 0.0015 respectively). For the ITT population during the pollen period, the 300 IR group had the lowest mean combined score and the placebo group had the highest (4.12 (SD 3.310) and 5.84 (SD 3.764) respectively).

The mean SPT wheal diameter at screening visit was between 8.83 mm (100 IR group) and 9.32 mm (500 IR group). It dropped to between 6.23 mm (500 IR group) and 7.4 mm (placebo group at Visit 7, end of treatment). Patients in the 500 IR group had the largest decrease from screening to Visit 7 and patients in the placebo the smallest.

Evaluator Comment

This is to be expected with the immunological effect of treatment.

Immunological markers – specific IgE and IgG 4

For IgG4, the value more than tripled from Visit 1 to 7 for 300 IR (ratio 3.2) and 500 IR (ratio 3.7) and almost tripled for the 100 IR (ratio 2.7) group while for placebo geometric means were similar on Visit 1 and 7.

The geometric mean for IgE more than doubled from Visit 1 to 7 for 300 IR (ratio 2.1), and 500 IR (ratio 2.2) and doubled for 100 IR (ratio 2.0) while placebo was similar at Visits 1 and 7 (ratio 1.7).

Ancillary analyses

After blinding of the data for the ITT population, results for the ANCOVA of the average RTSS with treatment and pooled sites as factors and retrospective RTSS, asthma and sensitisation status as covariants, a highly statistically significant difference between the 100 IR group versus the 300 IR group was seen with no significant difference between the 300IR group versus 500 IR group ($p = 0.0015$ and 0.6082 respectively). When the results for the 10 pooled sites with the highest pollen count were taken for comparisons of the primary efficacy variable between the placebo group and active groups there were statistically significant differences between the 300IR and 500 IR groups versus placebo ($p = 0.0025$ and 0.0303 respectively) and no difference between placebo and 100 IR group. This confirms the main analysis.

Summary of Efficacy Conclusions

Treatment with 300 IR and 500 IR are efficacious while 100 IR daily is not. Analysis of the primary efficacy variable shows patients in the 300 IR and 500 IR group had the lowest average RTSS during the pollen period on treatment while patients in the 100 IR and placebo groups had the highest average RTSS. The ANCOVA of the average RTSS showed a highly statistical significant difference between 300 IR and 500 IR group vs placebo. The level of mean improvement reached was 27.4% for the 300 IR group.

For the secondary efficacy measures, with respect to rescue medication usage during the pollen period and the worst pollen period there were no statistically significant differences in treatment groups and placebo. However the proportion of days on which rescue medication was used was different in the period of the worst pollen period between the 300 IR and 500 IR groups compared to placebo.

For individual average symptom scores there were statistically significant differences between the 300 IR and 500 IR groups vs placebo with mean improvement in the 300 IR group above 25% for the six individual symptom scores compared to placebo.

In the ITT population during the pollen period, 300 IR group had the highest mean proportion of symptom free days (26.22%) compared to placebo group having the lowest (16.71%).

ANCOVA of the overall quality of life scores showed statistically significant difference between the 300 IR and 500 IR groups vs placebo on Visits 5 and 7.

Overall difference in the global evaluation between 300 IR and 500 IR groups vs placebo was statistically significant with the 500 IR group having the highest proportion of patient success (89.5%) and placebo the lowest (73.3%).

In the ITT population during the pollen period there was a statistically significant difference between the 300 IR and 500 IR vs placebo with the combined score.

The treatment groups showed an expected decrease in the diameter of the skin prick test wheal from screening visit to the last visit in a dose response fashion.

IgG 4 and IgE levels showed an expected increase between Visit 1 and Visit 7 for all active treatment groups vs placebo.

Results - V052.06

Participant flow

A total of 278 patients were randomised 1:1 to either 300IR Oralair (139) or placebo (139) at Visit 2. Around 95.3% patients completed the final Visit of the study.

Baseline data

Approximately 58% of patients were between the ages of 5-11 years. There were no particular differences between the treatment and placebo groups. A total of 22 patients in the 300IR and 24 patients in the placebo were assessed as having asthma at Visit 1.

The mean RRTSS between the treatment groups at Visit 1 were as follows:

- 300IR -13.98 +/- 1.1671
- Placebo -13.98 +/- 1.650

Sensitisation was as follows:

Monosensitised to grass pollen:

- 300IR - 54 / 131 (41.2%)
- Placebo -55 / 135 (40.7%)

Polysensitisation :

- 300IR -77 / 131 (58.8%)
- Placebo -80 / 135 (59.3%)

Overall compliance with the usage of the investigational product was high in both treatment groups.

The numbers of patients in each group included in the ITT, PP and safety analyses are shown in Table 9.

Table 9: Numbers of patients in each group

| Population | Treatment Group | | | | | |
|------------|-----------------|--------|---------|--------|-----|--------|
| | 300 IR | | Placebo | | All | |
| | n | % | n | % | n | % |
| Safety | 139 | 100.0% | 139 | 100.0% | 278 | 100.0% |
| ITT | 131 | 94.2% | 135 | 97.1% | 266 | 95.7% |
| PP | 112 | 80.6% | 115 | 82.7% | 227 | 81.7% |

n = Number of patients; % = Percentage of patients; IR: Index of reactivity; ITT: Intention to Treat; PP: Per Protocol.
Source: Section 14, Table 14.1.1.2 (page 100).

Outcomes

For the primary efficacy variable, the difference between 300IR and placebo in average RTSS during both the pollen and worst pollen periods was highly statistically significant – $p \leq 0.0010$. Results for the PP population were similar to those obtained in the ITT population. The asthma status and sensitisation status co-variants were not statistically significant in the ANCOVA models.

The ANCOVA of the average RTSS showed the difference between 300IR and placebo was highly statistically significant ($p = 0.0010$ least square mean difference and 95% CI = -1.13 (-1.80: -0.46)). 300IR showed a mean improvement of 28% over placebo with a median improvement of 39.3% for the average RTSS.

Secondary Efficacy Parameters

The ANCOVA of the Rescue Medication Score (RMS) showed a highly statistically significant difference between 300IR and placebo for the average RMS ($p = 0.0064$). A total of 81.7% of patients in the 300IR group used at least one rescue medication compared to 85.2% in placebo group. This was not statistically significant. The mean proportion of days on at least one rescue medication during the pollen period was 35.4% for 300IR and 46.5% for placebo and this was statistically significant difference.

The ANCOVA for the Combined Score (CS) showed a highly statistically significant difference between 300IR and placebo ($p = 0.0004$). The CS is an adjusted RTSS compensating for rescue medication usage.

The ANCOVA results for four of six individual mean symptom scores showed a statistically significant difference between 300IR and placebo ($p \leq 0.0380$ for runny nose, nasal congestion, itchy eyes and watery eyes).

As for the first study, this study also showed more improvement in ocular symptoms than in nasal symptoms.

For the proportion of symptom free days for the ITT population during the pollen period subjects receiving 300IR had a higher mean proportion of symptom free days than subjects in placebo group; 22.6% compared to 12.7%.

The overall difference in the global evaluation between 300IR and placebo was highly statistically significant ($p = 0.0021$). The number of patients claiming treatment success was statistically significantly different between the 300IR group (83.2%) compared to placebo (68.1%) ($p = 0.0030$).

Exploratory Efficacy Parameters

IgG4, the geometric mean more than tripled from Visit 1 to endpoint for 300IR (ratio 3.37), placebo (ratio 1.41)

IgE, was similar at Visit 1 and endpoint for 300IR (ratio 1.35), slightly higher for placebo at endpoint compared to Visit 1 (ratio 1.64).

SPT diameter, patients in the 300IR had a larger mean decrease (-1.37 mm) in mean wheal diameter from Visit 1 to endpoint than patients on placebo (-0.77 mm).

Asthma evaluation–300IR group, 6 /20 patients no longer had symptoms of asthma at any point; placebo group 12 /24 patients no longer had symptoms of asthma at any point.

- 8 /109 patients in the 300IR who were considered not to have asthma symptoms at Visit 1 had symptoms at endpoint.
- 9 /111 patients in placebo group considered not to have asthma symptoms at Visit 1 had symptoms at endpoint.

There was no conclusion to be made. No particular trend in favour or against patients in either treatment group was found with respect to asthma.

VO52.06-Summary of Efficacy Conclusions

For this randomised double blind placebo controlled multicentre Phase III paediatric study investigating the efficacy and safety of SLIT tablets of 300IR with placebo in children aged 5-17 years, a total of 320 patients were screened and 278 patients were subsequently randomised at 28 study centres in Europe.

A total of 266 (95.7% of patients) completed the study. The overall mean duration of treatment was between 171.1 days in the 300IR group and 176 days in placebo group. Two thirds (57.9%) of patients were aged 5-11 years old. More males than females participated with 2.5% of patients had a reported medical history of asthma. The groups were well balanced at screening.

Highly statistically significant differences were observed between the 300IR and placebo for average RTSS, average RMS, average CS, global efficacy evaluation and 4 of the 6 individual symptom scores namely runny nose, nasal congestion, itchy eyes and watery eyes.

The mean improvement of 300IR compared with placebo for the primary efficacy variable was 28%. According to the World Allergy Organisation recommendations, the minimal clinically relevant efficacy should be at least 20% improvement compared with placebo so this finding is clinically relevant. This study confirms the finding in the adult study, that 300IR SLIT tablet is efficacious in children with grass pollen allergy.

In the ITT population during the pollen period, patients receiving 300IR had a higher mean proportion of symptom free days compared to placebo (22.6% versus 12.7%) 300IR treatment group had a statistically significant high proportion of patients with treatment success compared to placebo (83.2% versus 68.1%, P = 0.0030).

No particular trend in favour or against patients was found with respect to asthma.

Supportive studies

The studies submitted as “supportive” did not demonstrate efficacy with the dosage formulations used.

Evaluator’s overall conclusions on clinical efficacy

In the two pivotal studies (VO34.04 and VO52.06) sublingual immunotherapy treatment given as a tablet formulation, Oralair at a dose of 300IR has been shown to be efficacious in the amelioration of seasonal symptoms of AR/C in children from 5 years, in adolescents and in adults. In a European setting, administration pre- and co-seasonally appears an effective way to use the treatment. Symptom scores, medication use and number of symptom-free days were all improved with the active treatment.

Safety

Introduction

Immunotherapy as a treatment modality has been in use for almost 100 years. SCIT has been the major modality for the majority of this time. From reviews published on the subject, incidence of fatalities from anaphylaxis associated with SCIT has been calculated as 1 in 2 million injections.

In order to ensure safe use for SCIT, guidelines have been published regarding safety considerations and these are widely followed. In summary, the most important safety issues addressed by these guidelines concern the following:

Prescription of SCIT

Several guidelines recommend that SCIT should only be prescribed by those with expertise in the area of Allergic Diseases to minimise inappropriate use and risk adverse effects.

Observation time

Various recommendations exist regarding an appropriate observation period following SCIT administration because of the risk of a reaction post injection. Reviews of this risk suggest that the majority of immediate reactions occur within the first hour post injection although some have occurred after 2 hours.

Concomitant asthma

In all studies of adverse events following SCIT, uncontrolled asthma at the time of injection emerges as a major risk factor for death.

β blocker use

This is a risk factor because of the possible delay in recognition of the onset of anaphylaxis and because it renders the patient relatively resistant to the effects of adrenaline.

On the other hand, SLIT has been promoted because of its increased safety. In 2000, a published meta-analysis reported the total lack of severe side effects associated with SLIT. A Cochrane review by Wilson, 2003, also reported complete absence of systemic side effects.²⁵ Since that time only a few cases of anaphylaxis have been reported, most of which have occurred in situations where SLIT has been used in a non orthodox manner.

SLIT is associated with a range of mild, local sided effects, commonly reported in published studies. They are not of any great significance and rarely lead to cessation of treatment. They are expected and patients need to understand that they may occur. Local oropharyngeal itch, tingling and discomfort, with some minor swelling account for the majority of such local side effects.

In reviewing safety data for Oralair, particular note is taken of any report suggestive of systemic side effects, reasons for withdrawal from treatment and any other significant abnormality.

Patient exposure

Adults

The overall exposure was based on 4 clinical studies, VO33.04DK, VO34.04, GR02.97UK and VOX01.96F. All patients who had received at least one dose of study drug were included in the analyses (Table 10).

Table 10: Overall exposure

| Duration weeks | 0-100IR | 100-300IR | 300-500IR | Total-any dose | Percent |
|---------------------------|----------------|------------------|------------------|-----------------------|----------------|
| 0-1 | 1 | 3 | 2 | 6 | 1 |
| 1-2 | 0 | 13 | 12 | 25 | 4 |
| 2-4 | 4 | 5 | 1 | 10 | 2 |
| 4-12 | 2 | 2 | 4 | 8 | 1 |
| 12-24 | 83 | 20 | 17 | 120 | 18 |
| 24-48 | 131 | 124 | 134 | 389 | 59 |
| 48-96 | 0 | 57 | 0 | 57 | 9 |
| >96 | 0 | 45 | 0 | 45 | 7 |
| Total-any duration | 221 | 269 | 170 | 660 | 100 |
| percent | 33 | 41 | 26 | 100 | |

In the major pivotal study, V034.04, 628 subjects, age 18-45 years were enrolled; 258 subjects received 300IR or 500IR for more than 24 weeks. SLIT treatment was taken from Visit 2. From Visit 2 to Day 5; there was dose escalation as outlined in the study design. From Day 6 to Visit 7, patients took one tablet of the appropriate dose sublingually. Overall mean treatment duration was between 169.6 days (300IR group) and 180.6 days (placebo group). In the other studies, exposure was to the lower dose of 100IR.

Paediatric populations

In V052.06, 278 children age 5-17 years were enrolled; 131 received 300IR once daily (od) for greater than 24 weeks. (In VOX01.96F 23 subjects were under 18 years of age). The overall mean duration of treatment was between 171.1 days in the 300 IR group and 176 days in placebo group.

Adverse events

Adverse events were reported using MedDRA.⁶² Frequency classification was as follows:

- Very common (greater than or equal to 1: 10)
- Common (between 1 : 10 and 1 : 100)
- Uncommon (between 1 :100 and 1:1000)

V034.04

1,348 AEs were reported; all were in the mild to moderate category and all resolved. These were reported by 384 (61%) patients. The percentage of patients in each group reporting AEs were 68.2% for 100IR, 62.6% for 300IR, 64.4% for 500IR and 48.7% for placebo. Table 11 summarises treatment emergent adverse events reported by adults in study V034.

⁶² MedDRA = Medical Dictionary for Regulatory Activities

Table 11: Treatment emergent AEs reported by adults treated with 300IR and 500IR Oralair and considered “related” by the study investigators (Study V034.04)

| Organ system | Frequency | Undesirable effect |
|--|--------------------|--|
| Nervous system disorders | <i>Common</i> | Headache, paraesthesia |
| | <i>Uncommon</i> | Dysgeusia, dizziness |
| Eye disorders | <i>Common</i> | Conjunctivitis, eye pruritus |
| | <i>Uncommon</i> | Eyelids pruritus |
| Ear and labyrinth disorders | <i>Common</i> | Ear pruritus |
| | <i>Uncommon</i> | Vertigo |
| Respiratory, thoracic and mediastinal disorders | <i>Very common</i> | Throat irritation |
| | <i>Common</i> | Dyspnoea, oropharyngeal swelling, nasal congestion, rhinorrhoea, dry throat, sneezing, nasal discomfort |
| | <i>Uncommon</i> | Throat tightness, pharyngolaryngeal pain, larynx irritation, nasal dryness |
| Gastrointestinal disorders | <i>Very common</i> | Oral pruritus |
| | <i>Common</i> | Upper abdominal pain, nausea, dyspepsia, glossitis, glossodynia, swollen tongue, tongue oedema, oral mucosal blistering, paraesthesia oral, oedema mouth, oral pain, oral discomfort, dry mouth |
| | <i>Uncommon</i> | Colitis, stomatitis, oesophagitis, gastritis, dysphagia, hyperchlorhydria, salivary hypersecretion, abdominal discomfort, diarrhoea, eructation, hypoaesthesia oral, palatal oedema, tongue blistering, tongue disorder, lip blister |
| Skin and subcutaneous tissue disorders | <i>Common</i> | Face oedema, swelling face, pruritus, urticaria |
| | <i>Uncommon</i> | Angioedema, urticaria localised |
| General disorders and administration site conditions | <i>Common</i> | Fatigue, sensation of foreign body in the mouth |
| | <i>Uncommon</i> | Application site pain, local swelling, chest discomfort, oedema peripheral |
| Infections and infestations | <i>Common</i> | Rhinitis |
| Immune system disorders | <i>Uncommon</i> | Hypersensitivity |
| Psychiatric disorders | <i>Uncommon</i> | Anxiety |

The treatment emergent adverse events (TEAEs) with the highest incidence (> 10% in any group) expressed as percentages are shown in Table 12.

Table 12: Highest incidence expressed in percentages

| Dose | Oral pruritus | Headache | Throat irritation | Nasopharyngitis |
|----------------|----------------------|-----------------|--------------------------|------------------------|
| 100IR | 20 | 15 | 11 | 10 |
| 300IR | 26 | 14 | 9 | 8 |
| 500IR | 26 | 9 | 14 | 8 |
| Placebo | 5 | 13 | 3 | 7 |

As these local, expected side effects of SLIT are reported under the System Organ Class of *Gastrointestinal Disorders*, this was the organ system with the highest incidence of AE reporting (11-46% of all patients).

Most AEs were judged not to be related or unlikely to be related to the investigational product by the investigators.

V052.06

The overall incidence of TEAEs was similar between the treatment groups. The most notable difference between treatment groups was in the occurrence of TEAEs that may be considered the side effects of SLIT listed under *Gastrointestinal Disorders* – 50.4% of patients in 300IR and 16.5% patients in placebo. These symptoms consisted of oral pruritus, mouth oedema and lip swelling. The percentage of patients reporting *Respiratory, Thoracic and Mediastinal Disorders* and *Infections and Infestations* were similar in the two groups.

Oral pruritus was the only TEAE reported in greater than 1% of patients considered severe and related to administration of the investigational product.

A summary of common TEAEs including those that were considered related to study drug is seen in Table 13.

Table 13: Common TEAEs including those that were considered related to study drug

| Dose | <i>Respiratory Thoracic and Mediastinal Disorders</i> | Asthma | Dyspnoea | <i>Gastrointestinal Disorders</i> | Swollen tongue | Skin reaction | Urticaria |
|------------------------------|---|--------|----------|---------------------------------------|-------------------|------------------|-----------|
| 300IR (related) | 74 (25) | 10 (2) | 3 (2) | 70 (65) | 5 (5) | 15 (6) | 2 (0) |
| Placebo (related) | 70 (13) | 6 (0) | 6 (1) | 23 (4) | 1 (0) | 19 (4) | 4 (2) |

Study GR02. 97 UK in adult patients

In this study adverse events were recorded on diary cards by the subjects and noted at each study visit. Adverse events were subdivided into intercurrent events, allergic disease exacerbation and minor side effects of immunotherapy. Severe side effects of immunotherapy were noted as a separate category. Severity and relationship to study medication according to the investigator was not recorded.

There were many missing data entries regarding the safety data in this trial.

The safety population available for GR02.97 UK was 180 patients (121 active, 59 placebo). There were 3 serious adverse events (SAEs); 2 in the active group (one severe angioedema, one anaphylactic reaction) and one in the placebo group (severe asthma attack).

In the case of anaphylactic reaction, a 35 year old woman carried out the progression phase of dosing and then took her first tablet. She did not feel well immediately after dosing. She had a dry mouth, swollen throat, difficulty breathing and felt sick. She took one antihistamine tablet and some four hours later felt better. She was hospitalised. There were no objective data recorded.

The severe asthma attack in the placebo group patient was considered unrelated to treatment.

Overall the safety profile of 300IR three times per week was similar to that of the 100IR once a day group in the pivotal study V034.04.

Study VOX01.96F

In this study there was no record of the severity of reactions or any note of reaction relationship to the study medication. 100IR daily was used in the study and the safety profile was very similar to that found for this dose in the pivotal study VO34.04.

Serious adverse events and deaths

No deaths were recorded in the five controlled studies (V033.04DK, V034.04, GR02.97UK, VOX01.96F and V052.06).

V034.04

Three patients had a total of 4 SAEs, none of which were related to the study drug.

V052.06

Four patients reported 4 SAEs, none of which were related to the study drug. There were no cases of anaphylaxis reported.

Withdrawals from studies due to AE's

V034.04

TEAEs leading to withdrawal from the study occurred in 3 patients in the 100IR group, 6 patients in the 300IR group and 8 patients in the 500IR group. The majority of these events were moderate to severe and were considered to be related to administration of the product. There were no cases of anaphylaxis. There were no deaths during the study.

V052.06

Nine patients had TEAEs that led to withdrawal from the study; 7 in the 300IR group and 2 in the placebo group. There were no deaths.

Laboratory findings

V034.04

There were no significant abnormalities seen across the study in parameters in the full blood count, biochemical profile or vital sign measurements. There were two pregnancies detected on urine pregnancy test, one in the 300IR group and this woman was withdrawn at Day 1. One female in the placebo group revealed a positive urine pregnancy test at Visit 7 at the end of the study.

V052.06

There were no clinically relevant abnormalities in the clinical laboratory data in either treatment group.

Safety related to drug-drug interactions and other interactions

There were no problems with the concomitant use of medications used as rescue medications, for example, antihistamines, corticosteroids and asthma medication.

Evaluator's overall conclusions on clinical safety

In V034.04, the vast majority of reactions showing differences between the active treatment arms and the placebo arm were related to local reactions in the active treatment relevant to placebo particularly with oral and tongue oedema, oral pruritus, throat irritation as well as pruritus and swelling. A ratio of 97/155 (63%) patients with AR/C on 300IR od reported AEs compared to 76/156 (49%) receiving placebo. Oral pruritus was the most commonly reported AE in those on 300IR od (26% vs 5% placebo). Early

cessation of treatment as a result of AEs occurred in 4% in the treatment arm vs 0% receiving placebo.

The majority of AEs reported were mild to moderate in severity and did not require any action to be taken with resolution by the end of the study.

Three patients had a total of 4 SAEs, none of which were related to the study drug.

There were no deaths and no reports of anaphylaxis.

For the paediatric study V052.06, common and non serious frequent adverse events reported in children and adolescents receiving Oralair sublingual tablets were similar to the published data and did not differ significantly from the adult data. No particular age group appeared to have a specific profile of side effects. Oral pruritus occurred in 32% patients receiving 300IR od compared to 1.5% in placebo group and this was the most frequently reported AE. Given its frequency, future patients should be advised that it is a likely possible effect of treatment.

In summary, for the adult data the common and non serious frequent side effects are in keeping with expected side effects of a sublingual immunotherapy and are in accordance with published literature. There were no cases to suggest any relationship with production of asthma symptoms or exacerbations, no reports of anaphylaxis and no deaths.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a "list of questions" to the sponsor is generated.

Safety

1. Is there an analysis of respiratory AEs (particularly asthma exacerbation and dyspnoea for the subjects who also had asthma accompanying their AR/C condition?
2. Have there been any reported cases of anaphylaxis in the post marketing experience in Europe?
3. Has a procedure been established for post marketing surveillance of anaphylaxis or asthma exacerbation?
4. Are there more details available about the AE described as "blistering"? This reaction does not suggest an immediate hypersensitivity mechanism but either a delayed type immunological response or a toxic reaction?

Clinical Summary and Conclusions

The data presented support the claims for efficacy of Oralair 300IR tablets for immunotherapy in grass allergic subjects in the age range from 5 years to adult.

Studies demonstrate efficacy for those sensitised to northern-Poaceae grasses. IT is a specific therapy and targets allergy to the specific allergens in the IT formulation. In Australia many patients with AR/C are polysensitised with sensitisation to grasses of other families and thus the level of benefit with this particular formulation in an Australian population is untested.

Safety analyses support existing published data confirming the lack of systemic side effects. Local effects are very common but rarely result in cessation of treatment. Patients must be counselled to expect the local oral side effects.

From a comparison across all studies it is clear that 300IR once daily dose consistently showed optimal effective outcomes. Its superiority compared to placebo was supported by

clinically relevant efficacy with a decrease in both symptom scores (RTSS) and rescue medication use. In the studies where dosing was less than 300IR daily, there was no consistent superiority compared to the placebo.

The recommended dose based on Study V034.04 is an initial up dosing on Day 1 100IR, Day 2 200IR and from Day 3 onwards 300IR. The dosing schedule should be the same in paediatric patients based on the data from Study V052.06.

It is an advantage to have a convenient and safe IT formulation available in the Australian setting. There is a high prevalence of AR/C in the Australian community and there is a lack of suitable qualified specialists to service the need. SLIT does not need the same level of supervision and follow up that the more traditional SCIT formulation demanded. In addition, SLIT is a very convenient IT dose form for patients in rural and remote settings requiring IT for allergies as it is taken in the home and does not require frequent doctor presentations. The use of pre- and co-seasonal dosing will likely improve compliance and make the cost more attractive.

The evaluator recommended that the submission be approved for the indication:

Clinically relevant symptoms of AR/C with evidence of immediate hypersensitivity (using SPT and/or specific IgE measurement) to selected grass pollen of Poaceae family (Dactylis glomerata, Lolium perenne, Anthoxanthum odoratum, Phleum pratense, Poa pratensis)

- *In adults*
- *In adolescents*
- *In children from 5 years old*

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

No ongoing safety concerns were identified by the sponsor. There were no important identified or potential risks and no important identified or potential interactions. It was indicated that there were no interactions in clinical trials with Oralair sublingual tablets during which patients were able to take symptomatic medications (antihistamines and steroids), and that no interactions are expected.

No important missing information was identified by the sponsor.

The OPR evaluator noted that it was unclear why the sponsor has not specified important identified risks, potential risks and missing information as the proposed PI includes contraindications, precautions and adverse effects. The important identified risks, important potential risks and important missing information should be included in the relevant sections of the Safety Specification.

The Contraindications and Precautions refer to hypersensitivity, severe and/or unstable asthma, severe immune deficiency or autoimmune disease, malignant disease, oral inflammation and hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption, beta-blocker co-medication, simultaneous vaccination and treatment with Oralair, simultaneous immunotherapy with other allergens, pregnancy and lactation and use of adrenaline to treat severe allergic reactions in patients treated with tricyclic antidepressants and monoamine oxidase inhibitors. It was unclear to the OPR reviewer which of the above Contraindications and Precautions are important

identified risks and which, if any, are important potential risks. It was recommended to the Delegate that the sponsor be requested to specify such risks.

Of note, it was indicated in the RMP that asthma was considered a risk factor contributing to a proportion of deaths related to subcutaneous immunotherapy and that in a number of these cases the forced expiratory volume in one second (FEV₁) was less than 70% of predicted values. The sponsor stated that the safety of sublingual immunotherapy in high risk populations, such as patients with a degree of hypersensitivity, or patients experiencing exacerbations of their allergy symptoms, requires further evaluation. It was also stated that surveillance of the safety of sublingual immunotherapy should continue to assess and confirm the absence of severe systemic reaction. These issues were clearly important ongoing safety concerns.

It was recommended to the Delegate that the Sponsor be requested to:

- Specify important identified risks, important potential risks and important missing information for Oralair sublingual tablets and add them to the Safety Specification of the RMP
- Include the following as ongoing safety concerns in the Safety Specification of the RMP:
 - safety of sublingual immunotherapy in high risk populations, such as patients with a degree of hypersensitivity, or patients experiencing exacerbations of their allergy symptoms
 - severe systemic reaction
 - coagulation parameter abnormalities (important potential risk)
 - use of Oralair in pregnancy, lactation, with simultaneous vaccination, with simultaneous immunotherapy with other allergens, in patients aged over 46 years, and for periods longer than those studied in the pivotal clinical studies (important missing information)
 - overdose (missing information)

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The evaluator considered there were no remaining issues to be resolved and requested the PSC to provide a final recommendation on this application. The PSC resolved that there should be no objection on quality and pharmaceutical grounds to approval of the application to register Oralair tablet containing 100IR and 300IR of the extract of the five grasses provided all outstanding issues were addressed to the satisfaction of the TGA.

Nonclinical

The evaluator commented that the submitted non-clinical data (single and repeat dose toxicity, genotoxicity, reproductive toxicity and local tolerance) were generally adequate, apart from few limitations, and those submitted studies did not identify particular risks relating to general toxicity, local tolerance or reproductive toxicity, including teratogenicity. The weight of evidence indicated that Oralair presents no significant genotoxic potential at the maximum recommended clinical dose. The evaluator pointed out that although the nonclinical data were limited, this should be considered in light of the international clinical experience with the drug, including experience in Australia with

Alustal. There were no nonclinical objections to the registration of Oralair, provided the clinical data adequately address the efficacy of the product.

The sponsor proposed a Pregnancy Category C for Oralair, although the nonclinical data indicated that Pregnancy Category B2 was more appropriate.

Clinical

Efficacy

In support of this application, two pivotal studies (VO34.04 and VO52.06) and two supporting studies (VOX01.96F and GR02.97UK) were submitted.

The two pivotal studies were Study VO34.04 in adults and Study VO52.06 in children. The two pivotal studies used similar inclusion/ exclusion criteria, primary/secondary/ exploratory efficacy endpoints, and analysis populations. These were in general conformed to the current regulatory guideline⁶³. The submitted data only presented the treatment experience in one pollen season.

Study VO34.04

Study VO34.04 was a randomised, double blind placebo controlled multicentre Phase III study. The study evaluated the efficacy and safety of Oralair sublingual tablets in adult subjects. The study population consisted of male and female subjects between 18-45 years who suffering from seasonal grass pollen-related rhinoconjunctivitis for at least 2 years, as confirmed by radioallergosorbent test (RAST) and skin prick test (SPT).

Each patient received a sublingual dose once daily for about 4 months before the start of the pollen season, and continuing throughout the pollen season. An incremental dosage scheme was followed during the first 5 days and the dose was escalated by 100IR per day up to the randomized dose.

The primary efficacy endpoint was the average RTSS (Rhinoconjunctivitis Total Symptoms Score) during the pollen period while on treatment in the ITT population. RTSS is calculated as the sum of the 6 rhinoconjunctivitis symptoms – sneezing, rhinorrhoea, nasal pruritus, nasal congestion, ocular pruritus, watery eyes. These are assessed on a 4-point scale for the previous 24 hours. The average RTSS is a calculation of the daily average score during the pollen season on treatment. Analysis of the results was based on 569 evaluable patients.

The primary efficacy endpoint was analysed using ANCOVA with treatment and pooled centre as main effects and the RRTSS, presence and absence of asthma and sensitization (mono- versus poly-sensitized) status of the patient as covariates. The analysis in the ITT population showed that patients in the 300 IR and 500 IR groups had the lowest average RTSS during the pollen period (3.58 and 3.74) while patients in the 100 IR and placebo groups had the highest average RTSS (4.72 and 4.93). There was a statistical significant difference between 300 IR and 500 IR group versus placebo group (p-values of 0.0001 and 0.0006, respectively) in the average. The 300IR group showed a mean improvement (RTSS) of 27.4% over placebo with a median improvement of 37%. The results for the PP population were similar and confirm the results in the ITT population.

Rescue medication usage was assessed as one of the secondary efficacy measures. There was no significant difference between the active treatment groups and placebo groups in the proportion of patients who used at least one type of rescue medication during the

⁶³ EMEA. Committee for Medicinal Products for Human Use (CHMP), 20 November 2008. Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases, CPMP/EWP/2455/02. <http://www.tga.gov.au/docs/pdf/euguide/ewp/1850406en.pdf>

pollen period while on treatment (64.7% in 300IR group and 73.0% in the placebo group). However, there were significant differences for the proportion of days of rescue medication use between the 300IR group (19.72%) and the placebo group (27.85%) during the pollen period. With the individual average symptom scores, there were statistically significant differences between the active treatment groups vs placebo with the mean improvement in the 300 IR group above 25% four of the six individual symptom scores compared to placebo.

In the ITT population during the pollen period, there was a statistically significant difference between the active treatment groups vs placebo in the Global Evaluation as well as the Combined Score (a score taking into account the RTSS and rescue medication usage). The 300 IR group had the highest mean proportion of symptom free days (26.22%) while the placebo group had the lowest (16.71%). The overall quality of life scores showed statistically significant difference between the 300 IR and 500 IR groups vs placebo on Visits 5 and 7.

The treatment groups showed an expected decrease in the diameter of the skin prick test wheal from screening visit to the last visit in a dose response fashion. IgG₄ and IgE levels also showed an expected increase between Visit 1 and Visit 7 for all active treatment groups vs placebo. Overall, the treatment with 300 IR and 500 IR daily doses in adult subjects are efficacious in reducing the symptom scores (RTSS) while 100 IR daily is not. Safety results showed that the incidences of common adverse events were higher in the 500IR group compared to lower dose groups, 300IR was therefore selected as the dose of choice and this dose was then used in the paediatric study.

V052.06

V052.06 was a randomized double blind placebo controlled multicentre (in 28 study centres from 5 European countries) Phase III study conducted in paediatric subjects (5-17 years) with documented grass pollen allergic rhinoconjunctivitis. The study assessed the efficacy and safety of 300IR Oralair tablets and placebo.

The primary endpoint was the average RTSS during the pollen period while on treatment in the ITT population. Secondary endpoints include average Rescue Medication Score (RMS), average Combined Score (CS), and individual symptom scores, global efficacy evaluation, and proportion of symptom free days.

The primary endpoint was analysed using an ANCOVA. A point estimate and 95% CI for the difference in the adjusted means between 300IR and placebo was calculated. The results showed that there was a statistically significant differences between the 300IR and placebo for average RTSS (P =0.0010, Least square mean difference was -1.13 with 95% CI of -1.80 and -0.46).

The study also showed that there was a statistically significant differences between the 300IR and placebo for average RMS (p = 0.0064), average CS (p = 0.0004), global efficacy evaluation (p = 0.0021), and four of the six individual symptom scores (namely runny nose, nasal congestion, itchy eyes and watery eyes).

The mean improvement of 300IR compared with placebo for the primary efficacy variable was 28% (median improvement of 39.3%). According to the World Allergy Organisation recommendations⁶⁴, the minimal clinically relevant efficacy should be at least 20% improvement compared with placebo so this finding is clinically relevant.

⁶⁴ Canonica GW, Baena-Cagnani CE, Bousquet J, Bousquet PJ, Lockey RF, Malling HJ *et al.* Recommendations for standardization of clinical trials with allergen specific immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. *Allergy* 2007;62:317-324

In the ITT population during the pollen period, patients receiving 300IR had a higher mean proportion of symptom free days compared to placebo (22.6% versus 12.7%). The proportion of patients who used at least one rescue medication during the pollen period was slightly lower in 300IR group compared to placebo group (83.2% versus 68.1%). There was no particular trend in favour or against patients with respect to asthma.

Safety

The overall exposure of adult patients is based on four clinical studies (VO33.04DK, VO34.04, GR02.97UK, and VOX01.96F) while the overall exposure of paediatric subjects is based on Study VO52.06. The safety of SLIT was also considered in the context of published safety information on SLIT and SCIT.

In the adult pivotal study (VO34.04), the vast majority of reactions showing differences between the active treatment arms and the placebo arm were related to local reactions in the active treatment relevant to placebo particularly with oral and tongue oedema, oral pruritus, throat irritation as well as pruritus and swelling. Oral pruritus was the most commonly reported AE in subjects receiving 300IR once daily (26% vs 5% placebo group). Early cessation of treatment as a result of AEs occurred in 4% in treatment arm versus 0% in the placebo group. The majority of AEs reported was mild to moderate in severity and did not require any action to be taken with resolution by the end of the study. Three patients had a total of 4 SAEs, none of which were related to study drug. There were no deaths and no reports of anaphylaxis.

The safety population in adult study GR02.97UK was 180 patients (121 active, 59 in placebo group). In this study, there were 3 SAEs reported, one severe angioedema, one anaphylactic reaction and one in placebo group-severe asthma attack. There were no unusual findings from the adult study VOX01.96F.

For the paediatric study (VO52.06), common and non serious AEs reported in children and adolescents receiving Oralair sublingual tablets did not differ significantly from the adult data. No particular age group appeared to have a specific profile of side effects. Oral pruritus occurred in 32% patients in the 300IR group compared to 1.5% in placebo group and this was the most frequently reported AE.

Overall, the safety data from the submitted studies are based on limited subjects' exposure and the safety findings from these studies are in keeping with expected side effects of a sublingual immunotherapy and are in accordance with published literature. The trial data did not indicate any unusual risk associated with Oralair sublingual tablets and there were no cases to suggest any relationship with development of asthma symptoms or exacerbations.

Risk Management Plan

The RMP were evaluated by the Office of Product Review (OPR) and several recommendations were made. The sponsor's response to the RMP evaluation adequately addressed the issues raised and was considered acceptable by the OPR evaluator. The Delegate agreed that a severe laryngo-pharyngo-pharyngeal disorder should be considered as an important identified risk with anaphylactic shock / autoimmune disorders as potential risks. It was noted that there is an instruction in the PI stating that the first tablet of Oralair should be taken under medical supervision and that the patient should be monitored for 30 minutes after taking the first dose. The sponsor also proposed to provide training to physicians in relation to prescribe the product to the right patients and provide appropriate patients educations.

The information relating to the treatment in pregnant /lactating women is lacking. Routine and additional pharmacovigilance activities have been proposed for each of these identified safety concerns and missing information.

Risk-Benefit Analysis

Delegate Considerations

The Delegate agreed that the submitted data supported the efficacy and safety of Oralair 300IR tablets for the treatment of grass pollen allergic rhinitis with or without conjunctivitis in adults, adolescents and children (above the age of 5 years). The Delegate also considered that it would be an advantage to have a convenient and safer SLIT formulation available in the Australian market. As SLIT does not require the same level of supervision and follow up that the more traditional SCIT formulation demanded, SLIT is therefore convenient to use for patients in rural and remote settings where specialist services may be inadequate. The clinical evaluator pointed out that many Australian patients are poly-sensitised with sensitisation to grasses of other families, and the level of benefit with this particular SLIT formulation in the Australian population is untested.

The advisory committee was requested to comment and provide guidance as to whether it is acceptable to approve this product for use in the Australian population on the basis of efficacy and safety data from clinical studies conducted in the European countries.

The Delegate proposed to approve the submission for:

the treatment of grass pollen allergic rhinitis with or without conjunctivitis in adults, adolescents and children (above the age of 5) with clinically relevant symptoms, confirmed by a positive cutaneous test and/or a positive titre of the specific IgE to the grass pollen.

The recommended dose is an initial up dosing; 100IR on Day 1, 200IR on Day 2 and 300IR from Day 3 onwards. The dosing schedule is the same for adults and paediatric subjects. The treatment should be initiated about 4 months prior to the expected onset of the pollen season and must be maintained till the end of the pollen season.

The conditions of registration should include:

- Submitting the results of all ongoing clinical studies,
- Conducting the pharmacovigilance activities as agreed with the OPR.

Response from Sponsor

The sponsor agreed to the two proposed conditions of registration.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission for a new route of administration and new dosage form for the currently approved indication:

Treatment of grass pollen allergic rhinitis with or without conjunctivitis in adults, adolescents and children (above the age of 5) with clinically relevant symptoms, confirmed by a positive cutaneous test and/or a positive titre of the specific IgE to the grass pollen.

The ACPM noted that allergies are a significant and increasing problem in the community. This product is registered in Australia as a subcutaneous injection and contains five different species of grasses, four of which are common allergens in Australia.

It was acknowledged that sublingual immunotherapy (SLIT) provides convenience and possible safety advantages and published literature is supportive of SLIT mechanisms for tolerance induction.

In making this recommendation, the ACPM considered that nonclinical data, particularly on pharmacology, carcinogenicity and reproductive effects were extremely limited. This may be balanced by considerable post-market data in Europe and SC safety data in Australia.

The efficacy data from the two pivotal trials which were of appropriate design, selection of disease population, conduct and analyses showed symptom improvements were above accepted meaningfulness threshold and secondary measures were supportive. Safety data were in keeping with expected side effects of a sublingual immunotherapy and are in accordance with published literature. The ACPM, taking into account the submitted evidence of safety and efficacy, considered there is a favourable benefit-risk profile for this product.

The validity of the contraindication in cancer patients was questioned as the basis for it was not apparent. Pregnancy classification was now noted to be B2.

The ACPM considered the specific conditions of registration should include:

- The submission of the results of all ongoing clinical studies,

The ACPM noted that the sponsor had agreed to the evaluator's and Delegate's proposed pharmacovigilance activities and changes to the Product Information (PI) and Consumer Medicines Information (CMI). However, it was considered that the Dosage and Administration section should stress that treatment must be initiated about four months before the expected onset of the pollen season and that initiation of therapy must be undertaken with strict observation by a medical practitioner for potential hypersensitivity reactions, given the nature of the therapy and the site of administration.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Oralair Initiation Treatment Sublingual Tablets 100IR and Oralair Continuation Treatment Sublingual Tablets 300IR containing allergen pollen extract of 5 grasses indicated for:

Treatment of grass pollen allergic rhinitis with or without conjunctivitis in adults, adolescents and children (above the age of 5) with clinically relevant symptoms, confirmed by a positive cutaneous test and/or a positive titre of the specific IgE to the grass pollen.

Among the specific conditions of registration were:

- The implementation in Australia of the Risk Management Plan Version 3 (RMP) dated 22 September 2010, and any subsequent revisions, as agreed with the Office of Product Review (OPR) of the TGA .
- The provision of the results of all ongoing clinical studies and conducting pharmacovigilance activities as agreed with the Office of Product Review.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published.
For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

NAME OF MEDICINE

ORALAIR Initiation Treatment Sublingual Tablets 100 IR & 300 IR
(Allergen pollen extract of 5 grasses)

ORALAIR Continuation Treatment Sublingual Tablets 300 IR
(Allergen pollen extract of 5 grasses)

DESCRIPTION

Grass pollen allergen extract from: Cocksfoot (*Dactylis glomerata* L.), Sweet vernal grass (*Anthoxanthum odoratum* L.), Rye grass (*Lolium perenne* L.), Meadow grass (*Poa pratensis* L.) and Timothy (*Phleum pratense* L.) 100 IR* or 300 IR* per sublingual tablet.

* IR (Index of Reactivity) : The unit IR has been defined to measure the allergenicity of an allergen extract. The allergen extract contains 100 IR/ml when, on a skin prick-test using a Stallerpoint[®], it induces a wheal diameter of 7 mm in 30 patients sensitized to this allergen, (geometric mean). The cutaneous reactivity of these patients is simultaneously demonstrated by a positive skin prick-test to either 9 % codeine phosphate or 10 mg/ml histamine. The IR unit of Stallergenes is not comparable to the units used by other allergen manufacturers.

Excipients: Mannitol, Microcrystalline cellulose, Croscarmellose sodium, Colloidal anhydrous silica, Magnesium stearate and Lactose monohydrate.

One sublingual tablet of 100 IR contains 83.1 – 83.6 mg Lactose monohydrate.

One sublingual tablet of 300 IR contains 81.8 – 83.1mg Lactose monohydrate.

PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group: Allergen extract, grass pollen

ATC code: V01AA02

Mechanism of action

ORALAIR is used for treatment of patients with specific IgE-mediated allergy symptoms such as rhinitis with or without conjunctivitis caused by grass pollen.

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 ORALAIR has shown to induce a systemic competitive antibody response towards grass and induces an increase in specific IgG. The clinical relevance of these findings has not been established.

Pharmacokinetic properties

The majority of allergens in ORALAIR are a mixture of proteins and glycoproteins. There is no direct bioavailability of intact allergens in the blood. Therefore, no pharmacokinetic studies in animals or in humans have been carried out to investigate the pharmacokinetic profile and metabolism of ORALAIR.

CLINICAL TRIALS

Clinical experience in adults (VO34.04 study):

A European, multicentre, multinational, randomised, double-blind, placebo-controlled study was conducted.

The study included 628 patients with seasonal allergic rhinitis and/or rhinoconjunctivitis caused by grass pollen, as confirmed by cutaneous tests and/or a positive titre of the IgE specific to the grass pollen.

Patients were randomized to 4 groups: placebo (n=156), ORALAIR 100 IR/day (n=157), ORALAIR 300 IR/day (n= 155) and ORALAIR 500 IR/day (n=160).

Each patient received a sublingual dose once a day for about 4 months before the start of the pollen season, and continuing throughout the pollen season. Analysis of the results was based on 569 assessable patients (placebo, n=148; ORALAIR 100 IR, n=142; ORALAIR 300 IR, n=136; ORALAIR 500 IR, n=143). The efficacy was determined according to the Rhinoconjunctivitis Total Symptom Score (RTSS).

Results of this study showed a comparable efficacy of 500 and 300 IR, with safety data in favour of 300 IR, leading to a recommended dose of 300 IR per day.

The sensitisation status (poly/mono-sensitised) and the presence or absence of associated asthma have no impact on the results.

During the first season, the efficacy of the 300 IR group versus the placebo group (number of subjects included in the Intent to Treat (ITT) population were 136 and 148, respectively) showed the following results:

VO34.04 study: Efficacy results (during the pollen season)

Primary endpoint

| VO34.04 study | ORALAIR 300IR Mean (SD) <i>Median</i> | Placebo Mean (SD) <i>Median</i> | Absolute Adjusted Diff Mean [CI 95%] | Relative Diff.* % | P-value** |
|--|---|---|---|--------------------------|------------------|
| Rhinoconjunctivitis symptom score ^A | 3.58 (2.98) <i>2.91</i> | 4.93 (3.23) <i>4.62</i> | -1.39 [-2.09 ; -0.69] | 27.4% | 0.0001 |

*Relative Difference: Absolute Difference / Placebo

** p-value ANCOVA

^A Symptom Score: Average daily total rhinoconjunctivitis symptom scores for each patient during the grass pollen season. Rhinoconjunctivitis symptoms included sneezing, runny nose, itchy nose, nasal congestion, watery eyes and itchy eyes (0-18 range of score).

Secondary endpoints

| VO34.04 study | ORALAIR 300IR Mean (SD) <i>Median</i> | Placebo Mean (SD) <i>Median</i> | Absolute Adjusted Diff Mean [CI 95%] | Relative Diff.* % | p- value** |
|---------------------------------------|--|--|--|-------------------------|---------------|
| Rescue Medication use ^B | 19.7% (24.8) 10.6% | 27.9 % (29.3) 19.7% | - | - | |
| Quality of life score ^C | 1.15 (0.99) 0.90 | 1.45 (1.04) 1.27 | -0.26 [-0.36 ; -0.16] | 20.7% | <0.0001 |

*Relative Difference: Absolute Difference / Placebo

** p-value ANCOVA

^B Rescue medication use: Percentage of days per patient with at least one rescue medication intake, p-value 0.0194 NS (Wilcoxon).

^C Quality of life was assessed at the peak of the pollen season by the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). A higher score is reflecting a worse quality of life.

Global evaluation of the efficacy of the treatment by the patient: 119 patients (87%) in the ORALAIR 300IR group and 108 patients (73%) in the placebo group noted slight to moderate or good to excellent improvement relative to the previous pollen season.

The ANCOVA results on each of the six individual mean symptom scores showed a difference in favour of the 300 IR tablet with a statistical significance (p-values < 0.0102) for sneezing (-0.19), runny nose (-0.23), itchy nose (-0.23), nasal congestion (-0.28), itchy eyes (-0.24) and watery eyes (-0.21). The highest difference as compared to placebo was observed on nasal congestion and watery eyes.

The proportion of patients not using rescue medication were 35.3% in the 300 IR group and 27.0% in the placebo group (NS).

Sixty-one patients (45%) in the 300 IR group had presented more than 50% Symptom Controlled Days (with a symptom score not higher than 2 and without rescue medication) over the grass pollen season, versus 40 patients (27%) in Placebo group.

Clinical experience in children and adolescents (VO52.06 study):

A European, multicentre, multinational, randomised, double-blind, placebo-controlled study was conducted. The study included 278 patients aged 5 to 17 years suffering from seasonal allergic rhinitis and/or rhinoconjunctivitis caused by grass pollen, as confirmed by cutaneous tests and a positive titre of the IgE specific to the grass pollen.

Patients were randomized to 2 groups: placebo (n=139) or ORALAIR 300 IR/day (n= 139). Each patient received a sublingual dose once a day for about 4 months before the start of the pollen season, and continuing throughout the pollen season. An incremental dosing scheme was followed for the first 3 days of the treatment phase, where the dose was escalated by 100 IR per day from a starting dose of 100 IR up to daily dose of 300 IR. Analysis of the results was based on 266 assessable patients (placebo, n=135 and ORALAIR 300 IR, n=131). The efficacy was determined according to the Rhinoconjunctivitis Total Symptom Score (RTSS).

The sensitisation status (poly/mono-sensitised), the presence or absence of associated asthma and the age group (children 5-11 years versus adolescents 12-17 years) have no impact on the results.

During the first season, the efficacy analysis of the 300 IR group versus the placebo group (number of subjects included in the Intent to Treat ITT population were 131 and 135 respectively) showed the following results:

VO52.06 study: Efficacy results (during the pollen season):

Primary endpoint

| VO52.06 study | ORALAIR 300IR Mean (SD) <i>Median</i> | Placebo Mean (SD) <i>Median</i> | Absolute Adjusted Diff Mean [CI 95%] | Relative Diff.* % | p-value** |
|--|--|------------------------------------|--------------------------------------|-------------------|-----------|
| Rhinoconjunctivitis symptom score ^A | 3.25 (2.86) 2.48 | 4.51 (2.93) 4.08 | -1.13 [-1.80 ; -0.46] | 27.9% | 0.001 |

*Relative Difference: Absolute Difference / Placebo

** p-value ANCOVA

^A Symptom Score: Average daily total rhinoconjunctivitis symptom scores for each patient during the grass pollen season. Rhinoconjunctivitis symptoms included sneezing, runny nose, itchy nose, nasal congestion, watery eyes and itchy eyes (0-18 range of score).

Secondary endpoints

| VO52.06 study | ORALAIR 300IR Mean (SD) <i>Median</i> | Placebo Mean (SD) <i>Median</i> | Absolute Adjusted Diff Mean [CI 95%] | Relative Diff.* % | p-value** |
|--|--|------------------------------------|--------------------------------------|-------------------|-----------|
| Average Rescue Medication Score ^B | 0.60 (0.61) 0.39 | 0.79 (0.65) 0.76 | -0.20 [-0.34 ; -0.06] | 24.0% | 0.0064 |
| Rescue Medication use ^C | 35.4% (33.2) 26.8% | 46.5% (34.6) 49.0% | - | - | - |

*Relative Difference: Absolute Difference / Placebo

**p-value ANCOVA

^B Average Rescue Medication Score: Average daily rescue medication score for each patient during the grass pollen season. Medications used were scored as follows: no rescue medication = 0, antihistamines (oral and/or ocular) = 1, nasal corticosteroids = 2 and oral corticosteroids = 3.

^C Rescue medication use: Percentage of days per patient with at least one rescue medication intake, p-value 0.0146 NS (Wilcoxon).

Individual Symptom Scores: The ANCOVA results on each of the six individual mean symptom scores showed a difference in favour of the 300 IR tablet with a statistical significance (p-values ≤ 0.0380) for runny nose (-0.16), nasal congestion (-0.26), itchy eyes (-0.33) and watery eyes (-0.21). The highest difference as compared to placebo was observed on watery eyes, nasal congestion and itchy eyes.

The proportion of patients not using rescue medication were 18.3% in the 300 IR group and 14.8% in the placebo group (NS).

Forty-four patients (34%) in the 300 IR group had presented more than 50% Symptom-Controlled Days (with a symptom score not higher than 2 and without rescue medication) over the grass pollen season, versus 26 patients (19%) patients in Placebo group.

INDICATIONS

Treatment of grass pollen allergic rhinitis with or without conjunctivitis in adults, adolescents and children (above the age of 5) with clinically relevant symptoms, confirmed by a positive cutaneous test and/or a positive titre of the specific IgE to the grass pollen.

CONTRAINDICATIONS

- Hypersensitivity to any of the excipients;
- Beta-blocker co-medication;
- Severe and/or unstable asthma ($FEV_1 < 70$ % of predicted value);
- Severe immune deficiency or auto-immune disease;
- Malignant diseases (e.g. cancer);
- Oral inflammations (such as oral lichen planus, oral ulcerations or oral mycosis).

PRECAUTIONS

In case of oral surgery, including dental extraction, treatment with ORALAIR should be stopped for 7 days to allow healing of the oral cavity. Thereafter, treatment may be restarted with the previous dosage. Should the interruption period be longer, it is recommended to restart the treatment with the previous dosage under medical supervision.

Severe allergic reactions may be treated with adrenaline. The effects of adrenaline may be potentiated in patients treated with tricyclic antidepressants and mono amine oxidase inhibitors (MAOIs) with possible fatal consequences; this should be taken into consideration prior to initiating specific immunotherapy.

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

Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Carcinogenicity

No carcinogenicity studies were conducted in animals.

Genotoxicity

The purified 5 grasses pollen extract contained in ORALAIR showed no mutagenic or clastogenic potential in a series of *in vitro* assays (mouse lymphoma TK cells and bacterial reverse mutation).

Moreover, the same less purified extract of five grasses was not genotoxic *in vivo* in rats, using the two endpoints of chromosomal aberration and unscheduled DNA synthesis, at IP or SC doses resulting in exposures markedly greater than the maximum clinical exposure.

Effects on fertility

No fertility and early embryonic development studies were conducted with ORALAIR, however histopathological examination of the male and female reproductive organs in repeat-dose toxicity studies with the 5 grasses pollen extract of ORALAIR revealed no adverse findings.

Interaction with other medicinal products

No interactions were reported in clinical trials with ORALAIR, during which patients were able to take medications to treat allergic symptoms (antihistamines, steroids).

There are no data available on possible risks of simultaneous immunotherapy with other allergens during treatment with ORALAIR.

Use in Pregnancy (Category B2)

For ORALAIR no clinical data on exposed pregnancies are available.

It is not recommended to initiate immunotherapy during pregnancy. If pregnancy occurs during treatment, the treatment may continue with close supervision.

There was no evidence for embryofetal toxicity, including teratogenicity, following oral administration of ORALAIR to pregnant rats and rabbits during organogenesis, at exposures at least 76 times greater than the maximum clinical exposure, based on body surface area.

Use in Lactation

No clinical data are available for the use of ORALAIR during lactation. No effects on the breastfed infants are anticipated. It is not recommended to initiate immunotherapy during breast-feeding. However, if a patient is under treatment at delivery, she can breast-feed with close supervision.

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

Use in Children (< 5 years)

Clinical experience in younger children < 5 years is not performed

Effects on ability to drive and use machines

ORALAIR has no known influence on the ability to drive and use machines.

ADVERSE EFFECTS

During treatment with ORALAIR, patients are exposed to allergens that may cause local and/or systemic allergic symptoms.

Mild to moderate local allergic reactions (i.e. oral swelling or discomfort) may therefore be expected during the period of therapy. 50% of these reactions occur during the first three days of treatment (dose escalation).

If the patient experiences severe local adverse reactions during therapy, symptomatic treatment (e. g. with antihistamines) should be considered.

In very rare cases, stronger allergic reactions can occur, a feeling of swelling in the throat, difficulty swallowing or breathing and voice changes. In such cases a physician has to be consulted immediately and the treatment has to be discontinued immediately. Treatment may only be resumed on the doctor's advice.

The side effects are classified according to the MedDRA convention by system organ class and by frequency into:

- very common ($\geq 1/10$);
- common ($\geq 1/100$ to $<1/10$);

- uncommon ($\geq 1/1000$ to $<1/100$);
- rare ($\geq 1/10,000$ to $<1/1,000$);
- very rare ($<1/10,000$), not known (cannot be estimated from the available data).

Clinical experience in adults (VO34.04 study):

During a clinical trial conducted in adult patients with allergic rhinoconjunctivitis and receiving a dose of 300 IR per day, 97/155 patients (63 %) reported adverse reactions, compared to 76/156 patients (49 %) receiving a placebo.

The adverse effect most frequently reported in patients treated with 300 IR was oral pruritus in 26 % of patients (5 % in the placebo group).

The number of patients stopping their treatment prematurely due to an adverse effect was 6/155 (4 %) in the treated group and 0/156 in the placebo group.

The following side effects were reported by adult patients:

| Organ system | Frequency | Undesirable effect |
|---|--------------------|--|
| Nervous system disorders | <i>Common</i> | Headache, paraesthesia |
| | <i>Uncommon</i> | Dysgeusia, dizziness |
| Eye disorders | <i>Common</i> | Conjunctivitis, eye pruritus |
| | <i>Uncommon</i> | Eyelids pruritus |
| Ear and labyrinth disorders | <i>Common</i> | Ear pruritus |
| | <i>Uncommon</i> | Vertigo |
| Respiratory, thoracic and mediastinal disorders | <i>Very common</i> | Throat irritation |
| | <i>Common</i> | Dyspnoea, oropharyngeal swelling, nasal congestion, rhinorrhoea, rhinitis, dry throat, sneezing, nasal discomfort |
| | <i>Uncommon</i> | Throat tightness, pharyngolaryngeal pain, larynx irritation, nasal dryness |
| Gastrointestinal disorders | <i>Very common</i> | Oral pruritus |
| | <i>Common</i> | Upper abdominal pain, nausea, dyspepsia, glossitis, glossodynia, swollen tongue, tongue oedema, oral mucosal blistering, paraesthesia oral, oedema mouth, oral pain, oral discomfort, dry mouth |
| | <i>Uncommon</i> | Colitis, stomatitis, oesophagitis, gastritis, dysphagia, hyperchlorhydria, salivary hypersecretion, abdominal discomfort, diarrhoea, eructation, hypoaesthesia oral, palatal oedema, tongue blistering, tongue disorder, lip blister |
| Skin and subcutaneous | <i>Common</i> | Face oedema, swelling face, pruritus, urticaria |

| Organ system | Frequency | Undesirable effect |
|--|----------------------------------|---|
| tissue disorders | <i>Uncommon</i> | Angioedema, urticaria localised |
| Infections and infestations | <i>Common</i> | Rhinitis |
| General disorders and administration site conditions | <i>Common</i> <i>Uncommon</i> | Fatigue, sensation of foreign body in the mouth Application site pain, local swelling, chest discomfort, oedema peripheral |
| Immune system disorders | <i>Uncommon</i> | Hypersensitivity |
| Psychiatric disorders | <i>Uncommon</i> | Anxiety |

These reactions usually occurred during the first three days of treatment (dose escalation) and were all reversible.

Clinical experience in children and adolescents (VO52.06 study):

During a clinical trial conducted in children and adolescents (5 to 17 years of age) with allergic rhinoconjunctivitis and receiving a dose of 300 IR per day, 118/139 patients (85 %) reported adverse effects, compared to 114/139 patients (82 %) receiving placebo.

The most frequently reported adverse effect in children and adolescents treated with 300 IR was oral pruritus in 32 % of patients (1 % in the placebo group).

The number of patients stopping their treatment prematurely due to an adverse effect was 6/139 (4 %) in the 300 IR group and 1/139 (1.5 % in the placebo group).

The following side effects were reported by children and adolescents (5 to 17 years):

| Organ system | Frequency | Undesirable effect |
|--|--------------------|---|
| Nervous system disorders | <i>Uncommon</i> | Headache |
| Eye disorders | <i>Common</i> | Eye pruritus |
| | <i>Uncommon</i> | Ocular hyperaemia |
| Ear and labyrinth disorders | <i>Common</i> | Ear pruritus |
| | <i>Uncommon</i> | Ear congestion, ear discomfort |
| Respiratory, thoracic, and mediastinal disorders | <i>Common</i> | Throat irritation, nasal congestion, asthma, sneezing, nasal discomfort, dyspnoea, larynx irritation, throat tightness |
| | <i>Uncommon</i> | Cough, rhinorrhoea, dysphonia, laryngeal oedema, pharyngeal oedema |
| Gastrointestinal disorders | <i>Very common</i> | Oral pruritus, oedema mouth |
| | <i>Common</i> | Lip swelling, swollen tongue, oral mucosal blistering, stomatitis, vomiting, cheilitis, glossitis, oral discomfort |
| | <i>Uncommon</i> | Abdominal pain, abdominal pain upper, nausea, dyspepsia, dysphagia, hypoaesthesia oral, odynophagia, oral pain, tongue oedema |
| Skin and subcutaneous tissue disorders | <i>Common</i> | Dermatitis atopic, pruritus |
| | <i>Uncommon</i> | Eczema, circumoral oedema |
| Musculoskeletal and connective tissue disorders | <i>Uncommon</i> | Growing pains |
| Infections and infestations | <i>Uncommon</i> | Nasopharyngitis, tonsillitis, bronchitis, influenza |
| General disorders and administration site conditions | <i>Common</i> | Chest discomfort |
| | <i>Uncommon</i> | Asthenia, chest pain |
| Immune system disorders | <i>Uncommon</i> | Hypersensitivity |

DOSAGE AND ADMINISTRATION

Treatment should be initiated about 4 months before the expected onset of the pollen season and must be maintained throughout the pollen season.

Treatment with ORALAIR should only be prescribed and initiated by physicians with adequate training and experience in the treatment of allergic diseases. In case of paediatric treatment, the physicians should have the corresponding training and experience in children.

In order to enable patient and physician to discuss any side effects and possible actions it is recommended that the first tablet of ORALAIR is taken under medical supervision and that the patient is monitored for 30 minutes.

Dose regimen in adults, adolescents and children (above the age of 5):

The therapy is composed of an initiation treatment (including a 3-day dose escalation) and a continuation treatment.

The initiation treatment corresponds to the first month of treatment with ORALAIR 100 IR & 300 IR sublingual tablets:

| | | |
|---------------|--------|--------------------|
| Small blister | Day 1 | 1 x 100 IR tablet |
| | Day 2 | 2 x 100 IR tablets |
| | Day 3 | 1 x 300 IR tablet |
| Large blister | Day 4 | 1 x 300 IR tablet |
| | Day 5 | 1 x 300 IR tablet |
| | . | |
| | . | |
| | Day 30 | 1 x 300 IR tablet |

From the 2nd month onwards, the continuation treatment must be continued with one ORALAIR 300 IR sublingual tablet per day until the end of the pollen season.

The tablet must be placed under the tongue until complete dissolution (for at least 2 minutes) and then swallowed. On the second day of treatment 2 tablets 100 IR must be placed under the tongue simultaneously and then swallowed.

It is recommended to take the tablet in the morning, on an empty stomach.

No efficacy data on treatment with ORALAIR beyond one grass pollen season is available yet. If no relevant improvement of symptoms is obtained during the first pollen season, there is no indication for continuing the treatment.

Clinical experience on immunotherapy with ORALAIR in young children (< 5 years) and in patients over 45 years of age is lacking.

OVERDOSAGE

No case of overdosing has been reported.

If doses higher than the recommended daily dose are taken, the risk of undesirable effects, including systemic side effects or severe local adverse reactions, is increased. In the case of occurrence of severe symptoms, such as angioedema, difficulty in swallowing, difficulty in breathing, changes in voice, or feeling of fullness in the throat, a physician has to be consulted immediately.

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

Contact the Poisons Information Centre on 13 11 26 for advice on the management of overdose.

PRESENTATION AND STORAGE CONDITIONS

The following pack sizes are available:

Initiation treatment

1 x 3 sublingual tablets of 100 IR in a small blister + 1 x 28 sublingual tablets of 300 IR in a blister. Each blister (Alu/alu) is composed of a film (polyamide/aluminium/polyvinyl chloride) on one side and a heat-sealed foil (aluminium) coated with a varnish (vinyl) on the other side.

Continuation treatment

1 x 30 sublingual tablets of 300 IR in a blister (Alu/alu) composed of a film (polyamide/aluminium/polyvinyl chloride) on one side and a heat-sealed foil (aluminium) coated with a varnish (vinyl) on the other side. Pack of 30, 90 or 100 tablets.

Not all pack sizes may be marketed.

ORALAIR Initiation Treatment sublingual tablets 100 IR & 300 IR (Allergen pollen extract of 5 grasses) - (AUST R 167565)

ORALAIR Continuation Treatment Sublingual Tablets 300 IR (Allergen pollen extract of 5 grasses) - (AUST R 167566)

STORAGE

Store below 30°C.

Store in the original package in order to protect from moisture. Do not freeze.

SHELF LIFE

24 Months.

INCOMPATIBILITIES

Not applicable.

INSTRUCTIONS FOR USE AND HANDLING AND DISPOSAL

No special requirements.

NAME AND ADDRESS OF THE SPONSOR:

Distributed in Australia for Helex-A Pty Ltd by:

Link Medical Products Pty Ltd

5 Apollo Street

Warriewood NSW 2102

AUSTRALIA

Ph: 1800 824166

Fax: 1800 824199

POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE – S4

DATE OF APPROVAL

TGA approval: 28 / April / 2011.

Therapeutic Goods Administration

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[**www.tga.gov.au**](http://www.tga.gov.au)

Reference/Publication #